High Potential Disruption Report
May 2020

Prepared for:
Patient-Centered Outcomes Research Institute
1828 L St., NW, Suite 900
Washington, DC 20036

Contract No. MSA-HORIZSCAN-ECRI-ENG-2018.7.12

Prepared by:
ECRI
5200 Butler Pike
Plymouth Meeting, PA 19462

Investigators
Randy Hulshizer, MA, MS
Damian Carlson, MS
Christian Cuevas, PhD
Andrea Druga, PA-C
Marcus Lynch, PhD
Misha Mehta, MS
Brian Wilkinson, MA
Donna Beales, MLIS
Jennifer De Lurio, MS
Eloise DeHaan, BS
Eileen Erinoff, MLIS
Madison Kimball, MS
Maria Middleton, MPH
Diane Robertson, BA
Kelley Tipton, MPH
Rosemary Walker, MLIS
Karen Schoelles, MD, SM
High Potential Disruption Report
May 2020

Prepared for:
Patient-Centered Outcomes Research Institute
1828 L St., NW, Suite 900
Washington, DC 20036

Contract No. MSA-HORIZSCAN-ECRI-ENG-2018.7.12

Prepared by:
ECRI
5200 Butler Pike
Plymouth Meeting, PA 19462

Investigators:
Randy Hulshizer, MA, MS
Damian Carlson, MS
Christian Cuevas, PhD
Andrea Druga, PA-C
Marcus Lynch, PhD
Misha Mehta, MS
Brian Wilkinson, MA
Donna Beales, MLIS
Jennifer De Lurio, MS
Eloise DeHaan, BS
Eileen Erinoff, MSLIS
Madison Kimball, MS
Maria Middleton, MPH
Diane Robertson, BA
Kelley Tipton, MPH
Rosemary Walker, MLIS
Karen Schoelles, MD, SM
Statement of Funding and Purpose

This report incorporates data collected during implementation of the Patient-Centered Outcomes Research Institute (PCORI) Health Care Horizon Scanning System, operated by ECRI under contract to PCORI, Washington, DC (Contract No. MSA-HORIZSCAN-ECRI-ENG-2018.7.12). The findings and conclusions in this document are those of the authors, who are responsible for its content. No statement in this report should be construed as an official position of PCORI.

An intervention that potentially meets inclusion criteria might not appear in this report simply because the horizon scanning system has not yet detected it or it does not yet meet inclusion criteria outlined in the PCORI Health Care Horizon Scanning System: Horizon Scanning Protocol and Operations Manual. Inclusion or absence of interventions in the horizon scanning reports will change over time as new information is collected; therefore, inclusion or absence should not be construed as either an endorsement or rejection of specific interventions.

A representative from PCORI served as a contracting officer’s technical representative and provided input during the implementation of the horizon scanning system. PCORI does not directly participate in horizon scanning or assessing leads or topics and did not provide opinions regarding potential impact of interventions.

Financial Disclosure Statement

None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

Public Domain Notice

This document is in the public domain and may be used and reprinted without special permission. Citation of the source is appreciated.

All statements, findings, and conclusions in this publication are solely those of the authors and do not necessarily represent the views of PCORI or its Board of Governors. This publication was developed through a contract to support PCORI’s work. Questions or comments may be sent to PCORI at info@pcori.org or by mail to Suite 900, 1828 L Street, NW, Washington, DC 20036. ©2020 Patient-Centered Outcomes Research Institute. For more information see www.pcori.org.

Preface

The PCORI Health Care Horizon Scanning System (HCHSS) conducts horizon scanning of new and emerging health care technologies and innovations with high potential for disruption to the current standard of care to better inform patient-centered outcomes research investments at PCORI.

The HCHSS provides PCORI with a systematic process to identify and monitor technologies and innovations in health care that are in PCORI’s priority areas of interest and to create an inventory of interventions that have the highest potential for disruption to the current standard of care in terms of patient outcomes, health disparities, care delivery, infrastructure, access, and/or costs. It is also a tool for the public to identify information on selected new health care technologies and interventions. Any investigator or funder of research can use the PCORI HCHSS to help select research topics.

The health care technologies and innovations of interest for horizon scanning are those that have yet to become part of established health care practices. These interventions are in late stages of research and development or very early phases of adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the National Academy of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, PCORI is interested—at the outset of this project—primarily in innovations in drugs and biologics, medical devices, and procedures within its selected priority areas of interest for horizon scanning. PCORI may choose, upon future consideration, to expand its focus to include a wider range of interventions (eg, systems innovations).

Horizon scanning involves 2 processes. The first is identifying and monitoring new and evolving health care interventions that purportedly hold potential to diagnose, treat, or otherwise manage a disease or condition or to improve care delivery. The second is analyzing the relevant health care context in which these new and evolving interventions would exist to understand their potential for disruption to the standard of care. The goal of PCORI HCHSS is not to predict future utilization and costs of any health care intervention; rather, the reports are intended to help inform and guide planning and prioritization of research resources.

This edition of the High Potential Disruption Report is the first of 2 editions planned for 2020 and includes topics (ie, interventions intended for a specific use within a specific patient population) and trends (ie, high-level disruptions occurring within or across clinical areas from a combination of factors that, taken together, create a paradigm shift) that have been identified by stakeholders and the horizon scanning team as having high potential to cause disruption to health care.

We welcome comments on this report. Send comments by mail to William Lawrence, MD, MS, Patient-Centered Outcomes Research Institute, 1828 L St., NW, Suite 900, Washington, DC 20036, or by email to horizonscan@pcori.org.
Contents

Introduction ............................................................................................................................................................. 1

Background ............................................................................................................................................................. 1

System Overview ..................................................................................................................................................... 1
  Broad Scanning to Identify Topics and Trends ...................................................................................................... 1
  Developing Topic and Trend Profiles .................................................................................................................. 2
  Archiving Topics and Trends .................................................................................................................................... 2

Report Methods .................................................................................................................................................... 3
  Selecting Topics and Trends for the High Potential Disruption Report ............................................................. 3
  High Potential Disruption Report Topic Selection Meeting .................................................................................. 3
  Producing the High Potential Disruption Report .................................................................................................. 4

Reporting Period Summary .................................................................................................................................... 4

Chapter 1. Alzheimer’s Disease and Other Dementias ...................................................................................... 9

Chapter Summary .................................................................................................................................................... 9

Topic Summaries .................................................................................................................................................. 10
  Periodic Therapeutic Plasma Exchange (Alzheimer’s Management by Albumin Replacement Protocol) to Treat Mild to Moderate Alzheimer’s Disease .................................................................................. 10
  Highlights ............................................................................................................................................................................. 10

Chapter 2. Cancer .............................................................................................................................................. 13

Chapter Summary .................................................................................................................................................... 13

Topic Summaries .................................................................................................................................................. 15
  Avapritinib (Ayvakit) to Treat Advanced Systemic Mastocytosis ........................................................................ 15
  Capmatinib (INC280) to Treat Locally Advanced or Metastatic, MET-Altered Non–Small Cell Lung Cancer .............................................................................................................................................. 18
  Leflulceol (LN-144) as Second-Line Treatment for Locally Advanced or Metastatic Melanoma .......... 22
  MDNA55 to Treat First Recurrence of Recurrent Glioblastoma Multiforme .................................................. 26
  Nanoparticle Albumin-Bound Sirolimus (ABI-009) to Treat Locally Advanced or Metastatic Perivascular Epithelioid Cell Sarcoma .................................................................................................................. 28
  Oportuzumab Monatox (Vicinium) to Treat Non–Muscle Invasive Bladder Cancer (Third-line Setting) ............................................................................................................................................................................. 31
  Pembrolizumab (Keytruda) as First-Line Treatment for Locally Advanced or Metastatic, Recurrent Head and Neck Squamous Cell Carcinoma .............................................................................................................. 34
Pemigatinib (Pemazyre) to Treat Locally Advanced or Metastatic Cholangiocarcinoma Harboring FGFR2 Fusions or Rearrangements ............................................................................................................................ 38
Pexidartinib (Turalio) to Treat Tenosynovial Giant Cell Tumors ............................................................................................................................ 42
Remestemcel-L (Ryoncil) to Treat Pediatric Steroidal-Refractory Acute Graft-Versus-Host Disease ............................................................................................................................ 45
Sacituzumab Govitecan-hziy as Third-Line Treatment for Locally Advanced or Metastatic Triple-Negative Breast Cancer .............................................................................................................. 49
Selpercatinib (LOXO-292) to Treat Locally Advanced or Metastatic RET-Altered Thyroid Cancer ................................................................................................................................................................... 52
Sodium Thiosulfate (Pedmark) to Prevent Cisplatin-Mediated Ototoxicity ............................................................................................................................ 56
Tazemetostat (Tazverik) to Treat Locally Advanced or Metastatic Epithelioid Sarcoma ............................................................................................................................ 58

Chapter 3. Cardiovascular Diseases .................................................................................................................................................. 63

Chapter Summary ................................................................................................................................................. 63
Topic Summaries .................................................................................................................................................. 64
Neovasc Reducer to Treat Refractory Angina ....................................................................................................... 64
Organ Care System Heart to Treat End-Stage Heart Failure Requiring Transplantation ........................................................ 69
Paradise Renal Denervation System to Treat Resistant Hypertension ............................................................................ 73
Tafamidis (Vyndaqel, Vyndamax) to Treat Amyloid Transthyretin-Mediated Cardiomyopathy ............................................................................................................................ 78

Chapter 4. Mental and Behavioral Health Conditions ................................................................................................................................................. 82

Chapter Summary ............................................................................................................................................................................................................................................................................................................................................................................................ 82
Topic Summaries ............................................................................................................................................................................................................................................................................................................................................................................................ 83
3,4-Methylenedioxymethamphetamine-Assisted Psychotherapy to Treat Severe Posttraumatic Stress Disorder ............................................................................................................................................................................................................................................................................................................................................................................................ 83
SEP-363856 to Treat Schizophrenia ............................................................................................................................................................................................................................................................................................................................................................................................ 87

Chapter 5. Rare Diseases ................................................................................................................................................................................................................................................................................................................................................. 91

Chapter Summary .................................................................................................................................................................................................................................................................................................................................................. 91
Topic Summaries .................................................................................................................................................................................................................................................................................................................................................. 93
ABO-102 to Treat Sanfilippo Syndrome Type A ............................................................................................................................ 93
Afamelanotide (Scenesse) to Treat Erythropoietic Protoporphyr ia ............................................................................................................................ 98
Apremilast (Otezla) to Treat Behçet’s Disease ............................................................................................................................ 101
Arimoclomol (BRX-345) to Treat Niemann-Pick Disease Type C ............................................................................................................................ 104
CAP-1002 to Treat Duchenne Muscular Dystrophy ............................................................................................................................ 104
Casimersen to Treat Duchenne Muscular Dystrophy ............................................................................................................................ 110
Crizanlizumab-tmca (Adakveo) to Prevent Vaso-occlusive Crises in Sickle Cell Disease ............................................................................................................................................................................................................................................................................................................................................................................................ 114
Eculizumab (Soliris) to Treat Neuromyelitis Optica Spectrum Disorder ................................................................. 118
Elexacaftor/Tezacaftor/Ivacaftor and Ivacaftor (Trikafta) to Treat Cystic Fibrosis .......................................................... 122
Fenfluramine Hydrochloride Low-Dose (Fintepla) to Treat Dravet Syndrome ................................................................. 126
Galcanezumab-gnlm (Emgality) to Treat Episodic Cluster Headache ........................................................................ 130
Givosiran (Givlaari) to Prevent and Treat Acute Hepatic Porphyria .......................................................................... 133
Golodirsen (Vyonds 53) to Treat Duchenne Muscular Dystrophy ............................................................................. 137
Idebenone (Puldysa) to Treat Duchenne Muscular Dystrophy ..................................................................................... 141
LentiGlobin to Treat Transfusion-Dependent β-Thalassemia ......................................................................................... 146
Luspatercept-aamt (Reblozyl) to Treat Transfusion-Dependent β-Thalassemia ............................................................. 151
Onasemnogene Abeparvovec-xioi (Zolgensma) to Treat Spinal Muscular Atrophy ......................................................... 155
OTL-101 to Treat Adenosine Deaminase–Severe Combined Immunodeficiency .......................................................... 161
Palovarotene to Treat Fibrodysplasia Ossificans Progressiva ..................................................................................... 164
PTC-AADC to Treat Aromatic L-Amino Acid Decarboxylase Deficiency ........................................................................ 167
RVT-802 to Treat Pediatric Congenital Athymia (DiGeorge Syndrome Immunodeficiency, CHARGE Syndrome, FOXN1 Deficiency) ......................................................................................... 172
Valoctocogene Roxaparvovec to Treat Hemophilia A ................................................................................................. 174
Voxelotor (Oxbryta) to Treat Sickle Cell Disease ......................................................................................................... 178

Chapter 6. Potentially Disruptive Trends ................................................................................................................. 182

Chapter Summary ......................................................................................................................................................... 182

Trend Summaries .......................................................................................................................................................... 183

Artificial Intelligence Analysis of Imaging Scans to Screen for Cancer or Confirm a Cancer Diagnosis .......................................................... 183
Artificial Intelligence for Image Triage to Prioritize Emergency Cases ........................................................................ 184
Artificial Intelligence Operator Guidance for Cardiac Ultrasound Scans ....................................................................... 186
Artificial Pancreas Systems to Treat Type 1 Diabetes Mellitus ..................................................................................... 188
Comprehensive Genomic Profiling in Patients Who Have Cancer to Identify Targeted Therapy Options .............................................................. 190
Direct-to-Consumer Genetic Testing Partnerships With Pharmaceutical Companies to Facilitate Drug Development and Treatment ........................................................................................................ 192
Disease-Modifying Agents (Immunomodulators) to Mitigate Severe COVID-19 Symptoms .............................................................. 193
Emerging Antiviral Therapies for COVID-19 .............................................................................................................. 195
Integrated Electronic Health Solutions to Improve Cardiovascular Care ......................................................................... 197
N-of-1 Trials to Research Patient-Centered Outcomes ............................................................................................ 199
**Introduction**

**Background**

Horizon scanning identifies technology and systems innovations that could disrupt or cause significant shifts in health care. In health care, horizon scanning can identify new (and new uses of existing) diagnostic tests and procedures, health care delivery innovations, medical devices, mental and behavioral health interventions, pharmaceuticals, public health and health promotion activities, rehabilitation interventions, and therapeutic interventions.

Health care horizon scanning has typically informed strategic planning activities. Public and private entities around the world have long used formal or informal health care horizon scanning programs for purposes including commercial planning, health services research prioritization, financial or operational planning, controlled diffusion of technologies, and provision of information to policymakers, purchasers, and providers of health care.

**System Overview**

The PCORI Health Care Horizon Scanning System identifies and monitors topics (ie, interventions intended for a specific use within a specific patient population) likely to be available for clinical use (ie, outside the research environment) within 3 years and likely to cause significant disruption (ie, change or shift) in one or more key dimensions of health care in the United States. Examples of these dimensions include patient health outcomes, access to care, care setting and delivery processes, disparities, and costs of care. The HCHSS monitors topics for up to 1 year after initial clinical availability.

Initially, PCORI has defined its project scope as interventions with high potential for disruption in 5 priority areas: Alzheimer’s disease and other dementias, cancer, cardiovascular diseases, mental and behavioral health conditions, and rare diseases. In addition, the system captures high-level disruptive trends across all clinical areas, which may lead PCORI to expand the project scope to include other priority areas in the future.

**Broad Scanning to Identify Topics and Trends**

We scan information sources broadly within each priority area to detect leads for potential topics that meet criteria as described above. Analysts review leads to discover potential topics or trends and, if they meet inclusion criteria, create topic records—encompassing PICO (intended patient population, intervention, comparators to the intervention, and patient-oriented outcomes of interest) information and key regulatory information (if the topic is subject to a regulatory pathway)—or trend records, which include a description of the trend, potential clinical areas affected, and lists of potential threats and opportunities posed by the trend.

Analysts present potential topics and trends at nomination meetings. After a brief presentation and discussion, HCHSS team members vote in blinded fashion to include or exclude the topic or trend based on criteria described in the *PCORI Health Care Horizon Scanning System: Horizon Scanning Protocol and Operations Manual*. All included topics and trends are
reported in the quarterly Status Report (see the most recent volume, *Horizon Scanning Status Report, Volume 2, Issue 1, March 2020*).

**Developing Topic and Trend Profiles**

Included topics with late-phase clinical data are further developed as topic profiles—reports that rely on focused searches and more robust analysis. Each topic profile is sent to stakeholders for comment with the goal of obtaining a maximum of 9, but at least 5, sets of comments and ratings before a topic is eligible for consideration for this report. Stakeholders provide varied perspectives and/or areas of knowledge in health care (eg, clinical, health systems, research, nursing), ideally including at least one patient, patient representative, or caregiver. The commenter reads the topic profile and completes a 6-question survey, which elicits ratings—on a scale of 1 (low disruption potential) to 4 (high disruption potential)—about the intervention’s potential to disrupt a number of key areas of health care. Commenters provide a written rationale for each rating. ECRI follows strict conflict-of-interest policies and ensures that comments and ratings received from any stakeholder with potential conflicts of interest are balanced by inputs from other neutral parties, including ECRI experts. See the *PCORI Health Care Horizon Scanning System: Horizon Scanning Protocol and Operations Manual* for more details about ECRI’s conflict-of-interest policy.

Included trends are developed into trend profiles, revised based on comments from the nomination meeting (if needed) and edited before being sent to internal ECRI stakeholders for comment. Each trend profile is posted to an internal ECRI online bulletin board, and a pool of about 50 ECRI internal stakeholders—representing health care business and finance, clinical engineering, health systems, health care generalist, information technology, nursing, physician, physician assistant, and research perspectives—is invited to provide input on each trend. Any stakeholder from the pool may self-select to review a trend, based on his or her expertise and interest. The horizon scanning project manager monitors the process to ensure that at least 5 stakeholders representing appropriate perspectives review each trend. If a stakeholder chooses to review a trend, he or she reads a trend summary and then completes a brief online survey to elicit his or her perspectives on the trend’s potential to disrupt health care, the expected timing of the disruption, and the likelihood of the trend to cause disruption.

**Archiving Topics and Trends**

An included topic may be archived for one or more of the following reasons: (1) Comments from stakeholders overwhelmingly suggest that the intervention is unlikely to cause significant disruption in US health care in the next 3 years; (2) development of the intervention has ceased; or (3) the intervention has been clinically available outside the clinical research environment for longer than 1 year.

An included trend may be archived after stakeholder review, if ratings and comments from stakeholders overwhelmingly suggest that the trend is unlikely to cause significant disruption in US health care in the next 3 years.
**Report Methods**

The purpose of the stakeholder survey process is to help determine which topics and trends have the highest potential to significantly disrupt patient care in some manner, such as patient outcomes, access to care, health disparities, care delivery, staffing, and costs. Twice annually, the horizon scanning team reviews all stakeholder comments and ratings (for currently included topics and trends) received in the past 12 months. This review begins a process culminating in the production and delivery of the *High Potential Disruption Report*, which highlights topics and trends with high potential to be significantly disruptive to patient care in the United States within the next 3 years.

**Selecting Topics and Trends for the *High Potential Disruption Report***

To be considered for inclusion in the *High Potential Disruption Report*, topics and trends must be active (ie, not archived) and must have received a minimum of 5 stakeholder surveys within the past 12 months. Topics and trends selected for inclusion are those for which, based on review of stakeholder ratings, stakeholders generally agreed have high potential to be significantly disruptive to health care in the United States. Topics and trends selected for inclusion are assigned to analysts for report drafting.

Analysis of stakeholder comments must generally support conclusions suggested by ratings. Topics with borderline ratings, high variance, or questionable comments are scheduled for discussion at the *High Potential Disruption Report* topic selection meeting (see below). Each scheduled topic is reviewed by the analyst assigned to the applicable clinical priority area. The analyst rereads the topic profile and reviews each survey received for the topic, paying particular attention to stakeholder comments. The analyst prepares a summary of stakeholder comments to present at the topic selection meeting.

Trends with borderline ratings, high variance, or questionable comments are reviewed by a 3-member panel of senior horizon scanning team members to determine inclusion or exclusion. A majority affirmative vote by this panel selects the trend for inclusion.

See the *PCORI Health Care Horizon Scanning System: Horizon Scanning Protocol and Operations Manual* for a more complete description of the topic and trend selection processes.

**High Potential Disruption Report Topic Selection Meeting**

For topics for which consensus in stakeholder ratings is not clear regarding a topic’s disruptive potential (ie, there is wide variation among stakeholder opinions about whether the topic will be highly disruptive), the horizon scanning team meets to discuss and vote on whether to include these topics in the *High Potential Disruption Report*.

The assigned analyst for each topic presents a summary of stakeholder comments and ratings received for the topic. A brief discussion then takes place, during which team members may ask questions or provide perspectives regarding the topic’s disruptive potential. After the discussion, a blinded vote determines whether the topic should be included in the *High Potential Disruption Report*. The topic must receive a majority affirmative vote to be included. Topics selected for inclusion are assigned to analysts for report drafting.
Producing the High Potential Disruption Report

After topic and trend selection, the project manager creates a production schedule and assigns the selected topics and trends to the appropriate analysts for report drafting.

Analysts draft an analysis of each topic, which includes highlights, PICO information, an evidence development summary, manufacturer and regulatory information, cost information (if available), and a summary of key stakeholder perspectives. Likewise, analysts draft an analysis for each trend, which includes a trend description, a list of clinical areas potentially disrupted, lists of potential opportunities (ie, pros) and threats (ie, cons), and a summary of key stakeholder perspectives.

Summaries are compiled into chapters: one chapter for each of the 5 PCORI-defined priority areas and one chapter for potentially disruptive trends. After a chapter has been compiled, the project manager reviews all content and writes a chapter summary, which provides basic information and statistics about topics or trends included in the chapter and currently monitored or recently archived in the HCHSS. Each chapter is reviewed carefully by the medical copyeditor, senior technical reviewer, and project director before compilation into the final report. After compilation, the project manager reviews the content and writes the overall reporting period summary, which provides basic information and statistics about topics or trends included in the report and currently monitored or recently archived in the HCHSS.

Reporting Period Summary

The PCORI HCHSS began operating in December 2018. Since then, review of about 5000 information leads has led to the identification of about 530 potential topics across the 5 PCORI priority areas and 80 high-level trends occurring in all areas of health care.

As of April 3, 2020, after subjecting the potential topics to our inclusion criteria and nomination process, 311 topics have been selected. Of these, 227 topics are being actively monitored in the system; 84 topics have been archived. These 227 topics represent 132 diseases/conditions and span the PCORI-defined priority areas as follows (see also Figure 1):

- Alzheimer’s disease and other dementias: 10 topics (4%)
- Cancer: 79 topics (35%)
- Cardiovascular diseases: 23 topics (10%)
- Mental and behavioral health conditions: 16 topics (7%)
- Rare diseases: 99 topics (44%)
Across all priority areas, the 227 monitored topics represent the following therapeutic classes (also see Figure 2):

- Cell therapy: 21 topics (9.3%)
- Device (nonimplantable): 10 topics (4.4%)
- Gene therapy: 17 topics (7.5%)
- Immunotherapy: 3 topics (1.3%)
- Implant: 6 topics (2.6%)
- Monoclonal antibody: 11 topics (4.8%)
- Other biotechnology: 18 topics (7.9%)
- Pharmaceutical: 131 topics (57.7%)
- Procedure (nonsurgical): 1 topic (0.4%)
- RNA interference: 3 topics (1.3%)
- Viral vector therapy: 6 topics (2.6%)

*Note:* Total does not equal 100% because of rounding.
Of these 227 actively monitored topics, we have selected—based on the procedure described in Report Methods—44 topics for inclusion in this report, distributed across the PCORI priority areas as follows (see also Figure 3):

- Alzheimer’s disease and other dementias: 1 topic (2%)
- Cancer: 14 topics (32%)
- Cardiovascular diseases: 4 topics (10%)
- Mental and behavioral health conditions: 2 topics (5%)
- Rare diseases: 23 topics (51%)
Likewise, as of April 3, 2020, after subjecting potential trends to our inclusion criteria and nomination process, 32 trends occurring across clinical areas or within a clinical area that can potentially create a paradigm shift in health care (ie, large, high-level disruptions) have been selected and are being actively monitored in the system. Among these 32 trends, 4 themes have emerged (also see Figure 4):

- Artificial intelligence and machine learning: 10 trends (31%)
- Health information technology, apps, and smart devices: 5 trends (16%)
- Innovative treatment models: 10 trends (31%)
- Proteomics, genomics, and personalized medicine: 7 trends (22%)
Of these 32 actively monitored trends, we have selected—based on the procedure described in Report Methods—15 trends for inclusion in this report, distributed by theme as follows (see also Figure 5):

- Artificial intelligence and machine learning: 3 trends (20%)
- Health information technology, apps, and smart devices: 3 trends (20%)
- Innovative treatment models: 4 trends (27%)
- Proteomics, genomics, and personalized medicine: 5 trends (33%)

Figure 5. Percentage of Trends Selected for Report by Theme
Chapter 1. Alzheimer’s Disease and Other Dementias

Chapter Summary

For the Alzheimer’s disease and other dementias priority area, we considered for inclusion 2 topics for which (1) preliminary phase III data for drugs, phase II (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled and sent for stakeholder comment before March 10, 2020; and (3) we received at least 5 sets of comments and ratings from stakeholders between April 1, 2019, and March 20, 2020.

As of March 10, 2020, we were monitoring 10 topics in this priority area, including the 2 topics considered for inclusion in this report. These 10 topics will be listed in the June 2020 PCORI Health Care Horizon Scanning System: Horizon Scanning Status Report. We also archived one topic in November 2019. A description of that topic and the reason it was archived can be found in the March 2020 Status Report.

The 10 monitored topics encompass pharmaceuticals and biotechnologies for treating Alzheimer’s disease and/or related symptoms (eg, agitation). Of these, 8 topics are too early in development to meet criteria (as outlined above) for eligibility for this report.

Topic Considered for Inclusion in This Report

Table 1.1 lists the single topic selected for inclusion during the High Potential Disruption Report decision meeting. Most of the horizon scanning team voted that it had high potential for disruption, based on stakeholder ratings and comments and available data.

Table 1.1. Included Topic for Priority Area: Alzheimer’s Disease and Other Dementias

<table>
<thead>
<tr>
<th>Topic title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periodic therapeutic plasma exchange (Alzheimer’s management by albumin replacement protocol) to treat mild to moderate Alzheimer’s disease</td>
</tr>
</tbody>
</table>

Table 1.2 lists the single topic considered, but not selected, for inclusion during the High Potential Disruption Report decision meeting. A majority of the voting team agreed that the topic lacked high potential for disruption, based on stakeholder ratings and comments and available data. The record notes the reasons for exclusion.

Table 1.2. Topics Considered but Not Included for Priority Area: Alzheimer’s Disease and Other Dementias

<table>
<thead>
<tr>
<th>Topic title</th>
<th>Exclusion reason(s) and notes based on stakeholder comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pimavanserin (Nuplazid) to treat dementia-related psychosis</td>
<td>Data from late-phase trials showed some clinical effect for short-term health outcomes; however, concerns exist about the risk of adverse events. More data from longer trials are needed.</td>
</tr>
</tbody>
</table>
**Topic Summaries**

We present below one summary of a topic deemed to have high potential for disruption.

**Periodic Therapeutic Plasma Exchange (Alzheimer’s Management by Albumin Replacement Protocol) to Treat Mild to Moderate Alzheimer’s Disease**

**Highlights**

- Periodic therapeutic plasma exchange is an investigational therapy intended to slow cognitive decline and the progression of mild to moderate Alzheimer’s disease (AD).
- AD affects millions of Americans, particularly adults aged 55 to 85 years, and a significant unmet need exists for treatments.
- Although the use of human albumin in plasma exchange has been researched for more than 10 years, results from a recent clinical trial have generated renewed interest in this therapy.
- Stakeholders commenting on this topic thought this treatment could address the unmet need and improve patient-oriented health outcomes, including quality of life.
- Most stakeholders thought that the cost and delivery of the treatment (eg, infusion center resources, intravenous immunoglobulin [IVIG] shortages) would create disparities in access to care and/or add to the burden of care for these patients and caregivers.
- Stakeholders recommended further research to address the treatment’s long-term effectiveness and validate its purported mechanism of action.

**Patient Population**

Periodic therapeutic plasma exchange (Alzheimer’s management by albumin replacement [AMBAR] protocol) is intended for adults aged 55 to 85 years with mild to moderate AD.

**Intervention**

AD is the leading cause of dementia and has no effective cure and limited options for symptom management. No disease-modifying treatments are available.¹

AMBAR is a therapeutic approach under study that involves performing plasma exchange, using albumin to replace the plasma volume that is removed.² Researchers theorize that such replacement can lead to a shift of the dynamic equilibrium that exists between brain cerebrospinal fluid (CSF) and plasma amyloid-β peptide (Aβ; most of it is bound to albumin), thereby improving symptoms and delaying progression of cognitive decline in the intended population.²,³

Albumin infused as volume replacement would theoretically be able to bind and capture additional free-circulating Aβ. These processes purportedly reduce levels of free Aβ in plasma, resulting in a diffusion gradient that draws Aβ from the CSF and slows the progression of Aβ-driven AD pathogenesis.²

A neurologist refers a patient to an infusion center for the plasma exchange. During a 6-week intensive period, patients undergo weekly total plasma exchange (2.5 to 3 L plasma removal) and volume replacement with a 5% albumin solution (Albutein). A 12-month maintenance phase follows, during which patients undergo monthly low-volume plasma exchange (650 to 880 mL plasma removal) and volume replacement with a 20% albumin solution or IVIG.⁴
Three regimens are being tested that use some combination of albumin with or without IVIG as the replacement:

- Three 4-month cycles consisting of 20 g IVIG in month 1 and 40 g albumin in months 2 to 4
- Three 4-month cycles consisting of 10 g IVIG in month 1 and 20 g albumin in months 2 to 4
- Twelve 1-month cycles consisting of 20 g albumin

The Alzheimer’s Association website offers more information about AD.

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified no ongoing trials for this topic.

Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed late-phase trial with published results. We summarize this most recent and indication-relevant study with results as written in a news release.

The following abbreviations are used in this section: AD, Alzheimer’s disease; ADCS-CGIC, Alzheimer’s Disease Cooperative Study – Clinical Global Impression of Change; AMBAR, Alzheimer’s management by albumin replacement; CDR-Sb, Clinical Dementia Rating – Sum of Boxes.


- **Patient population/planned enrollment**: Adults (n = 347) aged 55 to 85 years who had mild to moderate AD
- **Study design**: A phase II/III, randomized controlled, parallel-assignment study to evaluate the efficacy and safety of short-term plasma exchange followed by long-term plasmapheresis with human albumin infusion combined with intravenous immunoglobulin in patients with mild to moderate AD
- **Primary outcome**: Cognitive performance from baseline to 14 months
- **Secondary outcomes**: Quality of life from baseline to 14 months and changes in cognitive function from baseline to 14 months
- **Results presented by study authors**: The following results were presented at the Alzheimer’s Association International Conference (AAIC) 2019 in Los Angeles:
  
  “These results showed a statistically significant reduction of 61% in disease progression in both primary efficacy endpoints, ADAS-Cog (Alzheimer’s Disease Assessment Scale – cognitive) and ADCS-ADL (Alzheimer’s Disease Cooperative Study – Activities of Daily Living) scales, in the cohort of moderate patients. Regarding specific cognitive aspects, the AMBAR treatment showed positive effects on memory in the moderate patients, and on language and processing speed in patients with the disease in a mild stage. The additional results presented today at the AAIC point in the same direction in all treated groups across the different relevant endpoints that combine assessments of cognitive status and daily functioning: CDR-Sb and ADCS-CGIC. In particular, the CDR-Sb scale — which assesses memory, orientation, judgment, community affairs, home and hobbies, and personal care — shows a statistically significant 71% less decline with respect to placebo in patients treated as a whole. This significance remains when analyzing the three study treatment arms separately, with less decline at 14 months that ranged 65-71%. Analysis of mild and moderate cohorts displays a statistically significant less decline of 53% in moderate patients and a statistically significant improvement in mild ones, suggesting that for
this endpoint the effect of the treatment might be higher in earlier phases of the disease. For the ADCS-CGIC scale, which assesses several domains of cognition, daily functioning and behavior from both the patient and the caregiver perspective, the results are in line with those of the CDR-Sb scale: a statistically highly significant stabilization is observed in all treated patients with respect to placebo. This effect remains in all three treatment arms when analyzed separately. As in the case of CDR-Sb scale, the positive and statistically significant effect is also observed for ADCS-CGIC in the moderate-patient cohort. Moreover, there’s a remarkable statistically significant improvement in the mild-patient cohort when compared with placebo at 14 months of treatment. All these effects are replicated when the three treatment arms are assessed against placebo.”

Manufacturers and Regulatory Status

The Albutein and IVIG (Flebogamma 5% DIF) treatment protocol (Grifols, SA, Barcelona, Spain) was evaluated in a phase II/III clinical trial for treating mild to moderate AD. FDA has not approved Albutein to treat AD, but it has been commercially available since 1978, and FDA has approved it for use in several other indications. IVIG also is not labeled for use in AD but is indicated for treating primary (inherited) immunodeficiency in adults and pediatric patients aged 2 years or older. Albutein and IVIG, as used in the AMBAR protocol, could be administered as an off-label treatment for mild to moderate AD. In a December 6, 2019, news release, the company announced that it would discuss the next steps for the AMBAR clinical development program with FDA.

Cost Information

According to ECRI’s PriceGuide database, member hospitals reported a median price paid of about $34 for 250 mL of 5% Albutein, $36 for 50 mL of 25% Albutein, and $836 for 10 g of 5% Flebogamma IVIG (as of August 29, 2019). Using these figures, the drug cost for 14 months would range from $5474 to $8501, depending on the prescribed dosing regimen. These costs do not include the costs of administration and other fees associated with an infusion procedure.

Key Stakeholder Perspectives

Ten stakeholders, reflecting caregiver, clinical, and health systems perspectives, provided comments and ratings on this periodic plasma exchange treatment. The list below provides a summary of key stakeholder perspectives.

- AMBAR protocol has the potential to slow AD progression with high potential to disrupt paradigm of care, because it is an infusion-based treatment rather than an oral drug.
- AMBAR might disrupt costs for payers and health care facilities depending on insurance reimbursement and copayments required of patients. The treatment would save overall costs because of decreased needs for home health aides or long-term care facilities.
- Concerns exist regarding AMBAR’s long-term effectiveness (beyond 14 months) as well as its purported mechanism of action of lowering cerebral amyloid.
- Given the absence of any other effective treatments addressing slow cognitive decline, this intervention might provide significant relief to caregivers by improving patients’ quality of life.
Chapter 2. Cancer

Chapter Summary

For the cancer priority area, we considered for inclusion 20 topics for which (1) preliminary phase III data for drugs, phase II (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled and sent for stakeholder comment before March 10, 2020; and (3) we received at least 5 sets of comments and ratings from stakeholder commenters between April 1, 2019, and March 20, 2020.

As of March 10, 2020, we were monitoring 83 topics in this priority area, including the 20 considered for inclusion in this report. These 83 topics will be listed in the June 2020 PCORI Health Care Horizon Scanning System: Horizon Scanning Status Report. We also archived 2 topics in February 2020. Descriptions of these topics and the reasons they were archived can be found in the March 2020 Status Report.

The 83 monitored topics encompass pharmaceuticals, gene and cellular therapies, viral vector therapies, monoclonal antibodies, and devices intended to treat 37 cancers and/or related conditions. Five topics were developed as topic profiles to be sent for stakeholder comment; however, fewer than 5 sets of stakeholder comments were received for these topics before March 10, 2020, so they were not considered for inclusion in this report. The remaining 58 topics are too early in development to meet criteria (as outlined above) for eligibility for this report.

Topics Considered for Inclusion in This Report

Table 2.1 lists 14 topics selected for inclusion during the High Potential Disruption Report decision meeting. A majority of the horizon scanning team voted that these topics had high potential for disruption, based on stakeholder ratings and comments and available data. Topics are listed and discussed alphabetically by title.

Table 2.1. Included Topics for Priority Area: Cancer

<table>
<thead>
<tr>
<th>Topic title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avapritinib (Ayvakit) to treat advanced systemic mastocytosis</td>
</tr>
<tr>
<td>Capmatinib (INC280) to treat locally advanced or metastatic, MET-altered non-small cell lung cancer⁴</td>
</tr>
<tr>
<td>Lifileucel (LN-144) as second-line treatment for locally advanced or metastatic melanoma</td>
</tr>
<tr>
<td>MDNA55 to treat first recurrence of recurrent glioblastoma multiforme</td>
</tr>
<tr>
<td>Nanoparticle albumin-bound sirolimus (ABI-009) to treat locally advanced or metastatic perivascular epithelioid cell sarcoma</td>
</tr>
<tr>
<td>Oportuzumab monatox (Vicinium) to treat non–muscle invasive bladder cancer (third-line setting)</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda) as first-line treatment for locally advanced or metastatic, recurrent head and neck squamous cell carcinoma</td>
</tr>
<tr>
<td>Pemigatinib (Pemazyre) to treat locally advanced or metastatic cholangiocarcinoma harboring FGFR2 fusions or rearrangements⁴</td>
</tr>
<tr>
<td>Pexidartinib (Turalio) to treat tenosynovial giant cell tumors</td>
</tr>
</tbody>
</table>
Table 2.2 lists 6 topics considered, but not selected, for inclusion during the High Potential Disruption Report decision meeting. A majority of the voting team agreed that these topics lacked high potential for disruption, based on stakeholder ratings and comments and available data. Each record contains a note explaining the reasons for exclusion.

<table>
<thead>
<tr>
<th>Topic title</th>
<th>Exclusion reason(s) and notes based on stakeholder comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remestemcel-L (Ryoncil) to treat pediatric steroid-refractory acute graft-versus-host disease</td>
<td></td>
</tr>
<tr>
<td>Sacituzumab govitecan-hziy as third-line treatment for locally advanced or metastatic triple-negative breast cancer</td>
<td></td>
</tr>
<tr>
<td>Selpercatinib (LOXO-292) to treat locally advanced or metastatic RET-altered thyroid cancer</td>
<td></td>
</tr>
<tr>
<td>Sodium thiosulfate (Pedmark) to prevent cisplatin-mediated ototoxicity</td>
<td></td>
</tr>
<tr>
<td>Tazemetostat (Tazverik) to treat locally advanced or metastatic epithelioid sarcoma</td>
<td></td>
</tr>
<tr>
<td>Enfortumab vedotin (Adcetris) to treat advanced or metastatic urothelial cancer (third-line setting)</td>
<td>Early clinical trial results for enfortumab vedotin suggest a small improvement to patient health outcomes, and a large disruption is unlikely. However, results from an ongoing phase III clinical trial for overall survival and progression-free survival are needed to evaluate its potential for disruption.</td>
</tr>
<tr>
<td>Lurbinectedin (Zepsyre) to treat extensive-stage small cell lung cancer (second-line setting)</td>
<td>Early data from a phase II trial appear to show that lurbinectedin has the potential to improve health outcomes, but the enrolled patients are not representative of the actual small cell lung cancer population. Additional data from the phase III ATLANTIS trial are needed to evaluate lurbinectedin’s safety and efficacy.</td>
</tr>
<tr>
<td>Melflufen (Ygalo) to treat relapsed and refractory multiple myeloma</td>
<td>Based on results in clinical trials, the risk-to-benefit ratio for melflufen is high, which would limit the likelihood of its approval and uptake. In addition, any potential benefit from melflufen would likely be incremental.</td>
</tr>
<tr>
<td>ONC201 to treat recurrent H3 K27M-variant glioma (second recurrence)</td>
<td>Results from a phase II trial suggest that ONC201 might have some activity against tumors without causing serious adverse events, but the data do not show that ONC201 substantially extends progression-free survival and overall survival. Additional data from a larger randomized trial are needed to evaluate ONC201’s disruptive potential.</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda) plus lenvatinib (Lenvima) to treat locally advanced, recurrent, or metastatic endometrial cancer (second-line setting)</td>
<td>Although this combination therapy has some potential to improve patient health outcomes, it is unlikely to be a preferred regimen because of the adverse events and a 19% discontinuation rate due to treatment-related adverse events. Therefore, its disruptive potential is small.</td>
</tr>
<tr>
<td>UGN-101 (MitoGel) to treat low-grade upper tract urothelial cancer (first-line setting)</td>
<td>UGN-101 administration is not curative and does not obviate the need for surgery once the disease progresses. Comparative effectiveness data are needed to support a substantial clinical effect.</td>
</tr>
</tbody>
</table>
**Avapritinib (Ayvakit) to Treat Advanced Systemic Mastocytosis**

**Highlights**

- Avapritinib (Ayvakit) is an oral small-molecule inhibitor of the receptor tyrosine kinase mast/stem cell growth factor receptor, Kit (KIT), and is under study for treating advanced systemic mastocytosis (SM), a rare blood cancer that lacks safe and effective treatment options.
- A specific mutation in the proto-oncogene *c-kit* is the molecular driver in nearly all patients with SM. By inhibiting the aberrant kinase activity of this mutated form of KIT, avapritinib purportedly has the potential to modify the disease.
- In a phase I, single-arm trial of avapritinib to treat patients with advanced SM, the overall response rate was 83%. Among responders, the duration of response lasted at least 12 months in 76% of patients.
- Stakeholders commenting on this topic thought that the preliminary clinical data for avapritinib suggest it might be more effective than current treatments for advanced SM and so has substantial potential to improve health outcomes for a patient population with a debilitating disease. However, commenters cautioned that this interpretation was based on a small amount of data from a small clinical trial with no control arm and that avapritinib’s effectiveness would need to be demonstrated in further studies.

**Patient Population**

Avapritinib is intended for adults aged 18 years or older with advanced SM, including aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL).

**Intervention**

Avapritinib is a small-molecule inhibitor of the receptor tyrosine kinase KIT that is being developed to treat advanced SM, a rare type of hematologic malignancy characterized by mast cell accumulation in skin, bone marrow, and internal organs (eg, gastrointestinal tract, liver, lymph nodes, spleen). SM is divided into 5 subtypes based on symptoms, presentation, and severity, with indolent SM and smoldering SM representing mild subtypes and ASM, SM-AHN, and MCL representing severe subtypes. The National Institutes of Health’s Genetic and Rare Diseases Information Center offers more information on SM.

SM is a clonal mast cell disease characterized by activating genetic variations in *c-kit*. These variants lead to decreased cell death (ie, apoptosis) and increased cell proliferation in malignant mast cells. Tyrosine kinase inhibitors (TKIs) capable of inhibiting the KIT protein (eg, imatinib, midostaurin) are used in treating SM; however, available TKIs have significant shortcomings.

For instance, imatinib is ineffective against a KIT variant (KIT D816V) that is present in more than 90% of SM cases; therefore, imatinib is suitable for use only in the minority of SM cases that test negative for KIT D816V. Although midostaurin has activity against KIT D816V, it is a nonselective TKI whose off-target effects on other tyrosine kinases are associated with adverse events including hematologic toxicity, gastrointestinal upset, and rare but serious cases...
of interstitial lung disease and pneumonitis. Therefore, new, safer, and more effective treatment options are needed for SM that have the potential to treat a larger percentage of patients.

Avapritinib is highly selective for KIT and is designed to act against a wide range of KIT-activating variants, including the D816V KIT isoform associated with imatinib resistance. Avapritinib purportedly inhibits KIT with high selectivity and low off-target activity to prevent SM cell proliferation, spread, and survival.

An oncologist prescribes avapritinib, an oral therapy that patients take once daily at a dose of 200 or 300 mg until disease progression or intolerable toxicity.

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 2 ongoing trials for this topic. We present these trials in Table 2.3.

Table 2.3. Ongoing Clinical Trials

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study of BLU-285 in Patients With Advanced Systemic Mastocytosis (AdvSM) and Relapsed or Refractory Myeloid Malignancies (EXPLORER) NCT02561988</td>
<td>Patients (n = 80) with AdvSM, ISM/SSM, or other R/R myeloid malignancies. Patients with AdvSM include those with ASM, SM-AHN, or MCL. Cohort 1: Patients treated with avapritinib orally, once daily, starting at 30 mg up to 400 mg Cohort 2: Patients treated with avapritinib orally, once daily, at a dose of 200 or 300 mg</td>
<td>Phase I, single-group assignment, multicohort, open-label trial to evaluate safety and efficacy of avapritinib in patients with AdvSM, ISM/SSM, or other R/R myeloid malignancies Primary endpoints: Maximum tolerated dose and adverse events Secondary endpoints: Objective response rate, duration of response, and quality of life</td>
<td>Primary completion November 2021 Study completion December 2021</td>
</tr>
<tr>
<td>Study to Evaluate Efficacy and Safety of Avapritinib (BLU-285), a Selective KIT Mutation-Targeted Tyrosine Kinase Inhibitor, in Patients With Advanced Systemic Mastocytosis (PATHFINDER) NCT03580655</td>
<td>Patients (n = 80) with AdvSM, including ASM, SM-AHN, or MCL, who will be treated with avapritinib orally, once daily, at a dose of 200 or 300 mg</td>
<td>Phase II, single-group assignment, open-label trial to evaluate the safety and efficacy of avapritinib in patients with AdvSM Primary endpoint: Objective response rate Secondary endpoints: Overall survival, progression-free survival, duration of response, time to response, quality of life, and adverse events</td>
<td>Primary and study completion May 2022</td>
</tr>
</tbody>
</table>

Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; ISM/SSM, indolent or smoldering systemic mastocytosis; MCL, mast cell leukemia; R/R, relapsed or refractory; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm.
Recently Completed and Ongoing Trials With Available Results

Our searches identified one recently completed late-phase trial with published results. We summarize this study with results as written in a conference abstract.

The following abbreviations are used in this section: AdvSM, advanced systemic mastocytosis; AE, adverse event; AML, acute myeloid leukemia; ASM, aggressive systemic mastocytosis; CR, complete response; CRh, complete response with partial hematologic recovery; DOR, duration of response; ISM/SSM, indolent or smoldering systemic mastocytosis; MCL, mast cell leukemia; mIWG-MRT-ECNM, modified International Working Group Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis criteria; ORR, objective response rate; OS, overall survival; PR, partial response; pts, patients; S/A/R, comutations in SRSF2, ASXL1, and/or RUNX1 genes; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm; TRAE, treatment-related adverse event.


- **Patient population/planned enrollment**: Patients (n = 67) with AdvSM (ASM [n = 23], SM-AHN [n = 30], and MCL [n = 7]) or ISM/SSM (n = 7) who underwent local testing for the KIT D816V mutation and were either untreated (40%) or previously treated (60%, including 23% with midostaurin). In cohort 1, patients were treated with avapritinib orally, once daily, starting at 30 mg up to 400 mg. In cohort 2, patients were treated with avapritinib orally, once daily, at a dose of 200 or 300 mg.

- **Study design**: Phase I, single-group assignment, multicohort, open-label trial to evaluate the safety and efficacy of avapritinib in patients with AdvSM or ISM/SSM

- **Primary outcomes**: Maximum tolerated dose of avapritinib; number of patients with adverse events, serious adverse events, and changes in physical findings, vital signs, clinical laboratory results, and electrocardiogram findings; and recommended phase II dose

- **Select secondary outcomes**: Overall response rate and patient-reported quality of life

- **Results presented by study authors**: "The ORR in 29 mIWG-MRT-ECNM evaluable pts was 83% and by subtype was 90% in ASM, 71% in SM-AHN, and 100% in MCL. CR or CRh was achieved in 24% of pts (2 pending confirmation). The median duration of response (DOR) was not reached, with a 12-month DOR rate of 76%, at a median follow up of 14 months. Six of the 7 (86%) pts previously treated with midostaurin achieved an objective response, including 5 PRs (2 pending confirmation). Fourteen of 17 (82%) pts with a mutated S/A/R genotype at baseline had an objective response, including 5 CR/CRh (2 pending confirmation). The median OS has not been reached among the 60 pts with AdvSM. The one-year OS rate in AdvSM subtypes was 96% (ASM), 77% (SM-AHN), and 100% (MCL). The one-year OS rate was 100% for known S/A/R negative patients (n = 28) and 78% for known S/A/R positive patients (n = 29). In the safety population (n = 67), the most common (>25%) treatment-emergent adverse events (AE; all grades; grade 3) included periorbital edema (67%; 4%), anemia (52%; 26%), fatigue (37%; 7%), nausea (36%; 4%), diarrhea (34%; 1%), peripheral edema (34%; 0%), thrombocytopenia (31%; 17%), vomiting (28%; 2%), and cognitive effects (28%; 1%). Hematological AEs were the most common reason for dose reduction. The majority of AEs were grades 1/2 and there were no grade 5 treatment-related AEs (TRAEs). 78% of pts remain on study up to 31 months, with discontinuations due to TRAEs (ascites, encephalopathy, and intracranial bleed) in 3/67 (4%) of pts. Four pts discontinued study for progression; 2 pts progressed with AML, 1 pt with MCL, and 1 pt with progressive thrombocytopenia due to AHN."

Manufacturers and Regulatory Status

Avapritinib is being developed by Blueprint Medicines Corp (Cambridge, Massachusetts). FDA granted avapritinib Breakthrough Therapy designation to treat severe subtypes of advanced SM that include ASM, SM-AHN, and MCL.27 Based on results from the phase I EXPLORER
trial, Blueprint Medicines plans to submit a New Drug Application to FDA in the second half of 2020.28

Blueprint Medicines also developed avapritinib for use in treating gastrointestinal stromal tumors (GIST). In January 2020, FDA approved avapritinib for treating unresectable or metastatic GIST in adults who have a platelet-derived growth factor receptor alpha exon 18 mutation.29

Cost Information

According to a US-based online aggregator of prescription drug prices, GoodRx, avapritinib’s retail price (as of April 1, 2020) was about $32 000 for thirty 200- or 300-mg tablets, which represents a 1-month supply of the drug.30 Thus, the yearly cost of avapritinib treatment would be about $384 000.

Key Stakeholder Perspectives

Nine stakeholders, reflecting clinical, physician assistant, nursing, research, and health systems perspectives, provided comments and ratings on this treatment.31-39 The list below provides a summary of key stakeholder perspectives.

- Avapritinib has a moderate to large potential to improve patient health outcomes because of the shortcomings of existing therapies in treating SM and the promising clinical trial results. However, these preliminary results were based on small clinical trials and need to be confirmed by additional follow-up and additional clinical trials.
- Avapritinib would not substantially disrupt the health care delivery system related to managing patients with advanced SM, because additional staff or facilities changes would not be needed for adoption of an orally administered drug, the familiarity of providers with other orally administered TKIs, and the small number of affected patients.
- Avapritinib will likely displace current treatments for advanced SM, potentially improving health outcomes and/or reducing side effects. However, patients treated with avapritinib will still require close monitoring of disease progression and potentially serious side effects.
- Avapritinib will likely be costly and, therefore, would increase the cost of care for this patient population. (Stakeholders reviewed the topic before cost information was available.) However, avapritinib’s overall cost impact on society and the health care system could be mitigated by the small number of patients affected by advanced SM and the potential for cost savings if avapritinib reduces the burden of managing SM symptoms.

Capmatinib (INC280) to Treat Locally Advanced or Metastatic, MET-Altered Non–Small Cell Lung Cancer

Highlights

- Capmatinib is an oral, highly selective, small-molecule inhibitor of the MET proto-oncogene, a receptor tyrosine kinase expressed by the MET proto-oncogene receptor tyrosine kinase gene, MET, which is involved in a pathway that promotes cell survival, cell proliferation, and tissue regeneration.
• *MET* alterations, including *MET* exon 14–skipping mutation and *MET* gene copy number amplification (GCN), occur in about 3% to 4% of non–small cell lung cancer (NSCLC) cases, and because of limited treatment options, patients usually have a poor prognosis.

• Stakeholders commenting on this topic thought that, compared with off-label treatment with crizotinib or cabozantinib, capmatinib has the potential to improve patient-oriented outcomes, which is supported by available data; however, they thought that confirmatory data from randomized controlled trials are needed.

• Stakeholders also thought that capmatinib has the potential to disrupt health care delivery because it will require incorporating *MET* genetic testing into the clinical workflow. Because capmatinib will likely be expensive, it could cause disparities for uninsured or underinsured patients.

**Patient Population**

Capmatinib is intended for adults aged 18 years or older with locally advanced or metastatic NSCLC harboring a *MET* exon 14–skipping mutation and/or *MET* GCN.

**Intervention**

NSCLC is the most common type of lung cancer, accounting for about 80% to 85% of all lung cancers. Treatment of NSCLC has been transformed the past 10 years by an increased understanding of the molecular events underlying the disease. In particular, FDA has approved multiple agents targeting specific NSCLC molecular drivers to treat NSCLC in patients with treatment-amenable mutations. Examples are mutations in the epidermal growth factor receptor gene, *EGFR*, and translocations in the anaplastic lymphoma kinase gene, *ALK*.

Investigators are seeking to identify additional molecular drivers that would lead to targeted therapy combinations with the potential to improve health outcomes for patients with other NSCLC molecular subtypes. One such potential target is the *MET* gene. The American Cancer Society offers more information on NSCLC.

*MET* encodes a receptor tyrosine kinase involved in a pathway that promotes cell survival, cell proliferation, and tissue regeneration in the presence of hepatocyte growth factor. *MET* exon 14–skipping mutation and/or *MET* GCN are types of *MET* gene alterations that dysregulate the pathway and may lead to cancer by causing uncontrolled cell proliferation, spread, and survival. *MET* alterations occur in about 3% to 4% of NSCLC cases and are associated with poor prognosis. Therefore, patients with *MET*-altered NSCLC need new treatment options that can improve health outcomes.

Capmatinib is a novel, highly selective, small-molecule inhibitor of the MET protein intended to treat patients with *MET*-altered NSCLC. Capmatinib’s antikinase activity prevents downstream MET signaling, purportedly blocking NSCLC proliferation and promoting tumor shrinkage.

An oncologist prescribes capmatinib, an oral therapy that patients take twice daily at a dose of 400 mg until disease progression or intolerable toxicity.

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified one ongoing trial for this topic. We present this trial in Table 2.4.
### Table 2.4. Ongoing Clinical Trial

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Study of Oral cMET Inhibitor INC280 in Adult Patients With EGFR Wild-Type Advanced Non-Small Cell Lung Cancer (GEOMETRY mono-1) NCT02414139</td>
<td>Patients (n = 373) with locally advanced or metastatic NSCLC harboring EGFR wild-type and ALK rearrangement-negative, as follows: Cohorts 1, 2, and 3: Pretreated patients stratified by MET GCN Cohort 4: Pretreated patients with MET exon 14 mutation regardless of MET GCN Cohort 5: Treatment-naïve patients with either MET GCN without MET exon 14 mutation or MET exon 14 mutation regardless of MET GCN Cohort 6: Pretreated patients with either MET GCN without MET exon 14 mutation or MET exon 14 mutation regardless of MET GCN Cohort 7: Treatment-naïve patients with MET exon 14 mutation regardless of MET GCN</td>
<td>Phase II, multicohort, parallel-assignment, open-label trial to evaluate the safety and efficacy of capmatinib in patients with MET-altered NSCLC. Patients will receive oral capmatinib at a dosage of 400 mg twice daily. Primary endpoint: Objective response rate Secondary endpoints: Overall survival, progression-free survival, disease control rate, duration of response, time to response, and adverse events</td>
<td>Primary completion May 2021 Study completion September 2022</td>
</tr>
</tbody>
</table>

Abbreviations: ALK, anaplastic lymphoma kinase gene; EGFR, epidermal growth factor receptor gene; GCN, gene copy number; MET, MET proto-oncogene receptor tyrosine kinase gene; NSCLC, non–small cell lung cancer.

### Recently Completed and Ongoing Trials With Available Results

Our searches identified one relevant, recently completed late-phase trial with published results.42,43 We summarize this study with results as written in a conference abstract and an article in OncLive.

The following abbreviations are used in this section: AE, adverse event; ALK, anaplastic lymphoma kinase gene; BIRC, blinded independent review committee; CI, confidence interval; DCR, disease control rate; DOR, duration of response; EGFR, epidermal growth factor receptor gene; GCN, gene copy number; IR, independent review; MET, MET proto-oncogene receptor tyrosine kinase gene; METΔex14-mutated, MET exon 14–skipping mutation; mo, month; NE, not evaluable; NSCLC, non–small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; pts, patients; TRAE, treatment-related adverse event.

- **Patient population/planned enrollment**: Patients (n = 373) with locally advanced or metastatic NSCLC harboring EGFR wild-type and ALK rearrangement-negative, as follows:
  - Cohorts 1, 2, and 3: Pretreated patients stratified by MET GCN
  - Cohort 4: Pretreated patients with MET exon 14–skipping mutation regardless of MET GCN
  - Cohort 5: Treatment-naïve patients with either MET GCN without MET exon 14–skipping mutation or MET exon 14–skipping mutation regardless of MET GCN
  - Cohort 6: Pretreated patients with either MET GCN without MET exon 14–skipping mutation or MET exon 14–skipping mutation regardless of MET GCN
  - Cohort 7: Treatment-naïve patients with MET exon 14–skipping mutation regardless of MET GCN

- **Study design**: Phase II, multicohort, parallel-assignment, open-label trial to evaluate the safety and efficacy of capmatinib in patients with MET-altered NSCLC. Patients received oral capmatinib at a dosage of 400 mg twice daily.

- **Primary outcome**: Objective response rate

- **Secondary outcomes**: Overall survival, progression-free survival, disease control rate, duration of response, time to response, and adverse events

- **Results presented by Wolf et al.**: "As of Nov 08, 2018, 97 pts with METΔex14-mutated NSCLC (Cohort 4: 69 pts; Cohort 5b: 28 pts) were evaluable for efficacy. ORR (95% CI) by BIRC was 39.1% (27.6-51.6) in Cohort 4 and 71.4% (51.3-86.8) in Cohort 5b. While still immature at the time of this analysis, data on durability are promising: median DOR (95% CI) by BIRC was 9.72 (4.27-11.14) and 8.41 (5.55-NE) mo for Cohorts 4 and 5b, respectively; median PFS (95% CI) by BIRC was 5.42 (4.17-6.97) and 9.13 (5.52-13.86) mo for Cohorts 4 and 5b, respectively. Safety profile remains favorable and unchanged. Most common AEs (≥25% all grades) across all cohorts (n = 315), were peripheral edema (49.2%), nausea (43.2%), and vomiting (28.3%); majority of the AEs were grade 1/2."

- **Results presented by OncLive**: "In pretreated patients [cohort 4], the ORR by IR with capmatinib was 40.6% (95% CI, 28.9%-53.1%). Moreover, DCR was 78.3% (95% CI, 66.7%-87.3%). The ORR by IR was 67.9% (95% CI, 47.6%-84.1%) for treatment-naïve patients [cohort 5b], and the DCR was 96.4% (95% CI, 81.7%-99.9%). Results also showed that the median DOR by IR was 9.72 months in pretreated patients and 11.14 months in those who received the agent upfront. The median PFS was 5.42 months in the pretreated group and 9.69 months for those treated in the frontline setting. Approximately half of the patients with brain metastases at baseline experienced an intracranial response with capmatinib (7 of 13; 54%). Of these patients, 4 had a complete resolution of brain lesions (31%), and the intracranial DCR was 92.3% (12 of 13). Safety, which was assessed across all cohorts examined in the study, also included patients with MET dysregulated NSCLC (N = 334). Grade 3 TRAEs occurred in 31.1% of patients and a grade 4 AE was seen in 4.5% of patients. The most common grade 3/4 AEs were peripheral edema (7.5%), fatigue (3.0%), and vomiting (18.9%)."

**Manufacturers and Regulatory Status**

Investigators at Novartis AG (Basel, Switzerland) are studying capmatinib in a phase II trial for treating NSCLC in patients with a MET exon 14–skipping mutation and/or MET amplification. FDA has granted Orphan Drug and Breakthrough Therapy designations to capmatinib for previously treated or treatment-naïve advanced NSCLC in patients with a MET exon 14–skipping mutation.44-46

Based on data from the phase II GEOMETRY mono-1 trial, Novartis submitted a New Drug Application to FDA, which was accepted and granted Priority Review in February 2020.47,48
Cost Information
Cost information is unavailable for this topic.

Key Stakeholder Perspectives
Eight stakeholders, reflecting clinical, health systems, nursing, patient representative, and research perspectives, provided comments and ratings on capmatinib.49-56 The list below provides a summary of key stakeholder perspectives.

- Patients with NSCLC who have a MET exon 14–skipping mutation have a poor prognosis, and off-label treatment with crizotinib or cabozantinib has yielded low response rates. Available data suggest that capmatinib has the potential to improve health outcomes. Because these results are from a nonrandomized trial, however, additional confirmatory data from randomized controlled trials are needed.

- As an oral drug, capmatinib is unlikely to affect health center infrastructure. But if trials demonstrate safety and efficacy, it has the potential to disrupt the health care delivery system by incorporating MET genetic testing into the patient’s clinical pathway and physician workflow. The therapy could also disrupt the current care paradigm as a viable therapy for patients who have few and ineffective treatment options.

- Capmatinib is expected to be expensive and has the potential to cause disparities for uninsured patients, underinsured patients, and patients living in rural areas or areas that have only community health centers with limited offerings that are not affiliated with large regional centers with access to MET genetic testing to determine eligibility.

- Capmatinib has the potential to increase costs associated with genetic testing, monitoring, and mitigating adverse events. But if trials demonstrate that it slows disease progression and improves quality of life, patients could potentially have fewer health care visits and hospitalizations, thus decreasing costs.

Lifileucel (LN-144) as Second-Line Treatment for Locally Advanced or Metastatic Melanoma

Highlights

- Lifileucel is a cell-based therapy that uses the patient’s own tumor-infiltrating lymphocytes (TILs) to enhance antitumor immune responses against melanoma.

- TIL therapy offers a new therapeutic paradigm for treating melanoma because it may address key challenges encountered with standard treatment options.

- Patients with metastatic melanoma need more effective options after standard therapies have failed.

- Stakeholders commenting on this topic thought lifileucel has the potential to improve patient health outcomes as a treatment option for progressive disease or after standard-of-care treatment has been exhausted.

- As a personalized, cell-based therapy, lifileucel availability would likely be limited to a small number of cancer centers of excellence and is expected to be very expensive, thus creating disparities that would restrict access for some patients.
Patient Population

Lifileucel is intended for adults aged 18 years or older who have unresectable or metastatic melanoma that has progressed after one or more lines of systemic therapy, including an immune checkpoint inhibitor (ICI). Patients with disease containing a BRAF (B homolog of the rapidly accelerated fibrosarcoma) gene V600 variation are given a BRAF inhibitor alone or in combination with a MEK (MAPKK [mitogen-activated protein kinase kinase]/ERK [extracellular signal–regulated kinase] kinase) inhibitor.

Intervention

Melanoma is a type of skin cancer that originates from melanocytes, which make the pigment melanin. Among skin cancers, melanoma is less common, but it is most likely to spread to other parts of the body. The American Cancer Society offers more information about melanoma.

Lifileucel (LN-144) is an autologous T-cell therapy that uses TILs, which are naturally occurring T cells that are embedded in and directed against the patient’s melanoma tumor. To produce lifileucel, a patient’s tumor sample is shipped to a centralized manufacturing facility where TILs are isolated from the sample and expanded (ie, multiplied) in the laboratory until a certain number are generated. The manufacturing process takes about 22 days from biopsy receipt to shipping lifileucel back to the treating institution. The patient is then given a pretreatment chemotherapy (fludarabine and cyclophosphamide), which neither destroys bone marrow nor reduces lymphocytes, to reduce the immunosuppressive tumor environment before giving the TIL infusion.

Lifileucel purportedly offers a new therapeutic paradigm for treating solid tumors because it addresses some of the key challenges encountered in treatment: (1) tumor cells that vary in makeup, with multiple gene variants driving the cancer; (2) critical gene variants that drive the cancer and are potential treatment targets but that are unclear to physicians; (3) tumors that resist treatments targeting a single variant; (4) tumor mechanisms that reduce the body’s immune response (ie, immunosuppression); and (5) immunosuppression that arises from standard-of-care treatment options.

After lifileucel has been manufactured, an infusion nurse gives a single intravenous infusion containing between $1 \times 10^9$ and $1 \times 10^{11}$ TILs in an outpatient setting. Patients also receive up to 6 doses of interleukin 2 (IL-2) immediately after infusing lifileucel to support TIL growth, activation, and efficacy.

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 4 ongoing trials for this topic. We present one phase II trial in Table 2.5. We excluded an unphased trial (NCT01701674), a phase I trial (NCT02652455), and a phase II trial (NCT03645928) because they focus on a different patient population (ie, patients who have not received an ICI).
### Table 2.5. Ongoing Clinical Trial

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>innovaTIL-01, Study of Lifileucel (LN-144), Autologous Tumor Infiltrating Lymphocytes, in the Treatment of Patients With Metastatic Melanoma (C-144-01) NCT02360579</td>
<td>Patients (n = 164) aged 18 years or older with unresectable or metastatic melanoma who have progressed after one or more lines of systemic therapy, including an immune checkpoint inhibitor and a BRAF inhibitor alone or in combination with a MEK inhibitor for patients with BRAF V600 mutation–positive melanoma</td>
<td>Phase II, open-label, nonrandomized, parallel-assignment study evaluating the safety and efficacy of lifileucel. Patients will be assigned to treatment with lymphodepletion with fludarabine and cyclophosphamide followed by lifileucel infusion with up to 6 doses of IL-2 (600 000 IU/kg) to support TIL replication and engraftment</td>
<td>Primary completion July 2020 Study completion December 2024</td>
</tr>
</tbody>
</table>

Abbreviations: BRAF, B homolog of the rapidly accelerated fibrosarcoma gene; IL-2, interleukin 2; MEK, MAPKK (mitogen-activated protein kinase kinase)/ERK (extracellular signal–regulated kinase) kinase; TIL, tumor-infiltrating lymphocyte.

### Recently Completed and Ongoing Trials With Available Results

Our searches identified one relevant, recently completed late-phase trial with published results.\textsuperscript{59} We summarize this study with results as written in a conference abstract.

The following abbreviations are used in this section: BRAF, B homolog of the rapidly accelerated fibrosarcoma gene; CR, complete response rate; IL-2, interleukin 2; MEK, MAPKK (mitogen-activated protein kinase kinase)/ERK (extracellular signal–regulated kinase) kinase; NE, not evaluated; ORR, objective response rate; PD, progressive disease; PR, partial response; SAE, serious adverse event; SD, stable disease; TEAE, treatment-emergent adverse event; TIL, tumor-infiltrating lymphocyte.

**innovaTIL-01, Study of Lifileucel (LN-144), Autologous Tumor Infiltrating Lymphocytes, in the Treatment of Patients With Metastatic Melanoma (C-144-01). NCT02360579. Sarnaik et al 2017.\textsuperscript{59}**

- **Patient population/planned enrollment**: Patients (n = 164) aged 18 years or older with unresectable or metastatic melanoma whose disease progressed after one or more lines of systemic therapy, including an immune checkpoint inhibitor and a BRAF inhibitor alone or in combination with a MEK inhibitor for patients with BRAF V600 mutation–positive melanoma
- **Study design**: Phase II, open-label, nonrandomized, parallel-assignment study evaluating the safety and efficacy of lifileucel. Patients were assigned to treatment with lymphodepletion with fludarabine and cyclophosphamide followed by lifileucel infusion with up to 6 doses of IL-2 (600 000 IU/kg) to support TIL replication and engraftment
- **Primary outcome**: Objective response rate
- **Secondary outcomes**: Duration of response and adverse events
- **Results presented by study authors**: Results are presented through 31 Jan 2017 for the first 9 infused patients evaluable by two assessments. Eight of 9 patients received all 6 doses of IL-2 per protocol. The most common (=3 patients) non-hematologic grade 3-4 TEAE was hypophosphatemia. No neurotoxicity of grade = 3 was reported. There were no deaths or discontinuations due to SAEs related to study treatment. ORR was 33% (CR = 11%, PR = 22%, SD = 22%, PD = 33%, NE = 11%). Mean time to best response was 3.0
months and median duration of follow up was 3.6 months (1.1+, 12.1). Responses were observed in patients with tumors carrying wild type or BRAF mutations. All patients demonstrated persistence of TIL on day 14 post-infusion.”

Manufacturers and Regulatory Status

Iovance Biotherapeutics Inc (San Carlos, California), in collaboration with the National Cancer Institute at the National Institutes of Health (Bethesda, Maryland), is studying lifileucel in a phase II clinical trial. The company reported receiving Fast Track designation and Regenerative Medicine Advanced Therapy designation from FDA for treating advanced melanoma.60,61 In an end-of-phase-II meeting, FDA indicated that the available data were insufficient for regulatory approval and recommended amending the ongoing C-144-01 trial to add a new cohort. This cohort, known as cohort 4, will enroll between 80 and 100 patients and its data will be the basis of a Biologics License Application, which Iovance planned to submit to FDA in the second half of 2020.61

Cost Information

Cost information is unavailable for this topic, but in general, costs of cell-based personalized therapies are expected to be very high because of complex manufacturing requirements and adjunctive treatment required (eg, IL-2).

Key Stakeholder Perspectives

Seven stakeholders, reflecting clinical, health systems, nursing, patient advocate, and research perspectives, provided comments and ratings on lifileucel.62-68 The list below provides a summary of key stakeholder perspectives.

- Lifileucel has the potential to improve health outcomes in heavily treated patients whose disease has failed to respond to previous lines of therapy and who lack effective treatment options.
- Lifileucel may create disparities for patients who cannot pay its anticipated high cost and who do not have access to large medical centers experienced in providing immunotherapies.
- Even though most health centers have the infrastructure to offer TIL therapies, the multistep process that involves manufacturing lifileucel and preparing patients will be more disruptive than giving an intravenous drug at an infusion center.
- Lifileucel is expected to very expensive and likely to be a cost burden to patients and payers. Patients receiving this therapy are at risk of developing grade 3 or 4 treatment-related adverse events, which will also increase costs associated with hospitalization and patient monitoring.
MDNA55 to Treat First Recurrence of Recurrent Glioblastoma Multiforme

Highlights

- MDNA55 is a genetically engineered therapy composed of a protein that binds the interleukin-4 receptor (IL4R) and a bacteria-derived endotoxin to kill cancer cells and immunosuppressive cells overexpressing IL4R.
- Patients with recurrent glioblastoma multiforme (GBM) have poor outcomes, short survival, and lack effective treatment options for recurrent disease.
- A neurosurgeon delivers the therapy through a thin tube (ie, cannula) inserted directly into the patient’s tumor during a minimally invasive procedure using stereotactic guidance.
- Stakeholders commenting on MDNA55 agreed that it offers a novel approach to treat GBM, with potential to improve patient health outcomes. Although available data seem promising, additional data from larger studies are needed to assess MDNA55’s potential for disruption.
- Stakeholders also thought that, because health centers offering MDNA55 would require changes in infrastructure, care setting, and personnel, the drug also has the potential to disrupt delivery and paradigms of care.

Patient Population

MDNA55 is intended for adults aged 18 years or older with recurrent or progressive GBM.

Intervention

GBM is a malignant brain cancer associated with poor outcomes and high mortality. GBM begins as stage IV disease with no evidence of a lower-grade precursor. The American Brain Tumor Association offers [more information about GBM](#).

Patients who have undergone primary treatment of surgery, radiation, and temozolomide chemotherapy typically experience disease recurrence in about 7 months. Even with treatment, patients with recurrent GBM have a median overall survival of 15 months and a 2-year survival rate of 27%,69 emphasizing the need for new therapies capable of treating recurrent disease and extending survival.

MDNA55 is a novel, genetically engineered fusion protein composed of a circularly permuted interleukin 4 (cpIL-4) molecule fused to *Pseudomonas aeruginosa* exotoxin A (PE), a protein-synthesis inhibitor. MDNA55 is designed to specifically target IL4R, a cell-surface receptor overexpressed in various types of cancer stem cells and immunosuppressive cells composing the tumor microenvironment. MDNA55 functions like a “molecular Trojan horse” because cpIL-4 binding to IL4R triggers receptor-mediated endocytosis to deliver the cytotoxic PE payload into the target cells’ cytoplasm. Via IL4R targeting, MDNA55 purportedly kills GBM stem cells and immunosuppressive cells in the tumor microenvironment with high specificity.70

A neuro-oncologist prescribes MDNA55, which is administered in a hospital by a neurosurgeon during a minimally invasive surgical procedure using a technique (ie, convection-enhanced delivery) that allows delivery of the drug through a thin tube (ie, cannula) inserted
directly into the tumor under stereotactic guidance. The starting dose is 63 μg. Depending on response to the initial dose, patients may be eligible for a second MDNA55 treatment.

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database did not identify any ongoing trials for this topic.

**Recently Completed and Ongoing Trials With Available Results**

Our searches identified one relevant, recently completed late-phase trial published as a conference abstract. We summarize this study with results as written in the abstract.

The following abbreviations are used in this section: CED, convection-enhanced delivery; GBM, glioblastoma multiforme; IL4R, interleukin 4 receptor; IL4R<sup>−ve</sup>, none to low interleukin 4 receptor expression; IL4R<sup>+ve</sup>, moderate to high interleukin 4 receptor expression; mOS, median overall survival; MRI, magnetic resonance imaging.


- **Patient population/planned enrollment**: Patients (n = 46) with GBM that has recurred or progressed after primary treatment
- **Study design**: Phase II, single-group assignment, open-label trial to evaluate the safety and efficacy of MDNA55 in patients with GBM. Patients will receive a single MDNA55 infusion via CED. Based on response, patients may receive a second MDNA55 infusion.
- **Primary outcome**: Overall survival
- **Secondary outcomes**: Objective response rate and adverse events
- **Results presented by study authors**: “Current safety data show similar profile to previous MDNA55 trials with no systemic toxicities or drug related deaths. Current mOS in subjects treated with low doses of MDNA55 (median 63µg; n=21) is 11.8 months. When stratified by IL4R expression, a biomarker for more aggressive GBM, IL4R<sup>−ve</sup> subjects (mOS 15.2 months; n=8) show a survival advantage of 7 months compared to IL4R<sup>+ve</sup> subjects (mOS 8.1 months; n=10). Updated survival and response outcomes including subjects receiving the high dose (median 180µg; n=25) and stratification by IL4R expression will be reported. Review of serial imaging within 90 days following MDNA55 treatment demonstrated tumor shrinkage or stabilization from baseline in 19/42 evaluable subjects (disease control rate of 45%). To account for initial pseudo-progression in some subjects, tumor response was also assessed from nadir: 83% (35/42) showed disease control. Multi-parametric MRI biomarkers including relative cerebral blood volume (rCBV) and apparent diffusion coefficient (ADC) measurements demonstrated distinct imaging phenotypes among different disease states (pseudo-progression vs true-progression, pseudo-response vs true-response) and improved response staging. This trial is advancing neurosurgical methods for CED, potential of IL4R expression as a biomarker to select GBM patients most likely to benefit from MDNA55 treatment, and optimal use of multi-parametric MRI as an adjunct to clinical decision making.”

**Manufacturers and Regulatory Status**

Medicenna Therapeutics Corp (Toronto, Ontario, Canada) is developing MDNA55 in an ongoing phase II trial. FDA has granted MDNA55 Orphan Drug and Fast Track designations for treating patients with recurrent GBM.

**Cost Information**

Cost information is unavailable for this topic, but stakeholders expect the therapy to be very costly.
**Key Stakeholder Perspectives**

Seven stakeholders, reflecting clinical, health systems, nursing, and research perspectives, provided comments and ratings on MDNA55. The list below provides a summary of key stakeholder perspectives.

- MDNA55 represents a new treatment approach with potential to improve health outcomes and quality of life for patients with recurrent GBM, a disease with a high mortality rate and short life expectancy, but evidence is insufficient to fully support these claims.
- MDNA55’s delivery via convection-enhanced delivery would be more disruptive to the health care delivery system and the paradigm of care than drugs taken orally because delivery requires changes in care setting, infrastructure, and personnel.
- Similar to many new specialty drugs and biologics, MDNA55 could be very expensive and have potential to create health disparities.
- Stakeholders thought that, if subsequent data from larger studies demonstrate its safety and efficacy, MDNA55 will have high overall potential to disrupt how GBM is treated, pointing out that patients with GBM are desperate for new therapies because current standard of care offers limited benefits.

**Nanoparticle Albumin-Bound Sirolimus (ABI-009) to Treat Locally Advanced or Metastatic Perivascular Epithelioid Cell Sarcoma**

**Highlights**

- Nanoparticle albumin-bound sirolimus (nab-sirolimus) is a novel formulation, given intravenously, of an inhibitor that targets a molecular pathway known as the mammalian target of rapamycin (mTOR) pathway. This pathway is involved in cell proliferation and is upregulated in perivascular epithelioid cell sarcoma (PEComa) tumors.
- PEComa is a rare soft tissue sarcoma with no FDA-approved therapy.
- Stakeholders commenting on this topic agreed that nab-sirolimus has the potential to improve health outcomes for patients with PEComa, but because it is expected to be costly, nab-sirolimus might create disparities for uninsured patients or those who cannot afford deductibles and/or copayments.
- Stakeholders also thought that nab-sirolimus is unlikely to disrupt the health care delivery system because it will use infrastructure that is already in place for intravenous treatments, but because of a lack of treatment options, it might disrupt current care paradigms.

**Patient Population**

Nab-sirolimus is intended for adults aged 18 years or older with locally advanced or metastatic PEComa.

**Intervention**

PEComa is a rare sarcoma that originates in the soft tissues of the stomach, intestines, lungs, and genitourinary organs. Although most PEComas are noncancerous benign tumors that grow slowly and are unlikely to spread to other organs, some are malignant, with potential to spread to
other parts of the body. The National Cancer Institute’s Physician Data Query offers more information about PEComa.

No targeted therapies are approved by FDA for use in treating malignant PEComas, and they usually do not respond well to cytotoxic chemotherapy. Therefore, patients with PEComa need new treatment options that can improve health outcomes.80

A molecular pathway called the mTOR pathway is involved in PEComa cell proliferation. Off-label use of commercially available mTOR-inhibitor drugs has shown some benefit for these patients. However, these mTOR inhibitors distribute widely in the body and affect normal cells as well as tumor cells, leading to adverse events.80,81

Nab-sirolimus is a novel mTOR inhibitor in a form that purportedly accumulates preferentially in cancer cells. The drug is a nanoparticle suspension, and each nanoparticle consists of several molecules of sirolimus (an mTOR inhibitor) bound to human albumin.81,82

Cancer cells take up blood albumin to support protein synthesis; thus, albumin may act as a carrier that helps sirolimus accumulate preferentially in tumor tissues.82 Once the nanoparticles enter cells and inhibit the mTOR pathway, nab-sirolimus purportedly prevents tumor cell growth, proliferation, nutrient metabolization, and blood vessel formation.80,81

An oncologist prescribes nab-sirolimus to be given at an infusion center. An infusion nurse administers intravenous nab-sirolimus weekly at a dose of 100 mg/m² in a 2-weeks-on, 1-week-off schedule until disease progression or intolerable toxicity.

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified one ongoing trial for this topic. We present this trial in Table 2.6.

Table 2.6. Ongoing Clinical Trial

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Phase 2 Study of ABI-009 in Patients With Advanced Malignant PEComa (AMPECT) <strong>NCT02494570</strong></td>
<td>Patients (n = 34) aged 18 years or older with locally advanced or metastatic PEComa</td>
<td>Phase II, single-group assignment, open-label trial to evaluate the safety and efficacy of nab-sirolimus in patients with PEComa. Patients receive weekly nab-sirolimus intravenously in a 2-week-on, 1-week-off schedule. Primary endpoint: Objective response rate Secondary endpoints: Overall survival, progression-free survival, duration of response, and adverse events</td>
<td>Primary completion September 2020 Study completion September 2021</td>
</tr>
</tbody>
</table>

Abbreviation: PEComa, perivascular epithelioid cell tumor.

Recently Completed and Ongoing Trials With Available Results

Our searches identified one relevant, recently completed late-phase trial with published results.83 We summarize this study with results as written in a conference abstract.
The following abbreviations are used in this section: AE, adverse event; CI, confidence interval; CR, control rate; DOR, duration of response; IRR, independent radiology review; ORR, objective response rate; OS, overall survival; PD, progressive disease; PEComa, perivascular epithelioid cell tumor; PFS, progression-free survival; PFS6, 6-month progression-free survival; PR, partial response; pts, patients; SD, stable disease; TRAE, treatment-related adverse event.

A Phase 2 Study of ABI-009 in Patients With Advanced Malignant PEComa (AMPECT).

**NCT02494570. Dickson et al 2019.**

- **Patient population/planned enrollment**: Patients (n = 34) aged 18 years or older with locally advanced or metastatic PEComa
- **Study design**: Phase II, single-group assignment, open-label trial to evaluate the safety and efficacy of nab-sirolimus in patients with PEComa. Patients received intravenous nab-sirolimus at a weekly dose of 100 mg/m² in a 2-week-on, 1-week-off schedule.
- **Primary outcome**: Objective response rate
- **Secondary outcomes**: Overall survival, progression-free survival, duration of response, and adverse events
- **Results presented by study authors**: "A total of 34 patients were treated. At the time of primary analysis (May 29, 2019), treatment was ongoing for 29% (10/34) patients. The most common primary site of tumors was the uterus (24%), pelvis (18%), retroperitoneum (18%), lung (12%), kidney (12%). 94% of patients had prior surgery and 21% had prior systemic therapy. Of the 34 enrolled pts, 29 (85%) had metastatic disease and 5 (15%) had locally advanced inoperable disease. 31 patients were evaluable for efficacy (ie, with centrally confirmed PEComa). The median time on treatment was 6.1 months (95% CI: 0.3, 28). The confirmed ORR by IRR was 39%, all partial responses (PR, 12/31, 95% CI: 21.8, 57.8), 52% stable disease (16/31, with 10/16 SD ≥12 weeks), and 10% progressive disease (PD 3/31); the disease control rate (CR + PR + SD ≥12 weeks) was 71%. One patient had an unconfirmed PR without subsequent scans and was assessed as SD ≥12 weeks. The majority of PRs (67%) were reached at the first post-baseline scan at week 6, with a median time to response of 1.4 months (95% CI: 1.3 to 2.8). The median DOR by independent review was not yet reached (range 4.2 to 27.7+ months), 75% (9/12) of PRs are ongoing, with 4 responders >1 year and 3 responders >2 year on therapy. Median PFS by IRR was 8.9 months (95% CI: 5.5; --) and PFS6 was 70%. Median OS was not reached, with 29 patients alive at the time of the primary analysis. One patient with locally advanced inoperable disease at study entry was able to undergo surgery after treatment for 6.9 months. Investigator-assessed confirmed responses were similar, with 42% ORR, 48% SD (10/15 SD ≥12 weeks), and 10% PD. The most common (>30%) nonhematologic treatment-related AEs (TRAEs) of any grade were mucositis (79%), fatigue (59%), rash (56%), nausea (47%), diarrhea/weight loss (38% each), hyperglycemia (35%), and hypertriglyceridemia/hypercholesterolemia/decreased appetite (32% each). The most common (>10%) grade 3 TRAEs were anemia (47%) and thrombocytopenia (32%). Pneumonitis (18%) was grade 1 or 2. The most common (>10%) grade 3 TRAEs were mucositis (18%), anemia (12%); No grade ≥4 TRAEs were observed. Mutational analysis was available for 25 patients and is reported separately."

**Manufacturers and Regulatory Status**

Investigators at Aadi Bioscience Inc (Pacific Palisades, California) are studying nab-sirolimus in a phase II clinical trial. FDA granted nab-sirolimus Orphan Drug, Fast Track, and Breakthrough Therapy designations to treat patients with PEComa.84,85 Based on results from the phase II AMPECT trial, Aadi Bioscience planned to submit a New Drug Application to FDA during the second quarter of 2020.85,86

**Cost Information**

Cost information is unavailable for this topic, but nab-sirolimus is expected to be more costly than generic mTOR inhibitors.
Key Stakeholder Perspectives

Seven stakeholders, reflecting clinical, health systems, nursing, physical therapy, and research perspectives, provided comments and ratings on nab-sirolimus. The list below provides a summary of key stakeholder perspectives.

- Data on nab-sirolimus show potential to improve health outcomes of patients with PEComa, who are in need of effective treatments, but additional patient-oriented outcomes are needed to evaluate the drug’s potential to improve health outcomes.
- Nab-sirolimus is expected to be more expensive than generic mTOR inhibitors and may cause disparities for uninsured patients who cannot afford to pay for treatment and insured patients who cannot afford the associated deductibles and copayments.
- As an intravenous drug, nab-sirolimus has little potential to disrupt the health care delivery system, but it may disrupt the paradigm of care because patients have no effective treatment options available.
- Although nab-sirolimus’ overall potential for disruption is based on the lack of treatment options for PEComa, its adoption will depend heavily on improving testing methods to diagnose PEComa, which is usually mistaken for other sarcomas, leading to mismanagement of patients.

Oportuzumab Monatox (Vicinium) to Treat Non–Muscle Invasive Bladder Cancer (Third-Line Setting)

Highlights

- Oportuzumab monatox (Vicinium) is a protein fusion drug administered through a catheter directly into the patient’s bladder to treat non–muscle invasive bladder cancer (NMIBC) that has not responded to bacillus Calmette-Guérin (BCG) treatment or has recurred after at least 2 courses of BCG.
- Oportuzumab monatox, if effective, might provide an alternative outpatient treatment option for patients who would otherwise undergo surgical removal of bladder tumor or intravesicular chemotherapy with one or more drugs.
- Stakeholders commenting on this topic thought that oportuzumab monatox has the potential to improve health outcomes and quality of life for patients with NMIBC whose disease has recurred or did not respond to BCG treatment.
- Stakeholders also thought that oportuzumab monatox use might create disparities because of its anticipated high cost and added burden of cystectomy for patients who do not respond to this treatment.

Patient Population

Oportuzumab monatox is intended for adults aged 18 years or older who have NMIBC that has not spread to any nearby tissues or has a high risk of spreading and whose disease has not responded to treatment with BCG or has recurred after at least 2 courses of BCG.

Intervention

NMIBC is one of the most common forms of cancer. It occurs when cells in the bladder’s inner layers become malignant. The Urology Care Foundation website offers more information on NMIBC.
Oportuzumab monatox is a new gene combination protein consisting of a humanized monoclonal infection-fighting fragment specific for the epithelial cell adhesion molecule (EpCAM) connected via a peptide to a shortened form of *Pseudomonas aeruginosa* exotoxin A (PE). EpCAM is purportedly highly expressed by more than 98% of high-grade NMIBCs, making it an attractive target for therapy.

The manufacturer designed the drug to selectively bind NMIBC cells through its EpCAM antibody fragment region and deliver the anticancer exotoxin directly into tumor cells. The cytotoxic part of the drug, PE, purportedly inhibits tumor protein synthesis by deactivating the translation factor elongation factor-2, which purportedly kills both rapid-growing and slow-growing cancer cells.

In an ongoing phase III trial, a clinician delivers the drug in an outpatient setting directly into the bladder using a sterile urethral catheter. The dose is 30 mg in 50 mL buffered saline. Patients receive the drug twice a week for 12 weeks (induction therapy), then once every 2 weeks for up to 2 years (maintenance therapy).

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified a single ongoing trial for this topic. We present this trial in Table 2.7. Our searches also identified an early-phase clinical trial (NCT03258593); however, we excluded it because oportuzumab monatox therapy is combined with an immune checkpoint inhibitor, which deviates from this topic.

**Table 2.7. Ongoing Clinical Trial**

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open-Label, Multicenter, Phase 3 Study to Evaluate the Efficacy and Tolerability of Intravesical Vicinium in Subjects With Non Muscle-Invasive Carcinoma in Situ and/or High-Grade Papillary Disease of the Bladder Treated With BCG (VISTA trial) NCT02449239</td>
<td>Adults (n = 134) aged 18 years or older with NMIBC relapsed or refractory to BCG treatment</td>
<td>Phase III, single-group assignment study to evaluate the efficacy and tolerability of intravesical oportuzumab monatox in adults with NMIBC previously treated with BCG Primary outcome: Complete response rate in patients with CIS with or without resected papillary disease up to 24 months after initiation of oportuzumab monatox therapy Secondary outcomes: Event-free survival at 104 weeks (events include disease recurrence, disease progression, or death) and the following, all measured up to 104 weeks: recurrence rate, frequency of adverse events (measured every 4 weeks), complete response rate, time to cystectomy, time to disease recurrence, time to progression, progression-free survival, and overall survival</td>
<td>Primary completion December 2020</td>
</tr>
</tbody>
</table>

Abbreviations: BCG, bacillus Calmette-Guérin; CIS, carcinoma in situ; NMIBC, non–muscle invasive bladder cancer.
Recently Completed and Ongoing Trials With Available Results

Our searches identified 2 relevant, recently completed late-phase trials with published results.97,98 We summarize these studies with results as written in an abstract of published study and a conference abstract.

The following abbreviations are used in this section: BCG, bacillus Calmette-Guérin; CI, confidence interval; CIS, carcinoma in situ; CR, complete response; DoR, duration of response; NE, not evaluable; NMIBC, non–muscle invasive bladder cancer; PFS, progression-free survival.

**Phase 3 Results of Vicinium in BCG-Unresponsive Non-Muscle Invasive Bladder Cancer (NIMBC).** NCT02449239. Shore et al 2019.97

- **Patient population/planned enrollment:** Adults (n = 134) aged 18 years or older who have NMIBC that has recurred or has not responded to BCG treatment. Patients were assigned to 1 of 3 cohorts:
  - Cohort 1: Patients with CIS with or without papillary disease that did not respond to BCG treatment or recurred within 6 months of their last course of adequate BCG
  - Cohort 2: Patients who had CIS with or without papillary disease that did not respond to BCG treatment or recurred 6 to 11 months after their last course of adequate BCG
  - Cohort 3: Patients who had high-risk papillary disease without CIS that did not respond to BCG treatment or recurred within 6 months of their last course of adequate BCG

- **Study design:** Phase III, open-label study to evaluate the safety and efficacy of intravesical oportuzumab monatox

- **Primary outcome:** Complete response rate in patients with CIS with or without resected papillary disease

- **Secondary outcomes:** Recurrence rate up to 104 weeks, event-free survival at 104 weeks (events include disease recurrence, disease progression, or death), frequency of adverse events up to 104 weeks, complete response rate up to 104 weeks, time to cystectomy up to 104 weeks, time to disease recurrence up to 104 weeks, time to progression up to 104 weeks, PFS up to 104 weeks, and overall survival up to 104 weeks

- **Results presented by study authors:** “Of the evaluable CIS patients (n = 89), the overall 3-month CR rate was 40% and the median DoR was 9.4 months (95% CI, 5.1-NE). Subgroup analysis showed the median DoR was not reached for patients that had received only two courses of BCG prior to enrollment (n = 42) vs. 5.1 months in those who have received more than 2 courses of BCG (n=51). Of the evaluable papillary patients (n = 38), the recurrence-free rate at 3 months was 71% and median time to recurrence was 13.2 months (95% CI, 5.6-NE). On average, responders disease-free at 3 months remained cystectomy-free for 34.0 months vs. 20.7 months for nonresponders (p = 0.001). Vicinium was well tolerated; approximately 50% of the patients (66 of 133) had treatment-related adverse events with the most common being dysuria (14%), hematuria (13%), urinary tract infection (12%), pollakuria (11%), micturition urgency (11%) and fatigue (8%). A total of 4 treatment-related severe adverse events were reported in 3 patients and included grade 4 cholestatic hepatitis, grade 5 renal failure, grade 3 acute kidney injury and grade 2 pyrexia. Only 3% of the patients discontinued treatment due to adverse events.”

**Study of Vicinium for Treating Patients With Non-invasive Urothelial CIS.** NCT00462488. Kowalski et al 2012.98

- **Patient population/planned enrollment:** Adults (n = 46) aged 18 years or older with NMIBC that had recurred or had not responded to BCG treatment

- **Study design:** Phase II, open-label, nonrandomized treatment study to evaluate the safety and efficacy of oportuzumab monatox for a 6-week (cohort 1) or 12-week (cohort 2) induction regimen of weekly intravesicular treatments followed by up to 3 maintenance cycles of 3 weekly intravesicular treatments every 3 months
• **Primary outcome**: Efficacy measured at 12 or 13 weeks

• **Results presented by study authors**: "A complete response to oportuzumab monatox was seen in 9 of 22 patients (41%) in cohort 1 and 9 of 23 (39%) in cohort 2 at the 3-month evaluation. A total of 20 patients (44%) achieved a complete response. Two other patients without CIS who achieved a CR were not included in the study due to the development of noninvasive papillary (Ta) disease. Median time to recurrence in patients who achieved a CR was 274 and 408 days in cohorts 1 and 2, respectively. Overall 7 patients (16%) remained disease-free. Post-study assessment demonstrated that these patients were still disease-free at last followup (18 to 25 months). The most common adverse events were mild to moderate reversible bladder symptoms."

** Manufacturers and Regulatory Status**

*Sesen Bio (Cambridge, Massachusetts)* is assessing the therapy in a phase III trial. FDA is considering this drug under an accelerated approval pathway with rolling review of accumulating data. The manufacturer announced plans to initiate a rolling Biologics License Application in the fourth quarter of 2019. In August 2018, FDA also granted Fast Track designation.

**Cost Information**

Cost information is unavailable for this topic, but stakeholders expect it to be very costly.

**Key Stakeholder Perspectives**

Five stakeholders, reflecting clinical, nursing, research, and health systems perspectives, provided comments and ratings on oportuzumab monatox. The list below provides a summary of key stakeholder perspectives.

- Oportuzumab monatox has the potential to improve health outcomes and quality of life for patients with NMIBC whose disease has recurred or did not respond to BCG treatment, because it might obviate the need for radical surgery.
- Insurance coverage might determine the potential for this treatment to disrupt health care costs and disparities. Medicare beneficiaries might face lower out-of-pocket costs than younger patients because of caps on those costs.
- If the data from comparative studies validate its effectiveness, this treatment would benefit affected patients who are older and are poor candidates for surgery.

**Pembrolizumab (Keytruda) as First-Line Treatment for Locally Advanced or Metastatic, Recurrent Head and Neck Squamous Cell Carcinoma**

**Highlights**

- Pembrolizumab is an immune checkpoint inhibitor given intravenously, alone or in combination with chemotherapy, to prevent tumor cells from downregulating cancer-specific immune responses.
- Because of a lack of effective treatments, locally advanced or metastatic, recurrent head and neck squamous cell carcinoma (HNSCC) is usually associated with poor outcomes.
- Pembrolizumab’s cost is about $9600 per cycle, which does not include the costs of administration and other fees associated with an infusion procedure.
- Stakeholders commenting on this topic agreed that pembrolizumab’s potential for disruption is based on it being a much-needed and important advancement for treating...
HNSCC and improving patient health outcomes, but its high cost could also increase disparities in access to care.

- Stakeholders also thought that additional data on short- and long-term adverse events are needed to further assess whether pembrolizumab’s benefits as monotherapy or in combination with chemotherapy outweigh its risks.

**Patient Population**

Pembrolizumab is intended for adults aged 18 years or older with previously untreated HNSCC that is unsuited for surgery, is metastatic, and has recurred. The cancer is located in the oral cavity, larynx, hypopharynx, or oropharynx. Pembrolizumab is also intended for patients with recurrent HNSCC who completed postoperative systemic therapy more than 6 months earlier. It may be used as a single agent or in combination with a platinum agent and 5-fluorouracil. Using pembrolizumab as a monotherapy for HNSCC requires the patient’s tumor to exhibit expression of programmed death-ligand 1 (PD-L1).

**Intervention**

Head and neck cancers encompass tumors that develop in the oral cavity, nasal cavity, paranasal sinuses, larynx, oropharynx, hypopharynx, nasopharynx, and salivary glands. Most head and neck cancers are squamous cell carcinomas that originate from the flat squamous cells on the surface of head and neck structures. The American Society of Clinical Oncology offers more information about HNSCC.

Programmed death-1 (PD-1) is an immune checkpoint protein on T cells and other immune cells that binds PD-L1 to downregulate immune cells and prevent runaway immune responses.\textsuperscript{106} Cancer cells overexpressing PD-L1 may avoid detection and destruction by immune cells infiltrating tumors. Although HNSCCs are highly immune-infiltrated tumors, suppressive mechanisms within the tumor microenvironment, including high PD-L1 expression, limit the anticancer immune response.\textsuperscript{107} A potential therapeutic target that prevents the interaction between PD-L1 in tumor cells and PD-1 in T cells could potentially induce an immune response against HNSCC by preventing T-cell downregulation.\textsuperscript{106,107}

Pembrolizumab is a humanized monoclonal immunoglobulin G4 antibody that binds the PD-1 receptor expressed in activated T cells. Pembrolizumab binding to PD-1 purportedly prevents interaction between PD-1 and PD-L1, inhibiting the immune checkpoint pathway and leading to an increase in anticancer immune response to HNSCC tumors.\textsuperscript{106,107}

An oncologist prescribes pembrolizumab to be given intravenously at an infusion center. An infusion nurse administers 200 mg of intravenous pembrolizumab on day 1 of each 21-day cycle for up to 24 months. Pembrolizumab may be given in combination with intravenous cisplatin (100 mg/m\textsuperscript{2} on day 1) or carboplatin (AUC 5 on day 1) plus 5-fluorouracil (1000 mg/m\textsuperscript{2} from day 1 to 4) for up to 6 cycles.

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified 2 ongoing trials for this topic. We present a phase III trial in Table 2.8. We excluded another phase III trial (NCT03358472) because it is evaluating pembrolizumab in combination with epacadostat (an investigational indoleamine 2,3-dioxygenase 1 inhibitor).
### Table 2.8. Ongoing Clinical Trial

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Study of Pembrolizumab (MK-3475) for First Line Treatment of Recurrent or Metastatic Squamous Cell Cancer of the Head and Neck (KEYNOTE-048) NCT02358031</td>
<td>Patients (n = 882) with unresectable or metastatic, recurrent HNSCC previously untreated in the recurrent/metastatic setting</td>
<td>Phase III, randomized, parallel-assignment, open-label trial to evaluate pembrolizumab’s safety and efficacy alone or in combination with chemotherapy (5-fluorouracil plus a platinum agent) in patients with HNSCC compared with those of the EXTREME regimen (5-fluorouracil plus cetuximab and cisplatin or carboplatin). Patients will be randomly assigned in a 1:1:1 ratio to treatment with pembrolizumab, pembrolizumab plus chemotherapy, or the EXTREME regimen. Primary endpoints: Overall survival and progression-free survival Secondary endpoints: Objective response rate and health-related quality of life</td>
<td>Primary completion February 2019 Study completion January 2021</td>
</tr>
</tbody>
</table>

Abbreviation: HNSCC, head and neck squamous cell carcinoma.

### Recently Completed and Ongoing Trials With Available Results

Our searches identified one relevant, recently completed late-phase trial with published results.\(^{108}\) We summarize this study with results as written in an abstract of the published study.

The following abbreviations are used in this section: CI, confidence interval; CPS, combined positive score; HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio.

**A Study of Pembrolizumab (MK-3475) for First Line Treatment of Recurrent or Metastatic Squamous Cell Cancer of the Head and Neck (KEYNOTE-048).**\(^{108}\) Burtness et al 2019

- **Patient population/planned enrollment:** Patients (n = 882) with unresectable or metastatic, recurrent HNSCC previously untreated in the recurrent/metastatic setting
- **Study design:** Phase III, randomized, parallel-assignment, open-label trial to evaluate pembrolizumab’s safety and efficacy alone or in combination with chemotherapy (5-fluorouracil plus a platinum agent) in patients with HNSCC compared with those receiving cetuximab in combination with chemotherapy. Patients were randomly assigned in a 1:1:1 ratio to treatment with pembrolizumab monotherapy, pembrolizumab plus chemotherapy, or cetuximab plus chemotherapy.
- **Primary outcomes:** Overall survival and progression-free survival
- **Secondary outcomes:** Objective response rate and health-related quality of life
- **Results presented by study authors:** "Between April 20, 2015, and Jan 17, 2017, 882 participants were allocated to receive pembrolizumab alone (n=301), pembrolizumab with chemotherapy (n=281), or cetuximab with chemotherapy (n=300); of these, 754 (85%) had CPS of 1 or more and 381 (43%) had CPS of 20 or more. At the second interim analysis, pembrolizumab alone improved overall survival versus cetuximab with chemotherapy in the CPS of 20 or more population (median 14.9 months vs 10.7 months, hazard ratio..."
[HR] 0.61 [95% CI 0.45–0.83], p=0.0007) and CPS of 1 or more population (12.3 vs 10.3, 0.78 [0.64–0.96], p=0.0086) and was non-inferior in the total population (11.6 vs 10.7, 0.85 [0.71–1.03]). Pembrolizumab with chemotherapy improved overall survival versus cetuximab with chemotherapy in the total population (13.0 months vs 10.7 months, HR 0.77 [95% CI 0.63–0.93], p=0.0034) at the second interim analysis and in the CPS of 20 or more population (14.7 vs 11.0, 0.60 [0.45–0.82], p=0.0004) and CPS of 1 or more population (13.6 vs 10.4, 0.65 [0.53–0.80], p<0.0001) at final analysis. Neither pembrolizumab alone nor pembrolizumab with chemotherapy improved progression-free survival at the second interim analysis. At final analysis, grade 3 or worse all-cause adverse events occurred in 164 (55%) of 300 treated participants in the pembrolizumab alone group, 235 (85%) of 276 in the pembrolizumab with chemotherapy group, and 239 (83%) of 287 in the cetuximab with chemotherapy group. Adverse events led to death in 25 (8%) participants in the pembrolizumab alone group, 32 (12%) in the pembrolizumab with chemotherapy group, and 28 (10%) in the cetuximab with chemotherapy group.

Manufacturers and Regulatory Status

Merck & Co Inc (Kenilworth, New Jersey) manufactures pembrolizumab. On June 11, 2019, FDA approved pembrolizumab, based on results from the KEYNOTE-048 trial, for the following indications:

- As first-line monotherapy for patients with unresectable or metastatic, recurrent HNSCC whose tumors express PD-L1 (combined positive score ≥ 1) as determined by an FDA-approved test (ie, the companion diagnostic test PD-L1 IHC 22C3 pharmDx [Agilent Technologies Inc])
- In combination with 5-fluorouracil plus a platinum agent as first-line therapy for patients with unresectable or metastatic, recurrent HNSCC, regardless of PD-L1 expression

FDA had granted accelerated approval to pembrolizumab to treat recurrent or metastatic HNSCC that has progressed on or after platinum-based chemotherapy (ie, second-line setting). According to Merck, results from the KEYNOTE-048 trial also served as confirmatory results to support pembrolizumab’s full approval in the second-line setting. FDA has also approved pembrolizumab to treat more than a dozen other cancer types. For those FDA-approved indications, see FDA prescribing information.

Cost Information

According to a US-based online aggregator of prescription drug prices, GoodRx, pembrolizumab’s retail price (as of March 25, 2020) was about $9600 for 4 vials of 50 mg, which is the amount (200 mg) a patient would use for each 3-week cycle. Thus, if a patient continued on treatment for a full year, the cost would be about $163 200 (17 cycles at $9600 per cycle). This estimate does not include the costs of administration and other fees associated with an infusion procedure.

Key Stakeholder Perspectives

Eight stakeholders, reflecting clinical, health systems, nursing, patient, and research perspectives, provided comments and ratings on pembrolizumab. The list below provides a summary of key stakeholder perspectives:

- Pembrolizumab used as a monotherapy or in combination with chemotherapy has the potential to improve patient health outcomes, but there is a need for more data reporting on the drug’s short- and long-term adverse events.
- Even if insurance reimburses most of the costs, pembrolizumab is an expensive therapy that will likely create disparities for patients who cannot afford the remaining treatment costs.
• As an intravenous drug, pembrolizumab is unlikely to disrupt the health care delivery system or the current paradigm of cancer care.
• Most stakeholders concluded that much of pembrolizumab’s potential for disruption is based on it being a sorely needed and important advancement for treating HNSCC, but it remains to be seen whether the benefits outweigh the risks and whether it will be cost effective.

Pemigatinib (Pemazyre) to Treat Locally Advanced or Metastatic Cholangiocarcinoma Harboring FGFR2 Fusions or Rearrangements

Highlights
• Pemigatinib (Pemazyre) is an oral small-molecule inhibitor of fibroblast growth factor receptor (FGFR) under study for treating advanced or metastatic cholangiocarcinoma in patients who have gene fusions or rearrangements involving the FGFR2 locus.
• About 10% to 16% of patients with intrahepatic cholangiocarcinomas have fusions or rearrangements in the fibroblast growth factor receptor 2 gene, FGFR2; these alterations are thought to drive multiple cancer-promoting processes. Pemigatinib purportedly inhibits these FGFR-dependent processes.
• In a phase II, single-arm trial of patients with previously treated cholangiocarcinoma, pemigatinib produced an overall response rate of 35.5%, including a complete response in 3 of 107 patients. Among responders, the median response duration was 7.5 months.
• Stakeholders commenting on this topic thought that pemigatinib has substantial potential to improve patient health outcomes, based on the lack of effective therapies for cholangiocarcinoma in the second-line setting and the initial results observed in the phase II trial.
• Stakeholders also envisioned small disruptions in health care delivery, treatment paradigm, and costs, mainly focusing on the incorporation of genetic testing into the cholangiocarcinoma treatment paradigm and a potential shift from use of drugs that are given intravenously to one taken orally.

Patient Population
Pemigatinib therapy is intended for adults aged 18 years or older with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 or other rearrangement as detected by an FDA-approved test.

Intervention
Cholangiocarcinoma, or bile duct cancer, is a rare malignancy, and about 8000 cases are diagnosed each year in the United States. These bile duct cancers represent a diverse group of tumors that can be broadly classified as intrahepatic (ie, originating in bile ducts within the liver) or extrahepatic (ie, originating in bile ducts exiting the liver [perihilar] or near the gall bladder, intestine, and pancreas [distal bile ducts]). The American Cancer Society offers more information on bile duct cancer.

Cholangiocarcinomas are typically diagnosed at late stages, and the standard of care is systemic therapy. However, systemic therapies have shown limited efficacy; median survival of
patients receiving systemic therapy for cholangiocarcinoma is about 12 months. Therefore, novel therapies are needed with the potential to improve health outcomes for these patients.

Genomic sequencing studies of cholangiocarcinoma have identified multiple, potentially actionable, genetic variants, including alterations in genes encoding FGFRs. About 10% to 16% of patients with intrahepatic cholangiocarcinomas have gene fusions or rearrangements involving the \( FGFR2 \) locus. These genetic alterations purportedly lead to aberrant FGFR signaling, which drives multiple cancer-promoting processes (eg, cell proliferation, cell migration, cell survival, angiogenesis). Therefore, inhibiting FGFR signaling in cholangiocarcinomas that have activating fusions or rearrangements in \( FGFR2 \) may therapeutically benefit the patient.

Pemigatinib (INCB54828) is a small-molecule competitive inhibitor of the kinase activity of FGFR1, FGFR2, and FGFR3. Pemigatinib is being tested in clinical trials as a first- and second-line systemic therapy for cholangiocarcinoma.

In these trials, pemigatinib was administered orally at a daily dose of 13.5 mg in a 2-week-on, 1-week-off schedule until disease progression or development of intolerable toxicity. To determine eligibility for pemigatinib treatment, clinicians will need to use a genetic test to assess a patient’s \( FGFR2 \) mutation status. FDA has approved a companion diagnostic test to confirm the presence of an \( FGFR2 \) fusion or rearrangement (FoundationOne CDX, Foundation Medicine Inc, Cambridge, Massachusetts).

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified 2 ongoing trials for this topic. We present these trials in Table 2.9.

**Table 2.9. Ongoing Clinical Trials**

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy and Safety of Pemigatinib in Subjects With Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma Who Failed Previous Therapy (FIGHT-202) NCT02924376</td>
<td>Patients (n = 147) who have locally advanced or metastatic cholangiocarcinoma harboring ( FGFR2 ) rearrangements or fusions (cohort A), other ( \text{FGF/FGFR} ) alterations (cohort B), or no ( \text{FGF/FGFR} ) alterations (cohort C), who have had at least one previous line of systemic therapy in the locally advanced/metastatic setting</td>
<td>Phase II, multicohort, parallel-assignment, open-label trial to evaluate the safety and efficacy of pemigatinib in patients who have advanced cholangiocarcinoma. Patients receive oral pemigatinib at a daily dose of 13.5 mg in a 2-week-on, 1-week-off schedule. Primary endpoint: Objective response rate Secondary endpoints: Progression-free survival and adverse events</td>
<td>Primary and study completion June 2020</td>
</tr>
<tr>
<td>Study name and National Clinical Trials identifier</td>
<td>Patient population and planned enrollment</td>
<td>Study design and outcomes</td>
<td>Estimated date of completion</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
<td>------------------------------------------</td>
<td>--------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td><strong>A Study to Evaluate the Efficacy and Safety of Pemigatinib Versus Chemotherapy in Unresectable or Metastatic Cholangiocarcinoma (FIGHT-302)</strong> NCT03656536</td>
<td>Patients (n = 432) who have locally advanced or metastatic cholangiocarcinoma harboring FGFR2 rearrangements or fusions and who have not been previously treated (prior adjuvant/neoadjuvant treatment completed at least 6 months before enrollment and treatment for locally advanced disease with transarterial chemoembolization or selective internal radiation therapy is permitted if clear evidence of radiologic progression is observed before enrollment)</td>
<td>Phase III, randomized, parallel-assignment, open-label trial to evaluate the safety and efficacy of pemigatinib in patients who have advanced cholangiocarcinoma. Patients are randomly assigned to receive either oral pemigatinib at a daily dose of 13.5 mg in a 2-week-on, 1-week-off schedule or intravenous gemcitabine (1000 mg/m²) plus cisplatin (25 mg/m²) given on days 1 and 8 of each 3-week cycle.</td>
<td>Primary completion October 2023 Study completion October 2024</td>
</tr>
</tbody>
</table>

Abbreviations: FGF, fibroblast growth factor gene; FGFR, fibroblast growth factor receptor gene; FGFR2, fibroblast growth factor receptor 2 gene.

**Recently Completed and Ongoing Trials With Available Results**

Our searches identified one relevant, recently completed late-phase trial with published results.\(^{125}\) We summarize this study with results as written in a conference abstract.

The following abbreviations are used in this section: AE, adverse event; CI, confidence interval; DCR, disease control rate; DOR, duration of response; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FGFR2, fibroblast growth factor receptor 2; m, median; mo, months; mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate; OS, overall survival; pts, patients.

**Efficacy and Safety of Pemigatinib in Subjects With Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma Who Failed Previous Therapy (FIGHT-202). NCT02924376. Vogel et al 2019.**\(^{125}\)

- **Patient population/planned enrollment:** Patients (n = 146) who have locally advanced or metastatic cholangiocarcinoma harboring FGFR2 rearrangements or fusions (cohort A), other FGF/FGFR gene alterations (cohort B), or no FGF/FGFR gene alterations (cohort C), who had at least one previous line of systemic therapy in the locally advanced/metastatic setting
- **Study design:** Phase II, multicohort, parallel-assignment, open-label trial to evaluate the safety and efficacy of pemigatinib in patients who had advanced cholangiocarcinoma. Patients received oral pemigatinib at a daily dose of 13.5 mg in a 2-week-on, 1-week-off schedule.
- **Primary outcome:** ORR in patients with FGFR2 translocations
- **Secondary outcomes:** Progression-free survival; ORR in patients with FGF/FGFR alterations other than FGFR2 translocations or no FGF/FGFR alterations
Results presented by study authors: “At data cutoff (Mar 22, 2019), 146 pts were enrolled (cohort A, n = 107; B, n = 20; C, n = 18; 1 pt undetermined). Median (range) age was 59 (26–78) years; 61% and 39% had 1 and ≥2 prior therapies, respectively. Fewer pts discontinued therapy in cohort A (71%) vs B and C (each 100%), mainly for progressive disease (53%, 75%, and 67%, respectively). ORR in cohort A was 35.5% (95% CI, 26.5%–45.4%), with 3 complete responses; median (m) DOR was 7.5 (95% CI, 7.3–14.5) months (mo), DCR was 82% (95% CI, 74%–89%), mPFS and mOS were 6.9 (95% CI, 6.2–9.6) and 21.1 (14.8–not reached) mo (OS not mature at cutoff). In cohorts B and C, no patient achieved a response. Overall, most common adverse events (AEs) were hyperphosphatemia (60%; grade ≥3, 0%), alopecia (49%; 0%), diarrhea (47%; 3%), fatigue (42%; 5%), nail toxicities (42%; 2%), and dysgeusia (40%; 0%). Hyperphosphatemia was managed with diet modifications, phosphate binders, if needed; diuretics or dose reductions/interruptions. Discontinuation, dose reduction and interruption due to AEs occurred in 9%, 14% and 42% of patients, respectively.”

Manufacturers and Regulatory Status

Pemigatinib is being developed by Incyte Corp (Wilmington, Delaware). On April 17, 2020, FDA granted accelerated approval to pemigatinib for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement. FDA had previously granted Breakthrough Therapy designation to pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma harboring FGFR2 rearrangements or fusions.

Cost Information

According to a US-based online aggregator of prescription drug prices, GoodRx, pemigatinib’s retail price (as of April 1, 2020) is about $36 000 for thirty 13.5-mg tablets. At the FDA-approved dosing regimen of 13.5 mg once daily for 14 consecutive days followed by 7 days off therapy, this represents a 1.4-month supply of the drug. In the FIGHT-202 trial, the median duration of therapy was 7.2 months, which would cost about $185 000.

Key Stakeholder Perspectives

Six stakeholders, reflecting clinical, health systems, and research perspectives, provided comments and ratings on pemigatinib for treating cholangiocarcinoma harboring FGFR2 fusions or rearrangements. The list below provides a summary of key stakeholder perspectives.

- Based on pemigatinib’s solid scientific rationale, the lack of available treatments for cholangiocarcinoma after initial therapy has stopped working, and the observed efficacy in the FIGHT-202 trial, pemigatinib has substantial potential to improve health outcomes in patients with FGFR2-mutated cholangiocarcinoma.
- Pemigatinib would cause minimal disruption to the health care delivery system because the drug is taken orally. Although pemigatinib would cause a shift from intravenously administered chemotherapy to an oral medication, this shift would be more disruptive if pemigatinib were to be used as a first-line treatment.
- High rates of hyperphosphatemia observed in the FIGHT-202 trial were concerning and would require dietary and pharmacologic intervention.
- The likely high cost of the drug as well as costs associated with genetic testing to determine treatment eligibility would increase costs of care. (Stakeholders reviewed the topic before cost information was available.) Conversely, the transition from intravenous chemotherapy to an orally administered drug could reduce health care facility costs for treating these patients by eliminating infusion-associated costs.
- The need to incorporate genetic testing to determine pemigatinib treatment eligibility could reduce the numbers of patients treated because of the precision oncology approach
represented by pemigatinib, as well as a learning curve for prescribing physicians about which patients are best suited for the treatment.

Pexidartinib (Turalio) to Treat Tenosynovial Giant Cell Tumors

**Highlights**

- Pexidartinib (Turalio) is an orally administered multikinase inhibitor intended to treat tenosynovial giant cell tumors (TGCTs).
- TGCTs are benign soft tissue sarcomas that arise from joint tissue. They can significantly deteriorate quality of life, and until FDA approved pexidartinib in August 2019, no FDA-approved systemic therapy had been available to address the needs of patients whose TGCTs are not amenable to surgery.
- In a phase III, randomized controlled trial, pexidartinib elicited a 39% overall response rate in patients with TGCT compared with a 0% response rate for patients who received a placebo.
- Stakeholders commenting on this topic generally agreed that pexidartinib, as the first systemic therapy approved by FDA for treating TGCT, might cause a paradigm shift in patient management by providing an option for patients ineligible for surgical resection or as an alternative to surgical resection.
- Stakeholders also voiced concerns about toxicity associated with pexidartinib (particularly liver toxicity), with some commenters suggesting that the risk-to-benefit ratio could limit uptake of pexidartinib.

**Patient Population**

Pexidartinib therapy is intended to treat adults aged 18 years or older with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery.

**Intervention**

Pexidartinib is a multikinase inhibitor under study for treating TGCTs. A type of benign soft tissue sarcoma, TGCTs arise from joint tissue, particularly the synovium, bursae, and tendon sheath. TGCTs typically remain localized to a single affected joint and are rarely fatal; however, they can be locally aggressive and substantially reduce quality of life because of resulting joint pain, inflammation, and dysfunction.

TGCTs are often amenable to treatment by surgical resection. However, patients (in particular, patients with the diffuse type of TGCT, also known as pigmented villonodular synovitis) often experience multiple recurrences, which can lead to substantial disease burden. Up until pexidartinib’s recent FDA approval, patients with TGCT who were ineligible for surgical resection had very few treatment options. The National Organization for Rare Disorders offers more information on TGCT.

TGCTs are characterized by the overexpression of a cytokine, the colony stimulating factor 1 (CSF-1). In many cases, CSF-1 overexpression is caused by a genetic base-pair translocation involving the colony stimulating factor 1 gene, *CSF-1*, which causes constitutive expression of the gene by neoplastic TGCT cells. Overexpression of CSF-1 causes recruitment of cells that express colony-stimulating factor-1 receptor (CSF-1R), such as macrophages, which compose most of the tenosynovial giant cell tumor’s mass.
Pexidartinib is a small-molecule inhibitor of multiple receptor tyrosine kinases, including CSF-1R, FLT3, and KIT. Inhibiting CSF-1R signaling by pexidartinib has the potential to disrupt the paracrine signaling loop that underlies the pathogenesis of TGCTs.

In clinical trials, pexidartinib was administered as 200-mg oral capsules. Patients take the capsules at a dosage of 1000 mg/day for 2 weeks followed by 800 mg/day for an additional 22 weeks. In the FDA approval, the recommended dose is 400 mg (2 capsules) orally, twice daily on an empty stomach.

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified one ongoing trial for this topic. We present this trial in Table 2.10.

### Table 2.10. Ongoing Clinical Trial

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3 Study of Pexidartinib for Pigmented Villonodular Synovitis (PVNS) or Giant Cell Tumor of the Tendon Sheath (GCT-TS) (ENLIVEN) NCT02371369</td>
<td>Adults aged 18 years or older (n = 120) with symptomatic TGCT that is unamenable to surgery</td>
<td>Phase III, randomized control trial of the safety and efficacy of pexidartinib in the treatment of TGCT. Patients will be randomly assigned to treatment with either pexidartinib (1000 mg/day for 2 weeks followed by 800 mg/day for 22 weeks) or placebo. Patients who complete the 24-week randomized controlled portion of the trial are eligible to continue into an open-label extension portion of the trial in which all patients received pexidartinib. Primary outcome: Overall response rate per RECIST Selected secondary outcome: Percentage of patients reporting frequent treatment-emergent adverse events</td>
<td>Primary completion March 2017 Study completion March 2021</td>
</tr>
</tbody>
</table>

**Abbreviations:** RECIST, Response Evaluation Criteria in Solid Tumors; TGCT, tenosynovial giant cell tumors.

**Recently Completed and Ongoing Trials With Available Results**

Our searches identified one relevant, recently completed late-phase trial with published results. We summarize this study with results as written in the abstract of the published study.

The following abbreviations are used in this section: CI, confidence interval; RECIST, Response Evaluation Criteria in Solid Tumors; TGCT, tenosynovial giant cell tumors.

**Phase 3 Study of Pexidartinib for Pigmented Villonodular Synovitis (PVNS) or Giant Cell Tumor of the Tendon Sheath (GCT-TS) (ENLIVEN). NCT02371369. Tap et al 2019.**

- **Patient population/planned enrollment:** Adults aged 18 years or older (n = 120) with symptomatic TGCT that is unamenable to surgery
• **Study design:** Phase III, randomized controlled trial of the safety and efficacy of pexidartinib in the treatment of TGCT. Patients were randomly assigned to treatment with either pexidartinib (1000 mg/day for 2 weeks followed by 800 mg/day for 22 weeks) or placebo. Patients who completed the 24-week randomized controlled portion of the trial were eligible to continue into an open-label extension portion of the trial in which all patients received pexidartinib.

• **Primary outcome:** Overall response rate per RECIST

• **Secondary outcome:** Percentage of patients reporting frequent treatment-emergent adverse events

• **Results presented by study authors:** “Between May 11, 2015, and Sept 30, 2016, of 174 patients assessed for eligibility, 120 patients were randomly assigned to, and received, pexidartinib (n=61) or placebo (n=59). There were 11 dropouts in the placebo group and nine in the pexidartinib group. Emergence of mixed or cholestatic hepatotoxicity caused the data monitoring committee to stop enrolment six patients short of target. The proportion of patients who achieved overall response was higher for pexidartinib than placebo at week 25 by RECIST (24 [39%] of 61 vs none of 59; absolute difference 39% [95% CI 27-53]; p<0.0001).

Serious adverse events occurred in eight (13%) of 61 patients in the pexidartinib group and one (2%) of 59 patients in the placebo group. Hair colour changes (67%), fatigue (54%), aspartate aminotransferase increase (39%), nausea (38%), alanine aminotransferase increase (28%), and dysgeusia (25%) were the most frequent pexidartinib-associated adverse events. Three patients given pexidartinib had aminotransferase elevations three or more times the upper limit of normal with total bilirubin and alkaline phosphatase two or more times the upper limit of normal indicative of mixed or cholestatic hepatotoxicity, one lasting 7 months and confirmed by biopsy.”

## Manufacturers and Regulatory Status

Pexidartinib was developed by Daiichi Sankyo (Tokyo, Japan). On August 2, 2019, FDA approved pexidartinib to treat “adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery.”

The FDA approval carries a black box warning regarding the potential for serious and fatal liver injury; because of this risk, pexidartinib is available only through a Risk Evaluation and Mitigation Strategy (REMS) program. The REMS requires that prescribing physicians enroll in the REMS and receive training, that patients prescribed pexidartinib enroll in a registry, and that pharmacies be certified by the program.

FDA had previously granted pexidartinib Breakthrough Therapy designation to treat TGCT.

## Cost Information

According to a US-based online aggregator of prescription drug prices, GoodRx, pexidartinib’s retail price (as of April 1, 2020) was about $20,000 for one hundred twenty 200-mg tablets, which represents a 30-day supply of the drug. Thus, a 1-year supply of pexidartinib would cost about $240,000. According to the manufacturer’s website, patient assistance programs are available in the form of copayment assistance, financial assistance for patients without insurance coverage for pexidartinib, and a free trial period for patients with a delay in obtaining a pexidartinib prescription.

## Key Stakeholder Perspectives

Six stakeholders, reflecting clinical, nursing, research, and health systems perspectives, provided comments and ratings on this TGCT treatment. The list below provides a summary of key stakeholder perspectives.

- Pexidartinib has moderate to large potential to disrupt patient-oriented outcomes because of limited nonsurgical treatment options for TGCT and the promising response rates and
symptom control observed in patients not amenable to surgery in the phase III trial. However, pexidartinib-associated liver toxicity might limit its benefits.

- Pexidartinib will moderately disrupt the current paradigm of TGCT care. Although pexidartinib’s immediate impact would be as the first FDA-approved systemic treatment of TGCTs not amenable to surgery, its largest impact might occur if used for patients with resectable TGCT, potentially making these tumors more amenable to surgical resection and reducing surgery-associated illness.
- Some commenters thought that pexidartinib might lead to changes in patient management due to a requirement to monitor patients’ liver function during use; however, most thought that pexidartinib’s impact on health care delivery would be minimal, citing its oral route of administration and the small number of TGCT patients.
- The low prevalence of TGCT will limit the overall impact of pexidartinib on health care costs. Direct costs to patients will likely be mitigated by insurance coverage or manufacturer patient assistance programs for underinsured or uninsured patients, although copayments might still be significant for some patients.

Remestemcel-L (Ryoncil) to Treat Pediatric Steroid-Refractory Acute Graft-Versus-Host Disease

**Highlights**

- Remestemcel-L (Ryoncil) is an off-the-shelf, intravenous, allogeneic mesenchymal stem cell therapy under study for treating pediatric patients with steroid-refractory acute graft-versus-host disease (GVHD).
- No FDA-approved therapy exists for children younger than 12 years of age who develop steroid-refractory acute GVHD after a bone marrow transplant, and 6-month survival rates are only about 50%, emphasizing the need for more effective treatments.
- Stakeholders commenting on this topic indicated that remestemcel-L has substantial potential to improve patient outcomes in children with steroid-refractory GVHD.
- Stakeholders suggested that the likely high cost of this cell therapy could have multiple consequences, including potential for slower adoption and the exacerbation of any existing health disparities based on socioeconomic status or access to health insurance coverage.

**Patient Population**

Remestemcel-L is intended for children aged 2 months to 17 years who have developed acute GVHD after a bone marrow transplant and whose GVHD has not responded adequately to steroid treatment.

**Intervention**

Allogeneic (from a donor) hematopoietic stem cell transplantation (allo-HSCT) is used in treating several cancerous and noncancerous blood disorders and metabolic diseases. Sometimes, donor cells launch an immune response against the recipient’s tissues in a condition called GVHD. Acute GVHD manifests as specific symptoms affecting the skin, gastrointestinal tract, and liver and can occur in the early posttransplantation period or later. 150-153 The Leukemia and Lymphoma Society offers more information on GVHD.
Acute GVHD dramatically impacts quality of life and is the second leading cause of death in patients who have undergone allo-HSCT, after disease recurrence. First-line treatment of acute GVHD typically uses corticosteroids to suppress the immune system; however, only a minority of patients experience a complete response to corticosteroid treatment. No FDA-approved therapy exists for patients younger than 12 years of age with steroid-refractory acute GVHD, and 6-month survival rates are only about 50%.150-153

Remestemcel-L (Ryoncil, formerly Prochymal) is an off-the-shelf preparation of allogeneic mesenchymal stromal cells (also known as mesenchymal stem cells). These cells purportedly have an immunomodulatory effect, regulating T-cell-mediated inflammation by inhibiting T-cell proliferation and downregulating production of inflammatory cytokines, including tumor necrosis factor-alpha and interferon gamma. Additionally, remestemcel-L purportedly secretes growth factors that might facilitate tissue repair. To produce remestemcel-L, adult human mesenchymal stem cells are isolated from donor bone marrow and expanded in culture.154,155

In clinical trials, patients receive remestemcel-L by intravenous infusion at a dose of $2 \times 10^6$ cells/kg twice a week for 4 consecutive weeks. Patients achieving a response at 4 weeks may receive up to 4 additional weekly infusions.156

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified no ongoing trials for this topic.

Recently Completed and Ongoing Trials With Available Results

Our searches identified 3 recently completed late-phase trials with published results.157-159 We summarize these 3 most recent and indication-relevant studies with results as written in an abstract of the published studies.

The following abbreviations are used in this section: aGVHD, acute graft-versus-host disease; CR, complete response; DCR, disease control rate; IV, intravenous; MSC, mesenchymal stem cell; OR, overall response; P, probability; PR, partial response, SR-aGVHD, steroid-refractory acute graft-versus-host disease.


- **Patient population/planned enrollment:** Children (n = 54) aged 2 months to 17 years with steroid-refractory aGVHD naive to other immunosuppressant therapies
- **Study design:** Phase III, single-group assignment, open-label trial to evaluate the safety and efficacy of remestemcel-L in patients with steroid-refractory aGVHD. Patients received 8 twice-weekly IV infusions of remestemcel-L (dose = 2 million cells/kg) over 4 weeks, with 4 more weekly infusions after day 28 in patients with a partial or mixed response.
- **Primary outcome:** Overall response at day 28
- **Secondary outcome:** Overall survival at 100 days after first infusion
- **Results presented by study authors:** "Remestemcel-L therapy significantly improved day 28 overall response rate (OR) compared with the prespecified control OR value of 45% (70.4% versus 45%, P = .0003). The statistically significant OR (70.4%) was sustained through day 100, including an increase in complete response from 29.6% at day 28 to 44.4% at day 100. Overall survival was 74.1% at day 100 and 68.5% at day 180. Overall response in all participants at day 28 was highly predictive of improved survival through 180
days, and survival was significantly greater in day 28 responders compared with nonresponders through day 100 (86.8% versus 47.1% for responders and nonresponders, respectively, P = .0001) and through day 180 (78.9% versus 43.8%, P = .003). Remestemcel-L was well tolerated with no identified infusion-related toxicities or other safety concerns. This study provides robust, prospective evidence of the safety, tolerability, and efficacy of remestemcel-L as first-line therapy after initial steroid failure in pediatric SR-aGVHD."

- Patient population/planned enrollment: Children (n = 241) aged 2 months to 17 years with steroid-refractory aGVHD
- Study design: Patients were given 8 twice-weekly IV infusions of remestemcel-L (dose = 2 million cells/kg) over 4 weeks, with 4 additional weekly infusions after day 28 in patients with a partial or mixed response
- Primary outcome: Overall response at day 28
- Results presented by study authors: "Across all subjects, a 28-day OR was observed in 157 patients (65.1%), with 34 (14.1%) achieving CR and 123 (51.3%) achieving PR. Stratified by aGVHD grade at baseline, the OR rate at day +28 was 72.9% for patients with aGVHD grade B, 67.1% for those with aGVHD grade C, and 60.8% for those with aGVHD grade D. Survival through day +100, a secondary endpoint of the study, was 66.9% (n = 160 of 239). Importantly, survival through day +100 was significantly greater in subjects who achieved a day +28 OR compared with nonresponders (82.1% versus 38.6%; P < .001, log-rank test). Remestemcel-L safety was generally well tolerated, with no infusional toxicity and no identified safety concerns."

- Patient population/planned enrollment: Patients (n = 260) aged 6 months to 70 years with steroid-refractory aGVHD
- Study design: Phase III, randomized, parallel-assignment, double-blind trial to evaluate the safety and efficacy of remestemcel-L in patients with steroid-refractory aGVHD. Patients were assigned in a 2:1 ratio to receive either 8 twice-weekly IV infusions of remestemcel-L (dose = 2 million cells/kg) or placebo over 4 weeks, with 4 more weekly infusions after day 28 in patients with a partial or mixed response.
- Primary outcome: Percentage of patients achieving a complete response of at least 28 days’ duration
- Secondary outcome: Overall survival at 180 days after first infusion
- Results presented by study authors: "Remestemcel-L did not meet the primary endpoint of greater DCR in the intent-to-treat population (35% versus 30%; P = .42). In post hoc analyses, patients with liver involvement who received at least 1 infusion of remestemcel-L had a higher DCR, and higher overall complete or partial response rate (OR) than those who received placebo (29% versus 5%; P = .047). Furthermore, pediatric patients had a higher OR with MSCs compared with placebo (64% versus 23%; P = .05). Similar rates of adverse events were observed between treatment groups. Remestemcel-L was safe and well tolerated. Results of this study did not demonstrate superior DCR compared with placebo when added to standard of care."

Manufacturers and Regulatory Status
Remestemcel-L is being developed by Mesoblast Ltd (Melbourne, Australia), which acquired the product from Osiris Therapeutics Inc in 2013. Mesoblast filed a Biologics License Application submission with FDA in January 2020.160 FDA had granted remestemcel-L to treat acute GVHD Fast Track designation in March 2017161 and Orphan Drug designation in December 2005.162
Cost Information
Cost information is unavailable for this topic, but stakeholders indicated they expected the cost to be high.

Key Stakeholder Perspectives
Nine stakeholders, reflecting clinical, patient advocate, research, and health systems perspectives, provided comments and ratings on the topic of remestemcel-L for treating pediatric steroid-refractory acute GVHD.163-171 The list below provides a summary of key stakeholder perspectives.

- Remestemcel-L has moderate to large potential to improve health outcomes for children with acute GVHD, given the lack of FDA-approved therapies for this potentially fatal condition.
- Similar improvement was not observed in the overall larger trial populations that included adults through 70 years of age.
- Remestemcel-L could give clinicians a standardized, off-the-shelf, and more effective option for treating children with acute GVHD instead of a cocktail of immunosuppressants used to manage the condition.
- As a stem cell–based therapy, remestemcel-L is likely to cost much more than the standard of care for acute GVHD; such high costs could hinder adoption, limit patient access, and increase disparities in care.
- Although delivering remestemcel-L is more labor intensive than oral immunosuppressant therapy for acute GVHD, the disruption to the health care delivery system is likely to be low relative to the overall management of this patient population.
Sacituzumab Govitecan-hziy as Third-Line Treatment for Locally Advanced or Metastatic Triple-Negative Breast Cancer

**Highlights**

- Sacituzumab govitecan-hziy, an intravenous therapy, consists of a chemotherapy drug coupled to a monoclonal antibody specific against trophoblast cell-surface antigen 2 (Trop-2), a protein expressed in about 85% of epithelial cancers, which includes triple-negative breast cancer (TNBC).
- TNBC is an aggressive cancer that constitutes about 15% of all breast cancer cases. The disease is associated with poor prognosis because it progresses rapidly and patients have limited treatment options. With targeted therapies, patients survive about 2 years.
- Stakeholders commenting on this topic thought that sacituzumab govitecan-hziy has the potential to improve health outcomes; however, they indicated that additional data from the ongoing phase III trial are needed.
- Stakeholders also thought that sacituzumab govitecan-hziy has the potential to disrupt health disparities and is expected to be more expensive than standard chemotherapy; however, some thought that a new treatment that lies outside the current 2 classes of targeted therapies might decrease disparities for some patients.

**Patient Population**

Sacituzumab govitecan-hziy is intended for adults aged 18 years or older with locally advanced or metastatic TNBC who have received at least 2 previous lines of systemic therapy.

**Intervention**

TNBC is a type of breast cancer that lacks overexpression of the 3 protein receptors—estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2—that drive growth of and provide therapeutic targets in other types of breast cancer. TNBC constitutes about 15% of all breast cancers. TNBC is an aggressive type of cancer associated with poor prognosis because it rapidly progresses into metastatic disease and develops resistance to chemotherapy. The site Breastcancer.org offers more information on breast cancer.

Historically, TNBC treatment has relied on cytotoxic chemotherapy regimens; however, these regimens induce relatively low tumor response rates and are associated with substantial toxicity. More recently, FDA has approved drugs in 2 classes of targeted therapies for TNBC: poly adenosine diphosphate (ADP) ribose polymerase inhibitors for TNBC in patients with germline BRCA1/BRCA2 mutations and an immune checkpoint inhibitor for TNBC expressing programmed death-ligand 1 (PD-L1). However, not all patients with TNBC are eligible for these therapies, and among eligible patients, the median overall survival reported in trials of these targeted therapies remains at about 2 years. Therefore, patients with TNBC need new treatment options that can improve health outcomes.

Sacituzumab govitecan-hziy is an antibody–drug conjugate consisting of a monoclonal antibody coupled via a cleavable linker to SN-38, an active metabolite of the chemotherapy drug irinotecan. The monoclonal antibody is specific for Trop-2, a cell-surface protein overexpressed in about 85% of epithelial cancers, including TNBCs. Sacituzumab govitecan-hziy purportedly kills Trop-2-expressing cells by binding to them and delivering SN-38.
An oncologist prescribes sacituzumab govitcan-hziy to be given in an infusion center. An infusion center nurse administers 10 mg/kg of intravenous sacituzumab govitcan-hziy on days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity.

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified 2 ongoing trials for this topic. We present these trials in Table 2.11.

**Table 2.11. Ongoing Clinical Trials**

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study of Sacituzumab Govitcan in Refractory/Relapsed Triple-Negative Breast Cancer (ASCENT) NCT02574455</td>
<td>Patients (n = 529) with histologically or cytologically confirmed, locally advanced or metastatic TNBC who have had 2 or more previous lines of systemic therapy in the locally advanced/metastatic setting</td>
<td>Phase III, randomized, parallel-assignment, open-label trial to evaluate the safety and efficacy of sacituzumab govitcan-hziy in patients with TNBC. Patients will be randomly assigned to treatment with either sacituzumab govitcan-hziy (10 mg/kg on days 1 and 8 of 21-day cycles) or physician’s choice consisting of eribulin, capecitabine, gemcitabine, or vinorelbine. Primary endpoint: Progression-free survival Secondary endpoints: Overall survival, objective response rate, duration of response, and time to onset of response</td>
<td>Primary completion April 2020 Study completion July 2020</td>
</tr>
<tr>
<td>Phase I/II Study of IMMU-132 in Patients With Epithelial Cancers (IM-T-IMMU-132-01) NCT01631552</td>
<td>Patients (n = 515) with locally advanced or metastatic TNBC and other types of epithelial cancers (eg, FTC, GBM, GC, HCC, HNSCC, NSCLC, RCC) who have had one or more previous lines of systemic therapy in the locally advanced/metastatic setting</td>
<td>Phase I/II, single-group assignment trial to evaluate the safety and efficacy of sacituzumab govitcan-hziy in patients with epithelial cancers. All patients will receive intravenous sacituzumab govitcan-hziy at various doses. Primary endpoint: Adverse events Secondary endpoints: Objective response rate, duration of response, and time to progression</td>
<td>Primary and study completion June 2020</td>
</tr>
</tbody>
</table>

Abbreviations: FTC, follicular thyroid cancer; GBM, glioblastoma multiforme; GC, gastric cancer; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; NSCLC, non–small cell lung cancer; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer.

**Recently Completed and Ongoing Trials With Available Results**

Our searches identified one relevant, recently completed late-phase trial with published results.172 We summarize this study with results as written in an abstract of the published study.
The following abbreviations are used in this section: CI, confidence interval; TNBC, triple-negative breast cancer.

**Study Phase I/II Study of IMMU-132 in Patients With Epithelial Cancers (IM-T-IMMU-132-01).**

*NCT01631552, Bardia et al 2019.172*

- **Patient population/planned enrollment:** Patients (n = 515) with previously treated locally advanced or metastatic epithelial cancers, including patients (n = 108) with TNBC who have had at least 2 previous lines of systemic therapy in the locally advanced/metastatic setting.

- **Study design:** Phase I/II, single-group assignment trial to evaluate the safety and efficacy of sacituzumab govitecan-hziy in patients with metastatic epithelial cancers. The 108 patients with TNBC in this analysis all received intravenous sacituzumab govitecan-hziy at a dose of 10 mg/kg on days 1 and 8 of each 21-day cycle.

- **Primary outcome:** Adverse events

- **Secondary outcomes:** Overall survival, progression-free survival, objective response rate, duration of response, and clinical benefit

- **Results presented by study authors:** "The 108 patients with triple-negative breast cancer had received a median of 3 previous therapies (range, 2 to 10). Four deaths occurred during treatment; 3 patients (2.8%) discontinued treatment because of adverse events. Grade 3 or 4 adverse events (in ≥10% of the patients) included anemia and neutropenia; 10 patients (9.3%) had febrile neutropenia. The response rate (3 complete and 33 partial responses) was 33.3% (95% confidence interval [CI], 24.6 to 43.1), and the median duration of response was 7.7 months (95% CI, 4.9 to 10.8); as assessed by independent central review, these values were 34.3% and 9.1 months, respectively. The clinical benefit rate was 45.4%. Median progression-free survival was 5.5 months (95% CI, 4.1 to 6.3), and overall survival was 13.0 months (95% CI, 11.2 to 13.7)."

**Manufacturers and Regulatory Status**

Sacituzumab govitecan-hziy is being developed by [Immunomedics Inc (Morris Plains, New Jersey)](https://www.immunomedics.com). On April 22, 2020, FDA granted accelerated approval to sacituzumab govitecan-hziy for the treatment of adults with locally advanced or metastatic TNBC who have received at least 2 previous lines of therapy. Its approval was based on data from the phase I/II IM-T-IMMU-132-01 trial, but its approval is contingent on verification of safety and efficacy in the confirmatory phase III ASCENT trial.

In April 2020, Immunomedics halted the phase III ASCENT study after an independent data safety monitoring committee determined that the study offered compelling evidence of efficacy. The company has not yet released data from the ASCENT study yet, but it could be presented at a future scientific meeting and annexed to the Biologics License Application. FDA has granted Fast Track and Breakthrough Therapy designations to sacituzumab govitecan-hziy for treating TNBC.

**Cost Information**

Cost information is unavailable for this topic.

**Key Stakeholder Perspectives**

Nine stakeholders, reflecting clinical, health systems, nursing, patient, patient representative, and research perspectives, provided comments and ratings on sacituzumab govitecan-hziy. The list below provides a summary of key stakeholder perspectives.

- Sacituzumab govitecan-hziy has the potential to improve health outcomes of patients with TNBC, which is an aggressive cancer that is resistant to treatment and lacks
therapeutic targets. However, data were not overwhelmingly positive; thus, more data from the ongoing phase III trial are needed to confirm findings.

- Sacituzumab govitecan-hziy’s likely high cost has the potential to cause disparities for uninsured patients. But if shown to improve health outcomes, this new drug that lies outside the current 2 classes of targeted therapies might decrease disparities in certain populations, such as African American women, in whom TNBC is more common than in Caucasian women.
- As an intravenous drug, sacituzumab govitecan-hziy would be given at infusion centers and use health care infrastructure that is already in place. If trials demonstrate efficacy for treating TNBC, clinicians may prescribe it more often, thus increasing both the use of infusion centers and the need for additional staff.
- Sacituzumab govitecan-hziy has the potential to disrupt health care costs because it is expected to be more expensive than current cytotoxic chemotherapy agents used in second- and third-line settings. If the drug is widely prescribed because of proven efficacy, it might increase costs for insurance companies, health centers, and patients.

Selpercatinib (LOXO-292) to Treat Locally Advanced or Metastatic RET-Altered Thyroid Cancer

**Highlights**

- Selpercatinib is an oral, highly specific tyrosine kinase inhibitor (TKI) that targets rearranged during transfection (RET), a protein expressed by the RET gene involved in division, growth, invasiveness, and survival of tumor cells.
- Depending on the type of thyroid cancer, up to 60% of cases harbor RET gene alterations that can be treated using multitarget TKIs, but their nonselective activity against the RET protein yields low response rates and high off-target toxicities.
- Stakeholders commenting on this topic agreed that selpercatinib shows potential to improve patient-oriented outcomes with minimal adverse events; however, they thought additional trials are needed to compare selpercatinib with multitarget TKIs.
- Stakeholders also thought that if trials demonstrate selpercatinib’s safety and efficacy, it might become standard of care for treating RET-altered thyroid cancer, but its high price and need for RET genetic testing might limit the access of uninsured patients and those living in underserved areas.

**Patient Population**

Selpercatinib is intended for children aged 12 years or older and adults with locally advanced or metastatic thyroid cancer harboring alterations in RET, including RET-mutant medullary thyroid cancer (MTC) or RET gene fusion–positive differentiated thyroid cancer (DTC).

**Intervention**

Thyroid cancer is a malignancy that originates when cells in the thyroid gland begin to grow out of control. MTC is a type of thyroid cancer that develops from C cells (cells that make calcium-regulating hormones). DTCs, including papillary, follicular, and Hürthle cell, are thyroid cancers that develop from follicular cells (cells that make metabolism-regulating hormones). The American Cancer Society offers [more information on thyroid cancer](https://www.cancer.org/cancer/types/thyroid/thyroid-cancer.html).
**RET** alterations have been reported to occur in various types of cancer. **RET** mutations affect more than 60% of MTC cases, and **RET** gene fusions occur in about 10% to 20% of DTCs, specifically follicular thyroid cancers.\(^{190,191}\) **RET** alterations promote cell division, growth, invasiveness, and survival and so represent a rational site for targeted therapy. However, treatment with multitarget TKIs with nonselective activity against the **RET** protein has yielded low response rates and high off-target toxicities.\(^{191}\) Therefore, new treatments are sought with improved targeting of **RET**-altered malignancies.

Selpercatinib is a novel, small-molecule TKI that is highly specific for **RET** and is intended to treat **RET**-altered MTC and DTC.\(^{190}\) Selpercatinib’s antikinase activity against **RET**-altered tumors purportedly promotes tumor shrinkage and has low potential to cause serious drug-related adverse events.\(^{190,192}\)

An oncologist prescribes selpercatinib, an oral therapy that patients take twice daily at a dose of 160 mg until disease progression or intolerable toxicity.

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified 2 ongoing trials for this topic. We present these trials in Table 2.12.

**Table 2.12. Ongoing Clinical Trials**

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1/2 Study of LOXO-292 in Patients With Advanced Solid Tumors, RET Fusion-Positive Solid Tumors, and Medullary Thyroid Cancer (LIBRETTO-001) NCT03157128</td>
<td>Patients (n = 970) with locally advanced or metastatic <strong>RET</strong>-mutant MTC, <strong>RET</strong> fusion–positive DTC (including follicular and papillary thyroid cancer), or <strong>RET</strong> fusion–positive solid tumors (including colorectal cancer and non–small cell lung cancer)</td>
<td>Phase I/II, multicohort, single-group assignment, open-label trial to evaluate the safety and efficacy of selpercatinib in patients with <strong>RET</strong>-altered solid tumor cancers. Patients will receive oral selpercatinib at a dose of 160 mg twice a day. Primary endpoint: Objective response rate Secondary endpoints: Overall survival, progression-free survival, disease control rate, duration of response, clinical benefit rate, and adverse events</td>
<td>Primary completion March 2022 Study completion May 2022</td>
</tr>
</tbody>
</table>
A Study of Selpercatinib (LY3527723) in Participants With RET-Mutant Medullary Thyroid Cancer (LIBRETTO-531) NCT04211337

- **Patient population and planned enrollment**: Patients (n = 400) with locally advanced or metastatic RET-mutant MTC who have received no previous TKI in the locally advanced or metastatic setting

- **Study design and outcomes**: Phase III, randomized, parallel-assignment, open-label trial to evaluate the safety and efficacy of selpercatinib in patients with RET-mutant MTC. Patients will receive either oral selpercatinib, cabozantinib, or vandetanib. Primary endpoint: Treatment failure–free survival. Secondary endpoints: Overall survival, progression-free survival, objective response rate, duration of response, and comparative tolerability

- **Estimated date of completion**: Primary completion February 2023. Study completion December 2024

Abbreviations: DTC, differentiated thyroid cancer; MTC, medullary thyroid cancer; RET, rearranged during transfection gene; TKI, tyrosine kinase inhibitor.

### Recently Completed and Ongoing Trials With Available Results

Our searches identified one relevant, recently completed late-phase trial with published results.\(^{193}\) We summarize this study with results as written in a conference abstract.

The following abbreviations are used in this section: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CEA, carcinoembryonic antigen; CI, confidence interval; CR, complete response; DoR, duration of response; MTC, medullary thyroid cancer; NE, not evaluable; ORR, overall response rate; PAS, primary analysis set; PR, partial response; RET, rearranged during transfection gene; US FDA, US Food and Drug Administration; V804M/L, valine 804 substituted with methionine or leucine.

### Phase 1/2 Study of LOXO-292 in Patients With Advanced Solid Tumors, RET Fusion-Positive Solid Tumors, and Medullary Thyroid Cancer (LIBRETTO-001). NCT03157128. Wirth et al 2019.\(^{193}\)

- **Patient population/planned enrollment**: Patients with RET-mutant MTC (n = 226) or RET fusion–positive thyroid cancer (n = 27), including follicular and papillary thyroid cancer

- **Study design**: Phase I/II, multicohort, single-group assignment, open-label trial to evaluate the safety and efficacy of selpercatinib in patients with RET-altered thyroid cancer. Patients received oral selpercatinib at a dose of 160 mg, twice daily.

- **Primary outcome**: ORR

- **Secondary outcomes**: DoR and AEs

- **Results presented by study authors**: “As of 17-June 2019, 253 RET–altered thyroid cancer patients (n = 226 RET-mutant MTC, n = 27 RET fusion+ thyroid cancer) were treated. The primary analysis set (PAS) for LOXO-292 registration in MTC, defined with the US FDA, consisted of the first 55 consecutively enrolled RET-mutant MTC patients who received prior cabozantinib and/or vandetanib. Among these previously treated RET-mutant MTC PAS patients, the investigator-assessed ORR was 56% (95% CI 42-70%, n = 31/55, 2 PRs pending confirmation), including 3 patients with a RET V804M/L gatekeeper mutation (1 CR, 2 PR, all confirmed). Median DoR has not been reached (6 DoR events, 95% CI 11.1 months-NE) with median follow-up of 10.6 months. Biochemical response rates (≥50% decrease lasting ≥4 weeks) were 91% for calcitonin (n = 49/54) and 64% for CEA (n = 34/53). The ORR in evaluable RET fusion+ thyroid cancer patients was 62% (95% CI 41-80%, n = 16/26, 2 PRs pending confirmation). In the safety data set of 531 patients, 5 treatment-
related AEs occurred in ≥15% of patients: dry mouth, diarrhea, hypertension, increased AST and increased ALT. Most AEs were grade 1-2. Only 9 of 531 (1.7%) patients discontinued LOXO-292 for treatment-related AEs.”

Manufacturers and Regulatory Status

Investigators at Loxo Oncology Inc (Stamford, Connecticut), a subsidiary of Eli Lilly and Co (Indianapolis, Indiana), are studying selpercatinib in a phase III trial for treating previously untreated RET-mutant MTC and in a phase I/II trial for treating RET-altered thyroid cancer that has progressed after one previous line of therapy (eg, vandetanib and/or cabozantinib). In September 2018, FDA granted Breakthrough Therapy designation to selpercatinib for treating RET-mutant MTC and RET fusion–positive thyroid cancer that has progressed after one previous line of therapy (eg, vandetanib and/or cabozantinib).194,195

Based on data from the LIBRETTO-001 trial,193 Loxo Oncology and Eli Lilly submitted a New Drug Application (NDA) to FDA. In January 2020, FDA accepted the NDA, granted Priority Review, and set a Prescription Drug User Fee Act–(PDUFA)-prescribed date in the third quarter of 2020.196

Cost Information

Cost information is unavailable for this topic.

Key Stakeholder Perspectives

Eight stakeholders, reflecting clinical, health systems, nursing, and research perspectives, provided comments and ratings on selpercatinib.197-204 The list below provides a summary of key stakeholder perspectives.

- Although treatments with nonselective TKIs have low response rates and high off-target adverse events, selpercatinib has the potential to improve patient-oriented outcomes with minimal adverse events. However, more data are needed, especially from trials comparing selpercatinib with multitarget TKIs.
- As an oral drug, selpercatinib will be delivered in a similar manner to standard treatment options and will not affect the way in which patients receive care. However, if trials demonstrate safety and efficacy, it could become the standard of care and decrease visits to infusion centers.
- Because selpercatinib is expected to be very expensive, it may create disparities for uninsured and underinsured patients, but it also has the potential to decrease costs associated with hospital admissions, delivery of intravenous drugs, and progressive disease.
- Selpercatinib’s adoption might depend on RET genetic testing availability, which will likely affect patients living in underserved areas with limited access to RET testing; thus, if they are not tested, they will not be eligible for selpercatinib treatment.
Sodium Thiosulfate (Pedmark) to Prevent Cisplatin-Mediated Ototoxicity

**Highlights**
- Pedmark, an intravenous infusion, is a proprietary form of sodium thiosulfate intended to reduce the risk of cisplatin-induced ototoxicity, which can lead to hearing loss, tinnitus, or vertigo, particularly in children undergoing chemotherapy.
- No effective treatment is available for preventing chemotherapy-induced ototoxicity.
- In 2 clinical trials, treatment with sodium thiosulfate significantly reduced hearing loss by 48% and 49% compared with standard care.
- Stakeholders commenting on this topic generally agreed that sodium thiosulfate use could meet an important unmet need—given the significant disease burden that children with cisplatin-induced ototoxicity experience and the lack of approved treatments—and that it could positively disrupt patient-oriented health outcomes, including quality of life.
- Stakeholders also thought that factors surrounding delivery of the treatment (eg, a 6-hour wait time after chemotherapy infusion) might create disparities in access to care and/or add to the burden of care for these patients.

**Patient Population**
Pedmark is intended for children aged 1 month to 18 years who have localized, nonmetastatic solid tumors eligible for cisplatin-based chemotherapy.

**Intervention**
Pedmark is a proprietary formulation of sodium thiosulfate intended to reduce the risk of cisplatin-induced ototoxicity. Ototoxicity, which can result in hearing loss, tinnitus, or vertigo, is a well-established risk factor of using cisplatin chemotherapy for various cancers. The Children’s Oncology Group offers more information on hearing loss related to chemotherapy use in children.

Pedmark’s antiototoxic effects have been attributed to multiple mechanisms of action, including inactivating platinum and/or platinum–protein complexes, which would reduce cisplatin’s direct cytotoxic effects, and inactivating reaction oxygen species (ROS) and/or elevating levels of endogenous reducing agents (eg, glutathione), which could inhibit ROS-induced apoptosis induced by cisplatin.

Because of Pedmark’s potential to interfere with cisplatin’s cytotoxic activity, clinicians delay giving Pedmark to allow cisplatin to exert its anticancer effects while remaining within the window for having an otoprotective effect.

A pediatric oncologist prescribes Pedmark and refers the patient to an infusion center. An infusion nurse gives intravenous Pedmark at a dose of 16 or 20 g/m², 6 hours after the patient receives cisplatin-based chemotherapy. Pedmark treatment continues with each round of cisplatin treatment until treatment is complete.

**Evidence Development Summary**

**Ongoing Trials**
Our searches of the National Clinical Trials database identified no ongoing trials for this topic.
Recently Completed and Ongoing Trials With Available Results

Our searches identified 2 recently completed late-phase trials with published results.208,209 We summarize these 2 most recent and indication-relevant studies with results as written in abstracts of published studies.

The following abbreviations are used in this section: CI, confidence interval; P or p, probability; vs, versus.

Cisplatin With or Without Sodium Thiosulfate in Treating Young Patients With Stage I, II, or III Childhood Liver Cancer (SIOPEL6). NCT00652132. Brock et al 2018.208

- **Patient population/planned enrollment**: Children (n = 109) who have standard-risk hepatoblastoma and are eligible for cisplatin-based chemotherapy
- **Study design**: Phase III, randomized, parallel-assignment, open-label trial to evaluate the safety and efficacy of sodium thiosulfate in patients with hepatoblastoma. Patients were randomly assigned in a 1:1 ratio to receive either intravenous cisplatin plus sodium thiosulfate (20 g/m²) or cisplatin alone.
- **Primary outcome**: Hearing loss
- **Secondary outcomes**: Event-free survival and overall survival
- **Results presented by study authors**: “Sodium thiosulfate was associated with fewer high-grade toxic effects. The absolute hearing threshold was assessed in 101 children. Hearing loss of grade 1 or higher occurred in 18 of 55 children (33%) in the cisplatin–sodium thiosulfate group, as compared with 29 of 46 (63%) in the cisplatin-alone group, indicating a 48% lower incidence of hearing loss in the cisplatin–sodium thiosulfate group (relative risk, 0.52; 95% confidence interval [CI], 0.33 to 0.81; P =0.002). At a median of 52 months of follow-up, the 3-year rates of event-free survival were 82% (95% CI, 69 to 90) in the cisplatin–sodium thiosulfate group and 79% (95% CI, 65 to 88) in the cisplatin-alone group, and the 3-year rates of overall survival were 98% (95% CI, 88 to 100) and 92% (95% CI, 81 to 97), respectively.”

Sodium Thiosulfate in Preventing Hearing Loss in Young Patients Receiving Cisplatin for Newly Diagnosed Germ Cell Tumor, Hepatoblastoma, Medulloblastoma, Neuroblastoma, Osteosarcoma, or Other Malignancy (ACCL0431). NCT00716976. Freyer et al 2017.209

- **Patient population/planned enrollment**: Children (n = 104) who had newly diagnosed germ cell tumor, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma, or other malignancy and were eligible for cisplatin-based chemotherapy
- **Study design**: Phase III, randomized, parallel-assignment, open-label trial to evaluate the safety and efficacy of sodium thiosulfate in patients with solid tumors. Patients were randomly assigned in a 1:1 ratio to receive either intravenous cisplatin plus sodium thiosulfate (16 g/m²) or cisplatin alone.
- **Primary outcome**: Hearing loss
- **Secondary outcome**: Adverse events
- **Results presented by study authors**: “Hearing loss was identified in 14 (28.6%; 95% CI 16.6–43.3) participants in the sodium thiosulfate group compared with 31 (56.4%; 42.3–69.7) in the control group (p=0.00022). Adjusted for stratification variables, the likelihood of hearing loss was significantly lower in the sodium thiosulfate group compared with the control group (odds ratio 0.31, 95% CI 0.13–0.73; P =0.0036). The most common grade 3–4 haematological adverse events reported, irrespective of attribution, were neutropenia (117 [66%] of 178 participant cycles in the sodium thiosulfate group vs 145 [65%] of 224 in the control group), whereas the most common non-haematological adverse event was hypokalaemia (25 [17%] of 149 vs 22 [12%] of 187). Of 194 serious adverse events reported in 26 participants who had received sodium thiosulfate, none were deemed probably or definitely related to sodium thiosulfate; the most common serious adverse event was decreased neutrophil count: 26 episodes in 14 participants.”
Manufacturers and Regulatory Status

Pedmark is manufactured by Fennec Pharmaceuticals Inc (Research Triangle Park, North Carolina). In December 2018, the company initiated a rolling New Drug Application (NDA) to FDA based on results from the phase III SIOPEL 6 and ACCL0431 trials. The company announced that submission of the rolling NDA was completed in February 2020. FDA has granted Orphan Drug, Breakthrough Therapy, and Fast Track designations for preventing cisplatin-induced ototoxicity in children.

Cost Information

Cost information is unavailable for this topic.

Key Stakeholder Perspectives

Seven stakeholders, reflecting clinical, nursing, audiology, research, and health systems perspectives, provided comments and ratings on sodium thiosulfate. The list below provides a summary of key stakeholder perspectives.

- In the absence of other options for preventing hearing loss, sodium thiosulfate use would likely positively disrupt patient health outcomes and quality of life in this patient population.
- Pedmark has the potential to reduce disparities by alleviating downstream burdens associated with hearing loss, which may be more difficult to manage in patients of low economic status.
- The 6-hour wait between cisplatin and Pedmark administration might lead to longer outpatient infusion visits, increasing demand on the health care system. This wait between treatments could also disrupt treatment paradigms because it will require keeping children at the facility and occupied.
- Sodium thiosulfate has the potential to be cost effective because preventing hearing loss is likely to reduce costs associated with hearing rehabilitation.
- Overall, Pedmark has the potential to improve patient-oriented outcomes and quality of life, but there are concerns that its adoption might be delayed because it is an intravenous drug requiring a 6-hour wait time after chemotherapy infusion.

Tazemetostat (Tazverik) to Treat Locally Advanced or Metastatic Epithelioid Sarcoma

Highlights

- Tazemetostat (Tazverik), an oral drug, is an inhibitor of methyltransferase EZH2 (enhancer of zeste homolog 2) that FDA recently approved to treat patients with locally advanced or metastatic epithelioid sarcoma (ES).
- ES is a rare soft tissue sarcoma characterized by aberrant histone methylation and oncogenic transformation driven by EZH2. Use of EZH2 inhibitors represents a novel mechanism of action in treating cancer and the first treatment option specifically approved by FDA to treat ES.
- FDA approval was based on a single-arm trial in which treatment with tazemetostat generated an overall response rate of 15%. Among patients achieving a response, the majority had a response that lasted at least 6 months.
• Stakeholders commenting on tazemetostat thought that it will likely disrupt the current treatment of ES patients, based on the lack of effective systemic therapies for this cancer, the preliminary data on the drug’s ability to improve patient health outcomes, and the likely high cost of the drug. However, they also noted that the small number of patients in whom ES is diagnosed would limit the magnitude of its disruption to the health care system as a whole.

Patient Population

Tazemetostat is intended for children aged 16 years or older and adults with metastatic or locally advanced ES not eligible for complete surgical resection.

Intervention

Tazemetostat is an inhibitor of the histone methyltransferase EZH2 intended to treat patients with ES, a rare sarcoma that typically originates in the soft tissues of the upper extremities. The Liddy Shriver Sarcoma Initiative offers more information about ES.

Historically, treatment of advanced ES ineligible for surgical resection has been limited to systemic therapies consisting of cytotoxic chemotherapy, which is associated with limited efficacy. Therefore, novel therapies with the potential to improve health outcomes in patients with advanced ES are needed.

EZH2 is the enzymatic subunit of polycomb repressive complex 2 (PRC2), a global regulator of gene expression that promotes silencing of gene transcription through histone modification. Gain-of-function EZH2 has been implicated in the pathogenesis of a wide range of cancers, including ES. Most ES cases demonstrate loss of expression of the integrase interactor 1 protein, a core component of a second global regulator of gene expression (SWI/SNF) that has an antagonistic relationship to PRC2. Therefore, loss of SWI/SNF activity leads to increased PRC2 activity, which drives oncogenesis. Tazemetostat purportedly inhibits the enzymatic activity of EZH2, potentially reducing PRC2 activity and reversing its oncogenic effects.

Tazemetostat is taken by mouth at a dose of 800 mg twice daily.

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 2 ongoing trials for this topic. We present these trials in Table 2.13.
### Table 2.13. Ongoing Clinical Trials

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Phase II, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects With INI1-Negative Tumors or Relapsed/Refractory Synovial Sarcoma (EZH-202) NCT02601950</td>
<td>Patients (n = 250) with INI1-negative tumors Cohort 1: Tumors with rhabdoid features Cohort 2: Relapsed or refractory synovial sarcoma Cohort 3: Any solid tumor with EZH2 gain of function Cohort 4: Renal medullary carcinoma Cohorts 5 and 6: Epithelioid sarcoma Cohort 7: Poorly differentiated chordoma</td>
<td>Phase II, multicohort, single-group assignment, open-label trial to evaluate the safety and efficacy of tazemetostat in patients with advanced soft tissue sarcomas, including epithelioid sarcoma. Patients will receive oral tazemetostat at a dose of 800 mg twice a day. Primary endpoints: Progression-free survival and overall response rate Secondary endpoints: Overall survival, progression-free survival, disease control rate, duration of response, and adverse events</td>
<td>Primary completion January 2022 Study completion February 2022</td>
</tr>
<tr>
<td>Tazemetostat in Combination With Doxorubicin as Frontline Therapy for Advanced Epithelioid Sarcoma NCT04204941</td>
<td>Patients (n = 154) with previously untreated epithelioid sarcoma with loss of INI1 or SMARCA4 confirmed by immunohistochemistry or bi-allelic loss of INI1 or SMARCA4 in the case of equivocal or unavailable immunohistochemistry result</td>
<td>Phase III, double-blind, randomized controlled trial of the safety and efficacy of tazemetostat in combination with doxorubicin. After a phase Ib portion of the trial to establish tazemetostat and doxorubicin dosing, patients will be randomly assigned to treatment with either tazemetostat plus doxorubicin or to placebo plus doxorubicin. Primary endpoint: Progression-free survival Secondary endpoints: Overall survival and quality of life</td>
<td>Primary completion (phase Ib portion) September 2020 Study completion May 2029</td>
</tr>
</tbody>
</table>

Abbreviations: EZH2, enhancer of zeste homolog 2; INI1, integrase interactor 1; SMARCA4, SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4.

**Recently Completed and Ongoing Trials With Available Results**

Our searches identified one relevant, recently completed late-phase trial with published results.225 We summarize this study with results as written in a conference abstract.

The following abbreviations are used in this section: AE, adverse event; BID, twice a day; CI, confidence interval; DCR, disease control rate; DOR, duration of response; ES, epithelioid sarcoma; EZH2, enhancer of zeste homolog 2; INI1, integrase interactor 1; ORR, overall response rate; OS, overall survival; PR, partial response; pts, patients; TEAE, treatment-emergent adverse event.

- **Patient population/planned enrollment**: Patients (n = 62) with locally advanced or metastatic INI1-deficient ES (cohort 6 of a multicohort trial)
- **Study design**: Phase II, multicohort, single-group assignment, open-label trial to evaluate the safety and efficacy of tazemetostat in patients with ES. Patients received oral tazemetostat at a dosage of 800 mg twice daily.
- **Primary outcomes**: Overall response rate and effects of tazemetostat on tumor immune priming
- **Select secondary outcomes**: Progression-free survival, overall survival, and incidence of treatment-emergent adverse events
- **Results presented by study authors**: "As of September 17, 2018, 62 INI1-negative ES pts were enrolled and treated with tazemetostat 800 mg BID. The median number of prior lines of therapy was 1 (range: 0-9). There were 9/62 (15%) confirmed partial responses (PRs) with an ORR of 15% and DCR of 26%. The DOR ranged from 7.1+ weeks to 103.0+ weeks (median: not reached) with a median OS of 82.4 weeks (95% CI: 47.4, not estimable) for all 62 pts. Tazemetostat was generally well tolerated. Treatment-emergent adverse events (TEAEs) were generally mild to moderate with the most commonly reported adverse events (AEs; ≥10% incidence) regardless of attribution being fatigue (24/62; 39%), nausea (22/62; 35%), and cancer pain (20/62; 32%). Any treatment-related TEAEs of grade ≥3 were reported in 10/62 (16%) pts. TEAEs grade ≥3 reported in ≥2 pts included anemia (6%) and decreased weight (3%). There were no drug-related deaths and a low discontinuation rate (1.7%)."

**Manufacturers and Regulatory Status**

Tazemetostat is being developed by Epizyme Inc (Cambridge, Massachusetts). In January 2020, FDA granted accelerated approval to tazemetostat to treat locally advanced or metastatic ES not eligible for complete resection.226 The indication is based on overall response rate and duration of response observed in the phase II EZH-202 trial (NCT02601950). Continued approval for this indication may be contingent on verification and description of clinical benefit in a confirmatory trial or trials.227 FDA had previously granted Orphan Drug designation to tazemetostat for treating soft tissue sarcomas.228

**Cost Information**

According to a US-based online aggregator of prescription drug prices, GoodRx, tazemetostat’s retail price (as of April 1, 2020) was about $7400 for one hundred twelve 200-mg tablets, which represents a 14-day supply of the drug.229 Thus, a 1-year supply of tazemetostat would cost about $200 000.

**Key Stakeholder Perspectives**

Seven stakeholders, reflecting clinical, nursing, health systems, and research perspectives, provided comments and ratings on tazemetostat for treating ES.230-236 The list below provides a summary of key stakeholder perspectives.

- Because of the lack of effective systemic therapies for ES, tazemetostat has the potential to improve patient health outcomes. In particular, patients responding to tazemetostat in a phase II trial exhibited a substantial duration of response and tazemetostat had a positive impact on ES symptoms.
- The evidence base consists of a small single-arm trial in which only a minority of patients exhibited a response to tazemetostat. Additionally, the ability of tazemetostat to produce responses of extended duration will need to be confirmed in additional studies.
• Tazemetostat will likely be adopted for treating patients with ES and, therefore, could disrupt the current treatment paradigm by providing a novel method of treating patients with ES and causing a switch from use of intravenous chemotherapy to an orally administered targeted therapy.

• The likely high cost of tazemetostat would increase the cost of treating ES and could exacerbate existing disparities based on socioeconomic status. (Stakeholders reviewed the topic before cost information was available.)

• Magnitude of impact on the health care system and health care costs will be limited by the small number of patients affected by ES.
Chapter 3. Cardiovascular Diseases

Chapter Summary

For the cardiovascular diseases priority area, we considered for inclusion 7 topics for which (1) preliminary phase III data for drugs, phase II (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled and sent for stakeholder comment before March 10, 2020; and (3) we received at least 5 sets of comments and ratings from stakeholder commenters between April 1, 2019, and March 20, 2020.

As of March 10, 2020, we were monitoring 28 topics in this priority area, including the 7 topics considered for inclusion in this report. These 28 topics will be listed in the June 2020 PCORI Health Care Horizon Scanning System: Horizon Scanning Status Report. We also archived one topic in February 2020. A description of that topic and the reason it was archived can be found in the March 2020 Status Report. We archived an additional topic in March 2020. A description of that topic and the reason it was archived will be included in the June 2020 Status Report.

The 28 monitored topics encompass pharmaceuticals, gene and cellular therapies, devices, and implants intended to treat 12 cardiovascular diseases and/or related symptoms. One topic was developed as a topic profile to be sent for stakeholder comment; however, fewer than 5 sets of stakeholder comments were received for this topic before March 10, 2020, so it was not considered for inclusion in this report. The remaining 20 topics are too early in development to meet criteria (as outlined above) for eligibility for this report.

Topics Considered for Inclusion in This Report

Table 3.1 lists 4 topics selected for inclusion during the High Potential Disruption Report decision meeting. A majority of the horizon scanning team voted that these topics had high potential for disruption, based on stakeholder ratings and comments and available data. Topics are listed and discussed alphabetically by topic title.

Table 3.1. Included Topics for Priority Area: Cardiovascular Diseases

<table>
<thead>
<tr>
<th>Topic title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neovasc Reducer to treat refractory angina</td>
</tr>
<tr>
<td>Organ Care System Heart to treat end-stage heart failure requiring transplantation</td>
</tr>
<tr>
<td>Paradise Renal Denervation System to treat resistant hypertension</td>
</tr>
<tr>
<td>Tafamidis (Vyndaqel, Vyndamax) to treat amyloid transthyretin-mediated cardiomyopathy</td>
</tr>
</tbody>
</table>

Table 3.2 lists 3 topics considered, but not selected, for inclusion during the High Potential Disruption Report decision meeting. A majority of the voting team agreed that these topics lacked high potential for disruption, based on stakeholder ratings and comments and available data. Each record notes the reasons for exclusion.
Table 3.2. Topics Considered but Not Included for Priority Area: Cardiovascular Diseases

<table>
<thead>
<tr>
<th>Topic title</th>
<th>Exclusion reason(s) and notes based on stakeholder comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bempedoic acid (ETC-1002) to treat high-risk atherosclerosis with statin intolerance</td>
<td>Because bempedoic acid will likely be used as a second- or third-line alternative to existing, generic nonstatin alternatives such as ezetimibe, it does not hold significant disruptive potential. (Note: Stakeholders rated bempedoic acid before FDA approved the drug in February 2020 as an adjunct to optimal statin therapy in patients who require additional cholesterol lowering.)</td>
</tr>
<tr>
<td>Revivent TC transcatheter ventricular enhancement system to treat heart failure</td>
<td>Although the concept of restoring a more natural shape to an enlarged left ventricle to improve heart function seemed theoretically sound, the high rate of serious adverse events in early trials would likely limit use of the Revivent TC device.</td>
</tr>
<tr>
<td>Shockwave intravascular lithotripsy system to treat coronary artery disease</td>
<td>The device and procedural techniques were similar to those used in other catheter-based cardiac interventions; thus, it would be unlikely to create significant disruption to patient management, costs, or the health care delivery system.</td>
</tr>
</tbody>
</table>

**Topic Summaries**

We present below 4 summaries on topics deemed to have high potential for disruption.

**Neovasc Reducer to Treat Refractory Angina**

**Highlights**

- Neovasc Reducer is a permanent implant placed in a large heart vein during a minimally invasive procedure and intended to relieve severe angina by increasing blood flow to areas of heart muscle with poor circulation.
- FDA has granted the technology Breakthrough Device designation and is reviewing the developer’s Premarket Approval (PMA) application submitted in December 2019.
- Only one small, randomized, phase II trial has compared Reducer device implantation to a sham procedure for treating refractory angina.
- Stakeholders commenting on this topic thought that the device has the potential to relieve angina and that demand could be high from patients for whom existing therapies are ineffective at reducing severe angina pain and improving quality of life.

**Patient Population**

The Neovasc Reducer device is intended to treat adults aged 18 years or older with Canadian Cardiovascular Society (CCS) grade III or IV chronic angina due to obstructive coronary artery disease that does not respond to optimal medical therapy and is unsuitable for conventional revascularization. (The 4-point CCS scale classifies angina based on severity, from grade I [no limitation/angina during ordinary physical activity such as walking] to grade IV [discomfort with any activity, angina may be present at rest].)237
**Intervention**

The Neovasc Reducer (herein referred to as the Reducer) is a stent-like, permanent implant intended to treat refractory angina by improving blood flow to ischemic heart tissue.\textsuperscript{238} Physicians implant the Reducer in the coronary sinus, the large vein that drains blood from heart muscle, to create a pressure backflow. This purportedly modulates blood flow through the coronary sinus and redistributes blood to areas of heart muscle that have poor circulation.\textsuperscript{238-240}

The minimally invasive procedure is performed in a cardiac catheterization laboratory. To deploy the balloon-expandable, hourglass-shaped device, a physician (ie, interventional cardiologist) inserts the delivery catheter at the patient’s jugular vein in the neck and advances it to the coronary sinus, located on the external heart wall between the left atrium and left ventricle.\textsuperscript{238-240} Implantation is typically performed as an outpatient procedure that purportedly takes about 20 minutes with patients under local anesthesia.\textsuperscript{238}

The American Heart Association website offers more information about angina.

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified 3 ongoing trials for this topic. We present these trials in Table 3.3.

**Table 3.3. Ongoing Clinical Trials**

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
</table>
| CoRONary SinuS Reducer implantatiOn for ischemiA reDuction (CrossRoad) NCT04121845 | Adults aged 18 to 85 years (n = 40) with CCS grade II to IV angina despite optimal medical therapy who have reversible myocardial ischemia | Unphased, randomized, double-blind, parallel-assignment trial comparing Neovasc Reducer implantation with sham procedure for treating refractory angina  
Primary outcome: Exercise capacity measured by VO\textsubscript{2}  
Selected secondary outcomes: Changes in CCS class, reversible myocardial ischemia, and QOL | Primary completion December 2021  
Study completion June 2022 |
<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>REDUCER-I: An Observational Study of the Neovasc Reducer System NCT02710435</td>
<td>Children and adults (n = 400, no ages specified) with refractory angina who demonstrate objective evidence of reversible myocardial ischemia, who have limited or no options for revascularization or who were previously implanted with a Neovasc Reducer device</td>
<td>Three-arm, prospective-retrospective observational study (phase not stated) of long-term safety and efficacy of Neovasc Reducer implant for treating refractory angina Primary outcomes: Improvement in CCS grade through 6 months, incidence of MACE and rate of device- or procedure-related serious adverse events, both through 30 days after implantation Selected secondary outcomes: Improvement in CCS grade and QOL, and MACE incidence, all through 5 years</td>
<td>Primary completion December 2022 Study completion December 2027</td>
</tr>
<tr>
<td>Use of the Neovasc Coronary Sinus Reducer System for the Treatment of Refractory Angina Pectoris in Patients With Angina Class 3-4 Who Are Not Candidates for Revascularization NCT01566175</td>
<td>Adults aged 18 years or older (n = 100) with CCS grade III or IV refractory angina and reversible myocardial ischemia</td>
<td>Prospective, single-arm, open-label study (phase not stated) to assess safety and efficacy of Neovasc Reducer implant for treating refractory angina in patients with reversible ischemia Primary outcome: Decrease of at least 2 CCS grades through 6 months after implantation</td>
<td>Primary completion December 2028 Study completion December 2029</td>
</tr>
</tbody>
</table>

Abbreviations: CCS, Canadian Cardiovascular Society; MACE, major adverse cardiac events; QOL, quality of life; VO2, maximal oxygen consumption.

Recently Completed and Ongoing Trials With Available Results

Our searches identified 4 relevant, recently completed late-phase trials with published results.239-242 We summarize these studies with results as written in abstracts of published studies, conference abstracts, or news releases.

The following abbreviations are used in this section: 6MWT, 6-minute walk test; CCS, Canadian Cardiovascular Society angina grade; CS, coronary sinus; SAQ, Seattle Angina Questionnaire quality-of-life survey.


- **Patient population/planned enrollment:** Adults (n = 50, ages not stated) with refractory angina
- **Study design:** Prospective, single-arm, single-center study to assess long-term safety and efficacy of Neovasc Reducer
- **Primary outcome:** Angina change assessed by CCS score
- **Secondary outcome:** Quality of life assessed by Seattle Angina Questionnaire score
- **Results presented by study authors:** “Canadian Cardiovascular Society (CCS) score improved of ≥1 class in 34 patients (75.6%), and of ≥2 classes in 16 patients (35.6%), translating into a significant mean CCS score reduction at 2-year follow-up (1.74 ± 0.86 vs. 2.98 ± 0.52; p < 0.001). Four out of five Seattle Angina
Questionnaire items improved significantly (p < 0.001 for all). Ten patients (22%) underwent percutaneous coronary intervention (PCI) during follow-up, three for acute coronary syndromes. Five patients died, two for cardiovascular causes (stroke and cardiac arrest).


- **Patient population/planned enrollment:** Adults (n = 141) with refractory angina consecutively treated with the Neovasc Reducer in general clinical practice
- **Study design:** Multicenter patient registry to assess the safety and efficacy of Reducer implantation to treat refractory angina in a real-world population through 14-month median follow-up
- **Primary outcomes:** Efficacy, reduction in angina symptoms measured by CCS and SAQ scores, safety, and successful device implantation without device-related adverse events
- **Results presented by study authors:** "Procedural success was achieved in 139 (98.6%) patients. Reducer implantation was not obtained in 2 (1.4%) patients because of unfavorable anatomy of the CS. There were no CS perforations, cardiac tamponade, peri-procedural death or myocardial infarction during a median follow-up of 14 months (range from 6- to 70-month). In patients undergoing Reducer implantation, mean CCS class improved from 3.05 ± 0.53 at baseline to 1.63 ± 0.98 at follow-up (p < 0.001). Overall, 113 (81%) patients experienced at least 1 CCS improvement, and 63 (45%) patients at least 2 CCS-class improvement. All SAQ items improved significantly (p < 0.001 for all) and translated into a significant reduction in the mean number of anti-ischemic drugs prescribed (2.37 ± 0.97 vs 2.17 ± 0.95; p = 0.003)."


- **Patient population/planned enrollment:** Adults with a mean age of 66.8 ± 8.9 years (n = 48) with CCS grade III or IV angina despite optimal medical therapy
- **Study design:** Prospective, nonrandomized, open-label, single-center registry of consecutive patients in whom Neovasc Reducer was implanted for refractory angina
- **Primary outcomes:** Efficacy, reduction in angina symptoms measured by CCS and SAQ scores, safety, and successful device implantation without device-related adverse events
- **Results presented by study authors:** "No periprocedural or long-term adverse events were recorded. CCS class diminished from a mean of 3.4±0.5 at baseline to 2.0±1 (p<0.001), and all domains of the SAQ improved significantly following Reducer implantation. Mean exercise duration increased from 03:43±01:30 to 04:36±02:18 min:sec (p=0.025) and 6MWT distance increased from 299.9±97.9 m to 352.9±75.3 m (p=0.002). Ejection fraction (EF%) at stress increased from 51.0±10 to 56.5±10 (p=0.004), and wall motion score index improved from 1.58±0.4 to 1.37±0.3 (p=0.004)."

**Coronary Sinus Reducer for Treatment of Refractory Angina (COSIRA).** *NCT01205893*. Verheyse et al 2015.239

- **Patient population/planned enrollment:** Adults aged 18 years or older (n = 104) with CCS grade III or IV angina and myocardial ischemia who were not candidates for revascularization
- **Study design:** Phase II, randomized, parallel-assignment, double-blind trial comparing safety and efficacy of Neovasc Reducer implantation with that of sham procedure (diagnostic coronary angiography) for treating refractory angina
- **Primary outcome:** Proportion of patients who improved by at least 2 CCS grades through 6 months
- **Secondary outcomes:** Exercise tolerance and proportion of patients who improved by at least one CCS grade, both through 6 months
- **Results presented by study authors:** "A total of 35% of the patients in the treatment group (18 of 52 patients), as compared with 15% of those in the control group (8 of 52), had an improvement of at least two
CCS angina classes at 6 months (P=0.02). The device was also associated with improvement of at least one CCS angina class in 71% of the patients in the treatment group (37 of 52 patients), as compared with 42% of those in the control group (22 of 52) (P=0.003). Quality of life as assessed with the use of the Seattle Angina Questionnaire was significantly improved in the treatment group, as compared with the control group (improvement on a 100-point scale, 17.6 vs. 7.6 points; P=0.03). There were no significant between-group differences in improvement in exercise time or in the mean change in the wall-motion index as assessed by means of dobutamine echocardiography. At 6 months, 1 patient in the treatment group had had a myocardial infarction; in the control group, 1 patient had died and 3 had had a myocardial infarction.”

Manufacturers and Regulatory Status

Neovasc Inc (Vancouver, British Columbia, Canada) manufactures the Reducer device. FDA granted Breakthrough Device designation in October 2018 to the Neovasc Reducer for treating refractory angina. On December 30, 2019, the company submitted a PMA application to FDA for the Neovasc Reducer for treating refractory angina; FDA accepted the PMA for review on January 15, 2020. The PMA is supported by data from the COSIRA trial, the REDUCER-I European postmarket study (with up to 5 years of follow-up), and other independent studies published in peer reviewed journals.

Cost Information

US cost information is unavailable for this topic.

Key Stakeholder Perspectives

Six stakeholders, reflecting clinical, nursing, and research perspectives, provided comments and ratings on the Reducer to treat refractory angina. The list below provides a summary of key stakeholder perspectives.

- The Reducer implant has moderate to high potential to provide relief from angina and improve quality of life for patients with few effective options remaining.
- Demand for Reducer implantation could be high if patients perceive the technology as an effective new therapy for treating severe angina pain that has not responded to limited available therapies.
- Emerging treatments that improve physical function and quality of life have potential to be cost effective and become adopted as standard of care, even if they do not affect endpoints such as survival or incidence of heart attack, stroke, or cardiovascular-related hospitalizations.
- Even with higher initial treatment costs, an effective new therapy for refractory angina could reduce emergency department visits or repeated cardiac catheterization procedures for severe chest pain.
Organ Care System Heart to Treat End-Stage Heart Failure Requiring Transplantation

Highlights

- The Organ Care System (OCS) Heart is a portable unit designed to maintain donor hearts for a longer period in a more functional state outside the body than the standard, static cold storage, during storage and transport.
- By keeping donor hearts beating and perfused with a blood-based solution in a protected environment, OCS Heart offers the potential for longer transport times that might reduce geographic limitations inherent with static cold storage.
- The technology might expand the pool of hearts available for transplantation by allowing expanded donor criteria, which could enable more patients on transplant waiting lists to receive a heart transplantation.
- Stakeholders commenting on this technology thought OCS Heart could substantially change the way donor hearts are preserved during transport and become a new standard of care, enabling more heart transplantations.

Patient Population

The OCS Heart is intended to preserve and allow outside-the-body assessment of donor hearts intended for transplantation into adults aged 18 years or older who are candidates for heart transplantation.

Intervention

Recent studies indicate that only about 40% of donor hearts are used, because of their poor condition after donation and transport. At the current levels of donor heart availability, a substantial number of patients remain on the transplant waiting list for extended periods, and the annual death rate among waiting patients is approaching 20%. Substantial interest exists in increasing the number of donor hearts that are suitable for use.

OCS is a portable system intended to maintain a donor organ—heart, lung, or liver grafts—252, 253—in a warm, functioning state outside the body for an extended period. This purportedly optimizes organ health and allows for continuous clinical evaluation of the donor organ and its suitability for transplantation.253

OCS Heart is optimized for preserving donor hearts.254 It is intended to increase the number of viable donor hearts for transplantation by making longer-distance transport possible. It also purportedly gives clinicians more clinical data to better assess donor organ suitability from a larger pool of donor hearts than are considered suitable for use with conventional cold storage.254

Like the other OCS systems, the OCS Heart comprises 2 principal components: a portable battery-powered console and an organ-specific perfusion kit that function together as a system.253,254 The system perfuses donor organs with a proprietary blood-based solution to replenish oxygen and essential nutrients.

After physicians harvest the donor heart, they place it in the perfusion module and revive it to a beating state. The self-contained perfusion module maintains the proper temperature and humidity, protects the organ from external contaminants, and allows sterile ultrasound
assessment of heart function and sterile blood sampling for laboratory analysis. A wireless monitor allows clinicians to assess the organ’s status and to control system functions.\textsuperscript{253,254}

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified 3 ongoing trials for this topic. We present these trials in Table 3.4. (Although the EXPAND Heart trial [NCT02323321] is listed as active, not recruiting [as of last update on August 14, 2019], we excluded it because final results were reported in April 2019 and published in the *Journal of Heart and Lung Transplantation*. See Schroder et al 2019 below.)

**Table 3.4. Ongoing Clinical Trials**

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart EXPAND Continued Access Protocol NCT03835754</td>
<td>Adults aged 18 years or older (n = 48) registered as candidates for primary heart transplantation</td>
<td>Unphased, single-arm, open-label protocol to provide transplant candidates expanded access to OCS Heart system (pending FDA regulatory review process) to preserve and assess donor hearts that do not meet current graft organ acceptance criteria Primary outcomes: Patient survival after transplantation; and absence of severe, primary right or left ventricular dysfunction of the donor heart within the first 24 hours</td>
<td>Primary completion November 2020 Study completion December 2020</td>
</tr>
<tr>
<td>Donors After Circulatory Death Heart Trial NCT03831048</td>
<td>Adults aged 18 years or older (n = 212) registered as candidates for primary heart transplantation</td>
<td>Unphased, randomized, single-group assignment, open-label trial comparing safety and efficacy of OCS Heart with that of static cold storage standard of care for preserving and assessing hearts from donors after circulatory death Primary outcome: Patient survival at 6 months after implantation Selected secondary outcomes: Patient and graft survival at 30 days; and initial hospital discharge, if longer than 30 days</td>
<td>Primary completion August 2021 Study completion December 2021</td>
</tr>
</tbody>
</table>
### Study name and National Clinical Trials identifier

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
</table>

Abbreviation: OCS, Organ Care System.

### Recently Completed and Ongoing Trials With Available Results

Our searches identified 3 relevant, recently completed late-phase trials with published results. We summarize these studies with results as written in an abstract of a published study and conference abstracts.

The following abbreviations are used in this section: CS, cold storage; DBD, donation after brain death; DCD, donation after circulatory death; DPP, direct procurement and perfusion; ECD, expanded criteria donor; ECMO, extracorporeal membrane oxygenation; EF, ejection fraction; ESHP, ex situ heart perfusion; ICU, intensive care unit; LV, left ventricular; LVH, left ventricular hypertrophy; NRP, normothermic regional perfusion; OCS, Organ Care System; PGD, primary graft dysfunction; RV, right ventricular; UNOS, United Network for Organ Sharing.


- **Patient population/planned enrollment:** Adults aged 18 years or older (n = 75) registered as candidates for heart transplantation.
- **Study design:** Single-arm, open-label trial to assess safety and efficacy of the OCS Heart system for preserving and assessing donor hearts (n = 93) that do not meet current standard heart graft acceptance criteria for transplantation (total ischemic time of 4 hours or more or total ischemic time of 2 to 4 hours plus one of the following risk factors: left ventricular hypertrophy, ejection fraction 40% to 50%, downtime of 20 minutes or more, and donor age older than 55 years).
- **Primary outcome:** Composite of patient survival at 30 days after transplantation and absence of severe primary heart graft dysfunction in the first 24 hours after transplantation.
- **Secondary outcomes:** Rate of ECD heart utilization after preservation and assessment on the OCS Heart system.
- **Results presented by study authors:** “Ninety-three eligible donor hearts with a mean UNOS match run of 66 declines were assessed on OCS Heart. Donor categories were as follows: x-clamp time ≥ 4 hours 37%, LVH 23%, EF 40-50% were 23%, downtime ≥ 20 minutes 28%, older age 13% and 33% met multiple inclusion criteria. 75 of the 93 donor hearts were successfully transplanted resulting in a utilization rate of 81%. Mean OCS perfusion time was 6.35 hours. Incidence of severe LV or RV PGD at 24 hours was 10.7%. 30-day and 6-month survival were 94.7% and 88% respectively.”
First to 50: Early Outcomes Following Heart Transplantation at Royal Papworth Hospital From Donation After Circulatory Determined Death (DCD) Donors. *The Journal of Heart and Lung Transplantation*. Messer et al 2019.257

- **Patient population/planned enrollment**: First 50 patients, ages not specified, to undergo DCD heart transplantation at a single center (Royal Papworth Hospital, Cambridge, United Kingdom) and a retrospective, matched cohort of patients who underwent standard DBD heart transplantation.

- **Study design**: Early outcomes analysis of DCD heart transplants compared with a retrospective cohort of DBD heart transplants. DCD hearts were retrieved by 1 of 3 methods: NRP followed by ESHP (NRP-ESHP), NRP followed by CS (NRP-CS), or DPP using only ESHP (DPP-ESHP). NRP indicates mechanical restoration of perfusion to the abdominal organs before donor heart removal. ESHP indicates external perfusion with the OCS Heart system. DPP indicates direct heart removal (ie, without abdominal perfusion) followed by OCS Heart perfusion outside the body.

- **Primary outcome**: Survival at 30 days after transplantation.

- **Secondary outcomes**: Posttransplantation inotrope dependence, mechanical support, initial cardiac performance, ventilator duration, intensive care duration, and length of hospital stay.

- **Results presented by study authors**: "Sixteen DCD hearts were transplanted following (NRP-ESHP), 32 hearts following (DPP-ESHP) and 2 hearts following (NRP-CS). The 30-day survival post transplant was 100% in both DCD and DBD groups. All other outcome variables were comparable between groups with the exception of Dopamine reliance post transplant."


- **Patient population/planned enrollment**: Adults (n = 126) who underwent heart transplantation using conventional donor graft preservation (n = 82, mean age 32.1 ± 22.9 years) or OCS Heart preservation (n = 44, mean age 46.4 ± 16.2 years).

- **Study design**: Two-center retrospective review of heart transplantation outcomes using OCS Heart donor heart preservation (group A) or standard cold storage (group B).

- **Primary outcomes**: Thirty-day survival and 1-year survival.

- **Secondary outcomes**: Donor heart preservation time, donor heart graft rejection, and ICU stays.

- **Results presented by study authors**: "Baseline characteristics in both groups: age (y) (A:46.4±16.2 vs. B:32.1±22.9; p<0.001), male gender (%) (A:75.0 vs. B:67.1, p=0.41), time on waiting list (d) (A:639±1100 vs. B:510±789, p=0.491), [high-urgency] status (%) (A:84.1 vs. B:91.5, p=0.241), previous [ventricular assist device] (%) (A:72.7 vs. B:62.2, p=0.324). Operative results: ex situ time (min) (Total preservation time Group A, ischemia for Group B) (A: 402±67 vs. B: 225±49, p<0.001), operation time (min) (A: 488±96.3 vs. B: 451±133, p=0.073), ventilation time (d) (A: 7.1±15.4 vs. B: 17.6±36.9, p=0.123), ICU stay (d) (A: 14.2±21 vs. B: 24.7±36.9, p=0.315), postoperative ECMO (%) (A: 18.2 vs. B: 28.4, p=0.279), bleeding requiring redo surgery (%) (A: 20.5 vs. B: 20.7, p=0.199), early graft rejection (%) (A: 9.3 vs. B: 20.0, p=0.199). 30-d-survival (%) (A: 99.6 vs. B: 91.2, p=0.263), 1-y-survival (%) (A: 88.6 vs. B: 78.2, p=0.222)."

Manufacturers and Regulatory Status

TransMedics Inc (Andover, Massachusetts) manufactures the OCS Heart system. TransMedics submitted a Premarket Approval (PMA) application to FDA for system in April 2014 based on results of the PROCEED II trial designed to demonstrate noninferiority of the OCS heart system to standard-of-care storage of donor hearts.258,259 In June 2019, TransMedics reported that FDA granted the company an investigational device exemption to begin a clinical trial, for the first time in the United States, that is evaluating the OCS Heart for preserving hearts obtained from donors after circulatory death.260,261
On March 17, 2020, TransMedics announced that FDA had postponed an Advisory Committee expert panel meeting to review the OCS Heart PMA, scheduled for April 16, 2020, because of impacts related to the COVID-19 pandemic, with no tentative reschedule date announced.262

In April 2018, FDA approved TransMedics’ PMA for similar technology, the OCS Lung system, for preserving donor lungs selected using standard lung graft acceptance criteria.263 In June 2019, FDA granted expanded approval for the OCS Lung for use in preserving donor lungs selected under expanded acceptance criteria.264

**Cost Information**

US cost information on OCS Heart is unavailable. However, the OCS Lung console, which is on the market, provides a useful analog. According to ECRI’s SELECTPlus database, member hospitals reported an average price paid of about $199,400 for the OCS Lung console unit plus about $79,000 for the single-use perfusion kit (as of March 26, 2020).265 Comparable pricing for the OCS Heart system would be anticipated.

**Key Stakeholder Perspectives**

Seven stakeholders, reflecting clinical, nursing, research, health systems, and caregiver perspectives, provided comments and ratings on the OCS Heart to treat end-stage heart failure requiring transplantation.266-272 The list below provides a summary of key stakeholder perspectives.

- Use of the OCS Heart system could become a new standard of care in preserving and transporting donor hearts for transplantation, if the encouraging data trends continue.
- The OCS Heart system could improve outcomes by potentially expanding the pool of donor hearts and allowing more patients on waiting lists to undergo heart transplantation.
- The technology would cause large disruption to existing procedures for donor organ transport that rely on static cold storage. Implementing the OCS Heart system would require additional staff, equipment, supplies, and training.
- One of the largest disruptions to the health care delivery system would be moving more patients off the waiting list if more donor hearts were to become available. If more patients undergo heart transplantation, hospitals might need more cardiac intensive care unit beds and staff to monitor and care for patients during recovery.

**Paradise Renal Denervation System to Treat Resistant Hypertension**

**Highlights**

- The Paradise Renal Denervation System is a minimally invasive, catheter-based system intended to treat resistant hypertension by eliminating the patient’s sympathetic nerves lining the kidney’s major arteries and believed to contribute to high blood pressure.
- Recent trials suggest Paradise renal denervation reduced average daytime systolic blood pressure by about 6 mm Hg over 2 months and about 4 mm Hg over 6 months.
- Stakeholders commenting on this topic believed renal denervation could shift hypertension management for some patients from office-based medical therapy to a one-time interventional procedure with high upfront costs and potential risks.
• Stakeholders suggested disparities could develop if patient access to renal denervation is restricted by insurance coverage or if the procedure is performed only at certain regional referral centers.

**Patient Population**

This intervention is intended for adults aged 18 to 75 years with average blood pressure (taken in a physician’s office) of 140/90 to 180/110 mm Hg (ie, stage 2 hypertension) who have previously tried antihypertensive medication and are currently taking 0 to 2 antihypertensive medications.

**Intervention**

The Paradise Renal Denervation System is a catheter-based system intended to treat difficult-to-manage hypertension, which can increase risk for heart attack and stroke. The American Heart Association defines treatment-resistant hypertension as blood pressure above treatment goals despite the concurrent use of 3 or more antihypertensive drug classes or blood pressure that reaches treatment targets with concurrent use of 4 or more antihypertensive medications. The American Heart Association website provides more information about hypertension.

The Paradise system offers a device-based approach to treating hypertension. Known as renal denervation, the system is used to destroy (ie, ablate) the renal sympathetic nerves that line the main renal arteries connecting the kidneys to the aorta. Research has suggested that overstimulation of the renal sympathetic nerves can contribute to resistant hypertension by increasing renin release, which leads to an increase in renal sodium reabsorption and a reduction of renal blood flow.

To deliver renal denervation, an interventional cardiology or interventional radiology team typically places the patient under conscious sedation with local anesthesia. The physician inserts a proprietary balloon catheter into the femoral artery in the groin and advances it into the left and right renal arteries, alternately. Each artery receives 2 to 4 applications of circumferentially (ie, in a 360-degree circular pattern) delivered ultrasound energy, of about 7 seconds each. The liquid-cooled balloon purportedly protects the artery walls from heat damage while the sympathetic nerves are ablated. The physician removes the catheter using standard interventional techniques after treating both renal arteries. Patients are typically kept overnight after the procedure for observation.

The Paradise system purportedly provides more complete ablation to more of the vessel by delivering energy circumferentially from the balloon. Earlier-generation renal denervation systems that failed in development typically delivered ablation point by point at the catheter tip, potentially increasing the chance of incomplete ablation.

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified 3 ongoing trials for this topic. We present these trials in Table 3.5. (Two other listed trials were excluded. One single-center German study [NCT01888315] listed as recruiting, but not updated since June 2013, was comparing the Paradise system with 3 other renal denervation systems that were commercially available in Europe but no longer in development for the US market. Another single-center German study [NCT02920034] listed as active, not recruiting, but not updated since April 2019, was comparing the Paradise system with a Medtronic renal denervation system.)
system and had results published in a peer reviewed journal *[Circulation]* in January 2019. See Fengler et al 2019 below.

**Table 3.5. Ongoing Clinical Trials**

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Study of the ReCor Medical Paradise System in Clinical Hypertension (RADIANCE-HTN) NCT02649426</td>
<td>Adults aged 18 to 75 years (n = 292) with average office BP ≥ 140/90 mm Hg despite stable regimen of at least 3 different antihypertensive medications including a diuretic (TRIO cohort) or average office BP ≥ 140/90 and &lt; 180/110 mm Hg despite lifestyle measures but no antihypertensive medications or average office BP &lt; 180/120 mm Hg on stable dose of 1 to 2 antihypertensive drugs (SOLO cohort)</td>
<td>Randomized, triple-blind, parallel-assignment trial (phase not stated) to compare safety and efficacy of Paradise system renal denervation with sham procedure (renal angiogram) for treating hypertension in 2 distinct populations Primary outcome: Mean reduction in average daytime ambulatory systolic BP</td>
<td>Primary completion March 2020 Study completion August 2021</td>
</tr>
<tr>
<td>A Pivotal Study of the ReCor Medical Paradise System in Stage II Hypertension (RADIANCE-II) NCT03614260</td>
<td>Adults aged 18 to 75 years (n = 225) with stable average office BP ≥ 140/90 and &lt; 180/120 mm Hg on 0 to 2 classes of previously or currently prescribed antihypertensive medications</td>
<td>Randomized, double-blind, parallel-assignment pivotal trial (phase not stated) to compare safety and efficacy of Paradise system renal denervation with sham procedure (renal angiogram) for treating stage II hypertension Primary outcomes: Change in average daytime ambulatory systolic BP, incidence of major adverse events</td>
<td>Primary completion December 2020 Study completion October 2024</td>
</tr>
<tr>
<td>Renal Denervation on Quality of 24-hr BP Control by Ultrasound In Resistant Hypertension (REQUIRE) NCT02918305</td>
<td>Adults aged 20 to 75 years (n = 140) with average office systolic BP ≥ 150 mm Hg, office diastolic BP ≥ 90 mm Hg, or 24-hr ambulatory systolic BP ≥ 140 mm Hg despite 3 or more different classes of antihypertensive medications including diuretics</td>
<td>Phase III, randomized, parallel-assignment, double-blind trial assessing safety and efficacy of Paradise system renal denervation with sham procedure (renal angiogram) for treating resistant hypertension Primary outcome: Decrease in average 24-hour ambulatory systolic BP through 3 months after intervention</td>
<td>Primary completion March 2021 Study completion May 2022</td>
</tr>
</tbody>
</table>

Abbreviation: BP, blood pressure.
Recently Completed and Ongoing Trials With Available Results

Our searches identified 3 relevant, recently completed late-phase trials with published results.\textsuperscript{281-283} We summarize these studies with results as written in abstracts of published studies.

The following abbreviations are used in this section: ACE, angiotensin-converting enzyme; ANOVA, analysis of variance; ARB, angiotensin receptor blocker; BP, blood pressure; CI, confidence interval; RDN, renal denervation; SD, standard deviation.

Note: Azizi et al report outcomes from the same patient group at 2 months without antihypertensive medication (2018) and after 6 months with addition of standardized stepped-care antihypertensive therapy (2019).

Randomized Comparison of Ultrasound Versus Radiofrequency Denervation in Patients With Therapy Resistant Hypertension (RADIOSOUND). \textbf{NCT02920034}. Fengler et al 2019.282

- **Patient population/planned enrollment**: Adults aged 18 to 75 years (n = 120) with systolic office blood pressure higher than 160 mm Hg despite stable regimen of 3 or more antihypertensive drugs including a diuretic, and renal artery anatomy amenable to catheter-based RDN
- **Study design**: Unphased, parallel-assignment, single-blind trial comparing Paradise ultrasound RDN with Medtronic Spyral radiofrequency RDN to treat resistant hypertension
- **Primary outcome**: Change in systolic daytime ambulatory blood pressure at 3 months
- **Secondary outcomes**: Change in systolic daytime and 24-hour average blood pressure at 6 and 12 months
- **Results presented by study authors**: “At 3 months, systolic daytime ambulatory blood pressure decreased by 9.5±12.3 mm Hg (P<0.001) in the whole cohort. Although blood pressure was significantly more reduced in the ultrasound ablation group than in the radiofrequency ablation group of the main renal artery (−13.2±13.7 versus −6.5±10.3 mm Hg; mean difference, −6.7 mm Hg; global P=0.038 by ANOVA, adjusted P=0.043), no significant difference was found between the radiofrequency ablation groups (−8.3±11.7 mm Hg for additional side branch ablation; mean difference, −1.8 mm Hg; adjusted P>0.99). Similarly, the blood pressure reduction was not found to be significantly different between the ultrasound and the side branch ablation groups. Frequencies of blood pressure response ≥5 mm Hg were not significantly different (global P=0.77).”

A Study of the ReCor Medical Paradise System in Clinical Hypertension (RADIANCE-HTN SOLO). \textbf{NCT02649426}. Azizi et al 2018.283

- **Patient population/planned enrollment**: Adults aged 18 to 75 years (n = 146) with average daytime ambulatory BP ≥ 135/85 and < 170/105 mm Hg after a 4-week cessation of up to 2 antihypertensive drugs (before interventional procedure) and suitable renal artery anatomy
- **Study design**: Randomized, parallel-assignment, triple-blind study (phase not stated) comparing the safety and efficacy of Paradise system RDN (n = 74) with those outcomes with sham procedure (renal angiogram; n = 72) to reduce hypertension in patients not taking antihypertensive medication
- **Primary outcome**: Mean change in average daytime ambulatory systolic BP through 2 months after RDN or sham procedure
- **Secondary outcome**: Procedural safety
- **Results presented by study authors**: “The reduction in daytime ambulatory systolic blood pressure was greater with renal denervation (−8.5 mm Hg, SD 9.3) than with the sham procedure (−2.2 mm Hg, SD 10.0; baseline-adjusted difference between groups: −6.3 mm Hg, 95% CI −9.4 to −3.1, p=0.0001). No major adverse events were reported in either group.”

- **Patient population/planned enrollment:** Adults aged 18 to 75 years (n = 146) who were randomly assigned to RDN or sham procedure at the end of the trial-mandated, 2-month antihypertensive medication–free follow-up period, who presented with an average daytime ambulatory BP ≥ 135/85 mm Hg

- **Study design:** Unphased, randomized, parallel-assignment, triple-blind study comparing the safety and efficacy of Paradise system RDN (n = 74) with those outcomes for sham procedure (renal angiogram; n = 72) to reduce hypertension. Patients with BP ≥ 135/85 mm Hg at 2 months after the procedure began standardized stepped-care antihypertensive therapy of sequentially added amlodipine 5 mg/day, a standard dose of an ACE inhibitor or ARB, and hydrochlorothiazide 12.5 mg/day, followed by sequential uptitration of hydrochlorothiazide to 25 mg/day and amlodipine to 10 mg/day.

- **Primary outcome:** Mean change in average daytime ambulatory systolic BP through 6 months adjusted for medications and baseline systolic BP

- **Secondary outcomes:** Procedural safety and medication burden at 6 months after RDN or sham procedure

- **Results presented by study authors:** “A total of 69/74 RDN patients and 71/72 sham patients completed the 6-month ambulatory BP measurement. At 6 months, 65.2% of patients in the RDN group were treated with the standardized stepped-care antihypertensive treatment versus 84.5% in the sham group (P=0.008), and the average number of antihypertensive medications and defined daily dose were less in the RDN group than in the sham group (0.9±0.9 versus 1.3±0.9, P=0.010 and 1.4±1.5 versus 2.0±1.8, P=0.018; respectively). Despite less intensive standardized stepped-care antihypertensive treatment, RDN reduced daytime ambulatory systolic BP to a greater extent than sham (−18.1±12.2 versus −15.6±13.2 mm Hg, respectively; difference adjusted for baseline BP and number of medications: −4.3 mm Hg, 95% confidence interval, −7.9 to −0.6, P=0.024). There were no major adverse events in either group through 6 months.”

**Manufacturers and Regulatory Status**

ReCor Medical Inc (Palo Alto, California) manufactures the Paradise system. In July 2018, FDA granted ReCor Medical’s request to begin the RADIANCE II pivotal trial (phase not stated) to support a regulatory submission. The company expected to complete the 225-patient pivotal trial by December 2020 but has not announced an anticipated timeline for submitting a Premarket Approval application to FDA.284,285

**Cost Information**

US cost information is unavailable for this topic.

**Key Stakeholder Perspectives**

Nine stakeholders, reflecting clinical, nursing, research, health systems, and patient perspectives, provided comments and ratings on renal denervation with the Paradise system to treat resistant hypertension.286-294 The list below provides a summary of key stakeholder perspectives.

- Renal denervation with the Paradise system could have moderate to high potential to improve patient outcomes and quality of life if it reduces or eliminates the need to take blood pressure medications.
- Renal denervation could largely disrupt patient care by shifting patients from office-based antihypertensive drug therapy to a (most likely) one-time interventional procedure.
- Disruption to the health care delivery system would be moderate because experienced interventional cardiology or interventional radiology teams would require additional training and would perform the procedures in existing interventional suites.
• Disparities could increase if third-party payer coverage is not widely available for renal
denervation or if large copayments or deductibles discourage some patients from seeking
the procedure.
• Potential concentration of renal denervation at high-volume regional centers could also
create disparities in access.

Tafamidis (Vyndaqel, Vyndamax) to Treat Amyloid Transthyretin-
Mediated Cardiomyopathy

Highlights
• Tafamidis is a drug intended to treat amyloid transthyretin-mediated cardiomyopathy
(ATR-CM), a rare and potentially fatal condition affecting heart muscle.
• FDA approved tafamidis in May 2019 as the first intervention specifically indicated for
treating ATR-CM, which traditionally has a poor prognosis.
• The daily oral therapy has a US retail list price of about $225 000 per year.
• Stakeholders commenting on this topic thought tafamidis has high potential to improve
patient outcomes and disrupt existing care paradigms for patients with ATR-CM.

Patient Population
Tafamidis is intended for adults aged 18 years or older with hereditary (ie, caused by a
genetic variant in the transthyretin gene, TTR) or wild-type (ie, not caused by any known genetic
variant) ATR-CM.

Intervention
A life-threatening disease, ATR-CM occurs as transthyretin-based amyloid fibrils
accumulate in the heart, leading to heart failure. Few treatments exist, and they typically involve
supportive measures to manage heart failure symptoms. Life expectancy for patients with ATR-
CM is about 2.5 years after diagnosis for the hereditary form of the disease and 3.6 years after
diagnosis of the wild-type form.295 Therefore, an unmet need exists for disease-modifying
treatments for this condition.

Tafamidis is a first-in-class oral drug intended to stabilize transthyretin tetramers (4-unit
molecules) and interfere with the process of amyloid creation that underlies ATR-CM.296,297 In
patients with ATR-CM, transthyretin tetramers dissociate into monomer (single-unit)
intermediates that misassemble into amyloid aggregates. Amyloid is a protein, and amyloid
aggregates gradually stiffen heart muscle, leading to heart failure.298 By stabilizing transthyretin
tetramers, tafamidis purportedly reduces levels of amyloidogenic transthyretin monomers,
potentially modifying the course of ATR-CM.

Tafamidis is available in 2 formulations, Vyndaqel and Vyndamax. Patients take one
formulation or the other but may not mix them. The recommended dosages are as follows:
tafamidis meglumine (Vyndaqel) taken as four 20-mg capsules once daily and tafamidis
(Vyndamax) taken as one 61-mg capsule daily (intended for patient convenience).296,297

The American Heart Association website offers more information about ATR-CM.
Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 2 ongoing trials for this topic. We present these trials in Table 3.6.

Table 3.6. Ongoing Clinical Trials

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vyndaqel Capsules Special Investigation (ATTR-CM) NCT04108091</td>
<td>Children and adults of any age (n = 360) with ATTR-CM</td>
<td>Unphased, observational postmarketing study in Japan to assess long-term safety and efficacy of oral tafamidis meglumine 80 mg to treat ATTR-CM Primary outcome: Adverse drug reactions through 30 months Secondary outcome: Survival through 30 months</td>
<td>Primary and study completion April 2024</td>
</tr>
<tr>
<td>Long-Term Safety of Tafamidis in Subjects With Transthyretin Cardiomyopathy NCT02791230</td>
<td>Adults aged 18 years or older (n = 2000) with hereditary or wild-type ATTR-CM</td>
<td>Phase III, single-arm, open-label extension study to assess the long-term safety of oral tafamidis meglumine 80 mg or tafamidis 61 mg daily to treat ATTR-CM Primary outcomes: All-cause mortality and treatment-emergent adverse events through 60 months Selected secondary outcomes: All-cause and cardiovascular hospitalizations, cardiovascular mortality, Kansas City Cardiomyopathy Questionnaire scores, and New York Heart Association functional class through 60 months</td>
<td>Primary completion December 2026 Study completion December 2027</td>
</tr>
</tbody>
</table>

Abbreviation: ATTR-CM, amyloid transthyretin-mediated cardiomyopathy.

Recently Completed and Ongoing Trials With Available Results

Our searches identified 2 relevant, recently completed late-phase trials with published results.295,299 We summarize these studies with results as written in abstracts of published studies.

The following abbreviations are used in this section: ATTR-CM, amyloid transthyretin-mediated cardiomyopathy; ATTRm, mutant amyloid transthyretin; ATTRwt, wild-type amyloid transthyretin; HF, heart failure; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall summary; NYHA, New York Heart Association; P/T, placebo/tafamidis (ie, patients who received placebo in the clinical trial and tafamidis in the extension); T/T, tafamidis/tafamidis (ie, patients who received tafamidis in both the clinical trial and the extension).
Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy (ATTR-ACT).
NCT01994889. Maurer et al 2018.295

- **Patient population/planned enrollment:** Adults aged 18 to 90 years (n = 441) with hereditary (n = 106) or wild-type (n = 335) ATTR-CM and at least one HF-related hospitalization or clinical evidence of HF requiring diuretic therapy for improvement
- **Study design:** Phase III, randomized, parallel-assignment, double-blind trial comparing safety and efficacy of once-daily tafamidis meglumine 20 or 80 mg (n = 264) against placebo (n = 177) for treating ATTR-CM
- **Primary outcome:** Hierarchical composite of all-cause mortality and frequency of cardiovascular-related hospitalizations through 30 months
- **Secondary outcomes:** All-cause mortality and frequency of cardiovascular-related hospitalizations through 30 months
- **Results presented by study authors:** "In the primary analysis, all-cause mortality and rates of cardiovascular-related hospitalizations were lower among the 264 patients who received tafamidis than among the 177 patients who received placebo (P<0.001). Tafamidis was associated with lower all-cause mortality than placebo (78 of 264 [29.5%] vs. 76 of 177 [42.9%]; hazard ratio, 0.70; 95% confidence interval [CI], 0.51 to 0.96) and a lower rate of cardiovascular-related hospitalizations, with a relative risk ratio of 0.68 (0.48 per year vs. 0.70 per year; 95% CI, 0.56 to 0.81). At month 30, tafamidis was also associated with a lower rate of decline in distance for the 6-minute walk test (P<0.001) and a lower rate of decline in KCCQ-OS score (P<0.001). The incidence and types of adverse events were similar in the two groups."

Interim Analysis of Data From a Long-Term, Extension Trial of Tafamidis Meglumine in Patients With Transthyretin Amyloid Cardiomyopathy. NCT01994889. Elliott et al 2019.299

- **Patient population/planned enrollment:** Adults aged 18 to 90 years (n = 441) with hereditary (n = 106) or wild-type (n = 335) ATTR-CM and at least one HF-related hospitalization or clinical evidence of HF requiring diuretic therapy for improvement who participated in ATTR-ACT and were also enrolled in a follow-up extension study
- **Study design:** Pooled analysis of a phase III, randomized, parallel-assignment, double-blind trial comparing safety and efficacy of once-daily tafamidis meglumine 20 or 80 mg (n = 264) against placebo (n = 177) for treating ATTR-CM and a long-term extension study comparing daily tafamidis meglumine 20 and 80 mg
- **Primary outcome:** All-cause mortality through 60 months
- **Results presented by study authors:** "All-cause mortality was significantly lower in the T/T group (n=264; 88 events, 33.3%) compared with the P/T group (n=177; 88 events, 50.3%); hazard ratio (95% CI), 0.64 (0.47, 0.85); P=0.001. In the subgroup of ATTRwt patients, all-cause mortality was significantly reduced in the T/T group (55/201; 27.4%) compared with the P/T group (60/134; 44.8%); 0.64 (0.44, 0.92); P=0.002. In the 106 (24.0%) ATTRm patients, there was a trend towards a reduction in all-cause mortality in the T/T group (33/63; 52.4%) compared with the P/T group (29/43; 67.4%); 0.66 (0.39, 1.09); P=0.17. In patients who were NYHA Class I or II at baseline, all-cause mortality was significantly reduced in the T/T group (38/186; 20.4%) compared with the P/T group (45/114; 39.5%); 0.49 (0.32, 0.75); P=0.001. In those patients with more severe symptoms at baseline (NYHA Class III), there were fewer deaths in the T/T group (50/78; 64.1%) compared with the P/T group (44/63; 69.8%); 0.80 (0.53, 1.21), but this difference was not statistically significant (P=0.50)."

Manufacturers and Regulatory Status

Pfizer Inc (New York, New York) manufactures tafamidis meglumine and tafamidis. On May 3, 2019, FDA approved tafamidis meglumine 20-mg capsules under the trade name Vyndaqel and tafamidis 61-mg capsules under the trade name Vyndamax for treating ATTR-CM.297,298 FDA had previously granted tafamidis Orphan Drug, Breakthrough Therapy, Fast Track, and Priority Review designations for treating ATTR-CM.297 It is the first drug approved to treat ATTR-CM.
Cost Information

Pfizer reportedly established a $225 000 per-year list price for tafamidis meglumine and tafamidis.\textsuperscript{300} The company has announced a patient-assistance program to help eligible patients afford tafamidis therapy for ATTR-CM.\textsuperscript{297}

Key Stakeholder Perspectives

Six stakeholders, reflecting clinical, research, and health systems perspectives, provided comments and ratings on tafamidis (Vyndaqel, Vyndamax) to treat ATTR-CM.\textsuperscript{301-306} The list below provides a summary of key stakeholder perspectives.

- Tafamidis has moderate to high potential to improve outcomes for patients with ATTR-CM, which traditionally has a poor prognosis.
- As a first-in-class therapeutic for a disease with no other approved or effective treatments, tafamidis has high potential to disrupt the care paradigm for patients with ATTR-CM.
- By slowing progressive heart damage, tafamidis could reduce the downstream need for more invasive treatments, such as implantable cardioverter-defibrillators or heart transplantation.
- Although tafamidis treats a rare condition, its estimated $225 000 annual retail cost could create disparities in patient access, depending on insurance coverage and reimbursement from third-party payers and patient copayments.
Chapter 4. Mental and Behavioral Health Conditions

Chapter Summary

For the mental and behavioral health conditions priority area, we considered for inclusion 4 topics for which (1) preliminary phase III data for drugs, phase II (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled and sent for stakeholder comment before March 10, 2020; and (3) we received at least 5 sets of comments and ratings from stakeholder commenters between April 1, 2019, and March 20, 2020.

As of March 10, 2020, we were monitoring 18 topics in this priority area, including the 4 considered for inclusion in this report. These 18 topics will be listed in the June 2020 PCORI Health Care Horizon Scanning System: Horizon Scanning Status Report. We also archived one topic in March 2020. A description of that topic and the reason it was archived can be found in the March 2020 Status Report.

The 18 monitored topics encompass pharmaceuticals and devices intended to treat 9 mental and behavioral health conditions. Two topics were developed as topic profiles to be sent for stakeholder comment; however, fewer than 5 sets of stakeholder comments were received for these topics before March 10, 2020, so they were not considered for inclusion in this report. The remaining 12 topics are still too early in development to meet criteria (as outlined above) for eligibility for this report.

Topics Considered for Inclusion in This Report

Table 4.1 lists 2 topics selected for inclusion during the High Potential Disruption Report decision meeting. A majority of the horizon scanning team voted that these topics had high potential for disruption, based on stakeholder ratings and comments and available data. Topics are listed and discussed alphabetically by title.

Table 4.1. Included Topics for Priority Area: Mental and Behavioral Health Conditions

<table>
<thead>
<tr>
<th>Topic title</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,4-methylenedioxymethamphetamine-assisted psychotherapy to treat severe posttraumatic stress disorder</td>
</tr>
<tr>
<td>SEP-363856 to treat schizophrenia</td>
</tr>
</tbody>
</table>

Table 4.2 lists 2 topics considered, but not selected, for inclusion during the High Potential Disruption Report decision meeting. A majority of the voting team agreed that these topics lacked high potential for disruption, based on stakeholder ratings and comments and available data. Each record contains a note explaining the reasons for exclusion.
Table 4.2. Topics Considered but Not Included for Priority Area: Mental and Behavioral Health Conditions

<table>
<thead>
<tr>
<th>Topic title</th>
<th>Exclusion reason(s) and notes based on stakeholder comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine (NRX-100)/cyclurad (NRX-101) to treat severe bipolar depression with acute suicidal ideation</td>
<td>More efficacy data are needed to determine the intervention’s potential to improve patient outcomes. Trials should investigate a larger patient sample size, a longer treatment period, and the outcome of suicidal ideation.</td>
</tr>
<tr>
<td>Dasotraline to treat moderate to severe binge eating disorder (BED)</td>
<td>Additional information is needed about overall efficacy and adverse events of dasotraline so new conclusions can be drawn about its potential disruption at this time. Results from an ongoing phase III trial need to be reviewed to determine whether this drug used for treating BED has potential for disruption.</td>
</tr>
</tbody>
</table>

**Topic Summaries**

We present below 2 summaries of topics deemed to have high potential for disruption.

3,4-Methylenedioxymethamphetamine-Assisted Psychotherapy to Treat Severe Posttraumatic Stress Disorder

**Highlights**

- MDMA (3,4-methylenedioxymethamphetamine) is an oral psychoactive drug given before an extended psychotherapy session that involves an overnight stay.
- The session is conducted by a specially trained therapist to enable the therapist and patient to efficiently establish a therapeutic relationship and increase 2-way communication during the session.
- Stakeholders commenting on this topic thought that MDMA has the potential to be a quicker and more effective treatment for severe posttraumatic stress disorder (PTSD) than standard psychotherapy and selective serotonin reuptake inhibitor drugs.
- Stakeholders also thought that several barriers would affect the widespread implementation of MDMA for treating severe PTSD. Barriers include the long duration of each therapy session, required clinical training for the therapist, infrastructure changes, cost, and concerns about appropriate patient selection.

**Patient Population**

This treatment is intended for adults aged 18 years or older who meet diagnostic criteria in the *Diagnostic and Statistical Manual of Mental Disorders, fifth edition* (DSM-5) for severe PTSD and who have had at least one unsuccessful attempt with either talk therapy or drug treatment.

**Intervention**

MDMA (also known by the street names Ecstasy and Molly) is a psychoactive drug under study for use during psychotherapy sessions led by specially trained therapists to improve symptoms of severe PTSD. MDMA works by activating the trace amine-associated receptor 1 (TAAR1) and inhibiting vesicular monoamine transporter 2, thereby increasing concentrations of...
these neurotransmitters, which are involved in the regulation of emotion, arousal, and memory.\textsuperscript{308}

MDMA is thought to produce a sense of euphoria, well-being,\textsuperscript{309} and “openness” that purportedly improves negative behaviors and feelings associated with PTSD, such as hostility, mistrust, and emptiness.\textsuperscript{310} When taken by the patient, MDMA purportedly enables the therapist to more efficiently establish a therapeutic relationship and increase 2-way communication during a prolonged psychotherapy session.\textsuperscript{311} Patients given MDMA have reported gaining greater access to their memories and helpful insights when revisiting traumatic events during therapy sessions.\textsuperscript{312} It produces its psychological and physical effects by increasing levels of neurotransmitters in the brain, including dopamine, norepinephrine, serotonin, oxytocin, prolactin, and cortisol\textsuperscript{307, 313-316}

In clinical trials, MDMA has been given to patients before an 8-hour psychotherapy session. The initial dose is 80 or 120 mg taken orally followed by a supplemental half-dose of 40 or 60 mg given 1.5 to 2 hours later, if necessary, totaling 80 to 180 mg per session. The treatment period consists of one session per month for 3 months. The psychotherapy session alternates between periods of patient introspection and engagement with the therapist. Patients are monitored overnight at the site and meet with their therapists for a 90-minute, follow-up therapy session the next day for further emotional reprocessing.\textsuperscript{317}

The National Institutes of Health’s National Institute of Mental Health website offers more information on PTSD.

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified 2 ongoing trials for this topic. We present these trials in Table 4.3.

**Table 4.3. Ongoing Clinical Trials**

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Multi-site Phase 3 Study of MDMA-Assisted Psychotherapy for PTSD (MAPP1) NCT03537014</td>
<td>Adults aged 18 years or older (n = 100) with severe PTSD</td>
<td>Phase III, randomized, double-blind, parallel-assignment trial assessing the efficacy and safety of MDMA-assisted manualized psychotherapy versus manualized psychotherapy with placebo for 3 monthly psychotherapy sessions Primary endpoint: Clinician-administered PTSD scale Secondary endpoint: Clinician-rated functional impairment disability scale</td>
<td>Primary completion June 2020</td>
</tr>
</tbody>
</table>
### Study name and National Clinical Trials identifier

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Multi-site Phase 3 Study of MDMA-Assisted Psychotherapy for PTSD (MAPP2) NCT04077437</td>
<td>Adults aged 18 years or older (n = 100) with severe PTSD</td>
<td>Phase III, randomized, double-blind, parallel-assignment trial assessing the efficacy and safety of MDMA-assisted manualized psychotherapy versus manualized psychotherapy with placebo for 3 monthly psychotherapy sessions. Primary endpoint: Clinician-administered PTSD scale. Secondary endpoint: Clinician-rated functional impairment disability scale.</td>
<td>Primary completion June 2021</td>
</tr>
</tbody>
</table>

**Abbreviations:** MDMA, 3,4-methylenedioxymethamphetamine; PTSD, posttraumatic stress disorder.

### Recently Completed or Ongoing Trials With Available Results

Our searches identified 6 recently completed late-phase trials reported in a pooled analysis (NCT01793610, NCT01689740, NCT01211405, NCT01958593, NCT00353938, NCT00090064).317 We summarize this pooled analysis of most recent and indication-relevant studies with results as written in a published study.

The following abbreviations are used in this section: BDI, Beck Depression Inventory; CAPS, Clinician-Administered PTSD Scale; MDMA, 3,4-methylenedioxymethamphetamine; MMRM, mixed model for repeated measures; PTSD, posttraumatic stress disorder; SAE, serious adverse event; SE, standard error; TEAE, treatment-emergent adverse event.

**MDMA-Assisted Psychotherapy for Treatment of PTSD.** NCT01793610, NCT01689740, NCT01211405, NCT01958593, NCT00353938, NCT00090064. Mithoefer et al 2019.317

- **Patient population/planned enrollment:** Adults (n = 103) aged 18 years or older with chronic, moderate to severe PTSD with at least one unsuccessful attempt at or inability to tolerate treatment for PTSD with either talk therapy or drugs.
- **Study design:** Six randomized, double-blind, controlled clinical trials at 5 study sites were conducted from April 2004 to February 2017. Active doses of MDMA (75 to 125 mg, n = 72) or placebo or controlled doses (0 to 40 mg, n = 31) were given to individuals with PTSD during manualized psychotherapy sessions consisting of two to three 8-hour sessions spaced 1 month apart. Three nondrug 90-minute therapy sessions preceded the first MDMA exposure, and 3 to 4 followed each experimental session.
- **Primary outcome:** PTSD symptoms.
- **Secondary outcomes:** Depression symptoms and severity, psychological distress, and quality of life.
- **Results presented by study authors:** "After two blinded experimental sessions, the active group had significantly greater reductions in CAPS-IV total scores from baseline than the control group [MMRM estimated mean difference (SE) between groups - 22.0 (5.17), \( P < 0.001 \)]. The between-group Cohen’s d effect size was 0.8, indicating a large treatment effect. After two experimental sessions, more participants in the active group (54.2%) did not meet CAPS-IV PTSD diagnostic criteria than the control group (22.6%). Depression symptom improvement on the BDI-II was greatest for the active group compared to the control group (22.6%). Depression symptom improvement on the BDI-II was greatest for the active group compared to the control group (22.6%).

**TEAEs** during the blinded treatment segment most commonly reported across all doses included events in the following MedDRA System Organ Classes: psychiatric disorders, gastrointestinal disorders, and general disorders. The most frequently reported psychiatric TEAEs were anxiety, depressed mood, irritability, and panic attack. On the day of blinded experimental sessions, reactions reported by ≥ 40% of participants in either group were anxiety, dizziness, fatigue, headache, jaw...
clenching/tight jaw, lack of appetite, and nausea. The majority of expected reactions were rated mild or moderate, and the frequency of reports decreased over the 7 days following an experimental session. No changes in neurocognitive function were detected. There were no unexpected MDMA-related SAEs. Four SAEs were reported during the blinded treatment period, including one instance of suicidal ideation (30 mg); one SAE of exacerbation of ventricular extrasystoles was reported during an open-label session (125 mg) and one SAE of suicidal behavior prior to MDMA exposure in the first experimental session. There was no suicidal behavior during the treatment period after dosing. At baseline, prior to any drug dosing, the active dose group (46%) had much higher rates of positive suicidal ideation than the control group (16.7%), but the lifetime reports were similar between groups. During the treatment phase, suicidal ideation transiently increased in some participants and was more common in the active MDMA group, although the causal relationship to the psychotherapeutic processing of traumatic memories or to MDMA itself, or to random group differences could not be determined.”

**Manufacturers and Regulatory Status**

MDMA-assisted psychotherapy is being investigated by Multidisciplinary Association for Psychedelic Studies (MAPS; Santa Cruz, California) in phase III trials for treating severe PTSD in adults. FDA granted Breakthrough Therapy designation to MDMA-assisted psychotherapy for severe PTSD in August 2017.318

After MDMA was designated a Schedule 1 controlled substance in 1985, the developer, MAPS, filed a Drug Master File application in 1986, followed by an Investigational New Drug application in 2001 for the use of MDMA in combination with psychotherapy.317

**Cost Information**

Cost information is unavailable for this topic.

**Key Stakeholder Perspectives**

Eight stakeholders, reflecting clinical, therapist, health systems, and research perspectives, provided comments and ratings on MDMA-assisted psychotherapy.319-326 The list below provides a summary of key stakeholder perspectives.

- The use of MDMA with psychotherapy might allow a rapid release of serotonin that could make it easier for patients to participate during their PTSD psychotherapy sessions.
- This intervention might lead to health care disparities for patients with PTSD that does not respond to standard treatments.
- Infrastructure changes would be needed to accommodate the 8-hour therapy sessions, overnight stays, and posttreatment follow-up that are recommended for MDMA administration.
- MDMA-assisted psychotherapy would moderately disrupt costs. Although short-term costs would likely increase, long-term costs could decrease if this medication is proved effective at facilitating therapy that results in resolution of symptoms.
- As a Schedule I drug, MDMA carries the potential for misuse and abuse, a particular risk for this patient population because of the rate of comorbid substance use disorders.
SEP-363856 to Treat Schizophrenia

Highlights

- SEP-363856 is a novel oral antipsychotic drug to treat schizophrenia that works without blocking dopamine receptors in the brain.
- Schizophrenia affects patients’ quality of life and overall health because the standard care can have substantial side effects that can lead to poor medication adherence and outcomes.
- Stakeholders commenting on this topic thought that SEP-363856 might lower long-term costs of patient care, given that it is an oral medication with an improved side effect profile compared with conventional antipsychotic drugs.
- Stakeholders also thought that fewer side effects might reduce emergency department visits and hospitalizations, as well as the burden of care to treat the side effects of obesity and diabetes caused by long-term use of dopamine-blocking medications.

Patient Population

SEP-363856 treatment is intended for adults aged 18 to 40 years with schizophrenia.

Intervention

Patients with schizophrenia report that undesirable effects—such as tremor, restlessness, difficulty sleeping, dizziness, sexual side effects, and weight gain—from available antipsychotic medications negatively affect their daily activities and quality of life. These negative side effects are one of the main reasons patients stop taking their medication, and nonadherence with recommended antipsychotic medication dosing reportedly occurs in 50% to 75% of patients.

SEP-363856 is an oral medication that purportedly treats both positive and negative schizophrenia symptoms, as well as depression symptoms, with fewer side effects than dopamine-blocking medications. It works differently from available antipsychotics because it does not block the D2 dopamine or serotonin 2A (5-HT2A) receptors. The exact way SEP-363856 produces its antipsychotic effect is unknown, but it is believed to activate trace amine-associated receptor 1 (TAAR1) and serotonin 1A (5-HT1A) receptors. SEP-363856 has not been found to cause tremors, involuntary muscle contractions, restlessness, or weight gain.

In clinical trials, SEP-363856 (25, 50, or 75 mg) has been given orally once daily for up to 26 weeks.

The National Institute of Mental Health website offers more information about schizophrenia.

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 4 ongoing trials for this topic. We present 3 of these trials in Table 4.4. One trial (DIAMOND 1, NCT04072354) was excluded for having a broad patient population in which children and adults are being evaluated.
Table 4.4. Ongoing Clinical Trials

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Clinical Trial That Will Study the Efficacy and Safety of an Investigational Drug in Acutely Psychotic People With Schizophrenia (DIAMOND 2) NCT04092686</td>
<td>Adults (n = 462) up to 65 years of age meeting DSM-5 criteria for schizophrenia</td>
<td>Phase III, multiregional, double-blind, parallel-group, long-term trial to assess safety and tolerability of once-daily SEP-363856 (75 or 100 mg) compared with placebo for 6 weeks Primary outcomes: Change in schizophrenia symptoms (positive and negative) and severity, and adverse events Secondary outcome: Time to relapse</td>
<td>Primary completion October 2021</td>
</tr>
<tr>
<td>A Study of the Long-Term Safety and Tolerability of an Investigational Drug in People With Schizophrenia. (DIAMOND 4) NCT04115319</td>
<td>Adults aged 18 to 65 years (n = 300) meeting DSM-5 criteria for schizophrenia</td>
<td>Phase III, multiregional, double-blind, parallel-group, long-term trial to assess safety and tolerability of once-daily SEP-363856 (50, 75, or 100 mg) compared with quetiapine XR (400, 600, or 800 mg/day) in a 2:1 ratio for 52 weeks Primary outcome: Adverse events Secondary outcome: Time to relapse</td>
<td>Primary completion March 2022</td>
</tr>
<tr>
<td>A Clinical Study to Evaluate the Long-Term Safety and Tolerability of an Investigational Drug in People With Schizophrenia DIAMOND 3 NCT04109950</td>
<td>Adults aged 18 to 40 years (n = 157) meeting DSM-5 criteria for schizophrenia who completed the 4-week double-blind treatment phase of study SEP361-201</td>
<td>Phase III, multiregional, open-label extension study to assess safety and tolerability of once-daily SEP-363856 (25, 50, or 75 mg) for 26 weeks Primary outcomes: Change in schizophrenia symptoms (positive and negative) and severity, and adverse events Secondary outcomes: Time to relapse and adverse events</td>
<td>Primary completion November 2022</td>
</tr>
</tbody>
</table>


Recently Completed and Ongoing Trials With Available Results

Our searches identified 2 recently completed late-phase trials with published results.\textsuperscript{330,334} We summarize the 2 most recent and indication-relevant studies with results as written in an abstract of a published study and a news release.

The following abbreviations are used in this section: BNSS, Brief Negative Symptom Scale; CGI Severity, Clinical Global Impressions severity scale; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition; PANSS, Positive and Negative Syndrome Scale.

**An Extension Study of Safety and Tolerability of SEP-363856 in Adult Subjects With Schizophrenia (SEP361-202). NCT02970929**, Sunovion 2019.\textsuperscript{334}

- **Patient population/planned enrollment:** Adults aged 18 to 40 years (n = 157) meeting DSM-5 criteria for schizophrenia who completed the 4-week double-blind treatment phase of study SEP361-201
• **Study design:** Phase II, multiregional, open-label extension study to assess safety and tolerability of once-daily SEP-363856 (25, 50, or 75 mg) for 26 weeks

• **Primary outcome:** Adverse events

• **Secondary outcomes:** Change in schizophrenia symptoms (positive and negative) and severity, change in depression symptoms and severity, and time to relapse

• **Results presented by study authors:** "The results of our six-month, open-label extension study in patients living with schizophrenia demonstrate that SEP-363856 has an excellent long-term safety profile, with continued, clinically meaningful improvement seen in the Positive and Negative Syndrome Scale (PANSS) total score"

**A Study to Evaluate the Efficacy and Safety of SEP-363856 in Acutely Psychotic Adults With Schizophrenia (SEP361-201).** [NCT02969382](https://clinicaltrials.gov/ct2/show/NCT02969382), Koblan et al 2019.330

• **Patient population/planned enrollment:** Hospitalized adults aged 18 to 40 years (n = 245) meeting DSM-5 criteria for schizophrenia and experiencing acute exacerbation of psychotic symptoms

• **Study design:** Randomized, double-blind, parallel-group, multicenter phase II trial comparing the efficacy and safety of flexibly-dosed SEP-363856 (50 or 75 mg/day) with placebo

• **Primary outcome:** Change in schizophrenia symptom (positive and negative) severity using PANSS

• **Secondary outcomes:** Change in depression symptom severity and incidence of adverse events

• **Results presented by study authors:** "Study treatment groups were similar at baseline: SEP-363856 (N=120; male, 64.2%; mean age, 30.0 years; PANSS total score, 101.4) and placebo (N=125; male, 63.2%; mean age, 30.6 years; PANSS total score, 99.7). Least-squares (LS) mean reduction from baseline to week 4 was significantly greater for SEP-363856 vs. placebo on the PANSS total score (-17.2 vs. -9.7; P=0.001; effect size, 0.45; primary endpoint), the PANSS positive subscale score (-5.5 vs. -3.9; P=0.019; effect size, 0.32), the PANSS negative subscale score (-3.1 vs. -1.6; P=0.008; effect size, 0.37), the PANSS general psychopathology subscale score (-9.0 vs. -4.7; P<0.001; effect size, 0.51), the CGISeverity score (-1.0 vs. -0.5; P<0.001; effect size, 0.52), and the BNSS total score (-7.1 vs. -2.7; P<0.001; effect size, 0.48). Overall discontinuation rates were similar for SEP363856 vs. placebo (21.7% vs. 20.8%) and for discontinuations due to an adverse event. The mean daily dose of SEP-363856 was 64.3 mg. Change in weight, lipids, glucose and prolactin was similar in SEP-363856 and placebo groups. Adverse events occurring with an incidence >2% on SEp363-856 or placebo (with SEP363- 856 incidence higher than placebo) were: somnolence (6.7% vs. 4.8%), agitation (5.0% vs. 4.8%), nausea (5.0% vs. 3.2%), diarrhea (2.5% vs. 0.8%), and dyspepsia (2.5% vs. 0%). The proportion of patients who reported any extrapyramidal symptom was 3.3% on SEP363856 and 3.2% on placebo."

**Manufacturers and Regulatory Status**

SEP-363856 is manufactured by Sunovion (Marlborough, Massachusetts), a subsidiary of Sumitomo Dainippon Pharma (Osaka, Japan), in collaboration with PsychoGenics (Paramus, New Jersey). Sunovion evaluated SEP-363856 to treat schizophrenia in the 2 phase II trials reported above: [NCT02969382](https://clinicaltrials.gov/ct2/show/NCT02969382), completed July 2018, and [NCT02970929](https://clinicaltrials.gov/ct2/show/NCT02970929), completed January 2019. In May 2019, FDA granted Breakthrough Therapy designation for SEP-363856 to treat patients with schizophrenia.335
Cost Information

Cost information is unavailable for this topic.

Key Stakeholder Perspectives

Nine stakeholders, reflecting clinical, nursing, health systems, and research perspectives, provided comments and ratings on SEP-363856.336-344 The list below provides a summary of key stakeholder perspectives.

- SEP-363856 might improve medication adherence by reducing long-term side effects, including weight gain, metabolic effects, and movement disorders, which could improve health outcomes for patients and lead to a reduction in emergency department visits.
- SEP-363856 might reduce the financial burden on the patient and health care delivery system in the long term, given that the drug seems to have improved tolerability and costs that might be saved by fewer hospital visits.
- Results from longer-term studies would validate the developer’s preliminary findings and determine SEP-363856’s duration of effects and cost-effectiveness.
Chapter 5. Rare Diseases

Chapter Summary

For the rare diseases priority area, we considered for inclusion 33 topics for which (1) preliminary phase III data for drugs, phase II (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled and sent for stakeholder comment before March 10, 2020; and (3) we received at least 5 sets of comments and ratings from stakeholder commenters between April 1, 2019, and March 20, 2020.

As of March 10, 2020, we were monitoring 112 topics in this priority area, including the 33 considered for inclusion in this report. These 112 topics will be listed in the June 2020 PCORI Health Care Horizon Scanning System: Horizon Scanning Status Report. We also archived 4 topics in February 2020. A description of those topics and the reason they were archived can be found in the March 2020 Status Report.

These 112 monitored topics encompass pharmaceuticals, gene and cellular therapies, monoclonal antibodies, viral vector therapies, RNA interference therapies, surgical procedures, and implantable devices intended to treat or prevent 79 rare diseases and/or related conditions. Ten topics were developed as topic profiles to be sent for stakeholder comment; however, fewer than 5 sets of stakeholder comments were received for these topics before March 10, 2020, so they were not considered for inclusion in this report. The remaining 69 topics are too early in development to meet criteria (as outlined above) for eligibility for this report.

Topics Considered for Inclusion in This Report

Table 5.1 lists 23 topics selected for inclusion during the High Potential Disruption Report decision meeting. A majority of the horizon scanning team voted that these topics had high potential for disruption, based on stakeholder ratings and comments and available data. Topics are listed and discussed alphabetically by title.

Table 5.1. Included Topics for Priority Area: Rare Diseases

<table>
<thead>
<tr>
<th>Topic title</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO-102 to treat Sanfilippo syndrome type Aa</td>
<td></td>
</tr>
<tr>
<td>Afamelanotide (Scenesse) to treat erythropoietic protoporphyriaa</td>
<td></td>
</tr>
<tr>
<td>Apremilast (Otezla) to treat Behçet disease</td>
<td></td>
</tr>
<tr>
<td>Arimoclomol (BRX-345) to treat Niemann-Pick disease type Caa</td>
<td></td>
</tr>
<tr>
<td>CAP-1002 to treat Duchenne muscular dystrophya</td>
<td></td>
</tr>
<tr>
<td>Casimersen to treat Duchenne muscular dystrophy</td>
<td></td>
</tr>
<tr>
<td>Crizanlizumab-tmca (Adakveo) to prevent vaso-occlusive crises in sickle cell disease</td>
<td></td>
</tr>
<tr>
<td>Eculizumab (Soliris) to treat neuromyelitis optica spectrum disordera</td>
<td></td>
</tr>
<tr>
<td>Elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta) to treat cystic fibrosisa</td>
<td></td>
</tr>
<tr>
<td>Fenfluramine hydrochloride low-dose (Fintepla) to treat Dravet syndrome</td>
<td></td>
</tr>
<tr>
<td>Galcanezumab-gnlm (Emgality) to treat episodic cluster headache</td>
<td></td>
</tr>
<tr>
<td>Givosiran (Givlaari) to prevent and treat acute hepatic porphyria</td>
<td></td>
</tr>
<tr>
<td>Topic title</td>
<td>Exclusion reason(s) and notes based on stakeholder comments</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Golodirsen (Vyondys 53) to treat Duchenne muscular dystrophy</td>
<td></td>
</tr>
<tr>
<td>Idebenone (Pul dysa) to treat Duchenne muscular dystrophy</td>
<td></td>
</tr>
<tr>
<td>Lentiglobin to treat transfusion-dependent β-thalassemia</td>
<td></td>
</tr>
<tr>
<td>Luspatercept-am (Reblozyl) to treat transfusion-dependent β-thalassemia</td>
<td></td>
</tr>
<tr>
<td>Onasemnogene Abeparvovec-xioi (Zolgensma) to treat spinal muscular atrophy</td>
<td></td>
</tr>
<tr>
<td>OTL-101 to treat adenosine deaminase–severe combined immunodeficiency</td>
<td></td>
</tr>
<tr>
<td>Palovarotene to treat fibrodysplasia ossificans progressiva</td>
<td></td>
</tr>
<tr>
<td>PTC-AADC to treat aromatic l-amino acid decarboxylase deficiency</td>
<td></td>
</tr>
<tr>
<td>RVT-802 to treat pediatric congenital athymia (DiGeorge syndrome immunodeficiency, CHARGE syndrome, FOXN1 deficiency)</td>
<td></td>
</tr>
<tr>
<td>Valoctocogene Roxaparvovec to treat hemophilia A</td>
<td></td>
</tr>
<tr>
<td>Voxelotor (Oxbryta) to treat sickle cell disease</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.2 lists 10 topics considered, but not selected, for inclusion during the High Potential Disruption Report decision meeting. A majority of the voting team agreed that these topics lacked high potential for disruption, based on stakeholder ratings and comments and available data. Each record contains a note explaining the reasons for exclusion.

**Table 5.2. Topics Considered but Not Included for Priority Area: Rare Diseases**

<table>
<thead>
<tr>
<th>Topic title</th>
<th>Exclusion reason(s) and notes based on stakeholder comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amifampridine (Ruzurgi) to treat Lambert-Eaton myasthenic syndrome</td>
<td>Although ambulatory function as measured by the Triple Timed Up &amp; Go test was encouraging, the available data lack patient-oriented outcomes. The frequent dosing schedule (3 to 4 times daily) might be a barrier to medication adherence for children.</td>
</tr>
<tr>
<td>Ataluren (Translarna) to treat Duchenne muscular dystrophy</td>
<td>More data are needed to evaluate efficacy in a larger-sized trial and over the long term. However, this intervention has moderate disruption potential, particularly in the areas of patient outcomes, quality of life, overall health, and health care costs.</td>
</tr>
<tr>
<td>Epidiolex (cannabidiol oral solution) to treat tuberous sclerosis complex</td>
<td>Although data demonstrate clinically efficacy in reducing seizures, the intervention is unlikely to significantly disrupt many areas, including health disparities, the health care delivery system, or health care costs.</td>
</tr>
<tr>
<td>Gaboxadol (OV101) to treat Angelman syndrome</td>
<td>Available data, which were limited, showed no improvements in behavior, sleep, or gait, which are important patient-oriented outcomes.</td>
</tr>
<tr>
<td>In utero percutaneous endoscopic repair to treat spina bifida</td>
<td>The surgical technique has low disruptive potential because it would be limited to a small number of centers already experienced in high-risk, technically challenging fetal surgery. Limited reported data without full transparency make this procedure controversial. The high rates of prematurity-related complications and fetal death raise concerns and are likely to severely limit adoption.</td>
</tr>
<tr>
<td>Nintedanib (Ofev) to treat interstitial lung disease in systemic sclerosis</td>
<td>Available data suggest nintedanib did not significantly improve most patient-oriented outcomes compared with placebo, and high adverse event rates prompted 20% of patients to quit trials. The drug’s high cost with modest benefit is likely to limit insurance coverage and patient access to it.</td>
</tr>
</tbody>
</table>
### Topic Title Exclusion reason(s) and notes based on stakeholder comments

<table>
<thead>
<tr>
<th>Topic title</th>
<th>Exclusion reason(s) and notes based on stakeholder comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-501 (Renexus) to treat macular telangiectasia type 2</td>
<td>The phase II clinical trial results for NT-501 showed some clinical effect for improved patient health outcomes. However, more data from longer trials are needed to assess the potential for disruption.</td>
</tr>
<tr>
<td>Setmelanotide (RM-493) to treat leptin receptor deficiency obesity</td>
<td>The small evidence base suggests some benefit but limits the drug’s potential impact. Further diminishing potential disruption are the anticipated high costs for yet another obesity drug with unclear insurance coverage and a need for daily injections that is likely to limit patient acceptance.</td>
</tr>
<tr>
<td>Trofinetide (NNZ-2566) to treat Rett syndrome</td>
<td>The available data are limited, particularly regarding symptom severity and disease progression, and the intervention might be cost prohibitive.</td>
</tr>
<tr>
<td>Vamorolone (VBP15) to treat Duchenne muscular dystrophy</td>
<td>Vamorolone is unlikely to significantly disrupt many areas, including health disparities, the health care delivery system, or the current paradigm of patient care.</td>
</tr>
</tbody>
</table>

### Topic Summaries

We present below 23 summaries on topics deemed to have high potential for disruption.

**ABO-102 to Treat Sanfilippo Syndrome Type A**

**Highlights**

- ABO-102 is an intravenous recombinant adeno-associated viral vector carrying a wild-type copy of the N-sulfoglucosamine sulfohydrolase gene, *SGSH*, that is responsible for encoding sulfamidase enzyme function important for breaking down the polysaccharide heparan sulfate.
- As a single dose, one-time gene therapy, ABO-102 might fix the underlying genetic defect that causes Sanfilippo syndrome type A and delay or halt disease progression, whereas current treatment is largely supportive care.
- Stakeholders commenting on ABO-102 thought that, based on interim clinical trial results, it has moderate potential to improve patient health outcomes, quality of life, and overall health; however, more data are needed to better assess its efficacy.
- Stakeholders also thought that ABO-102 is likely to be expensive and might be cost prohibitive; however, as a one-time treatment it could be less expensive than therapies that need to be given on an ongoing basis.

**Patient Population**

ABO-102 is intended for infants and children aged 6 months or older with a developmental quotient of 60 or higher and adults with biochemically and genetically confirmed Sanfilippo syndrome type A (mucopolysaccharidosis type III A [MPSIIIA]).

**Intervention**

ABO-102 is a recombinant adeno-associated viral vector carrying a wild-type copy of the *SGSH* gene. It is intended to treat Sanfilippo syndrome type A, a childhood-onset, progressive, inherited metabolic disorder caused by a loss-of-function variant in *SGSH*. Patients with the disorder cannot break down the polysaccharide heparan sulfate, a process normally mediated by the *SGSH*-encoded enzyme heparan-N-sulfamidase.
Buildup of heparan sulfate in cells of the central nervous system causes neural degeneration that manifests as behavioral problems, sleeplessness, loss of speech and cognitive skills, mental retardation, heart problems, seizures, and loss of mobility. No cure exists for Sanfilippo syndrome type A (about 60% of all Sanfilippo syndrome cases), and patients typically do not survive past their 20s with supportive care.

In these patients, ABO-102 purportedly restores sulfamidase enzyme function, which reduces levels of heparan sulfate and other glycosaminoglycans, thereby blocking central nervous system degeneration and reducing disease-related symptoms.345

In clinical trials, ABO-102 is given as a single intravenous infusion via a peripheral-limb vein at a low dose (0.5 \times 10^{13} \text{ viral genomes [vg]/kg}), middle dose (1 \times 10^{13} \text{ vg/kg}), or high dose (3 \times 10^{13} \text{ vg/kg}). Patients also receive a tapering course of prednisone or prednisolone to prevent an immune response to the viral vector.

The National MPS Society website provides more information on Sanfilippo syndrome type A/MPSIIIA.

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 2 ongoing trials for this topic. We present these trials in Table 5.3.
Table 5.3. Ongoing Clinical Trials

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
</table>
| Phase I/II Gene Transfer Clinical Trial of scAAV9.U1a.hSGSH for Mucopolysaccharidosis (MPS) IIIA (Transpher A) NCT02716246 See interim results by de Castro et al 2019 and Abeona Therapeutics 2019 under Recently Completed and Ongoing Trials With Available Results | Children (n = 22) aged 6 months or older with biochemically and genetically confirmed Sanfilippo syndrome type A Children aged ≥ 2 years must have a "DQ of ≥60 (as measured Bayley Scales of Infant and Toddler Development - Third Edition) and accepting values within the 95% CI of the Cognitive Developmental Age Equivalents." | Phase I/II, nonrandomized, open-label study to evaluate the safety and efficacy of ABO-102 at 1 of 3 doses: low (0.5 × 10^{13} vg/kg), middle (1 × 10^{13} vg/kg), or high (3 × 10^{13} vg/kg) Primary outcomes:  
• Incidence of 2 or more grade III or higher AEs or treatment-related AEs through 24 months  
• Change in age-equivalent developmental score from baseline to months 6, 12, 18, and 24 Secondary outcomes:  
• Change in CSF heparan sulfate levels, CSF, or plasma heparan-N-sulfamidase enzyme activity levels  
• Change in liver, spleen, and brain volume  
• Biologic outcomes measured from baseline to months 1, 6, 12, and 24  
• Change in plasma or urine heparan sulfate or other GAG levels, measured from baseline to months 1, 6, 12, 18, and 24  
• Change in cognitive age equivalent  
• Change in adaptive age equivalent  
• Change in developmental quotient  
• Change in the Sanfilippo Behavior Rating Scale  
• Change in Leiter International Performance Scale-Revised  
• Change in PedsQL total score  
• Cognitive outcomes measured from baseline to months 6, 12, 18, and 24 | Primary and study completion December 2022 |
A Phase I/II Open Label, Single-Dose, Gene Transfer Study of scAAV9.U1a.hSGSH (ABO-102) in Patients With Middle and Advanced Phases of MPS IIIA Disease

NCT04088734

Children and adults (n = 12) (age unspecified) with biochemically and genetically confirmed Sanfilippo syndrome type A and a DQ < 60

Phase I/II, nonrandomized, single-group, open-label study to evaluate the safety and efficacy of high-dose ABO-102 (3 × 10¹³ vg/kg)

Primary outcomes:
- AE and SAE incidence through 24 months
- Change in CSF heparan sulfate levels and liver or spleen volume, all measured from baseline to months 1, 6, 12, and 24

Primary and study completion December 2022

Abbreviations: AE, adverse event; CI, confidence interval; CSF, cerebrospinal fluid; DQ, developmental quotient; GAG, glycosaminoglycan; MPS, mucopolysaccharidosis; PedsQL, Pediatric Quality of Life Inventory; SAE, serious adverse event; vg, viral genomes.

Recently Completed and Ongoing Trials With Available Results

Our searches identified one ongoing clinical trial with interim results. We summarize this study with results as written in a conference abstract and news release.

The following abbreviations are used in this section: AE, adverse event; CI, confidence interval; CSF, cerebrospinal fluid; CFS-HS, cerebrospinal fluid-heparan sulfate; DQ, developmental quotient; GAG, glycosaminoglycan; MRI, magnetic resonance imaging; PedsQL, Pediatric Quality of Life Inventory; vg, viral genomes.


- **Patient population/planned enrollment**: Children (n = 22) aged 6 months or older with biochemically and genetically confirmed Sanfilippo syndrome type A. Children aged ≥ 2 years must have a "DQ of ≥60 (as measured Bayley Scales of Infant and Toddler Development - Third Edition) and accepting values within the 95% CI of the Cognitive Developmental Age Equivalents."

- **Study design**: Phase I/II, nonrandomized, open-label study to evaluate the safety and efficacy of ABO-102 at 1 of 3 doses: low (0.5 × 10¹³ vg/kg), middle (1 × 10¹³ vg/kg), or high (3 × 10¹³ vg/kg)

- **Primary outcomes**: Incidence of 2 or more grade III or higher AEs or treatment-related AEs through 24 months and change in age-equivalent developmental score from baseline to months 6, 12, 18, and 24

- **Secondary outcomes**: Change in CSF heparan sulfate levels; CSF or plasma heparan-N-sulfamidase enzyme activity levels; change in liver, spleen, and brain volume; biologic outcomes measured from baseline to months 1, 6, 12, and 24; change in plasma or urine heparan sulfate or other GAG levels, measured from baseline to months 1, 6, 12, 18, and 24; change in cognitive age equivalent; change in adaptive age equivalent; change in the Sanfilippo Behavior Rating Scale; change in Leiter International Performance Scale-Revised; change in PedsQL total score; and cognitive outcomes measured from baseline to months 6, 12, 18, and 24

- **Results presented by study authors**: "Fourteen patients have been enrolled (Cohort 1, 0.5 × 10¹³ vg/kg, n = 3; Cohort 2, 1 × 10¹³ vg/kg, n = 3; Cohort 3, 3 × 10¹³ vg/kg, n = 8). ABO-102 was well tolerated, without serious drug-related adverse events. Cohorts 1 and 2 have completed 24 months follow-up with 16.9 months median follow-up in Cohort 3 (8.7–23.9 months). Transient, mild elevation of liver transaminases resolved with protocol-prescribed corticosteroids and 8 out of 14 patients showed mild transient cellular immune responses (ELISpot). A rapid, sustained and dose-dependent reduction in CSF-HS was observed in all patients with a 65% decrease from pre-treatment levels at day 30 (n = 8), 77% at Month 6 (n = 7) and 71% at..."
Month 12 in Cohort 3. Abdominal MRI showed a rapid and sustained decrease in liver volume in all patients, with two patients in Cohort 3 normalizing liver volume by Month 6. In patients treated at younger age (<30 months), neurocognitive function tracked in the normal range at 12–18 months of follow up. Other patients showed signs of cognitive stabilization.346

“The three youngest patients enrolled in cohort 3 – ages 26 months, 19 months, and 14 months at dosing – continued to track within normal age equivalent development 12–18 months post treatment. . . . Dose dependent and sustained reductions in CSF heparan sulfate were observed in all three cohorts; levels reached lower limit of quantitation in all eight patients treated with higher ABO-102 dose in cohort 3. . . . No product-related serious adverse events were reported to date.”347

Manufacturers and Regulatory Status

ABO-102 is being developed by Abeona Therapeutics Inc (Dallas, Texas) and is in phase I/II clinical development. For the indication under study, FDA granted Orphan Drug designation in April 2014,348 Fast Track designation in October 2016,349 Regenerative Medicine Advanced Therapy (RMAT) designation in April 2018,350 and Rare Pediatric Disease designation (date not specified).350 In July 2019, the manufacturer announced plans to schedule an expedited meeting with FDA (per the drug’s RMAT designation) the second half of 2019 to discuss the next steps toward potential agency approval.347

Cost Information

Cost information is unavailable for this topic, but stakeholders anticipate the therapy would be costly if approved by FDA. Other single-administration gene therapies for rare diseases have been priced (eg, Zolgensma) or have had proposed pricing (eg, Valrox) of more than $2.1 million dollars.

Key Stakeholder Perspectives

Eight stakeholders, reflecting clinical, health systems, nursing, and research perspectives, provided comments and ratings on ABO-102.351-358 The list below summarizes key stakeholder perspectives.

- The theory behind ABO-102 to treat Sanfilippo syndrome type A is sound, and ABO-102 has significant potential to improve patient health outcomes, quality of life, and overall health for patients with an otherwise devastating disease; however, more data are needed from larger trials focused on patient-centered outcomes to better assess its efficacy.
- This intervention might have the most impact on patient health and outcomes if given before 3 years of age.
- As a gene therapy, ABO-102 is likely to be very expensive and could be cost prohibitive to many patients, potentially increasing health disparities in this population; however, as a one-time treatment, it could be less expensive than therapies that have to be given on an ongoing basis.
- As novel treatment option, ABO-102 might shift the paradigm of patient care from supportive to curative and from more outpatient care than inpatient, but patients might still need to seek supportive treatments.
Afamelanotide (Scenesse) to Treat Erythropoietic Protoporphyria

**Highlights**

- Afamelanotide (Scenesse) is a small implant (about the size of a grain of rice) containing an analogue of alpha-melanocyte-stimulating hormone (α-MSH). FDA approved afamelanotide in October 2019 to treat erythropoietic protoporphyria (EPP), and it allows patients to tolerate more sun exposure before experiencing pain or acute attacks.
- Afamelanotide disrupts treatment paradigms as the first approved treatment for EPP. Afamelanotide might reduce demands on the system because of fewer hospitalizations. But a specialist visit is required every 2 months for a new implant.
- Stakeholders commenting on this topic thought that afamelanotide is a clinically effective and well-tolerated option for treating EPP, but they highlighted the need for longer-term trials to determine afamelanotide’s impact on quality of life, acute attacks, duration of effects, tolerability, and cost-effectiveness.
- Stakeholders also thought that afamelanotide’s high cost (about $40,000 per implant or $240,000 annually) might increase health disparities.

**Patient Population**

Afamelanotide is indicated for treating adults aged 18 years or older with EPP.

**Intervention**

EPP is a type of porphyria, a rare genetic metabolic disorder that causes extreme sensitivity to sunlight that can be harmful (ie, sunburn, blistering, possible permanent lesions) when the patient’s skin is exposed to sunlight—even for very short periods.\(^{359}\)

The underlying cause of EPP is reduced activity of the enzyme ferrochelatase, typically caused by loss-of-function genetic variants in the ferrochelatase gene, \(FECH\), or gain-of-function variants in the aminolevulinic acid synthase 2 gene, \(ALAS2\). Ferrochelatase is required for insertion of iron into protoporphyrin to form heme, and reduced ferrochelatase activity results in accumulation of protoporphyrin in the body.

Sunlight exposure of protoporphyrin in the superficial blood vessels of the skin triggers the generation of free radicals that leads to severe pain, typically within 1 to 20 minutes of sun exposure. No effective treatments exist for EPP, and patients with the disorder must modify their lifestyle, usually substantially, to avoid sun exposure, compromising quality of life.

Afamelanotide is a chemically modified peptide analogue of α-MSH, a naturally occurring peptide hormone released by skin cells in response to ultraviolet radiation (UVR) that stimulates melanocytes to express melanin.\(^{359,360}\) Afamelanotide is a linear 13-amino-acid peptide with 2 modified amino acids intended to increase the peptide’s half-life. The peptide analogue purportedly works as a melanocortin 1 receptor agonist that increases the melanin content of skin without requiring exposure to damaging UVR.\(^{360,361}\) Melanin absorbs, scatters, and quenches ultraviolet light; increased melanin levels in the skin purportedly protect the skin from sun damage.\(^{360}\)

Scenesse is a controlled-release formulation of afamelanotide administered in a physician’s office as a subcutaneous, 16-mg implant (which is about the size of a grain of rice), once every 2 months with an implantation cannula.\(^{360,361}\)

The National Institutes of Health’s Genetic and Rare Diseases Information Center offers more information on EPP.
Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified no ongoing trials for this topic.

Recently Completed and Ongoing Trials With Available Results

Our searches identified 2 recently completed late-phase trials with published results that supported the regulatory filings. We summarize these studies with results as written in abstracts of published studies.

The following abbreviation is used in this section: EPP, erythropoietic protoporphyria.


- **Patient population/planned enrollment:** Patients in the European Union (n = 74) or the United States (n = 94) with EPP
- **Study design:** Two multicenter, randomized, double-blind, placebo-controlled trials of the safety and efficacy of afamelanotide 16 mg or placebo subcutaneously implanted every 60 days for a total of 5 implants in the EU study and 3 implants in the US study
- **Primary outcome:** Number of hours of direct exposure to sunlight without pain
- **Secondary outcomes:** Type and duration of sun exposure, number and severity of phototoxic reactions, quality of life, and adverse events
- **Results presented by study authors:** “In the U.S. study, the duration of pain-free time after 6 months was longer in the afamelanotide group (median, 69.4 hours, vs. 40.8 hours in the placebo group; *P* = 0.04). In the European Union study, the duration of pain-free time after 9 months was also longer in the afamelanotide group than in the placebo group (median, 6.0 hours vs. 0.8 hours; *P* = 0.005), and the number of phototoxic reactions was lower in the afamelanotide group (77 vs. 146, *P* = 0.04). In both trials, quality of life improved with afamelanotide therapy. Adverse events were mostly mild; serious adverse events were not thought to be related to the study drug.”

Note: We presume that the large variation in sun exposure times in the 2 studies relates to differences in time of year of exposure, extent of sunlight exposure, various types of exposures (eg, shade/partial shade/sunlight), and the way patients described their exposures in their diaries used for the trials.


- **Patient population/planned enrollment:** Ambulatory patients with EPP (n = 115)
- **Study design:** Observational, single-arm, longitudinal, observational study of the safety and efficacy of 1023 afamelanotide implants over a period of up to 8 years at a porphyria center in Rome, Italy, and another in Zurich, Switzerland
- **Primary outcome and secondary outcomes:** Meeting patient expectations for symptom improvement, discontinuations, quality of life, and adverse events
- **Results presented by study authors:** “Since the treatment first became available in 2006, the number of patients treated with 16 mg afamelanotide implants rose continuously until June 2014, when 66% of all patients with EPP known to the porphyria centers were treated. Only three patients considered afamelanotide did not meet their expectations for symptom improvement; 23% discontinued the treatment for other, mostly compelling, reasons such as pregnancy or financial restrictions. The quality of life (QoL) scores, measured by an EPP-specific questionnaire, were 31 ± 24% of maximum prior to afamelanotide treatment, rose to 74% after starting afamelanotide and remained at this level during the entire observation period. Only minor adverse events attributable to afamelanotide, predominantly nausea, were recorded.”
Manufacturers and Regulatory Status

Afamelanotide is manufactured by Clinuvel Pharmaceuticals Ltd (Melbourne, Australia) and was approved by FDA on October 8, 2019, for increasing pain-free light exposure in adults with a history of phototoxic reactions from EPP. FDA had granted afamelanotide Fast Track designation in July 2016 and Orphan Drug designation in 2008, and the agency reviewed the New Drug Application for afamelanotide under its Priority Review program.

Cost Information

According to a US-based online aggregator of prescription prices, GoodRx, afamelanotide’s retail price is about $40,000 for a single implant (as of May 1, 2020), yielding an annual cost of about $240,000.

One UK-based cost-effectiveness study projected that afamelanotidet was cost effective considering the country’s pricing, disease burden, and societal perspectives; over a lifespan time horizon; and with discount rates of 3.5% per annum for costs and benefits. The investigators reported that the base case lifetime disability-adjusted life-years (DALYs) averted with afamelanotide treatment was 1.87 and the incremental cost-effectiveness ratio was £373,000 per DALY averted. The investigators used hereditary angioedema as a benchmark condition, which had an incremental cost-effectiveness ratio of £401,000 per quality-adjusted life-year gained.

Key Stakeholder Perspectives

Six stakeholders, reflecting clinical, nursing, research, and health systems perspectives, provided comments and ratings on afamelanotide. The list below summarizes key stakeholder perspectives.

- Afamelanotide is a clinically effective and well-tolerated option for treating EPP that increases patients’ tolerance to sun exposure, improving quality of life. But the treatment does not cure the disease, thus still requiring patients to regulate their sun exposure to avoid acute attacks.
- Afamelanotide would disrupt treatment paradigms by requiring patients to travel to a specialist’s health care facility for treatment every 2 months for a new implant. Effective treatment might also reduce demands on the system because of fewer hospitalizations.
- Afamelanotide’s high cost might cause health disparities in patients with public insurance or who are uninsured or underinsured.
- Additional longer-term studies are needed to determine afamelanotide’s impact on quality of life, acute attacks, duration of effects, tolerability, and cost-effectiveness.
Apremilast (Otezla) to Treat Behçet Disease

**Highlights**

- Apremilast (Otezla) is an oral small-molecule drug that targets inflammation processes and was approved by FDA in July 2019 for treating Behçet disease–associated oral ulcers.
- Other treatment options for Behçet-associated ulcers are linked to toxicity and suboptimal efficacy.
- Although apremilast is less expensive than injectable tumor necrosis factor (TNF) inhibitors, it is substantially more expensive than generic agents like azathioprine.
- Stakeholders thought apremilast’s high cost (about $45 000 annually) might cause health disparities for patients without insurance, those whose insurance does not cover it, or those who have significant copays, but they thought apremilast’s oral route of administration might make the drug more accessible to some patients because it does not require self-injection.
- Stakeholders thought that apremilast is a clinically effective and well-tolerated option for treating oral ulcers and pain due to Behçet disease, but they highlighted the need for longer-term trials to compare the drug with standard of care.

**Patient Population**

Apremilast is indicated for adults aged 18 years or older with oral ulcers associated with Behçet disease.

**Intervention**

Apremilast is a small-molecule inhibitor of phosphodiesterase type 4, an intracellular signaling molecule responsible for converting the second messenger cyclic adenosine monophosphate (activated state) to adenosine monophosphate (inactivated state). Apremilast’s inhibition of phosphodiesterase type 4 promotes increases in intracellular cyclic adenosine monophosphate, which leads to decreased expression of proinflammatory mediators, such as TNF-α, interleukin (IL)-17, and IL-23.373

Blood vessel inflammation is a characteristic of Behçet disease. Investigators suspect this inflammation is linked to overactive Th17 cells, which produce IL-17 in response to inflammation, suggesting that apremilast might alleviate Behçet disease symptoms.374 In clinical trials, apremilast is administered orally as 30-mg tablets, twice daily.

The National Organization for Rare Disorders website offers more information on Behçet disease.

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified one ongoing trial for this topic. We present this trial in Table 5.4.
Table 5.4. Ongoing Clinical Trial

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Phase 3 Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of Apremilast (CC-10004) in Subjects With Active Behcet’s Disease (RELIEF) NCT02307513</td>
<td>Adults aged 18 years or older (n = 208) with Behçet disease and active oral ulcers that did not respond to previous treatment with at least one nonbiologic agent, such as a topical glucocorticoid or systemic treatment. Active oral ulcers are defined as 2 or more oral ulcers at the screening visit and 2 or more oral ulcers at random assignment to treatment, when randomization occurred at least 14 days after screening; or 2 or more oral ulcers at the screening visit and 3 or more oral ulcers at randomization, when randomization occurred at any time between 1 and 42 days after screening</td>
<td>Phase III, randomized, double-blind, placebo-controlled, parallel-assignment crossover study of the safety and efficacy of apremilast 30 mg, twice daily, for 52 weeks compared with placebo</td>
<td>Primary completion September 2017 Study completion March 2021</td>
</tr>
</tbody>
</table>

Recently Completed and Ongoing Trials With Available Results

Our searches identified one recently completed late-phase trial with published results.375 We summarize this study with results as written in an abstract of the published study.

The following abbreviations are used in this section: AUC, area under the curve; CI, confidence interval; PGA, physician global assessment; QOL, quality of life.

A Phase 3 Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of Apremilast (CC-10004) in Subjects With Active Behcet’s Disease (RELIEF). NCT02307513. Hatemi et al 2019.375

- **Patient population/planned enrollment:** Adults (n = 208) aged 18 years or older with Behçet disease and active oral ulcers that did not respond to previous treatment with at least one nonbiologic agent, such as a topical glucocorticoid or systemic treatment
- **Study design:** Phase III, randomized, parallel-assignment trial to evaluate the efficacy and safety of apremilast 30 mg twice daily versus placebo

Abbreviations: AEs, adverse events; PGA, physician global assessment; QOL, quality of life.
• **Primary outcome**: Oral ulcers at 12 weeks

• **Secondary outcomes**: Complete response rate for oral ulcers at 6 and 12 weeks, pain of oral ulcers, complete response rate for genital ulcers, pain of genital ulcers, disease activity, Behçet’s disease QOL score, Behçet’s Syndrome Activity Score, time to complete response of oral ulcers, no oral ulcers, time to recurrence of oral ulcers, static PGA of skin lesions at 12 weeks, and treatment emergent adverse events at 12 and 52 weeks

• **Results presented by study authors**: “A total of 207 patients underwent randomization (104 patients to the apremilast group and 103 to the placebo group). The AUC for the number of oral ulcers was 129.5 for apremilast, as compared with 222.1 for placebo (least-squares mean difference, -92.6; 95% confidence interval [CI], -130.6 to -54.6; P<0.001). The change from baseline in the Behçet’s Disease Quality of Life score was -4.3 points in the apremilast group, as compared with -1.2 points in the placebo group (least-squares mean difference, 3.1 points; 95% CI, -4.9 to -1.3). Adverse events with apremilast included diarrhea, nausea, and headache.”

**Manufacturers and Regulatory Status**

Apremilast is manufactured by Amgen Inc (Thousand Oaks, CA). It had been developed by Celgene Corp (Summit, New Jersey), which was acquired by Bristol-Myers Squibb (New York, New York) in November 2019. A requirement of this acquisition was divestiture of rights to Otezla, which were sold to Amgen in November 2019.

FDA approved apremilast for oral ulcers associated with Behçet disease on July 19, 2019. FDA had approved the drug for treating psoriatic arthritis in March 2014, and in September 2014 expanded the indication to include treating plaque psoriasis.

**Cost Information**

According to Drugs.com, an online medicine information aggregator, a 30-day supply of 60 apremilast 30-mg tablets costs about $3760 (as of May 1, 2020).

**Key Stakeholder Perspectives**

Six stakeholders, reflecting caregiver, clinical, nursing, and research perspectives, provided comments and ratings on apremilast. The list below summarizes key stakeholder perspectives.

- Apremilast is a clinically effective and well-tolerated option for treating oral ulcers and pain due to Behçet disease.
- Additional, longer-term studies are needed to determine apremilast’s efficacy compared with TNF inhibitors and immunosuppressive agents.
- Apremilast’s high cost may create disparities for insured patients who have high copayments and deductibles or do not qualify for copayment assistance programs.
- Apremilast’s oral route of administration might improve access to treatment for patients who are unable to or do not want to self-inject TNF inhibitors.
Arimoclomol (BRX-345) to Treat Niemann-Pick Disease Type C

**Highlights**

- Arimoclomol (BRX-345) is an oral small-molecule drug intended to treat Niemann-Pick disease type C (NPC) by amplifying the production of heat shock proteins (HSPs) that purportedly rescue misfolded proteins and clear abnormal protein collections, which would improve liposome function and slow disease progression.
- No cure or effective treatment is available for NPC, a rare progressive disease associated with mental and physical disability in infants and adults.
- Stakeholders commenting on this topic thought that, as a disease-modifying drug, arimoclomol might improve patient health outcomes and improve quality of life for patients with NPC and their caregivers.
- Stakeholders also thought that, if effective, arimoclomol might reduce the long-term cost to the patient and health care system by reducing hospitalizations and providing better disease management for these patients, who often suffer from disability and have poor survival.

**Patient Population**

Arimoclomol is intended for children aged 2 to 17 years with NPC subtypes NPC1 or NPC2.

**Intervention**

NPC is a rare, genetic, progressive disease characterized by abnormal accumulations of fats (cholesterol and other lipids) in the liver, spleen, lungs, or brain, which can eventually cause cell death in these tissues. NPC is caused by variations in the Niemann-Pick disease genes, either NPC1 or NPC2. These variant genes produce proteins that impair normal trafficking of fats related to lysosomes and endosomes in cells.\(^{386}\)

Signs and symptoms of NPC include difficulty with walking, motor coordination, swallowing, and eating; excessive muscle contractions or eye movements; recurrent pneumonia; and sleep disturbances.\(^{387}\) Age of onset spans infancy to adulthood. Symptoms vary widely and can be fatal. No known cure is available or approved for NPC, and therapies are needed.\(^{386}\) The Mayo Clinic website offers [more information about Niemann-Pick disease](https://www.mayoclinic.org/diseases-conditions/niemann-pick-disease/symptoms-causes/syc-20370548).

Arimoclomol is a small-molecule amine intended to treat NPC. It purportedly acts by amplifying and stabilizing heat shock factor 1 (HSF1), a transcription factor that regulates the production of HSPs in physiologically stressed cells. HSPs purportedly correct and promote recycling of misfolded or inappropriately aggregated proteins in cells. In NPC, abnormally folded and aggregated proteins contribute to abnormal lipid accumulation in affected cells. Arimoclomol purportedly decreases the presence of abnormal proteins in NPC, ultimately decreasing cellular stress and cell death contributing to NPC disease progression.\(^{388}\)

In the latest clinical trial, arimoclomol was given orally 3 times daily at a weight-based dose of 150 to 600 mg/day.

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified a single ongoing trial for this topic. We present this trial in Table 5.5.
### Table 5.5. Ongoing Clinical Trial

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arimoclomol Prospective Study in Patients Diagnosed With NPC NCT02612129</td>
<td>Children aged 2 to 17 years and adults aged 18 years (n = 50) with diagnosed NPC due to variants in the NPC1 or NPC2 genes with at least one active neurological symptom</td>
<td>Phase II/III, randomized, parallel-assignment, placebo-controlled study to assess the efficacy and safety of arimoclomol as an add-on therapy to standard care. Patients were randomly assigned to receive arimoclomol capsules orally 3 times daily at a dose of 150 to 600 mg/day (weight based) or matching placebo capsules. Primary outcome: Change in NPC disease severity score at 12 months Secondary outcomes: • Motor coordination/function change from baseline at 6, 12, 18, and 24 months • CGI change from baseline at 6, 12, 18, and 24 months • QoL change from baseline at 6, 12, 18, and 24 months</td>
<td>Primary completion June 2018 Study completion October 2020</td>
</tr>
</tbody>
</table>

Abbreviations: CGI, Clinical global impression; NPC, Niemann-Pick disease type C; QoL, quality of life.

### Recently Completed and Ongoing Trials With Available Results

Our searches identified a single relevant, recently completed late-phase trial with published results. We summarize this study with results as written in a news release.

**Arimoclomol Prospective Doubleblind, Randomised, Placebo-Controlled Study in Patients Diagnosed With Niemann-Pick Disease Type C.** NCT02612129. Orphazyme 2019.

- **Patient population/planned enrollment:** Children aged 2 to 17 years and adults aged 18 years (n = 50) diagnosed with Niemann-Pick disease type C due to variants in the NPC1 or NPC2 genes with at least one active neurological symptom
- **Study design:** Phase II/III, randomized, parallel-assignment, placebo-controlled study to assess the efficacy and safety of arimoclomol as an add-on therapy to standard care. Patients were randomly assigned to receive arimoclomol capsules orally 3 times daily at a dose of 150 to 600 mg/day (weight based) or matching placebo capsules.
- **Primary outcome:** Disease severity from baseline to 12 months as measured by the Niemann-Pick disease type C Clinical Severity Scale
- **Secondary outcomes:** Motor coordination/function change from baseline at 6, 12, 18, and 24 months; clinical global impression change from baseline at 6, 12, 18, and 24 months; and quality-of-life change from baseline at 6, 12, 18, and 24 months
- **Results presented by study authors:** “Treatment with arimoclomol adjunct to routine clinical care resulted in a 74% reduction in disease progression (p-value =0.0506) as measured by the primary endpoint, 5-domain Niemann-Pick disease type C Clinical Severity Scale (NPC-CSS). In the predefined subgroup of patients of 4 years and older (44 out of 50 randomized patients in the trial), the treatment difference was statistically significant with a minimal disease progression at month 12 in the arimoclomol-treated group (p-value
A highly statistically significant treatment difference was observed in another predefined subgroup analysis, requested by the European Medicines Agency (EMA), that compared arimoclomol to placebo control in patients receiving miglustat as a part of routine clinical care (p-value = 0.0071)." 

Manufacturers and Regulatory Status

Orphazyme A/S (Copenhagen, Denmark), which licensed rights from developer CytRx Corp (Los Angeles, California), is evaluating arimoclomol for NPC. The drug is in phase II/III development. Orphazyme announced plans to submit a New Drug Application to FDA in the first half of 2020.\textsuperscript{390} Arimoclomol for treating NPC received FDA Fast Track designation in June 2016\textsuperscript{391} and Orphan Drug designation in January 2015.\textsuperscript{392} It is also being developed for amyotrophic lateral sclerosis (ALS), Gaucher disease, and inclusion body myositis.

Cost Information

Cost information is unavailable for this topic, but arimoclomol is likely to be of high cost if approved as the first therapy to treat NPC.

Key Stakeholder Perspectives

Eight stakeholders, reflecting clinical, nursing, health systems, and research perspectives, provided comments and ratings on arimoclomol for treating NPC.\textsuperscript{393-400} The list below summarizes key stakeholder perspectives.

- Arimoclomol might improve patient health outcomes and quality of life by delaying disease progression and fatal reactions associated with NPC.
- Slowing disease progression (ie, mental and physical disability symptoms) could substantially decrease the burden on caregivers and the health care system.
- No treatments are approved for treating NPC. However, patients can be given miglustat off label; data are limited to comparing the drugs’ safety and efficacy at this point.
- Larger and longer-term studies are needed to evaluate the effectiveness of arimoclomol and side effects of the HSP lifecycle.

CAP-1002 to Treat Duchenne Muscular Dystrophy

Highlights

- CAP-1002 is an allogeneic cell therapy derived from donor human heart tissue given intravenously every 3 months that purportedly acts as an immunomodulator to decrease inflammation and muscle degeneration and promote muscle regeneration in patients with Duchenne muscular dystrophy (DMD).
- CAP-1002 is intended for all patients with DMD, whereas 2 disease-modifying therapies for DMD approved by FDA in recent years are available only to subsets of patients with specific genetic variants in the \textit{DMD} gene.
- Stakeholders commenting on this topic thought that CAP-1002 would significantly increase health care costs because it is expensive and requires infusions every 3 months.
- Stakeholders also thought that CAP-1002 could disrupt the current paradigm of patient care because of the clinician learning curve required to use it and its anticipated side effects and adverse event risks.
**Patient Population**

CAP-1002 is intended to treat males aged 10 years or older who have genetically confirmed DMD, are either ambulatory or nonambulatory, and are receiving stable doses of systemic glucocorticoids.

**Intervention**

CAP-1002 is a cell-based therapy intended for DMD, an inherited, chromosome X–linked genetic disorder caused by mutations or deletions in the dystrophin gene, DMD. DMD encodes the dystrophin protein, which helps promote muscle function. The absence of wild-type (ie, naturally produced) dystrophin protein causes progressive muscle fiber necrosis and eventual widespread muscle weakness. The Muscular Dystrophy Association website offers more information about DMD.

No cure for DMD exists, and first-line corticosteroid treatment addresses symptoms but does not prevent disease progression and has significant side effects. FDA has approved 2 gene therapies for patients who have specific mutations in DMD (ie, in exon 51 or 53); however, patients who have other DMD mutations do not qualify. Therefore, novel therapies for treating DMD are needed.

CAP-1002 consists of cardiosphere-derived cells (CDCs) from donor heart tissue. The CDCs in CAP-1002 purportedly secrete growth factors and exosomes that promote cellular regeneration by altering immune system activity.

Data from a completed phase I/II trial (ie, HOPE, NCT02485938), which enrolled patients with DMD-associated cardiomyopathy, suggest that a solution of CAP-1002 containing 75 million CDCs delivered directly into the heart improves both cardiac muscle and skeletal muscle function. Based on the systemic (ie, noncardiac) effects observed in this trial, further studies are delivering CAP-1002 by standard intravenous infusion.

In the ongoing phase II HOPE-2 clinical trial (Table 5.6), a solution of CAP-1002 containing 150 million CDCs is given intravenously once every 3 months, 4 times.

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified one ongoing trial for this topic. We present this trial in Table 5.6.
Table 5.6. Ongoing Clinical Trial

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Safety and Efficacy of Intravenous Delivery of Allogeneic Cardiosphere-Derived Cells in Subjects With Duchenne Muscular Dystrophy (HOPE-2) NCT03406780</td>
<td>Male children aged 10 years or older and adults (n = 18) who have genetically confirmed DMD, are ambulatory or nonambulatory, and are receiving stable doses of systemic glucocorticoids</td>
<td>Phase II, randomized, double-blind, parallel-assignment study to evaluate the safety and efficacy of CAP-1002 Patients were randomly assigned in a 1:1 ratio to receive CAP-1002 (150 million CDCs) via intravenous infusion, every 3 months for a total of 4 doses, or matching placebo Primary outcome: Change in the midlevel (elbow) dimension of the PUL 2.0 clinical scale, from baseline to month 12 Secondary outcomes: Change in the midlevel (elbow) dimension of the PUL 2.0 clinical scale, from baseline to months 3, 6, and 9 Change in regional systolic left ventricular wall thickening, as assessed by cardiac MRI, from baseline to months 6 and 12</td>
<td>Primary and study completion April 2020</td>
</tr>
</tbody>
</table>

Abbreviations: CDCs, cardiosphere-derived cells; DMD, Duchenne muscular dystrophy; MRI, magnetic resonance imaging; PUL, Performance of the Upper Limb.

Recently Completed and Ongoing Trials With Available Results

Our searches identified one recently completed late-phase trial with published results. We summarize this study with results as written in a news release.

The following abbreviations are used in this section: CDCs, cardiosphere-derived cells; DMD, Duchenne muscular dystrophy; MRI, magnetic resonance imaging; PUL, Performance of the Upper Limb.


- **Patient population/planned enrollment**: Male children aged 10 years or older and adults (n = 18) who have genetically confirmed DMD, are either ambulatory or nonambulatory, and are receiving stable doses of systemic glucocorticoids
- **Study design**: Phase II, randomized, double-blind, parallel-assignment study to evaluate the efficacy of CAP-1002 versus placebo. Patients were randomly assigned in a 1:1 ratio to receive CAP-1002 (150 million CDCs) via intravenous infusion, every 3 months for a total of 4 doses, or matching placebo.
- **Primary outcome**: Change in the midlevel (elbow) dimension of the PUL 2.0 clinical scale, from baseline to month 12
- **Secondary outcomes**: Change in the midlevel (elbow) dimension of the PUL 2.0 clinical scale, from baseline to months 3, 6, and 9; and change in regional systolic left ventricular wall thickening, as assessed by cardiac MRI, from baseline to months 6 and 12
• **Results presented by study authors:** Data reported in a table in the news release are summarized below:

<table>
<thead>
<tr>
<th></th>
<th>High/mid/distal</th>
<th>Mid/distal</th>
<th>Mid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PUL 2.0 score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CAP-1002</strong></td>
<td>0.5 (1.7)</td>
<td>0.4 (1.3)</td>
<td>0.1 (1.0)</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>–1.2 (1.7)</td>
<td>–0.4 (0.7)</td>
<td>–0.4 (0.5)</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>.06</td>
<td>.10</td>
<td>.22</td>
</tr>
</tbody>
</table>

\[\text{mean change from baseline at 3 months (SD)}\]

<table>
<thead>
<tr>
<th></th>
<th>High/mid/distal</th>
<th>Mid/distal</th>
<th>Mid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PUL 2.0 score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CAP-1002</strong></td>
<td>–0.3 (0.5)</td>
<td>0.2 (1.5)</td>
<td>–0.2 (1.2)</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>–2.3 (1.5)</td>
<td>–1.4 (0.9)</td>
<td>–1.1 (1.0)</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>.03</td>
<td>.02</td>
<td>.06</td>
</tr>
</tbody>
</table>

\[\text{mean change from baseline at 6 months (SD)}\]

**Manufacturers and Regulatory Status**

CAP-1002 is being developed by Capricor Therapeutics Inc (Beverly Hills, California) and is in phase II clinical development for treating DMD. For this indication, FDA granted the drug Orphan Drug designation in April 2015,\(^{406}\) Rare Pediatric Disease designation in July 2017,\(^{407}\) and Regenerative Medicine Advanced Therapy designation in February 2018.\(^{408}\)

In December 2018, Capricor Therapeutics placed a voluntary dosing hold on the ongoing HOPE-2 trial (NCT03406780) after a patient enrolled in the trial experienced a severe allergic reaction during drug infusion.\(^{409}\) The patient fully recovered from the event, and HOPE-2 trial dosing resumed in February 2019.\(^{410}\)

**Cost Information**

Cost information is unavailable for this topic, but stakeholders expected it to be costly (eg, priced similarly to other recently approved therapies for DMD).

**Key Stakeholder Perspectives**

Nine stakeholders, reflecting caregiver, clinical, health systems, patient representative, and research perspectives, provided comments and ratings on CAP-1002 for treating DMD.\(^{411-419}\) The list below summarizes key stakeholder perspectives.

- CAP-1002 has moderate to large potential to improve patient health outcomes, based on signs of efficacy observed in the HOPE and HOPE-2 trials; however, the trials were
small and outcomes were limited to upper limb function, and CAP-1002 demonstrated limited additional efficacy versus placebo.

- CAP-1002 will increase health care costs because it is expensive and requires infusions every 3 months.
- The intravenous delivery of CAP-1002 every 3 months could create barriers to patient access to treatment, might increase health disparities, and might disrupt the health care delivery system as more patients need to travel to infusion centers rather than taking current standard-of-care comparator corticosteroids at home (assuming most patients do not have access to home infusions).
- CAP-1002 might disrupt the current paradigm of patient care due to the clinician learning curve required to use it and its anticipated side effects and adverse event risks.

Casimersen to Treat Duchenne Muscular Dystrophy

**Highlights**

- Casimersen is a phosphorodiamidate morpholino oligomer (PMO) given intravenously that purportedly binds exon 45 of dystrophin pre-messenger RNA (pre-mRNA) and promotes skipping of exon 45 during mRNA processing to allow the synthesis of an internally truncated but functional dystrophin protein in patients with Duchenne muscular dystrophy (DMD).
- This intervention is intended for a subset of patients with DMD, about 9%, who have a mutation in the dystrophin gene, \( DMD \), amenable to exon 45 skipping.
- Treatment with casimersen requires weekly infusions in a health care setting.
- Stakeholders generally agreed that casimersen has potential to improve patient health outcomes and quality of life, but more data are needed to determine its clinical efficacy and potential impact on patient-centered outcomes.
- Stakeholders also thought casimersen might be cost prohibitive and controversial for use if effects are evident only after years of treatment.

**Patient Population**

Casimersen is intended for males aged 7 to 23 years who have DMD with an exon 45 rearrangement in the \( DMD \) gene and who are on a stable dose of corticosteroids.

**Intervention**

Casimersen, also known as SRP-4045, is a PMO intended for treating DMD, an inherited, chromosome X–linked genetic disorder caused by point mutations or deletions in the \( DMD \) gene. \( DMD \) encodes dystrophin, a protein that helps promote muscle function. In patients with DMD, the absence of wild-type dystrophin protein causes progressive muscle fiber death and eventual widespread muscle weakness.\(^4^0^1\) No cure for DMD is available, and while FDA has approved a dystrophin-replacement gene therapy for patients who have a specific mutation in \( DMD \) (ie, in exon 51), the therapy is not suitable for patients with other mutations.

Casimersen purportedly binds exon 45 of dystrophin pre-mRNA (precursor RNA composed of introns and exons) and promotes skipping of exon 45 during mRNA processing, which allows synthesis of an internally truncated but functional dystrophin protein.\(^9^2^0\) Therefore, casimersen treatment may promote skeletal muscle function and prevent or delay
In clinical trials, intravenous casimersen 30 mg/kg is given once weekly for up to 144 weeks. The Muscular Dystrophy Association website provides more information on DMD.

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified 2 ongoing trials for this topic. We present these trials in Table 5.7.

**Table 5.7. Ongoing Clinical Trials**

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Double-Blind, Placebo-Controlled, Multi-center Study With an Open-Label Extension to Evaluate the Efficacy and Safety of SRP4045 and SRP-4053 in Patients With Duchenne Muscular Dystrophy (ESSENCE) NCT02500381</td>
<td>Male children (n = 222) aged 7 to 13 years with genetically confirmed DMD who have a mutation in the DMD gene that is amenable to exon 45 or 53 skipping and who are on a stable dose of corticosteroids</td>
<td>Phase III, randomized, double-blind, parallel-assignment study to evaluate the efficacy and safety of casimersen (SRP-4045) 30 mg/kg and golodirsen (SRP-4053) 30 mg/kg versus placebo. The double-blind period will be followed by an open-label extension period, in which all patients will receive active treatment for 48 weeks (up to week 144 of study). Primary outcome: 6-minute walk test distance at baseline and week 96. Secondary outcomes:</td>
<td>Primary completion May 2022 Study completion May 2023</td>
</tr>
<tr>
<td>See preliminary results by Sarepta Therapeutics under Recently Completed and Ongoing Trials With Available Results</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

See preliminary results by Sarepta Therapeutics under Recently Completed and Ongoing Trials With Available Results.
Recently Completed and Ongoing Trials With Available Results

Our searches identified one relevant, recently completed late-phase trial with published results.\textsuperscript{422} We summarize this study with results as written in a news release.

The following abbreviations are used in this section: DMD, Duchenne muscular dystrophy; FVC, forced vital capacity; IHC, immunohistochemistry; mRNA, messenger RNA; NSAA, North Star Ambulatory Assessment; SAE, serious adverse event; WB, Western blot.

A Double-Blind, Placebo-Controlled, Multi-center Study With an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients With Duchenne Muscular Dystrophy (ESSENCE), \textbf{NCT02500381}. Sarepta Therapeutics 2019.\textsuperscript{422}

- **Patient population/planned enrollment:** Children (n = 222) aged 7 to 13 years with genetically confirmed DMD who have a mutation in the \textit{DMD} gene that is amenable to exon 45 or 53 skipping and who are on a stable dose of corticosteroids
- **Study design:** Phase III, randomized, double-blind, parallel-assignment study to evaluate the efficacy and safety of casimersen (SRP-4045) 30 mg/kg and golodirsen (SRP-4053) 30 mg/kg versus placebo
- **Primary outcome:** 6-minute walk test distance at baseline and week 96
- **Secondary outcomes:** Dystrophin expression at baseline and weeks 48 or 96, as measured by IHC and WB; ability to rise independently from the floor at week 96; time to loss of ambulation at week 96; ambulatory function at baseline and week 96, as measured by NSAA; and FVC percentage predicted at baseline and week 96
- **Results presented by study authors:** Patients amenable to exon 45 skipping were randomized to receive a once-weekly intravenous (IV) infusion of casimersen dosed at 30mg/kg (n=27) or placebo (n=16) for 96 weeks. The interim analysis was performed on data from biopsies of the bicep muscle at baseline and on-treatment at Week 48. Key findings from the interim analysis include:
  - In the casimersen arm, mean dystrophin protein (% normal dystrophin as measured by Western blot) increased to 1.736% of normal compared to a mean baseline of 0.925% of normal (p<0.001).
  - A statistically significant difference in the mean change from baseline to week 48 in dystrophin protein was observed between the casimersen-treated arm compared to the placebo arm (p=0.009).
  - Of the 22 patients receiving casimersen who have been tested for increased exon-skipping mRNA using reverse transcription polymerase chain reaction (RT-PCR), all have
displayed an increase in skipping exon 45 (p<0.001) over their baseline levels, representing a 100% response rate.
  o A statistically significant positive correlation between exon 45 skipping and dystrophin production was observed (Spearman rank correlation = 0.635, p<0.001).

The study is ongoing and remains blinded to collect additional efficacy and safety data."

Note: Data from only the casimersen (SRP-4045) and placebo arms of the trial were included in the news release.

**Manufacturers and Regulatory Status**

*Sarepta Therapeutics Inc (Cambridge, Massachusetts)* is developing casimersen to treat DMD. The drug is in phase III clinical development for this indication. In August 2019, Sarepta Therapeutics announced that it planned to submit in the first half of 2020 a New Drug Application for casimersen to treat DMD.423

In November 2019, Sarepta Therapeutics announced that, before pursuing regulatory approval for casimersen, it intended to address issues outlined in a Complete Response Letter from FDA regarding its New Drug Application for golodirsen, also in development for treating DMD.424 The developer announced golodirsen’s FDA approval in December 2019 but did not provide an update on its timeline for submitting a New Drug Application to FDA for casimersen.425

FDA granted the drug Orphan Drug designation for this indication in June 2019.426

**Cost Information**

Cost information is unavailable for this topic, but stakeholders expect the therapy to be costly (eg, priced similarly to other recently approved therapies for DMD).

**Key Stakeholder Perspectives**

Eight stakeholders, reflecting physical therapy, caregiver, clinical, research, and health systems perspectives, provided comments and ratings on casimersen.427-434 The list below summarizes key stakeholder perspectives.

- An increase in functional dystrophin production is theoretically likely to improve patient health outcomes and quality of life by slowing disease progression, and casimersen demonstrates efficacy in increasing functional dystrophin production, but more data are needed to determine what magnitude of increase in dystrophin production is clinically significant and whether casimersen reaches that threshold.
- The weekly infusions required for treatment with casimersen might disrupt patients’ lives and the paradigm of patient care, increase health care resource use related to the infusions, and increase health disparities because it might not be feasible for some patients to undergo the weekly infusions.
- The cost of casimersen will likely be high, its diffusion into clinical use might be cost prohibitive, and its use at a high cost might be controversial if its effects become evident only years after treatment.
- More data are needed to assess long-term efficacy of casimersen and should include outcomes that are more patient centered than dystrophin protein production.
**Crizanlizumab-tmca (Adakveo) to Prevent Vaso-occlusive Crises in Sickle Cell Disease**

**Highlights**
- Crizanlizumab-tmca (Adakveo) is a humanized monoclonal antibody approved by FDA and intended to reduce the frequency of painful vaso-occlusive crises (VOCs) in sickle cell disease (SCD).
- The therapy is given by monthly intravenous injections delivered in a sickle cell treatment center.
- Crizanlizumab-tmca has an average retail cost of about $100,000 per year.
- Stakeholders commenting on this intervention thought crizanlizumab-tmca could have a moderate to large improvement on outcomes by reducing painful crises by almost 50% per year.
- Stakeholders thought patients of lower socioeconomic status might have difficulty accessing the therapy due to its high cost and need for monthly intravenous infusions.

**Patient Population**
Crizanlizumab-tmca is indicated for patients aged 16 years or older to reduce the frequency of VOCs in people with SCD.

**Intervention**
Inherited SCD-inducing genetic rearrangements alter the shape of hemoglobin molecules, resulting in sickled red blood cells that are more susceptible to oxidative damage, inappropriate clumping (ie, adhesion), and vessel blockage, leading to severely painful VOCs, requiring hospitalization. The National Institutes of Health’s National Heart, Lung, and Blood Institute website offers more information on SCD.

VOCs are thought to be associated with several processes, including chronic inflammation, erythrocyte (ie, red blood cell) microvascular occlusion, impaired oxygen supply, and infarction-reperfusion injury. SCD progresses with age, and with it the frequency of VOCs and complications and an increasing risk of death. Patients may progress to thromboembolic events (ie, blood clots), stroke, organ failure, or early death.

An FDA-approved treatment for SCD, hydroxyurea, can reduce VOC incidence, but it is ineffective in about one-third of adult patients. Another FDA-approved treatment for SCD, L-glutamine (Endari), has not been proved to significantly reduce the frequency of sickle cell crises or related hospital visits, according to a negative opinion offered by the European Medicines Agency in May 2019.

Crizanlizumab-tmca is a humanized monoclonal antibody against P-selectin, blocking P-selectin’s interaction with glycoprotein ligand 1. P-selectin is expressed on the surface of endothelial cells and platelets and is thought to promote the inflammatory and adhesion processes involved in VOC. Crizanlizumab-tmca is administered by intravenous infusion at a dosage of 5 mg/kg over a period of 30 minutes on weeks 0 and 2, and every 4 weeks thereafter.
Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 3 ongoing trials for this topic. We present these trials in Table 5.8. (We excluded a phase II trial assessing the safety and pharmacokinetics and pharmacodynamics of crizanlizumab-tmca with or without hydroxyurea to treat SCD in children aged 16 years or older and adults up to 70 years of age [NCT03264989].)

Table 5.8. Ongoing Clinical Trials

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study of Dose Confirmation and Safety of Crizanlizumab in Pediatric Sickle Cell Disease Patients [NCT03474965]</td>
<td>Pediatric patients (n = 100) aged 6 months to 17 years with SCD and history of VOCs</td>
<td>Phase II, multicenter, open-label, single-arm study to optimize dosing and assess crizanlizumab’s safety with or without hydroxyurea Primary outcomes: Pharmacokinetics, pharmacodynamics, and adverse events at day 15 Selected secondary outcomes: Rates of VOC and VOC leading to health care visit (clinic, emergency department, or hospital), both at 6 months and 2 years</td>
<td>Primary completion June 2021 Study completion September 2023</td>
</tr>
<tr>
<td>Study of Two Doses of Crizanlizumab Versus Placebo in Adolescent and Adult Sickle Cell Disease Patients (STAND) [NCT03814746]</td>
<td>Children and adolescents aged 12 years or older and adults (n = 240) with SCD and history of VOCs leading to health care visits</td>
<td>Phase III, randomized, double-blind, placebo-controlled study to compare the efficacy, safety, and tolerability of 2 doses of crizanlizumab-tmca (5.0 and 7.5 mg/kg) versus placebo with or without hydroxyurea Primary outcome: Rate of VOC events leading to a health care visit at 1 year Selected secondary outcomes: • Rates of all VOCs through 1 and 5 years • VOCs leading to health care visit (clinic, emergency department, or hospital) through 1 year • Time to first and second VOC leading to health care visit through 1 year • Percentage of patients free from VOCs leading to health care visits through 1 year</td>
<td>Primary completion May 2022 Study completion December 2027</td>
</tr>
</tbody>
</table>
### Study Exploring the Effect of Crizanlizumab on Kidney Function in Patients With Chronic Kidney Disease Caused by Sickle Cell Disease (STEADFAST)

**NCT04053764**

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Exploring the Effect of Crizanlizumab on Kidney Function in Patients With Chronic Kidney Disease Caused by Sickle Cell Disease (STEADFAST)</td>
<td>Children aged 16 years or older and adults (n = 170) with SCD and estimated eGFR between 45 and 120 (inclusive) mL/min/1.73 m²</td>
<td>Phase II, randomized, unblinded, parallel-assignment study comparing crizanlizumab-tmca 5 mg/kg intravenous infusion plus standard of care with standard of care alone for preserving kidney function in patients with SCD Primary outcome: Percentage of patients with a 30% or greater decrease in albuminuria through 1 year Selected secondary outcomes: • Mean change in albuminuria through 1 year • Percentage change in eGFR through 1 year • Percentage of patients with progression to chronic kidney disease • Annualized rate of emergency department visits and hospitalizations</td>
<td>Primary completion June 2022 Study completion October 2022</td>
</tr>
</tbody>
</table>

**Abbreviations:** eGFR, estimated glomerular filtration rate; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

### Recently Completed and Ongoing Trials With Available Results

Our searches identified one relevant, recently completed trial with results published in 2 reports. We summarize this study with results as written in the abstract of a published study and a conference abstract.

The following abbreviations are used in this section: CI, confidence interval; HR, hazard ratio; VOC, vaso-occlusive crisis.

**Study to Assess Safety and Impact of SelG1 With or Without Hydroxyurea Therapy in Sickle Cell Disease Patients With Pain Crises (SUSTAIN). NCT01895361. Ataga et al 2017.**

- **Patient population/planned enrollment:** Patients (n = 198) aged 16 to 65 years with sickle cell disease who had had 2 to 10 VOCs in the 12 months before enrollment; some patients were also receiving concomitant hydroxyurea
- **Study design:** Phase II, randomized, double-blind, parallel-assignment study comparing crizanlizumab 2.5 or 5.0 mg/kg with placebo for reducing sickle cell pain crises through 52 weeks
- **Primary outcome:** Annual rate of sickle cell pain crises
- **Secondary outcomes:** Annual rate of days hospitalized, rate of VOC by concomitant hydroxyurea use, and time to first and second VOC, all up to 1 year
- **Results presented by study authors:** "The median rate of crises per year was 1.63 with high-dose crizanlizumab versus 2.98 with placebo (indicating a 45.3% lower rate with high-dose crizanlizumab, P=0.01). The median time to the first crisis was significantly longer with high-dose crizanlizumab than with placebo (4.07 vs. 1.38 months, P=0.001), as was the median time to the second crisis (10.32 vs. 5.09 months, P=0.02). The median rate of uncomplicated crises per year was 1.08 with high-dose crizanlizumab, as compared with
2.91 with placebo (indicating a 62.9% lower rate with high-dose crizanlizumab, P=0.02). Adverse events that occurred in 10% or more of the patients in either active-treatment group and at a frequency that was at least twice as high as that in the placebo group were arthralgia, diarrhea, pruritus, vomiting, and chest pain.”

Study to Assess Safety and Impact of SelG1 With or Without Hydroxyurea Therapy in Sickle Cell Disease Patients With Pain Crises (SUSTAIN). NCT01895361. Ataga et al 2019.442

- **Patient population/planned enrollment:** Patients (n = 198) aged 16 to 65 years with sickle cell disease who had had 2 to 10 VOCs in the 12 months before enrollment; some patients were also receiving concomitant hydroxyurea
- **Study design:** Post hoc analysis of SUSTAIN data to better characterize the differences between the crizanlizumab 5 mg/kg arm and the placebo arm
- **Primary outcome:** Difference in annual rate of hospitalized days between the crizanlizumab 5 mg/kg arm and the placebo arm
- **Secondary outcomes:** Comparative distribution of hospitalizations and time to first hospitalization
- **Results presented by study authors:** “[Results were presented in tables.] A greater proportion of patients in the crizanlizumab arm (46%) were not hospitalized during the trial period (up to end of treatment) than in the placebo arm (35%). Correspondingly, the percentage of patients with ≥1 hospitalization was lower in the crizanlizumab (54%) than the placebo arm (65%). . . . The median time to first hospitalization was greater with crizanlizumab 5 mg/kg than with placebo (6.3 vs 3.2 months; hazard ratio [HR] 0.683 [95% CI 0.437-1.066]). The apparent improvement in time to first hospitalization is consistent with previously published SUSTAIN results regarding median time to first VOC leading to healthcare visit. Patients treated with crizanlizumab 5 mg/kg were found to experience a longer median time to first VOC leading to healthcare visit than patients on placebo (4.07 vs 1.38 months; HR 0.50 [95% CI 0.33-0.74]).”

Manufacturers and Regulatory Status

**Novartis AG (Basel, Switzerland)** manufactures crizanlizumab-tmca. On November 15, 2019, FDA approved crizanlizumab-tmca, under the trade name Adakveo, for reducing the frequency of VOCs in children aged 16 years or older and adults with SCD.440 FDA previously granted crizanlizumab-tmca Breakthrough Therapy and Priority Review designations for this indication.439,443

Cost Information

Novartis reportedly set crizanlizumab-tmca’s wholesale acquisition cost at $2357 per vial.444 Weight-based dosing assumes most patients will require 3 or 4 vials per single monthly treatment (after 2 doses during the first month).444 GoodRx, an aggregator of prescription pharmaceutical pricing at US retail pharmacies, lists US retail pharmacy prices of about $2333 to $2471 for a single 10-mL vial (as of January 23, 2020).445 This suggests an annual cost of about $84 000 to $118 600 (for 12 monthly doses) after a first-year cost of about $91 000 to $128 500 (for 13 doses).

Key Stakeholder Perspectives

Nine stakeholders, reflecting clinical, research, nursing, patient, caregiver, and health systems perspectives, provided comments and ratings on crizanlizumab-tmca to prevent vaso-occlusive crises in sickle cell disease.446-454 The list below summarizes key stakeholder perspectives.

- A new therapy with potential to reduce the frequency of painful vaso-occlusive crises by almost one-half could have a large impact on improving patient health outcomes and quality of life.
• Crizanlizumab-tmca’s high cost and monthly intravenous infusion requirement could increase disparities for patients without adequate insurance coverage or convenient access to a specialized sickle cell treatment center.
• Significantly reducing the incidence of vaso-occlusive crises could lower incidence of emergency department visits for this patient population.
• The need for monthly intravenous infusions would be a major shift in care from standard oral therapy with hydroxyurea (hydroxycarbamide) and/or L-glutamine, for both patients and providers.

Eculizumab (Soliris) to Treat Neuromyelitis Optica Spectrum Disorder

Highlights
• Eculizumab (Soliris) is a recombinant humanized monoclonal antibody that binds to the complement protein C5 (a soluble component of the innate immune system) to purportedly relieve the autoimmune and neurodegenerative symptoms of neuromyelitis optica spectrum disorder (NMOSD).
• Eculizumab is the first FDA-approved therapy to prevent unpredictable relapses due to NMOSD, which might improve quality of life and health outcomes in patients with positive anti-aquaporin-4 (AQP4) antibodies.
• Stakeholders commenting on this topic thought that eculizumab has potential to reduce the occurrence of autoimmune attacks and disability due to NMOSD. They were encouraged by the published data, which showed that adjudicated relapses occurred in only 3 of 96 patients in the eculizumab group.
• Stakeholders also thought that this intervention will likely increase health disparities due to its high cost, inconvenient dosing regimen, and whether insurers cover it. (Note: As of April 2020, major third-party payers had policies providing coverage for the labeled NMOSD indication and required preauthorization before it can be administered.)

Patient Population
Eculizumab is indicated for adults aged 18 years or older with NMOSD who test positive for the AQP4 antibody.

Intervention
NMOSD is a rare and debilitating autoimmune disorder that attacks the central nervous system (CNS), including the eyes, brain, and spinal cord. Patients experience unpredictable relapses that can irreversibly damage the brain and spinal column, causing long-term disability and symptoms including optic neuritis (visual problems including blindness) and transverse myelitis (mobility problems including paralysis).455 The National Institutes of Health’s National Institute of Neurological Disorders and Stroke website offers more information on NMOSD.

The complement system is thought to play a key role in NMOSD pathogenesis. In particular, autoantibodies against the water channel protein AQP4 are present in about 73% of patients with NMOSD. AQP4 is expressed by astrocytes in the CNS, and antibodies to AQP4 are thought to trigger the complement cascade, leading to astrocyte destruction and neuronal injury through complement-dependent cytotoxicity (CDC) and induction of inflammation.455,456

Eculizumab is a recombinant humanized monoclonal antibody that binds to the complement protein C5 and inhibits C5’s cleavage to C5a and C5b. C5a is proinflammatory, and C5b is
required to form the CDC-inducing membrane attack complex. By inhibiting the complement cascade, eculizumab purportedly relieves the autoimmune and neurodegenerative symptoms of neuromyelitis optica.\textsuperscript{457,458} Eculizumab is the first FDA-approved therapy for NMOSD.\textsuperscript{455} It is given intravenously at a dosage of 900 mg weekly for 4 weeks, followed by 1200 mg on week 5 and every 2 weeks thereafter.\textsuperscript{458}

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified a single ongoing trial for this topic. We present this trial in Table 5.9.

**Table 5.9. Ongoing Clinical Trial**

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>An Open Label Extension Trial of Eculizumab in Relapsing NMO Patients NCT02003144</td>
<td>Adults (n = 119) aged 18 years or older who completed the PREVENT trial (NCT01892345), which required that patients have AQP4-IgG seropositive NMOSD and a historical relapse rate of at least 2 relapses in the past 12 months or 3 relapses in the past 24 months with at least one relapse in the 12 months before the screening</td>
<td>Phase III, open-label, single-arm study to confirm the long-term safety and efficacy of eculizumab in patients with relapsing NMOSD who completed the double-blind, randomized, placebo-controlled trial NCT01892345 Primary outcomes: Safety and tolerability as measured by TEAEs and SAEs (vital signs, clinical laboratory tests, and suicide risk as assessed with C-SSRS), and change from baseline Secondary outcomes: Long-term efficacy, measured by annualized relapse rate, disability, quality of life, and neurologic function, and change from baseline up to 4 years</td>
<td>Primary and study completion June 2020</td>
</tr>
</tbody>
</table>

**Recently Completed and Ongoing Trials With Available Results**

Our searches identified 2 relevant, recently completed late-phase trials with published results.\textsuperscript{459,460} We summarize these 2 studies with results as written in abstracts of published studies.

The following abbreviations are used in this section: AQP4-IgG, aquaporin-4 immunoglobulin G; CI, confidence interval; EDSS, expanded disability status scale; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; SD, standard deviation.
A Randomized Controlled Trial of Eculizumab in AQP4 Antibody-Positive Participants With NMO (PREVENT). NCT01892345. Pittock et al 2019.459

- **Patient population/planned enrollment**: Patients (n = 143) aged 18 years or older with AQP4-IgG seropositive NMOSD and a historical relapse rate of at least 2 relapses in the past 12 months or 3 relapses in the past 24 months with at least one relapse in the 12 months before the screening
- **Study design**: In a randomized, quadruple-blind (participant, care provider, investigator, outcomes assessor) clinical trial, patients were assigned in a 2:1 ratio to treatment with either intravenous eculizumab (900 mg weekly for 4 weeks followed by 1200 mg every 2 weeks) or matched placebo
- **Primary outcome**: Median number of attacks per year from baseline to up to 211 weeks
- **Secondary outcomes**: Adjudicated annualized relapse rate and quality-of-life measures on EDSS
- **Results presented by study authors**: “The trial was stopped after 23 of the 24 prespecified adjudicated relapses, given the uncertainty in estimating when the final event would occur. The mean (±SD) annualized relapse rate in the 24 months before enrollment was 1.99±0.94; 76% of the patients continued to receive their previous immunosuppressive therapy during the trial. Adjudicated relapses occurred in 3 of 96 patients (3%) in the eculizumab group and 20 of 47 (43%) in the placebo group (hazard ratio, 0.06; 95% confidence interval [CI], 0.02 to 0.20; P<0.001). The adjudicated annualized relapse rate was 0.02 in the eculizumab group and 0.35 in the placebo group (rate ratio, 0.04; 95% CI, 0.01 to 0.15; P<0.001). The mean change in the EDSS score was -0.18 in the eculizumab group and 0.12 in the placebo group (least-squares mean difference, -0.29; 95% CI, -0.59 to 0.01). Upper respiratory tract infections and headaches were more common in the eculizumab group. There was one death from pulmonary empyema in the eculizumab group.”


- **Patient population/planned enrollment**: Patients (n = 14) aged 18 years or older with AQP4-IgG seropositive NMOSD who experienced at least 2 attacks in the preceding 6 months or 3 attacks in the previous 12 months
- **Study design**: In a single-arm trial, all patients received treatment with intravenous eculizumab at a dosage of 600 mg weekly for 4 weeks, 900 mg in the fifth week, and then 900 mg every 2 weeks for 48 weeks
- **Primary outcome**: Median number of attacks per year from baseline to 12 months and safety
- **Results presented by study authors**: “We enrolled 14 patients, all of whom were women. After 12 months of eculizumab treatment, 12 patients were relapse free; two had had possible attacks. The median number of attacks per year fell from three before treatment (range two to four) to zero (zero to one) during treatment (p<0.0001). No patient had worsened disability by any outcome measure. Median score on the expanded disability status scale improved from 4.3 (range 1.0-8.0) before treatment to 3.5 (0-8.0) during treatment (p=0.0078). Two patients improved by two points and three improved by one point on the Hauser score; no change was recorded for the other patients. Visual acuity had improved in at least one eye by one point in four patients, and by two points in one patient; no change was recorded for other patients. One patient had meningococcal sepsis and sterile meningitis about 2 months after the first eculizumab infusion, but resumed treatment after full recovery. No other drug-related serious adverse events occurred. Eight attacks in five patients were reported within 12 months of eculizumab withdrawal.”

Manufacturers and Regulatory Status

Alexion Pharmaceuticals Inc (Boston, Massachusetts) assessed eculizumab for treating NMOSD in adults who test positive for AQP4 antibodies. FDA approved Alexion’s Biologics License Application submission on June 27, 2019.455 FDA granted Orphan Drug designation to eculizumab for the NMOSD indication in June 2013.461 FDA had previously approved eculizumab for treating paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, and generalized myasthenia gravis.458
The prescribing information carries a black box warning regarding the potential for serious meningococcal infections and offers guidance on managing the risk for these infections, including use of meningococcal vaccines and/or antibacterial drug prophylaxis. Because of this potential adverse event, eculizumab is available only through a Risk Evaluation and Mitigation Strategy (REMS).458

Cost Information

The wholesale acquisition cost of eculizumab is reportedly about $6543 per 300-mg vial (as of December 21, 2018) or about $706 600 per year per patient (ie, 900 mg weekly for 4 weeks, followed by 1200 mg in week 5 and every 2 weeks thereafter, which totals about 108 vials per year).462

Key Stakeholder Perspectives

Nine stakeholders, reflecting clinical, nursing, health systems, patient, and research perspectives, provided comments and ratings on eculizumab to treat relapsing neuromyelitis optica.463-471 The list below summarizes key stakeholder perspectives.

- Eculizumab has the potential to disrupt the health care delivery system while improving patient health outcomes by reducing the need for inpatient neurology clinic visits for costly, time-consuming plasmapheresis and recovery time for patients with this debilitating condition.
- Eculizumab might increase disparities due to limited availability of this treatment via a restricted program under a REMS.
- Patients eligible for this treatment might face access issues due to the logistics of administering intravenous infusions weekly or every 2 weeks.
- Adverse events, such as upper respiratory tract infections, headaches, and meningococcal sepsis, are possible due to eculizumab. However, the published data showed adjudicated relapses in only 3% of the treatment group patients compared with 43% of patients in the placebo group, which might improve patients’ health outcomes overall.
- Longer-term studies are needed to evaluate the improvement of autoimmune attacks due to neuromyelitis optica.
Elexacaftor/Tezacaftor/Ivacaftor and Ivacaftor (Trikafta) to Treat Cystic Fibrosis

**Highlights**
- Elexacaftor/tezacaftor/ivacaftor and ivacaftor is a daily oral therapy intended to treat cystic fibrosis by targeting mutations in the cystic fibrosis transmembrane conductance regulator gene, \( CFTR \), that cause the buildup of thick mucus in the lungs.
- FDA approved the drug in October 2019 for treating cystic fibrosis in patients who have at least one copy of the F508del variant in the \( CFTR \) gene.
- Elexacaftor/tezacaftor/ivacaftor has an estimated retail price about $313,000 per year.
- Stakeholders commenting on this topic thought that this drug combination could become a new standard of care, based on the significant improvements in lung function and quality of life seen in clinical trials.

**Patient Population**

Elexacaftor/tezacaftor/ivacaftor and ivacaftor (referred to as elexacaftor/tezacaftor/ivacaftor hereafter) is indicated for children aged 12 years or older and adults with cystic fibrosis that harbors an F508del variant in at least one copy of the \( CFTR \) gene.

**Intervention**

Cystic fibrosis is a progressive disease caused by loss-of-function variants in the \( CFTR \) gene in which missing or defective CFTR proteins contribute to thick mucus buildup in organs. The buildup in the lungs causes patients to experience difficulty breathing and persistent infections.\(^{472}\)

The Cystic Fibrosis Foundation (CFF) reports that, among genotyped patients in its registry, 84.7% had at least one copy of the F508del variant—44.2% with F508del on both copies (homozygous variation) and 40.5% with F508del on one copy (heterozygous variation).\(^{473}\) The CFF website offers [more information about cystic fibrosis](https://www.cff.org).

Elexacaftor/tezacaftor/ivacaftor is a triple combination drug therapy intended to increase both the quantity and activity of CFTR protein in patients with at least one F508del variant copy.\(^{474}\) Elexacaftor and tezacaftor are CFTR correctors, meaning they help defective CFTR proteins fold properly. Improved protein folding purportedly increases cell-surface levels of CFTR by improving intracellular trafficking of the protein. Ivacaftor is a potentiator, meaning it helps improve the function of the CFTR protein to allow for more normal passage of chloride and sodium through cells.\(^{475}\) Together, these 2 mechanisms purportedly improve water and salt balance across the cell surface, decreasing the buildup of the thick mucus characteristic of cystic fibrosis.\(^{476}\)

In vitro research has shown the triple combination therapy significantly improves CFTR protein processing, trafficking, and chloride transport more than any of the 2 drugs in dual combination.\(^{477}\)

Elexacaftor/tezacaftor/ivacaftor is taken as 2 fixed-dose combination tablets of elexacaftor 100 mg, tezacaftor 50 mg, and ivacaftor 75 mg in the morning and one ivacaftor 150-mg tablet in the evening, daily. The morning and evening doses must be taken 12 hours apart and with a fat-containing meal.\(^{474}\)
Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 5 ongoing trials for this topic. We present 2 of these trials in Table 5.10. (We excluded 3 trials [NCT03525574, NCT04043806, NCT04058366] that identified long-term safety and tolerability of elexacaftor/tezacaftor/ivacaftor as their primary outcomes.)

Table 5.10. Ongoing Clinical Trials

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
</table>
| A Study Evaluating the Efficacy and Safety of VX-445/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects, Homozygous for F508del NCT04105972 | Children aged 12 years or older and adults (n = 176) with cystic fibrosis with homozygous F508del mutation and FEV₁ value between 40% and 90% (inclusive) of predicted mean for age, sex, and height | Phase IIIb, double-blind, randomized, active-controlled study to evaluate the safety, efficacy, and pharmacodynamics of triple combination elexacaftor-tezacaftor-ivacaftor (mornings) plus ivacaftor separately (evenings) compared with dual combination tezacaftor-ivacaftor (mornings) plus ivacaftor separately (evenings) over 24 weeks. All doses are unspecified. Primary outcome: Change from baseline in CFQ-R respiratory score Secondary outcomes:  
- Change in ppFEV₁  
- Change in sweat chloride  
- Safety and tolerability | Primary and study completion September 2020 |
### Study name and National Clinical Trials identifier

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
</table>
| A Phase 3 Study of VX-445 Combination Therapy in Cystic Fibrosis (CF) Subjects Heterozygous for F508del and a Gating or Residual Function Mutation (F/G and F/RF Genotypes) NCT04058353 | Children aged 12 years or older and adults (n = 250) with cystic fibrosis with heterozygous F508del mutation and who have a gating or residual function mutation at the second CFTR locus. Patients must have a FEV₁ value between 40% and 90% (inclusive) of the predicted mean for age, sex, and height. | Phase III, triple-arm, double-blind, randomized, active-controlled study to evaluate the efficacy, safety, and pharmacodynamics of triple combination elexacaftor-tezacaftor-ivacaftor (mornings, dose not specified) plus additional ivacaftor 150 mg (evenings) compared with either dual combination tezacaftor-ivacaftor (mornings) plus additional ivacaftor 150 mg (evenings) or twice-daily ivacaftor 150-mg monotherapy (mornings and evenings) for treating cystic fibrosis Primary outcome: Change from baseline in ppFEV₁ Secondary outcomes:  
• Change in sweat chloride from baseline and compared with other treatment groups  
• Change in ppFEV₁ compared with other treatment groups  
• Change in CFQ-R respiratory score from baseline and compared with other treatment groups  
• Safety and tolerability | Primary and study completion October 2020 |

Abbreviations: CFQ-R, Cystic Fibrosis Questionnaire-Revised; CFTR, cystic fibrosis transmembrane conductance regulator; FEV₁, forced expiratory volume in 1 second; ppFEV₁, percent predicted forced expiratory volume in 1 second.

### Recently Completed and Ongoing Trials With Available Results

Our searches identified 2 relevant, recently completed late-phase trials with published results.⁴⁷⁸,⁴⁷⁹ We summarize these studies with results as written in abstracts of the published studies.

The following abbreviations are used in this section: CF, cystic fibrosis; CFQ-R RD, Cystic Fibrosis Questionnaire-Revised, respiratory domain; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; LSM, least squares mean; ppFEV₁, percent predicted forced expiratory volume in 1 second.


- **Patient population/planned enrollment**: Children aged 12 years or older and adults (n = 405) with cystic fibrosis that harbors a heterozygous F508del mutation and who have FEV₁ value between 40% and 90% (inclusive) of predicted mean for age, sex, and height
• **Study design**: Phase III, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of triple combination therapy elexacaftor/tezacaftor/ivacaftor compared with placebo for 24 weeks. Patients in the experimental group received daily treatment with one combination tablet of elexacaftor 200 mg, tezacaftor 100 mg, and ivacaftor 150 mg in the morning and one ivacaftor 150-mg tablet in the evening.

• **Primary outcome**: Change in FEV₁ from baseline to week 4

• **Secondary outcomes**: Change in FEV₁ from baseline to week 24, measures of pulmonary exacerbations, change in sweat chloride, measures of body weight and mass index, change in CFQ-R RD score, and safety and tolerability

• **Results presented by study authors**: “A total of 403 patients underwent randomization and received at least one dose of active treatment or placebo. Elexacaftor-tezacaftor-ivacaftor, relative to placebo, resulted in a percentage of predicted FEV₁ that was 13.8 points higher at 4 weeks and 14.3 points higher through 24 weeks, a rate of pulmonary exacerbations that was 63% lower, a respiratory domain score on the Cystic Fibrosis Questionnaire-Revised (range, 0 to 100, with higher scores indicating a higher patient-reported quality of life with regard to respiratory symptoms; minimum clinically important difference, 4 points) that was 20.2 points higher, and a sweat chloride concentration that was 41.8 mmol per liter lower (P<0.001 for all comparisons). Elexacaftor-tezacaftor-ivacaftor was generally safe and had an acceptable side-effect profile. Most patients had adverse events that were mild or moderate. Adverse events leading to discontinuation of the trial regimen occurred in 1% of the patients in the elexacaftor-tezacaftor-ivacaftor group.”


• **Patient population/planned enrollment**: Children aged 12 years or older and adults (n = 113) with cystic fibrosis that harbors a homozygous F508del mutation and who have FEV₁ value between 40% and 90% (inclusive) of predicted mean for age, sex, and height

• **Study design**: Phase III, double-blind, randomized, active-controlled study to evaluate the efficacy of triple combination therapy elexacaftor/tezacaftor/ivacaftor compared with dual combination therapy tezacaftor/ivacaftor for a period of 4 weeks. All participants took part in a run-in period before the experimental portion of the study, during which all patients received tezacaftor and ivacaftor daily for 4 weeks. Baseline is defined as the end of this 4-week run-in period. Patients in the experimental group then received daily treatment with one combination tablet of elexacaftor 200 mg, tezacaftor 100 mg, and ivacaftor 150 mg in the morning and one ivacaftor 150-mg tablet in the evening. Patients in the active comparator group received daily treatment with one combination tablet of tezacaftor 100 mg and ivacaftor 150 mg in the morning and one ivacaftor 150-mg tablet in the evening.

• **Primary outcome**: Change in ppFEV₁ from baseline at week 4

• **Secondary outcomes**: Change in CFQ-R RD score, change in sweat chloride, and safety and tolerability

• **Results presented by study authors**: “Between Aug 3 and Dec 28, 2018, 113 participants were enrolled. Following the run-in, 107 participants were randomly assigned (55 in the elexacaftor plus tezacaftor plus ivacaftor group and 52 in the tezacaftor plus ivacaftor group) and completed the 4-week treatment period. The elexacaftor plus tezacaftor plus ivacaftor group had improvements in the primary outcome of ppFEV₁ (least squares mean [LSM] treatment difference of 10.0 percentage points [95% CI 7.4 to 12.6], p<0.0001) and the key secondary outcomes of sweat chloride concentration (LSM treatment difference -45.1 mmol/L [95% CI -50.1 to -40.1], p<0.0001), and CFQ-R RD score (LSM treatment difference 17.4 points [95% CI 11.8 to 23.0], p<0.0001) compared with the tezacaftor plus ivacaftor group. The triple combination regimen was well tolerated, with no discontinuations. Most adverse events were mild or moderate; serious adverse events occurred in two (4%) participants receiving elexacaftor plus tezacaftor plus ivacaftor and in one (2%) receiving tezacaftor plus ivacaftor.”

Manufacturers and Regulatory Status

Vertex Pharmaceuticals Inc (Boston, Massachusetts) manufactures elexacaftor/tezacaftor/ivacaftor. FDA approved the triple combination therapy on October 21, 2019, for treating cystic
fibrosis in patients who have at least one F508del variant in the \textit{CFTR} gene.\textsuperscript{480} For this indication, FDA had granted Priority Review and Fast Track, Breakthrough Therapy, and Orphan Drug designations.\textsuperscript{480}

**Cost Information**

According to a US-based online aggregator of prescription prices, GoodRx, Trikafta’s retail price is about $24,000 for a 28-day supply (as of April 10, 2020), yielding an annual cost of about $313,000.\textsuperscript{481} Patient-assistance programs are available to help qualified patients defray costs of deductibles and copayments.\textsuperscript{482} The manufacturer provides patients and their families with patient-support specialists who “help you navigate questions about insurance, reimbursement, and potential co-pay assistance.”\textsuperscript{476}

**Key Stakeholder Perspectives**

Eight stakeholders, reflecting clinical, research, nursing, patient, and health systems perspectives, provided comments and ratings on elexacaftor/tezacaftor/ivacaftor and ivacaftor to treat cystic fibrosis.\textsuperscript{483-490} The list below summarizes key stakeholder perspectives.

- The anticipated improvements in breathing function and quality of life from elexacaftor/tezacaftor/ivacaftor as a simple, twice-daily oral therapy could prompt many patients to skip other lengthy, cumbersome treatments, such as nebulizers and airway clearance therapy.
- Because of its clinical and quality-of-life improvements over standard-of-care treatment, triple combination therapy with elexacaftor/tezacaftor/ivacaftor could become a new standard of care for cystic fibrosis.
- The drug’s estimated $313,000 annual cost could create disparities between patients with adequate insurance and those who are uninsured or underinsured.
- About 15% of patients with cystic fibrosis might be ineligible to receive elexacaftor/tezacaftor/ivacaftor because they lack the F508del genetic mutations that the triple combination therapy targets.
- Additional data are needed to establish whether the significant benefits seen after 1 to 6 months endure after long-term use of elexacaftor/tezacaftor/ivacaftor therapy.

**Fenfluramine Hydrochloride Low-Dose (Fintepla) to Treat Dravet Syndrome**

**Highlights**

- Low-dose fenfluramine (FFA) hydrochloride (Fintepla) is an amphetamine derivative taken twice daily in an oral solution that purportedly modulates serotonergic neurotransmission to block seizure activity.
- Low-dose FFA is being studied as an adjunct to patients’ current antiepileptic drug treatments.
- Stakeholders thought that, based on positive results in clinical trials, low-dose FFA has high potential to improve patient and caregiver quality of life and overall patient health.
- Stakeholders thought that FFA could decrease health disparities, disrupt the health care delivery system and current paradigm of patient care, and decrease costs over time.
Patient Population

FFA is intended for children and adults aged 2 to 35 years with Dravet syndrome who are taking one or more antiepileptic drugs.

Intervention

Low-dose FFA is an amphetamine derivative being developed as adjunctive therapy for treating Dravet syndrome. A rare, severe, infantile-onset form of epilepsy, Dravet syndrome is usually caused by a rearrangement in the sodium voltage-gated channel alpha subunit 1 gene, SCN1A. Patients with Dravet syndrome have prolonged seizures that are difficult to control with FDA-approved antiepileptic drugs and typically experience cognitive impairment, behavioral problems, muscle weakness, and sleep disorders.

FFA has been recognized as promoting serotonin release, but this alone is not believed to account for its purported beneficial effects on seizure activity, because other serotonin reuptake inhibitors have not shown benefits for managing epilepsy. Recent research found other activity that might account for effects observed in early studies after FFA administration for epilepsy treatment: FFA binds to sigma-1 receptors (Sig-1R) and acts as a positive allosteric modulator of Sig-1R and alters activity at the Sig-1R. This activity is thought to block seizure activity and modulate serotonergic neurotransmission.

In clinical trials, patients take or caregivers give an oral, sugar-free (ie, ketogenic diet–compatible) solution of FFA twice daily in equal doses totaling 0.2, 0.4, or 0.8 mg/kg (up to a maximum of 20 or 30 mg/day), for up to 156 weeks.

The Dravet Syndrome Foundation website offers more information on Dravet syndrome.

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified one ongoing trial for this topic. We present this trial in Table 5.11.

Table 5.11. Ongoing Clinical Trial

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride HCl) Oral Solution as an Adjunctive Therapy in Children and Young Adults With Dravet Syndrome (Study 1503) NCT02823145</td>
<td>Children and adults (n = 340) aged 2 to 35 years with clinically diagnosed Dravet syndrome who participated in Study 1501 or Study 1502. Note: The clinical trial record states that patients aged 18 to 35 years who did not participate in Study 1501 or Study 1502 may also be eligible for enrollment in this study.</td>
<td>Phase III, single-group, open-label extension study to assess the long-term safety and tolerability of a titrated effective dose of Fintepla (beginning with 0.2 mg/kg/day, up to a maximum of 30 mg/day) when used as an adjunctive therapy to antiepileptic drugs. Primary outcome: Incidence of treatment-emergent adverse events. Secondary outcomes: Change in monthly convulsive seizure frequency, from baseline to up to 156 weeks; and longest seizure-free interval during the 156-week study period.</td>
<td>Primary and study completion December 2020</td>
</tr>
</tbody>
</table>

See preliminary results by Lagae et al 2018 under Recently Completed and Ongoing Trials With Available Results.
Recently Completed and Ongoing Trials With Available Results

Our searches identified 4 recently completed late-phase trials with published results.\textsuperscript{493-495} We summarize the 3 most recent and indication-relevant studies with results as written in abstracts of a poster presentation and 2 published studies.

The following abbreviations are used in this section: CI, confidence interval; FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; OLE, open-label extension; SD, standard deviation; TEAE, treatment-emergent adverse event.

An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride HCl) Oral Solution as an Adjunctive Therapy in Children and Young Adults With Dravet Syndrome (Study 1503). NCT02823145. Lagae et al 2018.\textsuperscript{493}

- **Patient population/planned enrollment:** Children and adults (n = 340) aged 2 to 35 years with clinically diagnosed Dravet syndrome who participated in Study 1501 or Study 1502. (Note: The clinical trial record states that patients aged 18 to 35 years who did not participate in Study 1501 or Study 1502 may also be eligible for enrollment in this study.)

- **Study design:** Phase III, single-group open-label extension study to assess the long-term safety and tolerability of a titrated effective dose of FFA (beginning with 0.2 mg/kg/day, up to a maximum of 30 mg/day) when used as an adjunctive therapy to antiepileptic drugs.

- **Primary outcome:** TEAE frequency, from baseline to up to 156 weeks.

- **Secondary outcomes:** Percentage of patients with a clinically meaningful (≥50%) reduction in MCSF, from baseline to up to 156 weeks; and percentage of patients with a profound (≥75%) reduction in MCSF, from baseline to up to 156 weeks.

- **Results presented by study authors:** Adverse event rates (%) reported in a table within the poster are summarized below:

  - Decreased appetite: 15.9
  - Diarrhea: 10.8
  - Nasopharyngitis: 19.4
  - Pyrexia: 21.6
  - Upper respiratory tract infection: 10.3

  “Over the entire OLE interim analysis period (median 256 days), the median decrease in [monthly] convulsive seizure frequency was -66.8% (range, -100% to 234.9%; \(P<0.001\)). . . . The majority of patients responded to FFA over the entire OLE interim analysis period (median 256 days): 64.4% of patients demonstrated clinically meaningful (≥50%) reduction in convulsive seizure frequency; 41.2% of patients demonstrated profound (≥75%) reduction in convulsive seizure frequency.”

A Two-Part Study to Investigate the Dose-Ranging Safety and Pharmacokinetics, Followed by the Efficacy and Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children ≥2 Years Old and Young Adults With Dravet Syndrome (Study 1504). NCT02926898. Nabbout et al 2020.\textsuperscript{494}

- **Patient population/planned enrollment:** Children and adults (n = 87) aged 2 to 18 years with clinically diagnosed Dravet syndrome who were receiving stiripentol.

- **Study design:** Phase III, quadruple-blinded (participant, care provider, investigator, outcomes assessor), randomized controlled trial of FFA used as an adjunct to a stiripentol-containing anticonvulsive treatment regimen. After a 3-week dose-titration phase, patients were randomly assigned in a 1:1 ratio to adjunctive treatment with FFA (0.5 mg/day) or placebo.

- **Primary outcome:** Percentage difference from placebo in mean MCSF, from baseline to 12 weeks.

- **Secondary outcome:** Median percentage reduction from baseline in MCSF at 12 weeks.
Results presented by study authors: “A total of 115 eligible patients were identified; of these, 87 patients (mean [SD], age 9.1 [4.8] years; 50 male patients [57%]; mean baseline frequency of seizures, approximately 25 convulsive seizures per month) were enrolled and randomized to fenfluramine, 0.4 mg/kg/d (n = 43) or placebo (n = 44). Patients treated with fenfluramine achieved a 54.0% (95% CI, 35.6%-67.2%; P < .001) greater reduction in mean monthly convulsive seizure frequency than those receiving the placebo. With fenfluramine, 54% of patients demonstrated a clinically meaningful (≥50%) reduction in monthly convulsive seizure frequency vs 5% with placebo (P < .001). The median (range) longest seizure-free interval was 22 (3.0-105.0) days with fenfluramine and 13 (1.0-40.0) days with placebo (P = .004). The most common adverse events were decreased appetite (19 patients taking fenfluramine [44%] vs 5 taking placebo [11%]), fatigue (11 [26%] vs 2 [5%]), diarrhoea (10 [23%] vs 3 [7%]), and pyrexia (11 [26%] vs 4 [9%]). Cardiac monitoring demonstrated no clinical or echocardiographic evidence of valvular heart disease or pulmonary arterial hypertension.”

Manufacturers and Regulatory Status

FFA is being developed by Zogenix Inc (Emeryville, California). It is in phase III clinical development to treat Dravet syndrome. Its developer submitted a New Drug Application to FDA on February 6, 2019.496 FDA issued a refusal to file letter on April 8, 2019, citing missing nonclinical data and incorrect clinical data.497 Zogenix stated in June 2019 that FDA had agreed to proceed with resubmission of the New Drug Application without additional chronic-toxicity studies.498 Zogenix resubmitted the New Drug Application on September 26, 2019.499 FDA accepted the New Drug Application on November 25, 2019, granted Priority Review, and issued a Prescription Drug User Fee Act– (PDUFA)-prescribed target action date of March 25, 2020. The developer stated that FDA did not anticipate holding an advisory committee meeting to discuss the New Drug Application.500
FDA had granted FFA designations of Orphan Drug in December 2013, Breakthrough Therapy in February 2018, and Fast Track in January 2016 for treating Dravet syndrome. FFA is also in phase III clinical development for treating Lennox-Gastaut syndrome, a rare, severe form of infantile- or childhood-onset epilepsy.

**Cost Information**

Cost information is unavailable for this topic.

**Key Stakeholder Perspectives**

Seven stakeholders, reflecting caregiver, clinical, nursing, and research perspectives, provided comments and ratings on FFA. The list below summarizes key stakeholder perspectives.

- Clinical trial data demonstrate significant reductions in seizure frequency with FFA that might improve patient health outcomes and patient and caregiver quality of life—because of less risk for status epilepticus, patients being able to participate in more activities, patients and caregivers getting more uninterrupted sleep, and caregivers spending less time monitoring for and providing care during seizures.
- Seizure reduction with FFA might require fewer emergency department visits and hospital admissions, fewer rescue medications, and less intensive caregiving, thus potentially lowering health care costs and impacting the current paradigm of patient care and health care delivery system as use of supportive health care resources changes.
- Although cost might be a barrier to patient access to the medication, treatment with FFA might lower long-term health care costs and decrease health disparities, considering some comparators (eg, ketogenic diet) are more difficult to adhere to than an oral medication (ie, FFA).
- More data are needed regarding the cardiac safety of FFA and to assess what kind of cardiac monitoring patients might need to undergo treatment with FFA.

**Galcanezumab-gnlm (Emgality) to Treat Episodic Cluster Headache**

**Highlights**

- Galcanezumab-gnlm is the first FDA-approved drug to treat episodic cluster headache.
- Galcanezumab-gnlm is thought to work by stopping the calcitonin gene–related peptide (CGRP) from binding to its receptor, which can activate the trigeminal sensory nerve and lead to cluster headache development.
- Stakeholders commenting on this topic thought that the high cost of galcanezumab-gnlm (about $1375 per treatment episode) might present a significant barrier to access, but might be offset by improved health outcomes that reduce costs elsewhere.
- Stakeholders also thought that galcanezumab-gnlm might reduce the need for medical resources to manage symptoms and has the potential to significantly improve patient health outcomes, quality of life, and overall health.

**Patient Population**

Galcanezumab-gnlm injections are indicated for adults aged 18 years or older with episodic cluster headache.
**Intervention**

Galcanezumab-gnlm is a humanized monoclonal antibody specific for CGRP and is intended to prevent CGRP from binding to its receptors, which might reduce pain signaling of the trigeminal sensory nerve and prevent cluster headache onset. The recommended dose is 300 mg, which patients give themselves under the skin (ie, subcutaneously) as 3 consecutive injections of 100 mg each at the onset of the cluster headache period and then monthly until the end of the same cluster period.512

The American Migraine Foundation website offers [more information on cluster headache](https://www.migraineraw.com/cluster-headache).

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified a single ongoing trial for this topic. We present this trial in Table 5.12.

**Table 5.12. Ongoing Clinical Trial**

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Study of LY2951742 (Galcanezumab) in Participants With Cluster Headache CGAR NCT02797951</td>
<td>Adults (n = 300) aged 18 or older with episodic cluster headaches who completed 1 of the 2 phase III trials (CGAL [NCT02397473] or CGAM [NCT02438826])</td>
<td>Phase IIIb, single-arm, open-label trial to assess the long-term safety and tolerability of galcanezumab-gnlm in patients with episodic cluster headache and chronic cluster headache. Patients self-administer 300 mg of the drug via injections under the skin, up to once a month, for 4 years. Primary outcomes: SAE or TEAE incidence at baseline and 4 years; and patients experiencing suicidal ideation and behaviors, as measured by C-SSRS, at baseline and 4 years</td>
<td>Primary and study completion December 2020</td>
</tr>
</tbody>
</table>

Abbreviations: C-SSRS, Columbia – Suicide Severity Rating Scale; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

**Recently Completed and Ongoing Trials With Available Results**

Our searches identified 2 late-phase trials with available results.513,514 We summarize these 2 most recent and indication-relevant studies with results as written in an abstract of a published study and a conference abstract.

The following abbreviations are used in this section: CH, cluster headache; C-SSRS, Columbia – Suicide Severity Rating Scale; PGI-I, Patient Global Impression of Improvement; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event.


- **Patient population/planned enrollment:** Patients (n = 300) with chronic or episodic cluster headache who previously completed 1 of 2 phase III studies (NCT02397473 [CGAL study] or NCT02438826 [CGAM study])

  *Note:* The abstract reported data only from a subset of enrolled patients (those with episodic cluster...
headache who previously completed the CGAL study and were enrolled in the CGAR study at the time of the interim analysis).

- **Study design:** Phase III, single-group, open-label study to assess the long-term safety and efficacy of galcanezumab-gnlm. Patients self-administer galcanezumab-gnlm 300 mg subcutaneously up to once a month for 4 years.

- **Primary outcomes:** SAE or TEAE incidence at baseline and 4 years; and patients experiencing suicidal ideation and behaviors, as measured by C-SSRS, at baseline and 4 years

- **Results presented by study authors:** “Thirty-one patients completed CGAL and had entered the CGAR treatment phase at the time of this interim analysis. The majority of patients were male (71%) and European (67.7%). Mean age was 46.9 years with an average of 13.1 weekly CH attacks at CGAL baseline. All patients had a median (Quartile 1, Quartile 3) of 9 (5, 13) visits and 54.8%, experienced one active cluster period, while 29.0% and 12.9% experienced two, and more than two active periods, respectively. Median (Quartile 1, Quartile 3) duration of active periods was 2 visits (1, 3). [Galcanezumab] was administered in 98.1% of active status visits and 42.4% of remission visits. Among 26 patients who enrolled in active status with available data, 53.8% (14/26) reported feeling ‘very much/much better’ on the PGI-I scale at one month.”


- **Patient population/planned enrollment:** Adults (n = 106) aged 18 to 65 years with episodic cluster headaches with at least 2 cluster periods lasting from 7 days to 1 year when untreated and separated by pain-free remission periods of ≥1 month

- **Study design:** Phase III, randomized, double-blind, parallel-assignment study to assess the long-term safety and efficacy of galcanezumab-gnlm. Patients were randomly assigned to treatment with galcanezumab-gnlm or matching placebo. Patients were administered galcanezumab-gnlm 300 mg or placebo subcutaneously, at day 0 and at month 1.

- **Primary outcome:** Mean change in weekly cluster headache attack frequency from baseline to the average of weeks 1 to 3

- **Secondary outcomes:** Patients with ≥50% reduction in weekly number of cluster headache attacks from baseline through week 3; and patients reporting a score of 1 ("very much better") or 2 ("much better") on the PGI-I at week 4

- **Results presented by study authors:** "Recruitment was halted before the trial reached the planned sample size of 162 because too few volunteers met the eligibility criteria. Of 106 enrolled patients, 49 were randomly assigned to receive galcanezumab and 57 to receive placebo. The mean (±SD) number of cluster headache attacks per week in the baseline period was 17.8±10.1 in the galcanezumab group and 17.3±10.1 in the placebo group. The mean reduction in the weekly frequency of cluster headache attacks across weeks 1 through 3 was 8.7 attacks in the galcanezumab group, as compared with 5.2 in the placebo group (difference, 3.5 attacks per week; 95% confidence interval, 0.2 to 6.7; *P* = .04). The percentage of patients who had a reduction of at least 50% in headache frequency at week 3 was 71% in the galcanezumab group and 53% in the placebo group. There were no substantial between-group differences in the incidence of adverse events, except that 8% of the patients in the galcanezumab group had injection-site pain.”

Manufacturers and Regulatory Status

Galcanezumab-gnlm is being developed by [Eli Lilly and Co](https://www.eli-lilly.com) (Indianapolis, Indiana). FDA approved it on June 4, 2019, to treat episodic cluster headache.[512,515] FDA had granted the drug Priority Review for treating episodic cluster headache in March 2019 and Breakthrough Therapy designation for the same indication in September 2018.[516] Galcanezumab-gnlm was also approved by FDA to prevent migraine headache in September 2018.[517] It is in phase III clinical development for preventing chronic cluster headache; an open-label extension study (CGAM, [NCT02438826](https://clinicaltrials.gov/ct2/show/NCT02438826)) was scheduled to complete in July 2019.
Cost Information

Upon FDA approval for treating episodic cluster headache, the manufacturer announced, “The U.S. list price of Emgality . . . is the same per milligram as the migraine indication.”512 For preventing migraine headache, each 120-mg monthly dose of galcanezumab-gnlm (Emgality) provided in a single-use prefilled pen or syringe costs about $550 (as of April 16, 2019), or about $6600 per year.518 Therefore, we estimate that for treating episodic cluster headache, each 300-mg monthly dose of the drug, provided as 3 single-use prefilled syringes containing 100 mg each, will cost about $1375.

Key Stakeholder Perspectives

Nine stakeholders, reflecting clinical, nursing, patient, and research perspectives, provided comments and ratings on galcanezumab-gnlm.519-527 The list below summarizes key stakeholder perspectives.

- Patients with symptoms of suicidal ideation and behavior might benefit from this drug because reducing the frequency or intensity of episodic cluster headaches might help alleviate incidence of these symptoms.
- Galcanezumab-gnlm might reduce emergency department visits and off-label prescribing for cluster headache pain. It might offer an at-home solution, making it more convenient for both patients and health care providers, compared with current therapies.
- The high cost of this drug might limit access and increase health disparities, depending on insurance coverage of the drug.
- Patients might have a steep learning curve to be able to give themselves injections, which is a concern because the task can be affected by physical or cognitive limitations.
- Galcanezumab-gnlm’s convenient route of administration, taken at home, might make the drug an attractive option for patients and might improve work productivity and reduce time out of work.

Givosiran (Givlaari) to Prevent and Treat Acute Hepatic Porphyria

Highlights

- Givosiran is an interference RNA (RNAi) therapeutic given by subcutaneous injection and approved for treating acute hepatic porphyria (AHP) in adults. It reduces the expression of aminolevulinic acid synthase 1 (ALAS1), a liver enzyme in the heme biosynthesis pathway and involved in disease pathogenesis.
- This is the first treatment FDA has approved to treat adults with AHP, a group of rare, genetic, chronic, metabolic disorders that strongly induce ALAS1 and can lead to accumulation of neurotoxic heme intermediates, causing debilitating disease symptoms.
- Stakeholders commenting on this topic thought that givosiran might reduce demands on the health care system and considered it a clinically effective option for reducing incidence of AHP and related emergency care, but they highlighted the need for longer-term studies.
- Stakeholders also thought that givosiran’s high cost, estimated at about $575 000 per patient annually, might cause health disparities in patients who are uninsured or underinsured, or have high copayments.
Patient Population

Givosiran (Givlaari) is indicated for treating adults with AHP.

Intervention

AHPs are a group of rare metabolic disorders caused by genetic variants (usually autosomal dominant) in enzymes involved in heme biosynthesis in the liver. They include the manifestations of acute intermittent porphyria, aminolevulinic acid dehydratase-deficiency porphyria, hereditary coproporphyria, and variegate porphyria. The disorders are chronic, with no cure available, and are associated with serious burden of illness. Acute flares can be life threatening. AHP flares can be precipitated by many triggers that cause a strong induction of ALAS1, a liver enzyme in the heme biosynthesis pathway, which can lead to accumulation of neurotoxic heme intermediates that manifest in debilitating disease symptoms.

Givosiran is an RNAi therapeutic (ie, ESC-GalNAc-siRNA conjugate) intended to treat AHPs by reducing the expression of ALAS1. RNAi is a process of gene silencing that naturally occurs in cells, and researchers have adapted the process by developing targeted small interfering RNA (siRNA) molecules that mediate RNAi gene silencing activity in cells expressing messenger RNAs responsible for encoding pathogenic proteins. According to the developer, the ESC+GalNAc conjugate RNA improves specificity while maintaining potency and durability. The recommended givosiran dose according to product labeling is 2.5 mg/kg once monthly by subcutaneous injection. The Mayo Clinic website offers more information on AHPs.

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 2 ongoing trials for this topic. We present these trials in Table 5.13.
Table 5.13. Ongoing Clinical Trials

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
</table>
| ENVISION: A Study to Evaluate the Efficacy and Safety of Givosiran (ALN-AS1) in Patients With Acute Hepatic Porphyrias (AHP) NCT03338816 | Children aged 12 years or older and adults (n = 94) with acute hepatic porphyria | Phase III, double-blind, randomized controlled trial of the safety and efficacy of givosiran compared with placebo. Patients will be randomly assigned in a 1:1 ratio to treatment with givosiran (2.5 mg/kg once monthly) or matching placebo. After a 6-month double-blind period, all patients will receive once-monthly givosiran for up to 29 months during an open-label extension period. Primary outcome: Annualized rate of AIP attacks at 6 months Select secondary outcomes:  
  - Annualized rate of hemin administrations for AIP at 6 months  
  - Annualized rate of AHP attacks at 6 months  
  - Pain, nausea, and fatigue score changes at 6 months from baseline  
  - Quality-of-life PCS component of the SF-12 survey change from baseline to 6 months for AIP | Primary completion January 2019 Study completion May 2021 |
| A Study to Evaluate Long-Term Safety and Clinical Activity of Givosiran (ALN-AS1) in Patients With Acute Intermittent Porphyria (AIP) NCT02949830 | Adults aged 18 years or older (n = 17) with AIP who completed participation in part C of study ALN-AS1-001 and are not on a scheduled regimen of hemin | Phase I/II, open-label extension, single-group assignment to assess givosiran’s long-term safety, tolerability, and pharmacokinetics in patients with AIP Primary outcome: Safety of givosiran at month 37 Secondary outcomes:  
  - Pharmacodynamic effects of givosiran on urine ALA levels at 37 months  
  - Pharmacodynamic effect of givosiran on urine levels of porphobilinogen at month 37  
  - Frequency of porphyria attacks at month 37  
  - Frequency of hematin administrations through month 37 | Primary completion October 2020 Study completion October 2021 |

Abbreviations: AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, aminolevulinic acid; PCS, Physical Component Summary; SF-12, 12-item Short Form Survey.
Recently Completed and Ongoing Trials With Available Results

Our searches identified one relevant, recently completed late-phase trial with published results.531 We summarize this study with results as written in a news release.

The following abbreviations are used in this section: ADP, ALA dehydratase deficient porphyria; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, delta-aminolevulinic acid; HCP, hereditary coproporphyria; PBG, porphobilinogen deaminase; PCS, physical component summary; SF-12, 12-item Short Form Survey; VP, variegate porphyria.

ENVISION: A Study to Evaluate the Efficacy and Safety of Givosiran (ALN-AS1) in Patients With Acute Hepatic Porphyrias (AHP; ENVISION). NCT03338816. Alnylam Pharmaceuticals 2019.531

- **Patient population/planned enrollment:** Children aged 12 years or older and adults (n = 94) with AHP, (AIP, HCP, VP, ADP) with active disease, at least 2 porphyria attacks within the past 6 months, and elevated urinary or plasma PBG or ALA values within the past year
- **Study design:** Phase III, double-blind, randomized controlled, safety and efficacy study comparing givosiran (2.5 mg/kg once monthly) with placebo
- **Primary outcome:** Annualized rate of AIP attacks at 6 months
- **Secondary outcomes:** Annualized rate of hemin administrations for AIP at 6 months; annualized rate of AHP attacks at 6 months; pain, nausea, and fatigue score changes at 6 months from baseline; and quality-of-life PCS component of the SF-12 survey change from baseline to 6 months for AIP
- **Results presented by study authors:** "The full ENVISION results demonstrated a 74 percent mean and 90 percent median reduction in the primary endpoint measure of annualized rate of composite attacks in patients on givosiran relative to placebo during the six-month double-blind period. In addition, givosiran achieved statistically significant positive results for five of nine secondary endpoints, with an overall safety and tolerability profile that the Company believes is encouraging, especially in this high unmet need disease. Adverse events (AEs) were reported in 89.6 percent of givosiran patients and 80.4 percent of placebo patients; serious adverse events (SAEs) were reported in 20.8 percent of givosiran patients and 8.7 percent of placebo patients. Ninety-three of 94 patients, or 99 percent, enrolled in the open-label extension (OLE) period of the study."

Manufacturers and Regulatory Status

Givosiran is manufactured by Alnylam Pharmaceuticals Inc (Cambridge, Massachusetts). FDA approved givosiran on November 20, 2019, for treating AHP in adults.530 In May 2017, FDA granted givosiran Breakthrough Therapy designation.532 In August 2016, FDA had granted the drug Orphan Drug designation.533

Cost Information

Givosiran’s wholesale price is about $575 000 per patient annually, based on a list price of $39 000 per vial (as of November 20, 2019).534 Alnylam has stated that the price after mandatory discounts will be about $442 000 annually.534 According to the manufacturer, treating AHP with standard care can cost $400 000 to $650 000 annually, when considering treatment for attacks, including hospitalization, hemin administration, and supportive care.535

The manufacturer has announced plans to offer a novel framework for value-based agreements for givosiran payment.535 Participating public and private payers will pay the full value for givosiran only when it delivers real-world patient health outcomes similar to those reported in the ENVISION clinical trial. The manufacturer is also offering payers a prevalence-based adjustment rebate to help their plans manage members’ costs if the number of patients given givosiran exceeds a projected value derived from existing AHP prevalence models.535
Key Stakeholder Perspectives

Five stakeholders, reflecting clinical and research perspectives, provided comments and ratings on givosiran. The list below summarizes key stakeholder perspectives.

- Givosiran is a clinically effective option for reducing the incidence of AHP attacks causing patients to seek emergency care.
- Additional longer-term studies (1 to 5 years) are needed to determine givosiran’s efficacy compared with prophylactic hemin administration in preventing attacks.
- Givosiran’s high cost might cause health disparities in patients who are uninsured, underinsured, or have high copayments. Cost savings might be highly patient dependent, based on the severity of a patient’s disease symptoms.
- Givosiran might reduce demands on the health care system due to fewer AHP attacks. But additional studies are needed to understand the rate of adverse events in patients treated with givosiran.

Golodirsen (Vyondys 53) to Treat Duchenne Muscular Dystrophy

Highlights

- Golodirsen (Vyondys 53) is a phosphorodiamidate morpholino oligomer (PMO) given intravenously in weekly infusions. It purportedly binds exon 53 of dystrophin pre-messenger RNA (pre-mRNA) and promotes skipping of exon 53 during mRNA processing. This allows the synthesis of an internally truncated but functional dystrophin protein in patients with Duchenne muscular dystrophy (DMD).
- This intervention is FDA approved for a subset of patients with DMD, about 8% to 10%, who have a mutation in the dystrophin gene, DMD, amenable to exon 53 skipping.
- The cost is about $300,000 annually for the average patient, according to the manufacturer.
- Stakeholders commenting on this topic thought that, in clinical trials, golodirsen demonstrates significant increases in functional dystrophin production, which might improve patient health outcomes and quality of life.
- Stakeholders also thought that golodirsen has moderate potential to disrupt health disparities, the health care delivery system, the current paradigm of care, and health care costs; however, more data are needed to evaluate its overall disruptive potential.

Patient Population

Golodirsen is indicated for patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.

Intervention

Golodirsen is a PMO intended for treating DMD, an inherited, chromosome X–linked genetic disorder caused by insertion or deletion mutations in the DMD gene. DMD encodes dystrophin, a protein that helps promote muscle function. In patients with DMD, the absence of functional dystrophin protein causes progressive muscle fiber necrosis and eventual widespread muscle weakness. No cure exists for DMD. FDA previously approved a gene therapy for patients who have a specific mutation in DMD that is amenable to exon 51 skipping. Golodirsen is the second
FDA-approved gene therapy for patients with a specific mutation of DMD (ie, amenable to exon 53 skipping).

Golodirsen purportedly binds exon 53 of dystrophin pre-mRNA (precursor mRNA composed of introns and exons) and promotes skipping of exon 53 during mRNA processing. This allows synthesis of an internally truncated but functional dystrophin protein. Therefore, golodirsen treatment might promote skeletal muscle function and prevent or delay disease progression in patients with DMD who have DMD exon 53 mutations (about 8% to 10% of patients).

Golodirsen is given once weekly as an intravenous infusion over the course of 35 to 60 minutes at a dose of 30 mg/kg.

The Muscular Dystrophy Association website provides more information on DMD.

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 2 ongoing trials for this topic. We present these trials in Table 5.14.

Table 5.14. Ongoing Clinical Trials

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Double-Blind, Placebo-Controlled, Multi-center Study With an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients With Duchenne Muscular Dystrophy (ESSENCE) NCT02500381</td>
<td>Male children (n = 222) aged 7 to 13 years with genetically confirmed DMD who have a mutation in the DMD gene that is amenable to exon 45 or 53 skipping and who are on a stable dose of corticosteroids</td>
<td>Phase III, randomized, double-blind, parallel-assignment study to evaluate the efficacy and safety of casimersen (SRP-4045) 30 mg/kg and golodirsen (SRP-4053) 30 mg/kg versus placebo. The double-blind period will be followed by an open-label extension period, in which all patients will receive active treatment for 48 weeks (up to week 144 of study). Primary outcome: 6-minute walk test distance at baseline and week 96. Secondary outcomes: • Dystrophin expression at baseline and weeks 48 or 96, as measured by IHC and WB • Ability to rise independently from the floor at week 96 • Time to loss of ambulation at week 96 • Ambulatory function at baseline and week 96, as measured by NSAA • FVC percentage predicted at baseline and week 96</td>
<td>Primary completion May 2022 Study completion May 2023</td>
</tr>
</tbody>
</table>
Recently Completed and Ongoing Trials With Available Results

Our searches identified one relevant, recently completed late-phase trial with published results.\textsuperscript{542,543} We summarize this study with results as written in 2 abstracts of the published studies.

The following abbreviations are used in this section: AEs, adverse events; DMD, Duchenne muscular dystrophy; FVC, forced vital capacity; IHC, immunohistochemistry; mRNA, messenger RNA; RT-PCR, reverse transcription polymerase chain reaction; SAEs, serious adverse events; WB, Western blot.

A 2-Part, Randomized, Double-Blind, Placebo-Controlled, Dose-Titration, Safety, Tolerability, and Pharmacokinetics Study (Part 1) Followed by an Open-Label Efficacy and Safety Evaluation (Part 2) of SRP-4053 in Patients With Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping (4053-101 study). \textbf{NCT02310906. Muntoni et al 2018\textsuperscript{542} and Frank et al 2020.\textsuperscript{543}}

- **Patient population/planned enrollment**: Male children (n = 39) aged 6 to 15 years with genetically confirmed DMD who were on a stable dose of corticosteroids. Enrolled patients in one group had genetic deletions amenable to exon 53 skipping and in the other group were untreated patients whose DMD had genetic deletions not amenable to exon 53 skipping.
- **Study design**: Phase I/II, 2-part study. Part 1 was a randomized, double-blind, parallel-assignment study to evaluate the efficacy and safety of golodirsen (SRP-4053) at escalating dose levels as follows: weeks 1 to 2, 4 mg/kg/week; weeks 3 to 4, 10 mg/kg/week; weeks 5 to 6, 20 mg/kg/week; weeks 7 to 12, 30 mg/kg/week; versus placebo. Part 2 was an open-label evaluation of golodirsen in patients from part 1, along with newly enrolled patients whose DMD had genetic deletions amenable to exon 53 skipping and an untreated group of patients whose DMD had genetic deletions not amenable to exon 53 skipping.
- **Primary outcomes**: Incidence of AEs and SAEs at week 12; 6-minute walk test distance at baseline and week 144; and dystrophin expression at baseline and week 48, as measured by WB assay
- **Secondary outcomes**: Dystrophin expression at baseline and week 48, as measured by IHC; FVC percentage predicted at baseline through week 144; and exon 53 skipping at baseline and week 144, as measured by RT-PCR sequence verification of exon 53-skipped mRNA
- **Results presented by study authors**: "Mean percent of normal dystrophin protein increased from 0.095% at baseline to 1.019% at Week 48 (range: 0.09%–4.30%), a significant mean change of +0.924% (P<0.001). Muscle biopsy samples from all 25 patients displayed a significant increase from baseline in exon 53 skipping via RT-PCR at Week 48 (P<0.001), demonstrating the intended mechanism of action. A positive correlation between exon 53 skipping and de novo dystrophin production was observed (Spearman-r = 0.500; P=0.011)."
Analysis of mean fiber intensity demonstrated a significant increase from baseline in de novo dystrophin production ($P<0.001$) and confirmed dystrophin sarcolemma localization.  

“Twelve patients were randomized to receive golodirsen (n = 8) or placebo (n = 4) in part 1. All from part 1 plus 13 additional patients received 30 mg/kg golodirsen in part 2. Safety findings were consistent with those previously observed in pediatric patients with DMD. Most of the study drug was excreted within 4 hours following administration. A significant increase in exon 53 skipping was associated with ~16-fold increase over baseline in dystrophin protein expression at week 48, with a mean percent normal dystrophin protein standard of 1.019% (range, 0.09%-4.30%). Sarcolemmal localization of dystrophin was demonstrated by significantly increased dystrophin-positive fibers (week 48, $p < 0.001$) and a positive correlation (Spearman $r = 0.663; p < 0.001$) with dystrophin protein change from baseline, measured by Western blot and immunohistochemistry.”  

Manufacturers and Regulatory Status  

Golodirsen, developed by Sarepta Therapeutics Inc (Cambridge, Massachusetts), received accelerated FDA approval on December 12, 2019.  

Sarepta Therapeutics is required to conduct a confirmatory clinical trial and submit data demonstrating golodirsen’s clinical benefit to maintain the approval. The developer stated in December 2019 that it was enrolling patients into a placebo-controlled, postmarketing confirmatory trial (ESSENCE, NCT02500381), expected to conclude by 2024 (primary completion May 2022).  

The New Drug Application (NDA) was originally submitted on December 19, 2018, and accepted by FDA in February 2019 with Priority Review status. On the Prescription Drug User Fee Act– (PDUFA)-prescribed decision date (August 19, 2019), FDA issued a Complete Response Letter (CRL) rejecting the NDA. The developer stated that FDA had cited 2 concerns about infection risk and renal toxicity related to drug administration. The developer submitted a Formal Dispute Resolution Request on September 13, 2019; an Appeal Granted letter was issued on November 22, 2019; and the developer resubmitted the NDA on November 27, 2019. In January 2020, a month after the drug’s approval, FDA unexpectedly released the August 19, 2019, CRL, revealing the details of FDA’s safety and efficacy concerns, which are more extensive than those noted briefly by the developer in August. 

FDA had granted the drug Orphan Drug designation for this indication in May 2018.  

Cost Information  

Sarepta noted that golodirsen would be priced at parity to an existing DMD exon-skipping therapy it also developed (eteplirsen for skipping exon 51), which Sarepta stated at the time of FDA approval would cost about $300,000 annually for the average patient.  

Golodirsen’s cost has been estimated to be higher. An August 2019 evidence report, Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: Effectiveness and Value, from the Institute for Clinical and Economic Review (ICER) estimated the annual cost of eteplirsen for a 40-kg (88-pound) patient to be about $1 million. The ICER analysis was conducted before FDA approval and before pricing for golodirsen was announced. Therefore, it did not include an economic analysis specific to golodirsen. However, the report notes that were golodirsen to have the same costs as eteplirsen, then the performed assessment of cost-effectiveness for eteplirsen would hold true for golodirsen. In its analysis of eteplirsen, ICER noted that the data on the clinical efficacy of eteplirsen and golodirsen were insufficient because they were based on surrogate outcomes (ie, dystrophin protein levels) lacking a clear threshold for meaningful clinical improvement. Therefore, ICER’s cost-effectiveness assessment was based on the assumption of large positive impacts on both
patients and caregivers. However, even in the most optimistic scenario (full return to health for both the patient and 2 caregivers over a 40-year time frame), the incremental cost-effectiveness ratio remained above $450,000 per quality-adjusted life-year (QALY) gained, which is higher than what ICER considers to be an acceptable cost-effectiveness threshold.550

In April 2020, the New England Comparative Effectiveness Public Advisory Council (CEPAC), published a report, informed by the August 2019 ICER report. Its conclusions included the position that, even with an extreme curative treatment effect, golodirsen, if priced similarly to eteplirsen, “could never be cost-effective at commonly cited cost-effectiveness thresholds.”551

Key Stakeholder Perspectives

Eight stakeholders, reflecting caregiver, clinical, health systems, nursing, and research perspectives, provided comments and ratings on golodirsen.552-559 The list below summarizes key stakeholder perspectives.

- Clinical trial data demonstrate that golodirsen increases functional dystrophin, which has potential to greatly impact patient health outcomes and quality of life, although it remains to be seen whether the increase in dystrophin translates to clinically significant outcomes.
- Golodirsen might shift the current paradigm of patient care from supportive to preventive and might decrease or delay use of certain health care resources (eg, hospitalizations, wheelchairs, home care).
- The dosing regimen of weekly infusions is disruptive to patients’ lives and might be a barrier to access for some that could increase health disparities in this patient population.
- The high cost of golodirsen might also be a barrier to patient access that could increase health disparities, even if the drug could decrease health costs overall in the long run.

Idebenone (Puldysa) to Treat Duchenne Muscular Dystrophy

Highlights

- Idebenone is a benzoquinone with similarity to coenzyme Q-10 that is taken orally 3 times daily with meals. It purportedly facilitates electron transport within mitochondria to increase energy production within impaired nerve and muscle tissues in patients with Duchenne Muscular Dystrophy (DMD).
- Although idebenone does not cure DMD, data suggest that it might improve respiratory function.
- Stakeholders commenting on this topic generally agreed that idebenone might improve patient respiratory function and quality of life and disrupt the paradigm of patient care by decreasing hospitalizations, dependency on respiratory support staff and equipment, and medication treatment with steroids and antibiotics.
- Stakeholders thought that more data are needed to (1) determine whether improved respiratory function with idebenone translates to improved clinical function, and (2) compare the efficacy of idebenone to the current standard-of-care comparator, corticosteroids.
**Patient Population**

Idebenone is intended for males aged 10 years or older with DMD regardless of whether they are taking corticosteroids.

**Intervention**

DMD is an inherited, X chromosome–linked genetic disorder caused by point mutations or deletions in the dystrophin gene, \textit{DMD}. \textit{DMD} encodes the dystrophin protein, which helps promote muscle function. In patients with DMD, the absence of wild-type dystrophin protein causes progressive muscle death and eventual widespread muscle weakness.\textsuperscript{401}

Idebenone is a small-molecule, synthetic, short-chain benzoquinone with similarity to coenzyme Q-10 that purportedly facilitates electron transport within mitochondria. The developer asserts that maintaining correct electron balance is essential for normal energy metabolism—particularly in nerve and muscle cells, which demand more energy, making them more prone to rapid cell damage or death from mitochondrial dysfunction.\textsuperscript{560} Additionally, idebenone might protect cells from oxidative-stress signaling pathways that induce programmed cell death (ie, apoptosis), preserving mitochondrial function and cellular viability.\textsuperscript{561} These effects could increase energy production within impaired nerve and muscle tissue in patients with DMD.\textsuperscript{560}

Data from the phase II DELPHI trial (NCT\textsuperscript{00654784}) suggested that idebenone improved respiratory function but not cardiac function (defined as peak systolic radial strain values in the left ventricular inferolateral wall), shaping the selection of phase III respiratory function endpoints.\textsuperscript{562}

In clinical trials, patients take or caregivers give 900 mg of idebenone orally, daily, divided into 3 equal doses of two 150-mg tablets each, taken with meals.

The Muscular Dystrophy Association website offers more information on DMD.

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified 2 ongoing trials for this topic. We present these trials in Table 5.15.
### Table 5.15. Ongoing Clinical Trials

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III Double-Blind Study With Idebenone in Patients With Duchenne Muscular Dystrophy (DMD) Taking Glucocorticoid Steroids (SIDEROS) NCT02814019</td>
<td>Male patients (n = 266) aged 10 years or older with DMD who are taking corticosteroids</td>
<td>Phase III, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of idebenone compared with those of placebo Primary outcomes: Change in FVC %p from baseline to week 78, and delayed loss of respiratory function measured by changes in FVC %p from baseline to week 78 Secondary outcomes: Change in PEF %p, FVC, and IFR from baseline to week 78</td>
<td>Primary and study completion August 2021</td>
</tr>
<tr>
<td>Phase III Study With Idebenone in Patients With Duchenne Muscular Dystrophy (SIDEROS-E) (SIDEROS-E) NCT03603288</td>
<td>Male patients (n = 266) who completed the phase III SIDEROS trial</td>
<td>Phase III, open-label, single-group, multicenter extension study to assess the long-term safety and efficacy of idebenone Primary outcomes: Incidence and severity of AEs, number of discontinuations due to AEs, and abnormal laboratory safety parameters through week 78 Secondary outcomes: Change in FVC, PEF %p, and FEV1 %p from baseline through week 78</td>
<td>Primary completion December 2023 Study completion January 2024</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; DMD, Duchenne muscular dystrophy; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FVC %p, forced vital capacity percent predicted; IFR, inspiratory flow reserve; PEF %p, percent predicted peak expiratory flow.

### Recently Completed and Ongoing Trials With Available Results

Our searches identified one relevant, recently completed late-phase trial with published results.\(^563,564\) We summarize this study with results as written in an abstract of a published study and a conference abstract.

We identified but excluded 4 post hoc analyses of data from the phase III DELOS study (NCT01027884).\(^565-568\) We also identified but excluded 4 conference poster presentations containing data from a retrospective cohort study (ie, SYROS) and/or post hoc analyses of data from the phase II DELPHI trial (NCT00654784).\(^569-572\)

The following abbreviations are used in this section: BAE, bronchopulmonary adverse event; CI, confidence interval; DMD, Duchenne muscular dystrophy; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FVC %p, percent predicted forced vital capacity; ITT, intent to treat; mITT, modified intent to treat; PEF, peak expiratory flow; PEF %p, percent predicted peak expiratory flow; vs, versus.

- **Patient population/planned enrollment:** Male patients (n = 64) aged 10 to 18 years with DMD who were not taking corticosteroids
- **Study design:** Phase III, randomized, parallel-assignment, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of 900 mg idebenone daily compared with those of placebo
- **Primary outcome:** Change in PEF%p from baseline to week 52
- **Secondary outcomes:** Change in FVC%p, muscle strength, and quality of life, all from baseline to week 52, and adverse event incidence
- **Results presented by study authors:** 
  
  "Idebenone significantly attenuated the fall in PEF%p from baseline to week 52 in the mITT (-3.05%p [95% CI -7.08 to 0.97], p = 0.134, vs placebo -9.01%p [-13.18 to -4.84], p = 0.0001; difference 5.96%p [0.16 to 11.76], p = 0.044) and ITT populations (-2.57%p [-6.68 to 1.54], p = 0.215, vs 8.84%p [-12.73 to -4.95], p < 0.0001; difference 6.27%p [0.61 to 11.93], p = 0.031). Idebenone also had a significant effect on PEF (L/min), weekly home-based PEF, FVC, and FEV1. The effect of idebenone on respiratory function outcomes was similar between patients with previous corticosteroid use and steroid-naive patients. Treatment with idebenone was safe and well tolerated with adverse event rates were similar in both groups. Nasopharyngitis and headache were the most common adverse events (idebenone, eight [25%] and six [19%] of 32 patients; placebo, nine [26%] and seven [21%] of 34 patients). Transient and mild diarrhea was more common in the idebenone group than in the placebo group (eight [25%] vs four [12%] patients)."

  "More patients in the placebo group fell below any of the clinically relevant FVC%p thresholds (idebenone: 34%; placebo 57%) or experienced a BAE, resulting in a hazard ratio of 0.50 (95% CI: 0.26-0.97; p=0.039) in favor of idebenone."563

**Manufacturers and Regulatory Status**

Santhera Pharmaceuticals (Pratteln, Switzerland) is developing idebenone for treating DMD in phase III trials. Santhera intends to submit to FDA a New Drug Application for idebenone (Puldysa) to treat DMD.573 (The manufacturer formerly used the brand name Catena for this indication.)560 FDA has granted several designations to idebenone for treating DMD: Orphan Drug designation in August 2016,574 Rare Pediatric Disease designation in August 2015,575 and Fast Track designation in April 2015.560 Idebenone (Raxone) was approved by the European Medicines Agency in September 2015 for treating Leber’s hereditary optic neuropathy576 and is in phase IV clinical development (NCT02774005) in the United States for this indication.

**Cost Information**

Cost information is unavailable for this topic, but the therapy is expected to be costly.

**Key Stakeholder Perspectives**

Nine stakeholders, reflecting caregiver, clinical, health systems, nursing, patient representative, and research perspectives, provided comments and ratings on idebenone.577-585 The list below summarizes key stakeholder perspectives.

- Improved respiratory function is a significant, meaningful outcome for patients with DMD, and currently available clinical trial data demonstrate that idebenone is efficacious in improving respiratory function.
• Idebenone might disrupt the current paradigm of patient care by decreasing the number of hospitalizations, dependency on respiratory support staff and equipment, and medication treatment with steroids and antibiotics.

• Idebenone’s side effect profile appears to be low and milder in comparison with that of corticosteroids (which include an increased risk for infection, weight gain, and osteoporosis), although some side effects might still be inconvenient for patients (e.g., transient diarrhea if patient is wheelchair-bound, headaches).

• More data are needed on whether improved respiratory function with idebenone treatment leads to significant improvements in clinical function.

• Comparison efficacy data are needed between idebenone and corticosteroids to justify use of idebenone in place of current standard-of-care comparator corticosteroids, especially if idebenone will be more costly than corticosteroids.
LentiGlobin to Treat Transfusion-Dependent β-Thalassemia

**Highlights**

- LentiGlobin is an investigational gene therapy delivered in a single infusion that is intended to permanently enhance a patient’s ability to produce functional hemoglobin B (HBB), enhance red blood cell (RBC) production, and relieve transfusion-dependent β-thalassemia (TDT) symptoms in children and adults aged up to 50 years with β0/β0 genotype (no β-globin expression) as well as β+/β0 genotype (little β-globin expression).
- The company stated that it plans to price the therapy less than $2.1 million and will offer special financing options and a value-based payment plan tied to how well it works in a patient.
- TDT substantially affects patient’s quality of life, because standard care consists of lifelong, regular blood transfusions or allogeneic hematopoietic stem cell transplantation (HSCT), which is burdensome and can lead to complications.
- Stakeholders commenting on this topic thought that LentiGlobin might reduce transfusion dependence, improve quality of life, and reduce demands on the health care system, but that longer-term studies are needed comparing the therapy with standard care.
- Stakeholders also thought that LentiGlobin would carry a high upfront cost but reduce transfusion dependence, which might lead to cost savings over time.

**Patient Population**

LentiGlobin is intended for children and adults aged up to 50 years with TDT, also known as β-thalassemia major or Cooley anemia, who have a β0/β0 genotype (no β-globin expression) or a β+/β0 genotype (little β-globin expression).

**Intervention**

TDT is caused by variants in the hemoglobin B gene, *HBB*, leading to reduced or absent hemoglobin (Hb). Reduced Hb negatively affects RBC development, causing severe anemia and related complications. Standard supportive care for TDT consists of lifelong, regular blood transfusions. Iron chelation therapy manages iron overload from transfusions, which can cause serious complications and organ damage. The National Institutes of Health’s Genetics Home Reference website offers more information on β-thalassemia.

Allogeneic (from a donor) HSCT can address the underlying cause of TDT, but it carries the risk of HSCT-related death, graft failure, and development of graft-versus-host disease and opportunistic infections, particularly in recipients of HSCT that is not from a matched sibling donor. Thus, a therapy derived from the patient’s own cells (autologous) could avoid these complications.

As a gene therapy, LentiGlobin purportedly enhances the patient’s ability to produce functional *HBB* genes that subsequently improve RBC production. The therapy consists of bone marrow–derived CD34+ hematopoietic stem cells from the patient that are transduced in the laboratory with a lentiviral vector that inserts a functional, modified copy of the *HBB* gene, βA-T87Q-globin. This purportedly improves effectiveness and allows its expression in patients to be measured. Transduced cells are then expanded in the laboratory to facilitate uptake.

Hb consists of 4 protein subunits: 2 subunits of α-globin (encoded by the *HBA1* or *HBA2* genes) and 2 subunits of β-globin (encoded by the *HBB* gene). Patients with β0 thalassemia carry variants in *HBB* preventing the production of any β-globin. Patients with β+ thalassemia carry
HBB variants that allow reduced β-globin production. LentiGlobin is under study in patients with both β0 and β+ TDT.

In clinical trials, LentiGlobin is given as a single intravenous treatment, at an unspecified dose, after patients are treated with busulfan to destroy the β-thalassemia-causing blood cells.

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified 3 ongoing trials for this topic. We present these trials in Table 5.16.

**Table 5.16. Ongoing Clinical Trials**

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
</table>
| A Study Evaluating the Efficacy and Safety of the LentiGlobin BB305 Drug Product in Subjects With Transfusion-Dependent β-Thalassemia, Who Do Not Have a β0/β0 Genotype (Northstar-2 [HGB-207]) NCT02906202 | Patients (n = 23) aged 50 years or younger with TDT who do not have a β0 mutation at both alleles of the HBB gene | Phase III, open-label, single-arm, multisite, single-dose study to evaluate the efficacy and safety of LentiGlobin Primary outcome: Proportion of patients achieving Tl at 12 to 24 months after infusion Secondary outcome(s):
• Engraftment, defined as an absolute neutrophil count ≥ 500 cells/µL for 3 consecutive days at 24 months after transplantation
• Detection of vector-derived replication-competent lentivirus at 24 months after infusion
• Frequency of insertional mutagenesis events leading to clonal dominance or leukemia at 24 months after infusion
• Percentage of patients with a reduction of at least 50% from the 2-year pretrial average baseline annual mL/kg RBC transfused, at 12 to 24 months after infusion | Primary and study completion February 2022 |
<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
</table>
| A Study Evaluating the Efficacy and Safety of the LentiGlobin BB305 Drug Product in Subjects With Transfusion-Dependent β-Thalassemia, Who Have a β0/β0 Genotype (Northstar-3 [HGB-212]) NCT03207009 | Patients (n = 18) aged 50 years or younger with TDT who have a β0/β0 genotype | Phase III, multicenter, open-label, single-arm study to evaluate the efficacy and safety of LentiGlobin Primary endpoint: Proportion of patients meeting criteria for TR at 12 to 24 months after transplantation Secondary endpoints:  
• Proportion of patients meeting the criteria for TI at 12 to 24 months after infusion  
• Percentage of patients with a reduction of at least 50% from the 2-year pretrial average baseline annual mL/kg RBC transfused at 12 to 24 months after infusion  
• Engraftment, defined as an absolute neutrophil count ≥ 500 cells/µL for 3 consecutive days at 24 months after infusion  
• Detection of vector-derived replication-competent lentivirus at 24 months after transplantation  
• Frequency of insertional mutagenesis leading to clonal dominance or leukemia at 24 months after transplantation  
• Frequency of clinical adverse events at 24 months after infusion | Primary and study completion June 2022 |

See preliminary results by Schneiderman et al 2020 under Recently Completed and Ongoing Trials With Available Results
**Study name and National Clinical Trials identifier**  
Longterm Follow-up of Subjects With Hemoglobinopathies Treated With Ex Vivo Gene Therapy (LTF-303)  
*NCT02633943*

**Patient population and planned enrollment**  
Patients (n = 94) aged up to 50 years with β-thalassemia or severe sickle cell disease who were treated with LentiGlobin in manufacturer-sponsored clinical trials

**Study design and outcomes**  
Phase I/II, multicenter, open-label, randomized, parallel-assignment, follow-up study to assess the long-term safety and efficacy of LentiGlobin through 15 years  

**Estimated date of completion**  
Primary and study completion March 2031

Abbreviations: AEs, adverse events; MRI, magnetic resonance imaging; RBC, red blood cell; TDT, transfusion-dependent β-thalassemia; TI, transfusion independence (defined as a weighted average hemoglobin ≥ 9 g/dL without any packed red blood cell transfusions for a continuous period of ≥12 months at any time during the study after study drug infusion); TR, transfusion reduction (defined as demonstration of at least a 50% reduction in volume of red blood cell transfusion requirements, in mL/kg, in the posttreatment time period of months 12 to 24 compared with the average annual transfusion requirement in the 24 months before enrollment).

**Recently Completed and Ongoing Trials With Available Results**

Our searches identified 2 relevant, late-phase trials with interim results reported in one publication.588 We summarize these studies with results as written in a conference abstract. The following abbreviations are used in this section: AE, adverse event; AUC, area under the curve; Hb, hemoglobin; RBC, red blood cell; TDT, transfusion-dependent β-thalassemia; TI, transfusion independence (defined as a weighted average hemoglobin ≥ 9 g/dL without any packed red blood cell transfusions for a continuous period of ≥12 months at any time during the study after study drug infusion); TR, transfusion reduction (defined as demonstration of at least a 50% reduction in volume of red blood cell transfusion requirements, in mL/kg, in the posttreatment time period of months 12 to 24 compared with the average annual transfusion requirement in the 24 months before enrollment).

**Interim Results From the Phase 3 Hgb-207 (Northstar-2) and Hgb-212 (Northstar-3) Studies of Betibeglogene Autotemcel Gene Therapy (LentiGlobin) for the Treatment of Transfusion-Dependent β-Thalassemia. NCT02906202, NCT03207009. Schneiderman et al 2020.**588

- **Patient population/planned enrollment**: Patients (n = 31) with TDT and non-β°/β° genotypes (NCT02906202) or β°/β°, β°/β+ IVS-1-110 genotypes (NCT03207009)
- **Study design**: Two phase III, single-arm, multisite, single-dose safety and efficacy studies
• **Primary outcomes**: Northstar-2: The proportion of treated patients who become TI at 12 to 24 months after transplantation. Northstar-3: The proportion of treated patients achieving TR from 12 to 24 months after transplantation.

• **Secondary outcomes**: Northstar-2: Percentage of patients with a reduction in RBC transfused of at least 50% from baseline from months 12 through 24 after treatment; and engraftment, detection of vector-derived replication competent lentivirus, frequency of insertional mutagenesis events leading to clonal dominance or leukemia, or frequency of clinical adverse events at 24 months after transplantation. Northstar-3: Proportion of patients achieving TI from 12 to 24 months after transplantation; percentage of patients with at least a 50% reduction in RBC transfused from baseline through 12 or 24 month after treatment; and engraftment, detection of vector-derived replication competent lentivirus, and frequency of insertional mutagenesis events leading to clonal dominance or leukemia.

• **Results presented by study authors**: “As of 13 Dec 2018 and 12 Apr 2019, 31 patients were treated in HGB-207 and HGB-212 with a follow-up of 8.1 (0.5–22.2) and 4.6 (1.5–15.7) months, respectively. Daily average busulfan AUC was 4450 (3709–9087) μM*min. Neutrophil and platelet engraftment were achieved at 25 (13–38) and 44 (20–84) days, respectively. Hospitalization from conditioning to discharge ranged from 30–92 days. In HGB-207, 10/11 patients followed for ≥6 months have stopped transfusions for ≥5.9 months (Figure 1). HbAT87Q levels at Months 6 (n=11), 12 (n=8) and 18 (n=3) were 9.5, 9.2, and 9.5 g/dL, respectively, which contributed to total hemoglobin (Hb) of 11.9, 12.4, and 11.3 g/dL at these time points, respectively. Marrow myeloid:erythroid ratios in 7/8 patients at Month 12 were 0.63–1.90 versus 0.14–0.48 at baseline, indicating improved erythropoiesis. In HGB-212, 3/4 patients followed for ≥6 months stopped transfusions for ≥6 months. Total Hb at last visit ranged from 10.5–13.6 g/dL and HbAT87Q was 9.5–12.6 g/dL at last assessment. Transfusion independence (weighted average Hb ≥9 g/dL without transfusions for ≥12 months) was achieved in 4/5 evaluable patients in HGB-207 and in the only evaluable patient in HGB-212. Post-infusion non-hematologic grade ≥3 adverse events (AEs) in ≥3 patients in either study were stomatitis (n=17), febrile neutropenia (n=11), pyrexia (n=4), epistaxis (n=3), and veno-occlusive liver disease (VOD; n=3). VOD prophylaxis with ursodiol or ursodiol/defibrotide was used in 24/31 patients. One beti-cel [LentiGlobin]-related serious AE of thrombocytopenia was reported; platelet count was 63 × 109/L at last visit (Month 7). All patients remain alive.”

**Manufacturers and Regulatory Status**

LentiGlobin is manufactured by bluebird bio Inc (Cambridge, Massachusetts) and is in phase III development for treating TDT. The company has announced plans to complete a rolling Biologics License Application with FDA for LentiGlobin in mid-2021. FDA had granted LentiGlobin Breakthrough Therapy designation in February 2015 for treating TDT major.

**Cost Information**

The company has announced plans to price LentiGlobin below the $2.1 million in “intrinsic value” that it estimates the therapy delivers. Early estimates by a financial firm put LentiGlobin’s price at about $1.2 million in the United States and $900 000 in the European Union. However, on June 14, 2019, the company announced the EU list price would be €1.58 million ($1.78 million) after winning conditional EU approval.

The company has announced plans to offer payers annuity-based payment agreements that would allow insurers to delay paying about 80% of LentiGlobin’s costs for up to 5 years after an initial upfront payment. The company also announced plans to offer a value-based payment agreement, accepting payment only if the treatment works. Finally, the company announced plans for price stability, linking price increases to the Consumer Price Index.
Key Stakeholder Perspectives

Seven stakeholders, reflecting health systems, caregiver, clinical, patient, and research perspectives, provided comments and ratings on LentiGlobin. The list below summarizes key stakeholder perspectives.

- LentiGlobin interim data are encouraging, suggesting that it might provide a clinically effective and well-tolerated option for one-time or sustained treatment of TDT.
- LentiGlobin might improve patients’ quality of life and decrease demands on the health care system if the treatment can substantially reduce transfusion dependence.
- LentiGlobin’s high cost might lead to health disparities in patients with insufficient insurance or in patients with insurance who cannot afford their copayments. But the treatment might be cost saving over time by reducing costs related to transfusion dependence. Also, annuity-based payment structures might improve access to LentiGlobin.
- Additional longer-term studies are needed to determine LentiGlobin’s efficacy, duration of effects, and cost-effectiveness.

Luspatercept-aamt (Reblozyl) to Treat Transfusion-Dependent β-Thalassemia

Highlights

- Luspatercept-aamt is a subcutaneously injected biologic therapy intended to treat β-thalassemia by helping restore levels of red blood cells (RBCs) to prevent anemia.
- FDA approved luspatercept-aamt in November 2019 to treat anemia in adults with β-thalassemia who require regular RBC transfusions. The treatment is available only through authorized distributors and is delivered by a provider in a health care facility.
- The therapy has an estimated retail cost of about $14,000 per treatment every 3 weeks, or roughly $252,000 per year.
- Stakeholders commenting on this topic thought that luspatercept-aamt could disrupt how providers care for patients with β-thalassemia by reducing the dependence on repeated blood transfusions.
- Stakeholders also thought that the new therapy could improve patients’ quality of life by improving convenience of treatment through reduced transfusion burden.

Patient Population

Luspatercept-aamt is indicated for adults aged 18 years or older with transfusion-dependent β-thalassemia (TDT), also known as β-thalassemia major or Cooley anemia. The therapy is not indicated as a substitute for transfusions in anemia that require immediate treatment.

Intervention

Luspatercept-aamt is a first-in-class biologic intended to help erythrocytes (ie, RBCs) mature as a treatment for TDT. This disease is caused by a variant in the beta-globin gene that prevents normal erythrocyte maturation, resulting in severe anemia that requires regular blood transfusions for survival plus nightly iron chelation to prevent iron overload from the blood transfusions. The National Organization for Rare Disorders website offers more information on β-thalassemia.
Luspatercept-aamt purportedly neutralizes certain transforming-growth factor (TGF)-β superfamily ligands to prevent abnormal signaling of proteins known as Smad2/3, thereby enabling late-stage RBC maturation to restore normal RBC production.600,603,604 The TGF-β ligands signal by way of serine-threonine kinase receptors on the cell surface to Smad proteins that accumulate in the cell nucleus to regulate gene expression. TGF-β superfamily signaling has been linked to multiple pathologies, including cancer and cardiovascular diseases.

The recommended starting dose is 1 mg/kg of body weight, which can be increased to a maximum of 1.25 mg/kg, delivered by a health care provider through an injection under the skin every 3 weeks.605

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 2 ongoing trials for this topic for this indication and patient population. We present these trials in Table 5.17.

(An additional phase II trial [NCT03342404] is evaluating luspatercept-aamt to treat nontransfusion-dependent β-thalassemia in adults; another phase II trial [NCT04143724] is assessing the safety and pharmacokinetics of luspatercept-aamt for treating TDT in children aged 6 months to 18 years. A phase III trial [NCT04064060] is assessing the biologic’s long-term safety in adults previously enrolled in clinical trials of luspatercept-aamt for multiple indications, including myelodysplastic syndromes, myeloproliferative neoplasm-associated myelofibrosis, and β-thalassemia. We have excluded these trials.)

Table 5.17. Ongoing Clinical Trials

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>An Efficacy and Safety Study of Luspatercept Versus Placebo in Adults Who Require Regular Red Blood Cell Transfusions Due to Beta Thalassemia (BELIEVE) NCT02604433</td>
<td>Adults (n = 336) aged 18 years or older with β-thalassemia who require regular RBC transfusions</td>
<td>Phase III, randomized, double-blind, parallel-assignment study comparing safety and efficacy of luspatercept-aamt with placebo for treating transfusion-dependent β-thalassemia Primary outcome: Reduction of 33% or greater in transfusion burden, with a reduction of 2 or more RBC units during weeks 13 to 24, when compared with a 12-week baseline period</td>
<td>Primary completion November 2017 Study completion June 2025</td>
</tr>
<tr>
<td>See preliminary results by Viprakasit et al 2019606 under Recently Completed or Ongoing Trials With Available Results</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Study name and National Clinical Trials identifier
- **ACE-536 Extension Study – Beta Thalassemia**
  - **NCT02268409**

### Patient population and planned enrollment
- Adults (n = 64) aged 18 years or older with β-thalassemia previously enrolled in luspatercept study A536-04  
  - **(NCT01749540)**

### Study design and outcomes
- Phase II, open-label, single-group assignment, extension study to assess the safety, tolerability, and pharmacodynamic effects of luspatercept-aamt for treating β-thalassemia
  - Primary outcome: Safety and tolerability of luspatercept therapy up to 730 days, assessed by incidence and classification (clinical and laboratory) of all adverse events

### Estimated date of completion
- Primary and study completion
  - February 2020

**Abbreviation:** RBC, red blood cell.

---

**Recently Completed or Ongoing Trials With Available Results**

Our searches identified 3 recently completed late-phase trials with published results.  
We summarize the 2 most recent studies with results as written in an abstracts of a published study and a conference abstract. (We excluded results from Porter et al 2019, who reported changes in blood iron concentrations and other laboratory values among patients in the BELIEVE trial [NCT02604433]. See Viprakasit et al 2019 below.)

The following abbreviations are used in this section: AEs, adverse events; pts, patients; RBC, red blood cell; U, unit; vs, versus; wks, weeks.

**Study to Evaluate the Effects of ACE-536 in Patients With Beta-Thalassemia (Study A536-04). NCT01749540.** **ACE-536 Extension Study – Beta-thalassemia. NCT02268409.** **Piga et al 2019.**

- **Patient population/planned enrollment:** Adults (n = 64) aged 18 years or older with β-thalassemia who were transfusion-dependent, defined as requiring 4 or more RBC units transfused every 8 weeks (n = 31), or nontransfusion dependent, defined as requiring fewer than 4 RBC units transfused every 8 weeks (n = 33)
- **Study design:** Phase II, open-label, single-group assignment dose-escalation study, and phase II long-term single-arm extension study
- **Primary outcomes:** Study A536-04: proportion of patients with an erythroid response, defined as a hemoglobin increase of 1.5 g/dL or greater from baseline for 14 days or longer without RBC transfusions in nontransfusion-dependent patients, or a 20% or greater reduction in RBC transfusion burden compared with pretreatment in transfusion-dependent patients. Extension study: long-term (through day 730) safety and tolerability of luspatercept in patients enrolled in the A536-04 study.
- **Results presented by study authors:** "Eighteen non-transfusion-dependent patients (58%) receiving higher dose levels of luspatercept (0.6–1.25 mg/kg) achieved mean hemoglobin increase ≥1.5 g/dL over ≥14 days vs baseline. Twenty-six (81%) transfusion-dependent patients achieved ≥20% reduction in RBC transfusion burden. The most common grade 1 to 2 adverse events were bone pain, headache, and myalgia."

**An Efficacy and Safety Study of Luspatercept Versus Placebo in Adults Who Require Regular Red Blood Cell Transfusions Due to Beta Thalassemia (BELIEVE). NCT02604433.** **Viprakasit et al 2019.**

- **Patient population/planned enrollment:** Adults (n = 336) aged 18 years or older with transfusion-dependent β-thalassemia
- **Study design:** Phase III, randomized, double-blind, parallel-assignment study comparing the safety and efficacy of luspatercept with placebo for treating transfusion-dependent β-thalassemia
• **Primary outcomes:** Treatment responses, defined as reduction of 33% or greater from baseline in transfusion burden over any consecutive 24 weeks at median follow-up of 64.1 weeks; and duration of benefit

• **Selected secondary outcomes:** Percentage of patients who achieved a reduction of 50% or greater in transfusion burden, change from baseline in blood iron levels, and change from baseline in quality of life survey scores

• **Results presented by study authors:** “92/224 (41.1%) luspatercept-treated pts and 3/112 (2.7%) placebo-treated pts had achieved ≥ 33% reduction in RBC transfusion over any 24 wks; of these luspatercept responders, 55 (59.8%) had ≥ 2 separate responses, . . . 42 (45.7%) had ≥ 3, 29 (31.5%) had ≥ 4, and 19 (20.7%) had ≥ 5. Three (1.3%) pts receiving luspatercept re-responded at the same dose level after initially losing response. Median duration of clinical benefit . . . for luspatercept responders was 53.5 wks (range 24-93.7). Forty-seven (21.0%) pts receiving luspatercept had no loss of response within the entire study period. Five luspatercept responders achieved RBC transfusion independence for ≥ 24 wks (median total duration was 60.1 wks) and 3 achieved RBC transfusion independence for ≥ 48 wks (median duration was 66 wks). The average . . . RBC units saved over any 24 wks in all luspatercept responders was 6.55 U (0.27 U/wk) and was 8.16 U (0.34 U/wk) with transfusion burden > 15 U/24 wks, compared to baseline . . . “Frequent . . . [AEs] . . . included bone pain (19.7% vs 8.3%, respectively), arthralgia (19.3% vs 11.9%), and dizziness (11.2% vs 4.6%).”

**Manufacturers and Regulatory Status**

Luspatercept-aamt was developed by [Acceleron Pharma Inc (Cambridge, Massachusetts)](https://www.acceleron.com) in collaboration with [Celgene Corp (Summit, New Jersey)](https://www.celgene.com). On November 8, 2019, FDA approved luspatercept-aamt, under the trade name Reblozyl, to treat anemia in adults with TDT.608 FDA previously granted luspatercept-aamt Orphan Drug, Fast Track, and Priority Review designations for the TDT indication.609-611

Product labeling states that only a health care provider should prepare the medication (ie, reconstitution with sterile water) and deliver the injections.605 According to the manufacturer, luspatercept-aamt can be purchased only through authorized distributors for administration in health care facilities (eg, physician offices and hospital outpatient clinics).612

**Cost Information**

GoodRx, an aggregator of prescription drug pricing at US retail pharmacies, lists prices from about $10 200 to $10 800 with a coupon for a single 75-mg vial and about $3400 to $3600 with a coupon for a single 25-mg vial (as of February 7, 2020).613,614 Per product dosing instructions of 1 mg/kg, an average 30-year-old male patient weighing 97 kg (about 213 lb) would require a 97-mg dose for a single treatment.615 In this example, a single treatment would require both a 75-mg and a 25-mg single-use vial, suggesting a retail cost about $13 600 to $14 400 per treatment, delivered every 3 weeks.615 Over 54 weeks (18 treatments), treatment costs would approach $244 800 to $259 200 at retail prices.

**Key Stakeholder Perspectives**

Eight stakeholders, reflecting caregiver, clinical, health systems, patient, and research perspectives, provided comments and ratings on luspatercept-aamt to treat TDT.616-623 The list below summarizes key stakeholder perspectives.

- Luspatercept-aamt fills a treatment gap between regular blood transfusions and stem cell transplants, which are potentially curative but very limited in availability to patients.
- Luspatercept-aamt has great potential to disrupt patient management by shifting therapy from routine blood transfusions and chelation therapy to a regimen of regular injections.
The new therapy could substantially improve quality of life by reducing dependence on routine blood transfusions and their inherent disruptions to patients’ lives and by improving convenience of therapy for patients.

Reducing the need for routine blood transfusions, even for a small patient population, could positively disrupt health care delivery by reducing hospital admissions for transfusion-related complications, modifying staffing needs and resource use related to transfusion infrastructure and delivery, and reducing the need for lengthy specialty clinic visits.

Onasemnogene Abeparvovec-xioi (Zolgensma) to Treat Spinal Muscular Atrophy

**Highlights**

- Onasemnogene abeparvovec-xioi (Zolgensma) is an FDA-approved treatment for spinal muscular atrophy (SMA). It consists of an adeno-associated viral vector containing a functional copy of the human survival motor neuron 1 gene, *SMN1*, that is responsible for encoding SMN protein, which is important for motor neuron function and transmission of signals from the brain to the skeletal muscles.
- As an intravenously delivered, one-time gene therapy, it is intended to fix the underlying genetic defect that causes SMA and to delay or halt disease progression, whereas prior treatment options consisted only of supportive care.
- Priced at $2.1 million, the therapy’s cost might limit patient access to care, increasing health disparities, but treatment success might reduce significant costs associated with SMA disease progression (eg, hospitalizations, life-saving interventions, caregiving).
- Stakeholders commenting on this topic generally agreed that the therapy has high potential to disrupt patient health outcomes, quality of health, and overall health.

**Patient Population**

Onasemnogene abeparvovec-xioi is intended for infants aged 2 years or younger with SMA (type unspecified).

**Intervention**

SMA is a neuromuscular disorder caused by a genetic defect in the *SMN1* gene, which results in loss of function of the gene’s encoded SMN protein that is critical for motor neuron function and transmission of signals from the brain to skeletal muscles. Patients with SMA experience motor neuron loss, resulting in progressive muscle weakness and eventual paralysis. The related *SMN2* gene can also produce low levels of SMN protein. SMA disease severity generally correlates with the number of *SMN2* copies the patient has. SMA is classified into 1 of 4 types (1, 2, 3, 4), with type 1 being the most severe and having the earliest onset, at about 0 to 6 months.

Onasemnogene abeparvovec-xioi is an adeno-associated viral vector containing a functional copy of *SMN1* that FDA has approved for this indication. Delivery of a functional copy of *SMN1* might delay or halt disease progression. Patients receiving onasemnogene abeparvovec-xioi are likely to have SMA type 1 or 2 because onset of these types typically occurs before 2 years of age.
The FDA-recommended dose of onasemnogene abeparvovec-xioi is \(1.1 \times 10^{14}\) vg/kg of body weight, delivered intravenously via peripheral vein, once. Because of potential immune reactions and/or acute liver injury after onasemnogene abeparvovec-xioi treatment, patients also receive systemic corticosteroids equivalent to oral prednisolone at 1 mg/kg of body weight per day, starting 1 day before administration and continuing for 30 days. At the end of 30 days, patients with normal liver enzymes levels taper the corticosteroid dose over 28 days, while patients with persistent, elevated enzyme levels continue corticosteroid treatment until they normalize, and then taper.\(^{628}\)

The SMA Foundation website offers more information on SMA.

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified 3 ongoing trials for this topic. We present these trials in Table 5.18.

**Table 5.18. Ongoing Clinical Trials**

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
</table>
| Pre-symptomatic Study of Intravenous AVXS-101 in Spinal Muscular Atrophy (SMA) for Patients With Multiple Copies of SMN2 (SPR1NT) NCT03505099 | Infants (n = 30) aged 42 days or younger with presymptomatic, genetically confirmed SMA type 1, and 2 or 3 copies of SMN2 | Phase III, single-arm study to determine the efficacy of a one-time intravenous administration of \(1.1 \times 10^{14}\) vg/kg of onasemnogene abeparvovec-xioi Primary outcomes:  
• Achievement of independent sitting for at least 30 seconds at 18 months of age  
• Achievement of ability to stand without support for at least 3 seconds at 24 months of age Secondary outcomes:  
• Permanent ventilator support independence at 14 months of age  
• Maintenance of weight at or above the third percentile at 18 months of age  
• Achievement of the ability to walk independently at 24 months of age | Primary completion October 2020  
Study completion June 2023 |
<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
</table>
| Single-Dose Gene Replacement Therapy Clinical Trial for Patients With Spinal Muscular Atrophy Type 1 (STR1VE-EU) **NCT03461289**  
See preliminary results by Novartis 2019 under Recently Completed and Ongoing Trials With Available Results | Infants (n = 33) aged 6 months or younger with genetically confirmed SMA type 1, and 1 or 2 copies of the SMN2 gene | Phase III, single-arm study to determine the efficacy of an unspecified dose of onasemnogene abeparvovec-xioi  
Primary outcome: Achievement of sitting without support for at least 10 seconds through 18 months of age  
Secondary outcome: Overall survival through 14 months of age | Primary and study completion September 2020 |
| Long-Term Follow-up Study for Patients From AVXS-101-CL-101 **NCT03421977**  
**Recently Completed and Ongoing Trials With Available Results** | Infants (n = 15) aged 6 months or younger with genetically confirmed SMA type 1 who completed the START study (**NCT02122952**) | Long-term follow-up study of patients who underwent onasemnogene abeparvovec-xioi treatment in the phase I START study  
Primary outcome: Adverse event and serious adverse event incidence through 15 years after treatment | Primary and study completion December 2033 |

Abbreviation: SMA, spinal muscular atrophy.

**Recently Completed and Ongoing Trials With Available Results**

Our searches identified 3 relevant, recently completed late-phase trials with published results.\(^{629,630}\) We summarize these studies with results as written in news releases.

The following abbreviations are used in this section: BiPAP, bilevel positive airway pressure; CHOP-INTEND, Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CNS, central nervous system; MB, myocardial band; SMA, spinal muscular atrophy; \( \text{SMN2} \), spinal neuron 2 gene; vg, viral genomes.

**Pre-symptomatic Study of Intravenous AVXS-101 in Spinal Muscular Atrophy (SMA) for Patients With Multiple Copies of SMN2 (SPR1NT). ** **NCT03505099.** Novartis 2019.\(^{629}\)**

- **Patient population/planned enrollment:** Infants (n = 30) aged 42 days or younger with presymptomatic, genetically confirmed SMA type 1, and 2 to 4 copies of \( \text{SMN2} \)
- **Study design:** Phase III, single-arm study to determine the efficacy of a one-time intravenous administration of \( 1.1 \times 10^{14} \text{ vg/kg of onasemnogene abeparvovec-xioi} \)
- **Primary outcomes:** Achievement of independent sitting for at least 30 seconds at 18 months of age and achievement of ability to stand without support for at least 3 seconds at 24 months of age
- **Secondary outcomes:** Permanent ventilator support independence at 14 months of age, maintenance of weight at or above the third percentile at 18 months of age, and achievement of the ability to walk independently at 24 months of age
- **Results presented by study authors:** “As of May 31 [2019], 10 patients with two copies of \( \text{SMN2} \), 12 patients with three copies of \( \text{SMN2} \), and one patient with four copies of \( \text{SMN2} \) were treated. The mean age of patients in the two-copy cohort was 6.6 months at last follow up and 4.6 months for the three-copy cohort. Of the two- and three-copy patients who had completed their six-month swallow evaluation, all had normal swallow function and were fed exclusively by mouth; of the 22 patients being evaluated overall, all were alive
and free of permanent ventilation. All patients with two copies of SMN2 achieved or maintained a CHOP-INTEND score of greater than 50, with seven patients achieving a CHOP-INTEND score of greater than or equal to 60 and five patients reaching the maximum score of 64. Of patients with two copies of SMN2, six (60%) were able to sit without support for at least 30 seconds at an average age of 7.6 months. Three of these patients (30%) were able to stand with assistance at an average age of 10.1 months. The natural history of untreated patients with SMA indicates that patients with two copies of SMN2 will never sit without assistance. Thirteen of the 18 patients (72.2%) experienced at least one treatment-emergent adverse event (TEAE) and seven (38.9%) were reported to have a TEAE considered by the investigator to be related to Zolgensma. Three serious TEAEs were reported in three treated patients: croup (one patient), lethargy (one patient), and hypercalcemia (one patient). All serious TEAEs were resolved and considered unrelated to treatment. In addition, TEAEs of special interest were reported in four patients: hepatic enzyme increased (one patient), liver function test increased (two patients), transaminases increased (one patient). One patient had asymptomatic increases of blood creatine phosphokinase MB and troponin, both resolved.

**Gene Replacement Therapy Clinical Trial for Patients With Spinal Muscular Atrophy Type 1 (STR1VE-US).** NCT03306277. Novartis 2019.629,630

- **Patient population/planned enrollment:** Infants (n = 22) aged 180 days (≈6 months) or younger with genetically confirmed SMA type 1, and 1 or 2 copies of SMN2
- **Study design:** Phase III, open-label, single-arm study to determine the efficacy of an unspecified dose of onasemnogene abeparvovec-xioi
- **Primary outcomes:** Achievement of independent sitting for at least 30 seconds at 18 months of age and event-free survival at 14 months of age (defined as avoidance of either death or permanent ventilation)
- **Secondary outcomes:** Ability to thrive through 18 months of age and ventilator support independence through 18 months of age
- **Results presented by study authors:** “[As of May 31, 2019,] of the 22 patients enrolled in STR1VE-US, 20 were alive, without permanent ventilation, and continuing in the trial. Of 19 patients who had either reached 13.6 months of age or experienced an event, 17 patients (89.5%) survived without permanent ventilation. The mean age at the most recent visit was 15.8 months at an average follow-up time of 12.1 months. Natural history indicates that only 25% of patients [with SMA type I] will survive event-free by the time they reach 13.6 months of age. CHOP-INTEND scores increased by an average of 6.9 points one month and 11.7 points three months after gene therapy treatment. In the STR1VE-US trial, one patient died from respiratory failure, which was deemed by the investigator and an independent Data Safety Monitoring Board to be unrelated to treatment. Additionally, after the safety data cutoff (March 8, 2019) one patient in the STR1VE-US study was determined by the investigator to have required ≥ 16 hours of non-invasive BiPAP ventilator support for ≥ 14 consecutive days at the time of withdrawal from the study. Based on this report from the investigator, AveXis will consider this patient as having required permanent ventilatory support at the time of discontinuation.”629

**Single-Dose Gene Replacement Therapy Clinical Trial for Patients With Spinal Muscular Atrophy Type 1 (STR1VE-EU).** NCT03461289. Novartis 2019.629

- **Patient population/planned enrollment:** Infants (n = 33) aged 6 months or younger with genetically confirmed SMA type 1, and 1 or 2 copies of SMN2
- **Study design:** A phase III, single-arm study to determine the efficacy of an unspecified dose of onasemnogene abeparvovec-xioi
- **Primary outcome:** Achievement of sitting without support for at least 10 seconds through 18 months of age
- **Secondary outcome:** Overall survival through 14 months of age
- **Results presented by study authors:** “[As of May 31 [2019],] of the 10 patients who had reached 10.5 months of age or experienced an event, nine (90%) survived without permanent ventilation. The mean age at the most recent visit was 8.2 months at an average follow-up time of 4.2 months. CHOP-INTEND scores increased by an average of 6.4 points one month (n=25) and 10.6 points three months (n=22) after gene
therapy treatment. As previously reported, one patient in the STR1VE-EU trial died prior to the March 8th safety data cutoff. According to the Coroner's report, the immediate cause of death was hypoxic-ischemic brain damage with respiratory tract infection as the underlying cause. SMA type 1 was indicated as the underlying cause for the respiratory tract infection. In addition, there was no evidence of an inflammatory CNS process or a toxic or a treatment-related brain damage. Following the autopsy report findings, leukoencephalopathy, which was reassessed as hypoxic-ischemic brain damage, and respiratory distress are considered unrelated to the gene therapy by the investigator. The final autopsy report has indicated the gene therapy could have potentially contributed to the concurrent events of abnormal liver function tests (elevation of liver enzymes called transaminases), abnormal blood tests (low platelets) and low blood pressure. The serious adverse events (SAE) reports will be updated accordingly and submitted to the Health Authorities.

Manufacturers and Regulatory Status

AveXis Inc (Bannockburn, Illinois), a wholly owned subsidiary of Novartis AG (Basel, Switzerland), developed onasemnogene abeparvovec-xioi (Zolgensma) for treating SMA type 1. FDA approved the drug for this indication on May 24, 2019. Its approval was based on data from the ongoing phase III STR1VE-US trial and the completed phase I START trial. FDA approved the drug for this indication on May 24, 2019. Its approval was based on data from the ongoing phase III STR1VE-US trial and the completed phase I START trial. In August 2019, FDA released a statement regarding manipulation of data that were included in the manufacturer’s Biologics License Application but concluded that the product should remain on the market. FDA granted the drug Orphan Drug designation for treating any type of SMA and Breakthrough Therapy and Fast Track designations for treating SMA type 1.

Cost Information

Zolgensma’s wholesale acquisition cost is about $2.1 million. AveXis established the OneGene Program to provide patients with reimbursement assistance and support and created a worldwide expanded-access plan to allow uninsured or underinsured patients access to the drug.

An April 2019 evidence report from the Institute for Clinical and Economic Review (ICER), published before Zolgensma’s approval, evaluated the drug’s cost-effectiveness compared with that of best supportive care (no additional therapy). Because Zolgensma’s wholesale acquisition cost (WAC) was not yet available, ICER used a placeholder price of $2 million, which is similar to its actual WAC.

Compared with no additional treatment, Zolgensma’s estimated lifetime incremental cost-effectiveness ratio was about $243,000 per quality-adjusted life-year (QALY) gained, higher than the generally accepted cost-effectiveness threshold of $150,000 per QALY. Estimated cost per life-year gained was $182,000. Additionally, ICER estimated total costs of Zolgensma to be $3.7 million compared with $790,000 for best supportive care. In the same report, ICER also determined that Zolgensma’s comparator, Spinraza, was not cost effective, with a lifetime incremental cost-effectiveness ratio of about $1.1 million per QALY gained.

Key Stakeholder Perspectives

Seven stakeholders, reflecting caregiver, clinical, health systems, nursing, and research perspectives, provided comments and ratings on onasemnogene abeparvovec-xioi. The list below summarizes key stakeholder perspectives.

- Preliminary data as reported in news releases seem promising and suggest the drug might significantly improve patient health outcomes, quality of life, and overall health for patients with SMA who otherwise have a poor prognosis (eg, inability to walk,
respiratory failure, feeding difficulties, life expectancy often limited to childhood) by delaying or halting disease progression.

- At a price of $2.1 million, Zolgensma is very costly and might increase health disparities and access to care, although reimbursement assistance and/or access programs such as the developer’s OneGene Program might help. Additionally, treatment success with Zolgensma might reduce other significant health care costs associated with SMA (eg, hospitalizations, life-saving interventions, caregiving).

- The therapy has high potential to disrupt the current paradigm of patient care for reasons including it is a single-dose, one-time therapy (versus chronic therapy), it might shift the treatment model from supportive care to curative care, and the treatment setting might shift more toward outpatient (versus inpatient) if patients experience slower disease progression and fewer life-threatening symptoms.

- More data are needed on longer-term outcomes (eg, change in life expectancy, rate of disease progression).
OTL-101 to Treat Adenosine Deaminase–Severe Combined Immunodeficiency

Highlights
- OTL-101 is an investigational gene therapy given as a single intravenous infusion intended to permanently enhance a patient’s ability to produce a functional adenosine deaminase gene, *ADA*, and restore immune function in patients with adenosine deaminase–severe combined immunodeficiency (ADA-SCID).
- ADA-SCID is a rare inherited disorder that manifests as severe immunosuppression from a lack of functional lymphocytes (T cells and B cells), leaving patients perpetually susceptible to severe infections, affecting quality of life and overall survival.
- Stakeholders commenting on this topic thought that OTL-101 might eliminate the need for ADA enzyme replacement and immunoglobulin replacement therapies in patients without a suitable donor for hematopoietic stem cell transplantation (HSCT), improving quality of life, and reducing demands on the health care system.
- Stakeholders also thought that OTL-101 would carry a high upfront cost (more than $1 million) but that reduced need for supportive care might lead to cost savings over time.

Patient Population
OTL-101 is intended for infants and children aged 30 days to 17 years with ADA-SCID who are ineligible for allogeneic bone marrow transplantation from a matched family donor.

Intervention
ADA-SCID is a rare inherited disorder severely affecting the immune system due to genetic variants that inhibit the expression of the *ADA* gene, which encodes an enzyme crucial for lymphocyte (T cell and B cell) development. Patients with ADA-SCID do not produce functional lymphocytes and thus are perpetually susceptible to severe infections. The National Institutes of Health’s Genetics Home Reference website offers more information on ADA-SCID.

OTL-101 is a cell-based gene therapy made from patient-derived stem cells that have been transfected in the laboratory with a lentiviral vector encoding the human *ADA* gene. The therapy is intended for a deficiency in adenosine deaminase enzyme production, potentially restoring stable lymphocyte development and immunity in patients with ADA-SCID.

To prepare OTL-101, stem cells from the patient’s bone marrow are harvested and shipped to a manufacturing site, where the cells are purified and transduced with a lentiviral vector that will deliver the *ADA* gene into the stem cells. The genetically modified stem cells are frozen and shipped back to the infusion center. The patient then undergoes a pretreatment conditioning regimen with busulfan before the cryopreserved OTL-101 product is thawed and given as a single intravenous infusion.

Evidence Development Summary

Ongoing Trials
Our searches of the National Clinical Trials database identified 2 ongoing trials for this topic. We present these trials in Table 5.19.
### Table 5.19. Ongoing Clinical Trials

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
</table>
| A Clinical Study to Enable Process Validation of Commercial Grade OTL-101 [NCT04140539](NCT04140539) | Children aged 30 days to 17 years with ADA-SCID (n = 3) who did not have a medically eligible donor available for bone marrow transplantation | Phase II/III, single-arm, open-label, treatment study to validate the commercial manufacturing process of OTL-101 Primary outcomes:  
- ADA enzyme activity at 6 months after treatment  
- T-cell (CD3^+) count at 6 months after treatment  
- Absolute count of CD3^+ cells  
- Vector copy number at 6 months after treatment  
Secondary outcomes:  
- Overall survival at 12 months after infusion  
- Event-free survival at 12-months after OTL-101 infusion | Primary completion August 2020  
Study completion February 2021 |
| An Open Label Study to Assess the Safety and Efficacy of Gene Therapy for Patients With ADA-SCID [NCT03765632](NCT03765632) | Children aged up to 17 years with ADA-SCID (n = 10) who did not have a medically eligible donor available for bone marrow transplantation | Phase I/II, prospective, nonrandomized, single-group assignment study to assess the efficacy and safety of OTL-101 in infants and children with ADA-SCID Primary outcomes:  
- Overall survival at 12 months after OTL-101 infusion  
- Event-free survival at 12 months after OTL-101 infusion  
Secondary outcomes:  
- Overall survival at 24 months after infusion  
- Event-free survival at 24 months after infusion | Primary completion December 2020  
Study completion March 2021 |

Abbreviations: ADA, adenosine deaminase; ADA-SCID, adenosine deaminase–severe combined immunodeficiency.

### Recently Completed and Ongoing Trials With Available Results

Our searches identified 2 relevant, late-phase trials with interim results.646 We summarize these 2 studies with results as written in a conference abstract.

The following abbreviations are used in this section: ADA, adenosine deaminase; ADA-SCID, adenosine deaminase–severe combined immunodeficiency; ERT, enzyme replacement therapy; EvFS, event-free survival; FU, follow-up; GT, gene therapy; GvHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; HSPCs, hematopoietic stem and progenitor cells; mo, months; MRD, matched related donor; OS, overall survival; PEG-ADA,
polyethylene glycol–modified adenosine deaminase; UCLA, University of California, Los Angeles.

**Lentiviral Gene Therapy With Autologous Hematopoietic Stem and Progenitor Cells (HSPCs) for the Treatment of Severe Combined Immune Deficiency Due to Adenosine Deaminase Deficiency (ADA-SCID): Results in an Expanded Cohort.** [NCT01852071, NCT02999984](#), Kohn et al 2019.646

- **Patient population/planned enrollment:** Patients with ADA-SCID (NCT01852071, n = 20; NCT02999984, n = 10)
- **Study design:** Two phase I/II, single-arm, open-label, single-dose, safety and efficacy studies
- **Primary outcomes:** NCT01852071: Safety, overall survival, and event-free survival at 2 years. NCT02999984: Treatment success rate at 6 months, overall survival at 12 months, event-free survival at 12 months
- **Secondary outcomes:** NCT01852071: ADA enzyme activity in peripheral blood mononuclear cells, total adenine nucleotides in erythrocytes, antibody responses, and T lymphocyte reconstitution at 2 years. NCT02999984: overall survival and event-free survival at 24 months.
- **Results presented by study authors:** “Sustained engraftment of genetically modified HSPCs was observed in 29/30 GT subjects by 6-8 mo and persisted through FU in both studies, based on vector gene marking in granulocytes and CD3+ T cell reconstitution. Subjects who engrafted maintained long-term metabolic detoxification from deoxyadenosine nucleotides after stopping ERT approximately 1 mo post-GT. At last FU (median 24 mo; range 12-24 mo) in the GT group, overall survival (OS) was 30/30 (100%) and event-free survival (survival in the absence of ERT reinstitution or rescue allogeneic HSCT; EvFS) was 29/30 (97%). OS and EvFS were higher in the GT group at last FU compared with HSCT controls (with or without an MRD) at 2 years. One of 30 OTL-101 subjects (3%) did not engraft and was restarted on ERT; the subject was withdrawn from the study at 5.9 mo and subsequently received a rescue HSCT, whereas 42% of HSCT patients required rescue HSCT, PEG-ADA ERT or died. Among the 20 OTL-101 subjects in the UCLA Fresh Study who reached 2 years FU, 18 (90%) stopped immunoglobulin replacement therapy (IgRT), compared to 52% of HSCT patients. Preliminary results were observed in 5/7 (71%) OTL-101 subjects in the UCLA Cryo Study with more limited (18 mo) FU. Twelve OTL-101 subjects experienced one or more serious adverse events, most frequently infections and gastrointestinal events; only 1 of which was considered treatment-related (bacteremia due to product contamination). In the GT group, there were no events of autoimmunity with ≤24 mo FU. Due to the autologous nature of OTL-101, there was no incidence of graft vs host disease (GvHD); in contrast, 8 HSCT patients experienced GvHD events (5 acute, 3 chronic events), 1 of which resulted in death.”

**Manufacturers and Regulatory Status**

OTL-101 is manufactured by [Orchard Therapeutics Ltd (London, United Kingdom)](http://www.orchardtherapeutics.com) and is in phase II/III clinical development for treating ADA-SCID in infants and children aged 30 days to 17 years.647 The manufacturer has announced plans to delay the submission of a Biologics License Application to FDA planned for the first half of 2020 because of impacts related to the COVID-19 pandemic.648 FDA previously granted OTL-101 Orphan Drug, Rare Pediatric Disease, and Breakthrough Therapy designations.649,650

**Cost Information**

Cost information is unavailable for this topic, but stakeholders expect the gene therapy’s cost to be high. (Other FDA-approved gene therapies have costs exceeding $2 million.)

**Key Stakeholder Perspectives**

Six stakeholders, reflecting health systems, clinical, physician assistant, and research perspectives, provided comments and ratings on OTL-101.651-656 The list below summarizes key stakeholder perspectives.
OTL-101 interim data are encouraging, suggesting that it might provide a clinically effective and well-tolerated option for one-time or sustained treatment of ADA-SCID. OTL-101 might obviate the need for a matched donor for HSCT and improve patients’ overall survival and quality of life as well as reduce demands on the health care system compared with standard care HSCT, enzyme replacement therapy, or enzyme and immunoglobulin replacement therapy. OTL-101 is expected to have a high upfront cost (more than $1 million), which might lead to health disparities and controversy regarding patients with public insurance or who are uninsured or underinsured. But the treatment might save costs over time by reducing costs related to long-term management of ADA-SCID. Additional longer-term studies are needed to determine OTL-101’s efficacy, duration of effects, and cost-effectiveness.

Palovarotene to Treat Fibrodysplasia Ossificans Progressiva

Highlights

- Palovarotene is an investigational, oral, retinoic acid receptor gamma (RARγ) agonist intended to slow the progression of fibrodysplasia ossificans progressiva (FOP).
- FOP is a rare connective tissue disorder that leads to heterotopic ossification (HO) flares, characterized by abnormal bone growth in muscles, tendons, and ligaments leading to disability and death.
- Stakeholders commenting on this topic were generally optimistic about palovarotene’s preliminary clinical trial results, and they thought palovarotene might improve patient health outcomes and quality of life by slowing disease progression and decreasing dependence on supportive care.
- Stakeholders cautioned, however, that palovarotene’s benefits might not outweigh the risks, particularly in pediatric patients, and its overall disruptive potential depends on forthcoming safety and efficacy data.

Patient Population

Palovarotene is intended to treat FOP in children aged 14 years or older and adults.

Intervention

In patients with FOP, mutant activin receptor-like kinase-2 (ALK2) overactivates Smad 1/5/8 transcription factors in the bone morphogenetic protein 2 (BMP2) pathway. This leads to HO that manifests as abnormal bone growth in muscles, tendons, and ligaments.657,658 HO flares can occur spontaneously or follow physical trauma (eg, injury, infection).657,659 Once heterotopic bone forms, it cannot be surgically removed because tissue disruption causes additional HO episodes.

HO progressively interferes with normal body functions, including walking, bending, breathing, chewing, and swallowing. Patients typically require a wheelchair by about 20 years of age. Registry data suggest a median life span of about 40 years, with cardiorespiratory failure and pneumonia cited as the leading causes of death.657,659,660 The National Institutes of Health’s Genetic and Rare Diseases Information Center website offers more information on FOP.
Palovarotene is an orally administered selective RARγ agonist being developed to treat FOP, a rare connective tissue disorder caused by a mutation in the activin A receptor type I gene, ACVR1, that encodes the ACVR1/ALK2 receptor. ALK2 regulates the BMP pathway, which is responsible for cartilage regulation and bone growth and development. Palovarotene purportedly binds to and activates RARγ to decrease Smad 1/5/8 protein levels and reduce excess BMP signaling to prevent further HO development in patients with FOP.

In an ongoing phase III clinical trial, palovarotene is administered in a 5-mg dose, once daily, to manage chronic FOP. For an FOP disease flare, palovarotene is administered at a dose of 20 mg, once daily for 4 weeks, followed by 10 mg, once daily for 8 weeks.

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified 3 ongoing trials for this topic. We present these trials in Table 5.20.

**Table 5.20. Ongoing Clinical Trials**

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOVE Trial: An Efficacy and Safety Study of Palovarotene for the Treatment of FOP NCT03312634 MOVE trial (PVO-1A-301)</td>
<td>Children aged 4 years or older and adults (n = 90) with a clinical diagnosis of FOP and no flares in previous 4 weeks</td>
<td>Phase III, single-arm, open-label study to assess the efficacy of palovarotene in decreasing new HO in FOP. Data from this trial will be compared with historical data from a natural cohort study of FOP patients. Primary outcome: Annualized change in new HO volume</td>
<td>Primary completion September 2020 Study completion November 2020</td>
</tr>
<tr>
<td>An Open-Label Extension Study of Palovarotene Treatment in FOP NCT02279095 See preliminary results by Clementia Pharmaceuticals 2018 under Recently Completed and Ongoing Trials With Available Results</td>
<td>Children aged 6 to 17 years and adults aged up to 65 (n = 58) with a clinical diagnosis of FOP</td>
<td>Phase II, single-arm, open-label extension study assessing safety and efficacy of multiple palovarotene dosing regimens to treat chronic FOP and flares Primary outcome: Annualized change in new HO volume</td>
<td>Primary and study completion March 2021</td>
</tr>
<tr>
<td>An Open-Label Extension Study of Palovarotene Treatment in FOP in France NCT02979769</td>
<td>Children aged 6 to 17 years and adults aged up to 65 (n = 17) with a clinical diagnosis of FOP</td>
<td>Phase II, single-arm, open-label extension study in France assessing safety and efficacy of multiple palovarotene dosing regimens to treat chronic FOP and flares Primary outcome: Percentage of flares with no new HO</td>
<td>Primary and study completion March 2021</td>
</tr>
</tbody>
</table>

Abbreviations: FOP, fibrodysplasia ossificans progressiva; HO, heterotopic ossification.
Recently Completed and Ongoing Trials With Available Results

Our searches identified one recently completed late-phase trial with published results.\textsuperscript{663} We summarize this study below with results as written in a news release.

The following abbreviations are used in this section: FOP, fibrodysplasia ossificans progressiva; HO, heterotopic ossification; PROMIS, Patient-Reported Outcomes Measurement Information System; WBCT, whole body computed tomography.

An Open-Label Extension Study of Palovarotene Treatment in FOP. \textbf{NCT02279095}. Clementia Pharmaceuticals 2018.\textsuperscript{663}

- **Patient population/planned enrollment**: Children aged 6 to 17 years and adults aged up to 65 years (n = 53) with a clinical diagnosis of FOP
- **Study design**: Phase II, single-arm, open-label extension study assessing safety and efficacy of multiple palovarotene dosing regimens to treat chronic FOP and flares
- **Primary outcome**: Annualized change in new HO volume
- **Secondary outcomes**: Patients with new HO, the proportion of subjects with any new HO, range of motion, change in physical function using the FOP-Physical Function Questionnaire, change from baseline in mental and/or physical health function via age-appropriate PROMIS Global Health Scale, and incidence of adverse events from baseline up to 60 months
- **Results presented by study authors**: “New HO volume at the site of a flare-up at 12 weeks was a pre-specified secondary endpoint in the Phase 2 study, and is an objective measure that is analyzed using standardized procedures by blinded, independent central imaging readers. In a preliminary analysis of adults and skeletally mature children, we observed a statistically significant 91 percent reduction (p=0.01) in mean volume of new HO for the 29 flare-ups treated with the chronic/flare-up dosing regimen (719mm$^3$) in Part B as compared to the 60 untreated flare-ups (8,001mm$^3$). In addition to these data, Clementia analyzed data from those evaluable patients who had both 12-week flare-up scans and 12-month WBCT scans. For the 9 patients with no new HO at 12-weeks at the flare-up location, there was no new HO at 12-months anywhere in the body, including the assessed flare-up location. We believe these data suggest that flare-up data could potentially be predictive of longer term outcomes. In addition to the 12-week flare-up scans, new HO in adults and skeletally mature children receiving the chronic/flare-up dosing regimen was assessed by WBCT scan at 12 months compared to untreated patients in the natural history study, regardless of whether or not flare-up symptoms were present. This preliminary per protocol assessment included 33 evaluable patients, and a 28 percent reduction in whole body volume of new HO in treated patients (21,567mm$^3$) was observed as compared to the 55 untreated patients (29,731mm$^3$). Importantly, in this evaluation, one patient included in the analysis experienced multiple flare-ups which were not treated with the 20/10mg regimen because they did not meet the requirements for flare-up treatment according to the Part B protocol. Utilizing the MOVE Trial flare-up definition and treatment criteria, which require only one flare-up symptom, this patient would have qualified for high-dose treatment in the Phase 3 MOVE Trial. When we analyze these data without this one patient, treatment with palovarotene resulted in a 65 percent mean reduction of new HO by WBCT (10,682 mm$^3$) compared to the untreated control group (29,731mm$^3$).”

Manufacturers and Regulatory Status

Palovarotene is manufactured by \textbf{Clementia Pharmaceuticals Inc} (Montreal, Québec, Canada), an \textbf{Ipsen Group} company (Paris, France), and is in phase III development (MOVE trial, \textbf{NCT03312634}) for preventing FOP flares. The study is scheduled for primary completion in September 2020.\textsuperscript{662} On March 26, 2020, the manufacturer announced it would reinitiate palovarotene dosing in patients aged 14 years and older who were enrolled in FOP clinical trials, as FDA regulators confirmed they had no safety concerns about dosing patients in that cohort.\textsuperscript{664}

In January 24, 2020, Ipsen announced that the company would pause dosing patients in the phase III MOVE study as well as the ongoing phase II (PVO-1A-202/204) extension studies
based on results of a prespecified interim futility analysis by the Independent Data Monitoring Committee (IDMC). The futility analysis revealed that the phase III FOP trial was unlikely to meet its primary efficacy endpoint (annualized change in new HO volume compared with a separate ongoing natural history study control). However, the IDMC recommended not to discontinue the study due to disparate results, and the prespecified interim analysis revealed signals of encouraging therapeutic activity in a preliminary phase III post hoc analyses.

On December 6, 2019, Ipsen initiated a partial clinical hold for dosing pediatric patients aged 14 years and younger with palovarotene for treating chronic FOP due to safety reports submitted to FDA of cases of early growth plate closure in pediatric patients given the drug. FDA granted palovarotene Rare Pediatric Disease designation to treat FOP in February 2019. FDA has also granted palovarotene Breakthrough Therapy, Fast Track, and Orphan Drug designations for treating FOP.

**Cost Information**

Cost information is unavailable for this topic, but stakeholders expected the cost to be high.

**Key Stakeholder Perspectives**

Seven stakeholders, reflecting physical therapist, health systems, clinical, nurse practitioner, and research perspectives, provided comments and ratings on palovarotene. The list below summarizes key stakeholder perspectives.

- Palovarotene interim data are encouraging, suggesting that it might provide a clinically effective treatment option for slowing the progression of FOP. But the benefits might not outweigh the risks, particularly in pediatric patients in whom complications regarding growth plates, hearing, or vision might occur.
- Palovarotene might reduce demands on the health care system and caregivers by slowing disease progression and related needs for supportive care.
- Palovarotene is expected to have a high cost, which might lead to health disparities and controversy regarding patients with public insurance or who are uninsured or underinsured. But the treatment might provide cost offsets by reducing costs related to managing HO flares and supportive care.
- Additional longer-term studies are needed to determine palovarotene’s safety, efficacy, duration of effects, and cost-effectiveness.

**PTC-AADC to Treat Aromatic l-Amino Acid Decarboxylase Deficiency**

**Highlights**

- PTC-AADC is an adeno-associated viral vector containing a functional copy of the human dopa decarboxylase gene, DDC, that purportedly restores the gene’s encoded enzyme, aromatic l-amino acid decarboxylase (AADC), to correct the underlying genetic defect. It is intended to enhance neurotransmitter production, restore motor function, and delay or prevent other disease symptoms of aromatic l-amino acid decarboxylase deficiency (AADC). 
- PTC-AADC is administered in a one-time-only intracerebral infusion via stereotactic surgery.
- Stakeholders commenting on this topic generally agreed PTC-AADC has large potential to improve patient health outcomes, quality of life, and overall health.
• Stakeholders also thought PTC-AADC has moderate to large potential to disrupt the current paradigm of patient care and the health care delivery system because this therapy might shift care from supportive to curative and requires specialized personnel in a specialized health care setting for administration.

Patient Population

PTC-AADC is intended for children aged 2 years or older and adults with genetically confirmed, symptomatic AADCD.

Intervention

PTC-AADC (formerly known as AGIL-AADC, AAV2-hAADC, and GT-AADC) is an adeno-associated viral vector containing a functional copy of the \textit{DDC} gene.\cite{675} It is intended to promote \textit{DDC} gene expression in patients with AADCD, a childhood-onset, progressive, inherited neurometabolic disorder. AADCD is caused by variations in the \textit{DDC} gene, inherited in an autosomal recessive pattern, that result in the loss of the gene’s encoded enzyme AADC, which is critical for converting neurotransmitter precursors into dopamine, epinephrine, norepinephrine, or serotonin.\cite{676} Patients with AADCD experience many symptoms, including severe developmental delays, decreased muscle tone, involuntary arm and leg movements, and seizures. Treatments only manage symptoms and do not prevent disease progression.

Delivery of a functional copy of \textit{DDC} may enhance neurotransmitter production, restore motor function, and delay or prevent other disease symptoms.\cite{675} In clinical trials, patients received a single intracerebral infusion of PTC-AADC (1.8 \times 10^{11} \text{ viral genomes [vg]} or 2.4 \times 10^{11} \text{ vg}) via stereotactic surgery.

The National Institutes of Health’s Genetics Home Reference website offers more information on AADCD.

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 2 ongoing trials for this topic. We present these trials in Table 5.21.
### Table 5.21. Ongoing Clinical Trials

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Clinical Trial for Treatment of Aromatic L-Amino Acid Decarboxylase (AADC) Deficiency Using AAV2-hAADC – An Expansion (NTUH-AADC-011; MIND) NCT02926066 See preliminary results by Lee et al 2018677 and Chien et al 2019678 under Recently Completed and Ongoing Trials With Available Results</td>
<td>Children (n = 10) aged 2 to 6 years with genetically confirmed AADCD</td>
<td>Phase II, single-arm, open-label study to determine the safety and efficacy of a one-time intracerebral administration of 2.371 × 10¹¹ vg PTC-AADC (AAV2-hAADC) Primary outcomes: • Increase of PDMS-2 score of more than 10 points, from baseline to 13 months after gene therapy • 5-HIAA and HVA (neurotransmitter metabolite) levels in CSF 13 months after gene therapy Secondary outcomes: • Dyskinesia severity at 13 months after gene therapy • Other SAE incidence at 13 months after gene therapy</td>
<td>Primary and study completion December 2020</td>
</tr>
<tr>
<td>A Phase I/II Clinical Trial for Treatment of Aromatic L-Amino Acid Decarboxylase (AADC) Deficiency Using AAV2-hAADC NCT01395641 See preliminary results by Chien et al 2017675 under Recently Completed and Ongoing Trials With Available Results</td>
<td>Children and adults (n = 10) aged 24 months or older with genetically confirmed AADCD</td>
<td>Phase I/II single-arm, open-label study to determine the safety and efficacy of a one-time intracerebral administration of 1.8 × 10¹¹ vg PTC-AADC (AAV2-hAADC) Primary outcomes: • Increase of PDMS-2 score of more than 10 points, from baseline to 1 year after gene therapy • 5-HIAA and HVA (neurotransmitter metabolite) levels in CSF 1 year after gene therapy Secondary outcomes: • Dyskinesia severity at 12 months after gene therapy • Other SAE incidence at 12 months after gene therapy</td>
<td>Primary and study completion December 2020</td>
</tr>
</tbody>
</table>

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; AADCD, aromatic L-amino acid decarboxylase deficiency; CSF, cerebrospinal fluid; HVA, homovanillic acid; PDMS-2, Peabody Developmental Motor Scales, version 2; SAE, serious adverse event; vg, viral genomes.

Recently Completed and Ongoing Trials With Available Results

Our searches identified 3 relevant, recently completed late-phase trials with published results.675,677,678 We summarize these studies with results as written in an abstract of a published study and conference abstracts.

The following abbreviations are used in this section: 5-HIAA, 5-hydroxyindoleacetic acid; AADCD, aromatic L-amino acid decarboxylase deficiency; AE, adverse event; AIMS, Alberta
Infant Motor Scale; CSF, cerebrospinal fluid; HVA, homovanillic acid; IQR, interquartile range; PDMS-2, Peabody Developmental Motor Scales, version 2; SAE, serious adverse event; vg, viral genomes.

**Pooled Analysis of: A Clinical Trial for Treatment of Aromatic l-Amino Acid Decarboxylase (AADC) Deficiency Using AAV2-hAADC – An Expansion (NTUH-AADC-011; MIND), NCT02926066, and A Phase I/II Clinical Trial for Treatment of Aromatic L-Amino Acid Decarboxylase (AADC) Deficiency Using AAV2-hAADC, NCT01395641. Lee at al 2018,677 and Chien et al 2019.678**

- **Patient population/planned enrollment**: Children and adults (n = 25) aged 2 years or older with genetically confirmed AADCDD.
  
  *Note*: some of these patients are also included in data presented in the next recently completed trial.

- **Study design**: NCT02926066: Phase II, single-arm, open-label study to determine the safety and efficacy of a one-time intracerebral administration of $2.371 \times 10^{11}$ vg PTC-AADC (AAV2-hAADC). NCT01395641: Phase I/II, single-arm, open-label study to determine the safety and efficacy of a one-time intracerebral administration of $1.8 \times 10^{11}$ vg PTC-AADC (AAV2-hAADC).

- **Outcomes**: Developmental milestone achievement (ie, full head control, unassisted sitting, standing with support, and unassisted or assisted walking, as measured by AIMS, Bayley-III, and PDMS-2 scales) at 2 or 5 years after gene therapy; use of assistive devices; and AEs

  **Results presented by study authors**: “Patients received a total dose of either $1.8 \times 10^{11}$ vg total of AGIL-AADC [PTC-AADC] (n=21) or $2.4 \times 10^{11}$ vg total of AGIL-AADC (n=4). Of the 25 children given AGIL-AADC, 3 are now more than seven years post-gene therapy, 7 are more than six years post-gene therapy, and 16 are more than two years post-gene therapy. Clinical results of the first 18 patients given AGIL-AADC were compared to natural history cohort. At baseline, ages ranged from 21 months to 8.5 years and no child had developed full head control, sitting unassisted or standing capability, consistent with the published natural history cohort of severe AADC patients who never achieve these motor milestones over their lifetime. Compared to the natural history cohort, among the 18 patients receiving the $1.8 \times 10^{11}$ vg total dose of AGIL-AADC, 5/15 gain full head control ($P<.0001$), 4/15 gain sitting unassisted ($P = .0004$), and one subject achieved standing with support at 2 years. At five years, 4/7 gain full head control and sit unassisted ($P < .0001$), and 2/7 stand with support ($P=.0054$). Regarding ambulatory function, two patients are using wheeled walkers, one additional patient is able to take steps holding an examiner’s hand and one patient is walking independently. Adverse events in the first year after AGIL-AADC administration, in general, were associated with overall disease state.”677

  An update of this cohort reported, “. . . all patients had 2 years of posttreatment data; 8 patients had 5 years of posttreatment data. PDMS-2 total score and single-item motor developmental milestones demonstrated clinically meaningful improvements versus natural history controls. AIMS and Bayley-III total and cognitive and language subscale scores also improved. All patients demonstrated sustained de novo dopamine production. No new safety signals were observed.”678

**A Phase I/II Clinical Trial for Treatment of Aromatic l-Amino Acid Decarboxylase (AADC) Deficiency Using AAV2-hAADC, NCT01395641. Chien et al 2017,675**

- **Patient population/planned enrollment**: Children and adults (n = 10) aged 24 months or older with genetically confirmed AADCDD.

  *Note*: some of these patients are also included in data presented in the previous recently complete trial.

- **Study design**: Phase I/II, single-arm, open-label study to determine the safety and efficacy of a one-time intracerebral administration of $1.8 \times 10^{11}$ vg PTC-AADC

- **Primary outcomes**: Increase of PDMS-2 score of more than 10 points from baseline to 1 year after gene therapy and 5-HIAA and HVA (neurotransmitter metabolite) levels in CSF 1 year after gene therapy

- **Secondary outcomes**: Dyskinesia severity at 12 months after gene therapy and other SAE incidence at 12 months after gene therapy
Results presented by study authors: "Ten patients (median age 2.71 years, IQR 2.46-6.35) were enrolled from Oct 1, 2014, to Dec 2, 2015. All patients tolerated the surgeries and vector injections. One patient died from influenza B encephalitis during an endemic outbreak 10 months after treatment; therefore, 9 months of data were included in the analyses for this patient. All patients met the primary efficacy endpoint: 12 months after gene therapy, PDMS-2 scores were increased by a median of 62 points (IQR 39-93; P = .005) and HVA concentrations by a median of 25 nmol/L (IQR 11-48; P = .012); however, there was no significant change in 5-HIAA concentrations (median difference 0, IQR 0-5; P = .20). In total, 101 adverse events were reported, with the most common being pyrexia (16 [16%] of 101 events) and orofacial dyskinesia (ten [10%]). 12 serious adverse events occurred in six patients, including one death (treatment-unrelated encephalitis due to influenza B infection), one life-threatening pyrexia, and ten events that led to hospital admission. Transient post-gene therapy dyskinesia occurred in all patients but was resolved with risperidone. Of 31 treatment-related adverse events, only one (patient 1) was severe in intensity, and none led to hospital admission or death."

Manufacturers and Regulatory Status
PTC-AADC is being developed by PTC Therapeutics Inc (South Plainfield, New Jersey). It is in phase II clinical development. In January 2020, PTC Therapeutics announced a short delay in its plan to submit a biologics license application (BLA) because FDA requested “additional information concerning the use of the commercial delivery system for PTC-AADC in young patients” and announced anticipating submitting the BLA in the second quarter of 2020.679 FDA had granted Orphan Drug designation to PTC-AADC to treat AADCD in June 2016680 and Rare Pediatric Disease designation in November 2016.681

Cost Information
Cost information is unavailable for this topic, but as a gene therapy, stakeholders expect it will be high cost.

Key Stakeholder Perspectives
Seven stakeholders, reflecting clinical, health systems, nursing, and research perspectives, provided comments and ratings on PTC-AADC.682-688 The list below summarizes key stakeholder perspectives.

- PTC-AADC has large potential to improve patient health outcomes and quality of life because of significant efficacy data in clinical trials (ie, improvement in full head control, sitting without assistance, and ambulation compared with natural history data, and sustained de novo dopamine production) that support the underlying theory of PTC-AADC to treat AADCD.
- Stakeholders anticipate PTC-AADC will be expensive and potentially cost prohibitive, potentially increasing health disparities, but that the anticipated cost might be offset by a decrease in other, lifetime health care costs (eg, caregiving, therapy, medications).
- PTC-AADC has moderate to large potential to disrupt the current paradigm of patient care for reasons including it is purportedly curative compared with current treatment that is ongoing and supportive and it is administered in a highly specialized care setting as an intracerebral infusion via stereotactic surgery.
- PTC-AADC has moderate potential to disrupt the health care delivery system; although treatment requires a specialized care setting (and one reviewer noted that not every health facility has a Gamma Knife for this stereotactic surgery procedure), the treatment procedure is needed only once.
RVT-802 to Treat Pediatric Congenital Athymia (DiGeorge Syndrome Immunodeficiency, CHARGE Syndrome, FOXN1 Deficiency)

**Highlights**
- RVT-802 is a cell-based therapy derived from donor (i.e., allogeneic) infant thymus tissue; it is intended to restore thymus function in pediatric patients born without a thymus (i.e., athymia) so they can develop a functional immune system. The tissue is implanted in the patient’s quadriceps muscle.
- No FDA-approved treatments are available for pediatric congenital athymia, which often leads to death by 2 years of age.
- Stakeholders commenting on this topic thought that RVT-802 might be an effective one-time treatment that provides immune reconstitution for patients with congenital athymia without requiring matched donor tissue; however, larger, longer-term studies are needed to better understand RVT-802’s safety and effectiveness.
- Stakeholders also thought that, although the implantation procedure would be easier than a standard thymus transplantation, RVT-802’s high costs might limit access to therapy.

**Patient Population**

RVT-802 is intended for infants and children with pediatric congenital athymia, a condition associated with genetic syndromes including complete DiGeorge genetic anomaly (cDGA); coloboma, heart defects, atresia choanae, retarded growth and development, genital hypoplasia, and ear abnormalities and deafness (CHARGE) syndrome; and Forkhead Box N1 (FOXN1) deficiency.

**Intervention**

Pediatric congenital athymia is a very rare disorder associated with several rare, life-threatening genetic diseases (i.e., cDGA, CHARGE syndrome, and FOXN1 deficiency) that arise from genetic rearrangements that cause an affected individual to be born without a thymus. About 20 infants are born with congenital athymia each year in the United States. Affected infants cannot produce T cells, which are a critical part of a functioning immune system. Lack of T cells leads to a severe inability to fight infections and eventually results in death, typically by 2 years of age due to infection. No FDA-approved therapies are available for this collection of diseases. More information on disorders caused by athymia is offered by the Immune Deficiency Foundation (DiGeorge syndrome), National Institutes of Health’s Genetics Home Reference (CHARGE syndrome), and Orphanet Journal of Rare Diseases (FOXN1 deficiency).

RVT-802 is an allogeneic cell-based therapy derived from infant donor thymus tissue; it is intended to reconstitute thymus function in patients with athymia so they develop a working immune system. According to the manufacturer, these patients are still capable of producing bone marrow–derived precursor T cells that can migrate from the bone marrow to the implanted RVT-802 tissue product, where these precursors can grow into working thymus cells (i.e., thymopoiesis). RVT-802 is intended to be a one-time therapy to permanently restore normal immune function in patients.

Donor tissue composing RVT-802 is typically obtained from infants undergoing cardiac surgery, during which thymus tissue is frequently removed to gain access to the heart. After
tissue donation, RVT-802 is processed and cultured for 14 to 21 days in a manufacturing facility before the patient receives the implant at a specialized treatment center.

In clinical trials, RVT-802 is administered by placing a cultured thymus slice into a small incision in the patient’s quadriceps muscle that is then pulled over the slice using an insoluble stitch. Physicians implant between 4 and 18 g of thymus tissue per square meter of body surface area.

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database did not identify any ongoing trials for this topic.

Recently Completed Trials With Available Results

Thymic transplants have been performed at a single center in the United States since the mid-1990s and at a single European center beginning in 2009. Multiple papers covering partially overlapping patient populations from these studies have been published (Markert et al 1999,692 Markert et al 2004,693 Markert et al 2007,694 and Markert et al 2010695). We summarize the most recent, relevant data as written in a news release.

The following abbreviation is used in this section: BLA, Biologics License Application.

Enzyvant Announces FDA Acceptance of Biologics License Application (BLA) and Priority Review Status for RVT-802, a Novel Investigational Tissue-Based Regenerative Therapy for Pediatric Congenital Athymia. Enzyvant 2019.690

- **Patient population/planned enrollment**: Patients (n = 93) with pediatric congenital athymia
- **Study design**: Pooled patients from multiple single-arm trials of the safety and efficacy of RVT-802
- **Primary outcome**: Overall survival at 1 year after transplantation
- **Results presented by study authors**: “At the time of the BLA filing, a total of 93 patients received RVT-802 across multiple clinical studies, including 85 patients who met the criteria for inclusion in the efficacy analysis. The Kaplan-Meier estimates of survival [95% confidence interval] at year one and year two post treatment were 76% [66 - 84] and 75% [66 - 83], respectively. For patients surviving 12 months post-treatment, there was a 93% probability of surviving 10 years post-treatment. During clinical development, the most commonly (≥ 5%) reported RVT-802 related adverse events included thrombocytopenia (11%), neutropenia (8%), pyrexia (5%), and proteinuria (5%).”

Manufacturers and Regulatory Status

RVT-802 is being developed by Enzyvant Therapeutics GmbH (Basel, Switzerland), a subsidiary of Roivant Sciences GmbH (Basel, Switzerland), in collaboration with Duke University (Durham, North Carolina). In December 2019, Roivant entered into a strategic alliance with Sumitomo Dainippon Pharma (Osaka, Japan) in which ownership of Enzyvant and several other Roivant subsidiaries were transferred to a new company fully owned by Sumitomo Dainippon.696

FDA had accepted a Biologics License Application (BLA) for RVT-802 for treating pediatric congenital athymia; however, in December 2019, the company announced that FDA declined to approve the BLA.690,697 The developer indicated that FDA’s Complete Response Letter cited questions regarding RVT-802’s manufacturing process and other issues based on the agency’s inspection of the manufacturing site.
FDA had granted Rare Pediatric Disease designation to RVT-802 in September 2017 to treat primary immune deficiency resulting from congenital athymia associated with cDGA. FDA also granted RVT-802 Breakthrough Therapy and Regenerative Medicine Advanced Therapy designations in April 2017 to treat cDGA.

Cost Information

Although cost data are not yet available from the manufacturer, the Academy of Managed Care Pharmacy estimates that RVT-802 might have a budget impact of $1.5 million per treated patient.

Key Stakeholder Perspectives

Six stakeholders, reflecting clinical, health systems, nursing, and research perspectives, provided comments and ratings on RVT-802. The list below summarizes key stakeholder perspectives.

- RVT-802 might disrupt health outcomes by providing patients who have athymia a treatment option for immune reconstitution without needing sibling-matched donor tissue.
- RVT-802’s high cost (an estimated $1.5 million) and limited availability at only one US center (Duke University, Durham, North Carolina) and one center in the United Kingdom might cause disparities for families with insufficient financial resources who also cannot travel to one of those locations, or whose insurance coverage would not support treatment out of network in another state or country.
- If effective, RVT-802 might substantially reduce demands on hospitals related to serious infections compared with standard care, but staff training would be needed regarding pre- and postoperative management.
- Long-term controlled studies are needed to assess the safety and effectiveness of RVT-802 and donor-matched thymus transplantation, hemopoietic stem cell transplantation, and supportive care to better understand the therapies’ tradeoff between benefit (immune reconstitution) and risk (death or autoimmune complications).

Valoctocogene Roxaparvovec to Treat Hemophilia A

Highlights

- Valoctocogene roxaparvovec (BMN 270) is an adeno-associated viral vector gene therapy intended as a one-time intravenous infusion for hemophilia A.
- FDA is reviewing a Biologics License Application for the gene therapy product to treat hemophilia A, with a decision expected by August 21, 2020.
- FDA is also reviewing a Premarket Approval application for a companion diagnostic test to detect antibodies to the gene therapy’s viral delivery vector; if present, the antibodies would likely disqualify patients from receiving valoctocogene roxaparvovec.
- Stakeholders commenting on valoctocogene roxaparvovec thought it holds great potential to improve outcomes, convenience, and quality of life for patients as a one-time treatment.
Stakeholders also thought that valoctocogene roxaparvovec might cause substantial disruption to the health care delivery system by replacing multiple weekly factor replacement sessions with a presumably one-time gene therapy.

**Patient Population**

Valoctocogene roxaparvovec is intended for adults aged 18 years or older with severe hemophilia A (defined as baseline factor VIII [FVIII] levels of 1 international units per deciliter [IU/dL] or lower before treatment) who have been treated with FVIII replacement therapy for at least 150 exposure days and have no history of a detectable FVIII inhibitor.

**Intervention**

Hemophilia A is a congenital bleeding disorder caused by deficiency in coagulation FVIII, a protein essential to blood clot formation, that can trigger uncontrolled bleeding. The National Hemophilia Foundation website offers more information about hemophilia A. Hemophilia A therapy typically requires regular preventive or on-demand infusions of external FVIII replacement or emicizumab-kxwh, a drug that activates clotting pathways by different mechanisms. Hemophilia A treatment places substantial burdens on patients and providers due to the frequent (up to 3 times per week) treatments and high cost (about $200,000 per year).

Valoctocogene roxaparvovec, sometimes called valrox, is an adeno-associated virus type 5 (AAV5) vector gene therapy intended as a one-time treatment for hemophilia A. It is meant to eliminate or reduce the need for ongoing FVIII replacement or emicizumab-kxwh therapy. Valoctocogene roxaparvovec purportedly delivers a transgene encoding a functional version of coagulation FVIII to hepatocytes (a type of liver cell). Liver-based expression of the factor VIII transgene is intended to correct deficient FVIII levels that occur in hemophilia A. Candidates may first require a companion diagnostic test for antibodies to the AAV5 vector to determine their eligibility for valoctocogene roxaparvovec.

Hemophilia A treatment with replacement FVIII therapy can be complicated by development of inhibitory antibodies to FVIII, which occurs in about 30% of patients. Because valoctocogene roxaparvovec functions through restoring FVIII expression, the treatment may not work in patients who have developed FVIII inhibitors. So, clinical trials of valoctocogene roxaparvovec typically have excluded patients with FVIII inhibitors.

In phase III clinical trials, the agent is given as a single intravenous infusion at a dose of $4 \times 10^{13}$ to $6 \times 10^{13}$ vg/kg (vector genomes [ie, viral particles] per kilogram of body weight).

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database identified 4 ongoing trials for this topic. We present 3 of these trials in Table 5.22. (We excluded a phase I/II safety trial of valoctocogene roxaparvovec in patients with hemophilia A and antibodies to AAV5.)
## Table 5.22. Ongoing Clinical Trials

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gene Therapy Study in Severe Haemophilia A Patients</strong>&lt;br&gt;NCT02576795&lt;br&gt;See preliminary results from Pasi et al 2020&lt;sup&gt;719&lt;/sup&gt; under Recently Completed and Ongoing Trials With Available Results</td>
<td>Adult males aged 18 years or older (n = 15) with severe haemophilia A, defined as FVIII levels of 1 IU/dL or below, with no documented history of a detectable FVIII inhibitor</td>
<td>Phase I/II, single-group assignment study to assess the safety, tolerability, and efficacy of escalating doses (across patients) of a single valoctocogene roxaparvovec infusion to treat hemophilia A&lt;br&gt;Primary outcomes:&lt;br&gt;Number of patients with treatment-related adverse events through 61 months&lt;br&gt;Determination of which doses achieved FVIII expression at or above 5% of normal activity (greater than 5 IU/dL) at 16 weeks after the infusion</td>
<td>Primary completion and study completion February 2022</td>
</tr>
<tr>
<td><strong>Single-Arm Study to Evaluate The Efficacy and Safety of Valoctocogene Roxaparvovec in Hemophilia A Patients (BMN 270-301)</strong>&lt;br&gt;NCT03370913</td>
<td>Adult males aged 18 years or older (n = 134) with severe hemophilia A, defined as FVIII levels of 1 IU/dL or below despite FVIII replacement therapy for at least 1 year, with no documented history of a detectable FVIII inhibitor</td>
<td>Phase III, single-arm study to assess the safety and efficacy of a single dose of valoctocogene roxaparvovec (6 × 10&lt;sup&gt;13&lt;/sup&gt; vg/kg) to treat hemophilia A&lt;br&gt;Primary outcome: Change in median FVIII activity at 1 year&lt;br&gt;Secondary outcomes: Changes in bleeding episodes requiring FVIII replacement and FVIII replacement use (IU/kg), both through 1 year</td>
<td>Primary completion December 2022&lt;br&gt;Study completion September 2023</td>
</tr>
<tr>
<td><strong>Single-Arm Study to Evaluate The Efficacy and Safety of Valoctocogene Roxaparvovec in Hemophilia A Patients at a Dose of 4E13 vg/kg (BMN270-302)</strong>&lt;br&gt;NCT03392974</td>
<td>Adult males aged 18 years or older (n = 40) with severe hemophilia A, defined as FVIII levels of 1 IU/dL or below despite FVIII replacement therapy for at least 1 year, with no documented history of a detectable FVIII inhibitor</td>
<td>Phase III, single-arm study to assess the safety and efficacy of single dose valoctocogene roxaparvovec (4 × 10&lt;sup&gt;13&lt;/sup&gt; vg/kg) to treat hemophilia A&lt;br&gt;Primary outcome: Change in median FVIII activity at 1 year&lt;br&gt;Secondary outcomes: Changes in bleeding episodes requiring FVIII replacement and FVIII replacement use (IU/kg), both through 1 year</td>
<td>Primary completion December 2022&lt;br&gt;Study completion March 2024</td>
</tr>
</tbody>
</table>

Abbreviations: FVIII, clotting factor VIII; IU/dL, international units per deciliter; IU/kg, international units per kilogram of body weight; vg/kg, viral genomes per kilogram body weight.

### Recently Completed and Ongoing Trials With Available Results

Our searches identified one recently completed trial with published results<sup>719</sup>. We summarize this study’s results as written in the abstract of the published study.

The following abbreviations are used in this section: AAV, adeno-associated virus; FVIII, clotting factor VIII; hFVIII, human clotting factor VIII; IU/dL, international units per deciliter; vg, viral genomes.

- **Patient population/planned enrollment**: Adult males aged 18 years or older (n = 15) with severe hemophilia A, defined as FVIII levels of 1 IU/dL or below, and no history of factor VIII inhibitor development.
- **Study design**: Phase I/II, single-group assignment study assessing the safety, tolerability, and efficacy of escalating doses (across patients) of a single valoctocogene roxaparvovec infusion to treat hemophilia A.
- **Primary outcomes**: FVIII level, annualized rate of bleeding events, use of factor VIII replacement, safety, expression kinetics, and biologic markers of AAV transduction for up to 3 years.
- **Secondary outcomes**: Frequency of FVIII replacement therapy and number of bleeding episodes requiring treatment, both through 61 months.
- **Results presented by study authors**: "Three years after infusion, two participants (one who had received $6 \times 10^{12}$ vector genomes [vg] per kilogram of body weight and one who had received $2 \times 10^{13}$ vg per kilogram) had factor VIII expression of less than 1 IU per deciliter, as assessed on chromogenic assay. Seven participants (who had received $6 \times 10^{13}$ vg per kilogram) had a median factor VIII expression of 20 IU per deciliter; the median number of annualized treated bleeding events was 0, and the median use of exogenous factor VIII was reduced from 138.5 infusions to 0 infusions per year. Bleeding in all target joints (major joints with ≥3 bleeding events within 6 months) in this cohort resolved (≤2 bleeding events within 12 months). Two years after infusion, six participants (who had received $4 \times 10^{13}$ vg per kilogram) had a median factor VIII expression of 13 IU per deciliter; the median annualized rate of bleeding events was 0, and the median use of factor VIII was reduced from 155.5 infusions to 0.5 infusions per year. Bleeding in target joints resolved in five of six participants. The factor VIII pharmacodynamic profiles reflected cellular turnover in the blood and molecular events leading to episomal DNA stabilization for persistent expression, findings that are consistent with previous observations in two model systems. Transgene-derived human factor VIII (hFVIII) protein activity mirrored native hFVIII in hemostatic ability. No inhibitor development, thromboses, deaths, or persistent changes in liver-function tests were observed."

**Manufacturers and Regulatory Status**

BioMarin Pharmaceutical Inc (San Rafael, California) manufactures valoctocogene roxaparvovec. The company submitted a Biologics License Application to FDA for the gene therapy product to treat adults with hemophilia A in December 2019.720 FDA accepted the application for Priority Review and set a Prescription Drug User Fee Act (PDUFA)-prescribed action date of August 21, 2020; FDA has informed the company that it does not plan to hold an advisory committee meeting to discuss the application before making a final determination.713 FDA previously granted valoctocogene roxaparvovec Orphan Drug and Breakthrough Therapy designations for this indication.720 FDA also has accepted a Premarket Approval application from ARUP Laboratories (Salt Lake City, Utah) for its AAV5 total antibody assay, a companion diagnostic test for use with valoctocogene roxaparvovec, the AAV5 vector–based gene therapy product, to identify patients without existing antibodies to AAV5, who would be most likely to respond to valoctocogene roxaparvovec gene therapy.713

**Cost Information**

Cost information is unavailable for this topic, but stakeholders expect it to cost about $2 million per patient as a gene therapy.

**Key Stakeholder Perspectives**

Six stakeholders, reflecting clinical, research, nursing, and health systems perspectives, provided comments and ratings on valoctocogene roxaparvovec to treat hemophilia A.721-726 The list below summarizes key stakeholder perspectives.
• A single gene therapy that reduces or potentially eliminates the need for repeated factor replacement sessions could substantially improve outcomes and quality of life for patients with hemophilia A.
• Use of valoctocogene roxaparvovec could dramatically disrupt the health care delivery system and alter the paradigm of care for hemophilia A by replacing multiple weekly treatment sessions with a presumably one-time gene therapy.
• This treatment could significantly disrupt health care costs for this population, with upfront costs likely to approach $2 million per patient. However, if long-term safety and effectiveness are durable, the treatment might achieve cost-effectiveness in a few years because factor replacement therapy has estimated annual costs of about $200 000 per patient.
• More data are needed to establish definitively whether patients with FVIII inhibitors or antibodies to AAV5 would continue to be ineligible for valoctocogene roxaparvovec.

Voxelotor (Oxbryta) to Treat Sickle Cell Disease

Highlights
• Voxelotor (Oxbryta) is an oral drug intended to treat the underlying sickle cell disease (SCD) process by reducing or preventing the clumping of misshapen red blood cells (RBCs).
• FDA approved voxelotor, under the trade name Oxbryta, in November 2019 for use in treating SCD in children aged 12 years or older and adults.
• The drug has an estimated annual retail price between $123 000 and $130 000.
• Stakeholders commenting on this topic thought that voxelotor could change how physicians treat SCD by altering the disease process rather than managing symptoms.
• Stakeholders also thought that disparities could increase if insurance coverage is unavailable and access to voxelotor is limited to specialized SCD referral centers.

Patient Population
Voxelotor is indicated to treat children aged 12 years or older and adults with SCD.

Intervention
SCD is an inherited blood disorder caused by mutations in the hemoglobin subunit beta gene, HBB. It encodes a subunit (beta globin) of the oxygen-carrying protein hemoglobin present in RBCs. Mutated beta globin forms abnormal hemoglobin (sickle hemoglobin, or HbS) that polymerizes into rigid protein strands in low-oxygen conditions, leading to changes in the shape (ie, sickling) of RBCs. Sickled RBCs are prone to destruction (ie, hemolysis) and can block blood vessels, leading to hemolytic anemia and extremely painful veno-occlusive crises.435 The National Institutes of Health’s National Heart, Lung, and Blood Institute website offers more information on SCD.

Although some recently developed drugs target the root cause of SCD pathology—the HbS—by delaying its deoxygenation, they do not work in all patients and have side effects that many patients cannot tolerate. More effective disease-modifying treatments are needed.

Voxelotor has potential as a disease-modifying small-molecule drug. It acts as an inhibitor of sickle hemoglobin polymerization and is intended to prevent or reverse the sickling and
destruction of RBCs that characterizes SCD and causes vaso-occlusive crises. Voxelotor purportedly binds to variant hemoglobin (ie, sickle cell hemoglobin) and increases its affinity for oxygen. This process prevents polymerization of mutated hemoglobin and the sickling and clumping of RBCs that follow hemoglobin polymerization. Additionally, voxelotor purportedly reverses sickling of RBCs under conditions of low oxygen (ie, hypoxia).

Voxelotor is taken in oral tablets at a recommended dosage of 1500 mg (three 500-mg tablets) once daily.

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 5 ongoing trials for this topic. We present 3 of these trials in Table 5.23. (We excluded a phase II safety, pharmacokinetics-pharmacodynamics, and dose-escalation trial [NCT04247594] in adults aged 18 to 60 years and a phase II safety and pharmacokinetics study [NCT02850406] in children aged 9 months to 17 years.)

Table 5.23. Ongoing Clinical Trials

<table>
<thead>
<tr>
<th>Study name and National Clinical Trials identifier</th>
<th>Patient population and planned enrollment</th>
<th>Study design and outcomes</th>
<th>Estimated date of completion</th>
</tr>
</thead>
</table>
| Study to Assess the Effect of Long-Term Treatment With GBT440 in Participants Who Have Completed Treatment in Study GBT440-031 (034OLE) **NCT03573882** | Children aged 12 years or older and adults (n = 179) who have sickle cell disease and have participated in voxelotor study GBT440-031 | Phase III, single-arm, open-label extension study assessing long-term safety and effectiveness of once-daily oral voxelotor at 900 or 1500 mg to treat sickle cell disease Primary outcomes:  
• Number of patients with treatment-related adverse events through 5 years  
• Frequency of sickle cell disease–related complications through 5 years  
Secondary outcome: Response in hemolytic anemia measured by hemoglobin, bilirubin, and reticulocyte counts | Primary and study completion October 2024 |
| Pediatric Open-Label Extension of Voxelotor **NCT04188509** | Children aged 4 to 18 years (n = 50) with sickle cell disease who participated in a previous company-sponsored voxelotor pediatric trial | Phase III, single-arm, open-label study to assess long-term safety and efficacy of voxelotor for sickle cell disease in pediatric patients Primary outcomes: Treatment-related adverse events and serious adverse events, and frequency of sickle cell disease–related complications | Primary and study completion January 2026 |
Recently Completed and Ongoing Trials With Available Results

Our searches identified one relevant, recently completed late-phase trial with published results. We summarize this study with results as written in the abstract of the published study. (Subsequent post hoc analyses of this study reporting primarily nonpatient-oriented outcomes [eg, hemolysis markers] presented at scientific meetings were excluded.)

The following abbreviations are used in this section: CI, confidence interval; HbS, hemoglobin S; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

**Study to Evaluate the Effect of Voxelotor Administered Orally to Patients With Sickle Cell Disease (Hemoglobin Oxygen Affinity Modulation to Inhibit HbS PolymErization [HOPE]).** NCT03036813. Vichinsky et al 2019.

- **Patient population/planned enrollment:** Children aged 12 years or older and adults (n = 274) who had SCD with at least one VOC episode in the past 12 months
- **Study design:** Phase III, double-blind, parallel-assignment trial comparing the safety and efficacy of once-daily oral voxelotor (either 900 or 1500 mg) with placebo to treat SCD
- **Primary outcome:** Percentage of patients with a hemoglobin response, defined as an increase of more than 1.0 g/dL from baseline at week 24
- **Secondary outcomes:** Annualized VOC incidence rate, change in hemoglobin level from baseline to week 24, and hemolysis laboratory markers (indirect bilirubin level, absolute reticulocyte count, percentage of reticulocytes, and lactate dehydrogenase level)
- **Results presented by study authors:** “In the intention-to-treat analysis, a significantly higher percentage of participants had a hemoglobin response in the 1500-mg voxelotor group (51%; 95% confidence interval [CI], 84 to 61) than in the placebo group (7%; 95% CI, 1 to 12). Anemia worsened between baseline and week 24 in fewer participants in each voxelotor dose group than in those receiving placebo. At week 24, the 1500-mg voxelotor group had significantly greater reductions from baseline in the indirect bilirubin level and percentage of reticulocytes than the placebo group. The percentage of participants with an adverse event that occurred or worsened during the treatment period was similar across the trial groups. Adverse events of at least grade 3 occurred in 26% of the participants in the 1500-mg voxelotor group, 23% in the 900-mg voxelotor group, and 26% in the placebo group. Most adverse events were not related to the trial drug or placebo, as determined by the investigators.”
Manufacturers and Regulatory Status

Global Blood Therapeutics Inc (South San Francisco, California) manufactures voxelotor. On November 25, 2019, FDA granted Global Blood Therapeutics accelerated approval for voxelotor, under the trade name Oxbryta, to treat SCD in children aged 12 years or older and adults.\textsuperscript{734,735} Continued approval may be contingent on verification and description of clinical benefit in confirmatory trials.\textsuperscript{732,734} FDA previously granted Breakthrough Therapy, Fast Track, Orphan Drug, and Rare Pediatric Disease designations to voxelotor to treat SCD.\textsuperscript{736}

Cost Information

Global Blood Therapeutics reportedly priced voxelotor at $125,000 per year before unspecified discounts.\textsuperscript{737} GoodRx, an aggregator of prescription pharmaceutical pricing at US retail pharmacies, lists prices (as of January 23, 2020) from about $10,300 to $10,800 with a coupon for a typical 30-day supply of voxelotor (90 tablets, 500 mg each, recommended dose 1500 mg once daily), suggesting annual costs of about $123,600 to $129,600.\textsuperscript{738}

Key Stakeholder Perspectives

Nine stakeholders, reflecting clinical, research, nursing, health systems, caregiver, and patient perspectives, provided comments and ratings on voxelotor for treating SCD.\textsuperscript{739-747} The list below summarizes key stakeholder perspectives.

- As an effective disease-modifying therapy for SCD rather than a means to manage symptoms, voxelotor has great potential to improve outcomes and quality of life.
- Voxelotor could disrupt how clinicians manage SCD. The prospect of increasing hemoglobin levels could ultimately decrease painful crises and prevent long-term organ damage, although additional trials would be needed to track such outcomes.
- At an annual retail price of more than $120,000 per year, voxelotor could disrupt health care costs, especially in light of new competing SCD treatments with similarly high prices.
- Economic disparities could arise if insurance coverage is unavailable. Further disparities might develop if access to voxelotor is limited to SCD referral centers, at least until more clinicians become familiar with voxelotor.
- By improving hemoglobin levels and preventing sickling, voxelotor might reduce emergency department visits and hospitalizations. However, available data have not assessed these patient-oriented outcomes.
Chapter 6. Potentially Disruptive Trends

Chapter Summary

In addition to the topics included in the previous chapters, the PCORI HCHSS identifies and monitors trends (ie, large, high-level disruptions). These trends can occur across or within clinical areas and arise from a combination of factors that, taken together, create a paradigm shift in health care. Identification of these trends goes beyond the 5 priority areas PCORI initially defined as a focus.

Because of the different nature and focus of trends compared with the topics summarized in the previous chapters, the trend summaries that follow use a modified format. Each trend summary begins with a brief list highlighting key takeaways for the reader, followed by a description of the nature and importance of the trend, a listing of clinical areas potentially affected by the trend, a brief discussion of opportunities and threats (ie, potential positive and negative disruptions) posed by the trend, and a summary of key stakeholder comments.

As of April 3, 2020, we were monitoring 32 potentially disruptive trends. These 32 trends will be listed in the June 2020 PCORI Health Care Horizon Scanning System: Horizon Scanning Status Report. All 32 trends were sent for comment to internal ECRI stakeholders and each received at least 5 sets of ratings and comments from these stakeholders between March 1, 2020, and April 3, 2020. From among these 32 trends, 15 were selected that internal ECRI stakeholders indicated have high-moderate to high disruption potential and are likely to cause disruption within the next 3 years in the United States (see Table 6.1 below).

Table 6.1. Included Trends

<table>
<thead>
<tr>
<th>Trend title</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Artificial intelligence analysis of imaging scans to screen for cancer or confirm a cancer diagnosis</td>
<td></td>
</tr>
<tr>
<td>Artificial intelligence for image triage to prioritize emergency cases</td>
<td></td>
</tr>
<tr>
<td>Artificial intelligence operator guidance for cardiac ultrasound scans</td>
<td></td>
</tr>
<tr>
<td>Artificial pancreas systems to treat type 1 diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Comprehensive genomic profiling in patients who have cancer to identify targeted therapy options</td>
<td></td>
</tr>
<tr>
<td>Direct-to-consumer genetic testing partnerships with pharmaceutical companies to facilitate drug development and treatment</td>
<td></td>
</tr>
<tr>
<td>Disease-modifying agents (immunomodulators) to mitigate severe COVID-19 symptoms</td>
<td></td>
</tr>
<tr>
<td>Emerging antiviral therapies for 2019 novel coronavirus disease (COVID-19)</td>
<td></td>
</tr>
<tr>
<td>Integrated electronic health solutions to improve cardiovascular care</td>
<td></td>
</tr>
<tr>
<td>N-of-1 trials to research patient-centered outcomes</td>
<td></td>
</tr>
<tr>
<td>Proteomic profiling to diagnose cancer and guide personalized targeted therapy</td>
<td></td>
</tr>
<tr>
<td>Psychedelic drugs to treat mental health conditions</td>
<td></td>
</tr>
<tr>
<td>Smartphone-guided medical examinations and diagnostics for use by patients and caregivers</td>
<td></td>
</tr>
</tbody>
</table>
Trend title
Telehealth to assess and treat mental health conditions
Tissue-of-origin agnostic, molecularly targeted oncology drugs

a Trend appears for the first time in this edition of the High Potential Disruption Report.

**Trend Summaries**

We present below 15 summaries on trends deemed to have high potential for disruption. Trends are ordered alphabetically by trend title.

**Artificial Intelligence Analysis of Imaging Scans to Screen for Cancer or Confirm a Cancer Diagnosis**

**Highlights**

- Artificial intelligence (AI)–based image analysis is intended to help radiologists identify possible cancer cases by screening hundreds or thousands of images for abnormal lumps or nodules and flagging questionable/suspicious areas.
- AI is also intended to improve a radiologist’s diagnostic performance by identifying cancer lesions in early stages, which can lead to patients receiving appropriate care sooner.
- Stakeholders commenting on this trend thought that AI-assisted image analysis has the potential to improve health outcomes for patients. They suggested that if AI helps clinicians detect cancer in early stages, patient care can be streamlined to provide treatment before the disease progresses further.
- Stakeholders also thought that AI-assisted image analysis is expected to be expensive, but the fewer staff required to interpret images and treat patients with early stage cancer might offset these costs.

**Description**

In this application of AI, a software program analyzes magnetic resonance imaging, computed tomography, or ultrasound scans from patients suspected of having cancer and generates a probability-of-malignancy score. A standard risk score that could be used, for example, is BI-RADS (the Breast Imaging Reporting and Data System). The machine learning AI software (eg, convolutional neural networks) is used with conventional picture archiving and communications systems to learn the features of malignancy and point out problematic areas in images. This AI software is intended to improve radiologists’ ability to detect abnormal lumps and nodules and to help determine whether they are dangerous. It does this by scanning all dimension slices at once, homing in on regions of interest, and providing a cancer risk score. AI-based image analysis also might improve health outcomes if suspicious cases can be confirmed and patients can receive care sooner.

**Clinical Area(s) Potentially Disrupted**

This AI technology is most likely to disrupt radiology departments because it will screen for possible malignancies in hundreds or thousands of images to help radiologists focus their
attention on suspicious images that require follow-up. AI imaging algorithms also might disrupt surgery departments because early cancer detection might require that patients undergo surgery sooner to resect confirmed tumors if they are operable.

**Opportunities**

AI imaging algorithms might help detect cancer at earlier stages, thereby enabling earlier treatment and potentially improving patient health outcomes. From a radiologist’s perspective, AI-assisted image analysis might help prioritize cases with high risk of cancer, especially when radiologists have limited time to quickly triage large caseloads. This technology might also reduce human error rates in cancer detection and diagnosis.

**Threats**

Because of algorithmic detection errors, AI-assisted image analysis might lead to false-negative or false-positive reports that could have health and/or legal implications. This technology might also lead to overdiagnosis (ie, a true-positive diagnosis with little or no health consequences that could lead to unnecessary treatment or undue negative psychological impact on the patient). Even though AI algorithms are being developed to assist radiologists, some might view AI as a threat to their autonomy as clinicians.

**Key Stakeholder Perspectives**

Seven ECRI stakeholders, reflecting business and finance, clinical engineering, health care generalist, health systems, and research perspectives, provided comments and ratings on this trend.752-758 The list below summarizes stakeholder perspectives.

- AI-assisted image analysis has potential to improve patient outcomes because it might lead to earlier detection and diagnosis and allow patients to receive treatment sooner than if guided by the current clinical workflow.
- Adopting this AI technology has potential to disrupt radiologist staffing because health centers would need fewer staff to interpret images. AI may have the capacity to detect tumors that are imperceptible to the human eye. However, if the AI is too specific in its analysis, it could lead to a high false-positive rate that requires additional testing.
- Even with the expected high cost of implementing AI for image analysis, its adoption might offset costs by reducing the number of radiologists needed and by treating patients who have early stage cancer rather than late-stage disease.

**Artificial Intelligence for Image Triage to Prioritize Emergency Cases**

**Highlights**

- Artificial intelligence (AI)–assisted imaging triage uses software algorithms to screen high volumes of diagnostic imaging scans to detect subtle markers of urgent cases and redirect them for priority radiologist review.
- FDA has already granted 510(k) marketing clearance to several AI-assistance software products designed for specific indications, including detection of spinal fractures, brain aneurysms, and brain hemorrhages.
- Stakeholders commenting on this trend thought that this technology might improve throughput of urgent cases when radiologist coverage is limited and could help
overburdened and understaffed emergency department (ED) personnel improve care of urgent cases by removing existing bottlenecks in diagnostic imaging workflows.

Description

Several researchers and companies have developed AI software algorithms to screen imaging scans, including conventional X-rays, computed tomography (CT), and ultrasound, in high volumes in hospital EDs or other urgent care settings. These algorithms are designed to provide image triage—that is, to identify the most serious cases that might not be apparent based on traditionally recognized parameters or markers. The intent is to suggest giving these cases priority review by a radiologist. The AI algorithm pushes these cases to the front of the work queue based on identified markers learned by reviewing a multitude of images. Over time, some algorithms purportedly become more accurate at screening for certain indications as they review more images. Some products have already received FDA 510(k) clearance for specific indications using conventional X-rays, CT, and ultrasound, including identification of probable fractures in the cervical spine, intracranial hemorrhage, abdominal aortic tears, and brain aneurysms.759-763

Clinical Area(s) Potentially Disrupted

This AI technology is most likely to disrupt work routines in hospital emergency and radiology departments because it is intended to screen for the most urgent cases and redirect them for priority review by radiologists. These potential disruptions could extend to other units (eg, surgical, intensive care) based on possible changes in the acuity of patients’ conditions identified by AI imaging algorithms.

Opportunities

AI-assisted image triage might improve patient health outcomes if the technology effectively helps radiologists identify the most acute cases so these patients can receive appropriate care sooner. From a staffing perspective, AI-assisted image triage might improve workflow by enabling prioritization of higher-acuity cases more quickly when radiologist availability is limited. From a medico-legal perspective, implementation of AI-assisted image triage might provide a layer of protection against potential litigation for “missed” events or diagnoses in imaging scans.

Threats

From a resource perspective, the cost and complexity of AI-assisted image triage might limit its adoption to larger, high-volume imaging departments with sufficient resources and experienced staff to implement it. The availability of AI-assisted image triage could raise litigation risk for health care facilities that lack sufficient expertise and resources to implement these systems. Logistically, the availability of multiple AI-assisted image triage products or programs could complicate operations or system maintenance if many software products are required to work together. Such logistical issues might lead to imaging departments restricting use to a certain group of AI product vendors to minimize system compatibility problems, potentially excluding AI-assisted features offered by competing vendors.
Key Stakeholder Perspectives

Eight ECRI stakeholders, reflecting research, nursing, health care generalist, clinical engineering, health systems, and business and finance perspectives, provided comments and ratings on this trend. The list below summarizes stakeholder perspectives.

- Use of AI-assisted imaging triage could positively disrupt existing imaging bottlenecks that develop between ED evaluation and hospital admissions for appropriate patients.
- AI-assisted imaging triage could be particularly valuable in an overburdened or understaffed ED if implemented and used appropriately to improve clinical workflow.
- Radiology will likely continue to lead other clinical specialties in adoption of AI assistance due to the nature and high volume of imaging data that requires timely clinician review.
- Additional research is needed to investigate whether or to what extent AI-assisted imaging triage improves patient outcomes or whether it offers other benefits using different metrics.

Artificial Intelligence Operator Guidance for Cardiac Ultrasound Scans

Highlights

- Artificial intelligence (AI)–assisted operator guidance software for cardiac ultrasound scans is intended to allow nonexpert users to perform diagnostic-quality echocardiograms.
- FDA approved the first AI-assisted echocardiography guidance system in February 2020, and other developers are reportedly working on similar systems.
- The technology might allow detection of undiagnosed cardiac conditions in patients who lack access to expert echocardiographers.
- Stakeholders commenting on this technology thought it could impact staffing and costs if AI-assisted operator guidance allowed nonexperts to routinely perform diagnostic-quality cardiac ultrasound scans.
- Stakeholders also anticipated that wide adoption of AI-assisted operator guidance for echocardiography could encourage the use of this technology for nonexperts in other ultrasound applications, including telehealth and home use.

Description

Cardiac ultrasound (ie, echocardiography) is widely used to diagnose heart conditions. However, the diagnostic quality of echocardiograms is highly dependent on the operator’s ultrasound skills. New AI algorithms in development purportedly allow less-experienced operators to perform diagnostic-quality echocardiograms through real-time feedback that simulates guidance from an experienced sonographer in positioning the probe and capturing images.

In February 2020, FDA granted Caption Health Inc (Brisbane, California) De Novo marketing authorization for its Caption Guidance software as the first AI-assisted echocardiography operator guidance system. The software purportedly allows novice operators to record diagnostic-quality echocardiograms with system-generated instructions and
guidance. Other companies at earlier stages of developing similar AI-assisted ultrasound guidance software include EchoLogic Medical Ltd (Haifa, Israel), Ultromics Ltd (Oxford, United Kingdom), and TomTec Imaging Systems GmbH (Unterschleissheim, Germany).

**Clinical Area(s) Potentially Disrupted**

AI-assisted operator guidance could enable nonexpert providers to perform cardiac ultrasound to conduct diagnostic-quality echocardiograms. Depending on findings, patients might be referred for expert follow-up to review echocardiograms and conduct additional testing as warranted. The technology might eventually enable home use of portable ultrasound by patients or caregivers for some indications.

**Opportunities**

The use of AI-assisted ultrasound guidance software could reduce disparities by making diagnostic-quality echocardiograms available to more patients in lower-resource areas. Even in areas where echocardiography is more readily available, allowing primary care providers to offer diagnostic-quality echocardiography might enable them to more quickly refer appropriately selected patients to cardiologists for follow-up, based on initial echocardiogram findings. Earlier diagnosis of some cardiovascular conditions could enable clinicians to manage heart disease more conservatively and slow disease progression, at least initially, before more invasive and costly interventions become necessary.

**Threats**

Cardiology departments might experience increased workloads and demand for follow-up cardiac testing if primary care practices that adopt AI-assisted ultrasound guidance refer high volumes of patients after performing their own echocardiograms. Implementing AI-assisted operator guidance for echocardiography could increase the costs and complexity of health information technology in primary care practices and other noncardiology health care settings. In addition, more automation of health information technology systems might elevate security risks to patient data, thus requiring use of additional data protection measures.

**Key Stakeholder Perspectives**

Eight ECRI stakeholders, reflecting nursing, research, health systems, clinical engineering, and health care generalist perspectives, provided comments and ratings on this trend. The list below summarizes stakeholder perspectives.

- AI-assisted operator guidance could improve patient outcomes and reduce disparities by expanding access to echocardiography in rural or other areas lacking adequate cardiac ultrasound expertise.
- If real-world data demonstrate this technology definitively allows nonexpert providers to routinely perform high-quality echocardiograms, health care facilities could adjust staffing levels of personnel with and without cardiac ultrasound expertise. Such changes could have cost implications after incurring the initial costs for implementing the technology.
- Wide adoption of this technology for cardiac ultrasound by nonexpert providers could increase disruption by helping pave the way for further expansion of AI-assisted ultrasound in other clinical areas. Over the long term, it could have applications for telehealth and might facilitate home use by patients for other clinical indications.
example, ultrasound guidance could help patients with paralysis check their bladder capacity when deciding whether to change urinary catheters.

- AI-assisted operator guidance could alter ultrasound training and become integrated into training programs.

**Artificial Pancreas Systems to Treat Type 1 Diabetes Mellitus**

**Highlights**

- Artificial pancreas systems, also called closed loop systems, are wearable devices with embedded algorithms intended to continually measure and automatically adjust blood glucose levels to keep patients with type 1 diabetes mellitus (T1DM) within their target blood glucose ranges.
- Current FDA-approved artificial pancreas systems administer only the hormone insulin; the first device that might administer both insulin and glucagon is in late-phase clinical development.
- Stakeholders commenting on this trend thought that artificial pancreas systems have significant potential to improve patients’ health outcomes and quality of life and are likely to be widely adopted by patients with T1DM; however, they noted potential barriers to their clinical uptake, including high upfront costs and technology that is not fully autonomous.

**Description**

Patients with T1DM need to continually monitor and adjust their blood sugar levels to avoid extreme high or low levels that can cause serious immediate and/or long-term health problems. Historically this has been a time-consuming, manual task, which is now moving toward continuous, automated systems.

FDA approved the first artificial pancreas in 2016. This first-generation closed-loop system consisted of a sensor underneath the skin and an insulin pump. In automated mode, the system measured blood glucose every 5 minutes to automatically administer or withhold insulin according to its measurements. It did not accommodate adjustments for large meals or exercise, which strongly affect blood sugar levels. One study found that roughly 40% of patients stopped using the system in the first few months for reasons including difficulty keeping the system in the automated mode, frequent alarms, sensor failure, need for recalibration, skin adhesion issues, and sensor supply problems.

Since that time, researchers have been working toward improved artificial pancreas systems. Newer FDA-approved systems now integrate with smartphone apps that contain algorithms for more precise blood sugar control and have additional features, including predictive alerts (ie, impending highs or lows 10 to 60 minutes beforehand). Research is demonstrating that closed-loop systems help patients spend more time in target glycemic ranges, thus lowering risk of health complications. Patients have found algorithmic glucose monitoring to be significantly easier than traditional manual monitoring and have “hacked” old insulin pumps to integrate them with smartphone algorithms for this purpose.

One developer is working on a fully autonomous, novel bihormonal pancreas system, the iLet (Beta Bionics, Boston, Massachusetts), that can administer either insulin or glucagon (raises
blood sugar) to control blood sugar better than using insulin only, allowing patients to eat, work out, and sleep more freely. The manufacturer claims that its device could be clinically available in the United States within the next 3 years.\(^{795}\)

**Clinical Area(s) Potentially Disrupted**

Artificial pancreas systems are likely to disrupt management of T1DM, an endocrine disease.

**Opportunities**

Artificial pancreas systems might significantly improve patient health outcomes and improve quality of life by providing an easier and safer way for patients with T1DM to stay in their target blood glucose range. Patients will spend less time self-monitoring their blood glucose and will be able to engage in more activities (eg, exercise, sleep) without needing to pause to monitor their blood glucose or administer insulin. Staying in an optimal range will likely reduce serious long-term secondary complications of inadequately controlled blood glucose (ie, cardiovascular disease, neuropathy, nephropathy, retinopathy). Reducing these long-term health consequences is likely to help reduce health care costs associated with T1DM over time.

**Threats**

The use of artificial pancreas systems might increase health disparities if the technology is too costly for some patients or if reimbursement is unavailable. Health risks might be associated with the systems if the algorithms are imprecise or can be hacked for nefarious purposes. In the case of device or algorithm malfunction or a need to stop using the system, patients might be unfamiliar with and/or incompetent at manual blood glucose monitoring or insulin administration and might experience worse health outcomes as a result.

**Key Stakeholder Perspectives**

Ten ECRI stakeholders, reflecting clinical engineering, health care generalist, health systems, nursing, and research perspectives, provided comments and ratings on this trend.\(^{796-805}\) The list below summarizes stakeholder perspectives.

- Artificial pancreas systems are a significant improvement to the health care management of patients with T1DM and will positively disrupt health outcomes and quality of life; one commenter noted that this technology is the “holy grail” for T1DM.
- The possibility of catastrophic technology failure exists, including the possibility of serious adverse events (eg, death) for patients.
- High costs associated with this technology might be a barrier to patient access and might increase health disparities; however, its high upfront cost might be balanced by decreased long-term health costs associated with T1DM.
- Given that first-generation artificial pancreas devices are already available, the development of a fully autonomous artificial pancreas is likely.
Comprehensive Genomic Profiling in Patients Who Have Cancer to Identify Targeted Therapy Options

Highlights

- Comprehensive genomic profiling (CGP) analyzes DNA, RNA, or both isolated from a patient’s tumor or blood sample to detect actionable genomic alterations (AGAs) in a large panel of cancer-associated genes.
- CGP is intended to detect AGAs that increase inherited cancer risk or promote aggressive cancer growth that could be treated with FDA-approved targeted therapies or help clinicians refer patients to appropriate clinical trials of targeted therapies.
- Stakeholders commenting on this trend thought that implementing CGP into routine cancer care might improve patient health outcomes by helping to identify safer, more effective, targeted therapies that could decrease use of cytotoxic chemotherapy and biologic therapies, which may be less safe and effective.
- Stakeholders also thought that CGP’s cost might cause disparities for uninsured patients or patients whose insurance does not cover CGP. Even if criteria are met to cover CGP, insurance companies might not cover targeted therapies used to treat off-label indications.

Description

CGP involves sequencing a large panel (ie, thousands) of cancer-associated genes in DNA, RNA, or both isolated from a patient’s tumor tissue or blood sample. CGP is intended to detect AGAs known to be therapeutic targets. Clinicians are using CGP (in both germline and somatic testing scenarios) to determine the aggressiveness and inheritable factors of cancers upon initial diagnosis (germline testing) and to select targeted on- or off-label therapies along the patient’s clinical pathway (somatic testing) to benefit patients with cancers that harbor AGAs. CGP also is being used to help identify patients who are eligible for clinical trials of investigational therapies for cancers with specific AGAs.

Clinical Area(s) Potentially Disrupted

The technique of using CGP to identify AGAs has potential to disrupt oncology departments by strengthening collaborations between genetic counselors and clinicians when considering results of germline genetic testing and the expanding number of AGAs that affect the risk and aggressiveness of cancer. New gene variants that might drive oncogenesis and resistance to existing therapies are being identified continuously through research. The data provided by CGP can contribute to understanding which variants play a role and how they function to drive disease processes, as well as which therapies might target the pathogenic variants identified.

Opportunities

Having sufficient quantity and quality of a tumor sample to conduct multiple single-gene tests over time has been a long-standing problem in oncology. Next-generation sequencing of hundreds or thousands of genes at once, using a single tissue sample, has made CGP more feasible, as has the development of “liquid biopsy” methods that examine circulating tumor cells in the blood. Thus, CGP makes more information available to clinicians for future decisions about therapeutic targets. Compared with single-gene sequencing approaches, CGP also can identify AGAs quicker without the need for additional testing. In addition to improving patient
health outcomes, CGP and related management have the potential to be cost effective.\textsuperscript{806} In clinical practice, targeted therapy for treating cancers (eg, breast, lung, kidney) is associated with better outcomes and fewer adverse events for many patients than systemic chemotherapy.\textsuperscript{806, 809-811} In cancers such as gastric or pancreatic cancer, which lack effective targeted therapies, CGP might help identify gene variants that will be critical to developing effective treatments.\textsuperscript{807}

**Threats**

Clinically, CGP performed on heterogeneous tumors might not identify all relevant AGAs or offer information that would benefit patients.\textsuperscript{806} Also, the timing of blood sampling for liquid biopsy can affect the amount of circulating tumor DNA in the blood.\textsuperscript{812} As clinical effectiveness relates to cost, most FDA-approved targeted therapies are indicated for treating cancers that harbor specific genetic alterations, and third-party payers often reimburse for FDA-approved indications. However, third-party payers are reluctant to pay for genetic testing for variants that lack definitive evidence of being an effective target or that have not been approved by FDA as companion diagnostic tests for a labeled therapy. This might limit access to CGP and therapy options that could target some of the identified variants.\textsuperscript{808} Even if CGP is covered by insurance, disparities might increase because only patients with insurance might have access to testing, and when test results identify potential targeted therapies, patients without insurance might be unable to afford the out-of-pocket costs of therapy.\textsuperscript{806}

**Key Stakeholder Perspectives**

Six ECRI stakeholders, reflecting health care generalist, health systems, and research perspectives, provided comments and ratings on this trend.\textsuperscript{813-818} The list below summarizes stakeholder perspectives.

- If incorporated into the clinical workflow, CGP has potential to disrupt health care delivery by helping clinicians select targeted therapies, thus avoiding treatments that may be expensive or less effective.
- CGP has potential to improve health outcomes because it helps tailor a treatment that is based on the tumor’s genetic makeup. It might also improve a patient’s quality of life by leading to use of targeted therapies, which usually cause fewer adverse events than cytotoxic chemotherapy.
- CGP might also improve the clinical development of investigational drugs that target a specific AGA. Patients may benefit from investigational drugs when they are enrolled into trials based on CGP results.
- Even if insurance companies cover CGP, its high cost might create disparities for uninsured patients and prevent them from receiving this care. It might also increase costs when clinicians select off-label targeted therapies that insurance companies do not cover for unapproved indications.
Direct-to-Consumer Genetic Testing Partnerships With Pharmaceutical Companies to Facilitate Drug Development and Treatment

Highlights
- Laboratories offering direct-to-consumer (DTC) genetic testing services are establishing collaborations with drug manufacturers to share patients’ genetic data and volunteered genetic testing questionnaire data.
- Large data sets from DTC genetic testing might assist with drug development, enrollment in clinical trials, and, ultimately, patient access to targeted therapies.
- Stakeholders commenting on this trend thought that DTC genetic testing might improve patient outcomes by speeding up drug development but cautioned that it might increase disparities due to the out-of-pocket cost of testing.
- Stakeholders also expressed concern about inadequately managed collaborations posing substantial threats to patient health data privacy, possibly leading to higher insurance premiums or exploitation of personal health information.

Description
Laboratories that offer DTC genetic testing services are considering use of patients’ genetic data and patients’ volunteered genetic testing questionnaire data as a way to drive drug development and treatment. By partnering with pharmaceutical companies, DTC genetic testing companies can provide large data sets that might give insight into new disease targets worth pursuing by drug companies. The databases from DTC testing might also make it easier for pharmaceutical companies to identify people who have a disease, are asymptomatic, or are carriers for conditions of interest and recruit them for clinical trials in a cost-effective manner.

For example, genetic testing company 23andMe has established collaborations with GlaxoSmithKline, and another genetic testing company, Nebula Genomics, is collaborating with EMD Serono to use consumer data to drive the drug-development process.

Clinical Area(s) Potentially Disrupted
These collaborations could shift paradigms for drug development, drug target identification, and clinical trial recruitment, and might expedite these processes. Among the clinical areas being affected are medical genetics, neurology, cardiology, oncology, and rare and orphan diseases.

Opportunities
Effective collaboration between companies offering DTC genetic tests and drug developers might increase insights into the most promising targets to pursue for drug development, decreasing the cost and time needed to develop new agents. Such collaborations might also enable quicker and more cost-effective recruitment of patients and asymptomatic carriers with rare diseases into appropriate clinical trials. This, in turn, might result in additional new targeted therapies that address unmet needs and improve patient outcomes.

Threats
Poorly managed collaborations between DTC genetic test companies and drug developers might pose significant threats to patient health data privacy. Well-managed collaborations might put competing firms at a competitive disadvantage. Consumers who used DTC genetic test services and signed initial consents that their data could be used might not have realized
how companies would use or profit from their data: DTC companies can profit by selling the
data and drug-development companies can profit from the drugs they successfully develop
based on those data.

**Key Stakeholder Perspectives**
Seven ECRI stakeholders, reflecting health care generalist, nursing, business and finance,
and health systems perspectives, provided comments and ratings on this trend.822-828 The list
below summarizes stakeholder perspectives.

- DTC genetic testing might offer individuals the ability to identify health conditions early
  enough to make lifestyle changes, seek medical help, or delay progression to maintain
  their health.
- DTC genetic testing might promote self-diagnosis by individuals who may not be reading
  the fine print associated with genetic testing, which might lead to misdiagnosis and
  mistreatment.
- Effective collaboration might reduce development costs for drug developers. However,
  consumers could be unaware of the ways in which companies are profiting from their
  genetic data.
- DTC genetic testing might increase health care costs for individuals opting to pay for the
  testing; however, information gained from these tests may reduce long-term costs of
  treating certain health conditions.
- There might be ethical implications due to poor regulatory oversight if insurance
  companies gain access to genetic information of individuals and increase their insurance
  premiums.

**Disease-Modifying Agents (Immunomodulators) to Mitigate Severe COVID-19 Symptoms**

**Highlights**
- Numerous immunomodulators are being evaluated for mitigating immune-related
  pathological processes of severe coronavirus disease (COVID-19).
- Stakeholders commenting on this trend thought that effective immunomodulators might
  substantially improve health outcomes in high-risk patients (eg, seniors and
  immunocompromised people) and critically ill patients; however, untested, off-label use
  raises safety concerns.
- Stakeholders also thought that, because the COVID-19 treatment paradigm consists
  mainly of supportive care, effective immunomodulators might reduce infrastructure
  demands and costs to the system by shifting care to more outpatient settings.
- Stakeholders agreed that immunomodulators would be costly, and payers might limit
  coverage to only severe cases once efficacy is established.

**Description**
The recent COVID-19 pandemic has generated substantial interest in the rapid development
of effective treatments to manage severe immune complications from the disease, which can lead
to cytokine storm, organ damage, and death.829,830 Investigators are examining the use of
established immunomodulatory agents that might hold potential to mitigate some patients’ severe
immune reactions, which are linked with poor COVID-19 outcomes. At the time of stakeholder comment, investigators were examining small-molecule immunomodulators, including thalidomide, an antineoplastic with anti-inflammatory, antifibrotic, and antiangiogenesis properties. Thalidomide is in phase II development, with primary completion expected May 30, 2020.\textsuperscript{831,832} Fingolimod, a multiple sclerosis therapy, is in phase II development, with primary completion expected in July 2020.\textsuperscript{833} Tetrandrine, a Chinese plant–derived alkaloid and calcium channel blocker that purportedly inhibits mast cell degranulation, has phase IV data expected in March 2021.\textsuperscript{834} Additionally, antiviral/immunomodulatory cytokine interferon (IFN) therapies IFN-α2β and IFN-β1β are being evaluated, with phase I trials’ primary completion expected in March 2020 and May 2020.\textsuperscript{835,836}

Investigators are also examining a combination therapy with anti-PD-1 (programmed death-1) monoclonal antibodies and thymosin intended to promote T-cell survival and reduce sepsis and severe pneumonia risk in patients with COVID-19. Preclinical studies suggest that blocking the protein PD-1 or its ligand PD-L1 might regulate cytokine production, reduce organ dysfunction, and reduce death from sepsis.\textsuperscript{830,837} Thymosin also purportedly regulates cellular immunity in patients with sepsis, but the mechanism is unclear. The combination therapy has phase II primary completion expected in April 2020.\textsuperscript{838}

**Clinical Area(s) Potentially Disrupted**

Using immunomodulators for severe COVID-19 has potential to shift the treatment setting from supportive care in the emergency department and intensive care unit to enabling telemedicine and remote treatment of patients, with fewer demands on critical care resources. Although preauthorization might be required, primary care and urgent care facilities might also be better equipped to manage COVID-19 that begins to turn for the worse, and all clinical specialties would be more likely to resume normal operations if poor COVID-19 outcomes could be mitigated more effectively.

**Opportunities**

Effective immunomodulators might add to the current options of supportive care, reducing the death rate, duration, and costs of treating critical patients with COVID-19, relieving strain on the system, and freeing up critical care resources for other ailments. From a societal perspective, improved prognosis might reduce absenteeism and relax social distancing protocols.

**Threats**

Access to immunomodulators found to be effective against COVID-19 might be restricted to select patients due to global demand and the need for global manufacturing scale-up, particularly in the case of effective biologic agents. The off-label use of existing agents for COVID-19 without the usual vetting process might uncover new adverse events due to the complications from the disease or drug–drug interactions when used as part of a multidrug regimen. Extensive use of expensive off-label biologics to treat COVID-19 might increase health care costs.

**Key Stakeholder Perspectives**

Eight ECRI stakeholders, reflecting nursing, physician assistant, research, health systems, and health care generalist perspectives, provided comments and ratings on this trend.\textsuperscript{839-846} The list below summarizes stakeholder perspectives.
• A strong push to rapidly develop immunomodulators for managing complications from severe COVID-19 has substantially shortened development time frames, particularly for the use of off-label agents; however, untested use of these agents raises safety concerns.
• The COVID-19 treatment paradigm consists mainly of supportive care. Effective immunomodulators might reduce infrastructure demands and costs to the system, shifting care to outpatient settings.
• Effective immunomodulatory therapy might substantially improve health outcomes in high-risk patients (eg, seniors and immunocompromised people) and critically ill patients.
• Most immunomodulators discussed are costly, and payers might not cover treatment without severe disease symptoms and substantial evidence of efficacy; however, some costs might be offset by reduced inpatient care, illness, and death.

Emerging Antiviral Therapies for COVID-19

Highlights
• Numerous antiviral therapies are being evaluated for treating coronavirus disease (COVID-19; ie, severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection).
• Stakeholders commenting on this trend thought that effective antivirals would be very disruptive to the current COVID-19 treatment paradigm, which consists mainly of supportive care.
• Stakeholders also thought that effective antivirals might improve patient health and reduce infrastructure demands and costs to the system; however, they cautioned that untested, off-label use of antivirals raises serious safety concerns.

Description
The recent COVID-19 pandemic has generated substantial interest in the rapid development of effective therapies for targeting the infection. Investigators are pursuing novel agents and repurposing existing agents.

One of 2 novel agents is remdesivir (Gilead Sciences), a small-molecule nucleotide polymerase inhibitor, originally developed to treat Ebola and Marburg virus infections. Remdesivir is in phase III development for treating COVID-19, with positive initial data reported in April 2020. On May 1, 2020, Gilead received FDA Emergency Use Authorization for remdesivir to treat severely ill, hospitalized patients with COVID-19. The second novel therapy, meplazumab, is a humanized anti-CD147 monoclonal antibody that purportedly inhibits the binding of the SARS-CoV-2 Spike protein with CD147 on host cells, preventing binding or cell entry. Meplazumab is in phase I/II development, with primary completion expected in December 2020.

Various combination regimens that repurpose established antiviral agents for other clinical indications include the viral protease inhibitors lopinavir and ritonavir (HIV treatments), the viral RNA polymerase inhibitor favipiravir (approved in Japan for influenza), the neuraminidase inhibitor oseltamivir (influenza), and the immunomodulator chloroquine. A phase III trial of various combinations of these drugs has an expected primary completion in October 2020.
Clinical Area(s) Potentially Disrupted

Antiviral therapies for COVID-19 have potential to shift the treatment settings from self-quarantining and supportive care in the emergency department and intensive care unit to enabling telemedicine and remote treatment of patients, with shorter self-quarantines and fewer demands on critical care resources. Primary care facilities might also be better equipped to manage COVID-19, and all clinical specialties would be more likely to be able to resume normal operations.

Opportunities

Effective antiviral therapies might improve health outcomes in infected patients and reduce the likelihood of transmission to uninfected people. From a societal perspective, better expected outcomes and lower infection rates might reduce absenteeism and relax social distancing protocols. In critical care settings, effective antivirals might also reduce the morbidity, duration, and costs of treating critical patients, relieving strain on the system.

Threats

Antivirals found to be effective against COVID-19 might be restricted in access to select patients because of global demand and the need for global manufacturing scale-up, particularly in the case of effective antiviral agents. The off-label use of existing agents for COVID-19 might uncover new adverse events due to the complications from the infection or drug–drug interactions when used as part of a multidrug regimen. Extensive use expensive of off-label antivirals (eg, HIV therapies) might incur substantial cost to the system when used for treating COVID-19.

Key Stakeholder Perspectives

Ten ECRI stakeholders, reflecting health care generalist, research, nursing, physician assistant, health systems, clinical engineering, and business and finance perspectives, provided comments and ratings on this trend. The list below summarizes stakeholder perspectives.

- Effective antivirals might improve health outcomes and provide emotional and psychological benefits from ending self-isolation, as well as promoting economic activity. Strong demand to find effective antivirals has maximized efforts to pull the development and disruption time frame forward.
- The COVID-19 treatment paradigm consists mainly of supportive care. Effective antivirals would immediately reduce infrastructure demands and costs to the system, shifting care to outpatient and telemedicine settings, and reducing virus transmission.
- Effective antivirals might be most disruptive to outcomes in high-risk patients (eg, seniors and immunocompromised people).
- Off-label use of existing medications could accelerate treatment availability but raises serious long-term safety questions, while novel, FDA-approved therapies would likely not be available for at least another 6 to 9 months (ie, September to December 2020).
- Low-priced antivirals might reduce disparities and be highly disruptive globally for reducing demands and costs to the system for inpatient care (eg, equipment and beds). Higher-priced antivirals might still realize cost offsets from reduced inpatient care, illness, and death.
Integrated Electronic Health Solutions to Improve Cardiovascular Care

Highlights

- Smartphones and other personal electronic devices can collect increasingly more comprehensive physiologic data from cardiovascular patients and transfer it to clinicians, purportedly improving outcomes through more timely review and treatment adjustments.
- Published evidence establishing effectiveness and clinical importance of these technologies has mostly lagged behind product development and consumer marketing.
- The availability of substantial amounts of patient data raises several questions, including which clinicians are responsible for reviewing and acting on data and whether clinical practices will be compensated for that additional workload.
- Stakeholders commenting on this trend expected use of electronic health solutions to expand, although uncertain reimbursement could impact clinician uptake and increase disparities.
- Stakeholders thought regulation and professional consensus on which technologies work best could reduce disruption to the health care delivery system.

Description

Several products are available to collect physiologic data from cardiovascular patients through wearables or smartphones and transfer the data to clinicians. Most products are limited in scope (eg, blood pressure or electrocardiogram alone). Product availability and consumer marketing has largely outpaced clinical research on the true clinical utility of these technologies in cardiovascular care. Limited early data have suggested some integrated digital health interventions introduced during hospitalizations for heart attacks might reduce 30-day readmissions and related health care costs compared with historical controls.

The American College of Cardiology (ACC) has issued a set of principles to guide integration of e-health or mobile health technologies into cardiovascular care. ACC calls for more research of digital health applied to cardiovascular care to ensure patient safety, care quality, and positive health outcomes. ACC advises that these technologies should improve the patient experience, care quality, patient safety, and outcomes without hampering clinical workflow.

Clinical Area(s) Potentially Disrupted

Integrated electronic health solutions for cardiovascular care could disrupt patient management in cardiology and primary care practices. The availability of more physiologic patient data, nearly in real time, might require clinical staff to interact with patients more frequently to address changes in their health and adjust medications or other treatments as needed. Different clinicians might need to establish arrangements to permit adequate and secure data sharing to ensure optimal management of coexisting diseases while reducing redundancies (eg, duplicate testing). The most common cardiovascular conditions monitored with these technologies include high blood pressure, coronary artery disease, (past) myocardial infarction, and heart failure.

Opportunities

Combining several types of collected physiologic data into one integrated platform for cardiovascular patient monitoring in near real time could improve outcomes if clinicians and
patients can interact in a timely manner and adjust care as needed. An integrated patient monitoring system that tracks multiple physiologic parameters could also increase technical efficiencies compared with multiple separate systems that track blood pressure, heart rate, weight, and other vital statistics.

**Threats**

Collecting additional patient data might increase security risks and raise questions about who owns and stores the data. Greater data monitoring requirements could significantly increase the clinical staff’s workload. This additional workload could be controversial, depending on whether or how clinicians are compensated for data collection and monitoring. Depending on the technology and standards involved, the use of competing technologies with multiple components could create system compatibility problems, potentially limiting usefulness for effective patient monitoring. In addition to incompatibility, the use of multiple linked components within a single system might raise quality control concerns regarding device maintenance and data integrity. Cost concerns could emerge about who pays for the technology upfront and for its continued maintenance. The shift to integrated electronic health solutions could increase disparities if the technology’s cost or complexity filters out poorer, older, or less tech-minded patients, who theoretically would be most likely to benefit.

**Key Stakeholder Perspectives**

Eight ECRI stakeholders, reflecting research, nursing, health systems, health care generalist, and business and finance perspectives, provided comments and ratings on this trend. The list below summarizes stakeholder perspectives.

- Beyond giving clinicians more timely data to guide disease management and improve outcomes, use of electronic health solutions in cardiovascular care will continue to expand to better engage patients and improve convenience by reducing office visits (eg, for pacemaker evaluation).
- Better regulation of these technologies and consensus from cardiovascular specialists about which technologies actually provide benefit should reduce disruptions to the health care delivery system that can arise without standardization.
- More data are needed to clarify which clinical benefits are most likely and which technology combinations can best provide clinical improvements.
- Insurers will likely request more evidence on clinical efficacy and cost-effectiveness before reimbursement for these technologies becomes readily available, potentially increasing disparities.
- Patient education is needed to ensure appropriate technology operation and accurate data collection. Clinical personnel may need to engage patients to maintain adherence and follow-up with patients if data are not received.
N-of-1 Trials to Research Patient-Centered Outcomes

Highlights

- N-of-1 study designs, in which a single patient is studied, offer individualized treatment regimens to promote patient-centered research and can reveal how responses to treatments might vary among patients and within a patient.
- The results obtained from N-of-1 trials can guide specific treatment for a patient or be pooled with other such trials of the same drug and same experimental design to obtain population-level trends.
- Stakeholders commenting on this trend thought that N-of-1 trials have potential to improve patient outcomes by providing personalized treatment regimens for people who have difficult-to-treat diseases.
- Stakeholders were concerned about the ethical implications for human subject research and thought these kinds of trials might require robust protocols and regulatory procedures to safeguard patient safety.

Description

N-of-1 trials focus on collecting treatment-response data in a single patient and might represent the optimal form of clinical evaluation for patient-centered medicine. Researchers design a mini-investigation for an experimental drug’s safety and efficacy entirely around an individual patient’s response, to determine whether a particular treatment works for that individual.\(^7\) A patient might alternate between drug and placebo for a couple of weeks at a time, and researchers record the outcomes. These trial results can then be used to guide specific treatment for a patient or be pooled with other N-of-1 trials of the same drug and same experimental design to obtain population-level trends.\(^7\) An advantage of data from N-of-1 trials is that they can reveal how responses to treatments might vary among and within patients. N-of-1 trials are best used to evaluate treatments for chronic, slowly progressing conditions, or frequently recurring or relapsing diseases.\(^8\) The ideal treatments to test in N-of-1 trials would demonstrate substantial individual differences in treatment effects, uncertainty regarding the best treatment regimen, rapid onset of drug action, or brief and safe washout periods. N-of-1 trial outcomes should be validated, repeatable measures and might include the use of biomarkers.\(^7\)

Clinical Area(s) Potentially Disrupted

N-of-1 trials have potential to disrupt a wide range of clinical areas that involve chronic, stable, slowly progressing, or recurring illnesses such as behavioral health disorders, infectious disease, neurologic disorders, obesity, and other conditions.\(^7,8\)

Opportunities

Personalized study designs might provide insight into the best use of precision medicines, thereby improving health outcomes. They might also make patient-centered comparative data more accessible to patients and physicians.

Threats

N-of-1 trials might predispose patients to being treated unethically by manufacturers of poorly developed investigational agents with small budgets. They could also be viewed as a
threat by some stakeholders who benefit from large, population-based, randomized controlled trials and current data aggregation systems.

**Key Stakeholder Perspectives**

Seven ECRI stakeholders, reflecting health care generalist, nursing, health systems, and research perspectives, provided comments and ratings on this trend. The list below summarizes stakeholder perspectives.

- N-of-1 trials might provide individualized therapeutic regimens for patients with chronic and difficult-to-treat illnesses.
- Personalized trial designs might not produce generalizable results; thus, they are unlikely to make a very large impact on population health outcomes.
- Costs of running N-of-1 trials might be higher than traditional trials due to the personalized study design. This might increase health care disparities.
- N-of-1 trials might impact current research staff at study sites, affect patient recruitment and retention, and warrant changes in the regulatory requirements for obtaining FDA authorizations.

**Proteomic Profiling to Diagnose Cancer and Guide Personalized Targeted Therapy**

**Highlights**

- Proteomic profiling assesses tissue or blood samples to identify protein signatures that are associated with cancer.
- Proteomic profiling is intended to identify protein biomarkers that can help confirm a diagnosis of cancer, help guide selection of targeted therapies, or match patients to clinical trials.
- Stakeholders commenting on this trend thought that the cost of proteomic profiling is likely to be its most disruptive factor. It will be an expensive technology that might not receive reimbursement from insurance companies.
- Stakeholders also thought that, if proteomic profiling is used properly to detect cancer in its early stages and guides selection of safe and effective targeted therapies for patients, it could improve health outcomes and reduce health care costs for managing late-stage disease.

**Description**

Proteomic profiling involves the systematic separation, identification, and characterization of proteins in a patient’s tumor or blood sample. In patients suspected of having cancer, clinicians use proteomic profiling to identify a cancer-associated protein signature that might confirm the presence and origin of a specific cancer type. For these patients, proteomic profiling helps identify overexpressed proteins that are known to be therapeutic targets, such as those caused by chromosomal rearrangements. Clinicians then use this information to select a targeted therapy on label or off label that is most likely to benefit a patient who has cancer or to help enroll patients in clinical trials of investigational therapies.
Clinical Area(s) Potentially Disrupted

Proteomic profiling has potential to disrupt the oncology clinical area by simultaneously confirming a diagnosis of cancer and recommending targeted therapies that are likely to benefit patients. In patients suspected of having cancer (e.g., clinical features, family history), proteomic profiling might disrupt radiology departments by detecting cancers that have not progressed to a stage that medical imaging can detect.

Opportunities

Proteomic profiling has potential to improve health outcomes by diagnosing cancer earlier in patients suspected of having the disease and matching patients with targeted therapies or clinical trials likely to benefit them. In tumors that are composed of more than one cell type, proteomic analysis might identify several biomarkers that are involved in cancer growth.

Threats

As a novel testing approach, proteomics might add to clinician burden by requiring them to learn about protein signatures for different cancer types and understand which could be drug targets. Implementing proteomics into the clinical workflow has potential to increase disparities by being available only to patients who are insured or able to pay for treatment out of pocket.

Key Stakeholder Perspectives

Seven ECRI stakeholders, reflecting health care generalist, health systems, nursing, and research perspectives, provided comments and ratings on this trend.886-892 The list below summarizes stakeholder perspectives.

- If proteomic profiling can identify cancer at early stages and direct clinicians to targeted therapies for patients, it has potential to improve health outcomes and quality of life.
- Adopting proteomic profiling into clinical use has potential to disrupt health care delivery. Because the implementation of new technologies occurs regularly in clinical practice, proteomic profiling may be moderately disruptive.
- Proteomic profiling is likely to be an expensive procedure; unclear is whether insurance companies will cover it. Its use can also increase costs if clinicians prescribe off-label targeted therapies for unapproved indications, use proteomic profiling for all circumstances, or are unfamiliar with proper use of proteomic results to guide patient management.
- Even with its high cost, if proteomic profiling can inform decisions on targeted therapies that are safe and effective for treating early stage cancer, it might reduce overall health care costs, especially those associated with treating later-stage disease.

Psychedelic Drugs to Treat Mental Health Conditions

Highlights

- Psychedelic drugs (psychedelics) are being investigated as a novel drug class to treat a variety of mental health conditions, including depression and anxiety disorders.
- Psychedelics purportedly work by altering mood states, changing perception, and facilitating life-altering perspectives.
- Various psychedelics are being studied in clinical trials (including late-phase trials) in pursuit of FDA approval.
• Stakeholders commenting on this trend thought that psychedelics have potential to significantly improve patient health outcomes and quality of life, but, if approved, barriers to their clinical use might include concerns over adverse effects and ethical controversy.
• Stakeholders also thought the potential disruption this trend poses is most likely to occur at least 2 years from now (ie, 2022).

Description
Psychedelic drugs (eg, psilocybin, lysergic acid diethylamide [LSD], N,N-dimethyltryptamine [DMT], 3,4-methylenedioxymethamphetamine [MDMA], ketamine) alter one’s state of consciousness, purportedly by altering certain neurotransmitters in the brain. Their use might provide the patient with altered perception, increased introspection, feelings of closeness with others, and positive mood states. These experiences are often reported as deeply profound and life altering.

Although most psychedelics are currently designated as Schedule I drugs in the United States, researchers are investigating their potential to treat a variety of mental and behavioral health disorders that have not responded to conventional treatments.

Psilocybin is in clinical trials to investigate treatment for depression, anorexia nervosa, obsessive-compulsive disorder, alcohol use disorder, nicotine dependence, cocaine use disorder, and cancer-related anxiety. 893-898 LSD is being explored to treat anxiety associated with life-threatening illness, other anxiety disorders, and depression. 899-901 DMT, a drug present in a psychoactive brew called ayahuasca, is being researched to treat depression. 902,903 MDMA is in phase III clinical trials for use during psychotherapy to treat posttraumatic stress disorder (PTSD) and is being investigated as therapy for social anxiety in adults with autism. 904,905 Ketamine, while not traditionally considered a psychedelic drug, has some psychedelic properties and is being explored off label to treat PTSD. 906 A closely related molecule, esketamine (Spravato), has been FDA approved to treat depression. 907

In clinical trials, psychedelics are administered and patients are monitored under medical supervision.

Clinical Area(s) Potentially Disrupted
The use of psychedelics for treating mental health conditions could disrupt treatment models for practitioners of psychiatry and other mental health disciplines. The use of these drugs requires a learning curve; different approaches to prescribing, administering, and monitoring their effects; and changes in the duration and setting of psychotherapy and counseling sessions.

Opportunities
Psychedelics, as a novel drug class used to treat mental health conditions, might improve patient health outcomes and quality of life. They might also reduce the prevalence of treatment-resistant mental health conditions and reduce costs associated with long-term mental health treatment. Psychedelics might change the paradigm and infrastructure of mental health care. Their use might encourage continued research into additional potential therapeutic uses for psychedelics and might enhance understanding of mental health conditions.

Threats
Psychedelic use might result in negative health outcomes for some patients (eg, acute psychosis). For this reason, they are not recommended for every patient. Population health and
legal risks might arise from making controlled substances more accessible. Disparities in access to care might increase if clinicians hesitate to prescribe controlled substances that carry stigma or a significant risk of harm or mental deterioration. Treatment could be costly in the short term if significant costs are associated with building necessary infrastructure needed to deliver the treatments.

**Key Stakeholder Perspectives**

Ten ECRI stakeholders, reflecting business and finance, health care generalist, health systems, nursing, and research perspectives, provided comments and ratings on this trend. The list below summarizes stakeholder perspectives.

- Psychedelics have potential to significantly improve psychiatric health, particularly for mood disorders and anxiety disorders.
- Initial psychedelic research is promising, but more safety and efficacy data are needed.
- Psychedelics, if approved, will likely be applied to many different mental health conditions.
- The medical use of psychedelics is likely to be highly controversial and stigmatized, which might limit clinical uptake, although this might be attenuated by the recent wider acceptance of medical marijuana and popular culture surrounding psychedelics.
- Psychedelics might impact the treatment paradigm and care delivery because the drugs need to be given in a medically supervised health care setting.
- Stakeholders rated the potential disruption for this trend as most likely to occur at least 2 years from now (ie, 2022).

**Smartphone-Guided Medical Examinations and Diagnostics for Use by Patients and Caregivers**

**Highlights**

- Smartphone-based applications (apps; ie, mHealth) are expanding care delivery models by providing remote options for diagnosing conditions and identifying optimal treatments.
- These apps are accompanied by handheld examination kits that allow patients to perform guided medical examinations and share results with their providers in real time.
- Stakeholders commenting on this trend generally agreed that smartphone-guided medical examinations would improve patient outcomes by providing patients and their caregivers an option to receive medical care in a convenient and timely manner.
- Stakeholders also thought that this intervention will reduce health care costs while reducing disparities by giving health care access to underserved individuals who live in rural areas or have difficulty getting to a medical facility.

**Description**

An accurate diagnosis, when made in a timely manner, can provide the best insight into treatment options for patients. A recent telehealth and e-health case study highlighted a patient’s case in which acute appendicitis was diagnosed via telehealth that allowed timely surgery to take place. Smartphone apps are now capable of delivering examinations and diagnostic services to patients in remote areas by boosting the use of smartphones as diagnostic tools.
devices for multiple age groups. These apps are accompanied by handheld examination kits that allow patients to perform guided medical examinations and share results with their provider for an appropriate diagnosis and treatment options (eg, TytoCare, MoleScope, RetinaScope).920-922

Clinical Area(s) Potentially Disrupted

The practice of using physician-guided patient self-examinations using smartphones is likely to disrupt telehealth systems and influence the delivery of care to patients in both rural and urban locations. For patients who travel outside their usual care area and wish to be evaluated and receive treatment recommendations from their home clinicians, this technology could provide that option.

Opportunities

Smartphone-based medical self-examinations might decrease the overall cost related to both patient care and care delivery by reducing clinician office visits. These technologies might also reduce disparities in terms of access to care for patients in rural areas. Involving patients and caregivers in the diagnostic process might increase patient autonomy and satisfaction. In addition, mHealth app use might reduce burden on the health system, such as sequelae from overlooked symptoms for which patients did not have the time or opportunity to seek in-person evaluation.

Threats

Because of a lack of comprehensive privacy laws for telehealth systems and the fact that patients’ smartphones might not be sufficiently secure, personal health information might be at risk of being hacked, collected, used, or shared for unintended purposes. Additionally, user or device errors could lead to misdiagnosis or mistreatment. The move from in-person to virtual care might also adversely affect patient–clinician relationships.

Key Stakeholder Perspectives

Eight ECRI stakeholders, reflecting nursing, health care generalist, health systems, clinical engineering, and research perspectives, provided comments and ratings on this trend.923-930 The list below summarizes stakeholder perspectives.

- Smartphone-guided medical examinations might improve the decision-making process by giving patients and caregivers the ability to send reports to their provider in real time and receive medical care in a timely manner.
- They might also improve access to medical care for patients residing in rural areas and those who are unable to leave their home often. Conversely, it might increase disparities because of costs associated with device implementation and lack of a stable broadband connection.
- Due to a patient learning curve associated with the use of smartphones and the lack of quality control for the handheld examination kits, user or device errors could lead to misdiagnosis or mistreatment. Hence, many patients might still prefer an in-person visit with a health care professional.
- Smartphone-guided medical examinations might require additional trained staff if several patients opt for using these apps for their ongoing medical needs; however, this could be offset by the individuals cutting back on in-person doctor visits.
Telehealth to Assess and Treat Mental Health Conditions

*Note:* The use of telehealth increased significantly after COVID-19 was declared a national emergency in the United States. The commentary and associated stakeholder perspectives below do not specifically address these recent developments.

**Highlights**

- Telehealth to assess and treat mental health conditions is the use of digital communication modalities to provide patients with psychiatric and psychological assessment and treatment.
- It might be especially helpful in reducing patient access-to-care issues, which are affected by the limited number of health care providers available and geographic, financial, and psychosocial factors.
- Stakeholders commenting on this trend thought that using telehealth to assess and treat mental conditions might significantly improve patient outcomes, primarily because of its potential to increase patient access to care and treatment adherence.

**Description**

Telehealth, the use of digital communication modalities to provide health care, is being increasingly harnessed to provide patients with psychiatric and psychological assessment and treatment. A main driver for its adoption is the need to address access-to-care issues due to the limited number of health care providers and geographic, financial, and psychosocial factors.

Concerns are growing over the increasing shortage of psychiatrists and mental health professionals available to treat mental health conditions both now and in the future. A 2017 Merritt Hawkins report found that 77% of US counties reported a severe shortage of psychiatrists. The 2017 America’s Health Rankings data show a wide range of available mental health providers per 100,000 population, from as few as 85 providers per 100,000 population in Alabama to 547 providers per 100,000 population in Massachusetts, demonstrating disparities in current accessibility of mental health care. A 2015 Association of American Medical Colleges report of active physicians found that more than 60% of psychiatrists were aged 55 or older, touching on a concern that the shortage of providers is growing.

Telehealth might help narrow the provider-to-patient gap. Telehealth can also help facilitate faster and more convenient care for patients with other reasons delaying or preventing them from seeking mental health care.

Many telehealth platforms are available on the market.

**Clinical Area(s) Potentially Disrupted**

Telehealth to treat mental health conditions might disrupt the treatment of a range of mental health conditions, including anxiety disorders (e.g., generalized anxiety disorder, panic disorder, posttraumatic stress disorder), depression (e.g., major depression, bipolar depression, postpartum depression), attention-deficit/hyperactivity disorder, schizophrenia and other psychotic disorders, and substance abuse disorders (e.g., alcohol use disorder, opioid use disorder). It might disrupt the delivery of both psychiatry and auxiliary psychological services (e.g., psychological counseling) to patients.
Opportunities

Telehealth eliminates barriers to mental health care access, such as regional scarcity of providers and transportation difficulties, which might significantly decrease health disparities and improve patient health, outcomes, and quality of life. Patients who have been unable to travel to receive care or cannot seek care logistically might be more inclined to try telehealth than to not seek care at all. Certain mental health conditions make it more difficult for patients to seek mental health care in person (e.g., panic disorder triggered by driving, social anxiety in waiting rooms, depression that makes it hard to get dressed to go out). Telehealth might encourage patients with such conditions to seek care sooner and more often if telehealth is more convenient and comfortable. Additionally, some patients hesitate to seek care in person due to stigma. Telehealth offers more provider options to patients; therefore, a patient who does not establish an adequate therapeutic relationship with one provider could seek another more easily through telehealth instead of discontinuing treatment.

Threats

Telehealth poses a risk to patient confidentiality if communications are not secure. Patients without internet access might be unable to use telehealth. It might pose risks to patient health if medical providers (e.g., psychiatrists) are unable to collect crucial information such as vital signs or weight for medical decision making, as they would be able to in an in-person setting. It might be difficult to treat life-threatening health issues such as active suicidal ideation or alcohol withdrawal from a distance, especially if providers are unfamiliar with local inpatient facilities and mental health resources for referral. Telehealth might impede providers from establishing patient rapport as readily compared with in-person visits, and providers might lack full context of a patient’s geographical or cultural and psychosocial context as well.

Key Stakeholder Perspectives

Eleven ECRI stakeholders, reflecting clinical engineering, health care generalist, health systems, nursing, and research perspectives, provided comments and ratings on this trend. 

The list below summarizes stakeholder perspectives.

- Telehealth has significant potential to positively disrupt patient health outcomes for reasons including increased access to care, increased treatment rates, increased patient adherence, more comprehensive evaluation and data collection, more patients feeling comfortable seeking mental health care, and decreased wait times for appointments.
- The smartphone modality for telehealth is likely to be convenient for many patients but carries risks for maintaining patient confidentiality, and some patients might not have access to Wi-Fi or adequate cellular data in rural areas.
- Telehealth might positively impact patients in rural areas the most, and it could help decrease health disparities.
Tissue of Origin–Agnostic, Molecularly Targeted Oncology Drugs

**Highlights**

- FDA has recently approved 3 oncology drugs for use in indications defined solely by a molecular marker, irrespective of the cancer’s tissue of origin.
- This approach represents a departure from previous FDA oncology drug approvals whose indications pertained to cancers arising from a specific tissue.
- As additional molecular drivers shared across primary cancers are identified, additional tissue-agnostic approvals are likely, with the potential to disrupt clinical trial and treatment paradigms for cancer.
- Stakeholders commenting on this topic suggested that it might improve patient health outcomes, disrupt clinical trial design and regulatory pathways for oncology drugs, and disrupt the current paradigm of anatomy-based oncology specialization.

**Description**

Oncology drugs have traditionally been approved by FDA for cancers arising from specific tissues or organs (eg, breast, prostate, lung, blood). With the increasing recognition that some of the same genetic changes drive the development of cancers arising in different organs or tissues, investigators began defining patient populations in terms of their molecular subtype, irrespective of the organ or tissue in which the cancer arises. These observations were made in so-called basket trials or umbrella trials—the same clinical trial enrolled patients with different cancers, and researchers observed a signal of efficacy for a molecular target of a drug across those cancers. This led to expansion of cohorts or creation of tissue-of-origin trials with the intent that the manufacturer seek FDA drug approval for that tissue of origin (eg, ALK inhibitors for non–small cell lung cancer, BRAF inhibitors for melanoma or Erdheim Chester disease).

More recently, however, FDA approved 3 drugs for use in molecularly defined patient populations. That is, the cancer tissue of origin did not matter—eligibility for the drug rested on a molecular target. Examples include pembrolizumab (Keytruda), which received approval to treat unresectable or metastatic, microsatellite instability–high or mismatch repair–deficient solid tumors in adult and pediatric patients. Larotrectinib (Vitrakvi) and entrectinib (Rozlytrek) were approved to treat solid tumors that have a neurotrophic tyrosine receptor kinase gene fusion without a known acquired resistance mutation. This change in approach raises issues regarding clinical trial conduct to provide the supporting evidence for regulatory submissions as well as potential issues with the varied responses to molecularly targeted therapies across different cancer types, particularly for rare cancers or cancers in which a molecular target rarely occurs.

**Clinical Area(s) Potentially Disrupted**

These drugs have potential to disrupt treatment paradigms for cancer.

**Opportunities**

Conventional oncology clinical trial designs based on testing a drug only in cancers arising from a specific tissue of origin can be limited by the small number of eligible patients in rare cancers and rare molecularly defined cancer subtypes. Tissue-agnostic clinical trials that enroll cancer patients with a shared molecular subtype could provide a pathway to FDA approval in instances of indications that might be poorly suited for traditional clinical trial designs. Also, this...
approach creates new collaboration opportunities for laboratories and companies that offer whole genome and exome sequencing. More health care companies are collaborating with drug-development companies, and drug-development companies are acquiring genetic testing laboratories to enhance their research and development programs. Drug-development companies are also starting to partner with direct-to-consumer genetic test companies to acquire their large data sets and search for molecular targets for cancer therapy development.

**Threats**

An ever-increasing number of potential molecular targets might increase costs by requiring more widespread testing of tumors using whole genome sequencing or very large gene panels upon initial diagnosis of a cancer in a patient to identify all potential therapeutic targets. Additionally, evaluating a wider variety of molecular targets not tied to any specific type of cancer might involve a substantial learning curve for providers.

Although some targeted therapies have been shown to be therapeutically effective in targeting molecular drivers irrespective of cancer tissue of origin, the efficacy of other drug and molecular driver combinations depends on the tissue of origin. Therefore, drug approvals for tissue-agnostic indications might lead to poor outcomes in certain patients with a molecular driver/tissue-of-origin combination in which the targeted therapy is ineffective.

**Key Stakeholder Perspectives**

Five ECRI stakeholders, reflecting health systems, health care generalist, and research perspectives, provided comments and ratings on this trend. The list below summarizes stakeholder perspectives.

- Tissue-agnostic drug approvals could improve health outcomes by providing treatment alternatives for patients without available molecularly directed therapies. However, rapid development of these molecularly targeted therapies could lead to use in patient populations before high-quality evidence is available on their safety and efficacy, particularly in rare-cancer patient populations.
- For widespread development of drugs in tissue-agnostic indications to occur, clinical trial designs might need to be modified to address this approach, and FDA might need to provide guidance on clinical trial design and regulatory requirements specific to this approach.
- Availability of a large number of tissue-agnostic drugs could disrupt the organization of oncology departments, potentially shifting the focus from anatomy-based specializations to molecular pathway-based specializations.
- Shift in perspective to the use of tissue-agnostic therapies based on the underlying molecular biology could represent a substantial learning curve for some oncologists.
References


296. Vyndaqel (tafamidis meglumine) and Vyndamax (tafamidis) capsules, for oral administration. Package insert. Pfizer Inc; 2019.


https://www.mayoclinic.org/diseases-conditions/niemann-pick/symptoms-causes/syc-2035887

https://www.orphazyme.com/about-arimoclomol-


https://www.accessdata.fda.gov/scripts/opdlisting /oopd/detailedIndex.cfm?cfgridkey=458814


659. Keen R, Jacobs B. Fibrodysplasia ossificans progressiva (FOP) an unfamiliar disease that is now important to diagnose. Arch Dis Child. 2015;100(suppl 3):A87-A88. doi:10.1136/archdischild-2015-308599.199


