High Potential Disruption Report
May 2021

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 Institute
5200 Butler Pike
Plymouth Meeting, PA 19462

Investigators
Randy Hulshizer, MA, MS
Jennifer De Lurio, MS
Marcus Lynch, PhD, MBA
Brian Wilkinson, MA
Damian Carlson, MS
Christian Cuevas, PhD
Andrea Druga, MSPAS, PA-C
Misha Mehta, MS
Prital Patel, MPH
Donna Beales, MLIS
Eloise DeHaan, BS
Eileen Erinoff, MSLIS
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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.

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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 1828 L St, NW, Suite 900, 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 2021 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). These topics and trends 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.
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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 health care providers.

System Overview

The PCORI Health Care Horizon Scanning System (HCHSS) 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 settings and delivery processes, disparities, and costs of care. The HCHSS monitors topics for up to 1 year after initial clinical availability.

PCORI currently defines 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 or trend records. Topic records encompass 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). Trend records 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 3, Issue 1, March 2021*).

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 details about ECRI’s conflict-of-interest policy.

Included trends are developed into trend profiles, revised according to 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 that stakeholders generally agreed have high potential to significantly disrupt health care in the United States. Topics and trends selected for inclusion are assigned to analysts to draft topic summaries.

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 some topics, consensus in stakeholder ratings is unclear (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 to draft topic summaries.
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 topic summary 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.

**Topic Summaries**

Each topic summary begins with a brief paragraph highlighting key takeaways for the reader, followed by a description of the patient population likely to be affected by the intervention, a description of the intervention, an evidence development summary listing selected ongoing and/or recently completed clinical trials, a brief summary of manufacturers and regulatory status, cost information, and a summary of key stakeholder perspectives.

For concision, we generally limit the number of clinical trials reported in each of the evidence development summary tables to 3, although we may make exceptions. We normally report the latest, most complete, and/or largest trials relevant to the specific patient population, but we may apply different selection criteria when appropriate. In a case in which more than 3 trials are ongoing or more than 3 trials have recently been completed, we include a brief note explaining our selection criteria, and we provide references to relevant trials excluded from the tables.

In the table of recently completed trials in the evidence development summary, we present results as written in abstracts of published studies, conference abstracts, or company news releases. The reader should note that abstracts and news releases may not fully reflect the methods and findings of research presented in full published articles. We do not analyze the quality of the study designs, the reliability of the data reported on the outcomes assessed, or whether study investigators used appropriate statistical methods to analyze their data. In addition, we cannot warrant the validity of these results in the absence of such evaluations and analysis; therefore, the reader should review this information from abstracts and news releases cautiously.

**Trend Summaries**

Potentially disruptive 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. Each trend summary begins with a brief paragraph 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, and a brief discussion of opportunities and threats (ie, potential positive and negative disruptions) posed by the trend.
Report Compilation

Topic summaries are compiled into chapters: 1 for each of the 5 PCORI-defined priority areas and 1 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 6200 information leads has led to the identification of about 625 potential topics across the 5 PCORI priority areas and 130 high-level trends occurring in all areas of health care.

As of March 5, 2021, after subjecting the potential topics to our inclusion criteria and nomination process, 433 topics have been selected. Of these, 278 topics are being actively monitored in the system; an additional 155 topics have been archived. The 278 actively monitored topics represent 160 diseases and conditions and span the PCORI-defined priority areas as follows (Figure 1)*:

- Alzheimer’s disease and other dementias: 10 topics (4%)
- Cancer: 91 topics (33%)
- Cardiovascular diseases: 17 topics (6%)
- Mental and behavioral health conditions: 19 topics (7%)
- Rare diseases: 141 topics (51%)

* Total does not equal 100% because of rounding

Figure 1. Percentage of All Actively Monitored Topics by Priority Area
Across all priority areas, the 278 monitored topics represent the following therapeutic classes (Figure 2)*:

- Assistive technology: 1 topic (0.4%)
- Cell therapy: 17 topics (6%)
- Device (nonimplantable): 10 topics (4%)
- Gene therapy: 16 topics (6%)
- Immunotherapy: 4 topics (1%)
- Implant: 4 topics (1%)
- Monoclonal antibody: 34 topics (12%)
- Other biotechnology: 23 topics (8%)
- Pharmaceutical: 158 topics (57%)
- Procedure (nonsurgical): 2 topics (0.7%)
- Viral vector therapy: 9 topics (3%)

* Total does not equal 100% because of rounding

Figure 2. Percentage of All Currently Monitored Topics by Therapeutic Class
From the 278 actively monitored topics, we have selected—based on the procedures described in Report Methods—30 topics for inclusion in this report, distributed across the PCORI priority areas as follows (Figure 3):

- Alzheimer’s disease and other dementias: 2 topics (7%)
- Cancer: 12 topics (40%)
- Cardiovascular diseases: 1 topic (3%)
- Mental and behavioral health conditions: 2 topics (7%)
- Rare diseases: 13 topics (43%)

Figure 3. Percentage of Topics Selected for Report by Priority Area
Likewise, as of March 5, 2021, after subjecting potential trends to our inclusion criteria and nomination process, we have selected 77 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). Of these trends, 37 are being actively monitored in the system and 40 have been archived. Among the 37 actively monitored trends, 6 themes have emerged (Figure 4)*:

- Artificial intelligence and machine learning: 16 trends (43%)
- Health information technology, apps, and smart devices: 4 trends (11%)
- Innovative treatment models: 10 trends (27%)
- Preventive measures: 2 trends (5%)
- Proteomics, genomics, and personalized medicine: 3 trends (8%)
- Screening and diagnostics: 2 trends (5%)

* Total does not equal 100% because of rounding

Figure 4. Percentage of All Currently Monitored Trends by Theme
From the 37 actively monitored trends, we have selected—based on the procedure described in Report Methods—8 trends for inclusion in this report, distributed by theme as follows (Figure 5):

- Artificial intelligence and machine learning: 2 trends (25%)
- Health information technology, apps, and smart devices: 1 trend (12.5%)
- Innovative treatment models: 3 trends (37.5%)
- Proteomics, genomics, and personalized medicine: 2 trends (25%)

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 3 data for drugs, phase 2 (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 5, 2021; and (3) we received at least 5 sets of comments and ratings from stakeholders between March 20, 2020, and March 19, 2021.

As of March 5, 2021, we were monitoring 10 topics in this priority area, including the 2 topics considered for inclusion in this report. These 10 topics were listed in the March 2021 PCORI Health Care Horizon Scanning System: Horizon Scanning 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 2 topics selected for inclusion in this report based on stakeholder ratings and comments and available data. Topics are listed and discussed alphabetically by topic title.

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

<table>
<thead>
<tr>
<th>Topic title</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aducanumab (BIIB037) to treat early Alzheimer's disease</td>
<td></td>
</tr>
<tr>
<td>Periodic therapeutic plasma exchange (Alzheimer's management by albumin replacement protocol) to treat mild to moderate Alzheimer's disease</td>
<td></td>
</tr>
</tbody>
</table>
**Topic Summaries**

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

**Aducanumab (BIIB037) to Treat Early Alzheimer’s Disease**

**Highlights**

- Aducanumab is a recombinant human monoclonal antibody that is intended to reduce cognitive decline and the progression of Alzheimer’s disease (AD) in early and mild stages.
- AD affects millions of Americans, particularly adults aged 55 and older, and a significant unmet need exists for treatments.
- Stakeholders commenting on this topic thought aducanumab could be the first disease-modifying treatment for early AD that might improve patient-oriented health outcomes, including quality of life.
- Most stakeholders thought that both the cost (depending on insurance reimbursement) and delivery of the treatment (which occurs in infusion centers) would increase disparities in access and add to the burden of care for these patients and caregivers.
- Stakeholders recommended further research to evaluate the treatment’s long-term clinical effectiveness and address any drug safety issues in this high-risk patient population.

**Patient Population**

Aducanumab is intended for adults aged 50 years or older who have mild cognitive impairment or mild AD.

**Intervention**

AD causes up to 80% of dementia cases, has no cure, and has limited options for effective symptom management. No disease-modifying treatments are available, despite decades of research. The Alzheimer’s Association website offers [more information on AD](https://www.alz.org). The amyloid hypothesis of AD disease development suggests that the accumulation and deposition of oligomeric or fibrillary amyloid beta (Aβ) peptides are the primary cause of AD. However, no Aβ-targeted therapy has demonstrated improved outcomes in patients with AD.

Aducanumab is a recombinant human monoclonal antibody that preferentially binds aggregated forms of Aβ (ie, soluble oligomers and insoluble fibrils) that are hypothesized to cause the neurotoxic effects linked with AD. Aducanumab’s high degree of selectivity for aggregated forms of Aβ may differentiate it from other Aβ-targeting antibodies that failed to demonstrate clinical improvement in clinical trials. Although aducanumab’s exact mechanism of action is unclear, animal models suggest that the drug binds with aggregated Aβ isoforms, leading to their clearance by microglia. This might reduce cognitive decline in patients with early AD and improve their quality of life.

A clinician refers a patient to an infusion center for aducanumab therapy. In clinical trials, aducanumab is given intravenously at a dosage of 10 mg/kg every 4 weeks for 100 weeks.
Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified a single late-stage ongoing trial for this topic. We present it in Table 1.2.

Table 1.2. 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 to Evaluate Safety and Tolerability of Aducanumab in Participants With AD Who Had Previously Participated in the Aducanumab Studies 221AD103, 221AD301, 221AD302, and 221AD205 NCT04241068</td>
<td>Adults aged 50 to 90 years (n = 2400) who have AD and participated in an earlier trial of aducanumab</td>
<td>Phase 3b, randomized, open-label trial to evaluate the long-term safety and tolerability of aducanumab in patients with AD who had previously participated in aducanumab studies Primary outcome measures: • AEs and serious AEs up to week 118 Number of participants with ARIA up to week 102</td>
<td>Primary and study completion October 2023</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; AEs, adverse events; ARIA, amyloid-related imaging abnormalities.

Recently Completed and Ongoing Trials With Available Results

Our searches identified 2 recently completed late-phase trials with published results. We summarize the results of the most recent of these studies, as written in a company news release.

The following abbreviations are used in this section: AD, Alzheimer’s disease; ADAS-Cog 13, Alzheimer’s Disease Assessment Scale—cognitive subscale, 13 tasks; ADCS-ADL-MCI, Alzheimer’s Disease Cooperative Study—Activities of Daily Living inventory (mild cognitive impairment version); ARIA-E, amyloid-related imaging abnormalities—edema; CDR-SB, Clinical Dementia Rating scale—Sum of Boxes; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; P, probability.

Two Phase 3 Studies, 221AD302 EMERGE (NCT02484547) and 221AD301 ENGAGE (NCT02477800), of Aducanumab (BIIB037) in Early Alzheimer’s Disease. Biogen 2020.

- **Patient population/planned enrollment:** Adults aged 50 to 85 years with early AD enrolled in 2 cohorts, receiving either a low or high dose of aducanumab; EMERGE (n = 1638), ENGAGE (n = 1647)
- **Study design:** Two phase 3, randomized, double-blind, placebo-controlled studies to evaluate the efficacy and safety of aducanumab in patients with early AD
- **Primary outcome:** Change from baseline in CDR-SB score up to week 78
- **Secondary outcomes:** Change from baseline in MMSE score up to week 78, change from baseline in ADAS-Cog 13 score up to week 78, and change from baseline in ADCS-ADL-MCI score up to week 78
• Results presented by study authors: “In EMERGE, which met its pre-specified primary endpoint in the new analysis, patients treated with high dose aducanumab showed a significant reduction of clinical decline from baseline in CDR-SB scores at 78 weeks (23% versus placebo, P=0.01). In EMERGE, patients treated with high dose aducanumab also showed a consistent reduction of clinical decline as measured by the pre-specified secondary endpoints: the MMSE; 15% versus placebo, P=0.06, the AD ADAS-Cog 13; 27% versus placebo, P=0.01, and the ADCS-ADL-MCI; 40% versus placebo, P=0.001. Imaging of amyloid plaque deposition in EMERGE demonstrated that amyloid plaque burden was reduced with low and high dose aducanumab compared to placebo at 26 and 78 weeks (P<0.001). Additional biomarker data of tau levels in the CSF supported these clinical findings. Biogen believes that data from patients in ENGAGE who achieved sufficient exposure to high dose aducanumab supported the findings of EMERGE.

“In both studies, the most commonly reported adverse events were amyloid-related imaging abnormalities-edema (ARIA-E) and headache. The majority of patients with ARIA-E did not experience symptoms during the ARIA-E episode, and ARIA-E episodes generally resolved within 4 to 16 weeks, typically without long-term clinical sequelae.”

Cost Information

Aducanumab treatment has been projected to cost about $50 000 per year.8 This estimate excludes the cost of administration, tests needed to determine eligibility, and other fees associated with an infusion procedure.

Manufacturers and Regulatory Status

Biogen, Inc (Cambridge, Massachusetts), in collaboration with Eisai Co, Ltd (Tokyo, Japan), developed aducanumab. The drug is licensed from Neurimmune (Zurich, Switzerland).

In July 2020, Biogen submitted a biologics license application (BLA) to FDA for aducanumab to treat AD.5 FDA has accepted the BLA and will review it under the agency’s priority review program with a Prescription Drug User Fee Act (PDUFA)–prescribed decision date of March 7, 2021, which was later changed to June 7, 2021.9,10 The BLA was largely supported by data from the 2 phase 3 trials, EMERGE and ENGAGE (see above). In March 2019, the developers had stopped these trials after the preliminary results from futility analysis showed that the trials were unlikely to meet their primary end point of decrease in cognitive decline.11 However, in December 2019, the manufacturers presented additional data from the 2 phase 3 trials showing that a higher dose of the drug might clinically benefit patients with mild to moderate AD.2 On March 30, 2021, a few members of FDA’s advisory committee published concerns over the drug’s efficacy for the treatment of AD.12 Aducanumab is also being evaluated in a phase 3 long-term extension study for treatment of early AD.6

FDA has also granted aducanumab fast-track designation to treat AD.13

Key Stakeholder Perspectives

Between August 19, 2020, and September 4, 2020, ten stakeholders, reflecting caregiver, clinical, health systems, nursing, patient, and research perspectives, provided comments and ratings on this treatment. The list below provides a summary of key stakeholder perspectives.
• Given the absence of any other effective treatments addressing slow cognitive decline, aducanumab could be the first treatment to reduce the amyloid burden and alter the paradigm of care for adults with early AD.

• Aducanumab would disrupt costs for patients, 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.

• Aducanumab might disrupt health care delivery with additional clinic visits needed during the treatment period and increase the need for caregiver support in the short term. However, it might provide significant relief to caregivers by improving patients’ quality of life over the long term.

• If effective, aducanumab would increase health care disparities, given the large target population needing to visit infusion centers, which patients in rural areas might find difficult to reach.

• Concerns exist regarding aducanumab’s potential to be misused or overused. Longer-term studies are needed to evaluate its clinical effectiveness with comorbid medical conditions associated with aging.

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 years or older, 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, insurance coverage) would create disparities in access to care and add more burden for these patients and caregivers.

• Stakeholders expressed concern about a lack of reporting of the treatment’s side effects, of evidence related to long-term effectiveness, and of comparative studies with relation to oral drugs such as donepezil and memantine.
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 causes up to 80% of dementia cases, has no cure, and has limited options for effective symptom management. No disease-modifying treatments are available despite decades of research. The Alzheimer’s Association website offers more information about AD.

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

Albumin infused as volume replacement would theoretically 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 the Aβ-driven AD disease course.

A clinician refers a patient to an infusion center for the plasma exchange. During a 6-week intensive period, patients undergo weekly total plasma exchange (2.5-3 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 (650-880 mL plasma removal) and volume replacement with a 20% albumin solution or intravenous immunoglobulin (IVIG).

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

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 study with results as written in the abstract of the published study.

The following abbreviations are used in this section: AD, Alzheimer’s disease; ADAS-Cog, Alzheimer’s Disease Assessment Scale—cognitive subscale; ADCS-ADL, Alzheimer’s Disease Cooperative Study—activities of daily living; ADCS-CGIC, Alzheimer’s Disease Cooperative
A Randomized, Controlled Clinical Trial of Plasma Exchange With Albumin Replacement for Alzheimer’s Disease: Primary Results of the AMBAR Study. NCT01561053, Boada et al 2020.¹⁷

- **Patient population/planned enrollment:** Adults (n = 347) aged 55 to 85 years with mild to moderate, probable AD
- **Study design:** A phase 2b/3, randomized, controlled, parallel-assignment study to evaluate the efficacy and safety of short-term PE, 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: “PE-treated patients performed significantly better than placebo for the co-primary endpoints: change from baseline of Alzheimer’s Disease Cooperative Study-Activities of Daily Living (ADCS-ADL; P = .03; 52% less decline) with a trend for Alzheimer’s Disease Assessment Scale–Cognitive Subscale (ADAS-Cog; P = .06; 66% less decline) scores at month 14. Moderate-AD patients (baseline Mini-Mental State Examination [MMSE] 18-21) scored better on ADCS-ADL (P = .002) and ADAS-Cog (P = .05), 61% less decline both. There were no changes in mild-AD patients (MMSE 22-26). PE-treated patients scored better on the Clinical Dementia Rating Sum of Boxes (CDR-sb) (P = .002; 71% less decline) and Alzheimer’s Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) (P < .0001; 100% less decline) scales.”

Manufacturers and Regulatory Status

The Albutein and IVIG (Flebogamma 5% DIF) treatment protocol (Grifols, SA, Barcelona, Spain) was evaluated in a phase 2/3 clinical trial for treating mild to moderate AD.¹⁸ 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.¹⁹ 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.²⁰ 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.²¹ As of March 2021, the company had not announced any updates, although positive data from the phase 2/3 clinical trial were published in July 2020.¹⁷

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).²²⁻²⁴ Using these figures, the drug cost for 14 months would range from $5474 to $8501, depending on the prescribed dosing regimen.¹⁶,²²⁻²⁴ These costs do not include the costs of administration and other fees associated with an infusion procedure.
Key Stakeholder Perspectives

Between October 1, 2020, and October 16, 2020, ten stakeholders, reflecting caregiver, clinical, health systems, nursing, and research perspectives, provided comments and ratings on this periodic plasma exchange treatment. The list below provides a summary of key stakeholder perspectives.

- AMBAR protocol could slow AD progression, thereby improving patient health outcomes, and disrupt the paradigm of care, because it is an infusion-based treatment rather than an oral drug.

- AMBAR might increase 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 the lack of reporting on adverse events and long-term effectiveness (beyond 14 months) as well as the efficacy of AMBAR’s purported mechanism of action for lowering cerebral amyloid.

- AMBAR might increase disparities for those experiencing hardships due to social determinants of health, who have less access to health care and insurance coverage.

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 and cognition.
Chapter 2. Cancer

Chapter Summary

For the cancer priority area, we considered for inclusion 25 topics for which (1) preliminary phase 3 data for drugs, phase 2 (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 5, 2021; and (3) we received at least 5 sets of comments and ratings from stakeholders between March 20, 2020, and March 19, 2021.

As of March 5, 2021, we were monitoring 85 topics in this priority area, including the 25 considered for inclusion in this report. These 85 topics were listed in the March 2021 PCORI Health Care Horizon Scanning System: Horizon Scanning Status Report.

The 85 monitored topics encompass pharmaceuticals, gene and cellular therapies, viral vector therapies, monoclonal antibodies, and devices intended to treat 36 cancers and/or related conditions. Eleven 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 19, 2021, so they were not considered for inclusion in this report. The remaining 49 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 12 topics selected for inclusion in this report 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>131I-Omburtamab to treat leptomeningeal metastases from relapsed neuroblastoma*</td>
</tr>
<tr>
<td>Atezolizumab (Tecentriq) plus bevacizumab (Avastin) as first-line treatment for locally advanced or metastatic hepatocellular carcinoma</td>
</tr>
<tr>
<td>Axicabtagene ciloleucel (Yescarta) to treat indolent B-cell non-Hodgkin lymphomas</td>
</tr>
<tr>
<td>CAR T-cell therapies, idecabtagene vicleucel (Abecma) and ciltacabtagene autoleucel, to treat relapsed and refractory multiple myeloma</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 (nab-sirolimus; Fyarro) to treat locally advanced or metastatic perivascular epithelioid cell sarcoma</td>
</tr>
<tr>
<td>Omidubicel to treat hematologic malignancies eligible for hematopoietic stem cell transplantation</td>
</tr>
<tr>
<td>Onureg to treat acute myeloid leukemia (maintenance setting)</td>
</tr>
<tr>
<td>Oral paclitaxel plus encequidar (formerly oraxol) to treat locally advanced or metastatic breast cancer</td>
</tr>
<tr>
<td>Relugolix (Orgovyx) to treat relapsed, locally advanced, or metastatic androgen-sensitive prostate cancer*</td>
</tr>
<tr>
<td>Tazemetostat (Tazverik) to treat relapsed or refractory follicular lymphoma</td>
</tr>
</tbody>
</table>

Table 2.2 lists 13 topics considered, but not selected, for inclusion during the *High Potential Disruption Report* decision meeting. Most 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 2.2. Topics Considered but Not Included for Priority Area: Cancer

<table>
<thead>
<tr>
<th>Topic title</th>
<th>Exclusion reason(s) and notes based on stakeholder comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belumosudil (KD025) to treat chronic graft-vs-host disease</td>
<td>As another oral agent for treating chronic graft-vs-host disease, belumosudil might complement other orally administered alternatives (eg, ibrutinib, ruxolitinib) but is unlikely to cause substantial disruption of treatment paradigms or health care infrastructure. In addition, phase 2 trials lack control groups.</td>
</tr>
<tr>
<td>Belzutifan (MK-6482) to treat von Hippel-Lindau (VHL) disease-associated clear cell renal cell carcinoma (ccRCC)</td>
<td>Initial data from a small clinical trial suggest that belzutifan might improve health outcomes for patients with this rare form of ccRCC. However, outcomes were not expected to be substantially better than those with available multikinase inhibitors.</td>
</tr>
<tr>
<td>Burosumab-twza (Crysvita) to treat FGF23-related hypophosphatemia in tumor-induced osteomalacia</td>
<td>Preliminary data from a small clinical trial suggest that burosumab-twza might improve health outcomes in patients with limited treatment options, but the data are insufficient to assess burosumab-twza's disruptive potential at this time.</td>
</tr>
<tr>
<td>DCVax-L to treat glioblastoma multiforme (adjuvant setting)</td>
<td>Preliminary data suggest that the DCVax-L vaccine might lead to a slight increase in patients' overall survival. However, long-term results are needed to make a definitive statement about whether DCVax-L has potential to substantially improve health outcomes.</td>
</tr>
<tr>
<td>Fam-trastuzumab deruxtecan-nxki (Enhertu) to treat locally advanced or metastatic HER2-positive gastric cancer (second-line setting)</td>
<td>Data from the phase 2 DESTINY-Gastric02 trial showed that patients treated with fam-trastuzumab deruxtecan-nxki had a higher incidence of hematological adverse events than did similar patients treated with chemotherapy.</td>
</tr>
<tr>
<td>Iomab-B (apamistamab-I-131) to treat relapsed or refractory acute myeloid leukemia</td>
<td>Initial data for Iomab-B suggest that the intervention might increase the number of patients with acute myeloid leukemia eligible for a potentially curative hematopoietic stem cell transplant. However, data on the primary end point of complete durable remission and patient-oriented outcomes are lacking. More data are needed to assess disruptive potential.</td>
</tr>
<tr>
<td>Lu-PSMA-617 to treat metastatic castration-resistant prostate cancer (last-line setting)</td>
<td>Lu-PSMA-617 might improve survival and quality-of-life outcomes; however, early data are insufficient to support these claims.</td>
</tr>
<tr>
<td>Lurbinectedin (Zepzelca) to treat metastatic small cell lung cancer (second-line setting)</td>
<td>Data from a phase 2 clinical trial suggest that lurbinectedin might improve health outcomes, but the enrolled patients do not represent the small cell lung cancer population. Comparative data from the phase 3 ATLANTIS trial are needed to assess whether the safety and efficacy of lurbinectedin is better than that with standard of care.</td>
</tr>
<tr>
<td>Ofranergene obadenovec (VB-111) to treat recurrent platinum-resistant ovarian cancer (second-line setting)</td>
<td>Preliminary data suggest that ofranergene obadenovec might improve patient survival and quality of life; however, more data are needed to assess disruption in long-term patient outcomes, costs, and changes to the paradigm of care.</td>
</tr>
</tbody>
</table>
### Topic Summaries

We present below 12 summaries on topics deemed to have high potential for disruption.

#### 131I-Omburtamab to Treat Leptomeningeal Metastases From Relapsed Neuroblastoma

**Highlights**

- 131I-omburtamab is a monoclonal antibody conjugated with radiation-emitting iodine-131 that specifically targets neuroblastoma cells overexpressing the cell-surface protein B7-H3.

- In about 5% to 10% of cases, neuroblastoma cells migrate to the leptomeninges, tissues encasing the brain and spinal cord. Because leptomeningeal metastases are difficult to treat, patients who develop the disease survive for only 2 to 6 months.

- Stakeholders commenting on this topic thought that preliminary data suggest that 131I-omburtamab could improve patient survival but will likely be available only at large health centers, which have the specialists and resources to offer this treatment.

- Stakeholders also thought that this treatment is not expected to disrupt health care delivery or paradigm of care. If long-term data confirm the preliminary data findings, 131I-omburtamab might become the standard of care. However, there are also concerns about whether the treatment might cause adverse events over time.
Patient Population

131I-omburtamab is intended for children who have leptomeningeal metastases from relapsed, high-risk neuroblastoma.

Intervention

Neuroblastoma is a rare cancer that arises in immature nerve cells (ie, neuroblasts) of the sympathetic nervous system. Neuroblastoma typically originates in the adrenal glands but may also arise in the neck, chest, or spinal cord. The cancer most often affects infants and children younger than 10 years. The American Cancer Society website offers more information on neuroblastoma.

About 5% to 10% of patients with neuroblastoma will develop leptomeningeal metastases, a complication that occurs when the initial disease migrates to the tissues encasing the brain and the spinal cord (ie, leptomeninges). Leptomeningeal metastases are difficult to treat, and the survival of affected patients is from 2 to 6 months.25

131I-omburtamab (131I-8H9) is a conjugated drug, meaning that it joins a B7-H3–specific monoclonal antibody with radiation-emitting iodine-131.26,27 B7-H3 is a cell-surface protein involved in immune regulation that is highly expressed in neuroblastoma cells.27 131I-omburtamab is thought to bind B7-H3–expressing cells with high affinity and expose them to radiation emitted by iodine-131.26,27 Iodine-131 emits mainly short-range beta radiation that does not penetrate deeply into tissue, potentially sparing surrounding healthy tissue from harmful effects.27 This novel approach to target and kill leptomeningeal metastases could improve health outcomes in patients who have limited treatment options and a poor prognosis.25-27

A clinician prescribes 131I-omburtamab, which is injected directly into the cerebrospinal fluid at a dose of 50 mCi (millicurie; a unit of radioactivity). Eligibility for a second dose is evaluated 5 weeks after the first dose.
Evidence Development Summary

**Ongoing Trials**

Our searches of the National Clinical Trials database identified a single ongoing trial for this topic. We present this phase 2/3 trial 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>131I-Omburtamab Radioimmunotherapy for Neuroblastoma Central Nervous System/Leptomeningeal Metastases (Study 101) NCT03275402</td>
<td>Pediatric patients (n = 32) who have high-risk neuroblastoma with relapse in the leptomeninges</td>
<td>Phase 2/3, single-group assignment, open-label study to evaluate the safety and efficacy of 131I-omburtamab. Patients will receive intrathecal 131I-omburtamab at a dose of 50 mCi at week 1. Patients will be evaluated for eligibility for a second dose at week 5. Primary outcome: Overall survival. Secondary outcomes: Progression-free survival, objective response rate, and adverse events.</td>
<td>Primary completion December 2020 Study completion December 2026</td>
</tr>
</tbody>
</table>

Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed late-phase trial with published results.\(^{28,29}\) We summarize results as written in a conference abstract and a company news release.

The following abbreviations are used in this section: 131I, iodine-131; MBq, megabecquerels; mCi, millicurie; MSK or MSKCC, Memorial Sloan Kettering Cancer Center; mSv, millisievert; OLINDA, organ level internal dose assessment; p, probability; SAE, severe adverse event.

**131I-Omburtamab Radioimmunotherapy for Neuroblastoma Central Nervous System/Leptomeningeal Metastases (Study 101).** NCT03275402. Lisby et al 2020,\(^{28}\) Y-mAbs Therapeutics 2020.\(^{29}\)

- **Patient population/planned enrollment:** Pediatric patients (n = 32) who had high-risk neuroblastoma with relapse in the leptomeninges.
- **Study design:** Phase 2/3, single-group assignment, open-label study to evaluate the safety and efficacy of 131I-omburtamab. Patients received intrathecal 131I-omburtamab at a dose of 50 mCi at week 1. Patients were evaluated for eligibility for a second dose at week 5.
- **Primary outcome:** Overall survival.
- **Secondary outcomes:** Progression-free survival, objective response rate, and adverse events.
- **Results presented by Lisby et al:** “The interim analysis includes 17 patients (10 at MSKCC; 7 at other sites) who received at least one cycle of 131I-omburtamab before 30-Jun-2019 and have been followed...”
for at least six months. 8 patients received 1 cycle; 9 patients received two cycles. The median follow-up time for these patients is 179 days. 15 patients remain alive at the cut-off date. The OLINDA mean absorbed doses were 3.46 mSv/MBq in the brain and 5.97 mSv/MBq in the liver. Dosimetry level estimates in the cerebrospinal fluid at 0.56 Gray/mCi were orders of magnitude higher than those in the blood at 0.008 Gray/mCi. The most common SAEs were related to myelosuppression. Overall, the administration of 131I-Omburtamab was well tolerated.”

- **Results presented in a Y-mAbs news release:** “Preliminary Overall Survival (“OS”) data for the Company’s multicenter Study 101 for the first 18 months appears supportive of the conclusion from an earlier Study 03-133 at MSK on survival improvement for these patients, with 75% of patients surviving after 18 months. Additionally, the preliminary propensity score analysis of Study 03-133 compared to external control subjects, shows a significant difference in three years overall survival (p<0.001). Finally, an independent radiographic evaluation of the tumor responses in Study 101, shows that for ten evaluable patients with measurable disease, a total of 40% of the patients responded to omburtamab, 20% with complete response (“CR”) and 20% with partial response (“PR”), and another five patients had stable disease (“SD”). All nine patients with response or SD maintained these at six months follow up.”

### Manufacturers and Regulatory Status

Investigators at **Y-mAbs Therapeutics, Inc (New York, New York)**, are studying 131I-omburtamab in a phase 2/3 clinical trial to treat children who have high-risk neuroblastoma with relapse in the leptomeninges. Based on results from this study, Y-mAbs completed a rolling submission of a biologics license application (BLA) to FDA in August 2020.\(^{30}\) In October 2020, the company received a refusal-to-file letter from FDA regarding the BLA but planned to meet with the agency to amend and resubmit the BLA in the first half of 2021.\(^{29,31}\) FDA had previously granted 131I-omburtamab breakthrough therapy designation to treat leptomeningeal metastases from relapsed neuroblastoma.\(^ {32}\)

### Cost Information

Cost information is currently unavailable for this topic.

### Key Stakeholder Perspectives

Between January 26, 2021, and February 15, 2021, ten stakeholders, reflecting clinical, health systems, nursing, patient representative, and research perspectives, provided comments and ratings on 131I-omburtamab. The list below provides a summary of key stakeholder perspectives.

- Currently, patients with leptomeningeal metastases have very poor outcomes and are in urgent need of effective treatments. Preliminary data suggest that 131I-omburtamab might improve patient survival beyond the typical survival of 2 to 6 months. However, safety and quality-of-life data are needed to further evaluate this treatment.

- 131I-omburtamab is expected to be available only at large medical centers with specialists and resources that are needed to treat leptomeningeal metastases. Smaller health centers are unlikely to have the required infrastructure and personnel to offer this treatment.

- Even though 131I-omburtamab requires intensive surgical and medical interventions, it is not expected to disrupt large health centers that would offer treatment. The adoption of 131I-omburtamab is also not expected to disrupt the paradigm of care, because patients already undergo various intensive treatments.
If long-term data continue to show a clinical benefit for these patients, 131I-omburtamab could become the standard of care and have a positive impact for patients and their families. There are concerns about whether patients might experience adverse events over time, which depending on severity, can decrease quality of life.

**Atezolizumab (Tecentriq) Plus Bevacizumab (Avastin) as First-Line Treatment for Locally Advanced or Metastatic Hepatocellular Carcinoma**

**Highlights**

- Atezolizumab is an immune checkpoint inhibitor given intravenously in combination with bevacizumab, a drug that prevents new blood vessel formation, to prevent tumor cells from downregulating cancer-specific immune responses. FDA approved this combination therapy in June 2020 to treat hepatocellular carcinoma (HCC).
- Locally advanced or metastatic HCC is usually treated with multikinase inhibitors, but their benefit is incremental and associated with adverse events.
- The cost of atezolizumab plus bevacizumab is about $19,680 per cycle, which does not include administration costs and other fees associated with an infusion procedure. This is 10 times more costly than the oral multikinase sorafenib, a current standard of care.
- Stakeholders commenting on this topic thought that atezolizumab plus bevacizumab might have greater potential than multikinase inhibitors to improve patient outcomes and quality of life.
- Stakeholders also thought that this treatment combination could become the standard of care in the first-line setting; however, its high cost might increase disparities and be unaffordable for uninsured or underinsured patients.

**Patient Population**

Atezolizumab plus bevacizumab is intended for adults who have locally advanced or metastatic HCC and have had no previous systemic therapy.

**Intervention**

HCC is the most common type of liver cancer and often occurs in patients with chronic liver diseases, such as alcoholic cirrhosis, fatty liver disease, and viral hepatitis. HCC accounts for more than 800,000 deaths worldwide each year. Patients with HCC have a 5-year survival rate of 18%. The American Cancer Society website offers more information about HCC.

Historically, multikinase inhibitors (eg, sorafenib, lenvatinib) have been the most effective therapies for locally advanced or metastatic HCC. However, these drugs extend median survival by only 3 months and are associated with considerable adverse events.

In the body, programmed cell death protein 1 (PD-1) is an immune checkpoint protein on T cells and other immune cells that binds to programmed death ligand 1 (PD-L1) to downregulate immune cells and prevent runaway immune responses. Cancer cells overexpress PD-L1 to avoid detection and destruction by the immune system. Also, vascular endothelial growth factor...
(VEGF) is often overexpressed in cancer cells. This overexpression promotes blood vessel formation and suppresses immune response.\textsuperscript{35,38}

Atezolizumab (Tecentriq) is a humanized monoclonal antibody that selectively binds PD-L1 to prevent its interaction with the co-inhibitory receptor PD-1.\textsuperscript{36,37} This releases the brakes on the PD-1 and PD-L1 immune checkpoint pathway, and by so doing, atezolizumab purportedly enhances cancer-specific T-cell responses against HCC tumors.\textsuperscript{35,36} Bevacizumab (Avastin) is a humanized monoclonal antibody that blocks the VEGF pathway. This limits blood vessel formation and also helps overcome immune tolerance of HCC by helping cancer-specific T cells infiltrate the tumor.\textsuperscript{35,38}

A clinician prescribes atezolizumab and bevacizumab to be given at an infusion center. An infusion nurse gives 1200 mg of atezolizumab and 15 mg/kg of bevacizumab to the patient through a vein on day 1 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 a single ongoing trial for this topic. We present this phase 3 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>A Study of Atezolizumab in Combination With Bevacizumab Compared With Sorafenib in Patients With Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma (IMbrave150) NCT03434379</td>
<td>Patients (n = 480) who have locally advanced or metastatic HCC and have had no previous systemic therapy in the locally advanced/metastatic setting</td>
<td>Phase 3, randomized, parallel-assignment, open-label trial to evaluate the safety and efficacy of atezolizumab in combination with bevacizumab in patients with HCC</td>
<td>Primary completion June 2021 Study completion June 2022</td>
</tr>
</tbody>
</table>

Patients will be randomly assigned to treatment with either combination therapy with atezolizumab plus bevacizumab or monotherapy with sorafenib.

Primary end points: Overall survival and progression-free survival

Secondary end points: Objective response, duration of response, time to progression, and time to deterioration

Abbreviation: HCC, hepatocellular carcinoma.
Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed late-phase trial with published results.39,40 We summarize results as written in the abstract of a published study and a conference abstract.

The following abbreviations are used in this section: atezo, atezolizumab; bev, bevacizumab; CI, confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality-of-life questionnaire—core module; EORTC QLQ-HCC18, European Organization for Research and Treatment of Cancer quality-of-life questionnaire—primary liver cancer module; HCC, hepatocellular carcinoma; HR, hazard ratio; mo, month; P, probability; pt or pts, patient or patients; QOL, quality of life; sor, sorafenib; TTD, time to deterioration; tx, treatment.

A Study of Atezolizumab in Combination with Bevacizumab Compared With Sorafenib in Patients With Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma (IMbrave150). NCT03434379. Finn et al 2020,39 Galle et al 2020,40

- **Patient population/planned enrollment**: Patients (n = 501) who had locally advanced or metastatic HCC and who had no previous systemic therapy in the locally advanced/metastatic setting
- **Study design**: Phase 3, randomized, parallel-assignment, open-label trial to evaluate the safety and efficacy of atezolizumab in combination with bevacizumab in patients with HCC. Patients were randomly assigned in a 2:1 ratio to receive either intravenous atezolizumab (1200 mg) plus bevacizumab (15 mg/kg) on day 1 of each 21-day cycle or sorafenib (400 mg) taken by mouth twice daily. Patients completed the EORTC QLQ-C30 and EORTC QLQ-HCC18 questionnaires before treatment, every 3 weeks on treatment, and every 3 months after treatment discontinuation or disease progression.
- **Primary outcomes**: Overall survival and progression-free survival
- **Secondary outcomes**: QOL, duration of response, time to progression, TTD, and adverse events
- **Results presented by Finn et al**: “The intention-to-treat population included 336 patients in the atezolizumab-bevacizumab group and 165 patients in the sorafenib group. At the time of the primary analysis (August 29, 2019), the hazard ratio for death with atezolizumab-bevacizumab as compared with sorafenib was 0.58 (95% confidence interval [CI], 0.42 to 0.79; P<0.001). Overall survival at 12 months was 67.2% (95% CI, 61.3 to 73.1) with atezolizumab-bevacizumab and 54.6% (95% CI, 45.2 to 64.0) with sorafenib. Median progression-free survival was 6.8 months (95% CI, 5.7 to 8.3) and 4.3 months (95% CI, 4.0 to 5.6) in the respective groups (hazard ratio for disease progression or death, 0.59; 95% CI, 0.47 to 0.76; P<0.001). Grade 3 or 4 adverse events occurred in 56.5% of 329 patients who received at least one dose of atezolizumab-bevacizumab and in 55.1% of 156 patients who received at least one dose of sorafenib. Grade 3 or 4 hypertension occurred in 15.2% of patients in the atezolizumab-bevacizumab group; however, other high-grade toxic effects were infrequent.”
- **Results presented by Galle et al**: “Questionnaire completion rates were ≥ 92% in both arms from baseline through most of the tx period. Compared with sor, atezo + bev delayed TTD of pt-reported QOL (median TTD, 11.2 vs 3.6 mo; HR, 0.63 [95% CI: 0.46, 0.85]), physical functioning (median TTD, 13.1 vs 4.9 mo; HR, 0.53 [95% CI: 0.39, 0.73]), and role functioning (median TTD, 9.1 vs 3.6 mo; HR, 0.62 [95% CI: 0.46, 0.84]). Atezo + bev also delayed TTD in pt-reported appetite loss, fatigue, pain, and diarrhea vs sor; a lower proportion of pts on atezo + bev experienced clinically meaningful deterioration in each of these symptoms vs sor.”
Manufacturers and Regulatory Status

Genentech, Inc (South San Francisco, California), a subsidiary of F Hoffman-La Roche AG (Basel, Switzerland), manufactures atezolizumab. On June 2, 2020, FDA approved atezolizumab in combination with bevacizumab, based on results from the IMbrave150 trial, as first-line therapy for adults who have locally advanced or metastatic HCC. \(^{41}\) FDA earlier had granted atezolizumab in combination with bevacizumab orphan drug and breakthrough therapy designations for treating HCC. \(^{42,43}\)

Both atezolizumab and bevacizumab are commercially available because FDA has approved them for multiple indications other than HCC. For a list of FDA-approved indications, see the FDA prescribing information for atezolizumab and bevacizumab.

Cost Information

An online aggregator of US prescription drug prices, Drugs.com, reported a retail price of $9600 for one vial of 1200 mg of atezolizumab and $210 for one vial of 25 mg of bevacizumab (as of October 5, 2020). \(^{44,45}\) Patients with an average weight of 80 kg (176 lb) would receive 1200 mg of atezolizumab and 1200 mg (15 mg/kg) of bevacizumab once every 21 days.

At those prices, the estimated per-cycle cost of this combination regimen would be $19,680. On average, patients in the phase 3 IMbrave trial received about 7 months of treatment. \(^{39}\) Therefore, 10 cycles of this regimen would cost about $200,000. This estimate excludes the costs of administration and other fees associated with an infusion procedure.

The Department of Global Health Management and Policy at Tulane University (New Orleans, Louisiana) evaluated the cost-effectiveness of atezolizumab plus bevacizumab compared with the cost-effectiveness of sorafenib. For atezolizumab plus bevacizumab, the incremental cost-effectiveness ratio was about $89,807 per 0.531 quality-adjusted life year (QALY) gained compared with sorafenib’s $169,223 per QALY gained. Therefore, treatment with atezolizumab plus bevacizumab achieved a 35% probability of cost-effectiveness at a threshold of $150,000 per QALY net health benefit. \(^{46}\)

Key Stakeholder Perspectives

Between April 2, 2020, and June 1, 2020, nine stakeholders, reflecting clinical, health systems, patient, and research perspectives, provided comments and ratings on atezolizumab in combination with bevacizumab. The list below provides a summary of key stakeholder perspectives.

- Atezolizumab plus bevacizumab might improve patient survival and quality of life compared with multikinase inhibitors, which have been considered the standard of care for more than a decade.

- Atezolizumab plus bevacizumab might create disparities because it costs 10 times more than the multikinase sorafenib. This combination therapy could cause a significant financial burden for uninsured or underinsured patients.

- Although atezolizumab plus bevacizumab is given at an infusion center, multikinases are taken by mouth. This shift from a home setting to an infusion center might disrupt health care delivery because infusion centers require resources, space, and personnel to offer treatment for patients with HCC.
• Most stakeholders thought that atezolizumab and bevacizumab’s potential for disruption is based on data demonstrating superiority over multikinase inhibitors. Therefore, this combination is likely to become standard of care for patients with HCC.

Axicabtagene Ciloleucel (Yescarta) to Treat Indolent B-Cell Non-Hodgkin Lymphomas

Highlights

• Axicabtagene ciloleucel is an engineered chimeric antigen receptor (CAR) T-cell therapy produced by genetically modifying a patient’s own T cells to program them to generate an immune response to the patient’s cancer. Given as a single intravenous infusion, the therapy was approved in March 2021 to treat patients who have relapsed or refractory follicular lymphoma previously treated with 2 or more lines of systemic therapy.

• Patients with relapsed or refractory B-cell non-Hodgkin lymphoma that has progressed despite multiple treatments have limited treatment options. In particular, patients who experience early relapse after initial treatment have a poor prognosis with available treatments.

• Stakeholders commenting on this topic indicated that the rate and duration of response to axicabtagene ciloleucel observed in clinical trials suggested that the therapy has substantial potential to improve patient health outcomes. However, stakeholders also noted that the treatment was associated with a high burden of adverse events that could negatively impact quality of life.

• Stakeholders suggested that axicabtagene ciloleucel would likely substantially increase treatment costs for indolent non-Hodgkin lymphomas because it costs about $373 000 and the resource-intensive nature of its preparation, administration, and patient monitoring after treatment can bring total treatment costs to nearly $1 million.

Patient Population

Axicabtagene ciloleucel is intended for adults aged 18 years or older with relapsed or refractory indolent B-cell non-Hodgkin lymphomas (eg, follicular lymphoma, marginal zone lymphoma) that has been treated with at least 2 prior combination systemic therapies.

Intervention

Indolent B-cell lymphomas account for about 40% of non-Hodgkin lymphomas and are diagnosed in about 30 000 people each year in the United States. The most common forms of indolent B-cell lymphomas are follicular lymphoma and marginal zone lymphoma, which together account for about three-quarters of cases.

Indolent B-cell lymphomas requiring therapy typically respond to available treatments. However, most patients experience disease recurrence, and novel effective therapies are needed for patients who have undergone multiple rounds of treatment and for whom limited effective therapies are available.

Axicabtagene ciloleucel (Yescarta) is a CAR T-cell therapy that consists of patient-derived (ie, autologous) T cells that are genetically modified to express a CAR receptor. The CAR
receptor in axicabtagene ciloleucel targets CD19, an antigen expressed on the surface of normal and malignant B cells. The CAR protein construct contains an antibody-like region that binds CD19 linked to an intracellular T-cell signaling domain, which produces activating signals that induce CAR T-cell proliferation and tumor cell killing.\textsuperscript{49}

To produce axicabtagene ciloleucel, T cells are obtained from the patient’s blood and sent to the manufacturer’s facility to be genetically modified with the CAR construct. The cells are grown in number in culture and returned to the patient’s treatment facility.\textsuperscript{48}

CAR T-cell therapies are available only at specialist centers equipped to handle administration and manage adverse events associated with the treatment. To prepare for administration, patients undergo a cytotoxic chemotherapy-based conditioning regimen to deplete lymphocytes, which purportedly improves expansion, function, and persistence of CAR T cells through multiple mechanisms.\textsuperscript{50} After this regimen, patients receive a single infusion of the manufactured CAR T-cell therapy at a dose of about $2 \times 10^6$ CAR T cells/kg.\textsuperscript{51}

**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 2.5.

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>
</table>
| A Phase 2 Multicenter Study of Axicabtagene Ciloleucel in Subjects With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma (ZUMA-5) NCT03105336 | Patients (n = 160) with FL or MZL that has progressed after at least 2 lines of treatment with combination systemic therapy | Single-arm, phase 2 trial of the safety and efficacy of axicabtagene ciloleucel to treat relapsed or refractory indolent non-Hodgkin lymphomas
First, patients will undergo leukapheresis to collect white blood cells to manufacture axicabtagene ciloleucel. Next, patients will undergo 3 days of treatment with a conditioning regimen of cyclophosphamide and fludarabine. Finally, patients will receive an infusion of axicabtagene ciloleucel at an unspecified dose.
Primary outcome: Objective response rate
Selected secondary outcomes: Duration of response, progression-free survival, overall survival, and percentage of patients experiencing adverse events | Primary completion February 2022
Study completion February 2037 |

Abbreviations: FL, follicular lymphoma; MZL, marginal zone lymphoma.
Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed phase 2 trial with published results.\(^2\),\(^3\) We summarize results as written in a conference abstract.

The following abbreviations are used in this section: AEs, adverse events; AUC\(_{0-28}\), area under the curve between days 0 and 28; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CI, confidence interval; CR, complete response; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d’Etude des Lymphomes Folliculaires; iNHL, indolent non-Hodgkin lymphoma; MZL, marginal zone lymphoma; NE, neurologic event; ORR, objective response rate; OS, overall survival; P, probability; PFS, progression-free survival; POD24, progression of disease within 24 months of first treatment.

A Phase 2 Multicenter Study of Axicabtagene Ciloleucel in Subjects With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma (ZUMA-5). **NCT03105336**. Jacobson et al 2020.\(^3\)

- **Patient population/planned enrollment**: Patients (n = 160) with FL or MZL that had progressed after at least 2 lines of combination systemic therapy
- **Study design**: Single-arm, phase 2 trial of the safety and efficacy of axicabtagene ciloleucel to treat relapsed or refractory indolent non-Hodgkin lymphomas. First, patients underwent leukapheresis to collect the white blood cells needed to manufacture axicabtagene ciloleucel. Next, patients underwent 3 days of treatment with a conditioning regimen containing cyclophosphamide and fludarabine. Finally, patients received an infusion of axicabtagene ciloleucel at an unspecified dose.
- **Primary outcome**: ORR
- **Secondary outcomes**: DOR, OS, PFS, and percentage of patients experiencing AEs
- **Results presented by study authors**: As of 3/12/2020, 146 patients with iNHL (124 FL; 22 MZL) received axi-cel; 84 patients with FL had ≥ 12-months follow-up. The median age was 61 years (range, 34 – 79); 57% of patients were male. Thirty-eight percent of patients had ECOG 1, 86% had stage III/IV disease, 47% had ≥ 3 FLIPI, and 49% had high tumor bulk (GELF). Patients had a median 3 prior lines of therapy (range, 1 – 10); 64% had ≥ 3 prior lines. Progression < 2 years after initial chemoimmunotherapy (P) occurred in 55% of patients, and 68% were refractory to last prior treatment. Axi-cel was successfully manufactured for all enrolled patients. “With a median follow-up of 17.5 months (range, 1.4 – 31.6), the ORR was 92% among efficacy-evaluable patients with iNHL (n = 104), with a 76% CR rate. In patients with FL (n = 84), the ORR was 94% (80% CR rate); in those with MZL (n = 20), the ORR was 85% (60% CR rate). ORR was comparable across key risk groups analyzed by FLIPI, POD24, GELF, refractory status, and prior lines of therapy. As of the data cutoff, 62% of all treated patients had ongoing responses (64% for FL). The medians for DOR, PFS, and OS were not reached; 12-month estimated rates were 72% (95% CI, 61 – 80), 74% (95% CI, 63 – 82), and 93% (95% CI, 86 – 97), respectively.

“AEs of any grade occurred in 99% of all treated patients. Grade ≥ 3 AEs occurred in 86% of patients with iNHL (85% in FL; 95% in MZL), most commonly neutropenia (33%), decreased neutrophil count (27%), and anemia (23%). Grade ≥ 3 cytokine release syndrome (CRS; per Lee, et al, Blood. 2014) occurred in 7% of patients with iNHL (6% in FL; 9% in MZL). Grade ≥ 3 neurologic events (NEs; per CTCAE v4.03) occurred in 19% of patients with iNHL (15% in FL; 41% in MZL). Most CRS (118/119) and NEs (81/87) of any grade resolved by data cutoff. Grade 5 AEs occurred in 3 patients: multisystem organ failure in the context of CRS (Day 7; related to axi-cel; n = 1 FL), aortic dissection (Day 399; unrelated to axi-cel; n = 1 FL), and coccidioidomycosis infection (Day 327; unrelated to axi-cel; n = 1 MZL).
The median peak CART cell level was 38 cells/µL (range, 0 – 1415) in all treated patients with iNHL, with 36 cells/µL (range, 0 – 1415) in those with FL and 53 cells/µL (range, 2 – 453) in those with MZL. The AUC\(_{0-28}\) was 448 cells/µL × days (range, 6 – 19,900) in all treated patients with iNHL, with 422 cells/µL × days (range, 6 – 19,900) and 552 cells/µL × days (range, 13 – 6468) in those with FL and MZL, respectively. The median time to peak was 9 days (range, 8 – 371) in all patients, 8 days (range, 8 – 371) in patients with FL, and 15 days (range, 8 – 29) in patients with MZL. In efficacy-evaluable patients with FL, median peak CART cell levels were numerically greater in those with ongoing response at 12 months than in those who relapsed (P = .057). In all treated patients with FL, CART cell peak was associated with Grade ≥ 3 CRS (P = .031) and NEs (P = .005).

Manufacturers and Regulatory Status

Kite Pharma, a Gilead Company (South San Francisco, California), is developing axicabtagene ciloleucel. On March 5, 2021, FDA granted accelerated approval to axicabtagene ciloleucel to treat adult patients with relapsed or refractory follicular lymphoma after 2 or more lines of systemic therapy.\(^{54}\) This indication was approved based on response rate, and continued approval for this indication may be contingent upon verification and description of clinical benefit in 1 or more confirmatory trials.

The supplemental biologics license application Kite Pharma submitted had also pursued FDA approval for treating patients who have marginal zone lymphoma\(^{55}\); however, the scope of the accelerated approval was limited to treating patients who have follicular lymphoma.

FDA had previously granted both indications a breakthrough therapy designation.\(^{55}\) FDA earlier approved axicabtagene ciloleucel for a different indication, to treat relapsed or refractory diffuse large B-cell lymphoma.

The prescribing information carries a black box warning regarding the potential for cytokine release syndrome, which labeling indicates occurred in 88% of patients, and neurologic toxicities, which occurred in 81% of patients.\(^{51}\) Severe instances of these toxicities may threaten life and require supportive care or immunosuppressive treatment or both.

To mitigate the risk associated with these toxicities, axicabtagene ciloleucel is available only to facilities enrolled in a risk evaluation and mitigation strategy (REMS).\(^{56}\) The program requires that facilities enroll and comply with the REMS requirements and have onsite “immediate access to a minimum of 2 doses of tocilizumab for each patient for infusion within 2 hours after Yescarta infusion, if needed for treatment of [cytokine release syndrome]. Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense, or administer Yescarta are trained about the management of [cytokine release syndrome] and neurologic toxicities.”\(^{56}\)

Cost Information

According to an online aggregator of US prescription drug prices, Drugs.com, the list price of axicabtagene ciloleucel is $373 000 per treatment regimen.\(^{57}\) This price excludes additional costs for hospital care while the therapy is prepared and given and side effects managed, which can bring the total close to $1 million.\(^{58,59}\)

Key Stakeholder Perspectives

Between September 9, 2020, and September 16, 2020, five stakeholders, reflecting clinical, health systems, and patient perspectives, provided comments and ratings on axicabtagene ciloleucel to treat indolent non-Hodgkin lymphoma. The list below provides a summary of key stakeholder perspectives.
• Axicabtagene ciloleucel has moderate potential to improve health outcomes for patients with relapsed/refractory indolent non-Hodgkin lymphoma based on the high response rates observed in the ZUMA-5 trial and the potential for the therapy to generate prolonged remission.

• However, adverse events associated with the treatment limits axicabtagene ciloleucel’s potential to improve patient health outcomes. High rates of neurologic events and cytokine release syndrome and the potential for patients to develop long-lasting neuropathies are of concern.

• The CAR T-cell therapy procedure’s complex nature places substantial demands on patients and caregivers. Patients must travel to a major medical center, and treatment involves an inpatient stay, which has greater potential to negatively impact quality of life than outpatient treatment alternatives.

• Axicabtagene ciloleucel would likely substantially increase cost of care for patients because of the high cost of the therapy as well as procedural costs associated with the treatment.

• The therapy’s high cost and the likelihood that it would be given only at specialized facilities were seen as factors that could exacerbate disparities based on socioeconomic status or access to these facilities or both.

CAR T-Cell Therapies (Idecabtagene Vicleucel and Ciltacabtagene Autoleucel) to Treat Relapsed and Refractory Multiple Myeloma

Highlights

• Idecabtagene vicleucel (Abecma, formerly ide-cel) and ciltacabtagene autoleucel (cilta-cel) are engineered chimeric antigen receptor (CAR) T-cell therapies that use the patient’s own T cells to target multiple myeloma cells overexpressing the B-cell maturation antigen (BCMA). It is given as a single intravenous infusion. In March 2021, FDA approved ide-cel. In December 2020, cilta-cel’s developer initiated a rolling submission of a biologics license application to FDA.

• Most patients with multiple myeloma develop relapsed and refractory multiple myeloma (RRMM), which no longer responds to ongoing treatment and is unlikely to respond to subsequent standard treatments.

• Stakeholders commenting on this topic thought that preliminary data suggest that ide-cel and cilta-cel could improve outcomes and quality of life in patients whose disease no longer responds to standard treatments. However, their availability will be limited to large health centers with the necessary specialists and infrastructure to offer CAR T-cell therapies.

• Stakeholders also thought that these CAR T-cell therapies are expected to be very expensive (ie, $373,000 to $475,000, plus costs to administer the therapy, monitor patients, and manage complications). These costs might limit the availability of these therapies and increase disparities among patients of low and middle economic status.
Patient Population

Ide-cel and cilta-cel are intended for adults who have RRMM that has been treated with sequential or combination therapy, including a protease inhibitor, an immunomodulatory agent, and/or an anti-CD38 antibody.

Intervention

Multiple myeloma is the second most common hematologic malignancy, with about 32,000 new cases per year in the United States. It occurs when blood plasma cells (differentiated B cells) become malignant and grow out of control. The American Cancer Society website offers more information on multiple myeloma.

In the past 15 years, several new therapeutic agents for multiple myeloma have become available and, when used sequentially, have improved patient survival. However, most patients eventually have disease that no longer responds to standard therapies. Patients with heavily treated RRMM need new interventions to address this problem.

BCMA is a receptor expressed preferentially by plasma cells, with little or no expression in other blood cells or tissues. BCMA is highly overexpressed in malignant plasma cells from patients with multiple myeloma compared with plasma cells from healthy individuals, and its high levels are associated with cell proliferation, cell survival, and more progressive disease. Therefore, BCMA is a promising target for multiple myeloma therapies.

Ide-cel (Abecma) and cilta-cel are CAR T-cell therapies that have been engineered to target BCMA using the patient’s own T cells. T cells collected from a blood sample are sent to a laboratory to be genetically modified using a lentiviral vector encoding an anti-BCMA CAR. The genetically modified T cells that compose these therapies are grown in number and then reintroduced into the patient. The treatment purportedly targets malignant BCMA-expressing plasma cells to promote a robust immune response against these cells to treat the disease.

A clinician prescribes either ide-cel or cilta-cel to be given at a hospital that is capable of providing the specialized care required for CAR T-cell administration. A nurse gives the patient a single intravenous infusion of ide-cel at a dose ranging from \(300 \times 10^6\) to \(460 \times 10^6\) CAR T cells or cilta-cel at a dose of \(7.5 \times 10^5\) CAR T cells/kg. After treatment, the patient remains hospitalized and is monitored for cytokine release syndrome for 14 to 21 days.
Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 3 ongoing trials for ide-cel and 3 ongoing trials for cilta-cell. We present 4 of these trials with likely regulatory implications in Table 2.6. We excluded 2 phase 2 clinical trials (NCT03601078 and NCT04133636).

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>
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<tbody>
<tr>
<td>A Study of JNJ-68284528, a Chimeric Antigen Receptor T Cell (CAR-T) Therapy Directed Against B-Cell Maturation Antigen (BCMA) in Participants With Relapsed or Refractory Multiple Myeloma (CARTITUDE-1) NCT03548207</td>
<td>Patients (n = 126) who have RRMM that has been treated with at least 3 lines of therapy, including prior treatment with a protease inhibitor, an immunomodulatory agent, and an anti-CD38 antibody</td>
<td>Phase 1/2, single-group assignment, open-label trial to evaluate the safety and efficacy of cilta-cell in patients with RRMM. Patients will receive a single cilta-cell infusion at a dose of 7.5 × 10⁵ CAR T-cells/kg. Primary end point: Overall response rate and adverse events. Secondary end points: Overall survival, progression-free survival, clinical benefit rate, duration of response, time to response, time to progression, adverse events, and quality of life.</td>
<td>Primary completion February 2022 Study completion April 2022</td>
</tr>
<tr>
<td>Efficacy and Safety Study of bb2121 Versus Standard Regimens in Subjects With Relapsed and Refractory Multiple Myeloma (KarMMa-3) NCT03651128</td>
<td>Patients (n = 381) who have RRMM that has been treated with 2 to 4 lines of therapy, including treatment with a protease inhibitor, an immunomodulatory agent, and an anti-CD38 antibody</td>
<td>Phase 3, randomized, controlled, parallel-assignment, open-label trial to evaluate the safety and efficacy of ide-cel in patients with RRMM. Patients will be randomly assigned to receive either a single ide-cel infusion at a dose of 150 × 10⁶ to 450 × 10⁶ CAR T cells or investigator’s choice of antimyeloma therapy. Primary end point: Progression-free survival. Secondary end points: Overall survival, event-free survival, overall response rate, complete response rate, duration of response, time to response, time to progression, adverse events, and quality of life.</td>
<td>Primary completion May 2022 Study completion November 2025</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>
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<tr>
<td>Efficacy and Safety Study of bb2121 in Subjects With Relapsed and Refractory Multiple Myeloma (KarMMa) NCT03361748</td>
<td>Patients (n = 149) who have RRMM that has been treated with at least 3 lines of therapy, including prior treatment with a protease inhibitor, an immunomodulatory agent, and an anti-CD38 antibody</td>
<td>Phase 2, single-group assignment, open-label trial to evaluate the safety and efficacy of ide-cel in patients with RRMM Patients will receive a single ide-cel infusion at a dose of 150 × 10^6 to 450 × 10^6 CAR T cells Primary end point: Overall response rate Secondary end points: Overall survival, progression-free survival, complete response rate, duration of response, time to response, time to progression, adverse events, and quality of life</td>
<td>Primary and study completion November 2024</td>
</tr>
<tr>
<td>A Study Comparing JNJ-68284528, a CAR-T Therapy Directed Against B-Cell Maturation Antigen (BCMA), Versus Pomalidomide, Bortezomib and Dexamethasone or Daratumumab, Pomalidomide and Dexamethasone in Participants With Relapsed and Lenalidomide-Refractory Multiple Myeloma (CARTITUDE-4) NCT04181827</td>
<td>Patients (n = 400) who have RRMM that has been treated with 1 to 3 lines of therapy, including prior treatment with a protease inhibitor, an immunomodulatory agent, and an anti-CD38 antibody</td>
<td>Phase 3, randomized, parallel-assignment, open-label, multicohort trial to evaluate the safety and efficacy of cilta-cel in patients with RRMM Patients will receive a single cilta-cel infusion at a dose of 7.5 × 10^5 CAR T cells/kg Primary end point: Progression-free survival Secondary end points: Overall survival, overall response rate, complete response rate, minimal residual disease, time to worsening of symptoms, adverse events, and quality of life</td>
<td>Primary and study completion April 2026</td>
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</table>

Abbreviations: bb2121, idecabtagene vicleucel; CAR, chimeric antigen receptor; CAR-T, chimeric antigen receptor T-cell; cilta-cel, ciltacabtagene autoleucel; ide-cel, idecabtagene vicleucel; RRMM, relapsed and refractory multiple myeloma.
Recently Completed and Ongoing Trials With Available Results

Our searches identified 2 recently completed phase 2 trials with published results.\(^{66,67}\) We summarize results as written in the abstract of a published study and a conference abstract.

The following abbreviations are used in this section: AE, adverse event; bb2121, idecabtagene vicleucel; CAR, chimeric antigen receptor; CAR-T, chimeric antigen receptor T cell; CI, confidence interval; cilta-cel, ciltacabtagene autoleucel; CRS, cytokine release syndrome; d, days; gr, grade; ide-cel, idecabtagene vicleucel; mo, months; MRD, minimal residual disease; NR, not reached; OS overall survival; PFS, progression-free survival; pts, patients; RRMM, relapsed and refractory multiple myeloma; y, years.

Efficacy and Safety Study of bb2121 in Subjects With Relapsed and Refractory Multiple Myeloma (KarMMa). NCT03361748. Munshi et al 2021.\(^{66}\)

- **Patient population/planned enrollment:** Patients (n = 140) who had RRMM that was treated with at least 3 lines of therapy, including prior treatment with a protease inhibitor, an immunomodulatory agent, and an anti-CD38 antibody, either sequentially or in the same line.
- **Study design:** Phase 2, single-group assignment, open-label trial to evaluate the safety and efficacy of ide-cel in patients with RRMM. Patients received a single ide-cel infusion at a dose of \(150 \times 10^6\) to \(450 \times 10^6\) CAR T cells.
- **Primary outcome:** Overall response rate
- **Secondary outcomes:** Progression-free survival, complete response, duration of response, and adverse events
- **Results presented by study authors:** “Of 140 patients enrolled, 128 received ide-cel. At a median follow-up of 13.3 months, 94 of 128 patients (73%) had a response, and 42 of 128 (33%) had a complete response or better. Minimal residual disease (MRD)-negative status (<10\(^{-5}\) nucleated cells) was confirmed in 33 patients, representing 26% of all 128 patients who were treated and 79% of the 42 patients who had a complete response or better. The median progression-free survival was 8.8 months (95% confidence interval, 5.6 to 11.6). Common toxic effects among the 128 treated patients included neutropenia in 117 patients (91%), anemia in 89 (70%), and thrombocytopenia in 81 (63%). Cytokine release syndrome was reported in 107 patients (84%), including 7 (5%) who had events of grade 3 or higher. Neurotoxic effects developed in 23 patients (18%) and were of grade 3 in 4 patients (3%); no neurotoxic effects higher than grade 3 occurred. Cellular kinetic analysis confirmed CAR+ T cells in 29 of 49 patients (59%) at 6 months and 4 of 11 patients (36%) at 12 months after infusion.”

A Study of JNJ-68284528, a Chimeric Antigen Receptor T Cell (CAR-T) Therapy Directed Against B-Cell Maturation Antigen (BCMA) in Participants With Relapsed or Refractory Multiple Myeloma (CARTITUDE-1). NCT03548207. Madduri et al 2020.\(^{67}\)

- **Patient population/planned enrollment:** Patients (n = 126) who had RRMM that was treated with at least 3 lines of therapy, including prior treatment with a protease inhibitor, an immunomodulatory agent, and an anti-CD38 antibody, either sequentially or in the same line.
- **Study design:** Phase 1/2, single-group assignment, open-label trial to evaluate the safety and efficacy of cilta-cel in patients with RRMM. Patients received a single cilta-cel infusion at a dose of \(7.5 \times 10^5\) CAR T cells/kg.
- **Primary outcome:** Overall response rate
- **Secondary outcomes:** PFS, complete response, duration of response, and adverse events
- **Results presented by study authors:** “As of the May 20, 2020 clinical cutoff, 97 pts (58.8% male; median age 61.0 y [range 43–78]) with RRMM received cilta-cel (29 in phase 1b; 68 in phase 2). Median follow-up duration was 8.8 mo (range 1.5–20.4). Pts had received a median of 6 prior lines of therapy (range 3–18); 83.5% were penta-exposed, 87.6% were triple-refractory, 41.2% were penta-refractory,
and 97.9% were refractory to last line of therapy. Overall response rate per independent review committee (primary endpoint) was 94.8% (95% CI 88.4–98.3), with a stringent complete response rate of 55.7% (95% CI 45.2–65.8), very good partial response rate of 32.0% (95% CI 22.9–42.2), and partial response rate of 7.2% (95% CI 3.0–14.3). All pts achieved a reduction in M-protein. Median time to first response was 1.0 mo (range 0.9–5.8; 80.4% ≤ 1.0 mo), and median time to complete response or better was 1.8 mo (range 0.9–12.5; 74.1% ≤ 3.0 mo); responses deepened over time (Figure). Median duration of response was NR. Of 52 MRD-evaluable pts, 94.2% were MRD-negative at 10–5. The 6-mo PFS and OS rates (95% CI) were 87.4% (78.9–92.7) and 93.8% (86.7–97.2), respectively; median PFS and OS were NR. Ten deaths occurred during the study; 8 were due to AEs (both related and unrelated; CRS/hemophagocytic lymphohistiocytosis, neurotoxicity, respiratory failure, sepsis, septic shock, pneumonia, lung abscess, and acute myelogenous leukemia [n=1 each]), and 2 due to progressive disease. AEs reported in > 70% of pts were CRS (94.8%; grade [gr] 3/4 4.1%), neutropenia (90.7%; gr 3/4 90.7%), anemia (81.4%; gr 3/4 68.0%), and thrombocytopenia (79.4%; gr 3/4 59.8%). Median time to CRS onset was 7.0 d (range 1–12) and median duration 4.0 d (range 1–27, excluding n=1 with 97 d). CAR-T cell–related neurotoxicity was reported in 20.6% of pts (gr 3/4 10.3%). Cilta-cel CAR+ T cells showed maximum peripheral expansion at 14 d (range 9–43). Among pts with 6 mo' individual follow-up, 67% had cilta-cel CAR+ T cells below the level of quantification (2 cells/µL) in peripheral blood."

Manufacturers and Regulatory Status

Investigators at bluebird bio, Inc (Cambridge, Massachusetts), in collaboration with Bristol Myers Squibb Co (New York, New York), are studying ide-cel. On March 26, 2021, FDA approved ide-cel, based on results from the KarMMa trial, to treat adults who have RRMM that has been treated with at least 3 lines of therapy, including a protease inhibitor, an immunomodulatory agent, and an anti-CD38 antibody, either sequentially or in the same line.68 FDA earlier had granted ide-cel orphan drug and breakthrough therapy designations to treat RRMM.69,70

Janssen Pharmaceutical, LLC (Titusville, New Jersey), a subsidiary of Johnson & Johnson, Inc (New Brunswick, New Jersey), manufactures cilta-cel. Investigators are studying cilta-cel for treating adults who have RRMM in the phase 1/2 (CARTITUDE-1), phase 2 (CARTITUDE-2), and phase 3 (CARTITUDE-4) clinical trials. Based on results from the CARTITUDE-1 trial, the company initiated a rolling submission of a biologics license application to FDA in December 2020.71 FDA has granted cilta-cel orphan drug and breakthrough therapy designations to treat RRMM.71,72

Cost Information

Cost information is currently unavailable for this topic. Costs of other CAR T-cell therapies already approved by FDA range from $373 000 to $475 000 plus costs related to hospital care while the therapy is prepared and administered and side effects managed, which can bring the total close to $1 million.

Key Stakeholder Perspectives

Between September 4, 2020, and February 26, 2021, seventeen stakeholders, reflecting clinical, health systems, nursing, patient, patient representative, and research perspectives, provided comments and ratings on ide-cel (8 stakeholders) and cilta-cel (9 stakeholders). The list below provides a summary of key stakeholder perspectives.

- Because patients with RRMM have very few treatment options, ide-cel and cilta-cel could improve outcomes and quality of life. These therapies represent a novel treatment type that requires a single infusion to benefit patients. After treatment and hospital stay,
patients might have a long treatment-free period, as long as their disease stays in remission.

- As cell-based therapies, both ide-cel and cilta-cel are expected to create disparities because of high costs and additional costs for hospitalization and supportive care. Even with help from insurance, patients of low and middle economic status will likely have difficulty affording these treatments.

- Ide-cel and cilta-cel will be mostly offered at large health centers with the necessary infrastructure and personnel that have expertise with CAR T-cell therapies and management of cytokine release syndrome. Therefore, patients living in rural and remote areas might have difficulty accessing these treatments.

- Standard treatments for RRMM are given in an outpatient setting. However, ide-cel and cilta-cel have potential to shift care to a hospital setting, which is required to offer treatment and monitor patients for up to 3 weeks for cytokine release syndrome.

- Ide-cel and cilta-cel are promising treatments that might extend the life of patients who have exhausted their options. However, there are concerns about the high rate of serious adverse events, such as cytokine release syndrome and neurotoxicity, which might decrease patient quality of life. Overall, adopting CAR T-cell therapies could disrupt the paradigm of care, cause changes in infrastructure and personnel, and increase costs to health care systems and patients.

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

**Highlights**

- Lifileucel is a cell-based therapy that uses a patient’s own tumor-infiltrating lymphocytes (TILs) to enhance antitumor immune responses against melanoma. The developer expected to submit a biologics license application to FDA in 2021.

- 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 for progressive disease or after standard-of-care treatment has been exhausted.

- As a second-line, personalized, cell-based therapy, lifileucel is expected to be very expensive because of complex manufacturing requirements and required adjunctive treatment, 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 1 or more lines of systemic therapy, including an immune checkpoint inhibitor. 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 website 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 grown in numbers 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 receiving 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 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 treatments.

After lifileucel has been manufactured, a 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 the lifileucel infusion 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 2 trial in Table 2.7. We excluded an unphased trial (NCT01701674), a phase 1 trial (NCT02652455), and a phase 2 trial (NCT03645928) because they focus on a different patient population (ie, patients who have not received an immune checkpoint inhibitor).

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>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 = 178) aged 18 years or older with locally advanced or metastatic melanoma whose disease has progressed after 1 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 <em>BRAF</em> V600 mutation-positive melanoma, as follows: Cohort 1: First-generation TILs, not cryopreserved Cohort 2: Second-generation TILs, cryopreserved (closed) Cohort 3: Patients from cohorts 1, 2, and 4 who will receive a second dose of TILs Cohort 4: Second-generation TILs, cryopreserved</td>
<td>Phase 2, multicohort, open-label, parallel-assignment study evaluating the safety and efficacy of lifileucel Patients will be assigned to lymphocyte-depleting treatment with fludarabine and cyclophosphamide followed by lifileucel infusion and up to 6 doses of IL-2 (600 000 IU/kg) to support TIL replication and engraftment. Primary outcome: Objective response rate Secondary outcomes: Overall survival, progression-free survival, duration of response, disease control rate, and adverse events</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 a single recently completed phase 2 trial with published results. We summarize results as written in a conference abstract and company news release.

The following abbreviations are used in this section: BRAF, B homolog of the rapidly accelerated fibrosarcoma gene; CR, complete response; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DCR, disease control rate; IL-2, interleukin-2; LDH, lactate dehydrogenase; mDOR, median duration of response; MEK, MAPKK (mitogen-activated protein kinase) kinase; ORR, objective response rate; PD1, programmed cell death 1; PR, partial response; TIL, tumor-infiltrating lymphocyte; ULN, upper limit of normal.


• **Patient population/planned enrollment**: Patients (n = 178) aged 18 years or older with locally advanced or metastatic melanoma whose disease had progressed after 1 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, as follows:
  - Cohort 1: First-generation TILs, not cryopreserved
  - Cohort 2: Second-generation TILs, cryopreserved (closed)
  - Cohort 3: Patients from cohorts 1, 2, and 4 who will receive a second dose of TILs
  - Cohort 4: Second-generation TILs, cryopreserved

• **Study design**: Phase 2, multicohort, open-label, parallel-assignment study evaluating the safety and efficacy of lifileucel. Patients were assigned to lymphocyte-depleting treatment with fludarabine and cyclophosphamide followed by lifileucel infusion and up to 6 doses of IL-2 (600 000 IU/kg) to support TIL replication and engraftment.

• **Primary outcome**: ORR

• **Secondary outcomes**: Duration of response, DCR, and adverse events

• **Results presented for cohort 2 by study authors**: “[In 66 patients with unresectable melanoma, baseline statistics were as follows:] 3.3 mean prior therapies (anti-PD1 100%; anti-CTLA-4 80%; BRAF/MEK inhibitor 23%), high baseline tumor burden (106 mm mean target lesion sum of diameters), 44% liver/brain lesions, 40.9% LDH > ULN. ORR by investigator was 36.4% (2 CR, 22 PR) and DCR was 80.3%. Mean time to response was 1.9 months (range: 1.3-5.6). After a median study follow-up of 17.0 months, median DOR (mDOR) was still not reached. Six responders have progressed, 2 have died and 2 started other anti-cancer therapy without progression. The adverse event profile was consistent with the underlying advanced disease and the lymphodepletion and IL-2 regimens.”

• **Results presented for cohort 4 in a company news release**: “[In 68 patients with 2 radiological assessments] Lifileucel shows a 32.4% overall response rate (1 complete response and 21 partial responses, 2 of which are yet to be confirmed with follow up visits) and a disease control rate of 72.1% as of the data cut off of 16 Mar 2020. This data is consistent with what was noted in Cohort 2 at 6 months of median study follow up. The ORR was 33%.”
Manufacturers and Regulatory Status

Iovance Biotherapeutics, Inc (San Carlos, California), in collaboration with the National Institutes of Health’s National Cancer Institute (Bethesda, Maryland), is studying lifileucel in a phase 2 clinical trial. The company reported receiving fast track and regenerative medicine advanced therapy designations from FDA for treating advanced melanoma.78,79

In an end-of-phase-2 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, was to 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 2021.79,80

Cost Information

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

Key Stakeholder Perspectives

Between June 1, 2020, and August 30, 2020, six stakeholders, reflecting nursing, patient advocate, physician, and research perspectives, provided comments and ratings on lifileucel. The list below provides a summary of key stakeholder perspectives.

- Lifileucel could improve health outcomes in heavily treated patients whose disease has failed to respond to previous lines of therapy and who lack effective treatment options.
- Unanticipated issues with shipping the biopsies and returning the expanded TILs might create delays in treatment.
- Lifileucel is expected to be expensive and likely to be a cost burden to patients and payers.
- Lifileucel might create disparities for patients who cannot pay the anticipated high cost and who do not have access to large medical centers experienced in providing immunotherapies.
- Results from future randomized controlled trials are needed to provide better information on treatment benefits and to substantiate current findings.
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 (IL-4R) and a bacteria-derived endotoxin to kill cancer cells and immunosuppressive cells overexpressing IL-4R. It is in phase 2 development.
- Patients with recurrent glioblastoma multiforme (GBM) have poor outcomes and short survival and lack effective treatment options for recurrent disease.
- A clinician 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 could disrupt delivery and paradigms of care and be very costly.

Patient Population

MDNA55 is intended for adults who have a recurrent malignant glioma (eg, astrocytoma, GBM).

Intervention

GBM is a malignant brain cancer associated with poor outcomes and high death rates. GBM begins as stage IV disease with no evidence of a lower-grade precursor. The American Brain Tumor Association website 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%,81 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), which inhibits protein synthesis. MDNA55 is designed to target IL-4R, a cell-surface receptor overexpressed in various types of cancer stem cells and immunosuppressive cells that make up the tumor microenvironment. MDNA55 functions like a “molecular Trojan horse” because cpIL-4 binding to IL-4R triggers receptor-mediated cell take-up to deliver the cytotoxic PE payload into the target cells’ cytoplasm. Via IL-4R targeting, MDNA55 purportedly kills GBM stem cells and immunosuppressive cells in the tumor microenvironment with high specificity.82

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 total dose is between 18 and 240 μg.\textsuperscript{83}

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 phase 2 trial published as a conference abstract.\textsuperscript{84} We summarize results as written in the abstract.

The following abbreviations are used in this section: AEs, adverse events; CED, convection-enhanced delivery; CI, confidence interval; GBM, glioblastoma multiforme; IL4R, interleukin-4 receptor; KPS, Karnofsky Performance Status Scale; MGMT, O\textsubscript{6}-methylguanine-DNA methyltransferase; mOS, median overall survival; OS, overall survival; OS12, overall survival at 12 months; SCA, synthetic control arm; p, probability.

Convection-Enhanced Delivery (CED) of MDNA55 in Adults With Recurrent or Progressive Glioblastoma (MDNA55-05). \textbf{NCT02858895}. Sampson et al 2020.\textsuperscript{84}

- **Patient population/planned enrollment**: Patients (n = 46) with GBM that had recurred or progressed after primary treatment
- **Study design**: Phase 2, single-group assignment, open-label trial to evaluate the safety and efficacy of MDNA55 in patients with GBM. Patients received a single MDNA55 infusion via CED. Based on response, patients might have received a second MDNA55 infusion.
- **Primary outcome**: OS
- **Secondary outcomes**: Objective response rate, progression-free survival, and AEs
  - **Results presented by study authors**: “44 subjects comprise the MDNA55 per protocol analysis population: median age 56 (35 - 77); median dose 177 mg (range 18 – 240 mg), 50% had KPS ≤ 80. No systemic toxicities observed, drug-related AEs were primarily neurological and characteristic of GBM, no deaths attributed to MDNA55. Median OS was 11.6 months (95\% CI 7.9 – 15.2). When stratified by IL4R expression, mOS in IL4R High (n = 21) was 15 vs. 8.4 months in IL4R Low (n = 19); p = 0.2175. OS12 is 57\% vs. 33\%. When compared to the SCA (n = 81), MDNA55 subjects survived significantly longer: mOS 12.4 vs. 7.7 months; p = 0.0077. When comparing IL4R High groups, mOS in MDNA55 (n = 21) was 15.8 vs. 6.2 months in the SCA (n = 17); p = 0.0626. Subgroup analysis in unmethylated MGMT subjects also show better survival with MDNA55 (n = 23) than the SCA (n = 31); mOS 12.3 vs. 7.7 months (p = 0.0268), indicating that MDNA55 may be beneficial in patients resistant to temozolomide.”

Manufacturers and Regulatory Status

Medicenna Therapeutics Corp (Toronto, Ontario, Canada) is developing MDNA55 in an ongoing phase 2 trial. FDA has granted MDNA55 orphan drug and fast track designations for treating patients who have recurrent GBM.\textsuperscript{82}

Cost Information

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

Between May 28, 2020, and August 12, 2020, six stakeholders, reflecting health systems, nursing, physician, and research perspectives, provided comments and ratings on MDNA55. The list below provides a summary of key stakeholder perspectives.

- MDNA55 represents a new treatment with potential to improve health outcomes and quality of life for patients with recurrent GBM, a disease with a high death rate and short life expectancy. But larger trials are needed to fully support these claims.
- MDNA55’s convection-enhanced delivery would disrupt the health care delivery system and paradigm of care because, unlike drugs taken orally or in outpatient settings, MDNA55’s 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 need new therapy options because the current standard of care offers limited health benefits.

Nanoparticle Albumin-Bound Sirolimus (Nab-Sirolimus; Fyarro) to Treat Locally Advanced or Metastatic Perivascular Epithelioid Cell Sarcoma

Highlights

- Nanoparticle albumin-bound sirolimus (nab-sirolimus; Fyarro) is a novel form 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). The drug is given intravenously.
- PEComa is a rare soft tissue sarcoma with no FDA-approved therapy. Nab-sirolimus is in phase 2 development, and the company has initiated a rolling new drug application to FDA.
- Stakeholders commenting on this topic agreed that nab-sirolimus could improve health outcomes for patients with PEComa, but because it is expected to be more costly than other mTOR inhibitors, nab-sirolimus might create disparities for uninsured patients or those who cannot afford deductibles and copayments.
- Stakeholders also thought that nab-sirolimus is unlikely to substantially disrupt health care delivery because it will use infrastructure already in place for intravenous treatments. However, as potentially the first targeted therapy for PEComas, nab-sirolimus might impact 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. The National Cancer Institute’s Physician Data Query website offers more information about PEComa.

No targeted therapies are approved by FDA for use in treating malignant PEComas, and PEComas usually do not respond well to cytotoxic chemotherapy. Therefore, patients with PEComa need new treatments that can improve health outcomes.\(^5\)

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.\(^5,6\)

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.\(^6,7\)

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.\(^7\) Once the nanoparticles enter cells and inhibit the mTOR pathway, nab-sirolimus purportedly prevents tumor cell growth, proliferation, nutrient metabolization, and blood vessel formation.\(^5,6\)

A clinician prescribes nab-sirolimus to be given at an infusion center. A nurse administers intravenous nab-sirolimus weekly at a dose of 100 mg/m\(^2\) 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 2 ongoing trials for this topic. We present these trials in Table 2.8.

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>Nivolumab (Opdivo) Plus ABI-009 (Nab-rapamycin) for Advanced Sarcoma and Certain Cancers <a href="#">NCT03190174</a></td>
<td>Patients (n = 40) aged 12 years or older with a histologically confirmed diagnosis of Ewing sarcoma, PEComa, epithelioid sarcoma, desmoid tumor, chordoma, non–small cell lung cancer, small cell lung cancer, urothelial carcinoma, melanoma, renal cell carcinoma, squamous cell carcinoma of the head and neck, hepatocellular carcinoma, classic Hodgkin lymphoma, or MSI-H/dMMR metastatic colorectal cancer, and tumors with genetic mutations sensitive to mTOR inhibitors, that is either metastatic or locally advanced and for which surgery is not a recommended option.</td>
<td>Phase 1/2 single-group assignment, open-label trial to evaluate the safety, toxicity, and potential antitumor activity of sequential administration of nivolumab and escalating doses of the mTOR inhibitor nab-sirolimus in patients with diseases listed in the previous column. Patients will receive escalating doses of intravenous nab-sirolimus over 30 minutes for 2 of every 3 weeks beginning in week 2. Only nivolumab will be given in week 1. Following a cohort-of-3 design, 3 to 6 patients will receive dose level 1 of 56 mg/m²; 3 to 6 patients will receive dose level 2 of 75 mg/m²; and 3 to 6 patients will receive dose level 3 of 100 mg/m². Primary end point: Maximum tolerable dose. Secondary end points: Disease control rate and progression-free survival.</td>
<td>Primary completion February 2021 Study completion April 2021</td>
</tr>
</tbody>
</table>
Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed phase 2 trial with published results. We summarize results as written in a conference abstract.

The following abbreviations are used in this section: AEs, adverse events; CI, confidence interval; CR, complete response; DOR, duration of response; IRR, independent radiology review; ORR, objective response rate; OS, overall survival; PD, progressive disease; PEComa, perivascular epithelioid cell sarcoma; PFS, progression-free survival; PFS6, 6-month progression-free survival; PR, partial response; pts, patients; SD, stable disease; TRAEs, treatment-related adverse events.

A Phase 2 Study of ABI-009 in Patients With Advanced Malignant PEComa (AMPECT). NCT02494570. Dickson et al 2019.88

- **Patient population/planned enrollment:** Patients (n = 34) aged 18 years or older with locally advanced or metastatic PEComa
- **Study design:** Phase 2, 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-weeks-on, 1-week-off schedule.
- **Primary outcome:** ORR
- **Secondary outcomes:** OS, PFS, DOR, and AEs

**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 (>30%) hematologic 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 2 clinical trial. FDA has granted nab-sirolimus orphan drug, fast track, and breakthrough therapy designations to treat PEComa.\textsuperscript{89,90} Aadi Bioscience has initiated a rolling submission for a new drug application to FDA based on the results of the AMPECT study.\textsuperscript{91}

Cost Information

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

Key Stakeholder Perspectives

Between May 28, 2020, and July 29, 2020, five stakeholders, reflecting clinical, nursing, 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, comparative data are needed to support these claims.
- Nab-sirolimus is expected to be more expensive than generic mTOR inhibitors and might 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 limited treatment options available.
- Nab-sirolimus’ overall potential for disruption is based on the lack of treatment options for PEComa, but data show that this treatment caused adverse events in participants, and so risk-benefit analysis may be necessary before treatment is considered.
Omidubicel to Treat Hematologic Malignancies Eligible for Hematopoietic Stem Cell Transplantation

Highlights

- About 8500 patients undergo an allogeneic hematopoietic stem cell transplant (allo-HSCT) each year in the United States. The preferred source of graft material for HSCT is bone marrow or peripheral blood stem cells obtained from a matched, biologically related donor. However, not all patients in need of allo-HSCT have such an available donor, and alternative grafts are used in these patients.

- Omidubicel, an alternative source of hematopoietic cells, is derived from umbilical cord blood (UCB). Compared with unprocessed UCB, omidubicel purportedly decreases time to neutrophil engraftment, which could reduce treatment-related adverse events.

- The therapy is in phase 3 development, and the developer expects to submit a biologics license application to FDA in the fourth quarter of 2021.

- Stakeholders commenting on this topic thought that the observed improvement in time to neutrophil engraftment observed in the phase 3 trial of omidubicel compared with UCB suggested that omidubicel has substantial potential to improve patient health outcomes.

- Stakeholders also thought that omidubicel’s impact would be greatest for patients who would currently be treated with UCB and that omidubicel has the potential to disrupt the standard of care for these patients. They also thought the therapy would be expensive.

Patient Population

Omidubicel is intended for patients aged 12 years or older who have a blood, bone marrow, or lymph malignancy (ie, hematologic malignancy) and are eligible for treatment with allo-HSCT.

Intervention

Patients eligible for HSCT who lack matched donors require alternative graft sources. One such alternative is UCB, which is used in about 5% of allo-HSCTs. UCB transplants demonstrate efficacy in terms of relapse-related death; however, investigators have observed increased rates of treatment-related deaths. In particular, the lower cell counts present in a single-unit UCB transplant are thought to increase the time it takes for the transplant to engraft and restore blood cell levels in the recipient, which can lead to potentially life-threatening infections. Therefore, novel methods of increasing UCB cell counts to promote more rapid engraftment are sought.

Omidubicel (previously known as NiCord) is made up of UCB cells that have been grown to larger numbers in culture at a laboratory and is under study for use in allo-HSCT to treat hematologic malignancies.

To produce omidubicel, a sufficiently matched cord blood unit is selected from a cord blood bank and shipped to a centralized cell-processing facility. The cord blood unit is separated into fractions according to CD133 expression. The CD133-positive cell population, which contains immature immune cells such as CD34-positive stem cells, is cultured in the presence of growth factors and nicotinamide. Nicotinamide is an SIRT1 inhibitor that purportedly inhibits stem cell
differentiation and enhances the functionality of stem cells expanded in culture. The CD133-negative cell population, which contains mature immune cells such as T cells, is not cultured. Both fractions are cryopreserved and shipped to the transplantation center for infusion into the patient. Omidubicel processing takes about 24 days from identification of the UCB unit to receipt of the cryopreserved expanded graft.

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 2.9. Our searches also identified, but we excluded, an expanded access study for omidubicel (NCT04260698).

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>Stem Cell Transplantation With NiCord (Omidubicel) vs Standard Umbilical Cord Blood in Patients With Leukemia, Lymphoma, and Myelodysplastic Syndrome (MDS) NCT02730299</td>
<td>Patients (n = 124) undergoing allogeneic HSCT to treat hematologic malignancies and who lack an HLA-matched donor and have access to 1 or 2 partially HLA-matched cord blood units</td>
<td>Phase 3, open-label, randomized controlled trial of the safety and efficacy of omidubicel. Patients will be randomly assigned to treatment with either omidubicel or unmanipulated cord blood units. Primary end point: Time to neutrophil engraftment after transplantation.</td>
<td>Primary completion December 2019. Study completion March 2021</td>
</tr>
</tbody>
</table>

Abbreviations: HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation.

Recently Completed and Ongoing Trials With Available Results

Our searches identified 2 recently completed trials with published results. We summarize their results as written in a conference abstract, an abstract of a published study, and a manufacturer slide presentation.

The following abbreviations are used in this section: aGvHD, acute graft-vs-host disease; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CD34+, cluster of differentiation 34–positive; cGvHD, chronic graft-vs-host disease; CI, confidence interval; d, days; DRI, disease risk index; GVHD, graft-vs-host disease; HLA, human leukocyte antigen; HM, hematological malignancies; HSCT, hematopoietic stem cell transplant; P or p, probability; UCB, umbilical cord blood; y, year.

- **Patient population/planned enrollment:** Patients (n = 124) undergoing allogeneic HSCT to treat hematologic malignancies who lacked an HLA-matched donor and had access to 1 or 2 partially HLA-matched cord blood units.

- **Study design:** Phase 3, open-label, randomized controlled trial of the safety and efficacy of omidubicel. Patients were randomly assigned to treatment with either omidubicel or unmanipulated cord blood units.

- **Primary outcome:** Time to neutrophil engraftment after transplantation

- **Secondary outcomes:** Proportion of patients who achieved platelet engraftment by day 42, proportion of patients with grade 2 or grade 3 bacterial or invasive fungal infections in the first 100 days after transplantation, and number of days alive and out of the hospital in the first 100 days after transplantation.

- **Results presented by study authors:** “Between Jan 2017 and Dec 2019, 125 subjects were randomized at 33 sites in 7 countries to omidubicel (n=62) versus standard single (33%) or double (67%) UCB (n=63). Median age was 41 (range 13-65); 58% were male; most with AML (48%) or ALL (34%). DRI was moderate in 42% and high in 34%. The study population was diverse with 16% Black, 14% Asian, 3% multiracial and 13% Latino subjects. Demographics and baseline characteristics were well-balanced across the two arms. Median follow-up is 10 months. Median CD34+ cell dose for omidubicel recipients was 8 x 10^6/kg (124-fold expansion) and 0.3 x 10^6/kg for the controls. Median time to neutrophil engraftment was 12d (95% CI 10-15) in those randomized to omidubicel and 22d (95% CI 19-25) in controls (p<0.001). Cumulative incidence of engraftment is shown in the figure. Omidubicel recipients had a higher incidence of 42d platelet engraftment (55% vs. 35%, p=0.028), a lower incidence of infections (37% vs. 57%, p=0.027), and spent more time out of hospital (median 61 vs. 48d, p=0.005) than controls. Cumulative incidence of grade III/IV aGvHD was 14% vs. 21% (p=0.3), 1y-cGvHD was 35% vs. 29% (p=0.6) for omidubicel and control, respectively. Non-relapse mortality at 180d was 11% vs. 22% (p=0.1), 1y-relapse was 27% vs. 20% (p=0.4), and 1y-overall survival was 73% vs. 62% (p=0.16) for omidubicel and control, respectively.”


- **Patient population/planned enrollment:** Patients (n = 36) undergoing myeloablative HSCT to treat a hematologic malignancy who lack an HLA-matched donor and have access to 2 partially HLA-matched cord blood units.

- **Study design:** Phase 1/2, single-group assignment trial of the safety and efficacy of omidubicel. All patients received omidubicel as HSCT.

- **Primary outcome:** Rate of neutrophil engraftment at 42 days after transplantation

- **Results presented by study authors:** “The cumulative incidence of neutrophil engraftment at day 42 was 94%. Two patients experienced secondary graft failure attributable to viral infections. Hematopoietic recovery was compared with that observed in recipients of standard UCB transplantation as reported to the Center for International Blood and Marrow Transplant Research (n = 146). The median time to neutrophil recovery was 11.5 days (95% CI, 9 to 14 days) for recipients of nicotinamide-expanded UCB and 21 days (95% CI, 20 to 23 days) for the comparator (P < .001). The median time to platelet recovery was 34 days (95% CI, 32 to 42 days) and 46 days (95% CI, 42 to 50 days) for the expanded and the comparator cohorts, respectively (P < .001). The cumulative incidence of grade 2 to 4 acute graft-versus-host disease (GVHD) at day 100 was 44%, and grade 3 and 4 acute GVHD at day 100 was 11%. The cumulative incidence at 2 years of all chronic GVHD was 40%, and moderate/severe chronic GVHD was 10%. The 2-year cumulative incidences of nonrelapse mortality...”
and relapse were 24% and 33%, respectively. The 2-year probabilities of overall and disease-free survival were 51% and 43%, respectively.

Manufacturers and Regulatory Status

Gamida-Cell (Jerusalem, Israel) is developing omidubicel, which is under study in a phase 3 trial. The developer indicated that it intends to submit a biologics license application to FDA in the fourth quarter of 2021. In 2016, FDA granted omidubicel breakthrough therapy designation as a novel graft modality for bone marrow transplantation in patients with high-risk hematologic malignancies.  

Cost Information

Cost information is currently unavailable for this topic, but omidubicel’s cost is expected to be high because of its complex manufacturing requirements.

Key Stakeholder Perspectives

Between August 6, 2020, and August 24, 2020, six stakeholders, reflecting clinical, health systems, and research perspectives, provided comments and ratings on omidubicel to treat hematologic malignancies eligible for HSCT. The list below provides a summary of key stakeholder perspectives.

- Omidubicel has moderate to high potential to improve patient health outcomes, based on its reduction in the time to neutrophil engraftment compared with UCB. However, stakeholders noted that full study details on the magnitude of omidubicel’s effects on survival, infection rate, and adverse events are needed to fully assess the therapy’s potential impact.
- Omidubicel adoption should not require substantial changes to health care facilities or personnel. However, transplant teams would need to adjust procedures to accommodate the 24-day lead time associated with graft processing.
- Omidubicel would likely disrupt patient management. In particular, patients who would currently receive UCB transplants would instead receive omidubicel. Most stakeholders did not envision shifts to the care of patients receiving other forms of stem cell transplant.
- Omidubicel’s likely high cost and the fact that its use could be more predominant in specialized centers could exacerbate existing disparities based on insurance coverage and access to these facilities. Conversely, omidubicel could reduce disparities in patient populations that are less well represented in bone marrow transplant registries.
Onureg to Treat Acute Myeloid Leukemia (Maintenance Setting)

Highlights

- Onureg is an oral form of azacitidine, a small-molecule drug that acts as an antimetabolite and demethylating agent. In September 2020, FDA approved Onureg use as maintenance therapy for patients with acute myeloid leukemia (AML) who have responded to prior treatment.

- The cost for a typical Onureg treatment course is about $264,000.

- In a phase 3, randomized controlled trial, median overall survival was about 10 months longer in patients who received Onureg than in those who received placebo. Although patients receiving Onureg experienced increased rates of gastrointestinal events, neutropenia, and serious infections, overall health-related quality of life was reportedly not adversely affected.

- Stakeholders commenting on this topic agreed that Onureg is the first therapy to demonstrate a survival benefit when used in the maintenance setting after a first remission. Therefore, Onureg use in this setting would substantially disrupt the current AML treatment paradigm.

- Stakeholders also thought that, as an oral alternative to injected azacitidine in other treatment settings, Onureg could reduce treatment burden by shifting from an injected drug to a more convenient orally administered drug.

Patient Population

Onureg is intended for adults aged 18 years or older with AML who achieved first complete remission or complete remission with incomplete blood count recovery after intensive induction chemotherapy and are unable to complete intensive curative therapy.\(^{102}\)

Intervention

AML is a blood cancer characterized by the expansion of immature cells of the myeloid lineage. AML is an aggressive leukemia that is uniformly fatal unless treated. The American Cancer Society website offers more information on AML.\(^{102}\)

Treatment typically consists of a 2-phased approach, consisting of induction therapy intended to achieve remission and consolidation therapy intended to achieve long-term remission or cure. However, patients often experience disease relapse after a complete response to these treatments.\(^{103}\) In particular, older patients have high relapse rates because their disease is typically more aggressive and they might be ineligible for more intensive induction and consolidation therapies.\(^{104}\) Therefore, interest exists in novel methods of extending relapse-free and overall survival in patients with AML.

One such approach being explored is maintenance therapy, which consists of ongoing treatment with a low-intensity regimen to maintain the response to therapy. Although several agents have been studied in the maintenance setting, results to date have not demonstrated large enough effects on survival to become the standard of care.\(^{103}\)

Onureg (previously known as CC-486) is a demethylating agent under study as maintenance treatment for AML. The drug is a novel, orally bioavailable version of the intravenously administered hypomethylating agent azacitidine (Vidaza).\(^{104}\) FDA approved Vidaza in 2004 to
treat myelodysplastic syndrome, and it is widely used off-label in treating a range of hematologic malignancies, including AML.\textsuperscript{105} Onureg, like Vidaza, is a chemical analogue of the nucleoside cytosine and purportedly exerts its effects by inhibiting DNA methyltransferase after being incorporated into cellular DNA and by direct cytotoxic effect.\textsuperscript{106}

Onureg (300 mg) is taken by mouth once daily on days 1 through 14 of a 28-day treatment cycle until relapse or discontinuation for another reason.\textsuperscript{102,107}

**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 2.10.

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>Efficacy of Oral Azacitidine Plus Best Supportive Care as Maintenance Therapy in Subjects With Acute Myeloid Leukemia in Complete Remission (QUAZAR AML-001) NCT01757535</td>
<td>Patients (n = 472) with newly diagnosed AML who have achieved complete remission or complete remission with incomplete blood recovery with induction and consolidation therapy</td>
<td>Phase 3, quadruple-blind (participant, care provider, investigator, outcomes assessor), randomized controlled trial of the safety and efficacy of Onureg as maintenance therapy after standard induction and consolidation therapy Patients will be randomly assigned to treatment with either Onureg (300-mg oral tablet on days 1 through 14 of each 28-day cycle) or matching placebo Primary end point: Overall survival Secondary end points: Relapse-free survival, safety and tolerability, health care resource use, and patient-reported outcomes (FACT-Fatigue scale, EQ-5D)</td>
<td>Primary completion July 2019 Study completion December 2021</td>
</tr>
</tbody>
</table>

See preliminary results by Wei et al 2020 under Recently Completed and Ongoing Trials With Available Results
Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed phase 3 trial with published results.\textsuperscript{108} We summarize results as written in the abstract of a published paper.

The following abbreviations are used in this section: AML, acute myeloid leukemia; CC-486, Onureg; CR, complete remission; CRi, complete remission with incomplete blood recovery; EQ-5D, EuroQol-5D measure of health outcomes; FACT-Fatigue, Functional Assessment of Cancer Therapy—Fatigue; MDS, myelodysplastic syndrome.

Efficacy of Oral Azacitidine Plus Best Supportive Care as Maintenance Therapy in Subjects With Acute Myeloid Leukemia in Complete Remission (QUAZAR AML-001). \textsuperscript{108} Wei et al 2020.

- **Patient population/planned enrollment:** Patients (n = 472) with newly diagnosed AML who achieved CR or CRi with induction and consolidation therapy. Median age was 68 years (range 55-86), 91% of patients had \textit{de novo} AML, and 86% and 14% of patients, respectively, had intermediate-risk or poor-risk cytogenetics. After induction, 81% of patients achieved a CR and 19% achieved CRi; 80% of patients had received consolidation chemotherapy (45% received 1 consolidation cycle and 31% received 2 consolidation cycles).

- **Study design:** Phase 3, quadruple-blind (participant, care provider, investigator, outcomes assessor), randomized controlled trial of the safety and efficacy of Onureg as a maintenance therapy after standard induction and consolidation therapy. Patients were randomly assigned to treatment with either Onureg (300-mg oral tablet on days 1 through 14 of each 28-day cycle) or matching placebo.

- **Primary outcome:** Overall survival

- **Secondary outcomes:** Relapse-free survival, safety and tolerability, health care resource use, and patient-reported outcomes (FACT-Fatigue scale, EQ-5D)

- **Results presented by study authors:** “A total of 472 patients underwent randomization; 238 were assigned to the CC-486 group and 234 were assigned to the placebo group. The median age was 68 years (range, 55 to 86). Median overall survival from the time of randomization was significantly longer..."
with CC-486 than with placebo (24.7 months and 14.8 months, respectively; P<0.001). Median relapse-free survival was also significantly longer with CC-486 than with placebo (10.2 months and 4.8 months, respectively; P<0.001). Benefits of CC-486 with respect to overall and relapse-free survival were shown in most subgroups defined according to baseline characteristics. The most common adverse events in both groups were grade 1 or 2 gastrointestinal events. Common grade 3 or 4 adverse events were neutropenia (in 41% of patients in the CC-486 group and 24% of patients in the placebo group) and thrombocytopenia (in 22% and 21%, respectively). Overall health-related quality of life was preserved during CC-486 treatment.”

**Manufacturers and Regulatory Status**

Bristol Myers Squibb Co (New York, New York), which acquired original developer Celgene in November 2019, manufactures Onureg. On September 1, 2020, FDA approved Onureg for continued treatment of patients with AML who achieved first complete remission or complete remission with incomplete blood count recovery after intensive induction chemotherapy and are unable to complete intensive curative therapy.109 The drug’s application was reviewed under the agency’s priority review program. Onureg had previously been granted orphan drug designation for treating AML.

**Cost Information**

According to Drugs.com, an online aggregator of US prescription drug prices, a 14-day cycle of Onureg (300 mg) costs about $22,000.110 In the phase 3 QUAZAR AML-001 trial,107 patients received a median of 12 cycles of Onureg (range 1-80 cycles), and, therefore, a typical Onureg treatment course would cost about $264,000.

**Key Stakeholder Perspectives**

Between July 18, 2020, and September 4, 2020, seven stakeholders, reflecting clinical, health systems, and research perspectives, provided comments and ratings on Onureg for treating AML. The list below provides a summary of key stakeholder perspectives.

- Onureg has moderate to high potential to improve patient health outcomes, based on the significant improvement in overall survival and relapse-free survival observed with Onureg treatment relative to placebo in the QUAZAR AML-001 trial.

- Although treatment toxicity is a concern for a drug being used in a setting in which patients do not typically receive therapy, Onureg appears generally well tolerated. Additionally, the burden associated with treatment administration is low because the drug is taken by mouth.

- As the first maintenance therapy to demonstrate a survival advantage in the maintenance setting, Onureg use would cause a shift in the AML treatment paradigm. Additionally, extending remission for patients with AML could decrease costs and resource requirements for downstream care to treat disease recurrence.

- If Onureg were to be used as a replacement for injected azacitidine, it could facilitate improved treatment adherence, improve access to treatment, and reduce injection-related adverse events. However, because of a lack of head-to-head trials, questions remain regarding the relative safety and efficacy of Onureg compared with injected azacitidine.
Oral Paclitaxel Plus Encequidar (formerly Oraxol) to Treat Locally Advanced or Metastatic Breast Cancer

**Highlights**

- Oral paclitaxel plus encequidar is a novel combination of a solubilized paclitaxel capsule and an encequidar tablet that can be taken by mouth with similar efficacy to that of intravenous paclitaxel and with fewer adverse events. After accepting a new drug application for oral paclitaxel plus encequidar, FDA issued a complete response letter in March 2021 to indicate that the oral combination therapy was not ready for approval.

- In contrast to this therapy’s oral paclitaxel, intravenous paclitaxel contains additives that increase the risk of neuropathy and hypersensitivity, which leads about 10% to 30% of patients to stop treatment.

- Compared with intravenous paclitaxel outcomes, clinical data demonstrate that treatment with oral paclitaxel plus encequidar led to improved health outcomes. Patients treated with the oral combination therapy also had fewer adverse events, but some, such as neutropenia, were more common with oral paclitaxel plus encequidar than with intravenous paclitaxel.

- Stakeholders commenting on this topic thought that the oral combination therapy could decrease disparities, because it is taken by mouth and patients might have broad access to it through retail pharmacies.

- Stakeholders also thought that oral paclitaxel plus encequidar could shift the care setting from an infusion center to the home. This shift might also decrease the burden on infusion centers, with fewer patients traveling to receive treatment.

**Patient Population**

Oral paclitaxel plus encequidar (formerly oraxol) is intended for adults who have locally advanced or metastatic breast cancer for whom treatment with intravenous paclitaxel has been recommended.

**Intervention**

Breast cancer is the most common type of cancer diagnosed in women, and it can arise from different parts of the breast (ie, ductal, lobular). The American Cancer Society website offers more information on breast cancer.

Intravenous paclitaxel, a taxane that inhibits cell division, is the most widely used chemotherapy agent for treating breast cancer. Historically, paclitaxel has been given intravenously because the drug is a substrate of P-glycoprotein (P-gp), an active transport protein on the gastrointestinal (GI) tract’s surface that pumps paclitaxel back into the GI tract. This limits systemic exposure to paclitaxel taken by mouth.111

Because paclitaxel is not soluble in water, it is diluted in an oily solvent (ie, Cremophor EL) and alcohol, which allows it to be given intravenously. However, these additives increase the risk of neuropathy, hypersensitivity, and other adverse events.112 These adverse effects can require stopping the regimen, thereby interrupting the planned treatment cycle. Studies have reported a paclitaxel discontinuation rate between 10% and 30% because of treatment-related adverse
Patients and clinicians are interested in forms of taxanes with the potential to improve safety and health outcomes.

Oral paclitaxel plus encequidar is a novel combination taxane therapy composed of a solubilized paclitaxel capsule and an encequidar tablet, both taken by mouth. Adding the P-gp inhibitor encequidar to paclitaxel purportedly prevents P-gp–mediated GI retention of paclitaxel. The oral combination therapy could increase paclitaxel’s accumulation in the body. Its use could also decrease the burden of infusion clinic visits, premedication, and potentially dangerous infusion-related reactions. Additionally, oral paclitaxel plus encequidar might improve the rates at which paclitaxel is taken up in the body, distributed, and eliminated, avoiding the high peak concentrations and low trough concentrations associated with periodic intravenous doses.

A clinician prescribes oral paclitaxel plus encequidar, and patients take it for 3 consecutive days per week at a dose of 205 mg/m² solubilized paclitaxel plus 15 mg encequidar until disease progression or intolerable toxicity.

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 2.11.

Table 2.11. 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>Ph3 Study to Determine Safety, Tolerability &amp; Tumor Response of Oraxol Compared to Taxol In Metastatic Breast Cancer (KX-ORAX-001) NCT02594371</td>
<td>Patients (n = 402) who have locally advanced or metastatic breast cancer for whom paclitaxel monotherapy has been recommended</td>
<td>Phase 3, randomized, parallel-assignment, open-label trial to evaluate the safety and efficacy of oral paclitaxel plus encequidar in patients with breast cancer Patients will be randomly assigned to treatment with either oral paclitaxel (205 mg/m²) plus encequidar (15 mg) for 3 consecutive days per week or intravenous paclitaxel (175 mg/m²) once every 3 weeks Primary end points: Tumor response and adverse events Secondary end points: Overall survival and progression-free survival</td>
<td>Primary completion July 2019 Study completion December 2021</td>
</tr>
</tbody>
</table>
Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed phase 3 trial with published results.\textsuperscript{117} We summarize results as written in a conference abstract.

The following abbreviations are used in this section: AEs, adverse events; ITT, intention-to-treat; IV, intravenous; mBC, metastatic breast cancer; mITT, modified intention-to-treat; oraxol, oral paclitaxel plus encequidar; OS, overall survival; p, probability; Pac, paclitaxel; Pac+E, oral paclitaxel plus encequidar; PFS, progression-free survival; Ph3, phase 3.

**Ph3 Study to Determine Safety, Tolerability & Tumor Response of Oraxol Compared to Taxol in Metastatic Breast Cancer (KX-ORAX-001) NCT02594371. Umanzor et al 2019.\textsuperscript{117}**

- **Patient population/planned enrollment:** Patients (n = 402) who have locally advanced or metastatic breast cancer for whom paclitaxel monotherapy has been recommended
- **Study design:** Phase 3, randomized, parallel-assignment, open-label trial to evaluate the safety and efficacy of oraxol in patients with breast cancer. Patients were randomly assigned in a 2:1 ratio to receive either oral paclitaxel (205 mg/m\textsuperscript{2}) plus encequidar (15 mg) for 3 days per week or intravenous paclitaxel (175 mg/m\textsuperscript{2}) every 3 weeks.
- **Primary outcomes:** Tumor response and AEs
- **Secondary outcomes:** OS and PFS
- **Results presented by study authors:** “A total of 402 mBC patients were enrolled (Pac+E 265 vs IV Pac 137); demographics were balanced. A similar percentage of subjects in each treatment group received prior taxane therapy (Pac+E, 28%; IV Pac, 31%). For the ITT population, final analysis of the primary endpoint of confirmed tumor response demonstrated a statistically significant difference between treatments; Pac+E 35.8% vs IV Pac 23.4%, a difference of 12.4%, p=0.011, favoring Pac+E. For the protocol defined mITT population (baseline evaluable scans and received at least 75% of the first cycle of dosing) the confirmed response rates were 40.4% for Pac+E vs 25.6% for IV Pac (p=0.005). For the population with evaluable post-baseline scan, the confirmed response rates were 50.3% for Pac+E vs 29.6% for IV Pac (p=0.0005). Tumor response in all clinically important subgroups was consistent with the overall confirmed response profiles. Responses were durable. Ongoing analysis of duration of confirmed response showed the median durations were 39.0 weeks for Pac+E vs 30.1 weeks for IV Pac. Ongoing analysis of OS in the prespecified mITT population favors Pac+E (p=0.035) with a median of 27.9 months vs 16.9 months for Pac+E and IV Pac, respectively. Ongoing analysis of PFS in the prespecified mITT population shows a strong trend favoring Pac+E (p=0.077) with a median of 9.3 months vs 8.3 months. The Pac+E group had a lower incidence of alopecia and a lower incidence and severity of neuropathic AEs compared to IV Pac (17% versus 57% respectively to Week 23), with Grade 3 neuropathic symptoms observed in 1% for Pac+E vs 8% for IV Pac. The toxicity profile of Pac+E was generally similar to IV Pac. However higher rates of neutropenia, infection and gastrointestinal AEs were observed in Pac+E group. The risk of serious AEs on both treatments was highest among subjects with pre-treatment evidence of hepatic impairment and the protocol was amended to address this issue.”
Manufacturers and Regulatory Status

Investigators at Athenex Pharmaceuticals, Inc (Buffalo, New York), are studying oral paclitaxel plus encequidar in the phase 3 KX-ORAX-001 trial to treat locally advanced or metastatic breast cancer. Athenex submitted a new drug application (NDA) to FDA, based on results from this trial.118

FDA accepted the NDA on September 1, 2020, granted priority review, and issued a Prescription Drug User Fee Act (PDUFA)—prescribed action date of February 28, 2021.119 On March 1, 2021, FDA issued a complete response letter indicating that oral paclitaxel plus encequidar’s NDA was not ready for approval. FDA expressed concerns about oral paclitaxel plus encequidar increasing neutropenia-related sequelae and uncertainty over the 19-week objective response rate data. FDA recommended that Athenex conduct a new phase 3 clinical trial to verify oral paclitaxel plus encequidar’s safety and efficacy.120

Cost Information

Cost information is currently unavailable for this topic.

Key Stakeholder Perspectives

Between June 1, 2020, and June 22, 2020, eight stakeholders, reflecting clinical, health systems, nursing, patient, patient representative, and research perspectives, provided comments and ratings on oral paclitaxel plus encequidar. The list below provides a summary of key stakeholder perspectives.

- Oral paclitaxel plus encequidar could improve health outcomes and quality of life, because patients treated with it had overall improved health vs patients treated with intravenous paclitaxel.
- If patients manifest fewer adverse events with the oral drug than with intravenous paclitaxel, the oral regimen also could reduce hospital admissions to manage neuropathy and hypersensitivity. However, oral paclitaxel plus encequidar raises concerns about specific adverse events such as neutropenia.
- Unlike intravenous drugs that are available through infusion centers, oral paclitaxel plus encequidar could reduce health disparities by being broadly accessible to patients, including those living in rural areas, through retail pharmacies.
- If oral paclitaxel plus encequidar becomes available and is more expensive than intravenous drugs, the oral regimen might increase disparities for uninsured and underinsured patients. But it might decrease costs associated with treatment at infusion centers, such as supplies, labor, and personnel.
- The transition of patient care from an intravenous drug to an oral medication decreases the burden on infusion centers and reduces the patient’s burden of traveling to an infusion center once every 3 weeks.
Relugolix (Orgovyx) to Treat Relapsed, Locally Advanced, or Metastatic Androgen-Sensitive Prostate Cancer

Highlights

- Relugolix is an FDA-approved drug that selectively antagonizes the gonadotropin-releasing hormone (GnRH) receptor by binding with high affinity to the pituitary GnRH receptors. Relugolix purportedly reduces testosterone to surgery- or drug-mediated castration levels, preventing prostate cancer cells from growing.

- Androgen (ie, testosterone) deprivation therapy (ADT) increases risk of hormonal flares and cardiovascular events, and the only other available GnRH antagonist increases risk of injection-site reactions. Effective oral treatments are needed.

- Stakeholders commenting on this topic thought that data from the phase 3 trial showed that relugolix could improve patient outcomes while reducing side effects but will likely be accessible only to those with good insurance coverage.

- Stakeholders were concerned that the drug’s cost of $2400 for a 30-day supply might be cost-prohibitive for many; however, some stakeholders noted that taking an oral pill will reduce treatment time and transportation costs.

Patient Population

Relugolix is intended for adult males who have androgen-sensitive, advanced prostate cancer.

Intervention

After skin cancer, prostate cancer is the most common type of cancer in men, and it is the second leading cause of cancer-related death in men. About 192,000 new cases of prostate cancer are diagnosed each year in the United States. The American Cancer Society website offers more information on prostate cancer.

ADT deprives prostate cancer cells of growth-stimulating androgens either by surgery or by drug therapy. It is considered the standard of care for androgen-sensitive prostate cancer. The most commonly used ADTs are GnRH agonists (eg, leuprolide, goserelin). However, GnRH agonists, or activators, have substantial shortcomings, including the need for periodic injections (once every 3 to 6 months) and possible increased risk of cardiovascular events. Additionally, after GnRH agonist therapy is started, testosterone surges. To suppress the potential adverse events of this surge, an androgen-receptor antagonist (eg, bicalutamide, flutamide) is typically given at the same time.

GnRH antagonists represent an alternative means of ADT. However, the available GnRH antagonist, degarelix (Firmagon), has not been widely adopted, which might be because of the need for monthly injections and the high incidence of injection-site reactions.

Relugolix (Orgovyx) is a selective, GnRH antagonist that binds with high affinity to the pituitary GnRH receptors. This interaction causes the pituitary gland to decrease production of gonadotropin hormones, which are responsible for testosterone production in the testes. Relugolix purportedly reduces testosterone to surgery- or drug-mediated castration levels, preventing prostate cancer cells from growing. Thus, the drug could improve health-related
outcomes. Upon ending relugolix therapy, testosterone levels are expected to recover to prevent loss of bone density and cardiac events and to establish glycemic control.\textsuperscript{125}

The other GnRH antagonist, degarelix, is given as a monthly under-the-skin injection. In contrast, relugolix is taken by mouth, which might reduce the number of clinic visits and avoid injection-site adverse events.\textsuperscript{121,122} Additionally, relugolix it thought to have a lower risk of cardiac events than GnRH agonists.

A clinician prescribes relugolix tablets. According to the FDA-approved label, this drug is taken by mouth at a dosage of 120 mg once daily, after a single loading dose of 360 mg on day 1.\textsuperscript{125}

**Evidence Development Summary**

**Ongoing Trials**

Our searches of the National Clinical Trials database for ongoing trials for this patient population and clinical indication identified a single ongoing trial. We briefly describe it 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>A Study to Evaluate the Safety and Efficacy of Relugolix in Men With Advanced Prostate Cancer (HERO) <a href="#">NCT03085095</a></td>
<td>Patients (n = 1100) with prostate cancer that has relapsed after local primary intervention with curative intent (eg, surgery, radiation therapy); locally advanced prostate cancer unlikely to be cured by local primary intervention; or newly diagnosed metastatic androgen-sensitive prostate cancer</td>
<td>Phase 3, randomized, parallel-assignment, open-label trial to evaluate the safety and efficacy of relugolix in patients with prostate cancer Patients will be randomly assigned in a 2:1 ratio to receive either oral relugolix at a daily dose of 120 mg (after a loading dose of 360 mg on day 1) or subcutaneous leuprolide at a dose of 22.5 mg every 3 months Primary end point: Sustained castration rate Secondary end points: Castration resistance–free survival, quality of life, PSA response rate, and time to PSA progression</td>
<td>Primary completion October 2019 Study completion November 2021</td>
</tr>
</tbody>
</table>

Abbreviation: PSA, prostate-specific antigen.

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

Our searches identified a single recently completed late-phase trial with published results.\textsuperscript{124,126} We summarize the results, as written in an abstract of a published study and a company news release.

The following abbreviations are used in this section: CI, confidence interval; HR, hazard ratio; P, probability; PSA, prostate-specific antigen.
A Study to Evaluate the Safety and Efficacy of Relugolix in Men With Advanced Prostate Cancer (HERO). NCT03085095, Shore et al 2020.\textsuperscript{124}

- **Patient population/planned enrollment:** Patients (n = 930) with prostate cancer that had relapsed after local primary intervention with curative intent (eg, surgery, radiation therapy); locally advanced prostate cancer unlikely to be cured by local primary intervention; or newly diagnosed metastatic androgen-sensitive prostate cancer
- **Study design:** Phase 3, randomized, parallel-assignment, open-label trial to evaluate the safety and efficacy of relugolix in patients with prostate cancer. Patients were randomly assigned in a 2:1 ratio to receive either oral relugolix at a daily dose of 120 mg (after a loading dose of 360 mg on day 1) or subcutaneous leuprolide at a dosage of 22.5 mg every 3 months
- **Primary outcome:** Sustained castration rate
- **Secondary outcomes:** Castration resistance–free survival, quality of life, PSA response rate, and time to PSA progression
- **Results presented by study authors:** “A total of 622 patients received relugolix and 308 received leuprolide. Of men who received relugolix, 96.7% (95% confidence interval [CI], 94.9 to 97.9) maintained castration through 48 weeks, as compared with 88.8% (95% CI, 84.6 to 91.8) of men receiving leuprolide. The difference of 7.9 percentage points (95% CI, 4.1 to 11.8) showed noninferiority and superiority of relugolix (P<0.001 for superiority). All other key secondary end points showed superiority of relugolix over leuprolide (P<0.001). The percentage of patients with castrate levels of testosterone on day 4 was 56.0% with relugolix and 0% with leuprolide. In the subgroup of 184 patients followed for testosterone recovery, the mean testosterone levels 90 days after treatment discontinuation were 288.4 ng per deciliter in the relugolix group and 58.6 ng per deciliter in the leuprolide group. Among all the patients, the incidence of major adverse cardiovascular events was 2.9% in the relugolix group and 6.2% in the leuprolide group (hazard ratio, 0.46; 95% CI, 0.24 to 0.88).”

Results for the secondary end point of castration resistance–free survival were reported in a Myovant 2020 news release, as follows\textsuperscript{126}:

- “In the subgroup of men with metastatic disease treated with relugolix, 74% were castration-resistance free through 48 weeks compared to 75% men treated with leuprolide acetate (HR = 1.03 [95% CI: 0.68–1.57]; p = 0.84).”

Manufacturers and Regulatory Status

Myovant Sciences, Ltd (Basel, Switzerland), manufactures relugolix. On December 18, 2020, Myovant received FDA approval for relugolix to treat adult patients who have advanced prostate cancer.\textsuperscript{127} This approval was based on results from the phase 3 HERO trial.\textsuperscript{128}

Cost Information

An online aggregator of US-based prescription drug prices, Drugs.com, reported a retail price of $2424 for a 30-day supply of relugolix oral tablets (as of April 12, 2021).\textsuperscript{129} A 1-year supply costs about $29 250.

Key Stakeholder Perspectives

Between January 23, 2021, and February 15, 2021, nine stakeholders, reflecting clinical, health systems, nursing, patient representative, and research perspectives, provided comments and ratings on relugolix. The list below provides a summary of key stakeholder perspectives.

- Relugolix could improve patient outcomes because it reduces risk of hormone flares associated with ADT, injection errors or trauma at the injection site, and cardiovascular events.
This drug will likely be partially covered under insurance plans such as Medicare part D but could have substantial copayments compared with other prostate cancer treatments, such as leuprolide acetate injection (Lupron) or degarelix.

In the absence of effective oral drugs, relugolix could decrease health disparities for many because it does not require transportation, reduces office visits, and limits lost wages for caregivers. However, the cost of $2424 for a 30-day supply is much more than for other prostate cancer treatments, which might be barrier for many.

Relugolix will reduce the use of health care resources (eg, infrastructure, staff requirements), because patients would not need repeated clinic visits. However, monitoring is required for medication compliance, which can be done using telehealth.

Tazemetostat (Tazverik) to Treat Relapsed or Refractory Follicular Lymphoma

Highlights

- Tazemetostat, an oral drug, inhibits methyltransferase EZH2 (enhancer of zeste homolog 2), which is involved in the development of about 20% of follicular lymphomas.
- FDA approved the drug in June 2020 to treat relapsed or refractory follicular lymphoma, an incurable type of non-Hodgkin lymphoma that can transform into a more aggressive form, diffuse large B-cell lymphoma.
- Stakeholders commenting on this topic thought that, based on results from a single-group phase 1/2 trial, tazemetostat showed promise for improving health outcomes and could be adopted by patients whose disease has progressed within 24 months.
- Stakeholders also thought that tazemetostat might decrease disparities for patients who lack effective oral treatments. Because tazemetostat represents the first molecularly directed treatment for follicular lymphoma, it also could disrupt the current paradigm of care.
- The drug cost is listed as $15,300 for a 30-day supply of tazemetostat; the annual cost would be about $183,600.

Patient Population

Tazemetostat is intended to treat relapsed or refractory follicular lymphoma in adults whose tumors are positive for an EZH2 gene mutation as detected by an FDA-approved test and who have received at least 2 previous lines of systemic therapy.

Intervention

Follicular lymphoma is an indolent B-cell non-Hodgkin lymphoma that is considered incurable. It has the potential to transform into more aggressive diffuse large B-cell lymphoma. Although many patients with follicular lymphoma respond well to available therapies, certain patients, such as those whose disease progresses within 24 months of diagnosis or after treatment with multiple agents, have limited effective treatment options and poor prognosis. The American Cancer Society website offers more information on follicular lymphoma.
Tazemetostat (Tazverik) is a first-in-class, small-molecule inhibitor of EZH2 under study for treating relapsed or refractory follicular lymphoma. EZH2 regulates gene expression by modifying the methylation status of DNA-associated proteins called histones. Histone methylation patterns promoted by EZH2 activity are thought to promote cell proliferation and the growth and development of lymphoma. Specifically, EZH2 is thought to maintain a highly proliferative cell fate (ie, what type of cell the cell could become at maturity) that closely resembles that of germinal center B cells, which take part in an immune response in the body. Tazemetostat inhibition of EZH2 may reverse this cell fate specification, leading to exit of lymphoma cells from the germinal center and reducing their proliferation.

About 20% of follicular lymphomas harbor gain-of-function mutations in the EZH2 gene, which may provide a biomarker that indicates which patients are likely to respond to tazemetostat. However, EZH2 activity may also play a role in the growth and development of follicular lymphomas lacking EZH2 mutations, and tazemetostat studies have tested the drug’s activity in patients with either EZH2 mutations or wild-type EZH2.

A clinician prescribes tazemetostat. According to the FDA-approved label, this drug is intended to be taken by mouth at a dosage of 800 mg twice daily until disease progression or intolerable toxicity.
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 2.13. We excluded a phase 2 clinical trial that is being conducted in Japan (NCT03456726).

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>
</table>
| Open-Label, Multicenter, Phase 1/2 Study of Tazemetostat (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Adv. Solid Tumors or With B-Cell Lymphomas and Tazemetostat in Combination With Prednisolone in Subjects With DLBCL (EZH-101) [NCT01897571](#) | Patients (n = 420) with relapsed or refractory advanced solid tumors or B-cell lymphomas, including patients (n = 99) with relapsed or refractory follicular lymphoma who have received at least 2 prior systemic therapies | Phase 1/2, single-group trial of the safety and efficacy of tazemetostat in treating relapsed or refractory malignancies
Patients with relapsed/refractory follicular lymphoma received oral tazemetostat at a dosage of 800 mg twice daily.
Primary outcomes: Maximum tolerated dose of tazemetostat and objective response rate | Primary and study completion May 2021 |

^[NCT01897571](#): See preliminary results by Morschhauser et al 2020 under Recently Completed and Ongoing Trials With Available Results.
<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 in Subjects With Relapsed/Refractory Follicular Lymphoma (EZH-302) NCT04224493</td>
<td>Patients (n = 518) with relapsed or refractory follicular lymphoma who have received at least 1 prior systemic therapy</td>
<td>Phase 3, randomized controlled trial of the safety and efficacy of tazemetostat plus lenalidomide and rituximab The trial consists of 3 stages: (1) a safety run-in stage to determine the recommended phase 3 dose, (2) a safety and efficacy stage with 2 futility analyses assessing overall response rate and progression-free survival, and (3) a safety and efficacy stage that may enroll patients irrespective of EZH2 mutation status or patients with only EZH2 gain-of-function mutation, depending on the results of stage 2. Primary outcomes: Recommended phase 3 dose and progression-free survival</td>
<td>Primary completion June 2022 Study completion December 2024</td>
</tr>
<tr>
<td>Tazemetostat Rollover Study (TRuST): An Open-Label Rollover Study NCT02875548</td>
<td>Patients (n = 300) who have demonstrated clinical benefit from tazemetostat in an antecedent clinical trial of the drug</td>
<td>Phase 2, single-group trial of the safety and efficacy of extended tazemetostat dosing Patients will receive tazemetostat at the dose specified in the antecedent trial Primary outcome: Long-term safety profile of tazemetostat Secondary outcome: Overall survival</td>
<td>Primary completion December 2023 Study completion April 2024</td>
</tr>
</tbody>
</table>

Abbreviations: Adv, advanced; DLBCL, diffuse large B-cell lymphoma; EZH2, enhancer of zeste homolog 2 gene.

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

Our searches identified a single recently completed phase 1/2 trial with published results. We summarize results as written in the abstract of a published study.

The following abbreviations are used in this section: Adv, advanced; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; EZH2, enhancer of zeste homolog 2; EZH2mut, EZH2 activating mutation–positive; EZH2WT, EZH2 activating mutation–negative; IQR, interquartile range; NE, not estimable.

- **Patient population/planned enrollment:** Patients (n = 420) with relapsed or refractory advanced solid tumors or B-cell lymphomas, including patients (n = 99) with relapsed or refractory follicular lymphoma who had received at least 2 prior systemic therapies
- **Study design:** Phase 1/2, single-group trial of the safety and efficacy of tazemetostat in treating relapsed or refractory malignancies. Patients with relapsed/refractory follicular lymphoma received oral tazemetostat at a dosage of 800 mg twice daily.
- **Primary outcomes:** Objective response rate and maximum tolerated dose
- **Secondary outcomes:** Progression-free survival, duration of response, and adverse events
- **Results presented by study authors:** “Between July 9, 2015, and May 24, 2019, 99 patients (45 in the EZH²mut cohort and 54 in the EZH²WT cohort) were enrolled in the study. At data cutoff for the analysis (Aug 9, 2019), the median follow-up was 22.0 months (IQR 12.0-26.7) for the EZH²mut cohort and 35.9 months (24.9-40.5) for the EZH²WT cohort. The objective response rate was 69% (95% CI 53-82; 31 of 45 patients) in the EZH²mut cohort and 35% (23-49; 19 of 54 patients) in the EZH²WT cohort. Median duration of response was 10.9 months (95% CI 7.2-not estimable [NE]) in the EZH²mut cohort and 13.0 months (5.6-NE) in the EZH²WT cohort; median progression-free survival was 13.8 months (10.7-22.0) and 11.1 months (3.7-14.6). Among all 99 patients, treatment-related grade 3 or worse adverse events included thrombocytopenia (three [3%]), neutropenia (three [3%]), and anemia (two [2%]). Serious treatment-related adverse events were reported in four (4%) of 99 patients. There were no treatment-related deaths.”

### Manufacturers and Regulatory Status

Epizyme, Inc (Cambridge, Massachusetts), manufactures tazemetostat. On June 18, 2020, FDA granted accelerated approval to tazemetostat to treat patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as determined by an FDA-approved test and who have received at least 2 prior systemic therapies.¹³⁷ The submission was based on data from the phase 2 EZH-101 trial. At the same time, FDA also approved the cobas EZH2 Mutation Test (Roche Molecular Systems, Basel, Switzerland) to determine EZH2 mutation status.

Tazemetostat received accelerated approval in January 2020 to treat a different indication, metastatic or locally advanced epithelioid sarcoma that is ineligible for complete resection.¹³⁸ For a list of FDA-approved indications, see the FDA prescribing information for tazemetostat.

### Cost Information

An online aggregator of US-based prescription drug prices, GoodRx, reported a retail price of $15 300 for a 30-day supply of tazemetostat (as of October 5, 2020). If patients take the drug for a year, it would cost about $183 600.¹³⁹

### Key Stakeholder Perspectives

Between July 22, 2020, and September 1, 2020, seven stakeholders, reflecting clinical, health systems, nursing, patient, and research perspectives, provided comments and ratings on tazemetostat. The list below provides a summary of key stakeholder perspectives.

- Data from a small number of patients showed that tazemetostat improved response rates and was well tolerated. These outcomes could increase tazemetostat’s adoption rate in
patients whose disease progresses within 24 months compared with other salvage therapies, such as kinase inhibitors and T-cell–based therapies.

- In the absence of other effective oral drugs, tazemetostat could decrease disparities by allowing patients to be treated outside large medical centers. However, its high cost and need for genetic profiling might increase disparities.

- Implementing tazemetostat for clinical use is not expected to disrupt health care delivery because it is an oral drug used in the third-line setting to treat only about 20% of patients with relapsed or refractory follicular lymphoma.

- As the first molecularly directed therapy to treat follicular lymphoma, tazemetostat could disrupt the paradigm of care. Patient care might be further disrupted if follow-up studies of tazemetostat show safety and efficacy in earlier lines of treatment.
Chapter 3. Cardiovascular Diseases

Chapter Summary

For the cardiovascular diseases priority area, we considered for inclusion a single topic for which (1) preliminary phase 3 data for drugs, phase 2 (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 5, 2020; and (3) we received at least 5 sets of comments and ratings from stakeholders between March 20, 2020, and March 19, 2021.

As of March 5, 2021, we were monitoring 17 topics in this priority area, including the topic considered for inclusion in this report. These 17 topics were listed in the March 2021 PCORI Health Care Horizon Scanning System: Horizon Scanning Status Report.

The 17 monitored topics encompass pharmaceuticals, gene and cellular therapies, devices, and implants intended to treat 10 cardiovascular diseases and/or related symptoms. Of these, 16 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 the topic selected for inclusion in this report based on stakeholder ratings and comments and available data.

Table 3.1. Included Topics for Priority Area: Cardiovascular Diseases

<table>
<thead>
<tr>
<th>Topic title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ Care System Heart to treat end-stage heart failure requiring transplantation</td>
</tr>
</tbody>
</table>

Topic Summaries

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

Organ Care System Heart to Treat End-Stage Heart Failure Requiring Transplantation

Highlights

- Only about 35% of donor hearts can be used because of the hearts’ poor condition after donation and transport. This issue leads to a substantial number of patients remaining on the transplant waiting list for long periods and an annual death rate of nearly 20% in these patients.

- 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 waiting lists to receive a heart transplant.

• Stakeholders commenting on this technology thought OCS Heart could improve outcomes by enabling more patients on waiting lists to undergo heart transplantation sooner and saving overall care costs by reducing posttransplant complications and rehospitalizations for end-stage heart failure.

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 35% of donor hearts are used because of the hearts’ poor condition after donation and transport.\textsuperscript{140,141} 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%.\textsuperscript{142} 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 graft\textsuperscript{143,144}—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.\textsuperscript{144}

OCS Heart is optimized for preserving donor hearts.\textsuperscript{145} 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.\textsuperscript{145}

Like the other OCS systems, the OCS Heart is made up of 2 principal components: a portable battery-powered console and an organ-specific perfusion kit that function together as a system.\textsuperscript{144,145} 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{144,145}
Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 4 ongoing trials for this topic. We present these trials in Table 3.2.

Table 3.2. 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>Donors After Circulatory Death Heart Trial NCT03831048</td>
<td>Adults aged 18 years or older (n = 180) 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 at initial hospital discharge, if longer than 30 days, and utilization rate of eligible DCD donor hearts.</td>
<td>Primary completion August 2021 Study completion December 2021</td>
</tr>
<tr>
<td>Heart EXPAND Continued Access Protocol NCT03835754</td>
<td>Adults aged 18 years or older (n = 52) 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) to preserve and assess donor hearts that fail to 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 December 2021 Study completion December 2022</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>
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</tbody>
</table>
| Observational Study of the Clinical Use of the OCS Heart NCT03687723 | Children and adults, ages not specified (n = 100), who require heart transplantation | Unphased, single-arm, 2-center, prospective observational trial to observe clinical use of OCS Heart for patients who require heart transplantation  
Primary outcome: Patient survival at 12 months after transplantation  
Secondary outcome: Patient and graft organ survival at 30 days after transplantation | Primary completion December 2021  
Study completion October 2022 |
| Donor After Circulatory Death Heart CAP Trial NCT04615182 | Adults aged 18 years or older (n = 90) registered as candidates for primary heart transplantation | Unphased, single-arm, open-label protocol to provide transplant candidates continued access to DCD heart transplantation and collect additional performance data on OCS Heart system to preserve and assess DCD hearts’ ability to increase the donor heart pool  
Primary outcome: Patient survival at 6 months after transplantation  
Selected secondary outcomes: Utilization rate of eligible DCD donor hearts and primary graft dysfunction after 24 hours | Primary completion December 2021  
Study completion December 2025 |

Abbreviations: CAP, continued access protocol; DCD, donors after circulatory death; OCS, Organ Care System.

Recently Completed and Ongoing Trials With Available Results

Our searches identified 3 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; d, days; 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; min, minutes; NRP, normothermic regional perfusion; OCS, Organ Care System; p, probability; PGD, primary graft dysfunction; RV, right ventricular; UNOS, United Network for Organ Sharing; x-clamp, cross-clamp (a surgical instrument that closes off the aorta); y, years.

- **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 fail to 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 1 of the following risk factors: LVH, EF 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 2019.147

- **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. On April 6, 2021, TransMedics announced that FDA’s Circulatory Systems Device Advisory Panel voted to recommend approval of the premarket approval (PMA) application for the OCS Heart system. The panel voted 12 to 5, with 1 abstention, that the device’s benefits outweighed the risks of its use. The panel voted 10 to 6, with 2 abstentions, that available data demonstrated reasonable assurance that the OCS Heart was effective for the proposed indication. Further, the panel voted 9 to 7, with 2 abstentions, that reasonable assurance exists of the system’s safety.

The advisory panel meeting had been postponed twice during 2020 because of impacts related to the COVID-19 pandemic. TransMedics had submitted the PMA application to FDA 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. 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. The trial is evaluating the OCS Heart for preserving hearts obtained from donors after circulatory death.

FDA previously approved TransMedics’ PMA for similar technology in April 2018 to preserve donor lungs (OCS Lung system) selected using standard lung graft acceptance criteria. Approval was further expanded in June 2019 for OCS Lung use in preserving donor lungs selected under expanded acceptance criteria.

**Cost Information**

According to ECRI’s SELECTPlus database, member hospitals reported an average price of $308,200 for the OCS Heart console unit (as of April 9, 2021); US cost information for the single-use perfusion kit is currently unavailable.

**Key Stakeholder Perspectives**

Between July 9, 2020, and September 28, 2020, eight stakeholders, reflecting caregiver, clinical, health systems, nursing, patient, and research perspectives, provided comments and ratings on this topic. 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 dramatically improve outcomes by potentially expanding the pool of donor hearts and reducing deaths of patients on waiting lists.
• The technology represents a large shift from existing donor organ transport procedures that rely on static cold storage. Implementing the OCS Heart system would require additional staff, equipment, supplies, and training.

• The higher initial equipment costs could lower downstream care costs if posttransplant complications are reduced.

• Smaller waiting lists with shorter wait times might reduce overall care costs for this population. Growing donor heart scarcity, relative to demand, has increased the degree of illness of patients on the waiting list, resulting in recurrent rehospitalizations and increasingly costly and complex outpatient care, including use of ventricular assist devices and intravenous inotropes.
Chapter 4. Mental and Behavioral Health Conditions

Chapter Summary

For the mental and behavioral health conditions priority area, we considered for inclusion 7 topics for which (1) preliminary phase 3 data for drugs, phase 2 (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 5, 2021; and (3) we received at least 5 sets of comments and ratings from stakeholders between March 20, 2020, and March 19, 2021.

As of March 5, 2021, we were monitoring 18 topics in this priority area, including the 7 considered for inclusion in this report. These 18 topics were listed in the March 2021 PCORI Health Care Horizon Scanning System: Horizon Scanning Status Report.

The 18 monitored topics encompass pharmaceuticals and devices intended to treat 9 mental and behavioral health conditions. Of these, 11 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 4.1 lists 2 topics selected for inclusion in this report 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>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3,4-Methylenedioxyamphetamine (MDMA)-assisted psychotherapy to treat severe posttraumatic stress disorder</td>
<td></td>
</tr>
<tr>
<td>SEP-363856 to treat schizophrenia</td>
<td></td>
</tr>
</tbody>
</table>
Table 4.2 lists 5 topics considered but not selected for inclusion in this report, based on stakeholder ratings and comments and available data. Each record notes 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>BXCL501 to treat acute agitation in bipolar disorder and schizophrenia</td>
<td>Clinical use of BXCL501 might be limited by unwillingness of health care providers to administer an under-the-tongue medication to acutely agitated patients, because of the risk of being injured. If it is used clinically, this intervention is unlikely to significantly disrupt health care costs compared with current treatments and might only minimally impact the current paradigm of care and the health care delivery system.</td>
</tr>
<tr>
<td>EndeavorRx to treat attention-deficit/hyperactivity disorder (ADHD)</td>
<td>Data from clinical trials of this intervention did not demonstrate meaningful, patient-centered effects (ie, improvement of ADHD symptoms). Stimulant medication is likely to remain the standard of care. Additional and long-term efficacy data are needed.</td>
</tr>
<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 meaningful, patient-centered outcomes (eg, lowering suicidal behavior) and safety (ie, incidence of serious side effects such as hallucinations). Future clinical trials should investigate a larger patient sample size, a longer treatment period, and additional outcomes including suicidal ideation.</td>
</tr>
<tr>
<td>NightWare to treat nightmares associated with nightmare disorder or posttraumatic stress disorder</td>
<td>The current standard of care is unlikely to be impacted, considering NightWare is intended for use with existing pharmacotherapy. Its use might be limited because of patients who find a watch uncomfortable to wear to bed, have difficulty learning to use the technology, and face a potentially high cost of the device. Currently available efficacy data are limited and insufficient to support a large potential for improving patient outcomes, compared with current therapies.</td>
</tr>
<tr>
<td>PH94B to treat social anxiety disorder</td>
<td>PH94B might be used as an adjunctive therapy rather than monotherapy, therefore impacting only incrementally the current paradigm of care and patient outcomes. It is likely to be prescribed and self-administered in the same settings as current treatments, thus not impacting the current health care delivery system. It is likely to be more costly than current treatments that are available as generics, which might be cost-prohibitive for some patients and impact its clinical use.</td>
</tr>
</tbody>
</table>
3,4-Methylenedioxymethamphetamine (MDMA)–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 in the clinic.
- The session is conducted by a specially trained therapist so the therapist and patient can 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, and because fewer sessions could be needed overall, it might treat more patients earlier.
- 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*, for severe PTSD and who have had at least one unsuccessful attempt at either talk therapy or drug treatment.

**Intervention**

MDMA 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 and inhibiting vesicular monoamine transporter 2, thereby increasing concentrations of neurotransmitters (eg, dopamine, norepinephrine, serotonin) involved in the regulation of emotion, arousal, and memory.

MDMA is thought to produce a sense of euphoria, well-being, and “openness” that purportedly improves negative behaviors and feelings associated with PTSD, such as hostility, mistrust, and emptiness. 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. Patients given MDMA have reported gaining greater access to their memories and helpful insights when revisiting traumatic events during therapy sessions. MDMA produces its psychological and physical effects by increasing levels of neurotransmitters in the brain, including dopamine, norepinephrine, serotonin, oxytocin, prolactin, and cortisol.

In clinical trials, MDMA has been given to patients before an 8-hour psychotherapy session. The initial dose is 80 or 120 mg taken by mouth 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.169

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 a single ongoing trial for this topic. We present this trial 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 (MAPP2) NCT04077437</td>
<td>Adults aged 18 years or older (n = 100) with severe PTSD</td>
<td>Phase 3, randomized, double-blind, parallel-assignment trial assessing the efficacy and safety of MDMA-assisted manualized psychotherapy vs manualized psychotherapy with placebo for 3 monthly psychotherapy sessions Primary end point: Clinician-administered PTSD scale Secondary end point: Clinician-rated functional impairment disability scale</td>
<td>Primary completion November 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 7 recently completed late-phase trials. Data from 6 of these trials (NCT01793610, NCT01689740, NCT01211405, NCT01958593, NCT00353938, NCT00090064) were published in 2 pooled analyses, one initial and one longer term.169,170 Data from 3 of those trials (NCT01793610, NCT01211405, NCT01958593) were published in another pooled analysis.171 We summarize the 3 most recent studies’ results as written in the published studies.

We excluded a completed phase 2, open-label trial (NCT03282123) for brevity and a phase 3, placebo-controlled trial (NCT03537014) because no data are available yet.

The following abbreviations are used in this section: BDI-II, Beck Depression Inventory-II (revised); CAPS-IV, Clinician-Administered PTSD Scale for DSM IV; CI, confidence interval; LS, least-squares; LTFU, long-term follow-up; MDMA, 3,4-methylenedioxymethamphetamine; MMRM, mixed model for repeated measures; P or p, probability; PTG, posttraumatic growth; PTSD, posttraumatic stress disorder; SE, standard error.

- **Patient population/planned enrollment**: Adults (n = 103) aged 18 years or older with chronic, moderate to severe PTSD with at least one unsuccessful treatment attempt at or inability to tolerate treatment for PTSD with either talk therapy or drugs
- **Study design**: Six randomized, double-blind, controlled, phase 2 clinical trials at 5 study sites were conducted from April 2004 to February 2017. Active doses of MDMA (75-125 mg; n = 72) or placebo or controlled doses (0-40 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, although only trended towards significant group differences [MMRM, estimated mean difference (SE) between groups − 6.0 (3.03), P = 0.053]. All doses of MDMA were well tolerated, with some expected reactions occurring at greater frequency for the active MDMA group during experimental sessions and the 7 days following.”

Long-Term Follow-up Outcomes of MDMA-Assisted Psychotherapy for Treatment of PTSD: A Longitudinal Pooled Analysis of Six Phase 2 Trials. [NCT01793610, NCT01689740, NCT01211405, NCT01958593, NCT00353938, NCT00090064]. Jerome et al 2020.170

- **Patient population/planned enrollment**: Adults (n = 105) aged 18 years or older with chronic, moderate to severe PTSD with at least one unsuccessful treatment attempt at or inability to tolerate treatment for PTSD with either talk therapy or drugs
- **Study design**: Six randomized, double-blind, controlled, phase 2 clinical trials investigated long-term change in PTSD symptoms and additional benefits and harms after MDMA-assisted psychotherapy to treat PTSD. Participants were randomly assigned to either active-group doses of 75, 100, or 125 mg or control-group doses of 25, 30, or 40 mg or placebo at the beginning of 8-hour therapy sessions. An optional supplemental dose of MDMA was given 1.5 to 2.5 hours after the initial dose. Three nondrug therapy sessions followed the experimental sessions. Control participants received MDMA during an open-label crossover phase.
- **Primary outcome**: PTSD symptoms
- **Secondary outcomes**: Suicidal ideation and behavior, relapse of PTSD symptoms, current treatment, substance use
- **Results presented by study authors**: “There was a significant reduction in CAPS-IV total severity scores from baseline to treatment exit (LS mean (SE) = − 44.8 (2.82), p < .0001), with a Cohen's $d$ effect size of 1.58 (95% CI = 1.24, 1.91). CAPS-IV scores continued to decrease from treatment exit to LTFU (LS mean (SE) = − 5.2 (2.29), p < .05), with a Cohen's $d$ effect size of 0.23 (95% CI = 0.04, 0.43). The number of participants who no longer met PTSD criteria increased from treatment exit (56.0%) to LTFU (67.0%). The majority of participants reported benefits, including improved relationships and well-being, and a minority reported harms from study participation.”

- **Patient population/planned enrollment**: Adults (n = 60) aged 18 years or older with chronic, moderate to severe PTSD with at least one unsuccessful treatment attempt at or inability to tolerate treatments for PTSD with either talk therapy or drugs
- **Study design**: Three randomized, triple-blind, crossover phase 2 clinical trials investigated 3 different active doses of MDMA to treat PTSD: 75, 100, and 125 mg compared with active control doses of 30 or 40 mg or placebo. Participants were randomly assigned to receive 8 hours of manualized psychotherapy in 2 experiment sessions spaced 3 to 5 weeks apart. An optional supplemental dose of MDMA was given 1.5 to 2.5 hours after the initial dose. Three nondrug therapy sessions followed the experimental sessions.
- **Primary outcomes**: PTG and PTSD symptoms
- **Results presented by study authors**: “At primary endpoint, the MDMA group demonstrated more PTG, Hedges’ g = 1.14, 95% CI [0.49, 1.78], p < .001; and a larger reduction in PTSD symptom severity, Hedges’ g = 0.88, 95% CI [-0.28, 1.50], p < .001, relative to the control group. Relative to baseline, at the 12-month follow-up, within-subject PTG was higher, p < .001; PTSD symptom severity scores were lower, p < .001; and two-thirds of participants (67.2%) no longer met criteria for PTSD. MDMA-assisted psychotherapy for PTSD resulted in PTG and clinical symptom reductions of large-magnitude effect sizes. Results suggest that PTG may provide a new mechanism of action warranting further study.

**Manufacturers and Regulatory Status**

MDMA-assisted psychotherapy is being investigated by Multidisciplinary Association for Psychedelic Studies (MAPS; Santa Cruz, California) in phase 3 trials for treating severe PTSD in adults. MAPS anticipates completing the phase 3 trial program and filing for FDA regulatory approval in 2022.172 FDA granted breakthrough therapy designation to MDMA-assisted psychotherapy for severe PTSD in August 2017.173

After MDMA was designated a Schedule I 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.169

**Cost Information**

Cost information is currently unavailable for this topic.

**Key Stakeholder Perspectives**

Between July 2, 2020, and August 2, 2020, nine stakeholders, reflecting allied health, clinical, health systems, nursing, and research perspectives, provided comments and ratings on MDMA-assisted psychotherapy. The list below provides a summary of key stakeholder perspectives.

- MDMA-assisted psychotherapy might reduce the number of therapy sessions needed to treat PTSD compared with traditional psychotherapy. This reduction in therapy sessions might result in more patients being treated more quickly.
- This intervention might lead to health care disparities for patients with PTSD that does not respond to standard treatments because all patients might not have access to this treatment, which requires certain infrastructure and specially trained staff.
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 (ie, due to longer sessions, overnight monitoring, and cost of the drug), long-term costs could decrease if this intervention results in quicker resolution of symptoms, leading to less long-term health care utilization.

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 intended to treat schizophrenia without blocking dopamine receptors in the brain.
- Standard-of-care antipsychotic drug treatment for schizophrenia affects patients’ quality of life and overall health because it can have substantial side effects that can lead to poor medication adherence and outcomes.
- Stakeholders commenting on this topic thought that with fewer side effects, SEP-363856 might significantly improve patient health outcomes and quality of life.
- Stakeholders thought SEP-363856 might lower long-term costs of patient care, considering that its more favorable side effect profile might improve medication adherence and reduce use of costly health care resources to treat uncontrolled symptoms.

Patient Population

SEP-363856 treatment is intended for adolescents and adults aged 13 to 65 years with schizophrenia.

Intervention

Patients with schizophrenia report that undesirable effects from available antipsychotic medications—such as tremor, restlessness, difficulty sleeping, dizziness, sexual side effects, and weight gain—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 receptors. The exact way SEP-363856 produces its antipsychotic effect is unknown, but it is believed to activate trace amine–associated receptor 1 and serotonin 1A receptors. SEP-363856 has not been found to cause tremors, involuntary muscle contractions, restlessness, or weight gain.
A clinician prescribes SEP-363856, to be taken by mouth at a dosage of 25, 50, or 75 mg once daily for up to 26 weeks.\textsuperscript{179,180} The National Institutes of Health’s 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 these trials in Table 4.4.

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 to Study the Efficacy and Safety of an Investigational Drug in Acutely Psychotic People With Schizophrenia (DIAMOND 1) NCT04072354</td>
<td>Adolescents and adults (n = 525) aged 13 to 65 years who meet DSM-5 criteria for schizophrenia</td>
<td>Phase 3, double-blind, randomized, 3-arm, placebo-controlled study to assess the efficacy and safety of 2 doses of SEP-363856, either 50 or 75 mg, taken orally once daily, vs placebo over a period of 6 weeks. Primary outcome: Change in schizophrenia symptoms (positive and negative symptoms) from baseline. Secondary outcome: Change in CGI-S score from baseline.</td>
<td>Primary and study completion September 2021</td>
</tr>
<tr>
<td>A Clinical Trial That Will Study the Efficacy and Safety of an Investigational Drug in Acutely Psychotic People With Schizophrenia (DIAMOND 2) NCT04092586</td>
<td>Adults (n = 462) aged up to 65 years who meet DSM-5 criteria for schizophrenia</td>
<td>Phase 3, 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 symptoms) 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) who meet DSM-5 criteria for schizophrenia</td>
<td>Phase 3, multiregional, randomized, double-blind, parallel-group, long-term trial to assess safety and tolerability of once-daily SEP-363856. Patients will be randomly assigned in a 2:1 ratio to receive SEP-363856 (50, 75, or 100 mg) or quetiapine XR (400, 600, or 800 mg/day) for 52 weeks. Primary outcome: Adverse events. Secondary outcome: Time to relapse.</td>
<td>Primary completion March 2022</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>
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</tr>
<tr>
<td><strong>A Clinical Study to Evaluate the Long-term Safety and Tolerability of an Investigational Drug in People With Schizophrenia (DIAMOND 3) NCT04109950</strong></td>
<td>Adolescents and adults aged 13 to 65 years (n = 555) who meet DSM-5 criteria for schizophrenia and have completed DIAMOND 1 or DIAMOND 2 trials</td>
<td>Phase 3, multiregional, open-label, long-term trial to assess safety and tolerability of once-daily SEP-363856. Patients will receive SEP-363856 (25, 50, 75, or 100 mg) for 52 weeks. Primary outcome: Adverse events. Secondary outcome: Time to relapse.</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.\(^{177,181}\) We summarize these 2 most recent studies with results as written in an abstract of a published study and a poster presentation.

The following abbreviations are used in this section: AE, adverse event; BNSS, Brief Negative Symptom Scale; CGI-S or CGI-S; Clinical Global Impressions–severity scale; C-SSRS, Columbia–Suicide Severity Rating Scale; DB, double-blind; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; EPS, extrapyramidal; LDL, low-density lipoprotein; LOCF, last observation carried forward; msec, millisecond; OL, open-label; P, probability; PANSS, Positive and Negative Syndrome Scale; PSQI, Pittsburgh Sleep Quality Index; QTcF, Fridericia corrected QT interval; SAE, serious adverse event.


- **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 2, 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:** AEs
- **Secondary outcomes:** Change in schizophrenia symptoms (positive and negative symptoms) and severity, change in depression symptoms and severity, and time to relapse
- **Results presented by study authors:** “A total of 193 patients completed the 4-week DB study, and 156 (80.8%) entered the OL extension study and received at least one dose of SEP-363856 (safety population); 52 patients (33.3%) discontinued, and 18 (11.5%) discontinued due to an AE. A total of 15 patients (9.6%) experienced an SAE; schizophrenia was the only SAE to occur in more than one patient (n = 7, in the group switched from DB placebo to SEP-363856; n = 4, in the group continuing SEP-363856). There were no deaths in the study. Suicidal ideation (assessed using the C-SSRS) was reported by 3 patients, and 1 patient made an attempt. A total of 88 patients (56.4%) experienced at least one AE; individual AEs with an incidence ≥2% were schizophrenia (12.2%), headache (11.5%), insomnia (8.3%), anxiety (5.1%), somnolence (4.5%), nasopharyngitis (4.5%), nausea (3.8%), irritability (3.2%), influenza (3.2%), weight decreased (3.2%), and prolactin increased (2.6%). Extrapyramidal (EPS)-related symptoms were reported by 5 patients. Mean month 6 change from DB/OL baseline in PSQI global score was -4.2/-2.0. Mean month 6 change from DB/OL baseline in weight was -0.26/-0.32 kg. No
clinically meaningful median changes were observed at week 26 in metabolic laboratory parameters (total and LDL cholesterol, triglycerides, hemoglobin A1c) or in prolactin levels. During 6 months of OL treatment, no patient had an increase in QTcF ≥60 msec and a prolonged QTcF interval (≥450 msec in men; ≥475 msec in women). Treatment with SEP-363856 was associated with significant improvement from OL baseline to week 26 (observed/LOCF-endpoint) in the PANSS total score (-22.6/-13.8), positive subscale score (-7.3/-4.5), negative subscale score (-5.2/-3.5), and general psychopathology score (-10.2/-5.8); and in the CGI-Score (-1.0/-0.6) and BNSS total score (-11.3/-8.0)."

A Study to Evaluate the Efficacy and Safety of SEP-363856 in Acutely Psychotic Adults With Schizophrenia (SEP361-201). NCT02969382, Koblan et al 2020.183

- **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 2 trial comparing the efficacy and safety of flexibly-dosed SEP-363856 (50 or 75 mg/day) with placebo
- **Primary outcome:** Change in schizophrenia symptom severity (positive and negative symptoms), using PANSS
- **Secondary outcomes:** Change in depression symptom severity and incidence of AEs
- **Results presented by study authors:** "A total of 120 patients were assigned to the SEP-363856 group and 125 to the placebo group. The mean total score on the PANSS at baseline was 101.4 in the SEP-363856 group and 99.7 in the placebo group, and the mean change at week 4 was −17.2 points and −9.7 points, respectively (least-squares mean difference, −7.5 points; 95% confidence interval, −11.9 to −3.0; P=0.001). The reductions in the CGI-S and BNSS scores at week 4 were generally in the same direction as those for the primary outcome, but the results were not adjusted for multiple comparisons. Adverse events with SEP-363856 included somnolence and gastrointestinal symptoms; one sudden cardiac death occurred in the SEP-363856 group. The incidence of extrapyramidal symptoms and changes in the levels of lipids, glycated hemoglobin, and prolactin were similar in the trial groups."

Manufacturers and Regulatory Status

SEP-363856 is manufactured by Sunovion (Marlborough, Massachusetts), a subsidiary of Sumitomo Dainippon Pharma (Osaka, Japan). It is in phase 3 clinical development. In May 2019, FDA granted breakthrough therapy designation for SEP-363856 to treat patients with schizophrenia.184

Cost Information

Cost information is currently unavailable for this topic.

Key Stakeholder Perspective

Between September 9, 2020, and September 21, 2020, seven stakeholders, reflecting allied health, clinical, nursing, and research perspectives, provided comments and ratings on SEP-363856. The list below provides a summary of key stakeholder perspectives.

- SEP-363856 appears effective at improving schizophrenia symptoms, although the magnitude of these effects might be similar to that of current standard-of-care therapies.
- SEP-363856 might improve patient health and quality of life by causing fewer side effects (eg, weight gain, movement disorders) than standard-of-care therapies.
- A more favorable side effect profile with SEP-363856 might result in more patients able to take medication to treat schizophrenia, better medication adherence once treatment is
initiated, and less use of costly health care resources for uncontrolled symptoms (eg, emergency department visits or hospitalization for acute exacerbations). 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 29 topics for which (1) preliminary phase 3 data for drugs, phase 2 (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 5, 2021; and (3) we received at least 5 sets of comments and ratings from stakeholders between March 20, 2020, and March 19, 2021.

As of March 5, 2021, we were monitoring 134 topics in this priority area, including the 29 considered for inclusion in this report. These 134 topics were listed in the March 2021 PCORI Health Care Horizon Scanning System: Horizon Scanning Status Report.

These 134 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 89 rare diseases and/or related conditions. Eleven 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 19, 2021, so they were not considered for inclusion in this report. The remaining 94 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 13 topics selected for inclusion in this report 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>Arimoclomol (BRX-345) to treat Niemann-Pick disease type C</td>
<td></td>
</tr>
<tr>
<td>Betibeglogene autotemcel (beti-cel, formerly LentiGlobin) to treat transfusion-dependent β-thalassemia</td>
<td></td>
</tr>
<tr>
<td>CAP-1002 to treat Duchenne muscular dystrophy</td>
<td></td>
</tr>
<tr>
<td>Casimersen (Amondys 45) to treat Duchenne muscular dystrophy</td>
<td></td>
</tr>
<tr>
<td>Fosdenopterin (Nulibry) to treat molybdenum cofactor deficiency type A</td>
<td></td>
</tr>
<tr>
<td>Human plasminogen (Ryplazim) to treat congenital plasminogen deficiency a</td>
<td></td>
</tr>
<tr>
<td>Lumasiran (Oxlumo) to treat primary hyperoxaluria type 1 a</td>
<td></td>
</tr>
<tr>
<td>Mepolizumab (Nucala) to treat hypereosinophilic syndrome</td>
<td></td>
</tr>
<tr>
<td>MT1621 to treat thymidine kinase 2 deficiency</td>
<td></td>
</tr>
<tr>
<td>Olibudase alfa (GZ402665) to treat acid sphingomyelinase deficiency</td>
<td></td>
</tr>
<tr>
<td>Palovarotene to treat fibro dysplasia ossificans progressiva</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>Setmelanotide (Imcivree) to treat proopiomelanocortin deficiency obesity</td>
<td></td>
</tr>
</tbody>
</table>

*Topic appears for the first time in this edition of the High Potential Disruption Report.*
Table 5.2 lists 16 topics considered but not selected for inclusion in this report, based on stakeholder ratings and comments and available data. Each record notes 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>Arimoclomol (BRX-345) to treat amyotrophic lateral sclerosis (ALS)</td>
<td>Similar to the standard of care, arimoclomol is taken by mouth and is likely to be taken at home. Thus, its potential to disrupt is limited in terms of the current paradigm of ALS treatment, the health care delivery system, and health disparities, compared with current treatments.</td>
</tr>
<tr>
<td>Ataluren (Translarna) to treat Duchenne muscular dystrophy</td>
<td>More data are needed to evaluate ataluren’s 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>Efgartigimod (ARGX-113) to treat generalized myasthenia gravis</td>
<td>Efgartigimod is unlikely to significantly disrupt the current health care delivery system because giving it via infusion is unlikely to require significant infrastructure or staffing changes. Initial efficacy data are promising, but it remains to be seen whether efgartigimod can produce clinically meaningful outcomes, such as fewer hospitalizations and surgeries, and whether it could replace current treatments instead of being prescribed as an adjunctive treatment.</td>
</tr>
<tr>
<td>Ganaxolone (CCD-1042) to treat seizures associated with CDKL5 deficiency disorder</td>
<td>Ganaxolone could reduce but likely not eliminate the seizure burden on patients with CDKL5 deficiency disorder, and seizures are only one symptom of the disorder. Ganaxolone is taken by mouth and is likely to be taken at home, similar to traditional antiepileptic drugs, and so is not a significant departure from the current paradigm of care or health care delivery system.</td>
</tr>
<tr>
<td>Inebilizumab (Uplizna) to prevent attacks from neuromyelitis optica spectrum disorder (NMOSD)</td>
<td>Results from the N-Momentum trial showed reduced NMOSD attacks. However, its uptake is questionable because this patient population is being treated with other therapies that cost much less than inebilizumab. This intervention might reduce hospitalization rates, but it might increase the risk of side effects, disparities in access, and health care costs.</td>
</tr>
<tr>
<td>Maralixibat (LUM001) to treat Alagille syndrome</td>
<td>The limited available data, with multiple dose levels studied, do not consistently demonstrate a significant improvement from maralixibat compared with standard of care. Further, the relatively high rates of adverse events and patient withdrawals raise concerns about efficacy and safety.</td>
</tr>
<tr>
<td>Narsoplimab (OMS721) to treat hematopoietic stem cell transplant–associated thrombotic microangiopathy (TMA)</td>
<td>Additional data are needed from larger-sized trials that incorporate control groups to assess narsoplimab’s potential to improve patient outcomes.</td>
</tr>
<tr>
<td>Nomacopan (rVA576) to treat bullous pemphigoid</td>
<td>Efficacy data suggest that nomacopan might not benefit all patients or be more efficacious than current treatments, thus limiting its potential to improve patient outcomes and change the current paradigm of bullous pemphigoid care. Further, its clinical use might be limited by both its daily subcutaneous administration, which is invasive and likely to be cumbersome for many patients, and by an anticipated high cost.</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>Odevixibat (A4250) to treat progressive familial intrahepatic cholestasis</td>
<td>Available data suggest moderate improvement in some symptoms compared with placebo. However, odevixibat's efficacy compared with available off-label oral treatments or avoidance of biliary diversion surgery or liver transplantation remains unknown.</td>
</tr>
<tr>
<td>Oleogel-S10 (Filsuvez) to treat epidermolysis bullosa</td>
<td>Oleogel-S10 is applied topically, similar to other wound treatments, and is unlikely to disrupt the current health care delivery system, paradigm of care, or health disparities. The gel might only incrementally improve wound-closure time.</td>
</tr>
<tr>
<td>Omaveloxolone (RTA 408) to treat Friedreich ataxia</td>
<td>Although there is an unmet need for treatments for Friedreich ataxia, more data are needed to determine the short- and long-term efficacy and clinical significance of treatment with omaveloxolone. It might only incrementally slow disease progression, and patients in later stages of the disease might have difficulty swallowing the medication.</td>
</tr>
<tr>
<td>Rilzabrutinib (PRN1008) to treat moderate to severe pemphigus vulgaris and pemphigus foliaceus</td>
<td>Preliminary data are insufficient to determine how the efficacy of rilzabrutinib might compare with that of current treatments, and, therefore, it might be used much less often than current treatments. Because it is taken by mouth, rilzabrutinib is likely to be a convenient medication to prescribe and take and so unlikely to significantly change the current paradigm of care or the health care delivery system.</td>
</tr>
<tr>
<td>Sodium phenylbutyrate-taurursodiol to treat amyotrophic lateral sclerosis (ALS)</td>
<td>Sodium phenylbutyrate-taurursodiol might improve side effects compared with current treatments but overall has little potential to disrupt patient outcomes, because a cure for the disease is what is most needed. This intervention is another oral drug to treat ALS (ie, similar to riluzole) and so is not a significant departure from the current paradigm of care and is unlikely to disrupt the health care delivery system or health disparities.</td>
</tr>
<tr>
<td>Sutimlimab (BIVV009) to treat cold agglutinin disease</td>
<td>The preliminary trial showed some clinical effect, but it was a very small and unpublished trial. Larger trials and more data are needed to determine the safety and efficacy of this treatment.</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>Vosoritide (BMN 111) to treat achondroplasia</td>
<td>Although preliminary clinical data demonstrating increased growth velocity are promising, it is unknown whether this will translate to increased adult height or patient quality-of-life outcomes. Vosoritide might have a high cost up-front, but it might be balanced by long-term health care cost savings related to fewer surgeries and treatments for health complications of the disorder. Health disparities are unlikely to be impacted because patients are receiving specialized care already.</td>
</tr>
</tbody>
</table>
Topic Summaries

We present below 13 summaries on topics deemed to have high potential for disruption.

Arimoclomol (BRX-345) to Treat Niemann-Pick Disease Type C

Highlights

- Arimoclomol is an oral small-molecule drug intended to treat Niemann-Pick disease type C (NPC), a rare, progressive disease associated with mental and physical disability in infants and adults. The therapy is meant to amplify 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.

- FDA accepted the company’s marketing application for the therapy in September 2020 and, in December 2020, updated a previously set decision date of March 17, 2021, to June 17, 2021.

- 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.

- Stakeholders thought that arimoclomol might become the standard of care if it becomes the first FDA-approved treatment for NPC.

- Stakeholders also thought that arimoclomol is likely to be expensive—although it is not clear how its price might compare with that of off-label miglustat—but that the cost of the drug might be offset by less use of health care resources because of slowed disease progression (eg, fewer hospitalizations or follow-up visits).

Patient Population

Arimoclomol is intended for children and young adults aged 2 to 18 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 that 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.\(^{185}\)

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.\(^{186}\) Age of onset spans infancy to adulthood. Symptoms vary widely and can be fatal. Because no known cure is available or approved for NPC, therapies are needed.\(^{185}\)

The Mayo Clinic website offers more information about NPC.

Arimoclomol (BRX-345) is a small-molecule amine intended to treat NPC. It purportedly acts by amplifying and stabilizing heat shock factor 1, a transcription factor that regulates the production of HSPs in physiologically stressed cells. HSPs are thought to 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.\(^{187}\)

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 5.3.

**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>
<tbody>
<tr>
<td>Arimoclomol Prospective Study in Patients Diagnosed With NPC NCT02612129</td>
<td>Children and adults aged 2 to 18 years (n = 50) with diagnosed NPC due to variants in the NPC1 or NPC2 genes with at least 1 active neurological symptom</td>
<td>Phase 2/3, randomized, parallel-assignment, placebo-controlled study to assess the efficacy and safety of arimoclomol as an add-on therapy to standard care. Patients are 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 Note: The National Clinical Trials database lists this trial as ongoing.</td>
</tr>
</tbody>
</table>

Abbreviations: CGI, Clinical Global Impression; NPC, Niemann-Pick disease type C; NPC1, NPC1 like intracellular cholesterol transporter 1 gene; NPC2, NPC intracellular cholesterol transporter 2 gene; QOL, quality of life.
Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed phase 2/3 trial with reported results.\textsuperscript{188,189} We summarize this study with results as written in 2 news releases. Although the National Clinical Trials database lists this trial as ongoing, the company indicated in a news release that this is the full data set.

The following abbreviations are used in this section: NPC, Niemann-Pick disease type C; \textit{NPC1}, NPC1 like intracellular cholesterol transporter 1 gene; \textit{NPC2}, NPC intracellular cholesterol transporter 2 gene; NPC-CSS or NPCCSS, Niemann-Pick Disease Type C Clinical Severity Scale; \textit{p}, probability.

Arimoclomol Prospective Study in Patients Diagnosed With Niemann-Pick Disease Type C. \textbf{NCT02612129}. Orphazyme 2019,\textsuperscript{188} Orphazyme 2020.\textsuperscript{189}

- **Patient population/planned enrollment:** Children and adults aged 2 to 18 years (\textit{n} = 50) with diagnosed NPC due to variants in the \textit{NPC1} or \textit{NPC2} genes with at least 1 active neurological symptom
- **Study design:** Phase 2/3, randomized, parallel-assignment, placebo-controlled study to assess the efficacy and safety of arimoclomol as an add-on therapy to the standard of care. Patients were randomly assigned to receive arimoclomol capsules orally 3 times daily at a dosage of 150 to 600 mg/day (weight based) or matching placebo capsules for a double-blinded treatment period of 12 months. Participants had the option of continuing into a 12-month open-label extension study.
- **Primary outcome:** Disease severity from baseline to 12 months, as measured by the NPC-CSS
- **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 (\textit{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 (\textit{p}-value =0.0219). 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 (\textit{p}-value =0.0071).”\textsuperscript{188}

“Results from the 12-month open-label extension of the phase 2/3 randomized placebo-controlled trial (CT-ORZY-NPC-002) demonstrate sustained benefit of arimoclomol over a two-year period and further evidence of its efficacy and safety profile. Forty-one patients completed the 12-month double-blinded part of the CT-ORZY-NPC-002 trial and continued into the open-label extension, where all patients received arimoclomol treatment. Patients who switched from placebo to arimoclomol treatment experienced similar reduction of disease progression as observed earlier in those patients randomized to arimoclomol treatment in the placebo-controlled trial as measured by the 5-domain NPCCSS (0.23 progression in the open-label extension vs 2.0 progression in the placebo-controlled trial). Patients who received arimoclomol for a total of two years showed greater progression in the open-label extension compared to the placebo-controlled part. This was mainly due to patients under 4 years with continued aggressive disease course. In the predefined subgroups of patients 4 years and older and patients receiving miglustat as part of their routine clinical care, early treatment initiation with arimoclomol resulted in greater benefit than delayed start of treatment, indicating that the disease course was modified by the treatment. Arimoclomol was safe and well-tolerated over 24 months.”\textsuperscript{189}
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 2/3 development. In January 2020, arimoclomol became available to patients who have NPC through an early access program in the United States.190

Orphazyme announced in July 2020 that it had completed a rolling new drug application (NDA) submission to FDA for arimoclomol to treat NPC.191 The developer announced in September 2020 that FDA had accepted the NDA, granted priority review, and issued a Prescription Drug User Fee Act (PDUFA)–prescribed decision date of March 17, 2021.192 In December 2020, Orphazyme announced FDA had extended the review period of the NDA by a standard 3 months, with a new PDUFA target action date of June 17, 2021.193

Arimoclomol for treating NPC received FDA breakthrough therapy designation in December 2019,194 rare pediatric disease designation in January 2018,195 fast track designation in June 2016,196 and orphan drug designation in January 2015.197

Cost Information

Cost information is currently unavailable for this topic, but stakeholders thought arimoclomol would likely be expensive if approved as the first therapy to treat NPC.

Key Stakeholder Perspectives

Between September 8, 2020, and September 18, 2020, eight stakeholders, reflecting clinical, health systems, nursing, and research perspectives, provided comments and ratings on arimoclomol to treat NPC. The list below summarizes key stakeholder perspectives.

- Arimoclomol has potential to meet a large unmet need in patients with NPC and, if FDA approves it, to become the standard of care as the first approved treatment.
- The 74% reduction in disease progression reported from clinical trials with arimoclomol suggests it might significantly improve patient health outcomes and quality of life. The largest effect is likely to be in patients who begin this treatment early in their disease progression.
- More data are needed to assess whether arimoclomol will increase life expectancy in patients with NPC and how it might compare with off-label treatment with miglustat.
- The health care delivery system is unlikely to change dramatically because of arimoclomol, which would conveniently be taken by mouth at home. However, some health care use, such as hospitalizations, routine follow-up visits, and supportive treatment, might decrease in this patient population.
- Arimoclomol is likely to be expensive, although it might not differ much from the off-label comparator miglustat. Thus, it is unclear whether treatment cost will be significantly disrupted. Overall health care cost might be offset by less use of health care resources (see previous bullet point).
Betibeglogene Autotemcel (beti-cel, formerly LentiGlobin) to Treat Transfusion-Dependent β-Thalassemia

Highlights

- Betibeglogene autotemcel is a gene therapy in phase 3 trials and is delivered in a single infusion. The gene therapy is intended to permanently enhance a patient’s ability to produce functional hemoglobin B (HBB) and enhance red blood cell (RBC) production, as well as relieve transfusion-dependent β-thalassemia (TDT) symptoms. It is intended for use in children and adults aged up to 50 years with little to no β-globin expression.

- The developer has plans to submit a licensing application to FDA in mid-2021. However, recent reports of adverse events in clinical trials of a related gene therapy product for treating sickle cell disease has the potential to delay this timeline. The developer has stated that it would price betibeglogene autotemcel, administered as a one-time infusion, at less than $2.1 million per patient and will offer special financing options and a value-based payment plan tied to how well the therapy works in a patient.

- TDT substantially affects a patient’s quality of life because the standard of care consists of lifelong, regular blood transfusions or allogeneic hematopoietic stem cell transplantation (HSCT), which are burdensome and can lead to complications.

- Stakeholders commenting on this topic thought that betibeglogene autotemcel might reduce transfusion dependence, improve quality of life, and reduce demands on the health care system but that data from more patients would be needed before the drug’s potential could be fully assessed.

- Stakeholders also thought that this gene therapy would carry a high up-front cost but reduce transfusion dependence, which might lead to cost savings over time.

Patient Population

Betibeglogene autotemcel 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 overload from the transfusions can cause serious complications and organ damage, and iron chelation therapy is used to manage the overload. The National Library of Medicine’s MedlinePlus Genetics website offers more information on β-thalassemia.

Donor-derived (ie, allogeneic) HSCT can address the underlying cause of TDT, but it carries the risk of HSCT-related death, graft failure, graft-vs-host disease, and opportunistic infections, particularly in recipients of HSCT that is not from a matched sibling donor. A therapy derived from the patient’s own cells (ie, autologous) could avoid these complications.
As a gene therapy, betibeglogene autotemcel (beti-cel, formerly LentiGlobin) purportedly enhances the patient’s ability to produce functional HBB genes that subsequently improve RBC production.

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 that prevent the production of any β-globin. Patients with β+ thalassemia carry HBB variants that allow reduced β-globin production. Betibeglogene autotemcel is under study in patients with both β0 and β+ TDT.

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 grown in number in the laboratory to facilitate uptake.

In clinical trials, patients are treated with busulfan to destroy the β-thalassemia-causing blood cells and then betibeglogene autotemcel is given as a single intravenous treatment, at an unspecified dose.
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 5.4.

Table 5.4. 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 Study Evaluating the Efficacy and Safety of the LentiGlobin BB305 Drug Product in Subjects With Transfusion-Dependent β-Thalassemia, Who Do Not Have a β°/β° Genotype (Northstar-2 [HGB-207]) NCT02906202</td>
<td>Patients (n = 23) aged 50 years or younger with TDT who do not have a β° mutation at both alleles of the HBB gene</td>
<td>Phase 3, open-label, single-arm, multisite, single-dose study to evaluate the efficacy and safety of betibeglogene autotemcel Primary outcome: Proportion of patients achieving TI at 12 to 24 months after infusion Secondary outcomes: • 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</td>
<td>Primary and study completion February 2022</td>
</tr>
<tr>
<td>See preliminary results by Porter et al 2020 under Recently Completed and Ongoing Trials With Available Results</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The table lists ongoing clinical trials focusing on the efficacy and safety of LentiGlobin BB305 drug product for subjects with transfusion-dependent β-thalassemia who do not have a β°/β° genotype. The trials are designed to evaluate various outcomes including engraftment, vector-derived replication-competent lentivirus detection, and clonal dominance or leukemia. One trial is expected to be completed in 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>
<tbody>
<tr>
<td>A Study Evaluating the Efficacy and Safety of the LentiGlobin BB305 Drug Product in Subjects With Transfusion-Dependent β-Thalassemia(Northstar-3 [HGB-212]) NCT03207009</td>
<td>Patients (n = 18) aged 50 years or younger with TDT who have a β^0/β^0 genotype</td>
<td>Phase 3, multicenter, open-label, single-arm study to evaluate the efficacy and safety of betibeglogene autotemcel Primary outcome: Proportion of patients meeting criteria for TR at 12 to 24 months after transplantation Secondary end points: • 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 AEs at 24 months after infusion</td>
<td>Primary and study completion June 2022</td>
</tr>
</tbody>
</table>
Study name and National Clinical Trials identifier

Longterm Follow-up of Subjects With Hemoglobinopathies Treated With Ex Vivo Gene Therapy (LTF-303)

NCT02633943

See preliminary results by Kwiatkowski et al 2020 under Recently Completed and Ongoing Trials With Available Results

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 betibeglogene autotemcel in manufacturer-sponsored clinical trials

Study design and outcomes

Unphased, multicenter, open-label, randomized, parallel-assignment, follow-up study to assess the long-term safety and efficacy of betibeglogene autotemcel through 15 years

Primary outcomes:
- Overall survival 15 years after infusion
- AEs and serious AEs at 15 years after infusion
- Vector persistence at 15 years after infusion
- Monitoring of βA-T87Q-globin at 15 years after infusion
- Transfusions required at 15 years after infusion

Iron content in the liver and heart, measured by cardiac MRI and blood draws at 15 years after infusion

Estimated date of completion

Primary and study completion March 2031

Abbreviations: AEs, adverse events; β0, HBB mutation preventing the production of any β-globin; HBB, hemoglobin B gene; 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 phase 3 trials and 1 unphased trial with interim results. We summarize these studies with results as written in conference abstracts.

The following abbreviations are used in this section: AEs, adverse events; β0, HBB mutation preventing the production of any β-globin; β+IVS-I-110, β-globin mutation producing minimal adult hemoglobin; beti-cel, betibeglogene autotemcel; CD34+, cluster of differentiation 34-positive; EQ-5D, EuroQoL-5 dimension quality-of-life instrument; Hb, hemoglobin; HbA\textsuperscript{T87Q}, drug-delivered β globin gene; HBB, hemoglobin B gene; LIC, liver iron concentration; PB VCN, peripheral blood vector copy number; RBCs, red blood cells; RCL, replication-competent lentivirus; 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); yrs, years.

- **Patient population/planned enrollment:** Patients (n = 23) aged 50 years or younger with TDT who do not have a β⁰ mutation at both alleles of the HBB gene

- **Study design:** Phase 3, open-label, single-arm, multisite, single-dose study to evaluate the efficacy and safety of betibeglogene autotemcel

- **Primary outcome:** The proportion of treated patients who become TI at 12 to 24 months after transplantation

- **Secondary outcomes:** Percentage of patients with a reduction of at least 50% in RBCs transfused, from baseline to 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, and frequency of clinical AEs at 24 months after transplantation

- **Results presented by study authors:** “As of 12 June 2019, 21 patients were treated and followed for 11.6 (0.9–26.3) months. The median age at enrollment was 15 (8–34) years; 6 patients were <12 years old. All patients engrafted. Ten patients with sufficient follow-up were evaluable for TI and 9 of these patients achieved transfusion independence for an ongoing duration of 15.2 (12.1–21.3) months. The weighted average Hb during TI was 12.2 (11.4–12.8) g/dL.

  “At Month 12, the 9 patients who achieved transfusion independence had improved bone marrow cellularity compared to baseline (44% vs 11% normocellular) and improved myeloid:erythroid ratios (baseline: 1.7:3–1:1.4; Month 12: 1:1.6–1.9:1). Seven of 9 patients had reticulocyte counts within normal range vs 44% (4/9) at baseline. Soluble transferrin receptor levels decreased from 171.8 (66-235) nmol/L at baseline to 49.4 (34-68) nmol/L with 78% (7/9) of patients within normal range at last follow-up (vs 44% [4/9] at baseline). Erythropoietin levels in patients achieving TI decreased 61.4% from 33.2 (10.8-73.4) U/L at baseline (n=9) to 12.8 (4.9-21.8) U/L at Month 12 (n=7). Finally, the hepcidin:ferritin ratio improved from 0.01 (0.00-0.06) at baseline (n=9) to 0.03 (0.01-0.4) at Month 12 (n=9).

  “Post-infusion non-hematologic grade ≥3 treatment-emergent adverse events (AEs) reported in ≥3 patients included stomatitis (n=12), febrile neutropenia (n=7), epistaxis (n=3), pyrexia (n=3), and veno-occlusive liver disease (n=3). Adverse events considered related to beti-cel by the investigator included thrombocytopenia (n=2, one event was serious), abdominal pain (n=1), and pain in extremity (n=1). There were no deaths and no evidence of insertional oncogenesis or clonal dominance.”

Updated results were presented at the conference and in a June 12, 2020, bluebird bio news release, as follows:

- **As of March 3, 2020, all 23 patients in HGB-207 were treated and have been followed for a median of 19.4 months. These patients ranged in age from four to 34 years, including eight pediatric (<12 years of age) and 15 adolescent/adult (>12 years of age) patients. Only 19 patients were evaluable for transfusion independence; four additional patients do not yet have sufficient follow-up to be assessed for transfusion independence.

  “Eighty-nine percent of evaluable patients (17/19) achieved transfusion independence, with median weighted average total Hb levels of 11.9 g/dL (min-max: 9.4 – 12.9 g/dL) over a median of 19.4 months of follow-up to date (min-max: 12.3 – 31.4 months). These 17 patients previously required a median of 17.5 transfusions per year (min-max: 11.5 – 37 transfusions per year).

  “Improved iron levels, as measured by serum ferritin and hepcidin levels (proteins involved in iron storage and homeostasis), were observed and trends toward improved iron management were seen. Over half of patients stopped chelation therapy, which is needed to reduce excess iron caused by chronic blood transfusions. Seven out of 23 patients began using phlebotomy for iron reduction.”
A Study Evaluating the Efficacy and Safety of the LentiGlobin BB305 Drug Product in Subjects With Transfusion-Dependent β-Thalassemia, Who Have a β^0/β^0 Genotype (Northstar-3 [HGB-212]). NCT03207009. Yannaki et al 2020.201

- **Patient population/planned enrollment:** Patients (n = 18) aged 50 years or younger with TDT who have a β^0/β^0 genotype
- **Study design:** Phase 3, multicenter, open-label, single-arm study to evaluate the efficacy and safety of betibeglogene autotemcel
- **Primary outcome:** Proportion of treated patients achieving TR from 12 to 24 months after transplantation
- **Secondary outcomes:** Proportion of patients achieving TI from 12 to 24 months after transplantation; percentage of patients with at least a reduction of at least 50% in RBCs transfused from baseline through 12 or 24 months 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 30 September 2019, 13 patients were treated (8 β^0/β^0, 3 β^+IVS1-110/β^+IVS1-110, 2 β^0/β^+IVS1-110 genotypes) and were followed for 8.8 (2.5-20.0) months. Median age at enrollment was 17 (7-33) years; 4 patients were younger than 12 years of age. Median cell dose infused was 9.6 (5.9-15.8) x10^6 CD34+ cells/kg. Nine of 11 patients followed for ≥6 months have discontinued transfusions for ≥3 months. Total unsupported Hb in these patients ranged from 8.3 to 14.2 g/dL at last visit, including 3 patients with total Hb >12.5 g/dL. Beti-cel-derived HbA^T87Q in these 9 patients was 3.8-12.4 g/dL at last visit, contributing 38-92% to total Hb. Soluble transferrin receptor, a marker of ineffective erythropoiesis, improved in these 9 patients at Month 6 (51.8 [35.3-177.7] nmol/L) compared to baseline (109.4 [34.1-214.1] nmol/L). Only two patients had sufficient follow-up to be evaluable for TI and both achieved transfusion independence. The two patients with ≥6 months follow-up who continue to receive RBC transfusions had HbA^T87Q levels of 4.6 g/dL and 0.0 g/dL at last visit (Month 9 and 6, respectively).

“Neutrophil and platelet engraftment occurred at 26 (14-38) days and 41 (21-64) days, respectively. Post-infusion non-hematologic grade ≥3 adverse events (AEs) in ≥3 patients included febrile neutropenia (n=7) and stomatitis (n=5). AEs considered possibly related to beti-cel included abdominal pain (n=2), thrombocytopenia (n=1), leukopenia (n=1) and neutropenia (n=1). There were no deaths, graft failure, or cases of insertional oncogenesis.”

Updated results were presented at the conference and in a June 12, 2020, bluebird bio news release, as follows203:

“As of March 3, 2020, 15 patients (genotypes: 9 β^0/β^0, 3 β^+IVS1-110/β^+IVS1-110, 3 homozygous IVS-1-110 mutation) were treated and had a median follow-up of 14.4 months (min-max: 1.1-24.0 months). Median age at enrollment was 15 (min-max: 4 – 33 years).

“Six of eight evaluable patients achieved transfusion independence, with median weighted average total Hb levels of 11.5 g/dL (min-max: 9.5 - 13.5 g/dL), and continued to maintain transfusion independence for a median duration of 13.6 months (min-max: 12.2 – 21.2 months) as of the data cutoff.

“Eighty-five percent of patients (11/13) with at least seven months of follow-up had not received a transfusion in more than seven months at time of data cutoff. These 11 patients previously required a median of 18.5 transfusions per year (min-max: 11.0 – 39.5 transfusions per year). In these patients, gene therapy-derived HbA^T87Q supported total Hb levels ranging from 8.8-14.0 g/dL at last visit.”
Longterm Follow-up of Subjects With Hemoglobinopathies Treated With Ex Vivo Gene Therapy (LTF-303). Kwiatkowski et al 2020.202

- **Patient population/planned enrollment:** Patients (n = 94) aged up to 50 years with β-thalassemia or severe sickle cell disease who were treated with betibeglogene autotemcel in manufacturer-sponsored clinical trials

- **Study design:** Unphased, multicenter, open-label, randomized, parallel-assignment, follow-up study to assess the long-term safety and efficacy of betibeglogene autotemcel through 15 years

- **Primary outcomes:** Overall survival 15 years after infusion, AEs and serious AEs at 15 years after infusion, vector persistence at 15 years after infusion, monitoring of βA-T87Q-globin at 15 years after infusion, transfusions required at 15 years after infusion, and iron content in the liver and heart, measured by cardiac MRI and blood draws at 15 years after infusion

- **Results presented by study authors:** “As of 3 March 2020, all 32 patients who completed the parent studies (age at enrollment in parent study: 20 [12 – 35] yrs) enrolled in LTF-303 (22 treated in phase 1/2 studies, 10 treated in phase 3 studies). Follow-up post-infusion was 49.1 (23.3 – 71.8) months. PB VCN was detected in all patients at last follow-up (Phase 1/2: 0.4 [0.07 – 4.0] c/dg; Phase 3: 2.0 [0.13 – 3.0] c/dg). Gene therapy-derived Hb, HbA1T87Q, in patients treated in the phase 1/2 studies was stable over time: 6.4 (0.5 – 10.1), 6.7 (0.4 – 10.1), 6.6 (0.5 – 10.7), and 7.1 (2.8 – 11.2) g/dL at months 24 (n=22), 36 (n=22), 48 (n=22), and 60 (n=10). Median HbA1T87Q at month 24 in patients treated in the phase 3 studies was 9.5 (0.9 – 12.4) g/dL (n=10).

  “Of the 32 patients enrolled in LTF-303, TI (defined as a weighted average Hb ≥9 g/dL) without packed red blood cell transfusions for ≥12 months) was achieved in 14/22 (64%) patients treated in phase 1/2 (12 achieved TI during parent study, 2 during LTF-303) and in 9/10 (90%) patients treated in phase 3 (all achieved TI in parent study). All patients remain TI at last follow-up for 39.4 (19.4 – 69.4) months. Weighted average Hb during TI was 10.4 (9.4 – 13.3) and 12.5 (11.9 – 13.5) g/dL in patients treated in the phase 1/2 and phase 3 studies, respectively. In patients who achieved TI in the phase 3 studies, soluble transferrin receptor decreased from 144.1 (65.9 – 235.3) nmol/L at baseline to 54.1 (24.7 – 67.1) nmol/L at Month 24. Patients who achieved TI in HGB-207 had an improved health state today score from 65 – 96 at baseline to 90 – 100 at month 24 (n=8) on the EQ-5D-3L or EQ-5D-Y instrument.

  “All patients were on iron chelation before beti-cell infusion, but post-infusion, only 26/32 (81%) patients restarted iron chelation; of these, 11 have since discontinued chelation. Phlebotomy was used for iron removal in 7/32 patients (22%; 3 patients treated in phase 1/2, 4 patients treated in phase 3) including 3 patients who also used iron chelation. Following an initial increase in liver iron concentration (LIC) after infusion, LIC in patients who achieved TI decreased, particularly in patients with an elevated baseline LIC (Figure). The median decrease in LIC from baseline to month 48 in patients who achieved TI was a 38% reduction (85% reduction to 269% increase; n=13).

  “No drug-product-related AEs were reported >2 years post-infusion. Serious AEs during LTF-303 included gonadotropin insufficiency, ectopic pregnancy, gall bladder wall thickening/polyp, bacteremia with neutropenia, and major depression (all n=1). No deaths, RCL, or insertional oncogenesis were reported. Insertion site analysis as assessed every 6 months until month 60 showed unique insertions accounted for <30% of all insertions indicating polyclonal hematopoiesis.”

**Manufacturers and Regulatory Status**

Betibeglogene autotemcel is manufactured by bluebird bio, Inc (Cambridge, Massachusetts), and is in phase 3 development for treating TDT. FDA had granted betibeglogene autotemcel breakthrough therapy designation in February 2015 for treating TDT major.204

On February 16, 2021, the company announced that a suspected unexpected serious adverse reaction (SUSAR) of acute myeloid leukemia had occurred in a patient treated in a bluebird bio-sponsored trial of LentiGlobin gene therapy for sickle cell disease.205 A second SUSAR of myelodysplastic syndrome was also reported in a LentiGlobin-treated patient. Because
betibeglogene autotemcel is based on the same lentiviral platform as LentiGlobin, FDA placed a clinical hold on the ongoing phase 3 trials of betibeglogene autotemcel. Additionally, bluebird bio suspended marketing of betibeglogene autotemcel in Europe, where it has been approved as Zynteglo.

On February 23, 2021, the company indicated that it was still on track to complete a regulatory filing for betibeglogene autotemcel for treating TDT by mid-2021, pending resolution of FDA safety concerns. On March 10, 2021, bluebird reported that the company’s analysis of the acute myeloid leukemia case suggested that it was unlikely that betibeglogene autotemcel had caused the malignancy and indicated that the company is in dialogue with FDA to resume clinical studies. The company is still investigating the reported case of myelodysplastic syndrome.

**Cost Information**

The company has announced plans to price betibeglogene autotemcel below the $2.1 million in “intrinsic value” that it estimates the therapy delivers. Early estimates by a financial firm put the gene therapy’s price for a one-time infusion 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 betibeglogene autotemcel’s costs for up to 5 years after an initial up-front 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**

Between April 29, 2020, and July 12, 2020, five stakeholders, reflecting caregiver, clinical, and research perspectives, provided comments and ratings on betibeglogene autotemcel. The list below summarizes key stakeholder perspectives.

- Betibeglogene autotemcel interim data are encouraging, suggesting that it might provide a clinically effective and well-tolerated option as a one-time treatment for TDT with potential long-term efficacy.

- Betibeglogene autotemcel might improve patients’ quality of life and decrease demands on the health care system, if the treatment can substantially reduce transfusion dependence, because of the substantial burden that repeat transfusions place on patients in terms of health care facility visits and side effects.

- Betibeglogene autotemcel’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 save costs over time by reducing costs related to transfusion dependence.

- Additional data on all patients who received the gene therapy in the Northstar-2 and Northstar-3 trials as well as longer-term studies are needed to determine betibeglogene autotemcel’s efficacy, duration of effects, and cost-effectiveness. (Stakeholders commented before the December 2020 publication of long-term [49-month] results by Kwiatkowski et al.)
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. The therapy is thought to modulate the immune system to decrease inflammation and muscle degeneration and promote muscle regeneration in patients with Duchenne muscular dystrophy (DMD). It is in phase 2 development.

- 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 *DMD* gene.

- Stakeholders commenting on this topic thought that CAP-1002 might disrupt the care paradigm by shifting from supportive therapy that primarily treats symptoms to the first disease-modifying therapy that might alter the natural history of DMD.

- Stakeholders also thought that CAP-1002 has moderate to large potential to improve patient outcomes and quality of life by preserving upper body strength and reducing heart muscle damage, provided the early demonstrated benefit endures over a longer term.

**Patient Population**

CAP-1002 is intended to treat males aged 10 years or older who have genetically confirmed DMD, can be 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 point mutations or deletions in the dystrophin gene, *DMD*. *DMD* encodes the dystrophin protein, which helps promote muscle function. In patients, the absence of naturally produced (ie, wild-type) dystrophin protein causes progressive muscle fiber cell death (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 signs and symptoms but does not prevent disease progression and has significant side effects. Although FDA has approved 2 gene therapies for patients who have specific mutations in *DMD* (ie, in exon 51 or 53), 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 1/2 trial (ie, HOPE, NCT02485938), which enrolled patients with DMD-associated heart disease, 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 a more usual route, standard intravenous infusion.

In the completed phase 2 HOPE-2 clinical trial, 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 a single ongoing trial for this topic. We present this trial in Table 5.5.1.

Table 5.5.1. 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 Extension of the HOPE-2 Trial (HOPE-2-OLE) NCT04428476</td>
<td>Male children aged 10 years or older and adults (n = 14) who have genetically confirmed DMD, were enrolled in the HOPE-2 trial, and completed 12 months of follow-up</td>
<td>Phase 2, open-label, single-arm extension study to assess continued safety and efficacy of an additional 4 intravenous infusions of CAP-1002 (150 million CDCs) given every 3 months to treat DMD Primary outcomes: Safety—incidence and severity of treatment-emergent AEs; efficacy—change in functional capacity measured on full PUL 2.0 clinical scale, from baseline to 12 months • Secondary outcomes: Changes in midlevel (elbow) and distal-level (wrist/hand) dimensions of the PUL 2.0 clinical scale from baseline to 12 months</td>
<td>Primary and study completion October 2021</td>
</tr>
</tbody>
</table>

Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed phase 2 trial with published results. We summarize this study with results as written in a company 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, can be either ambulatory or nonambulatory, and are receiving stable doses of systemic glucocorticoids
- **Study design**: Phase 2, randomized, double-blind, parallel-assignment study to evaluate the efficacy of CAP-1002 vs 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:** Top-line efficacy data reported in a table in the news release are shown in Table 5.5.2 and Table 5.5.3.

Table 5.5.2. Upper Limb Function Results (12-Month Time Point)\(^a\)

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>CAP-1002(^b) (n = 8)(^c)</th>
<th>Placebo(^b) (n = 12)(^c)</th>
<th>(P) value(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midlevel PUL (version 1.2)</td>
<td>−2.1 (3.63)</td>
<td>−4.9 (2.57)</td>
<td>0.08</td>
</tr>
<tr>
<td>Shoulder + mid + distal PUL (version 1.2)</td>
<td>−2.3 (3.86)</td>
<td>−6.4 (3.84)</td>
<td>0.03</td>
</tr>
<tr>
<td>Shoulder + mid + distal PUL (version 2.0)</td>
<td>−1.3 (2.14)</td>
<td>−3.7 (1.50)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Abbreviations: \(P\), probability; PUL, Performance of the Upper Limb.

\(^a\)Mixed model repeated measures analysis.

\(^b\)Mean change from baseline to 12 months (standard deviation).

\(^c\)Intent-to-treat population.

\(^d\)Nominal values unadjusted for multiple testing.

Table 5.5.3. Cardiac Function Results (12-Month Time Point)\(^a\)

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>CAP-1002(^b) (n = 8)(^c)</th>
<th>Placebo(^b) (n = 12)(^c)</th>
<th>(P) value(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV ejection fraction, %</td>
<td>−0.33 (2.01)</td>
<td>−1.89 (2.23)</td>
<td>0.004</td>
</tr>
<tr>
<td>LV end-diastolic volume, indexed mL/m(^2)</td>
<td>−7.35 (6.10)</td>
<td>0.00 (7.34)</td>
<td>0.07</td>
</tr>
<tr>
<td>LV end-systolic volume, indexed mL/m(^2)</td>
<td>−3.10 (1.68)</td>
<td>1.70 (5.02)</td>
<td>0.01</td>
</tr>
<tr>
<td>Creatine Kinase-MB (% of total CK)</td>
<td>−0.50 (0.55)</td>
<td>2.00 (1.00)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Abbreviations: CK, creatine kinase; LV, left ventricular; MB, myocardial; \(P\), probability.

\(^a\)Mixed model repeated measures analysis.

\(^b\)Mean change from baseline to 12 months (standard deviation).

\(^c\)Intent-to-treat population.

\(^d\)Nominal values unadjusted for multiple testing.

**Manufacturers and Regulatory Status**

CAP-1002 is being developed by [Capricor Therapeutics, Inc (Beverly Hills, California)](https://www.capricor.com), and is in phase 2 clinical development for treating DMD. For this indication, FDA granted the drug orphan drug designation in April 2015,\(^{215}\) rare pediatric disease designation in July 2017,\(^{216}\) and regenerative medicine advanced therapy designation in February 2018.\(^{217}\)

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.\textsuperscript{218} The patient recovered fully from the event, and the HOPE-2 trial dosing resumed in February 2019.\textsuperscript{219}

Cost Information

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

Key Stakeholder Perspectives

Between December 10, 2020, and January 11, 2021, nine stakeholders, reflecting caregiver, health systems, nursing, patient representative, physician, and research perspectives, provided comments and ratings on CAP-1002 for treating DMD. The list below summarizes key stakeholder perspectives.

- CAP-1002 has moderate to large potential to improve patient health outcomes and quality of life by preserving upper body strength and reducing heart muscle damage. However, additional data will be needed to demonstrate that these improvements can be maintained over a longer term.

- In one respect, CAP-1002 could reduce disparities in access because it might offer an effective therapeutic option to patients with more advanced DMD (ie, nonambulatory), a traditionally underserved group with limited options.

- Conversely, it could increase disparities based on a patient’s insurance coverage, given the anticipated high treatment cost and possible limited geographic availability at only specialty DMD programs.

- CAP-1002 could disrupt the care paradigm by moving beyond treating signs and symptoms to offer the first approach that can potentially change the natural history of DMD.

- CAP-1002 widens the treatment scope to all patients with DMD, compared with exon-skipping therapies targeted only to population subsets with specific genetic mutations.

Casimersen (Amondys 45) to Treat Duchenne Muscular Dystrophy

Highlights

- Casimersen is a DNA analogue given to patients with Duchenne muscular dystrophy (DMD). Casimersen purportedly binds exon 45 of dystrophin pre-messenger RNA (pre-mRNA) and promotes skipping of exon 45 during mRNA processing. These molecular actions allow synthesis of a shorter, but functional, dystrophin protein.

- In February 2021, FDA granted accelerated approval for casimersen to treat patients with DMD who have a confirmed mutation of the dystrophin gene, $DMD$, that is amenable to exon 45 skipping (a subset of about 8\%). Continued approval might require verification of clinical benefit in confirmatory trials.

- Treatment with casimersen requires weekly intravenous infusions in a health care setting.
• Estimated annual treatment costs, based on weight, range from about $350,000 for a child weighing about 23 kg (50 lb), to $1 million or more for an adult.

• Stakeholders commenting on this topic generally agreed that casimersen could improve patient health outcomes and quality of life, but more data are needed to determine its clinical efficacy and potential impact on patient-oriented outcomes.

• Stakeholders also thought that 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 (Amondys 45, also known as SRP-4045) is a phosphorodiamidate morpholino oligomer, or DNA analogue. It is intended to treat DMD, an inherited, chromosome X–linked genetic disorder caused by point mutations or deletions in the dystrophin gene, DMD. DMD encodes the dystrophin protein, which helps promote muscle function. The absence of naturally produced (ie, wild-type) dystrophin protein causes progressive muscle fiber death (necrosis) and eventual widespread muscle weakness. The Muscular Dystrophy Association website provides more information on DMD.

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

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. These molecular actions allow synthesis of a shorter, but functional, dystrophin protein. Therefore, casimersen treatment might promote skeletal muscle function and prevent or delay disease progression in patients with DMD who have DMD exon 45 mutations (about 8% of these patients).

According to FDA-approved labeling, the recommended dose of casimersen is 30 mg/kg given once weekly as an intravenous infusion over 35 to 60 minutes.
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 5.6.

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>Study of SRP-4045 and SRP-4053 in DMD Patients (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 3, multicenter, randomized, double-blind, parallel-assignment study to evaluate the efficacy and safety of casimersen (SRP-4045) 30 mg/kg or golodirsen (SRP-4053) 30 mg/kg vs 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>
<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>
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</tr>
<tr>
<td>An Extension Study to Evaluate Casimersen or Golodirsen in Patients With Duchenne Muscular Dystrophy <a href="https://clinicaltrials.gov/ct2/results?term=NCT03532542">NCT03532542</a></td>
<td>Male children (n = 260) aged 7 to 23 years with genetically confirmed DMD, who have a mutation in the DMD gene that is amenable to exon 45 or 53 skipping, who are on a stable dose of corticosteroids, and who completed a prior study on casimersen or golodirsen</td>
<td>Phase 3, nonrandomized, open-label, parallel-assignment study to evaluate the safety and tolerability of long-term (144-week) treatment with casimersen 30 mg/kg or golodirsen 30 mg/kg</td>
<td>Primary and study completion August 2026</td>
</tr>
</tbody>
</table>

Abbreviations: DMD, Duchenne muscular dystrophy; DMD, dystrophin gene; FVC, forced vital capacity; IHC, immunohistochemistry; NSAA, North Star Ambulatory Assessment; SAEs, serious adverse events; WB, Western blot.

Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed phase 3 trial with published results. We summarize this study with results as written in a company news release.

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


- **Patient population/planned enrollment:** 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
- **Study design:** Phase 3, randomized, double-blind, parallel-assignment study to evaluate the efficacy and safety of casimersen (SRP-4045) 30 mg/kg or golodirsen (SRP-4053) 30 mg/kg vs 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.

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), manufactures casimersen. On February 25, 2021, FDA granted accelerated approval to the new drug application (NDA) for casimersen injection, under the trade name Amondys 45, to treat DMD in patients with a confirmed genetic mutation amenable to skipping exon 45.\(^{222,225}\)

The accelerated approval was based on an increase in dystrophin production in skeletal muscle observed in patients treated with casimersen. Continued approval might be contingent on verification of a clinical benefit in confirmatory trials.\(^{223}\) According to FDA, this is the first targeted treatment it has approved for patients with a mutation amenable to exon 45 skipping, who make up about 8% of all patients with DMD.\(^{222}\)

FDA previously granted casimersen drug orphan drug, fast track, and priority review designations for this indication.\(^{222,226}\)

Sarepta received FDA approval for another DMD therapy, golodirsen, in December 2019.\(^{227}\)

Cost Information

The treatment cost for casimersen is based on patient weight, with an annual retail price for a child weighing between 20 and 23 kg (45 and 50 lb) averaging $300,000 to $350,000. Treatment for an adult may approach an estimated $1 million or more per year. These costs are reportedly comparable to other, similar treatments approved for subsets of patients with DMD.\(^{228,229}\)

Key Stakeholder Perspectives

Between August 25, 2020, and September 4, 2020, and before FDA approval of casimersen, 9 stakeholders, reflecting caregiver, health systems, patient, physician, and research perspectives, provided comments and ratings on casimersen. 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. However, more data are needed to determine the magnitude of increased dystrophin production that 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 and its diffusion into clinical use might be cost-prohibitive, placing strain on payers, health care facilities, and patients, especially if there are insurance coverage challenges.

• More data are needed to assess long-term efficacy of casimersen and should include outcomes that are more patient-oriented than dystrophin protein production.

Fosdenopterin (Nulibry) to Treat Molybdenum Cofactor Deficiency Type A

Highlights

• Molybdenum cofactor deficiency (MoCD) type A is an ultra-rare, life-threatening genetic metabolic disorder characterized by loss of the molybdenum cofactor (MoCo).

• MoCD causes catastrophic and irreversible neurologic damage within the first weeks of life, and no effective treatments exist for MoCD type A. Care is mostly supportive.

• Fosdenopterin is a substrate replacement therapy that restores levels of a compound absent in patients with MoCD type A that is an essential precursor in MoCo biosynthesis.

• In February 2021, FDA approved fosdenopterin to treat patients who have MoCD type A.

• Stakeholders commenting on this topic thought that, as the first disease-modifying therapy for MoCD type A, fosdenopterin has substantial potential to improve patient outcomes and disrupt the current paradigm of care.

• Stakeholders also thought that clinical trial results had been reported for only a small number of patients and that results from ongoing trials would need to confirm the results observed in this small patient population.

Patient Population

Fosdenopterin is intended for patients with MoCD type A.

Intervention

MoCD type A is caused by loss-of-function variants in a gene called the molybdenum cofactor synthesis 1 gene, MOCS1. These genetic variants prevent the conversion of guanosine triphosphate into cyclic pyranopterin monophosphate (cPMP), an essential metabolic intermediate needed to produce sufficient levels of MoCo.230,231

MoCo is a major component of the enzyme sulfite oxidase, which normally helps clear sulfite, a potent neurotoxin, from the body. Buildup of sulfite is believed to cause the rapid, severe damage to the central nervous system seen in patients with MoCD type A.230-232 The National Library of Medicine’s MedlinePlus Genetics website offers more information about MoCD.

Fosdenopterin (Nulibry, formerly ORGN001 or BBP-870) is a synthetic cPMP intended for use as a substrate replacement therapy. By restoring cPMP levels, fosdenopterin is thought to increase MoCo biosynthesis, which would, in turn, restore sulfite oxidase activity to allow sulfite removal and prevent neurotoxicity.233,234
According to the FDA-approved prescribing information, fosdenopterin is given daily, intravenously, at an initial dose of 0.4 mg/kg for preterm neonates and 0.55 mg/kg for term neonates. Daily fosdenopterin dose is increased at months 1 and 3 to a maximum dose of 0.9 mg/kg once 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 5.7.

**Table 5.7. 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>Safety &amp; Efficacy Study of ORGN001 (Formerly ALXN1101) in Pediatric Patients With MoCD Type A Currently Treated With rcPMP NCT02047461 See results summarized from the Nulibry prescribing information under Recently Completed and Ongoing Trials With Available Results</td>
<td>Children (age not specified; n = 7) with a genetically confirmed diagnosis of MoCD type A being treated with rcPMP infusions at time of enrollment (rcPMP was an investigational cPMP replacement therapy available to a small number of patients on a named-patient basis)</td>
<td>Phase 2, open-label, single-arm, dose-escalation study to assess the safety and efficacy of fosdenopterin to treat MoCD type A Primary outcome: Safety, measured by type, number, and frequency of AEs and SAEs</td>
<td>Primary and study completion December 2021</td>
</tr>
<tr>
<td>Study of ORGN001 (Formerly ALXN1101) in Neonates With Molybdenum Cofactor Deficiency (MoCD) Type A NCT02629393 See results summarized from the Nulibry prescribing information under Recently Completed and Ongoing Trials With Available Results</td>
<td>Children aged up to 28 days (n = 5) with a diagnosis of MoCD type A</td>
<td>Phase 2/3, open-label, single-arm study evaluating the safety and efficacy of fosdenopterin to treat MoCD type A Primary outcome: Treatment response, defined as patients alive and able to sit upright independently for at least 30 seconds at 12 months</td>
<td>Primary and study completion December 2021</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency; rcPMP, recombinant Escherichia coli-derived cyclic pyranopterin monophosphate; SAE, serious adverse event.
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 study with results as written in an abstract of a published study. We also present data from 2 additional trials as summarized in the fosdenopterin prescribing information.

The following abbreviations are used in this section: cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency; rcPMP, recombinant *Escherichia coli*–derived cyclic pyranopterin monophosphate; SD, standard deviation; SSC, S-sulfocysteine.

Safety & Efficacy Study of ORGN001 (Formerly ALXN1101) in Pediatric Patients With MoCD Type A Currently Treated With rcPMP NCT02047461 and Study of ORGN001 (Formerly ALXN1101) in Neonates With Molybdenum Cofactor Deficiency (MOCD) Type A NCT02629393, Origin Biosciences, Inc.

- **Patient population/planned enrollment:** Newborn children with clinical and biochemical evidence of MoCD type A, including 8 patients enrolled in study NCT02047461 (study 1), 1 patient enrolled in study NCT02629393 (study 2), and 4 patients treated in an observational study of rcPMP (see data by Schwahn et al, below). Note that the patients represented here partially overlap with those presented by Schwahn et al.
- **Study design:** Prospective, observational, single-arm studies to assess the use of fosdenopterin or rcPMP to treat patients who have MoCD type A. The rcPMP was an investigational cPMP replacement therapy available to a small number of patients on a named-patient basis.
- **Primary outcomes:** Safety and efficacy
- **Results presented by study authors:** “Efficacy was assessed by comparing overall survival in pediatric patients treated with NULIBRY or rcPMP (n=13) with an untreated natural history cohort of pediatric patients with genetically confirmed MoCD Type A who were genotype-matched to the treated patients (n=18). Patients treated with NULIBRY or rcPMP had an improvement in overall survival compared to the untreated, genotype-matched, historical control group (Table 4 and Figure 1). Results were similar when comparing treated patients with all patients in the untreated natural history cohort 10 with genetically confirmed MoCD Type A (n=37, includes the 18 genotype-matched untreated patients as well as 19 additional untreated patients who were not genotype-matched).

“Treatment with NULIBRY resulted in a reduction in urine concentrations of SSC in patients with MoCD Type A and the reduction was sustained with long-term treatment over 48 months. The baseline level of urinary SSC normalized to creatinine was characterized in one patient (Study 2) with a value of 89.8 µmol/mmol. Following treatment with NULIBRY in Studies 1 and 2 (n=9), the mean ± SD levels of urinary SSC normalized to creatinine ranged from 11 (±8.5) to 7 (±2.4) µmol/mmol from Month 3 to Month 48.

Efficacy and Safety of Cyclic Pyranopterin Monophosphate Substitution in Severe Molybdenum Cofactor Deficiency Type A: A Prospective Cohort Study. Schwahn et al 2015.

- **Patient population/planned enrollment:** Newborn children with clinical and biochemical evidence of MoCD type A (n = 11) or type B (n = 5). Note that data for the patients represented here partially overlap with those presented in the Nulibry prescribing information, above.
- **Study design:** Prospective, observational, single-arm study to assess compassionate use of intravenous rcPMP (80 to 320 µg/kg/day) to treat MoCD type A or B. The rcPMP was an investigational cPMP replacement therapy available to a small number of patients on a named-patient basis.
- **Primary outcomes:** Safety and efficacy
- **Results presented by study authors:** “Between June 6, 2008, and Jan 9, 2013, intravenous cPMP was started in 16 neonates diagnosed with MoCD (11 type A and five type B) and continued in eight type A
patients for up to 5 years. We observed no drug-related serious adverse events after more than 6000 doses. The disease biomarkers urinary S-sulphocysteine, xanthine, and urate returned to almost normal concentrations in all type A patients within 2 days, and remained normal for up to 5 years on continued cPMP substitution. Eight patients with type A disease rapidly improved under treatment and convulsions were either completely suppressed or substantially reduced. Three patients treated early remain seizure free and show near-normal long-term development. We detected no biochemical or clinical response in patients with type B disease.”

Manufacturers and Regulatory Status

Origin Biosciences (Palo Alto, California), an affiliate of BridgeBio Pharma (Palo Alto, California), manufactures fosdenopterin. On February 26, 2021, FDA approved fosdenopterin, under the trade name Nulibry, for injection to reduce the risk of death due to MoCD type A. The new drug application for fosdenopterin was reviewed under FDA’s priority review program. The agency had previously granted fosdenopterin orphan drug and breakthrough therapy designations for this indication.

Cost Information

According to a media report, fosdenopterin costs about $500 000 per patient per year of treatment.

Key Stakeholder Perspectives

Between May 8, 2020, and July 27, 2020, six stakeholders, reflecting health systems, nursing, research, and physician perspectives, provided comments and ratings on fosdenopterin to treat MoCD type A. The list below provides a summary of key stakeholder perspectives.

- Fosdenopterin represents a promising disease-modifying treatment for a disease with no such therapy. As such, fosdenopterin has substantial potential to improve patient health outcomes.

- Although promising, results are available for only a small number of cPMP-treated patients. For fosdenopterin to be adopted, the 2 ongoing studies of fosdenopterin (synthetic cPMP) would need to confirm results observed for recombinant cPMP in earlier trials.

- As a disease-modifying therapy, fosdenopterin might cause substantial disruption of MoCD type A treatment paradigms. In addition, the requirement for daily intravenous dosing might place a substantial treatment burden on patients and caregivers.

- Fosdenopterin is likely to be very costly, which could increase existing disparities based on socioeconomic status. Effects of fosdenopterin adoption on the health care system would be minimized by the small number of patients affected by MoCD type A. Additionally, fosdenopterin, if effective, could reduce costs associated with supportive care.
Human Plasminogen (Ryplazim) to Treat Congenital Plasminogen Deficiency

Highlights

• Ryplazim is an intravenously administered, purified plasminogen concentrate under study for treating patients with congenital plasminogen deficiency.

• A rare disease, congenital plasminogen deficiency is caused by genetic variants in the plasminogen gene and characterized by the formation of fibrin-rich lesions in mucous membranes throughout the body.

• No treatments are FDA-approved for treating congenital plasminogen deficiency, and untreated lesions can cause long-term consequences that impact patient quality of life.

• Stakeholders commenting on this topic thought that the available clinical data on human plasminogen suggest that it has substantial potential to improve outcomes in patients with congenital plasminogen deficiency, basing their opinions on the observed improvement in plasminogen levels and effect on congenital plasminogen deficiency-related lesions.

• Stakeholders also thought that human plasminogen would substantially disrupt the treatment of patients with congenital plasminogen deficiency because it is the first FDA-approved treatment and because of its requirement for frequent, ongoing intravenous infusions.

Patient Population

Human plasminogen is intended for children aged 2 years or older and adults with a diagnosis of congenital plasminogen deficiency.

Intervention

Congenital plasminogen deficiency is a genetic disease caused by loss-of-function variants in the plasminogen gene, PLG.239 A rare disease, congenital plasminogen deficiency occurs in an estimated 1.6 cases per 1 million population.

The disease leads to a deficiency in plasminogen, a zymogen (an inactive form of an enzyme) whose active form is plasmin. Plasmin serves a key role in lysis of the protein fibrin. The main clinical manifestation of this deficiency is the formation of fibrin-rich, woody extravascular lesions in mucous membranes throughout the body.240,241

Patients with congenital plasminogen deficiency can develop lesions in the conjunctival membranes of the eye and eyelid, which can lead to vision impairment or blindness if left untreated. Lesions can also form in the respiratory tract, possibly leading to respiratory failure, and in the central nervous system, potentially leading to occlusive hydrocephalus. Other affected tissues include mucous membranes in the ears, nasopharynx, oral cavity, gastrointestinal tract, and genitourinary tract. No FDA-approved treatments are available for patients with this disease.242

Human plasminogen replacement therapy (Ryplazim) is under study for treating patients who have congenital plasminogen deficiency. It consists of a purified Glu-plasminogen concentrate isolated from human plasma.242 The replacement therapy is intended to restore adequate levels of plasminogen activity in these patients, correcting symptoms of the disease. Glu-plasminogen,
characterized by a glutamate residue at its amino terminus, is the predominant form of circulating plasminogen and is rapidly converted to the more easily cleaved Lys-plasminogen upon binding to a fibrin clot.

In clinical trials, Glu-plasminogen is given intravenously at a dose of 6.6 mg/kg. Dosing frequency is once every 2, 3, or 4 days, depending on a patient’s individual pharmacokinetic profile (ie, level of drug activity based on its absorption, distribution, metabolization, and excretion).243

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 phase 2/3 trial with published results.242 We summarize results as written in the abstract of a published paper.

The following abbreviation is used in this section: IV, intravenous.

A Study of Prometic Plasminogen IV Infusion in Subjects With Hypoplasminogenemia. NCT02690714. Shapiro et al 2018.242

- **Patient population/planned enrollment:** Children and adults (n = 15) aged 2 to 80 years with a diagnosis of congenital plasminogen deficiency and a plasminogen activity level ≤ 45%
- **Study design:** Phase 2/3, single-arm, open-label trial of the safety and efficacy of IV plasminogen divided into 3 segments. In segment 1, patients received a single IV infusion of plasminogen (6.6 mg/kg) to determine the individual's pharmacokinetic profile. In segment 2, patients received repeated doses of IV plasminogen every second, third, or fourth day for 12 weeks. In segment 3, patients continued receiving repeat doses of plasminogen at established dosing.
- **Primary outcomes:** Trough plasminogen activity levels during segment 2, number of lesions after 48 weeks of treatment, size of lesions after 48 weeks, spirometry results after 48 weeks in patients with bronchial lesions

**Results presented by study authors:** “Reported here are data on 14 patients who completed at least 12 weeks of treatment. The primary end point was an increase in trough plasminogen activity levels by at least an absolute 10% above baseline. The secondary end point was clinical success, defined as ≥50% improvement in lesion number/size or functionality impact from baseline. All patients achieved at least an absolute 10% increase in trough plasminogen activity above baseline. Clinical success was observed in all patients with clinically visible (conjunctiva and gingiva), nonvisible (nasopharynx, bronchus, colon, kidney, cervix, and vagina), and wound-healing manifestations of the disease. Therapeutic effects were rapid, as all but 2 lesions resolved or improved after 4 weeks of treatment. Human Glu-plasminogen was well tolerated in both children and adults.”

Manufacturers and Regulatory Status

Liminal BioSciences (Laval, Québec, Canada), previously known as Prometic Life Sciences, is developing Ryplazim. The developer has submitted a biologics license application (BLA) to FDA for Ryplazim to treat patients with congenital plasminogen deficiency. The Prescription Drug User Fee Act (PDUFA)–prescribed decision date for the BLA is June 5, 2021.244

The BLA was originally submitted in 2017 and received a complete response letter from FDA that purportedly identified the need for changes to the chemistry, manufacturing, and controls section of the application.245,246 FDA accepted a resubmission of the BLA in September

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FDA had previously granted Ryplazim orphan drug and rare pediatric disease designations to treat congenital plasminogen deficiency.\textsuperscript{246}

**Cost Information**

Cost information is currently unavailable for this topic. However, as a drug intended to treat a rare orphan disease, Ryplazim is likely to have a high per-patient cost.

**Key Stakeholder Perspectives**

Between February 5, 2021, and March 4, 2021, eight stakeholders, reflecting clinical, health systems, nursing, and research perspectives, provided comments and ratings on human plasminogen to treat congenital plasminogen deficiency. The list below provides a summary of key stakeholder perspectives.

- Human plasminogen could address a substantial unmet need in patients with congenital plasminogen deficiency, given the lack of available treatments for this condition.
- Initial data on human plasminogen replacement therapy demonstrated an increase in plasminogen levels and a decrease in the number and size of disease-related lesions, suggesting that the rationale behind the treatment is sound and that the treatment has substantial potential to improve patient health outcomes. However, published data covers only 12 weeks of treatment and the long-term efficacy of the treatment is unclear.
- If Ryplazim is approved by FDA, it would represent the first treatment approved for patients with congenital plasminogen deficiency and, therefore, substantially disrupt patient management. Additionally, the requirement for repeated intravenous infusions could require frequent visits to infusion centers for treatment, which would cause substantial disruption for patients and caregivers.
- Although approval of Ryplazim would substantially disrupt the management of patients with congenital plasminogen deficiency, the small number of patients affected by this disease would limit the magnitude of disruption to the overall health care system.

**Lumasiran (Oxlumo) to Treat Primary Hyperoxaluria Type 1**

**Highlights**

- Lumasiran is an RNA interference (RNAi) therapeutic intended to prevent kidney stone formation, kidney damage, and eventual dialysis by reducing accumulation of harmful oxalate crystals.
- In November 2020, FDA approved lumasiran for reducing urinary oxalate levels in children and adults. A health care provider delivers the drug as an injection under the skin every 1 to 3 months, according to weight-based dosing recommendations.
- The drug has a reported average list price of about $493 000 per year, although the manufacturer asserts that rebates would likely cut the average net cost per patient to about $380 000 per year. The manufacturer is reportedly working with third-party payers on value-based agreements that outline payments to manufacturers for achieving treatment...
success milestones and rebates to payers if actual primary hyperoxaluria type 1 (PH1) diagnoses and drug use exceed anticipated levels.

- Stakeholders commenting on this topic thought that lumasiran could largely shift PH1 management to a disease prevention model and away from managing complications from progressive stone formation and kidney damage.

Patient Population

Lumasiran is intended for patients of any age who have PH1.

Intervention

PH1 is a rare inherited disorder characterized by development of kidney and bladder stones from the buildup of excessive oxalate crystals. As the disease progresses, kidney function declines, and the excessive oxalate buildup in plasma becomes life-threatening.\textsuperscript{247,248} Before lumasiran’s FDA approval, no drug treatments were available for PH1, and disease management included treatment of symptoms and organ transplantation.\textsuperscript{247,249,250} The National Institutes of Health’s Genetic and Rare Diseases Information Center website offers more information about PH1.

Lumasiran (Oxlumo) is an RNAi therapeutic intended to reduce glycolate oxidase (GO) expression.\textsuperscript{251} GO is a key enzyme in the oxalate metabolic pathway that catalyzes oxalate formation and its precursor glyoxylate. Lumasiran purportedly targets the messenger RNA of the hydroxyacid oxidase 1 gene, \textit{HAO1}, that encodes GO in the liver, thereby reducing oxalate production and buildup. Lumasiran is intended to improve health outcomes and reduce disease burden in patients with PH1 who have oxalate accumulation in the kidneys and the urinary tract.\textsuperscript{247,250}

According to the FDA-approved labeling, lumasiran is given by a health care professional as an injection under the skin. Dosage is 3 or 6 mg/kg once monthly for 3 months and then 3 or 6 mg/kg once every 1 or 3 months. Dose and frequency depend on patient weight.\textsuperscript{252}
Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 4 ongoing trials for this topic. We present them in Table 5.8.

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>A Study to Evaluate Lumasiran in Children and Adults With PH1 ILLUMINATE-A NCT03681184 See preliminary results by Garrelfs et al 2021 and Alnylam Pharmaceuticals 2020 under Recently Completed and Ongoing Trials With Available Results</td>
<td>Patients aged 6 years or older (n = 39) with a diagnosis of PH1 and an eGFR &lt; 30 mL/min/1.73 m²</td>
<td>Phase 3, double-blind, randomized trial to compare the efficacy and safety of lumasiran injection compared with placebo to treat PH1 Primary outcome: Percentage change in 24-hour UOx excretion corrected for BSA up to 6 months Selected secondary outcomes: • Percentage change in 24-hour UOx to creatinine ratio from baseline up to 6 months • Percentage of patients with 24-hour UOx corrected for BSA at or below ULN or at or below 1.5 times ULN up to 6 months • Change in eGFR up to 6 months • Change in plasma oxalate up to 6 months Rate of kidney stone events</td>
<td>Primary completion November 2019 Study completion January 2024</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>
</tbody>
</table>
| A Study of Lumasiran in Infants and Young Children With PH1 ILLUMINATE-B NCT03905694 | Infants and children aged up to 5 years (n = 18) with a diagnosis of PH1 | Phase 3, single-group, open-label study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran injection  
Primary outcome: Percentage change in UOx excretion up to 6 months  
Selected secondary outcomes:  
• Percentage change in UOx excretion up to 60 months  
• Percentage of patients with UOx excretion at or below the ULN and at or below 1.5 times the ULN up to 60 months  
• Change in eGFR up to 60 months  
• Frequency of AEs up to 60 months | Primary completion June 2020  
Study completion August 2024 |
| A Study to Evaluate Lumasiran in Patients With Advanced PH1 ILLUMINATE-C NCT04152200 | Patients of all ages (n = 21) with a diagnosis of PH1 and eGFR ≤ 45 mL/min/1.73 m² for patients 12 months of age or older. Patients younger than 12 months must have serum creatinine considered elevated for their age. | Phase 3, single-group, open-label study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran injection  
Primary outcomes:  
• Percentage change in plasma oxalate up to 6 months  
• Percentage change in predialysis plasma oxalate up to 6 months  
Select secondary outcomes:  
• Absolute change in plasma oxalate up to 60 months  
• Change in frequency of dialysis up to 60 months  
• Change in eGFR up to 60 months  
• Change in Quality of Life eGFR assessed on PedsQL and KDQOL up to 60 months | Primary completion May 2021  
Study completion July 2025 |
Study name and National Clinical Trials identifier | Patient population and planned enrollment | Study design and outcomes | Estimated date of completion
---|---|---|---
An Extension Study of an Investigational Drug, Lumasiran (ALN-GO1), in Patients With Primary Hyperoxaluria Type 1  NCT03350451  
See preliminary results by Alnylam Pharmaceuticals 2020 under Recently Completed and Ongoing Trials With Available Results | Patients (n = 20) aged 6 years or older with confirmed PH1 who completed a previous lumasiran trial within the past 12 months | Phase 2, single-group, open-label extension study to evaluate the long-term safety and tolerability of lumasiran injection to treat PH1  
Primary outcome: Incidence of AEs up to about 1600 days (4.4 years)  
Selected secondary outcomes:  
- Change in 24-hour UOx corrected for BSA over time  
- Change in 24-hour UOx to creatinine ratio over time  
Change in eGFR over time | Primary and study completion June 2023

Abbreviation: AE, adverse event; BSA, body surface area; eGFR, estimated glomerular filtration rate; KDQOL, Kidney Disease Quality of Life; PedsQL, Pediatric Quality of Life Inventory; PH1, primary hyperoxaluria type 1; ULN, upper limit of normal; UOx, urinary oxalate.

Recently Completed and Ongoing Trials With Available Results
Our searches identified 3 recently completed late-phase trials with published results.\textsuperscript{250,253} We summarize results as written in the abstract of a published study and a company news release.

The following abbreviations are used in this section: AE, adverse event; BSA, body surface area; DB, double-blind; eGFR, estimated glomerular filtration rate; ISR, injection-site reaction; P, probability; PH1, primary hyperoxaluria type 1; SAE, serious adverse event; ULN, upper limit of normal; UOx, urinary oxalate.

A Study to Evaluate Lumasiran in Children and Adults With Primary Hyperoxaluria Type 1 (ILLUMINATE-A).  
NCT03681184. Garrelfs et al 2021,\textsuperscript{250} Alnylam Pharmaceuticals 2020.\textsuperscript{253}

- **Patient population/planned enrollment:** Patients (n = 39) aged 6 years or older with PH1 randomly assigned to lumasiran injection (n = 26) or placebo (n = 13)
- **Study design:** Phase 3, double-blind, randomized trial to compare the efficacy and safety of lumasiran injection compared with placebo to treat PH1
- **Primary outcome:** Percentage change in 24-hour UOx excretion corrected for BSA up to 6 months
- **Selected secondary outcomes:** Percentage change in 24-hour UOx to creatinine ratio from baseline up to 6 months, percentage of patients with 24-hour UOx corrected for BSA at or below ULN or below 1.5 times ULN up to 6 months, change in eGFR up to 6 months, change in plasma oxalate up to 6 months, and rate of kidney stone events
- **Results presented by study authors:** “The least-squares mean difference in the change in 24-hour urinary oxalate excretion (lumasiran minus placebo) was −53.5 percentage points (P<0.001), with a reduction in the lumasiran group of 65.4% and an effect seen as early as month 1. The between-group differences for all hierarchically tested secondary end points were significant. The difference in the percent change in the plasma oxalate level (lumasiran minus placebo) was −39.5 percentage points (P<0.001). In the lumasiran group, 84% of patients had 24-hour urinary oxalate excretion no higher than 1.5 times the upper limit of the normal range at month 6, as compared with 0% in the placebo
group (P<0.001). Mild, transient injection-site reactions were reported in 38% of lumasiran-treated patients.250

“As of the data cut-off date of May 1, 2020, results from the extension period of the ILLUMINATE-A Phase 3 study showed that patients initially randomized to lumasiran in the 6-month double-blind (DB) period who continued treatment with lumasiran through Month 12 (“lumasiran/lumasiran”; N=24) maintained their reduction in 24-hour urinary oxalate excretion, with a 64 percent mean reduction relative to baseline. The majority (88 percent) of patients in this group reached normal or near-normal levels (at or below 1.5x ULN) of urinary oxalate. In patients who were originally randomized to placebo in the DB period but crossed over to lumasiran (“placebo/lumasiran”; N=13), treatment with lumasiran led to a 57 percent mean reduction in 24-hour urinary oxalate excretion after six months of treatment; 77 percent of these patients reached urinary oxalate levels at or below 1.5 x ULN.”253

A Study of Lumasiran in Infants and Young Children With Primary Hyperoxaluria Type 1 (ILLUMINATE-B). NCT03905694. Alnylam Pharmaceuticals 2020.253

- Patient population/planned enrollment: Infants and children aged up to 5 years (n = 18) with a diagnosis of PH1
- Study design: Phase 3, single-group, open-label study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran injection in young children
- Primary outcome: Percentage change in UOx excretion up to 6 months
- Selected secondary outcomes: Percentage change in UOx excretion at or below the ULN and at or below 1.5 times the ULN up to 60 months, change in eGFR up to 60 months, and frequency of AEs up to 60 months
- Results presented by study authors: “Treatment with lumasiran in ILLUMINATE-B led to a 72 percent mean reduction in spot urinary oxalate:creatinine ratio from baseline to Month 6, averaged across months 3 to 6 – the primary endpoint of the study. Lumasiran also demonstrated positive results across secondary endpoints, including proportion of patients (9/18 or 50 percent) achieving urinary oxalate levels at or below 1.5 times ULN.

“Preliminary analysis of exploratory endpoints indicated improvements in nephrocalcinosis in 8 out of 18 patients (44 percent), while estimated glomerular filtration rates (eGFR) remained stable. At baseline, 14 of 18 patients had nephrocalcinosis. After 6 months of lumasiran treatment, no patients worsened, 10 remained stable, and eight showed bilateral (3 out of 8) or unilateral (5 out of 8) improvements in nephrocalcinosis. As expected, given the 6-month duration of the study, there was no change in the rate of renal stone events (RSEs).

“The most common drug-related adverse events (AEs) were mild and transient injection site reactions (ISRs) reported in 3 of 18 (17 percent) patients. No clinically relevant changes in laboratory measures (including liver function tests), vital signs, or electrocardiograms related to lumasiran were observed.”

An Extension Study of an Investigational Drug, Lumasiran (ALN-GO1), in Patients With Primary Hyperoxaluria Type 1. NCT03350451. Alnylam Pharmaceuticals 2020.253

- Patient population/planned enrollment: Patients (n = 20) aged 6 years or older with confirmed PH1 who completed a previous lumasiran trial within past 12 months
- Study design: Phase 2, single-group, open-label extension study to evaluate the long-term safety and tolerability of lumasiran injection to treat PH1
- Primary outcome: Incidence of AEs up to about 1600 days (4.4 years)
- Selected secondary outcomes: Change in 24-hour UOx corrected for BSA over time, change in 24-hour UOx:creatinine ratio over time, and change in eGFR over time

Results presented by study authors: “As of January 30, 2020, data cut-off date, patients continued to experience sustained reductions in urinary oxalate excretion, with similar responses across dosage regimens. Specifically, ongoing treatment with lumasiran resulted in 74 percent (range: 35.7–88.3
percent) mean maximal reduction in urinary oxalate relative to Phase 1/2 baseline (N=17), and 17/18 (94 percent) of patients achieved normal or near-normal levels of urinary oxalate. Mean eGFR levels remained stable over time. Lumasiran had an acceptable safety profile. There were no deaths, severe AEs, or AEs leading to discontinuation of treatment. There were no drug-related SAEs. The most common drug-related AEs were mild ISRs. No clinically significant laboratory changes related to lumasiran were reported."

Manufacturers and Regulatory Status

Alnylam Pharmaceuticals (Cambridge, Massachusetts) manufactures lumasiran. On November 24, 2020, FDA approved the new drug application (NDA) for lumasiran injection, under the trade name Oxlumo, to lower urinary oxalate levels in children (aged from birth or older) and adults who have PH1. Lumasiran injection is intended to be delivered by a health care professional.254

FDA previously granted lumasiran breakthrough therapy, orphan drug, priority review, and rare pediatric disease designations for treating patients who have PH1.251

Cost Information

Alnylam Pharmaceuticals has reportedly set a list price of about $493 000 per patient per year for lumasiran, with an average annual net price about $380 000 after rebates.255 The company has announced it would work with several health plans and pharmacy benefit managers to create value-based agreements for lumasiran therapy. Under these agreements, the manufacturer will receive certain payments if patients respond to therapy and achieve predefined treatment success targets. Also under such agreements, payers are eligible for rebates if more PH1 diagnoses and requests for lumasiran treatment occur than expected, based on epidemiologic estimates. Further, payers may receive rebates if a patient exceeds an established volume of lumasiran vials over time for the weight-based dosing therapy.255,256

Key Stakeholder Perspectives

Between October 1, 2020, and March 15, 2021, nine stakeholders, reflecting allied health, health systems, nursing, physician, and research perspectives, provided comments and ratings on lumasiran to treat PH1. The list below provides a summary of key stakeholder perspectives.

- Lumasiran use has demonstrated substantial reductions in urine oxalate levels that should correlate with reduced kidney stone formation and less kidney injury over the longer term.

- Lumasiran injections could disrupt PH1 treatment by shifting to disease prevention and away from management of complications after stone formation and long-term renal injury requiring more invasive procedures.

- Treatment costs with lumasiran are likely to be high but could translate into reduced long-term treatment costs if the drug prevents kidney stone formation, kidney injury, and eventual need for dialysis and kidney transplantation.

- Improvements in patient outcomes and quality of life could be greatest for younger patients who currently face a longer duration of illness from increased oxalate levels.
Mepolizumab (Nucala) to Treat Hypereosinophilic Syndrome

Highlights

- Mepolizumab is a humanized monoclonal antibody approved by FDA in September 2020 to treat severe eosinophilic asthma, eosinophilic granulomatosis, and hypereosinophilic syndrome (HES).
- The drug is injected under the skin once every 4 weeks, a treatment patients can give to themselves at home.
- Mepolizumab has an average retail cost of $124,800 per patient per year.
- Stakeholders commented on this treatment 3 to 4 months before FDA approval and thought that mepolizumab might have a moderate to high impact on patient outcomes and overall health by reducing HES flares, improving quality of life, and sparing corticosteroid use.
- Stakeholders thought that, although the cost of treatment might increase disparities if payers do not cover treatment, long-term hospital and care costs might be lower because of slower HES disease progression.

Patient Population

Mepolizumab is intended for children aged 12 years or older and adults with HES.

Intervention

HES represents a collection of rare disorders characterized by chronically elevated levels of a class of innate immune cells known as eosinophils (ie, hypereosinophilia). HES is associated with end-organ damage caused by eosinophilic tissue infiltration and mediator release. The American Partnership for Eosinophilic Disorders website offers more information on HES.

Three goals of HES treatment are decreasing eosinophil counts, reducing signs and symptoms of the disorder, and preventing disease progression. Standard first-line treatment of HES involves corticosteroids (except in the case of certain clonal eosinophilias, which may respond to treatment with tyrosine kinase inhibitors specific to the molecular driver in that clonal disease).

Although HES in many patients responds to corticosteroids, HES in other patients stops responding, and long-term steroid treatment carries substantial side effects. Alternative approaches using cytoreductive agents (eg, cyclophosphamide, hydroxyurea, vincristine) are also associated with substantial adverse events, do not address the underlying disease, and are ineffective in some patients. Therefore, effective new approaches to treating HES are needed.

Mepolizumab (Nucala) is a humanized monoclonal antibody that acts as an antagonist to interleukin-5 (IL-5), a key eosinophilopoietic cytokine that promotes eosinophil proliferation. Increased serum IL-5 levels have been implicated in various forms of HES; therefore, IL-5 represents a rational target for treating HES.

According to the FDA-approved labeling, mepolizumab is injected under the skin once every 4 weeks at 3 doses of 100 mg each. Treatment is given in a doctor’s office or by patients themselves at home.
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 phase 3 trials with published results.\textsuperscript{260,263} We summarize the 2 most recent studies with results as written in the abstracts of published studies.

The following abbreviations are used in this section: AE, adverse event; CI, confidence interval; HES, hypereosinophilic syndrome; P, probability.

Efficacy and Safety of Mepolizumab in Hypereosinophilic Syndrome: A Phase III, Randomized, Placebo-Controlled Trial (Study 200622). \textbf{NCT02836496}, Roufosse et al 2020.\textsuperscript{263}

- **Patient population/planned enrollment**: Patients (n = 108) aged 12 years or older with a diagnosis of HES for at least 6 months at random assignment and who had a history of 2 or more HES flares within the past 12 months
- **Study design**: Phase 3, randomized, double-blind study of the safety and efficacy of mepolizumab in treating patients who have HES. Patients were randomly assigned to 32 weeks of treatment with either mepolizumab (300-mg subcutaneous injection once every 4 weeks) or matching placebo. Patients continued on baseline standard-of-care therapy.
- **Primary outcome**: Percentage of patients who experienced an HES flare or withdrew from the study during the 32-week study period
- **Secondary outcomes**: Time to first HES flare, the proportion of patients with a flare during weeks 20 to 32, annualized rate of HES flares, and fatigue score per Brief Fatigue Inventory
- **Results presented by study authors**: “The proportion of patients experiencing 1 or more flares/withdrawing from the study was 50% lower with mepolizumab versus placebo (15 of 54 [28%] vs 30 of 54 [56%]; P = .002). Logistic regression analysis was consistent with the primary analysis (odds ratio, 0.28; 95% CI, 0.12–0.64; P = .003). Similar proportions of patients in the mepolizumab and placebo groups experienced on-treatment adverse events (48 of 54 [89%] vs 47 of 54 [87%]).”

An Open-Label Extension of Intravenous Mepolizumab in Patients With Hypereosinophilic Syndrome (Study 100901). \textbf{NCT00097370}, Roufosse et al 2013.\textsuperscript{260}

- **Patient population/planned enrollment**: Patients (n = 78) with HES who completed a phase 2 trial of mepolizumab (Study 100185, \textbf{NCT00086658}, reported by Rothenberg et al\textsuperscript{259} 2008)
- **Study design**: Phase 3, single-group assignment study of the long-term safety and efficacy of mepolizumab in treating patients who have HES. All patients received intravenous mepolizumab (750 mg) either monthly or on an individualized dosing schedule.
- **Primary outcome**: Frequency of AEs
- **Secondary outcomes**: Number of participants achieving a prednisone level of \(\leq 10\) mg and number of participants achieving an eosinophil level of \(<600\) cells/\(\mu\)L
- **Results presented by study authors**: “Seventy-eight subjects received 1 to 66 mepolizumab infusions each (including mepolizumab infusions received in the placebo-controlled trial). Mean exposure was 251 weeks (range, 4–302 weeks). The most common dosing interval was 9 to 12 weeks. The incidence of AEs was 932 events per 100 subject-years in the first year, declining to 461 events per 100 subject-years after 48 months. Serious AEs, including 1 death, were reported by the investigator as possibly due to mepolizumab in 3 subjects. The median daily prednisone dose decreased from 20.0 to 0 mg in the first 24 weeks. The median average daily dose for all subjects over the course of the study was..."
1.8 mg. Sixty-two percent of subjects were prednisone free without other HES medications for ≥ 12 consecutive weeks. No neutralizing antibodies were detected. Twenty-four subjects withdrew before study completion for death (n = 4), lack of efficacy (n = 6), or other reasons.”

Manufacturers and Regulatory Status
Alexion Pharmaceuticals Inc (Boston, Massachusetts) assessed eculizumab for treating Mepolizumab was developed by GlaxoSmithKline plc (Brentford, United Kingdom). On September 25, 2020, FDA approved mepolizumab under the trade name Nucala for adults and children aged 12 years or older with HES for 6 months or longer without another identifiable nonblood-related cause of the disease. FDA had earlier granted mepolizumab orphan drug and fast track status for this indication.

Mepolizumab is commercially available in the United States, having been initially approved in 2015 for treating eosinophilic asthma and subsequently for treating eosinophilic granulomatosis with polyangiitis.

Cost Information
According to a US-based online aggregator of prescription drug prices, GoodRx, mepolizumab’s retail price (as of March 25, 2021) was about $3200 for a 100-mg vial. At the required dosing of 300 mg every 4 weeks, a 1-year course of treatment would cost about $124 800. Dosing of mepolizumab in treating HES is 3 times higher than that of other indications (eg, eosinophilic asthma).

Key Stakeholder Perspectives
Between May 3, 2020, and June 19, 2020, and before FDA approval, 6 stakeholders, reflecting nursing, patient safety, physician, and research perspectives, provided comments and ratings on mepolizumab to treat HES. The list below provides a summary of key stakeholder perspectives.

- Clinical trial data of mepolizumab demonstrate significant reductions in the frequency of HES flares, as well as an improvement in fatigue scores, which might improve patient outcomes, quality of life, and overall health.
- Mepolizumab might allow patients to reduce or stop standard-of-care corticosteroids, which have substantial side effects and long-term tolerability issues. A treatment reducing corticosteroid use might significantly disrupt patient outcomes.
- Mepolizumab might significantly disrupt the paradigm of patient care because it is the only IL-5 agonist that is available as an injection patients can give themselves, allowing treatment in the home setting.
- Although cost might be a barrier to patient access and could result in disparities if not covered by insurance, treatment with mepolizumab might lower long-term hospital and care costs associated with HES disease progression.
- The clinical trials also revealed serious adverse events that might need to be considered when selecting the drug for a patient.
MT1621 to Treat Thymidine Kinase 2 Deficiency

Highlights

- MT1621 is an oral combination drug of deoxycytidine and deoxythymidine, precursors (nucleosides) to the building blocks of genetic material (nucleotides).
- The drug is in phase 3 development and is used to correct the underlying cause of thymidine kinase 2 deficiency (TK2d), a rare, inherited, mitochondrial DNA depletion disorder. It addresses the cause of TK2d by making DNA building blocks (ie, nucleotides) available for normal DNA synthesis.
- Current standard of care for TK2d is supportive, and FDA has not approved any treatments for the disorder.
- Stakeholders commenting on this topic thought that MT1621 might significantly improve patient health outcomes and quality of life by increasing survival, reducing disability, and reducing need for supportive care, and that, if approved, it is likely to become the standard of care for TK2d.
- Stakeholders also thought that, because MT1621 is taken by mouth, it is likely to be convenient for patients and lessen potential disparities in treatment access.

Patient Population

MT1621 is intended for children and adults with TK2d due to a confirmed genetic mutation in the thymidine kinase 2 gene, TK2.

Intervention

An ultra-rare disorder with no approved treatments, TK2d is caused by a genetic variation in the TK2 gene. This gene normally produces the protein TK2, a metabolic enzyme that is necessary for maintaining a balanced pool of DNA building blocks (ie, nucleotides) in the mitochondria, cellular organelles often described as the power generators inside cells.\(^{266,267}\)

TK2d-induced nucleotide imbalance causes impaired DNA synthesis in mitochondria. This leads to progressive, severe muscle weakness that affects movement, breathing, and eating and can be fatal, most often from respiratory failure.\(^{266-268}\) The National Library of Medicine’s MedlinePlus Genetics website offers more information about TK2d.\(^{267}\)

MT1621 is a drug taken by mouth and intended to address the underlying cause of TK2d. The drug consists of a combination of the nucleosides deoxycytidine and deoxythymidine, precursors of 2 nucleoside triphosphates that are incorporated into DNA.\(^{269}\) By providing an external source of deoxycytidine and deoxythymidine, MT1621 purportedly restores balance to the nucleotide pool, potentially restoring mitochondrial DNA synthesis and mitochondrial function in patients with TK2d.\(^{270}\)

In clinical trials, MT1621 is taken by mouth as a dissolved solution at a dosage up to 400 mg/kg daily.\(^{271}\)
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 5.9.

Table 5.9. 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>An Open-Label Study of Continuation Treatment With Combination Pyrimidine Nucleosides in Patients With TK2 NCT03845712</td>
<td>Children and adults (n = 47) with a confirmed genetic mutation in the TK2 gene, without other genetic or polygenic disease</td>
<td>Phase 2, open-label, single-arm study to assess the safety and efficacy of MT1621 to treat TK2d taken by mouth 3 times daily at a total dosage of up to 400 mg/kg daily for up to 36 months. Annual assessments of safety and efficacy will continue annually after the 36-month treatment period. Primary outcome: Safety, measured by adverse events, laboratory measurements, and electrocardiograms. Selected secondary outcome: Efficacy, measured by lung function and motor function tests.</td>
<td>Primary and study completion January 2022</td>
</tr>
<tr>
<td>Treatment of TK2 Deficiency With Thymidine and Deoxycytidine NCT03639701</td>
<td>Children and adults (n = 20) with a confirmed genetic mutation in the TK2 gene, without other genetic or polygenic disease</td>
<td>Phase 1/2, open-label, single-arm study to assess the safety and efficacy of MT1621 to treat TK2d taken by mouth 3 times daily at a total dosage of up to 400 mg/kg daily for up to 60 months. Primary outcome: Safety, measured by adverse events, laboratory measurements, electrocardiograms, and diarrhea incidence. Selected secondary outcomes: Event-free survival, Motor function, Lung function.</td>
<td>Primary and study completion April 2024</td>
</tr>
</tbody>
</table>
A Study of the Efficacy and Safety of MT1621 in Thymidase Kinase 2 (TK2) Deficiency  
**NCT04581733**

<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 of the Efficacy and Safety of MT1621 in Thymidase Kinase 2 (TK2) Deficiency | Children and adults (n = 25) with a confirmed genetic mutation in the TK2 gene, without other genetic or polygenic disease | Phase 3, open-label, double-arm study to assess the safety and efficacy of MT1621 to treat TK2d taken by mouth 3 times daily at a total dosage of up to 400 mg/kg daily for up to 24 months (participants 12 years or younger) or for up to 39 months after a 9-month run-in period (participants older than 12 years)  
Primary outcome: time to loss of any motor milestone  
Secondary outcomes:  
- Time to acquisition of any motor milestone  
- Survival | Primary completion March 2025  
Study completion April 2025 |

Abbreviations: TK2, thymidine kinase 2; TK2d, thymidine kinase 2 deficiency; TK2, thymidine kinase 2 gene.

Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed late-phase trial. We summarize this study with results as written in a company news release and a poster presentation.

The following abbreviations are used in this section: BMI, body mass index; p, probability; TK2d, thymidine kinase 2 deficiency.

A Retrospective Study of Patients With TK2d (RETRO). **NCT03701568.** Zogenix 2019, Quan et al 2019.

- **Patient population/planned enrollment:** Children and adults, no ages specified (n = 38), with TK2d and who were previously treated with deoxycytidine and deoxythymidine
- **Study design:** Retrospective, observational study to review data from patients previously treated with deoxycytidine and deoxythymidine. Participants were given a fixed combination of deoxycytidine and deoxythymidine at an unknown dose for a median of 77 weeks.
- **Primary outcomes:** Safety and tolerability of deoxycytidine and deoxythymidine therapy for TK2d
- **Secondary outcomes:** BMI, clinical course (achievement, loss, or regain of developmental motor milestones), motor function, and ambulatory assessments
- **Results presented by study authors:** “All treated patients remain alive. A survival analysis using a time-dependent Cox regression model showed that the difference in probability of survival between treated patients and untreated natural history control patients was highly statistically significant (p<0.0006). . . the vast majority of treated patients (94.7%) had either improved (68%) or stabilized (26%) responses in major functional domains.”

A subset of responders regained lost most motor milestones, including the following:

“Ambulation: 3 subjects who had lost ambulation prior to treatment regained ambulation; 1 subjects who had never walked gained ambulation.”
“Respiratory function: 1 subject receiving 24 hours/day of invasive mechanical ventilation prior to treatment discontinued all respiratory support following treatment.
“Feeding Support: 3 subjects had their feeding tubes removed, out of a total of 8 subjects on feeding tubes at study start.”

Manufacturers and Regulatory Status
MT1621 is being developed by Modis Therapeutics (Oakland, California), a subsidiary of Zogenix (Emeryville, California). It is in phase 3 clinical trials for treating TK2d. Zogenix announced in August 2020, after meeting with FDA about a regulatory pathway forward, that it anticipated having all necessary clinical trial data by 2021 and submitting a new drug application in the first half of 2022.274
MT1621 received FDA breakthrough therapy designation in February 2019 and orphan drug designation in July 2016 for this indication.275,276

Cost Information
Cost information is currently unavailable for this topic.

Key Stakeholder Perspectives
Between April 24, 2020, and June 23, 2020, five stakeholders, reflecting clinical, nursing, and research perspectives, provided comments and ratings on MT1621 to treat TK2d. The list below provides a summary of key stakeholder perspectives.

• Clinical trial data suggest that MT1621 has significant potential to improve patient health outcomes and quality of life by increasing survival, reducing disability, and reducing the use of supportive care, although the data were observational, retrospective, and unpublished, and more data are needed.

• MT1621 is likely to become the standard of care for TK2d if FDA approves it, considering that the current standard of care is supportive and a large unmet need exists for treatments.

• The oral delivery route of MT1621 is likely to be convenient for many patients and unlikely to cause disparities in patient access to the treatment.

• MT1621 could shift the paradigm of care from supportive to preventive and, therefore, impact the treatment goals and management of patients with TK2d.

• A reduction in the need for supportive care (eg, ambulatory devices, respiratory support, feeding support) is likely to result in significant health care cost savings.
Olipudase Alfa (GZ402665) to Treat Acid Sphingomyelinase Deficiency

**Highlights**

- Olipudase alfa is a human recombinant form of acid sphingomyelinase (ASM), an enzyme that helps break down the lipid sphingomyelin. It is in phase 3 development as an enzyme replacement therapy.

- It is intended to treat patients with acid sphingomyelinase deficiency (ASMD) by replacing insufficient levels of ASM that contribute to serious health effects, including liver and spleen enlargement, neurologic disease, and early death.

- The standard of care for ASMD is supportive, and FDA has not approved any treatments for the disease.

- Stakeholders commenting on this topic thought that olipudase alfa might significantly improve health and quality of life for patients with ASMD and might become the standard of care, if FDA approves it.

- Stakeholders thought this intervention might increase health disparities in this patient population if it is cost-prohibitive to some patients or some patients are unable to travel to health care facilities to receive the biweekly infusions.

**Patient Population**

Olipudase alfa is intended for children and adults with the ASMD form of Niemann-Pick disease type B (NPB) or Niemann-Pick disease type A/B (NPA/B).

**Intervention**

ASMD is a rare, autosomal recessive, lysosomal storage disease in which a variation in the **SMPD1** gene causes a deficiency or absence of ASM. An enzyme, ASM is normally found in lysosomes and is responsible for breaking down the lipid sphingomyelin. ASMD leads to excessive accumulation of sphingomyelin in cells, causing cell death, organ enlargement, and malfunction of major organ systems.

ASMD severity exists along a spectrum historically known, in order of decreasing severity, as Niemann-Pick disease type A (NPA), NPA/B, and NPB. A patient with NPA presents with health complications including liver and spleen enlargement and neurologic disease that results in death in childhood. Conversely, NPB presents without neurologic involvement, and patients typically survive into adulthood with health complications, including delayed growth, enlarged liver and spleen, and breathing problems. NPA/B is an intermediate form characterized by slower progression of neurologic symptoms and longer survival than NPA. The National Niemann-Pick Disease Foundation website offers more information on ASMD.

No FDA-approved treatments are available for ASMD, and treatment consists of supportive care and symptom management.

Olipudase alfa (GZ402665), a human recombinant ASM, is an enzyme replacement therapy intended to correct the underlying ASM deficiency to help break down sphingomyelin. It is intended to treat NPA/B or NPB, the forms of ASMD with little to no neurologic involvement. Preclinical research indicated that olipudase alfa is unlikely to prevent neurodegeneration in
patients with ASMD but might reduce sphingomyelin levels in the heart, liver, spleen, and to a lesser degree, the lungs.\textsuperscript{280}

In clinical trials, olipudase alfa is given intravenously once every 2 weeks at a dose of up to 3 mg/kg (dosing is the same for children and adults).

**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 5.10.

Table 5.10. 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>Efficacy, Safety, Pharmacodynamic, and Pharmacokinetics Study of Olipudase Alfa in Patients With Acid Sphingomyelinase Deficiency (ASCEND) (NCT02004691)</td>
<td>Adults (n = 36) aged 18 years or older with documented ASMD and DLco of 70% or less of the predicted normal value, spleen volume of 6 times or more than normal, and an SRS of at least 5</td>
<td>Phase 2/3, placebo-controlled, randomized study to evaluate the efficacy and safety of olipudase alfa administered intravenously at a dosage of up to 3 mg/kg once every 2 weeks for 52 weeks Primary outcomes: • Percentage predicted DLco • Spleen volume Secondary outcomes: • Liver volume • Fatigue severity • Pain severity • Dyspnea severity • SRS • Adverse events</td>
<td>Primary completion October 2019 Study completion October 2023</td>
</tr>
</tbody>
</table>

See data from Sanofi 2020 (2 trials) under Recently Completed and Ongoing Trials With Available Results
<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 Long-Term Study of Olipudase Alfa in Patients With Acid Sphingomyelin Deficiency</td>
<td>Children and adults (n = 25) with ASMD who completed a prerequisite clinical trial of olipudase alfa</td>
<td>Phase 2, open-label, single-group assignment study to evaluate the long-term safety and efficacy of olipudase alfa given intravenously at the dose each patient was receiving at the end of their previous study (ie, up to 3 mg/kg) once every 2 weeks for up to 9 years</td>
<td>Primary and study completion September 2023</td>
</tr>
</tbody>
</table>

Abbreviations: ASMD, acid sphingomyelinase deficiency; DLco, diffusing capacity of the lungs for carbon monoxide; SRS, splenomegaly related score.

Recently Completed and Ongoing Trials With Available Results

Our searches identified 3 recently completed phase 2 and phase 2/3 trials with published results.279,281,282 We summarize these 3 studies with results as written in the abstracts of published studies and a company news release.

The following abbreviations are used in this section: ALT, alanine aminotransferase; ASMD, acid sphingomyelinase deficiency; DLco, diffusing capacity of the lungs for carbon monoxide; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; lyso-SM, sphingosylphosphorylcholine; MN, multiples of normal; p, probability; PK, pharmacokinetic; PRO, patient-reported outcome; SM, sphingomyelin; SRS, splenomegaly related score; VLDL-C, very-low-density lipoprotein cholesterol.
Safety, Tolerability, PK, and Efficacy Evaluation of Repeat Ascending Doses of Olipudase Alfa in Pediatric Patients < 18 Years of Age With Acid Sphingomyelinase Deficiency (ASCEND-Peds). NCT02292654. Sanofi 2020.279

- **Patient population/planned enrollment:** Children (n = 20) aged up to 17 years with documented ASMD with spleen volume of 5 times of normal or more
- **Study design:** Phase 2, single-arm, open-label study to primarily assess the safety and tolerability and secondarily characterize the PK profile and evaluate the pharmacodynamics and exploratory efficacy of olipudase alfa given intravenously to pediatric patients at a dosage of up to 3 mg/kg every 2 weeks for 64 weeks
- **Primary outcomes:** Adverse events, laboratory parameters, and physical examination findings
- **Secondary outcomes:** PK parameters, pharmacodynamic parameters, sphingomyelin levels, lung disease, and spleen size
- **Results presented by study authors:** “Over the 64-week treatment period, all patients experienced at least one adverse event. These events were mostly mild and moderate, with one patient experiencing a severe and serious anaphylactic reaction that was considered related to olipudase alfa. Five treatment-related serious adverse events were observed in three patients: two cases of transient, asymptomatic alanine aminotransferase (ALT) increase in one patient, one case each of urticaria and rash in one patient, and one anaphylactic reaction in one patient. No patients had to permanently discontinue treatment due to an adverse event. The most common adverse events (as defined by percentages of events greater than or equal to 2% and number of patients greater than or equal to two in all olipudase alfa treated patients) seen in this trial were pyrexia, cough, vomiting, nasopharyngitis, diarrhea, headache, upper respiratory tract infection, contusion, abdominal pain, nasal congestion, rash, urticaria, scratch, and epistaxis.

“The study also explored secondary endpoints of progressive lung disease and enlarged spleen. After one year of treatment (52 weeks), the percent predicted DLco increased by a mean of 33% in nine patients who were able to perform the test at baseline (children over the age of five were assessed if they were able to perform the test). Additionally, at 52 weeks, the spleen volumes decreased by 49% as assessed by mean MN (individual patient decreases ranged from 23% to 61%).”


- **Patient population/planned enrollment:** Adults (n = 36) aged 18 years or older with documented ASMD with Dlco of 70% or less of the predicted normal value, spleen volume of 6 times of normal or more, and an SRS of at least 5
- **Study design:** Phase 2/3, placebo-controlled, randomized study to evaluate the efficacy and safety of olipudase alfa given intravenously at a dosage of up to 3 mg/kg once every 2 weeks for 52 weeks
- **Primary outcomes:** Percentage predicted DLco and spleen volume
- **Secondary outcomes:** Liver volume, fatigue severity, pain severity, dyspnea severity, SRS, and adverse events
- **Results presented by study authors:** “The first independent primary endpoint measuring improvement in lung function, using the percent predicted diffusing capacity of carbon monoxide (DLco), was met; therefore, ASCEND is declared positive. The relative improvement from baseline to week 52 was 22% for the olipudase alfa arm compared with 3% for the placebo arm. The difference between the two treatment arms (19%) was statistically significant (p=0.0004).

“The other independent primary endpoint measuring the effect of olipudase alfa on spleen size, assessed as percent change from baseline in multiples of normal (MN) of spleen volume, was met per the study protocol. In the olipudase alfa arm, spleen volume was reduced by 39.5%, compared with a 0.5% increase in the placebo arm. The difference between the two treatment arms (40%) was statistically significant (p<0.0001).
“For the U.S., the spleen volume endpoint was further combined with a patient-reported outcome (PRO) measurement of symptoms associated with enlarged spleen called Splenomegaly Related Score (SRS). Compared to baseline, the SRS was reduced by 8.0 points in the olipudase alfa arm and 9.3 points in the placebo arm (p=0.70); therefore, this combination endpoint was not met.

“Over the 52-week period, all patients in both the placebo and olipudase alfa arms experienced at least one adverse event. The number of events was lower in the olipudase alfa arm (242 events) compared with the placebo arm (267 events). Severe adverse events were less frequent in the olipudase alfa arm (3 events) compared with the placebo arm (13 events). There were five serious adverse events in the olipudase alfa arm and 11 in the placebo arm, none of which were treatment related. There were no adverse events that led to treatment discontinuation or study withdrawal. The most common adverse events (as defined by percentages of events greater than or equal to 2% and number of patients greater than or equal to two in all olipudase alfa treated patients; occurring with higher percentages in olipudase alfa patients compared to placebo patients) seen in this trial were headache, nasopharyngitis, upper respiratory tract infection, cough, and arthralgia.”


- **Patient population/planned enrollment:** Children and adults (n = 20) with ASMD who completed a prerequisite clinical trial (NCT02292654 for children and NCT01722526 for adults) of olipudase alfa
- **Study design:** Phase 2, open-label, single-group assignment study to evaluate the long-term safety and efficacy of olipudase alfa given intravenously at the dose each patient was receiving at the end of their previous study (ie, up to 3 mg/kg) once every 2 weeks for up to 9 years
- **Primary outcomes:** Treatment-emergent adverse events, physical examination findings, vital signs, and various laboratory and imaging tests
- **Secondary outcomes:** Spleen and liver volumes, lung imaging and function tests, hematology and lipid profiles, health outcome questionnaire items, and growth measures (children)
- **Results presented by study authors:**
  
  *Note:* Data were given for adult participants only.

“This ongoing, open-label, long-term study (NCT02004704) assessed safety and efficacy of olipudase alfa following 30 months of treatment in five adult patients with ASMD. There were no deaths, serious or severe events, or discontinuations during 30 months of treatment. The majority of adverse events were mild and included headache, nausea, and abdominal pain. No patient developed anti-drug antibodies and there were no clinically significant adverse changes in vital signs, hematology, or cardiac safety parameters. Statistically significant reductions in liver (31%) and spleen (39%) volumes were maintained through 30 months of treatment. There was a mean increase in lung diffusing capacity of 35%, and clinically relevant improvements in infiltrative lung disease parameters. Lipid profiles improved in all patients. Improvements in bone mineral density of the spine were observed in some patients. Chitotriosidase in serum and lyso-sphingomyelin in dried blood spots decreased with olipudase alfa treatment, suggesting utility as biomarkers for monitoring treatment efficacy.281

“Five adult patients with chronic visceral ASMD were enrolled in a 26-week phase 1b trial of enzyme replacement therapy (ERT) with olipudase alfa (NCT01722526) followed by an ongoing long-term extension study (NCT02004704). We compare the changes in hepatic SM levels, plasma lyso-SM, and lipoprotein profiles after 42 months of treatment. Progressive clearance of histologic SM storage was observed throughout the trial, along with similar reductions in plasma lyso-SM. Improvements in liver enzymes were observed at 6 months and remained stable at 42 months. Progressive reductions from baseline in pro-atherogenic lipid profiles (total cholesterol, LDL-C, VLDL-C, triglycerides) were observed at month 6 and 42. Conversely, there were progressive increases in anti-atherogenic markers, HDL-C and apolipoprotein A-1, with HDL-C increases up to 200% over baseline levels after 42 months of treatment.”282
Manufacturers and Regulatory Status

Olipudase alfa to treat ASMD is being developed by Sanofi Genzyme (Cambridge, Massachusetts) and is in phase 3 clinical development. It received FDA orphan drug designation in August 2000 and breakthrough therapy designation in June 2015 for this indication.\textsuperscript{283,284} Sanofi stated in a January 2020 news release that it expected to begin global regulatory submissions in the second half of 2021 with data from the phase 2/3 ASCEND and phase 2 ASCEND-Peds clinical trials.\textsuperscript{279}

Cost Information

Cost information is currently unavailable for this topic, although stakeholders thought that olipudase alfa would likely be expensive.

Key Stakeholder Perspectives

Between April 24, 2020, and July 5, 2020, five stakeholders, reflecting clinical, health systems, nursing, and research perspectives, provided comments and ratings on olipudase alfa for treating ASMD. The list below provides a summary of key stakeholder perspectives.

- Clinical trial data suggest meaningful patient-oriented outcomes and significant improvement in surrogate disease markers including spleen size and lung disease.
- Long-term efficacy and safety data were positive and significant, although the trial sizes were small.
- Given the positive clinical trial data and olipudase alfa’s potential to become the first FDA-approved treatment for ASMD, it is likely to have a significant impact on improving patient health outcomes, including life expectancy and quality of life. Further, treatment with this drug is likely to become the standard of care.
- Olipudase alfa is likely to be expensive and might be cost-prohibitive to some patients.
- The biweekly intravenous administration of olipudase alfa might be burdensome to patients who need to travel to receive the infusions and might increase health disparities in this population if this mode of delivery is not feasible for some patients.
Palovarotene to Treat Fibrodysplasia Ossificans Progressiva

Highlights

- Palovarotene is an oral, retinoic acid receptor gamma agonist (ie, activator) intended to slow the progression of fibrodysplasia ossificans progressiva (FOP). It is in phase 3 development.
- 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 that palovarotene might improve patient health outcomes and quality of life by slowing disease progression and decreasing dependence on supportive care.
- Stakeholders cautioned, however, that its overall disruptive potential depends on forthcoming safety and efficacy data, particularly regarding adverse events.

Patient Population

Palovarotene is intended to treat FOP in children aged 14 years or older and adults.

Intervention

FOP is a rare connective tissue disorder caused by a mutation in a gene called activin A receptor type I, ACVR1, which encodes the ACVR1/ALK2 receptor.\(^{285,286}\) This mutation leads to HO that manifests as abnormal bone growth in muscles, tendons, and ligaments.\(^{287,288}\) HO flares can occur spontaneously or after physical trauma (eg, injury, infection). Once heterotopic bone forms, it cannot be surgically removed because tissue disruption causes additional HO episodes.\(^{289,290}\)

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.\(^{285,286,289,290}\) The National Institutes of Health’s Genetic and Rare Diseases Information Center website offers more information on FOP.

Palovarotene is a selective retinoic acid receptor gamma (RARγ) activator that is taken by mouth. It is being developed to treat FOP.\(^{291}\) In patients with FOP, mutant activin receptor–like kinase-2 (ALK2) overactivates Smad 1/5/8 transcription factors in the bone morphogenetic protein (BMP) 2 pathway. This pathway is responsible for cartilage regulation and bone growth and development.\(^{286,288}\) Palovarotene activation of RARγ is thought to decrease Smad 1/5/8 protein levels, reducing excess BMP signaling to prevent further HO development in patients with FOP.\(^{288,291}\)

In an ongoing phase 3 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.\(^{292}\)
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 5.11.

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 Efficacy and Safety Study of Palovarotene for the Treatment of FOP (MOVE) NCT03312634 (PVO-1A-301) See preliminary results by Ipsen Group 2020 under Recently Completed and Ongoing Trials With Available Results</td>
<td>Children aged 4 years or older and adults (n = 110) with a clinical diagnosis of FOP and no flares in the previous 4 weeks</td>
<td>Phase 3, 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 patients with FOP Primary outcome: Annualized change in new HO volume</td>
<td>Primary completion January 2020 Study completion November 2022</td>
</tr>
<tr>
<td>An Open-Label Extension Study of Palovarotene Treatment of FOP in France NCT02979769</td>
<td>Children and adults aged 6 to 65 years (n = 9) with a clinical diagnosis of FOP</td>
<td>Phase 2, single-arm, open-label extension study in France assessing the 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 July 2021</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 and adults aged 6 to 65 years (n = 54) with a clinical diagnosis of FOP</td>
<td>Phase 2, single-arm, open-label extension study assessing the 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 October 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 phase 2 trial and one phase 3 trial with published results.\textsuperscript{293,294} We summarize these studies below with results as written in company news releases.

The following abbreviations are used in this section: FOP, fibrodysplasia ossificans progressiva; HO, heterotopic ossification; p or p-value, probability; PROMIS, Patient-Reported Outcomes Measurement Information System; RARγ, retinoic acid receptor gamma; WBCT, whole body computed tomography.

An Efficacy and Safety Study of Palovarotene for the Treatment of FOP (MOVE). \textsuperscript{294} Ipsen Group 2020.

- **Patient population/planned enrollment**: Children aged 4 years or older and adults (n = 90) with a clinical diagnosis of FOP and no flares in the previous 4 weeks
- **Study design**: Phase 3, single-arm, open-label study to assess the efficacy of palovarotene in decreasing new HO in FOP. Data from this trial were compared with historical data from a natural cohort study of patients with FOP.
- **Primary outcome**: Annualized change in new HO volume
- **Secondary outcomes**: Proportion of patients with any new HO, number of body regions with HO, proportion of patients with flares, rate of flares, and adverse events
- **Results presented by study authors**: “Dosing of palovarotene in the MOVE clinical trial was paused when futility criteria were met at a pre-specified interim analysis. However, subsequent post hoc analyses showed the RARγ agonist oral investigational therapy palovarotene reduced mean annualized new heterotopic ossification (HO) volume in pediatric and adult participants with FOP. This was compared with untreated patients from a natural history study over 24 months. Results from the MOVE trial demonstrated a 62% reduction in mean annualized new HO volume in participants treated with palovarotene (8,821 mm\textsuperscript{3}) (n=97) versus untreated (23,318 mm\textsuperscript{3}) (n=98) patients (nominal weighted linear mixed effects [wLME] model est. \(-11,611\) mm\textsuperscript{3}, p-value = 0.0292). Premature physeal closure (PPC) (n=18) or epiphyseal disorder (n=1) was observed in 27.1% (19/70) of participants who were skeletally immature at baseline. Palovarotene safety data were otherwise generally consistent with the known adverse event (AE) profile of retinoids.”

An Open-Label Extension Study of Palovarotene Treatment in FOP. \textsuperscript{293} Clementia Pharmaceuticals 2018.

- **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 2, 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 (719 mm\textsuperscript{3}) in Part B as compared to the 60 untreated flare-ups (8,001 mm\textsuperscript{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 (21,567mm³) was observed compared to the 55 untreated patients (29,731mm³). 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 (10,682mm³) compared to the untreated control group (29,731mm³).

Manufacturers and Regulatory Status

The Ipsen Group (Paris, France) is developing palovarotene, after acquiring the original developer, Clementia Pharmaceuticals, Inc (Montreal, Québec, Canada), in April 2019.291,295 Palovarotene is in phase 3 development (MOVE trial, NCT03312634) for preventing FOP flares. Primary data collection for the study was completed in January 2020.292 On January 24, 2020, Ipsen announced that the company would pause dosing patients in the phase 3 MOVE study as well as the ongoing phase 2 (PVO-1A-202/204) extension studies because of results of a prespecified interim futility analysis by the Independent Data Monitoring Committee (IDMC). The futility analysis revealed that the phase 3 FOP trial was unlikely to meet its primary efficacy end point (annualized change in new HO volume compared with a separate ongoing natural history study control).296 However, the IDMC recommended against discontinuing the study because of disparate results, and a prespecified interim analysis revealed signals of encouraging therapeutic activity in preliminary phase 3 post hoc analyses.296 Data using a modified statistical analysis were presented in August 2020.294 In addition, on December 6, 2019, Ipsen initiated a partial clinical hold for dosing pediatric patients aged 14 years or younger with palovarotene for treating chronic FOP because of safety reports submitted to FDA of cases of early growth plate closure in pediatric patients given the drug.297 On March 26, 2020, the manufacturer announced it would reinitiate palovarotene dosing in patients aged 14 years or older who were enrolled in FOP clinical trials because FDA regulators confirmed they had no safety concerns about dosing patients in that cohort.298 FDA had granted palovarotene rare pediatric disease designation to treat FOP in February 2019.288 FDA has also granted palovarotene breakthrough therapy, fast track, and orphan drug designations for treating FOP.291,299

Cost Information

Cost information is currently unavailable for this topic, but stakeholders expected the drug to be expensive.
Key Stakeholder Perspectives

Between June 10, 2020, and August 28, 2020, six stakeholders, reflecting health systems, nursing, physician, and research perspectives, provided comments and ratings on palovarotene. Stakeholder comments were received before the August 2020 release of data from the phase 3 MOVE trial. The list below summarizes key stakeholder perspectives.

- Palovarotene has substantial potential to improve patient outcomes in a disease with no effective disease-modifying treatments. The mechanism of action directly influencing the disease course of FOP has demonstrated reduction in flare rate and could improve long-term bone health and joint function. However, data have not yet been published in peer reviewed journals, and full reporting of the drug’s adverse event profile is needed.

- The availability of a disease-modifying therapy for HO would cause a shift in the patient treatment paradigm, potentially reducing the need for some supportive care and hospitalizations related to disease flares.

- As a drug taken by mouth, palovarotene should not cause substantial disruption to the health care delivery system.

- Palovarotene will likely be very expensive, like other drugs for rare orphan diseases. However, costs to the health care system could be mitigated by reduced costs related to supportive care, and cost burden on the overall health care system will be limited by the small number of affected patients.

RVT-802 to Treat Pediatric Congenital Athymia (DiGeorge Syndrome Immunodeficiency, CHARGE Syndrome, FOXP1 Deficiency)

Highlights

- RVT-802 is a cell-based therapy derived from donor (ie, allogeneic) infant thymus tissue; it is intended to restore thymus function in children born without a thymus (ie, 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 is often fatal by 2 years of age. The developer plans to resubmit a biologics license application (BLA) for RVT-802 to treat pediatric congenital athymia in 2021. In December 2019, FDA declined to approve a BLA for this indication, citing concerns about the developer’s manufacturing process and other issues.

- 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. However, they also thought that larger, longer-term studies are needed to better understand RVT-802’s safety and effectiveness relative to other treatments such as hematopoietic stem cell transplantation.
• Stakeholders further thought that RVT-802’s likely high cost and the likelihood that thymus transplants would be available at relatively few facilities 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 (ie, cDGA, CHARGE syndrome, and FOXN1 deficiency) that arise from gene 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 athymic diseases. 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 (ie, thymopoiesis). RVT-802 is intended to be a one-time therapy to permanently restore normal immune function in patients.

The 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 grams of thymus tissue per square meter of body surface area.

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

Thymus transplants have been performed at a single center in the United States since the mid-1990s and at a single European center since 2009. Multiple papers covering partially overlapping patient populations from these studies have been published (Markert et al 1999, Markert et al 2004, Markert et al 2007, and Markert et al 2010). We summarize the most recent data as written in a company 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

- 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 was transferred to a new company, Sumitovant Biopharma, Inc (New York, New York), which is fully owned by Sumitomo Dainippon.

In March 2021, Sumitovant Biopharma announced plans to resubmit to FDA a biologics license application (BLA) for RVT-802 for treating pediatric congenital athymia in 2021. In June 2019, FDA had accepted a BLA for RVT-802 for treating pediatric congenital athymia. However, in December 2019, FDA declined to approve the BLA and issued a complete response letter that cited concerns about RVT-802’s manufacturing process and other issues, after FDA’s inspection of the manufacturing site. FDA in September 2017 had granted rare pediatric disease designation to RVT-802 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 currently unavailable from the manufacturer, a presentation at the Academy of Managed Care Pharmacy Nexus 2018 conference estimated that RVT-802 might have a budget impact of $1.5 million per treated patient.
Key Stakeholder Perspectives

Between June 14, 2020, and August 3, 2020, six stakeholders, reflecting health systems, nursing, physician, 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 a treatment option for patients with athymia. In particular, athymic patients who lack a suitable donor for hematopoietic stem cell transplant could benefit substantially from another available treatment.

- RVT-802’s high cost (an estimated $1.5 million per patient) might create disparities for families that are underinsured or lack sufficient financial resources. In addition, RVT-802 transplants will likely be offered only at specialty facilities like major children’s hospitals and, therefore, RVT-802 would likely increase disparities for patients who live far from these facilities.

- If effective, RVT-802 could disrupt the paradigm of patient care by causing a shift from mainly palliative care and treatment of opportunistic infections to an approach that reconstitutes the patient’s immune system. In addition, health care facilities offering RVT-802 transplantation would need to develop protocols to ensure the timely acquisition of the thymus graft and appropriate preoperative and postoperative patient management.

- Long-term controlled studies are needed to assess the safety and effectiveness of RVT-802 and donor-matched thymus transplantation, hematopoietic stem cell transplantation, and supportive care to better understand the therapies’ trade-off between benefit (immune reconstitution) and risk (death or autoimmune complications).

Setmelanotide (Imcivree) to Treat Proopiomelanocortin Deficiency Obesity

Highlights

- Setmelanotide is an injectable drug intended to treat proopiomelanocortin (POMC) deficiency obesity, a rare form of obesity caused by mutations in certain genes regulating hunger. Setmelanotide purportedly activates melanocortin-4 (MC4) receptors in the brain to help restore normal appetite and energy regulation pathways.

- In November 2020, FDA approved the new drug application for setmelanotide injection for chronic weight management in adults and children aged 6 years or older with obesity related to deficiency of POMC, proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR).

- Candidates for setmelanotide therapy require genetic testing to identify whether they carry the genetic variants that the drug targets.

- Stakeholders reviewing this topic thought that early results reported in a small patient group were impressive, with average weight loss of about 32 kg (70 lb) per patient over 1 year.
• Stakeholders also thought that additional data in a larger patient sample are needed to better define the long-term safety and effectiveness of setmelanotide to treat POMC deficiency obesity.

**Patient Population**

Setmelanotide is intended to treat patients aged 6 years or older with genetically confirmed POMC deficiency obesity.

**Intervention**

A rare disease, POMC deficiency obesity is caused by variants in the proopiomelanocortin gene, *POMC*, or the proprotein convertase subtilisin/kexin type 1 gene, *PCSK1*. Variants in these 2 genes lead to deficient production of proopiomelanocortin protein, a precursor required to synthesize the peptides adrenocorticotropic hormone (ACTH), α-melanocyte-stimulating hormone (α-MSH), and β-MSH in the brain. ACTH stimulates cortisol release from the adrenal glands, which helps maintain blood glucose levels.\(^{316,317}\)

In the brain, α-MSH and β-MSH maintain the balance of energy from food intake and energy expenditure\(^{316}\) by activating MC4 receptors. Inadequate activation of MC4 receptors may disrupt hunger regulation.\(^{317}\) The National Library of Medicine’s MedlinePlus Genetics website offers more information on POMC deficiency.

Setmelanotide (Imcivree), a peptide, is a selective MC4 receptor agonist (ie, activator) intended to treat POMC deficiency obesity. Setmelanotide purportedly activates MC4 receptors, restoring function to the MC4 pathway to reduce hunger and lead to weight loss.\(^{318,319}\)

According to the FDA-approved label, setmelanotide is given as a daily injection under the skin. The dose is 1 to 3 mg (depending on patient age, weight, and drug tolerance). If not tolerated, starting dose is 0.5 mg, gradually increased to 1 mg and up to 2 mg, if tolerated, for more weight loss.\(^{320}\) Candidates require genetic testing to confirm the presence of variants in the *POMC, PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance.\(^{320}\)
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 5.12.

Table 5.12. 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>Setmelanotide (RM-493) Phase 2 Treatment Trial in Patients With Rare Genetic Disorders of Obesity NCT03013543</td>
<td>Patients aged 6 years or older (n = 150) with rare genetic disorders of obesity, including POMC deficiency, leptin receptor deficiency, Bardet-Biedl syndrome, Alström syndrome, and Smith-Magenis syndrome</td>
<td>Phase 2/3, single-group, open-label study to determine the effect on weight of once-daily under-the-skin injections of setmelanotide (at an unspecified dose) over the course of 1 year • Primary outcome: Body weight reduction</td>
<td>Primary completion May 2021 Study completion August 2021</td>
</tr>
<tr>
<td>Long Term Extension Trial of Setmelanotide NCT03651765</td>
<td>Patients aged 6 years or older (n = 100) with obesity associated with defects in leptin-melanocortin pathways who completed a previous setmelanotide clinical trial</td>
<td>Phase 2/3, single-group, open-label study to assess the safety and tolerability of continued once-daily under-the-skin injections of setmelanotide (at an unspecified dose) over the course of 2 years Primary outcome: Safety and tolerability Selected secondary outcomes: • Weight loss • Hunger • Body fat mass • Waist circumference • Change in total body mass, nonbone lean mass, and bone density • Quality of life Measure of health status</td>
<td>Primary and study completion March 2023</td>
</tr>
</tbody>
</table>

Abbreviation: POMC, proopiomelanocortin.

Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed late-phase trial with reported results.321,322 We summarize this study with results as written in 2 company news releases.

The following abbreviations are used in this section: p, probability; PCSK1, proprotein convertase subtilisin/kexin type 1 gene; POMC, proopiomelanocortin; POMC, proopiomelanocortin gene.
Setmelanotide for the Treatment of Early-Onset POMC Deficiency Obesity. \textit{NCT02896192}. Rhythm Pharmaceuticals 2019.$^{321}$

- **Patient population/planned enrollment:** Patients aged 6 years or older with POMC deficiency obesity due to biallelic \textit{POMC} or \textit{PCSK1} gene mutations

- **Study design:** Phase 2/3 single-group study to evaluate the effect of once-daily under-the-skin injections of setmelanotide (dose unspecified) on weight and other factors. All patients received setmelanotide for 12 weeks, followed by an 8-week double-blind withdrawal period during which patients received placebo treatment for a randomly timed 4-week window. After the placebo withdrawal period, all patients received setmelanotide for another 32 weeks.

- **Primary outcome:** Weight loss

- **Secondary outcomes:** Treatment-related adverse events and changes in body fat mass, hunger, insulin resistance, waist circumference, and weight during withdrawal phase

- **Results presented by study authors:** “Eight of 10 patients with POMC deficiency obesity achieved the primary endpoint of greater than 10 percent weight loss over approximately one year (p<0.0001). The mean reduction from baseline in body weight for POMC deficiency obesity patients was -25.4 percent (p=0.0001), and the mean reduction from baseline in most hunger rating for POMC deficiency obesity patients was -27.8 percent (p=0.0005). In addition, 50 percent of the POMC deficiency obesity patients in the trial met or exceeded a 25 percent improvement in self-reported hunger scores (p=0.0004). Mean weight loss for these patients was 31.9 kg, or 70.2 pounds, over one year on therapy.”

In a November 2020 news release, the manufacturer reported additional data from 5 patients with POMC deficiency obesity who reached 89 weeks on setmelanotide therapy: “The mean percent reduction in body weight from pivotal trial baseline at week 89 of the extension was -30.2%, a -0.1% change from the conclusion of the pivotal trial; the mean absolute reduction in body weight at week 89 of the extension was -40.2kg, a change of -0.5kg from the conclusion of the pivotal trial; the mean percent reduction in body mass index at week 89 of the extension was -32.5%, a change of -0.4% from the conclusion of the pivotal trial; the mean percent change in most hunger score from pivotal baseline was consistent through week 89 of the extension at -8.2%, a change of 10% from the conclusion of the pivotal trial.”$^{322}$

**Manufacturers and Regulatory Status**

\textbf{Rhythm Pharmaceuticals, Inc (Boston, Massachusetts)}, manufactures setmelanotide. On November 27, 2020, FDA approved setmelanotide for injection, under the trade name Imcivree, for chronic weight management in adults and children aged 6 years or older with obesity due to deficiency of \textit{POMC}, \textit{PCSK1}, or \textit{LEPR}, confirmed by genetic testing.$^{323}$ FDA previously had granted setmelanotide breakthrough therapy, orphan drug, and rare pediatric disease designations for these indications.$^{324}$

Setmelanotide is also in phase 3 clinical development to treat Bardet-Biedl syndrome and Alström syndrome, and it is in phase 2 clinical development to treat other rare, genetically linked forms of obesity.$^{318}$

**Cost Information**

Setmelanotide reportedly has a retail list price of $330 per milligram. For an adult at the recommended dose of 3 mg per day, that would mean an annual treatment cost of about $360,000.$^{325}$
Key Stakeholder Perspectives

Between March 20, 2020, and September 13, 2020, nine stakeholders, reflecting clinical, health systems, nursing, patient, and research perspectives, provided comments and ratings on this topic. The list below provides a summary of key stakeholder perspectives.

- Initial results for setmelanotide, including average weight loss of about 32 kg (70 lb) per patient in 1 year, appear impressive, and no apparent safety concerns have been reported thus far.

- Most patients and family caregivers would welcome a new treatment for POMC obesity that is more effective than diet modification and less invasive than bariatric surgery.

- Although POMC is a rare condition, the scarcity of available data, based on company reporting for only very few patients, can limit the ability to extrapolate or make strong projections about this intervention.

- Longer-term data in a larger patient group are needed to fully establish the safety and duration of effect of setmelanotide to treat POMC deficiency obesity and to identify any unexpected adverse events related to its mechanism of action.

- Some ongoing trials include patients with different genetically linked obesity types, potentially complicating analysis of findings.
Chapter 6. Potentially Disruptive Trends

Chapter Summary

In addition to the topics included in the previous chapters, the PCORI HCHSS identifies and monitors trends, which are 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, 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 March 5, 2021, we were monitoring 34 potentially disruptive trends. These 34 trends were listed in the March 2021 *PCORI Health Care Horizon Scanning System: Horizon Scanning Status Report*.

All 34 monitored 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 20, 2020, and March 19, 2021. From among these 34 trends, 8 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 (Table 6.1).

Table 6.1. Included Trends

<table>
<thead>
<tr>
<th>Trend title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artificial intelligence to predict antidepressant treatment response</td>
</tr>
<tr>
<td>Bacteriophages to treat bacterial infections*</td>
</tr>
<tr>
<td>Direct-to-consumer genetic testing collaborations with pharmaceutical companies to facilitate drug development and treatment</td>
</tr>
<tr>
<td>Gene editing to treat or prevent disease*</td>
</tr>
<tr>
<td>Identifying drug synergies with artificial intelligence to optimize regimens</td>
</tr>
<tr>
<td>Proteomic profiling to diagnose cancer and guide personalized targeted therapy</td>
</tr>
<tr>
<td>Psychedelic drugs to treat mental health conditions</td>
</tr>
<tr>
<td>Smartphone-guided medical examinations and diagnostics for use by patients and caregivers</td>
</tr>
</tbody>
</table>

*Trend appears for the first time in this edition of the *High Potential Disruption Report*. 

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*HIGH POTENTIAL DISRUPTION REPORT • MAY 2021*
Trend Summaries

We present below 8 summaries on trends deemed to have high potential for disruption. Trends are ordered alphabetically by trend title.

Artificial Intelligence to Predict Antidepressant Treatment Response

Highlights

- Researchers are studying whether artificial intelligence (AI) can identify which antidepressant drugs are most likely to work for individual patients, based on AI-assisted analysis of brain examinations.

- Fewer than half of patients with depression have treatment success with their first-prescribed antidepressant drug, leaving many discouraged enough to stop further treatment.

- Early research suggests AI-assisted analysis of electroencephalography (EEG) results before treatments are prescribed might help predict whether patients will benefit from certain drugs or other interventions such as transcranial magnetic stimulation (TMS).

- Stakeholders commenting on this trend thought that, if AI assistance could successfully personalize antidepressant therapy, it might improve adherence to therapy and reduce emergency department visits and hospitalizations. Thus, overall treatment costs might be lower.

- Stakeholders also thought AI assistance might allow more patients to access scarce mental health resources if fewer office visits to adjust medications were required.

Description

In the United States almost 10% of youth have experienced severe major depression, and even before the COVID-19 pandemic, almost 20% of adults experienced a mental illness. Access to behavioral health care continues to be a challenge for many Americans, and stress from the COVID-19 pandemic has increased the need for mental health services. AI has been proposed as a means to leverage limited resources to benefit more patients across several clinical specialties, and applying AI to behavioral health is an emerging field of research.

Results from the STAR*D trial suggest that fewer than half of patients who have major depressive disorder achieve remission with use of a first-line antidepressant medication. This might be because major depressive disorder is a biologically varied mental health condition that has demonstrated distinct neurophysiological subtypes. Researchers are investigating whether AI techniques might predict a patient’s response to an antidepressant medication, particularly when applied to EEG results.

One study developed an EEG computation model to predict treatment outcomes with sertraline to lay the groundwork for machine learning approaches. The researchers found that participants who were unlikely to respond to sertraline treatment were more likely to respond to treatment with TMS. Another study, investigating the application of machine learning to EEG to predict response to escitalopram treatment, found a prediction accuracy of 79.2% using...
baseline EEG data. Other researchers who did not use AI-based EEG analysis suggested that a machine learning algorithm that analyzed treatments, symptoms, and baseline characteristics might help predict an individual patient’s response to antidepressant treatment.

**Clinical Area(s) Potentially Disrupted**

Applying AI to the selection of appropriate drugs or other interventions could disrupt patient management, the clinician learning curve, and treatment models for mental health indications and affect which providers deliver care. Patient outcomes could improve if the most effective interventions are identified sooner. AI-assisted treatment selection could increase initial costs by requiring additional tests, such as EEGs; however, it could decrease long-term treatment costs if multiple ineffective drug regimens and ineffective care leading to hospitalization are avoided and patient outcomes improve. The intervention could also impact understanding of disease and varying responses to treatment among different patients.

**Opportunities**

The use of AI assistance to identify antidepressant interventions most likely to work for individual patients could greatly improve patient outcomes. By finding the most effective drugs sooner, patients are less likely to become discouraged with their antidepressant treatment regimen and less likely to stop their treatment. Adding AI assistance to treatment selection might decrease overall costs by avoiding the use of several ineffective drugs before an effective one is identified. The use of AI assistance in selecting appropriate antidepressants could change the care paradigm by making depression treatment more personalized. Better therapy targeting might also improve providers’ understanding of depression treatment and why different patients respond differently to various antidepressant interventions.

**Threats**

Economic disparities might arise if the costs to perform EEG or brain imaging examinations for AI-assisted antidepressant treatment selection prevent some patients from accessing this intervention. Additional disparities in access might develop if machine learning applied to EEG, brain imaging, or other tests is restricted to research institutions, where most psychiatrists and other behavioral health specialists experienced in this technology are likely to be concentrated.

**Key Stakeholder Perspectives**

Between June 17, 2020, and April 12, 2021, sixteen ECRI stakeholders, reflecting clinical engineering, health care generalist, health systems, nursing, and research perspectives, provided comments and ratings on this topic. The list below provides a summary of key stakeholder perspectives.

- Societal influences could trigger depressive conditions, so any innovations that can improve behavioral health care will likely have impact.
- Using AI to identify drugs most likely to benefit patients could help personalize mental health treatment, potentially improving adherence to therapy, and represents a major advance compared with standard care.
- Applying AI to identify appropriate drug therapy could increase up-front costs because of the need to conduct EEG or other testing for drug selection.
• However, AI assistance might lower long-term costs by reducing emergency department visits and hospitalizations and restoring lost productivity.

• If it improves timely antidepressant selection, AI assistance might ease workload on overstretched mental health providers by reducing office visits to adjust medications. Consequently, this might allow more patients to access scarce office visits.

• Adding biomarker analysis and pharmacogenomics information to algorithms might improve effectiveness of AI-assisted antidepressant selection.

Bacteriophages to Treat Bacterial Infections

Highlights

• Bacteriophages, viruses that specifically infect bacterial cells, are being investigated in clinical trials to treat various bacterial infections.

• They might be an important treatment, considering that rates of bacterial infections that are multidrug-resistant are increasing and that some infections are characteristically difficult to treat with antibiotics.

• Stakeholders commenting on this trend generally agreed bacteriophages are a promising treatment, especially considering increasing concerns over antibiotic drug resistance, and that bacteriophages have significant potential to improve patient health outcomes if they result in quicker infection resolution, fewer chronic infections, and fewer infection-related deaths.

• Stakeholders also expressed concerns about the safety of bacteriophages and stated that more research is needed to determine their safety and any potential unanticipated consequences of their use.

Description

Bacteriophages are viruses that infect only bacterial cells and might help treat bacterial infections. They were discovered more than a century ago but were not pursued as a treatment in the United States because of safety concerns and the increased availability of antibiotics. However, with increasing rates of antibiotic resistance and better understanding of bacteriophage biology, researchers are now considering using bacteriophages to treat infections that are multidrug-resistant or characteristically hard to treat with antibiotics. Multiple bacteriophages might diffuse clinically in the United States within the next 2 to 3 years, and they offer a novel treatment for bacterial infections.

Bacteriophages are in clinical trials to treat primary immune deficiency disease, hyper-IgM syndrome, urinary tract infections, gastrointestinal tract infections, diabetic foot ulcers, leg ulcers, wound infections, *Pseudomonas aeruginosa* infections, and *Staphylococcus aureus* infections. The University of California San Diego’s Center for Innovative Phage Applications and Therapeutics (IPATH) treats patients who have life-threatening multidrug-resistant infections with bacteriophages on a case-by-case basis through FDA’s compassionate use program. IPATH intends to conduct phase 1/2 trials for chronic infections in cystic fibrosis and infections associated with implantable hardware such as pacemakers and prosthetic joints. Another synthetic phage, AP-PA02, targeting the pathogen *P. aeruginosa*, is in a
phase 1/2 trial in 48 participants with cystic fibrosis and chronic pulmonary *P. aeruginosa* infection, with estimated completion in March 2022.337

**Clinical Area(s) Potentially Disrupted**

Bacteriophages have a novel mechanism of action to treat bacterial infections compared with standard-of-care antibiotic medications and, therefore, could disrupt patient outcomes and many aspects of the health care delivery system. Considering that bacteriophages are live viruses, their use might require significant infrastructure changes to implement, especially to accommodate any potential changes in storage requirements or administration setting. There might be a significant learning curve for clinicians to understand how to use them. Bacteriophages could change how patients are managed and disrupt the current bacterial infection treatment model. Because they might require many or all of the changes above, implementing them clinically could disrupt health care costs.

**Opportunities**

Bacteriophages might improve patient health outcomes by effectively and safely treating bacterial infections. They might have additional benefits compared with antibiotic treatments, which face unique limitations such as multidrug-resistant bacteria or difficulty achieving therapeutic concentrations in certain areas of the body. It might help reduce new drug-resistant bacterial strains and improve antibiotic stewardship. If bacteriophages are more effective than antibiotic drugs, bacteriophages might reduce length of hospitalization or result in fewer deaths in patients with severe infection. The study and use of bacteriophages might add to the body of scientific knowledge surrounding infection and its treatment and might contribute to further treatment innovation.

**Threats**

Bacteriophages might pose a health risk to patients if they fail to work as intended or cause side effects. There is a theoretical risk of bacterial resistance to bacteriophages. Bacteriophages might add significant short-term health care costs to infection treatment, because of both the cost of the treatment and any costs related to infrastructure or staffing changes needed to administer the treatment. There might be a significant learning curve for clinicians to use this treatment, which might result in additional health care costs related to clinician education. Health disparities might increase if the treatment is available only in certain areas or if some clinicians cannot undertake the necessary training, due to either financial or time restrictions.

**Key Stakeholder Perspectives**

Between March 25, 2020, and April 9, 2021, eleven ECRI stakeholders, reflecting health care generalist, health systems, nursing, and research perspectives, provided comments and ratings on this trend. The list below provides a summary of key stakeholder perspectives.

- Bacteriophages have significant potential to impact patient health outcomes if they result in quicker resolution of infection, reduce the rate of chronic infections, or decrease infection-related deaths, and especially if they are effective against multidrug-resistant bacteria.

- If used clinically, they would be an important treatment option, considering increasing rates of multidrug-resistant bacteria.
- Additional data are needed to assess the safety of treatment with bacteriophages and potential for unexpected, unintended consequences of their use.
- Preventing chronic infections and reducing length of hospitalization for infections could result in significant health care cost savings.

Direct-to-Consumer Genetic Testing Collaborations 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 enhance drug development, enrollment in clinical trials, and, ultimately, patient access to targeted therapies.
- The first new experimental treatments created through some of these collaborations have entered early testing.
- Stakeholders commenting on this trend thought that DTC genetic testing might improve patient outcomes by speeding drug development and patient identification but cautioned that it might increase disparities because of the out-of-pocket cost of testing. That is, this approach to drug development and subsequent clinical trials might tend to favor those with high enough socioeconomic status to afford DTC genetic testing and exclude populations that cannot afford DTC genetic testing but that might benefit from newly discovered therapies.
- 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 using patients’ genetic data and data that patients volunteer on questionnaires 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. 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.

Multiple DTC testing companies are forming research collaborations for treating chronic conditions with unmet medical needs that might substantially disrupt clinical care in the next 3 years. For example, genetic testing company 23andMe has established a collaboration with GlaxoSmithKline to develop treatments for conditions such as cancer, Parkinson’s disease, and inflammatory conditions. Another genetic testing company, Nebula Genomics, is collaborating with EMD Serono to use consumer data to drive the drug-development process.
The number of collaborations is growing. In January 2020, 23andMe reported it granted Almirall, SA (Barcelona, Spain), worldwide rights to develop a 23andMe-designed monoclonal antibody targeting the interleukin (IL)-36 cytokine subfamily for dermatologic indications. In July 2020, GlaxoSmithKline announced the start of a phase 1 trial of its first-in-class monoclonal antibody targeting the CD96 immune checkpoint receptor, codeveloped with 23andMe, to treat advanced solid tumor cancers. The website of 23andMe also lists collaborations with Pfizer for treating inflammatory bowel disease and systemic lupus erythematosus; with Celmatix for treating infertility in females; and with H Lundbeck A/S for treating major depressive disorder or bipolar disorder.

**Clinical Area(s) Potentially Disrupted**

Collaborations between companies offering DTC genetic tests and drug developers 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**

These collaborations 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 help investigators recruit patients and asymptomatic carriers with rare diseases into clinical trials faster and more cost-effectively. 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 consent forms allowing their data to 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 create based on those data.

**Key Stakeholder Perspectives**

Between March 25, 2020, and April 12, 2021, thirteen ECRI stakeholders, reflecting business and finance, clinical engineering, health care generalist, health systems, nursing, and research perspectives, provided comments and ratings on this topic. The list below provides a summary of key stakeholder perspectives.

- DTC genetic testing might help individuals identify health conditions early enough to make lifestyle changes, seek medical help, or delay disease progression. Also, the future impacts of these collaborations might extend beyond rare diseases.
- DTC genetic testing might promote self-diagnosis, misdiagnosis, or inappropriate treatment without adequate follow-up from a health care provider.
- Effective collaboration might reduce development costs for drug developers and reach patients who would otherwise not consider enrolling in clinical trials. However, consumers could be unaware that 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 might reduce long-term costs of treating certain health conditions. Further, this approach to drug development might prioritize testing for people who can afford DTC testing and related treatments while excluding populations that cannot, creating disparities.

• Poor regulatory oversight might allow insurance companies to gain access to consumers’ genetic information and raise their insurance premiums.

• Companies trading consumers’ genetic data might raise more privacy risks by creating new targets for hackers.

Gene Editing to Treat or Prevent Disease

Highlights

• Gene modification using CRISPR (clustered regularly interspaced short palindromic repeats) is intended to target and repair the mutated region in affected genes to restore regular function and help treat or prevent diseases.

• This technology is being evaluated in several clinical trials for genetic disorders in which the patient’s DNA is permanently modified to provide a durable treatment effect.

• Stakeholders commenting on this trend generally agreed that this technology would be life-changing for those who lack effective treatments for their genetic conditions; however, its uptake would largely depend on insurance coverage and access.

• Stakeholders were concerned about ethical implications: Using this technology in human embryos might have unintended long-term consequences to humanity.

Description

The Genetic Disease Foundation lists more than 6000 genetic disorders that either are fatal or cause serious illness in humans. Gene editing technology holds great promise for treating and/or preventing several such diseases and conditions. Clinical trials using gene editing technology are underway to provide effective treatment options for those who have debilitating genetic disorders.

CRISPR is a gene-editing tool that can be programmed to target specific stretches of the genetic code and edit DNA at precise locations in the human genome. The technology allows researchers to permanently modify genes and has the potential to create therapies with a durable treatment effect. NTLA-2001 is one such treatment being evaluated in a phase 1 clinical trial to treat patients who have transthyretin amyloidosis, a progressive neurodegenerative disorder. AGN-151587 is another example of a CRISPR-based medicine being evaluated, in this case to treat vision impairment due to Leber congenital amaurosis in children and adults.

Clinical Area(s) Potentially Disrupted

Gene-editing technology might disrupt patient health outcomes and influence the delivery of treatment. Other than influencing future treatment models, gene editing might also improve our understanding of various rare genetic disorders for which our knowledge is limited. This technology could be costly for patients who may not have the resources to pursue these
treatments. However, it might reduce caregiver burden and costs associated with lost wages and repeated clinic visits. It is unclear whether this technology would be a one-time treatment or require several procedures.

Opportunities

Gene-editing technology might improve survival outcomes as well as quality of life for patients who have limited treatment options or are ineligible for available treatments. It might reduce overall treatment costs for patients and the health care system by providing a one-time, curative treatment, although further research is needed to validate the curative nature of gene-editing technology. It might also reduce societal burden and health care costs by preventing and/or eliminating certain genetic disorders.

Threats

Because gene editing technology is in early development stages, much is still unknown about possible adverse events in patients. Any unintended consequences could impact these patients’ health over the long term. The technology also raises significant ethical and societal threats (eg, unethical alteration of human embryos).

Key Stakeholder Perspectives

Between March 16, 2020, and April 12, 2021, thirteen 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 provides a summary of key stakeholder perspectives.

- If proven safe and effective, gene-editing technology (eg, CRISPR) could improve patient outcomes for those who have diseases caused by genetic mutations with limited effective treatments available.
- Because of the clinician learning curve and special training associated with the use of gene editing, it will likely disrupt care delivery and staffing.
- Treating and preventing genetic diseases would reduce long-term costs that include the cost of hospitalizations, repeated treatments, and other care. Conversely, these therapies might be cost-prohibitive for patients who are uninsured and those with limited insurance coverage.
- It might increase disparities if patients are unable to access gene-editing therapies.
  - Ethical guidelines and policies would need to clarify the potential applications of gene-editing technology. In the absence of such policies, there might be unauthorized uses of gene editing for altering human embryos that can have substantial ethical and societal consequences.
Identifying Drug Synergies With Artificial Intelligence to Optimize Regimens

Highlights

- Artificial intelligence (AI) algorithms are being developed to identify potentially beneficial new drug combinations in much less time than that needed for traditional, preclinical drug research and development.
- Use of AI assistance to find new drug combinations might particularly benefit rare-disease research, because the small number of patients with rare diseases challenges researchers conducting clinical trials to recruit enough participants for meaningful results.
- Relying too heavily on AI assistance up-front to find new drug combinations might not identify the potential for adverse events that could harm patients.
- Stakeholders commenting on this trend thought that AI assistance to identify potential drug synergies could speed drug development and reduce research costs.
- Stakeholders also thought that ensuring the safety and efficacy of new drug combinations to improve patient outcomes should take precedence over cutting drug-development costs and shortening time to market.

Description

AI algorithms that analyze gene expression signatures from available databases might help scientists predict which drugs could be combined to better treat diseases with high unmet needs, including SARS-CoV-2, cancer, and tuberculosis. These AI algorithms might promote, inform, and accelerate studies putting existing drugs to new uses or creating new drug combinations for patients who need more options.

In one AI-based model, investigators found that predicted synergies for treating tuberculosis could be confirmed in a laboratory test tube or culture dish 88% of the time. Researchers purport that AI algorithms based on laboratory studies have successfully identified synergistic regimens confirmed in human studies. These findings suggest that AI might save scientists valuable research time in identifying optimized treatment regimens, expediting these options for patients.

Clinical Area(s) Potentially Disrupted

Reducing the total research time to identify potential new drug combinations could positively affect both individual patient and population health outcomes. Using AI to find effective drug combinations sooner might disrupt costs. New drug synergies identified with AI help could change treatment models and patient management for diseases of interest. Including AI protocols in the research process could disrupt clinician learning curves and the understanding of certain disease processes.

Opportunities

Adding AI assistance to find new drug synergies might shorten the time needed to discover the safest and most effective drug combinations. AI’s help might also reduce the costs of drug development by identifying the compounds most likely to succeed before proceeding with costly clinical trials. Further, using AI to find the most effective drug combinations could improve
outcomes for patients with hard-to-treat conditions or rare diseases. For many rare diseases or
small subgroups of common conditions, researchers have difficulty recruiting enough patients for
clinical trials that can produce statistically meaningful results.

**Threats**

Overuse of AI to identify the most effective drug combinations, especially to lower research
costs, could cause researchers to abandon other effective methods of drug development. Further,
AI assistance to find promising new drug combinations might not detect or predict adverse
events that could harm patients.

**Key Stakeholder Perspectives**

Between May 20, 2020, and April 9, 2021, nine ECRI stakeholders, reflecting clinical
engineering, health care generalist, health systems, nursing, and research perspectives, provided
comments and ratings on this topic. The list below provides a summary of key stakeholder
perspectives.

- AI assistance might substantially shorten preclinical research time to select the most
  promising drugs for clinical testing and eventual treatment, thereby allowing patients
  access to these treatments more quickly.
- Because the risk of future pandemics is high, the use of AI to speed preclinical research
  to identify the most promising agents for clinical testing will become more important.
- The driving principle behind wider use of AI to help select and develop drugs should be
  improving patient outcomes and safety, rather than lowering drug-development costs and
time to market.
- Effectiveness of AI in this setting could increase, provided that high-quality data continue
to be available and that only the best-quality data are used to train algorithms for drug
selection.
- AI might be useful in finding alternative indications for existing drug products, leading to
easier approval pathways for these new combinations.

**Proteomic Profiling to Diagnose Cancer and Guide Personalized
Targeted Therapy**

**Highlights**

- Proteomic profiling uses test results from tissue or blood samples to identify proteins that
  are associated with cancer.
- VeriStrat and Stroma Liquid Biopsy are examples of proteomic profiling tests. They are
  intended to identify protein biomarkers that can help confirm a diagnosis of cancer and
  help guide selection of targeted therapies or match patients to clinical trials.
- Stakeholders commenting on this trend thought that proteomic profiling is beginning to
diffuse. If used properly to detect early-stage cancer and guide targeted therapy selection
for patients, proteomic profiling could improve health outcomes. However, some patients
might not benefit from proteomic profiling because their disease develops resistant mutations against the selected targeted therapies.

- Stakeholders also thought that the cost of proteomic profiling is likely to be the most disruptive factor. It will be an expensive technology that insurance companies might not reimburse without sufficient evidence of clinical utility. But even with its high cost, proteomic profiling might reduce health care costs, such as those for managing late-stage disease.

Description

Proteomic profiling involves the systematic separation, identification, and characterization of proteins present in a patient’s tumor or blood sample.\(^{357,358}\) In patients with suspected cancer, clinicians use proteomic profiling to identify a cancer-associated protein that might confirm the presence and origin of a specific cancer type.\(^{358}\) 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 an on-label or off-label targeted therapy that is most likely to benefit a patient with cancer or help enroll patients in clinical trials of investigational therapies.\(^{357,359}\) Proteomic tests, such as VeriStrat (Biodesix, Inc, Boulder, Colorado)\(^{360}\) and Stroma Liquid Biopsy (Biotech Support Group LLC, Monmouth Junction, New Jersey),\(^{361}\) analyze specific protein biomarkers in patients with suspected cancer to determine the tissue origin of a solid tumor and help develop personalized treatment plans.

Clinical Area(s) Potentially Disrupted

Proteomic profiling could disrupt the oncology clinical area by simultaneously confirming a diagnosis of cancer and recommending targeted therapies that are likely to benefit patients.\(^{359}\) In patients suspected of having cancer (eg, 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.\(^{358}\)

Opportunities

Proteomic profiling could improve health outcomes by detecting cancer early in patients suspected of having the disease and matching patients with targeted therapies or clinical trials likely to benefit them. If used in routine screening, proteomic profiling might also detect early-stage cancers before they can be properly identified using medical imaging.\(^{358,359}\) In tumors that are composed of more than one cell type, proteomic analysis might identify several biomarkers that are involved in cancer growth.\(^{362}\)

Threats

As a novel testing approach, proteomics might add to clinician burden by requiring physicians to learn about protein signatures for different cancer types and understand which could be drug targets.\(^{359,362}\) Implementing proteomics into the workflow could increase disparities by being available only to patients who are insured or able to pay for treatment out of pocket.\(^{362}\)

Key Stakeholder Perspectives

Between March 11, 2020, and April 9, 2021, eight ECRI stakeholders, reflecting health care generalist, health systems, nursing, and research perspectives, provided comments and ratings on this trend. The list below provides a summary of key stakeholder perspectives.
• Proteomic profiling to identify cancer at its early stages and direct clinicians to targeted therapies for patients is beginning to diffuse. Protein expression–based targeted therapies could improve health outcomes and quality of life, but in some cases, resistant mutations will arise and the therapies’ efficacy might be no better than systemic chemotherapy.

• Adopting proteomic profiling into clinical use could disrupt health care delivery. If evidence demonstrates that proteomic profiling will be an important tool for the diagnosis and treatment of cancer, it might be moderately disruptive.

• Proteomic profiling is likely to be very expensive; it is unclear 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 late-stage disease.

Psychedelic Drugs to Treat Mental Health Conditions

Highlights

• Psychedelic drugs (psilocedibles) are being investigated as a novel drug class to treat a variety of mental health conditions, including depression and anxiety disorders.

• Psychedelics are thought to 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 could improve patient health outcomes, especially for those who have found other treatments to be ineffective, and that the controlled settings prescribed for their use might improve their safety.

• Stakeholders also thought that psychedelics might significantly impact health care delivery because of changes needed in staffing, training, and infrastructure for their clinical use.

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 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. Multiple psychedelics to treat
mental health conditions are in clinical trials and might diffuse clinically in the United States in the next 2 to 3 years.

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. LSD is being explored to treat anxiety associated with life-threatening illness, other anxiety disorders, and depression. DMT, a drug present in a psychoactive brew called ayahuasca, is being researched to treat depression. MDMA is in phase 3 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.

Ketamine, while not traditionally considered a psychedelic drug, has some psychedelic properties and is being explored off-label to treat PTSD. A closely related molecule, esketamine (Spravato), is FDA-approved to treat depression.

In clinical trials, psychedelics are given 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 approach to treat mental health conditions, might improve patient health outcomes and quality of life by providing new and quicker mechanisms for emotional and cognitive reframing compared with traditional drug treatments and psychotherapy. Psychedelics might be an important additional treatment as demand for mental health care grows in the wake of the COVID-19 pandemic.

Psychedelics might reduce the prevalence of treatment-resistant mental health conditions and, thus, reduce costs associated with longer-term mental health treatment. Special considerations for implementing psychedelic treatment (eg, specialized clinician training, tight drug dispensing, patient monitoring) might significantly change the paradigm and infrastructure of mental health care.

The use of psychedelics for mental health conditions might encourage continued research into additional potential therapeutic uses for psychedelics and might enhance understanding of mental health conditions.

**Threats**

Psychedelics can cause serious negative mental health effects for some patients (eg, acute psychosis) not commonly observed with current standard-of-care psychiatric medications. Greater availability of these drugs might increase the risk of diversion to people the drug is not intended for, posing population health risks and legal consequences.

Disparities in access to care might increase if clinicians hesitate to prescribe psychedelics (for reasons such as stigma), making the treatment option less readily available to those who might benefit. Disparities might also increase for patients with underlying psychiatric illnesses (eg, schizophrenia, bipolar disorder), who are generally advised not to take psychedelics due to increased risk of negative adverse events (eg, acute psychosis, exacerbation of underlying illness).
Psychedelic treatment could be costly in the short term to build the infrastructure needed to deliver the treatments (eg, areas for patient monitoring, increased clinician training).

**Key Stakeholder Perspectives**

Between June 3, 2020, and April 9, 2021, twelve 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.

- Psychedelics given in a controlled setting could improve mental health conditions and decrease sequelae of mental health disorders for some patients, especially in those who have not had success with currently available treatments, although some patients might not agree to their use because of stigma surrounding psychedelics.
- The controlled settings used for administration and monitoring might improve the safety of psychedelics.
- Treating mental health conditions with psychedelics is likely to disrupt health care delivery because of changes in staffing (eg, more clinicians for medical supervision), clinician training (ie, special therapist training for psychedelic-assisted sessions), and infrastructure (eg, adequate space for longer therapy sessions and patient monitoring).
- The initial cost of treatment might be high because of necessary infrastructure changes and because mental health treatments such as therapy are costly, but psychedelics might decrease costs associated with long-term mental health treatment or complications.

**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 thought that this intervention would reduce health care costs while reducing disparities by enabling health care access to underserved individuals who have internet access and live in rural areas or have difficulty getting to a medical facility.
- Stakeholders also thought that these smartphone apps would be useful in situations in which routine clinic visits are reduced or postponed, like the COVID-19 pandemic. However, stakeholders were concerned that user or device errors could lead to misdiagnosis and mistreatment.
Description

An accurate diagnosis, when made in a timely manner, can provide the best insight into treatment options for patients.\textsuperscript{380} For instance, in August 2019, a case study highlighted a patient for whom acute appendicitis was diagnosed via telehealth, allowing timely surgery to take place.\textsuperscript{381}

Smartphone apps can deliver examinations and diagnostic services to patients in remote areas for multiple age groups. These apps are accompanied by handheld kits that allow patients or caregivers to perform guided medical examinations and share results with their provider for an appropriate diagnosis and treatment.

For example, in August 2020, Avram et al\textsuperscript{382} reported that smartphones using an optical measurement of blood flow in small blood vessels performed with a fingertip pulse oximeter and coupled with artificial intelligence could detect diabetes. Other examples include TytoCare for ear infections, heart and lung sounds, and throat infection diagnosis; MoleScope for skin screening; and RetinaScope for diabetic eye disease screening.\textsuperscript{383-385} Chan et al\textsuperscript{386} suggested that smartphone apps accompanied with otoscopes show promise as screening tools for ear diseases in pediatric patients.

These apps can be used in acute-care situations but are not recommended for emergency or life-threatening situations. Moreover, the visit cost depends on the individual’s health care provider and insurance coverage.\textsuperscript{387}

Clinical Area(s) Potentially Disrupted

The practice of using physician-guided patient self-examinations with 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 secure, personal health information might be at risk of being hacked, collected, used, or shared for unintended purposes. Additionally, lack of stringent regulation and 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

Between March 23, 2020, and April 12, 2021, sixteen ECRI stakeholders, reflecting clinical engineering, health care generalist, health systems, nursing, and research perspectives, provided
comments and ratings on this topic. The list below provides a summary of key stakeholder perspectives.

- Smartphone-guided medical examinations might improve the decision-making process by allowing patients and caregivers 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, particularly to specialists, for patients residing in rural areas and those who have difficulty leaving their homes. Conversely, they might increase disparities because of costs associated with device implementation and lack of a stable broadband connection.

- Health literacy, disability, and cultural issues could also contribute to a patient’s learning curve associated with the use of smartphones for telehealth. These issues might increase user errors, which would give inaccurate information to health care providers.

- The lack of quality control for the handheld examination kits, as well as 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 allocated to conduct the examinations for patients who prefer this modality for receiving ongoing care; however, this could be offset by the individuals who reduce in-person doctor visits because of situations like the COVID-19 pandemic.
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