PCORI HEALTH CARE HORIZON SCANNING SYSTEM

High Potential Disruption Report
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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 Institute 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 may 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 is neither endorsement nor 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 have any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

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

The HCHSS provides PCORI with a systematic process to identify and monitor the technologies and innovations that are in PCORI's priority areas of interest. It also creates 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, providing information on selected new health care technologies and interventions. Any research investigator or funder can use the PCORI HCHSS to help select research topics.

Of interest for horizon scanning are health care technologies and innovations 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 (e.g., 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 manage a disease or condition or to improve care delivery. The second is analyzing the health care context in which these new and evolving interventions would exist to understand their potential for disruption to the standard of care. It is not the goal of the PCORI HCHSS to predict future use and costs of any health care intervention. Rather, the reports are intended to help inform and guide planning and prioritization of research resources.

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 system 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 been performed to inform a variety of 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, financial, or operational planning; prioritization of health services research; controlled diffusion of technologies; and provision of information to policy makers, purchasers, and providers of health care.

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 of the research environment) within 3 years and likely to cause a significant disruption (ie, change, shift) in one or more key dimensions of health care in the United States. Examples of these dimensions include patient health outcomes, access to care, care setting and delivery processes, disparities, and costs of care. HCHSS continues to monitor topics for up to 1 year after initial clinical availability.

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

We scan information sources broadly within each priority area to detect leads for potential topics meeting criteria as described above. Analysts review leads to discover potential topics and, if they meet inclusion criteria, create topic records encompassing PICO (intended patient population, intervention, comparators to the intervention, and patient-oriented outcomes of interest) information and key regulatory information (if the topic is subject to a regulatory pathway).

Analysts present potential topics at topic nomination meetings. After a brief presentation and discussion, HCHSS team members vote in blinded fashion to include or exclude the topic based on criteria described in the PCORI Health Care Horizon Scanning System: Horizon Scanning Protocol and Operations Manual. All included topics are reported in the quarterly Status Report (see the first volume, March 2019 Horizon Scanning Status Report).
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 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 1 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.

It is possible, even likely, that a particularly knowledgeable expert or patient commenter could have a personal, intellectual, or financial conflict of interest related to a topic on which he or she provides comments. Commenters are asked to declare all potential conflicts of interest on the structured comment form we send to record their ratings and comments. Those who declare potential conflicts of interest for a topic are not necessarily disqualified from participating. Their views are balanced by inputs from other neutral parties, including ECRI Institute experts.

Individuals with vested interests in new technologies, services, and innovations typically provide critical insights and information about the areas in which they have a vested interest. Their perspectives may include their vision and plans for how they intend to carry out adoption of a technology, service, or innovation.

From the total number of commenters per topic (5 to 9), we limit the number of participants with potential conflicts of interest to 2. Equally important is identifying whether any commenters represent special interests against a technology or service. If they are involved in some manner in developing a competing intervention, their views must be balanced by other commenters without special interests.

Twice a year, analysts review all topics for which stakeholder comments have been received in the previous 15 months. Based on stakeholder rationales and ratings, analysts nominate topics deemed to have the highest potential for disruption to be included in the *High Potential Disruption Report*. See Report Methods below for a detailed description of the process.

At any point, 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, (2) development of the intervention has ceased, or (3) the intervention has been clinically available outside of the clinical research environment for longer than 1 year.

The PCORI HCHSS began operating in December 2018. Since then, review of about 420 leads has led to identification of about 260 potential topics across the 5 PCORI priority areas. After subjecting these potential topics to our inclusion criteria and nomination process, more than 165 topics have been selected and are being actively monitored in the system.

**Report Methods**

A primary goal of the PCORI HCHSS is to identify health care interventions likely to cause significant disruption to patient health care in the United States. To that end, twice a year the Horizon Scanning team prepares a *High Potential Disruption Report* detailing interventions from
among those it has identified and is monitoring that are deemed to have high potential to cause disruption.

Every 6 months, all actively monitored topics receiving at least 5 sets of stakeholder comments and ratings (described above) within the past 15 months are considered for inclusion in a *High Potential Disruption Report*. Stakeholder comments and ratings serve as critical input into the HCHSS process for determining which interventions have the highest potential for disruption. Several weeks before delivery of each *High Potential Disruption Report*, the horizon scanning team reviews all stakeholder comments and ratings, then convenes to decide which topics to include in the report.

To provide an initial sorting order for the data, ECRI calculates the mean and median ratings for each of the 6 parameters that commenters provided for each eligible topic. The summary data are exported to a spreadsheet for the analysts, who assess the comments for each eligible topic as a starting point. Comments take priority over ratings because prior HCHSS experience has shown that individual commenters with similar rationales may rate a topic differently. Thus, ratings are used only as a preliminary signal of potential for disruption. Furthermore, comments for all eligible profiles are read—including those whose ratings are below the mean or median in a priority area—to ensure that no topic with important potential is missed because of a rating anomaly.

After review of stakeholder comments, the HCHSS team meets to decide which topics have the highest potential for disruption. The analyst for each priority area presents the results of the comments and ratings on all their respective topics that have at least 5 sets of stakeholder comments from the prior 15 months. Analysts make recommendations based on ratings and comments. Rating scores alone are not the sole criterion for inclusion—rather, commenter rationales are the main drivers for consideration of the topic’s disruption potential. All topics chosen for inclusion in this report have rating scores *and/or* supporting rationales at or above the average for all topics considered for inclusion in this priority area.

Each team member votes using a blinded voting system (simple majority rules) on topics to include in the report. The current voting team includes 10 to 12 participants. A vote to include indicates that the voter thinks the intervention has high potential for disruption, based on stakeholder ratings/comments and available data at the time. The decision data for each topic that an analyst presents is recorded, as is the reason for exclusion or changes to the topic. If the topic was included in a *High Potential Disruption Report* but is subsequently excluded, the reason for the change is recorded and stated in the current report. Topics selected for inclusion are subject to updated searches for the latest information and are assigned to analysts for report drafting.

After the decision meeting, analysts synthesize the stakeholder comments in a written analysis on each topic to compose the chapter(s) in their respective priority areas. This analysis provides a brief overview (see Report Summary) of each priority area and all the topics considered, followed by more detailed information on each topic designated as having high potential for disruption. The Project Manager, Medical Copyeditor, Senior Technical Advisor, and Project Director carefully review each chapter before it undergoes final preparation for delivery.

For additional details on methods, please refer to the *PCORI Health Care Horizon Scanning System: Horizon Scanning Protocol and Operations Manual*. 
Chapter 1. Alzheimer’s Disease and Other Dementias

Chapter Summary

For the Alzheimer’s Disease and Other Dementias priority area, no topics met criteria to be considered for inclusion in this report at this time. Topics meeting criteria are those for which: (1) preliminary phase III data for drugs, phase II (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled and sent for stakeholder comment before May 1, 2019; and (3) we received at least 5 sets of comments and ratings from stakeholder commenters between April 1, 2019, and May 7, 2019.

As of May 1, 2019, we were monitoring 7 topics in this priority area. These topics encompass novel pharmaceutical and biotechnologic interventions for treating Alzheimer’s disease and/or related symptoms (eg, agitation). However, these topics are still too early in development to meet criteria (as outlined above) for eligibility for this report. We archived 1 additional topic, Aducanumab for Treating Alzheimer’s Disease, in this priority area on March 21, 2019. This was done because its developers (Biogen, Cambridge, Massachusetts, and Eisai Co., Ltd., Tokyo, Japan) announced discontinuation of their phase III clinical trials of the drug, stating that aducanumab was unlikely to meet its primary endpoints.¹ These 8 topics will be described briefly in the June 2019 PCORI Health Care Horizon Scanning System: Horizon Scanning Status Report.
Chapter 2. Cancer

Chapter Summary

For the Cancer priority area, we considered for inclusion 6 topics for which (1) preliminary phase III data for drugs, phase II (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled and sent for stakeholder comment before May 1, 2019; and (3) we received at least five sets of comments and ratings from stakeholder commenters between April 1, 2019, and May 7, 2019.

As of May 1, 2019, we were monitoring 76 topics in this priority area, including those considered for inclusion in this report. The topics encompass pharmaceuticals, biotechnologies, and devices intended to treat 35 cancers and/or related conditions. Fourteen more topics in this priority area are undergoing or have been queued for stakeholder comment; however, fewer than 5 sets of stakeholder comments were received for those topics before May 7, and they were not considered for inclusion in this report. The remaining 56 topics are still too early in development to meet criteria (as outlined above) for eligibility for this report. The 76 topics we are monitoring will be listed in the June 2019 PCORI Health Care Horizon Scanning System Status Report.

Topics Considered for Inclusion in this Report

Table 1 lists 4 topics selected for inclusion during the High Potential Disruption Report decision meeting. Included topics are those that a majority of the voting team agreed had high potential for disruption, based on stakeholder ratings and comments and available data. Topics are listed alphabetically by Topic Title. The report below follows the same organization.

Table 1. Included Topics for Priority Area: Cancer

<table>
<thead>
<tr>
<th>Topic Title</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>DCVax-L for Treating Glioblastoma Multiforme (Adjuvant Setting)</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda) for Treating Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (First-Line Setting)</td>
<td></td>
</tr>
<tr>
<td>Pexidartinib for Treating Tenosynovial Giant Cell Tumors</td>
<td></td>
</tr>
<tr>
<td>Sodium Thiosulfate (Pedmark) for Preventing Cisplatin-Mediated Ototoxicity</td>
<td></td>
</tr>
</tbody>
</table>
Table 2 lists 2 topics considered but not selected for inclusion during the High Potential Disruption Report decision meeting. Topics considered but not included are those that a majority of the voting team agreed did not have high potential for disruption, based on stakeholder ratings and comments and available data. Each record contains a note explaining the reasons for exclusion. Topics are listed alphabetically by Topic Title.

Table 2. Topics Considered but Not Included for Priority Area: Cancer

<table>
<thead>
<tr>
<th>Topic Title</th>
<th>Exclusion Reason(s) and Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etirinotecan Pegol (Onzeald) for Treating Advanced Breast Cancer and Brain Metastases (Second-Line Setting)</td>
<td>Stakeholder commenters agreed that results from an ongoing phase III trial need to be reviewed to determine whether etirinotecan pegol has potential for disruption. We continue to actively monitor this topic.</td>
</tr>
<tr>
<td>Margetuximab for Treating Metastatic, Relapsed, or Refractory HER2-Positive Breast Cancer (Third-Line Setting)</td>
<td>Stakeholder commenters indicated that preliminary results from a randomized, controlled trial were promising in terms of efficacy. But they thought the approach offered by margetuximab for treating HER2-positive breast cancer was incremental or equivalent to existing HER2-targeted treatments in terms of health outcomes, patient management, health care delivery, and costs. We have archived this topic.</td>
</tr>
</tbody>
</table>

**Topic Summaries**

We present below 4 summaries on topics deemed to have high potential for disruption. Topics are ordered alphabetically by topic title.

**DCVax-L for Treating Newly Diagnosed Glioblastoma Multiforme**

**Highlights**

DCVax-L is an immunotherapy made from activated dendritic cells derived from the patient’s monocytes obtained during pheresis and then loaded with patient-derived tumor antigens that were obtained from the patient’s tumor during surgery. The therapy is intended as an adjunct to standard initial therapy for newly diagnosed glioblastoma multiforme (GBM). Most of the 8 stakeholders commenting on this topic agreed that DCVax-L has potential to improve outcomes, quality of life, and overall health of patients with GBM. Because DCVax-L is anticipated to be costly relative to standard of care, it also has potential to disrupt health care costs for patients and payers. DCVax-L’s high cost might also increase disparities because copayments even for insured patients could be high and uninsured and underinsured patients could have difficulty accessing DCVax-L.

**Patient Population**

The intended patients for DCVax-L treatment are adults aged 18 to 70 years with newly diagnosed, unilateral, stage IV GBM, astrocytoma, or glioma. Patients must not have had disease progression after completing primary therapy consisting of surgical resection (gross or near total resection) and external beam radiation therapy with or without concurrent temozolomide chemotherapy.
Intervention

GBM is a malignant brain cancer associated with poor outcomes and high mortality that begins as a stage IV disease with no evidence of a lower-grade precursor (the American Brain Tumor Association offers more information about GBM). Patients who have undergone primary treatment including surgery, radiation, and temozolomide typically experience disease recurrence in about 7 months and have a median overall survival between 14 and 17 months. An unmet need exists for new GBM treatments capable of delaying disease recurrence and extending survival.\(^2,3\)

DCVax-L is an autologous immunotherapy that consists of activated dendritic cells loaded with patient-derived tumor antigens. DCVax-L is manufactured from monocytes obtained from the patient through leukapheresis (ie, extracted from the patient’s blood) at a hospital, cancer center, or blood center (eg, the Red Cross).\(^4\) The sample is collected using a kit containing a shipping box and a special grinder vial (that grinds and homogenizes the sample) prefilled with enzymes. After tumor excision, a nurse or technician places pieces of the tissue sample into the vial, and ships the sample to the manufacturer.\(^4\) The isolated monocytes are differentiated into dendritic cells in vitro, activated and loaded with tumor-derived antigens obtained from a lysate of the surgically resected GBM tumor,\(^5\) frozen into single doses, and shipped back to the treatment facility. The product must remain frozen until just before it is administered to the patient.\(^4\) According to the manufacturer, facilities might need to “adopt new requirements for handling, distribution and delivery of DCVax.”\(^4\)

When DCVax-L is injected into the patient, the tumor lysate–pulsed dendritic cells purportedly activate T cells and B cells to elicit an adaptive immune response against GBM tumor cells.\(^5\) Intended as an adjunct to standard initial therapy for newly diagnosed GBM, DCVax-L could disrupt patient management and improve health outcomes.\(^2,5\)

At least 2 weeks after patients undergo primary therapy, a clinician administers DCVax-L containing \(2.5 \times 10^6\) tumor lysate–pulsed dendritic cells as an intradermal injection in the upper arm at days 0, 10, and 20 and at weeks 8, 16, 32, 48, 72, 96, and 120. DCVax-L is intended to be used in combination with adjuvant temozolomide chemotherapy. Patients self-administer oral tablets of adjuvant temozolomide (150-200 mg/m\(^2\)) taken for 5 days every 28 days until disease progression or development of intolerable toxicity.

Evidence Development Summary

DCVax-L is being evaluated in the GBM (NCT00045968) clinical trial for treating newly diagnosed GBM. GBM is a phase III, randomized, parallel-assignment, quadruple-blinded trial to evaluate the safety and efficacy of DCVax-L. Patients (\(n = 348\)) are randomly assigned in a 2:1 ratio to treatment with either DCVax-L plus temozolomide or placebo plus temozolomide. Upon progression, patients in the placebo arm cross over to the DCVax-L arm. The primary endpoint is progression-free survival (PFS) and the secondary endpoints are overall survival (OS), and time to disease progression.

Preliminary results from the GBM trial\(^2\) reported a median OS of 23.1 months from surgery in intent-to-treat (ITT) patients (\(n = 331\)). However, about 90% of ITT patients have received DCVax-L because of the trial’s cross-over design. At the time of analysis, 67 (30%) patients lived 30 months or more among 223 patients whose surgery date was at least 30 months earlier. Among 182 patients whose surgery occurred at least 36 months earlier, 44 (24.4%) lived 36 or more months. The median OS was 34.7 months in patients (\(n = 131\)) whose tumors contained a
methylated MGMT promoter (O⁶-methylguanine-DNA methyltransferase; associated with better prognosis). The median OS was 40.5 months in a subpopulation (n = 100) of extended survivors with currently unknown prognostic factors. Grade 3 or 4 adverse events were reported in 7 (2.1%) patients.

The primary endpoint of PFS has not yet been evaluated and will be the subject of later analyses by an expert panel. Because PFS can be complex to determine and pseudo-progression is a known confounding phenomenon in patients with GBM, investigators should perform a central and multifactorial assessment that uses criteria currently emerging as appropriate for immune therapy.

Manufacturers and Regulatory Status

Northwest Biotherapeutics, Inc. (Bethesda, Maryland) is developing DCVax-L, which is being evaluated in a phase III trial.

Results and Discussion of Stakeholder Comments

Eight stakeholder commenters, reflecting clinical, health technology, health systems, nursing, and research perspectives, provided comments and ratings on the topic of DCVax-L for treating newly diagnosed GBM.⁶⁻¹³ We have organized the following discussion of stakeholder comments by the parameters on which they commented.

Patient outcomes, quality of life, and overall health: A commenter with a clinical perspective emphasized the unmet need for this patient population, “In spite of advances in earlier diagnosis, the standard of care and adjuvant therapy for GBM have remained essentially the same since 2005. The continued absence of preventative measures, poor prognosis and relatively young age at presentation, for many in the mid-50’s, with a mean OS for newly diagnosed GBM of 14 to 15 months and mean OS of 7 to 8 months for recurrent GBM makes this disease not only devastating for the individual and family, but socioeconomically significant.”⁷ Basing their opinions on preliminary results and the poor prognosis of patients with GBM, 6 commenters thought DCVax-L has potential to improve patient health outcomes.⁶⁻⁸,¹⁰,¹²,¹³ But a commenter with a health systems perspective thought that available results suggest DCVax-L has a small potential to improve health outcomes. Still, this commenter indicated that if the mature data demonstrate better efficacy, DCVax-L could have greater impact on health outcomes in patients with GBM.⁹

Health disparities: Commenters unanimously agreed that DCVax-L does not have potential to improve health disparities. Six commenters with clinical, health systems, nursing, and research perspectives anticipate that DCVax-L will be very expensive, and even if insurance offers reimbursement, copayments could be high for anyone with insurance, and uninsured and underinsured patients with low socioeconomic status especially would have difficulty paying for DCVax-L.⁷⁻¹² In terms of access to DCVax-L, 2 commenters with health systems and research perspectives suggested that DCVax-L use might initially be limited to large research or academic medical centers. Thus, many patients, especially those living in remote rural areas, might have difficulty accessing hospitals that offer DCVax-L treatment.⁶,¹²

Health care delivery system: Most commenters thought DCVax-L has small to no potential to disrupt the health care delivery system, indicating that DCVax-L would not be burdensome because it is administered as intradermal injection in combination with standard adjuvant
therapy. But a commenter with a clinical perspective expects DCVax-L implementation to cause moderate disruption in restructuring of multifunctional staffs and clinical facilities in hospitals, which would be similar to changes experienced by hospitals employing immunotherapy protocols.\textsuperscript{7}

**Current paradigm of patient care:** Because DCVax-L is administered via intradermal injection and would be used in addition to standard therapy instead of as a replacement, most commenters expect DCVax-L to have small to no potential to disrupt current patient care paradigms.\textsuperscript{6,7,10-13} A commenter with a clinical perspective suggests that as a personalized medicine, DCVax-L may cause specific adverse effects that clinicians will need to monitor closely.\textsuperscript{8}

**Health care costs:** Although 4 commenters with health systems and research perspectives anticipate DCVax-L to be expensive relative to standard of care,\textsuperscript{6,9,12,13} 3 commenters with clinical and nursing perspectives indicated that they could not directly comment on DCVax-L’s potential to disrupt health care costs.\textsuperscript{7,8,10} The commenters with a research perspective specified that DCVax-L is likely to disrupt costs for patients and payers, but because the overall population eligible for DCVax-L treatment is not large, it will likely have less impact on health care providers and facilities.\textsuperscript{12,13}

**Overall disruption potential:** Four commenters with clinical, health systems, nursing, and research perspectives thought that DCVax-L is more likely to disrupt patient health outcomes by potentially improving them than any other aspect of health care delivery.\textsuperscript{6,7,10,12} Commenters with health systems, nursing, and research perspectives noted DCVax-L has potential to improve survival of patients with this difficult-to-treat disease.\textsuperscript{6,10,12} The commenter with a nursing perspective also pointed out that extending life might not be disruptive if the overall quality of life is low, indicating that if a patient lives longer with DCVax-L than with standard of care, but treatment causes serious adverse events, DCVax-L use would not benefit the patient.\textsuperscript{10} The commenter with a clinical perspective indicated the therapy could improve outcomes, thereby being a positive disruption. Based on the way DCVax-L was developed, resection of a patient’s tumor is essential, and DCVax-L must be administered in combination with standard adjuvant therapy. Because DCVax-L is considered an immunotherapy, it purportedly elicits an adaptive immune response against GBM tumor cells. However, the biology of immune responses in the brain involving B cells, T cells, and circulating tumor cells is not well understood.\textsuperscript{7} With the available clinical data, 4 commenters with clinical, health systems, and research perspectives thought that additional results from the ongoing trial are needed to fully assess whether DCVax-L has potential for disruption.\textsuperscript{8,9,11,13}

Pembrolizumab (Keytruda) for Treating Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (First-Line Setting)

**Highlights**

Pembrolizumab is an immune checkpoint inhibitor that prevents tumor cells from downregulating cancer-specific immune responses. It is intended as a first-line therapy for treating recurrent or metastatic head and neck squamous cell carcinoma (HNSCC). Most of the 6 stakeholders commenting on this topic agreed that pembrolizumab’s high cost has potential to
disrupt health care costs for third-party payers and patients of low socioeconomic status, who would have difficulty paying for treatment. This could lead to increased disparities in access to care. Some commenters thought that pembrolizumab has potential to improve outcomes, quality of life, and overall health of patients with recurrent or metastatic HNSCC. However, although data suggest that pembrolizumab might be better than standard chemotherapy for extending patient survival, commenters agreed that additional results from the ongoing clinical trial are needed to evaluate pembrolizumab’s overall potential for disruption.

Patient Population

The intended patients for pembrolizumab treatment are adults aged 18 years or older with untreated recurrent or metastatic HNSCC located in the oral cavity, larynx, hypopharynx, or oropharynx. Patients with recurrent HNSCC who completed postoperative systemic therapy more than 6 months earlier, given as part of multimodal treatment for locally advanced disease, are also eligible for pembrolizumab treatment. Like other immune checkpoint inhibitor indications, pembrolizumab’s use in HNSCC may require the patient’s tumor to exhibit expression of programmed death ligand 1 (PD-L1).

Intervention

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

Cancer cells have developed immune-tolerance mechanisms to avoid detection and destruction. These mechanisms involve the overexpression of ligands that limit T-cell responses. These so-called immune checkpoints are thought to have evolved to prevent runaway immune responses; however, by aberrantly activating these immune checkpoints, cancers reportedly can reduce the body’s anticancer immune response.

One of these checkpoint pathways is programmed death-1 (PD-1), a receptor expressed by many immune system cells, including high expression on activated T cells, which has a central role in T-cell downregulation. In many types of cancer, PD-L1, the ligand for PD-1, is highly expressed by cells in the tumor. Binding of PD-L1 to PD-1 causes the inactivation of cancer-specific T cells, which allows the tumor to evade immune responses.14

HNSCC tumors can reduce anticancer immune responses because they express high levels of PD-L1, thus preventing T cells from targeting tumor cells.15 A potential therapeutic target that prevents the interaction between PD-L1 in tumor cells and PD-1 in T cells could potentially induce an immune response against HNSCC by preventing T cell downregulation.14,15

Pembrolizumab is a humanized monoclonal immunoglobulin G4 (IgG4) antibody that binds the PD-1 co-inhibitory receptor expressed in activated T cells. Preclinical studies performed in animal cancer models have shown that antibody-mediated inhibition of the PD-1/PD-L1 pathway increases T-cell antitumor response. Pembrolizumab binding to PD-1 purportedly prevents interaction between PD-1 and its ligands, inhibiting the immune checkpoint pathway and leading to an increase in anticancer immune response to HNSCC tumors.14,15 Because antibody binding to PD-1–expressing immune cells has the potential to deplete these immune cells,
pembrolizumab’s Fc region has also been modified to reduce the induction of antibody-dependent cellular cytotoxicity and complement mediated cytotoxicity.14

For several indications, pembrolizumab has been jointly approved with the PD-L1 IHC 22C3 pharmDx companion diagnostic. Most of the KEYNOTE trials of pembrolizumab, including KEYNOTE-048, have used PD-L1 IHC 22C3 pharmDx to determine the PD-L1 status of tumors. The companion diagnostic test is billed separately from pembrolizumab.16

An oncologist prescribes pembrolizumab and refers the patient to an infusion center. An infusion nurse will administer 200 mg of intravenous pembrolizumab on day 1 of each 21-day cycle for up to 24 months. Pembrolizumab may be administered in combination with intravenous cisplatin (100 mg/m² on day 1) or carboplatin (AUC 5 on day 1) plus 5-fluorouracil (1000 mg² from day 1 to 4) for up to 6 cycles.

Evidence Development Summary

Pembrolizumab is being studied in the KEYNOTE-048 (NCT02358031) clinical trial for treating recurrent or metastatic HNSCC in the first-line setting. KEYNOTE-048 is a phase III, randomized, parallel-assignment, open-label trial to evaluate pembrolizumab’s safety and efficacy alone or in combination with a platinum agent in patients with HNSCC compared with those of the EXTREME regimen (5-fluorouracil plus cetuximab and cisplatin or carboplatin). Patients (n = 882) are randomly assigned in a 1:1:1 ratio to treatment with either pembrolizumab, pembrolizumab and a platinum agent plus 5-fluorouracil, or the EXTREME regimen. The primary endpoints are OS and PFS and the secondary endpoints are objective response rate (ORR) and health-related quality of life.

While the KEYNOTE trial is still ongoing, preliminary results are available for evaluation. In the KEYNOTE-048 trial17 patients were stratified by PD-L1 combined positive score (CPS), derived from the PD-L1 IHC 22C3 pharmDx test to evaluate PD-L1 expression in both tumor cells and tumor-associated immune cells. Preliminary results demonstrated that in the pembrolizumab versus EXTREME regimen groups, pembrolizumab was superior to the EXTREME regimen in patients (n = 255) with CPS ≥ 20 (median OS 14.9 versus 10.7 months; hazard ratio [HR] 0.61; 95% confidence interval [CI], 0.45 to 0.83; P < .001). Patients (n = 512) with CPS ≥ 1 had median OS of 12.3 versus 10.3 months (HR, 0.78; 95% CI, 0.64 to 0.96; P = .009). Pembrolizumab did not prolong PFS in patients with CPS ≥ 20 (P = .5), and PFS was not analyzed in patients with CPS ≥ 1.17

In the total population (n = 601), pembrolizumab was noninferior to the EXTREME regimen. Even though pembrolizumab did not have better ORR than the EXTREME regimen for patients with CPS ≥ 20 (23% versus 36%), with CPS ≥ 1 (19% versus 35%), or the total population (17% versus 36%), pembrolizumab improved the duration of response for patients with CPS ≥ 20 (20.9 versus 4.2 months), with CPS ≥ 1 (20.9 versus 4.5 months), and the total population (20.9 versus 4.5 months).17

Patients treated with pembrolizumab also experienced fewer grade 3 or 4 adverse events than those treated with the EXTREME regimen (17% versus 69%).17

Pembrolizumab in combination with chemotherapy (platinum agent plus 5-fluorouracil) was superior to the EXTREME regimen for OS (median OS 13.0 versus 10.7 months; HR 0.77, 95% CI, 0.63 to 0.93; P = .003). But in the total population (n = 559), it did not statistically significantly prolong PFS (P = .2). Pembrolizumab’s combination therapy also did not improve
ORR (36% versus 36%) or duration of response (6.7 versus 4.3 months) and increased the rate of grade 3 or 4 adverse events (71% versus 69%).

Manufacturers and Regulatory Status

Merck & Co., Inc. (Kenilworth, New Jersey) manufactures pembrolizumab. In August 2016, FDA granted accelerated approval to pembrolizumab for treating recurrent or metastatic HNSCC that has progressed on or after platinum-based chemotherapy (ie, second-line setting). FDA has also approved pembrolizumab for treating several other cancer types. For more FDA-approved indications, see FDA prescribing information.

In February 2019, FDA accepted a supplemental Biologics License Application (sBLA) for first-line pembrolizumab based on results from the KEYNOTE-048 trial. FDA granted the sBLA priority review and assigned a Prescription Drug User-Fee Act action date of June 10, 2019. According to Merck, the sBLA may also serve as confirmatory results to support pembrolizumab’s full approval in the second-line setting.

If pembrolizumab gains FDA marketing approval for treating HNSCC, PD-L1 IHC 22C3 pharmDX will likely be approved as its companion diagnostic.

Cost Information

According to a US-based, online aggregator of prescription drug prices, GoodRx, pembrolizumab’s retail price as of May 2019 was about $9,000 for 4 vials of 50 mg, which is the amount (200 mg) a patient would use for each 3-week cycle. Thus, if a patient continued on treatment for a full year, the cost would be about $153,000 (17 cycles at $9,000 per cycle).

Results and Discussion of Stakeholder Comments

Six stakeholder commenters, reflecting clinical, health systems, nursing, and research perspectives, provided comments and ratings on pembrolizumab for treating recurrent or metastatic HNSCC. We have organized the following discussion of stakeholder comments by the parameters on which they commented.

Patient outcomes, quality of life, and overall health: Most commenters indicated pembrolizumab has potential to improve patient health outcomes and appears to be an advancement for treating HNSCC. One commenter with a clinical perspective considered the improvement of 5 months in OS to be a breakthrough for HNSCC but still thought that it was a small benefit. Another commenter with a nursing perspective expressed concerns about pembrolizumab treatment not being consistently better than the EXTREME regimen when offered alone or in combination.

Health disparities: Most commenters with health systems, clinical, and nursing perspectives agreed that pembrolizumab is unlikely to improve health disparities. Among these, 3 commenters with health systems, clinical, and nursing perspectives indicated that pembrolizumab is a more expensive option, even if insurance offers reimbursement and that costs, including copayments, could be high for insured, underinsured, and uninsured patients. It is likely that only patients with high socioeconomic status would not have difficulty paying for pembrolizumab. A commenter with a research perspective thought that when newly
approved, pembrolizumab might increase disparities because some payers might offer reimbursement, while others might not, thus limiting access to pembrolizumab treatment.\textsuperscript{26}

**Health care delivery system:** As another intravenous intervention in the arsenal of chemotherapy agents, pembrolizumab use would not greatly disrupt the health care delivery system, most commenters agreed. However, a commenter with a clinical perspective thought the change from using pembrolizumab in second-line therapy to first-line therapy has potential to disrupt treatment offerings.\textsuperscript{22}

**Current paradigm of patient care:** Most commenters agreed that, because pembrolizumab would be administered intravenously at infusion centers, it would cause very little or no disruption in the current paradigm of patient care. A commenter with a clinical perspective expected pembrolizumab to become an alternative to the standard-of-care treatment, platinum-based chemotherapy. Even though both are administered intravenously at infusion centers, pembrolizumab use might lead to different adverse events that would need to be monitored by clinicians.\textsuperscript{23}

**Health care costs:** Most commenters agreed that, with a cost of about $150,000 per year, pembrolizumab is an expensive intervention that can disrupt health care costs, in particular by placing a burden on third-party payers. A commenter with a clinical perspective pondered whether payers would reimburse an expensive intervention such as pembrolizumab, indicating that if they did not, only patients with very high socioeconomic status would have access to treatment. This commenter also noted that with pembrolizumab treatment being limited to patients expressing PD-L1, its potential to disrupt health care costs overall could be reduced, although individual patient costs would still be affected.\textsuperscript{23}

**Overall disruption potential:** Although 2 commenters with clinical perspectives concluded that much of pembrolizumab’s potential for disruption is based on it being a much-needed and important advancement for treating HNSCC, one of these also thought that pembrolizumab’s cost is likely to be the most important disruptor to the health care system.\textsuperscript{22,24} According to 3 commenters with clinical, nursing and research perspectives, pembrolizumab is not consistently effective and in some outcomes, such as PFS, pembrolizumab was not superior to standard of care. Additional results from the ongoing clinical trial may help evaluate pembrolizumab’s overall potential for disruption.\textsuperscript{23,25,26}

### Pexidartinib for Treating Tenosynovial Giant Cell Tumors

**Highlights**

Pexidartinib is a multikinase inhibitor under study for treating tenosynovial giant cell tumors (TGCTs). TGCTs are benign soft-tissue sarcomas that arise from joint tissue. They can significantly deteriorate quality of life, and no FDA-approved systemic therapy is available. The 6 stakeholders commenting on this topic agreed that pexidartinib would represent the first systemic therapy approved by FDA for treating the rare disease TGCT and, therefore, could represent a paradigm shift in managing these patients. It would do so by providing a treatment option for patients ineligible for surgical resection or a treatment alternative to surgical resection. However, most commenters voiced concerns regarding toxicity associated with pexidartinib treatment (particularly hepatic toxicity). Some also thought the small number of patients affected...
by the disease could limit pexidartinib’s disruption of TGCT treatment and the broader health care system.

**Patient Population**

The intended population is adults aged 18 years or older with a TGCT (also known as a giant cell tumor of the tendon sheath) that is unamenable to surgical resection because surgery would likely cause significant morbidity or functional limitation.

**Intervention**

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

TGCTs are often amenable to treatment by surgical resection. However, patients (in particular, patients with the diffuse type of TGCT, also known as pigmented villonodular synovitis) often experience multiple recurrences, which can lead to substantial morbidity. FDA has not approved any systemic therapy for treating TGCTs, and patients ineligible for surgical resection have few treatment options. For more information on TGCT, see the National Organization for Rare Diseases.

TGCTs are characterized by the overexpression of the cytokine colony stimulating factor-1 (CSF-1). In many cases, CSF-1 overexpression is caused by a genetic base-pair translocation involving the CSF-1 gene, which causes constitutive expression of the gene by neoplastic TGCT cells. Overexpression of CSF-1 causes recruitment of cells that express colony-stimulating factor-1 receptor (CSF-1R), such as macrophages, which compose most of the tenosynovial giant cell tumor’s mass.

Pexidartinib (PLX3397) is a small-molecule inhibitor of multiple receptor tyrosine kinases, including CSF1R, FLT3, and KIT. Inhibition of CSF-1R signaling by pexidartinib has the potential to disrupt the paracrine signaling loop that underlies the pathogenesis of TGCTs.

In clinical trials, pexidartinib was administered as 200-mg oral capsules. Patients self-administered 1000 mg/day for 2 weeks followed by 800 mg/day for an additional 22 weeks.

**Evidence Development Summary**

Results from the phase III, randomized, controlled ENLIVEN trial (NCT02371369) were presented at the 2018 American Society of Clinical Oncology annual meeting. In this study, 120 adults aged 18 years or older with symptomatic TGCTs for whom surgery would be associated with reduced joint function or substantial morbidity were randomly assigned to treatment with either pexidartinib (61 patients at 1000 mg/day for 2 weeks followed by 800 mg/day for 22 weeks) or to placebo (59 patients). Patients completing the randomized, controlled portion of the study were eligible to continue into an open-label extension portion of the trial in which all patients received pexidartinib.

The trial’s primary efficacy endpoint was overall response rate by Response Evaluation Criteria in Solid Tumors (RECIST) in the randomized, controlled portion of the trial; 39.3% of
patients receiving pexidartinib achieved a response compared with 0% of patients receiving placebo ($P < .001$). Patients in the pexidartinib arm of the trial also experienced increased improvements in measures of joint function such as range of motion (+15.1% pexidartinib versus +6.2% placebo, $P = .0043$), PROMIS (Patient-Reported Outcomes Measurement Information System) physical function scale (+4.06 versus -0.89, $P = .002$), worst stiffness (-2.45 versus -0.28, $P < .001$), and pain response (31.1% versus 15.3%, 1-sided $P = .03$).\textsuperscript{30}

Hepatic toxicities were observed in patients receiving pexidartinib, and trial enrollment was halted by the trial’s data monitoring committee 6 patients short of the target enrollment after nonfatal, serious hepatic toxicity was reported in 2 patients. In all, 8 patients discontinued pexidartinib treatment because of hepatic toxicity. Other adverse events reported in at least 15% of patients receiving pexidartinib included hair-color changes, vomiting, fatigue, dysgeusia (distortion in sense of taste), and periorbital edema.\textsuperscript{30}

Manufacturers and Regulatory Status

Pexidartinib is being developed by Daiichi Sankyo (Tokyo, Japan). The manufacturer sponsored a phase III randomized, controlled trial of pexidartinib for treating TGCTs and, based on data from this trial, submitted a New Drug Application (NDA) to FDA. On May 14, 2019, the FDA’s Oncologic Drugs Advisory Committee reviewed the pexidartinib NDA with panel members voting 12-3 in favor on the question “Does the demonstrated benefit of pexidartinib outweigh the risks of the drug in the proposed indication?”\textsuperscript{31}

FDA has granted the pexidartinib NDA priority review status with a Prescription Drug User Fee Act designated decision date of August 3, 2019.\textsuperscript{32} FDA had previously granted pexidartinib Breakthrough Therapy designation for treating TGCT.\textsuperscript{33}

Results and Discussion of Stakeholder Comments

Six stakeholder commenters, representing clinical, research, and health systems perspectives, provided comments and ratings on this TGCT treatment.\textsuperscript{34-39} We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Most commenters indicated that pexidartinib would have moderate to large potential to improve patient outcomes, quality of life, and overall health.\textsuperscript{35-38} These commenters suggested that the ENLIVEN trial results indicated that pexidartinib led to a radiographic response in a significant number of patients as well as positively affecting parameters of joint function with the potential to improve quality of life. However, multiple commenters noted that the hepatic toxicity observed in the trial could limit pexidartinib’s potential impact. In particular, 2 commenters with research and health systems perspectives indicated that the toxicity issues meant pexidartinib has only a small potential to improve patient health outcomes.\textsuperscript{34,39}

**Health disparities:** Commenters generally agreed that pexidartinib would have only a small potential to disrupt health disparities, and the disruption relates to exacerbation of existing socio-economic disparities.

**Health care delivery system:** Several commenters thought that pexidartinib would have a moderate to large potential to disrupt the health care delivery system, citing the shift from surgical management to an orally administered, systemic therapy.\textsuperscript{36-38} Conversely, in the context
of the entire health care system, commenters with health systems and research perspectives thought that the drug would have no or only small potential to disrupt the health care delivery system, citing the small number of patients affected by TGCTs and that no special infrastructure would be needed for the orally administered drug.\textsuperscript{34,35,39} One commenter with a research perspective suggested that the fact that pexidartinib is intended for use in patients who are ineligible for surgical resection would mitigate the drug’s potential impact on health care delivery system.\textsuperscript{39}

**Current paradigm of patient care:** Most commenters thought that pexidartinib has a moderate to large potential to disrupt the current treatment paradigm for patients with TGCTs, citing the potential for the first FDA-approved systemic therapy for TGCT to shift the treatment for some patients from surgery to an orally administered drug. In particular, one commenter with a clinical perspective noted that this could cause a shift in patient management towards medical oncology and/or multidisciplinary oncology-orthopedic surgery tumor boards. Additionally, this commenter noted that managing pexidartinib hepatic toxicity might require close monitoring that could increase the potential impact of pexidartinib use.\textsuperscript{36} But one commenter with a research perspective suggested that this hepatic toxicity would limit uptake of the drug to such an extent that its potential to disrupt patient management would be only minimal.\textsuperscript{39}

**Health care costs:** Most commenters thought that pexidartinib was likely to cause only minimal disruption to health care costs, citing the small number of patients affected by the condition and the fact that pexidartinib costs would be offset by decreased use of surgical resection and/or off-label use of other systemic therapies.\textsuperscript{34,35,37,39} Alternatively, one commenter with a research perspective suggested that pexidartinib use might decrease costs by better controlling morbidity associated with TGCTs,\textsuperscript{38} and one commenter with a clinical perspective suggested that pexidartinib use might increase costs due to the introduction of costly targeted therapy and associated adverse-event monitoring.\textsuperscript{36}

**Overall disruption potential:** Overall, commenters thought that pexidartinib, as the first FDA-approved systemic therapy for treating TGCTs, has the potential to improve patient health and alter patient management. However, experts cautioned that the observed hepatic toxicity might limit use of the drug and noted that the effects of pexidartinib on the health care system more generally were limited by the small number of patients in whom TGCTs are diagnosed.\textsuperscript{34-39}

**Sodium Thiosulfate (Pedmark) for Preventing Cisplatin-Mediated Ototoxicity**

**Highlights**

Pedmark is a proprietary formulation of sodium thiosulfate intended to reduce the risk of cisplatin-induced ototoxicity, which can lead to hearing loss, tinnitus, or vertigo, particularly in children undergoing chemotherapy. In 2 clinical trials, treatment with sodium thiosulfate significantly reduced hearing loss by 48% and 49%, compared with standard care. The 7 stakeholders commenting on this topic generally agreed that sodium thiosulfate could meet an important unmet need—given the significant morbidity that children with cisplatin-induced ototoxicity experience and the lack of approved treatments—and that it could positively disrupt patient-oriented health outcomes, including quality of life. However, most commenters thought
that factors surrounding delivery of the treatment (eg, the 6-hour wait time) might create disparities in access to care and/or add to the burden of care for these patients.

Patient Population

The intended population for this intervention is children aged 1 month to 18 years with localized, nonmetastatic solid tumors eligible for cisplatin chemotherapy.

Intervention

Pedmark is a proprietary formulation of sodium thiosulfate intended to reduce the risk of cisplatin-induced ototoxicity.\(^40,41\) Development of ototoxicity, which can result in hearing loss, tinnitus, or vertigo, is a well-known risk of using cisplatin chemotherapy for various cancers.\(^42\) Anti-ototoxic (protective) effects of sodium thiosulfate have been attributed to multiple mechanisms of action—including inactivation of platinum and/or platinum-protein complexes to reduce cisplatin’s direct cytotoxic effects, inactivation of reactive oxygen species (ROS), and/or elevation of levels of endogenous reducing agents (eg, glutathione)—which could inhibit the ROS-induced cell death (apoptosis) induced by cisplatin.\(^41\)

Because of sodium thiosulfate’s potential to interfere with cisplatin’s cytotoxic activity, sodium thiosulfate administration is delayed to allow cisplatin to exert its anticancer effects while remaining within a time window that allows an otoprotective effect. In clinical trials, sodium thiosulfate is administered intravenously, \(16 \text{ g/m}^2\) or \(533 \text{ mg/kg}\), 6 hours after the patient receives cisplatin-based chemotherapy. Sodium thiosulfate treatment is given with each round of cisplatin until treatment is complete.\(^40,41\)

Evidence Development Summary

Investigators have reported results from 2 trials of sodium thiosulfate, SIOPEL6 (NCT00652132) and ACCL0431 (NCT00716976), to reduce the risk of cisplatin-induced ototoxicity.

In the phase III SIOPEL6 randomized, controlled trial, pediatric patients (\(n = 109\)) aged 1 month to 18 years with stage I to III liver cancer (hepatoblastoma) were assigned to treatment with cisplatin alone or cisplatin plus sodium thiosulfate infusion 6 hours after chemotherapy, for 4 preoperative and 2 postoperative courses. The study evaluated the safety and efficacy of sodium thiosulfate for reducing absolute hearing loss (Brock grade 1 or higher) in patients treated with cisplatin chemotherapy.

The investigators reported that 33% of children receiving cisplatin with sodium thiosulfate experienced hearing loss compared with 63% of children receiving cisplatin alone (48% lower incidence of hearing loss; relative risk, 0.52; \(P = .002\)).

At a median 52 months of follow-up, both groups had similar 3-year rate of event-free survival rates (cisplatin and sodium thiosulfate 82% [95% CI, 69% to 90%] versus 79% for cisplatin alone [95% CI, 65% to 88%]). Patients in both groups also had similar 3-year overall survival rates (98% for cisplatin and sodium thiosulfate [95% CI, 88% to 100%] vs. 92% for cisplatin alone [95% CI, 81% to 97%]).\(^43\)

In the phase III, open label, ACCL0431 randomized, controlled trial, pediatric patients (\(n = 104\)) aged 1 to 18 years with newly diagnosed germ cell tumor, hepatoblastoma,
medulloblastoma, neuroblastoma, osteosarcoma, or other malignancy who were eligible for
cisplatin therapy were assigned 1:1 to treatment with sodium thiosulfate or observation (control
group). The investigators reported hearing loss in 28.6% of patients given sodium thiosulfate
compared with 56.4% of patients in the control group ($P < .001$), and when adjusted for
stratification variables, the likelihood of hearing loss remained lower in the sodium thiosulfate
group compared with control (odds ratio 0.31, 95% CI, 0.13 to -0.73; $P = .004$).

Of the 194 serious adverse events reported in patients given sodium thiosulfate, none were
attributed to the drug. The most common grade 3 to 4 hematologic adverse event was
neutropenia (66% of 178 participant cycles in the sodium thiosulfate group versus 65% of 224
cycles in the control group). The most common nonhematologic adverse event observed was
hypokalemia (17% of 149 cycles in the sodium thiosulfate group versus 12% of 187 cycles in the
control group).44

Manufacturers and Regulatory Status

Sodium thiosulfate is being developed by Fennec Pharmaceuticals, Inc. (Research Triangle
Park, North Carolina). In December 2018, Fennec Pharmaceuticals initiated a rolling New Drug
Application for Pedmark for preventing cisplatin-induced ototoxicity in children aged 1 month to
18 years who have localized, nonmetastatic, solid tumors.45 In March 2018, FDA granted the
drug Breakthrough Therapy designation for preventing cisplatin-related ototoxicity in pediatric
patients with standard-risk hepatoblastoma.46 FDA has also granted sodium thiosulfate Orphan
Drug and Fast Track designations for preventing cisplatin-induced ototoxicity in children.45,46

Results and Discussion of Stakeholder Comments

Seven stakeholder commenters reflecting clinical, nursing, allied health, research, and health
systems perspectives provided comments and ratings on sodium thiosulfate.47-53 We have
organized the following discussion of stakeholder comments by the parameters on which they
commented.

Patient outcomes, quality of life, and overall health: Commenters agreed that data from a
clinical trial showed that sodium thiosulfate substantially reduced the incidence of hearing loss in
children concomitantly treated with cisplatin. A commenter with a nursing perspective thought a
need exists for a hydration plan accompanying this intervention during the 6-hour waiting period
due to the risk of renal toxicity that chemotherapeutic drugs like cisplatin are known to cause.51
Several commenters with allied health and health systems perspectives thought that, in the
absence of other options for preventing hearing loss, sodium thiosulfate would likely positively
disrupt patient health outcomes and quality of life in this population.47,48,53

Health disparities: Most commenters noted that the cost of sodium thiosulfate and changes
in transportation accommodations due to the 6 hours between treatments might be difficult for
some patients and caregivers and thereby increase disparities. However, 2 commenters with
clinical and allied health perspectives thought that sodium thiosulfate might reduce disparities by
alleviating downstream burdens associated with life-long hearing loss, which could be even more
difficult to manage for patients of low economic status or who have limited resources.47,50

Health care delivery system: Commenters with clinical and health systems perspectives
thought that the 6-hour wait between cisplatin and sodium thiosulfate administration would
likely lead to longer outpatient infusion visits or hospital stays, increasing demands on the
Conversely, a commenter with an allied health perspective noted that preventing hearing loss and related lifelong supportive care could substantially improve health outcomes and reduce cost of care and long-term system burden. Current paradigm of patient care: Most commenters thought sodium thiosulfate has little potential to disrupt treatment paradigms. However, two commenters with clinical and nursing perspectives agreed that a longer chemotherapy stay could disrupt current treatment paradigms because treatment with sodium thiosulfate involves keeping children at the facility and occupied. Health care costs: Most commenters agreed that sodium thiosulfate would be cost saving because the costs for hearing rehabilitation (hearing devices, educational services, speech-language services) would likely outweigh the costs of hearing-loss prevention—and hearing-technology costs might not be covered by insurance. Two commenters with health systems and clinical perspectives thought that disruption in costs would depend on insurance reimbursement for patients and providers for this treatment. Overall disruption potential: Noting that no other options are available for preventing cisplatin-related ototoxicity, most commenters thought that sodium thiosulfate has large overall potential to disrupt health care delivery, particularly in regards to patient-oriented health outcomes and quality of life. Two commenters with research and health systems perspectives expressed concerns about how quickly this intervention would be adopted by clinicians and patients because of the intravenous administration route for Pedmark.
Chapter 3. Cardiovascular Diseases

Chapter Summary

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

As of May 1, 2019, we were monitoring 17 topics in this priority area, including the one considered for inclusion in this report. The topics encompass pharmaceuticals, biotechnologies, devices, and implants intended to treat 10 cardiovascular diseases and/or related symptoms. One topic, WEB Embolization System for Treating Intracranial Wide-Necked Bifurcated Aneurysms, approved for marketing by FDA in December 2018, is currently undergoing stakeholder comment; however, fewer than 5 sets of stakeholder comments were received for the topic before May 7, and it was not considered for inclusion in this report. The remaining 15 topics are still too early in development to meet criteria (as outlined above) for eligibility for this report. These 17 topics will be described briefly in the June 2019 PCORI Health Care Horizon Scanning System Status Report.

Topics Considered for Inclusion in this Report

Table 1 lists 1 topic selected for inclusion during the High Potential Disruption Report decision meeting. Included topics are those that a majority of the voting team agreed had high potential for disruption, based on stakeholder ratings/comments and available data.

Table 1. Included Topic for Priority Area: Cardiovascular Diseases

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<tr>
<th>Topic Title</th>
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<tr>
<td>Cardiac Contractility Modulation (Optimizer) for Treating Moderate to Severe Chronic Heart Failure</td>
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Topic Summaries

We present below 1 summary on this topic, which was deemed to have high potential for disruption.

Cardiac Contractility Modulation (Optimizer) for Treating Moderate to Severe Chronic Heart Failure

Highlights

Most of the 9 stakeholders commenting on this topic thought that cardiac contractility modulation with the implantable Optimizer device has moderate to large potential to disrupt care for patients with heart failure. This was across several domains, including patient outcomes,
treatment costs, health care disparities, patient management, and the health care delivery system. Commenters reflecting patient and nursing perspectives rated this technology as having large disruptive potential, especially given the existing lack of heart failure treatment options along the clinical pathway between medical management and highly invasive interventions, such as left-ventricular assist devices and heart transplantation.

**Patient Population**

Intended patients for the Optimizer are adults aged 18 years or older with a diagnosis of New York Heart Association (NYHA) functional class III heart failure. Further, these are patients who remain symptomatic while on guideline-directed medical therapy and are in normal sinus rhythm (ie, not candidates for cardiac resynchronization therapy) with left ventricular ejection fraction (LVEF) between 25% and 45%.

**Intervention**

Cardiac contractility modulation (CCM) with the implantable Optimizer device delivers nonexcitatory electrical pulses to the heart during the myocardial absolute refractory period to improve systolic contraction in the weakened heart muscle of patients with moderate to severe heart failure. CCM purportedly normalizes phosphorylation of regulatory proteins to improve calcium handling, thereby interrupting the remodeling cascade to reverse left ventricular enlargement and improve left ventricular contractile strength.

Physicians place the implantable pulse generator (IPG) in a subcutaneous pocket in the patient’s right pectoral region using techniques similar to implanting conventional pacemakers and defibrillators. Clinicians place 2 standard pacemaker leads through the subclavian vein on the right ventricular septum: one lead to sense local electrical activity and the second to deliver CCM therapy. Physicians may also implant a third lead in the right atrium for additional electrical sensing.

Physicians program and interrogate the Optimizer IPG with the Omni II Programmer System, which includes a magnetic induction telemetry wand, a programmer interface box, and a touchscreen tablet or laptop computer with proprietary software.

The Optimizer IPG delivers pulses at regular intervals during the day, purportedly unnoticed by patients. Patients recharge the IPG’s battery at home for about 60 to 90 minutes once a week, using a noninvasive charging system placed over the implant.

**Evidence Development Summary**

The manufacturer continues to evaluate the Optimizer device in 2 ongoing studies in the United States. One nonrandomized study (NCT03339310), scheduled for completion in November 2019, is evaluating the Optimizer with a 2-lead configuration in up to 60 adults with moderate to severe heart failure. This study is assessing change in exercise tolerance and device-related adverse events (primary outcomes) and efficacy of CCM delivery with the Optimizer device using 2 leads versus 3 leads.

A second prospective, nonrandomized study (NCT03102437), scheduled for completion in January 2020, was designed to allow controlled access to the Optimizer Smart System in up to 350 adults with moderate to severe heart failure until FDA granted the device regulatory...
approval. The study is assessing serious device-related adverse events (primary outcome) and change in NYHA functional class and quality of life.62

A nonrandomized European pilot study (NCT03240237), scheduled for completion in March 2021, is evaluating the Optimizer device in a different population: adults who have heart failure with preserved ejection fraction (ie, LVEF ≥ 50%).63

In October 2018, Abraham et al reported that CCM with the Optimizer Smart device plus optimal medical therapy improved exercise tolerance and quality of life and reduced heart-failure related hospitalizations through 6 months compared with optimal medical therapy alone. The randomized FIX-HF-5C trial (NCT01381172) compared treatments among 160 adults aged 18 years or older with NYHA functional class III to IV heart failure and LVEF between 25% and 45% enrolled at more than 40 centers across the United States and Germany.64

In this trial, exercise tolerance quantified by peak oxygen consumption (VO2) improved by 0.84 mL O2/kg/min (95% Bayesian credible interval, 0.123-1.552) in the Optimizer plus optimal medical therapy group compared with the control group, satisfying the primary endpoint. The Optimizer treatment group also showed significant improvement compared with the control group in Minnesota Living With Heart Failure Questionnaire (MLHFQ) scores (-21.3 points versus -10.2 points, respectively, \(P < .001\)), NYHA functional class (≥1 class change, 81.4% versus 42.7%, respectively, \(P < .001\), and 6-minute hall walk distance (43.0 ± 80.7 m versus 9.3 ± 87.4 m, respectively, \(P = .009\)).64 (In a 2017 systematic review, Bohannon and Crouch found that a change of 14.0 m to 30.5 m in 6-minute hall walk distance may be clinically important across multiple patient groups.65 Clinically meaningful changes in MLHFQ scores between 5 and 19 have been reported.66-68) The composite rate of cardiovascular death and heart-failure-related hospitalizations was significantly lower in the Optimizer group compared with the control group, 2.9% versus 10.8%, respectively (\(P = .048\)). Seven device-related events occurred, yielding a lower bound of 80% of patients free from device-related events, satisfying the primary safety endpoint.64

In January 2019, Anker et al reported that Optimizer therapy in real-world practice demonstrated improvement similar to that seen in clinical trials.69 Investigators measured changes in heart-failure-related hospitalization, NYHA functional class, MLHFQ scores, and mortality among 140 adults with NYHA class III to IV heart failure and LVEF between 25% and 45% treated at 31 centers in a European patient registry. Hospitalizations decreased by 75%, from 1.2/patient-years at baseline to 0.35/patient-years at 2 years after Optimizer implantation (\(P < .0001\)) in the entire patient group and similarly in subgroups. After 3 years, observed mortality was similar to that predicted by the Seattle Heart Failure Model for the entire patient group (82.8% versus 76.7%, respectively, \(P = .16\)) and the subgroup with LVEF between 25% and 34% (79.4% versus 78.0%, \(P = .81\), respectively). However, 3-year mortality was better than predicted in the subgroup with LVEF of between 35% and 45% (88.0% versus 74.7%, respectively, \(P = .046\)). NYHA functional class and MLHFQ scores showed progressive improvement over time in the overall group and both subgroups (\(P < .002\)).69

Manufacturers and Regulatory Status

Impulse Dynamics (USA), Inc. (Orangeburg, New York), manufactures the Optimizer device. FDA approved the company’s premarket approval (PMA) application for the Optimizer Smart System on March 21, 2019.70,71 The device is indicated to improve 6-minute hall walk
distance, NYHA functional class, and quality of life in patients with NYHA class III heart failure and LVEF between 25% and 45%, who remain symptomatic despite guideline-directed medical therapy and who are in normal sinus rhythm (ie, not candidates for cardiac resynchronization therapy).70,71 FDA had granted the Optimizer device a Breakthrough Device designation in July 2015.57 In 2016, the latest model, the Optimizer Smart, replaced (i.e., for new device implantations) all earlier Optimizer versions (II, III, IV) used in clinical trials.57

Cost Information

According to ECRI Institute’s PriceGuide database, member hospitals reported an average price paid of $16 500 for the Optimizer Smart device (as of April 2, 2019).72 Estimated implantation costs at US centers have not been widely reported since the device became commercially available in March 2019.

Results and Discussion of Stakeholder Comments

Nine stakeholder commenters, reflecting clinical, research, nursing, systems, and patient perspectives, provided comments and ratings on CCM with the Optimizer implant.73-81 We have organized the following discussion of stakeholder comments by the parameters on which they commented.

Patient outcomes, quality of life, and overall health: Three commenters with clinical73 and research perspectives74,81 expressed skepticism about the technology’s ability to durably improve outcomes, given the general lack of long-term data demonstrating fewer heart-failure-related hospitalizations or reduced mortality. However, the other 6 commenters reflecting patient,76 nursing,75,77 research,78,79 and systems80 perspectives considered Optimizer therapy to be an important new therapeutic option with moderate to large potential to improve outcomes for a large portion of the population with heart failure whose condition continues to deteriorate despite optimal medical therapy.

Health disparities: Overall, commenters expressed concern that this technology might increase disparities among the population with heart failure, many of whom are of lower socioeconomic status and may be uninsured or underinsured. Most commenters noted that patients with more generous private health insurance might be most likely to receive the Optimizer device, whereas patients with public insurance (i.e., Medicare or Medicaid) could be less likely to receive it.73-81 A patient commenter noted the general lack of available data on Optimizer safety and efficacy in populations other than white men and called for more research of the technology in women and underrepresented ethnic groups.76 A clinical commenter noted that in addition to potential disparities related to insurance coverage, the technology might be accessible or offered only at large tertiary medical centers, creating further disparities, at least initially.73

Health care delivery system: Three commenters with clinical73 and research perspectives79,81 anticipated that the Optimizer would represent a small disruption to the health care delivery system, mostly because they predicted low use of the technology. However, one of these commenters anticipated the disruption would gradually increase if more long-term efficacy data became available and the device were to become a more established technology.79 The other 6 commenters reflecting patient,76 nursing,75,77 research,74,78 and systems80 perspectives noted that implementing a program to offer Optimizer therapy would represent a moderate to large
disruption to the care delivery system, ultimately depending on the number of patients who receive the technology.

Commenters generally expected the same clinicians and centers that implant pacemakers and defibrillators to implant the Optimizer devices, resulting in less disruption to those services unless use and demand were substantial. Three commenters with patient, nursing, and research perspectives anticipated that more staff would likely be needed, initially to screen candidates and train patients how to recharge and care for the devices at home and over the long term to monitor the implanted devices. Two commenters with patient and nursing perspectives suggested that more home care nurses would be required to safely monitor patients at home, at least during an introductory period, especially if remote monitoring and management were available and patients had fewer office visits to evaluate the devices and their health status.

One commenter with a nursing perspective suggested an Optimizer program might be an attractive new revenue stream for some hospitals, potentially creating a risk of overutilization, given how it would shift office-based medical management to an interventional cardiology procedure. Two commenters with research and nursing perspectives noted that if Optimizer therapy demonstrates clinical benefit in general practice similar to that seen in clinical trials, some hospitals might see fewer heart-failure-related hospitalizations and reduced use of more aggressive heart failure interventions (e.g., left ventricular assist devices, heart transplantation), which are needed because heart failure traditionally progresses over time.

**Current paradigm of patient care:** Most commenters expected Optimizer therapy would have moderate to large disruptions to management of heart failure, shifting from office-based medical management to an interventional procedure that requires regular follow-up visits to monitor device performance and safety. Commenters with patient and nursing perspectives expected more disruption than other commenters to current heart failure care models from adding Optimizer therapy. A commenter with a patient perspective suggested that requiring patients to recharge the device weekly could make care more inclusive and give patients more sense of control and involvement in their own care, potentially improving satisfaction and quality of life. However, 2 commenters with clinical and research perspectives anticipated low adoption of this technology, resulting in little disruption to how heart failure is managed in most patients with the condition.

**Health care costs:** Commenters generally thought adding Optimizer therapy could disrupt the costs of heart failure care. Device implantation would increase short-term costs due to device implantation. However, over the long term, Optimizer therapy could help lower total costs if the implants reduce the need for heart-failure-related hospitalizations and more aggressive interventions, such as left ventricular assist devices and heart transplantation. One commenter with a clinical perspective anticipated a substantial increase in heart failure treatment costs if Optimizer therapy were to be widely used among the population with heart failure with reduced ejection fraction, adding “This, especially without any clear survival/mortality benefits, would be highly controversial in an environment where the focus is on reducing health care costs.”

**Overall disruption potential:** Most commenters thought the Optimizer device was an important additional therapeutic option for patients with heart failure that has potential to improve quality of life and slow disease progression and the need for more aggressive interventions. Commenters with patient, nursing, and research backgrounds
expressed the strongest support for the Optimizer’s overall disruptive potential, especially given the treatment gap between medical therapy and highly invasive options, such as left ventricular assist devices and heart transplantation. Commenters with clinical, research, patient, nursing, and systems perspectives called for additional clinical trials to better identify or stratify patient subgroups most likely to benefit from Optimizer therapy and to evaluate the technology in a more diverse population of patients with heart failure than the patients observed in available trials. These commenters also suggested a need for longer-term trials that could more clearly identify a possible mortality benefit, which in turn could lead to wider utilization and a disruptive potential.
Chapter 4. Mental and Behavioral Health Conditions

Chapter Summary

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

As of May 1, 2019, we were monitoring 15 topics in this priority area, including the 2 considered for inclusion in this report. The topics encompass pharmaceuticals and devices intended to treat 8 mental and behavioral health conditions. Four more topics in this priority area are undergoing or have been queued for stakeholder comment; however, fewer than 5 sets of stakeholder comments were received for those topics before May 7, and they were not considered for inclusion in this report. The remaining 9 topics are still too early in development to meet criteria (as outlined above) for eligibility for this report. These 15 topics will be described briefly in the June 2019 PCORI Health Care Horizon Scanning System: Horizon Scanning Status Report.

Topics Considered for Inclusion in this Report

Table 1 lists 1 topic selected for inclusion during the High Potential Disruption Report decision meeting. Included topics are those that a majority of the voting team agreed had high potential for disruption, based on stakeholder ratings and comments and available data.

<table>
<thead>
<tr>
<th>Topic Title</th>
</tr>
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<tbody>
<tr>
<td>Esketamine [Intranasal] (Spravato) for Treating Treatment-Resistant Major Depressive Disorder</td>
</tr>
</tbody>
</table>
Table 2 lists 1 topic considered but not selected for inclusion during the High Potential Disruption Report decision meeting. Topics considered but not included are those that a majority of the voting team agreed did not have high potential for disruption, based on stakeholder ratings and comments and available data. Each record contains a note explaining the reason(s) for exclusion.

Table 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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasotraline for Treating Moderate to Severe Binge Eating Disorder (BED)</td>
<td>Stakeholder commenters agreed that additional information was needed about overall efficacy and adverse events of dasotraline. Results from an ongoing phase III trial need to be reviewed to determine whether this drug used for treating BED has potential for disruption. We continue to actively monitor this topic.</td>
</tr>
</tbody>
</table>

**Topic Summaries**

We present below 1 summary on a topic deemed to have high potential for disruption.

**Esketamine (Spravato) for Treating Treatment-Resistant Major Depressive Disorder**

**Highlights**

Esketamine HCL is the only FDA-approved formulation of the anesthetic ketamine available for treating major depressive disorder (MDD); intravenous and intranasal ketamine were studied and used off-label for treatment-resistant MDD for about 10 years before esketamine approval. Esketamine’s cost is substantially higher than that of intravenous (IV) or intranasal ketamine—$36 500 versus an estimated $3600 per treatment. Five stakeholders commenting on this topic were cautiously optimistic that noninvasive, rapid delivery of esketamine might lead to a net improvement in patient outcomes. However, they also thought that the FDA requirement for certified facilities, physician-supervised administration, posttreatment monitoring, and vehicle-driving restrictions might limit patient acceptance and diffusion or negatively disrupt some aspects of health care delivery. For example, esketamine’s cost relative to off-label ketamine and limited access to certified facilities might increase health disparities unless the drug receives widespread reimbursement.

**Patient Population**

This treatment is intended for adults with treatment-resistant MDD (ie, inadequate response to 2 or more oral antidepressants of adequate dose and duration in the current episode of depression).
Intervention

Esketamine HCL nasal spray is the (S+)-enantiomer of ketamine, delivered through a single-use intranasal device. The drug is indicated for use in combination with an oral antidepressant for treatment-resistant depression in adults.\(^{82}\) Esketamine is absorbed by the lining of the nasal passages and into the bloodstream, purportedly leading to rapid (within hours) improvement in depression-symptom severity in patients with MDD.\(^{83}\) The Mayo Clinic website offers more information about treatment-resistant MDD.

Esketamine’s mechanism of action is noncompetitive antagonism to the N-methyl-D-aspartate (NMDA) receptor.\(^{82}\) Blocking activation of the NMDA receptor facilitates sensory input, moderates emotional responses, and may increase dopamine, norepinephrine, and serotonin levels in the brain.\(^{83}\)

The single-use nasal spray device contains 28 mg of esketamine HCL and delivers two 14-mg sprays per device. Treatment is initiated in the induction phase at weeks 1 to 4 at a dose of 56 mg on day one and 56 or 84 mg subsequently, twice weekly. During the maintenance phase, from weeks 5 to 8, esketamine is administered once weekly at a dose of 56 or 84 mg, and from week 9 and subsequently it is given every 1 or 2 weeks at a dose of 56 or 84 mg. A 5-minute rest is indicated between the use of each 28-mg device to allow the body to absorb the medication.\(^{82}\)

Patients take the intranasal spray themselves but in a health care setting certified to provide the treatment under the supervision of a health care professional. Its use requires patient monitoring in that health care setting for 2 hours after administration. Patients are also advised to not drive or operate machinery until the next day, after sleep.\(^{82}\) Esketamine is quickly metabolized and the majority is eliminated from the body within 24 hours.\(^{83}\)

Esketamine was approved with a boxed warning about risk of suicidal thoughts and behaviors in young adults and carries the potential for misuse and abuse.\(^{82}\) Therefore, it is not dispensed directly to patients and is available only through enrollment in the Spravato Risk Evaluation and Mitigation Strategy (REMS) program.

Evidence Development Summary

The manufacturer has reported data from 5 completed phase III clinical trials that evaluated esketamine in combination with an oral antidepressant to treat adults with treatment-resistant MDD.

In the phase III, active control, double-blind TRANSFORM-1 trial (n = 346), adults aged 18 to 64 years with treatment-resistant MDD received fixed-dose intranasal esketamine twice weekly for 4 weeks (56 mg or 84 mg) or placebo, and all arms initiated a new oral antidepressant.\(^{84}\)

Although the results numerically favored esketamine over placebo for both dosages, the change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline to day 28 was not statistically significant (\(P = .088\)) for the 84-mg esketamine group based on a mixed-effects model for repeated measures (MMRM) analysis. The 56-mg esketamine group and secondary endpoints could not be formally evaluated.\(^{84}\)

Overall response rates (\(\geq 50\%\) improvement from baseline) and remission rates (MADRS total score \(\geq 12\)) at day 28 were higher for both esketamine groups than for the placebo group. Response rates at day 28 were 53.1\% and 54.1\% in patients treated with 84 mg and 56 mg of
esketamine, respectively, compared with 38.9% for placebo. Remission rate at day 28 was 38.8% and 36.0% in patients treated with 84 mg and 56 mg of esketamine, respectively, compared to 30.6% of patients receiving placebo. The most common adverse events reported were dysgeusia, nausea, vertigo, and dizziness (incidence 20.9% to 26.1%).

In the phase III, randomized, double-blind TRANSFORM-2 trial (n = 197), adults aged 18 to 64 years, with moderate to severe, recurrent or persistent MDD and a history of no response to 2 or more antidepressants in the current episode of depression similarly received fixed-dose intranasal esketamine twice weekly for 4 weeks (56 mg or 84 mg) or placebo, and all arms initiated a new oral antidepressant.

The mean change (LS mean [SE] difference) in MADRS total score for intranasal esketamine was numerically superior to placebo at day 28 (-4.0 [1.69]; 95% confidence interval [CI], -7.31 to -0.64; one-sided $P = .01$), and was statistically significant 24 hours after the dose (one-sided $P = .009$).

In the phase III, active control, double-blind TRANSFORM-3 trial (n = 138), patients aged 65 years or older with treatment-resistant MDD received flexible-dose intranasal esketamine twice weekly for 4 weeks (28 mg, 56 mg, or 84 mg) or placebo, and all arms initiated an oral antidepressant.

Patients treated with esketamine did not achieve statistically significant improvement in the primary outcome of depression severity at 28 days based on change from baseline in MADRS total scores. The mean (SD) change in MADRS total scores from baseline to day 28 was -10.0 (12.74) for esketamine and -6.3 (8.86) for placebo. Based on MMRM analysis, the median-unbiased estimate of the difference between esketamine and placebo was -3.6 (95% CI, -7.20 to 0.07; one-sided $P = .029$).

In the phase III, randomized, double-blind SUSTAIN-1 trial (n = 703), adults aged 18 to 64 years with treatment-resistant MDD received flexible-dose intranasal esketamine twice weekly for 4 weeks (56 mg or 84 mg) and then once weekly or every other week or placebo, and all arms initiated an oral antidepressant.

Relapse was reported for 26.7% of patients in the esketamine group and 45.3% of patients in the placebo group (2-sided $P = .003$, weighted-combination test). The weighted estimate of hazard ratio (HR) showed that treatment with esketamine decreased the risk of relapse by 51% compared with placebo among stable remitters (HR, 0.49; 95% CI, 0.29 to 0.84). The most common adverse events reported were dysgeusia, vertigo, dissociation, somnolence, and dizziness (incidence 20.4% to 27.0%).

In the phase III, long-term safety and efficacy trial, SUSTAIN-2 (n = 802), adults aged 65 years or older with MDD and a history of nonresponse to 2 or more antidepressants in the current episode of depression received flexible-dose intranasal esketamine twice weekly for 4 weeks (28 mg, 56 mg or 84 mg) and then once weekly or every other week for 48 weeks in conjunction with an oral antidepressant. Participants who entered the study directly received a newly initiated oral antidepressant, and those entering from the TRANSFORM-3 trial continued the same antidepressant.

The mean (SD) change in MADRS total score from the induction phase to the endpoint was -16.4 (8.76) and 0.3 (8.12) from the optimization/maintenance phase to the endpoint. At the end of the induction phase, the response rate was 78.4% and the remission rate was 47.2%; of
responders proceeding to the optimization/maintenance phase, the response rate was 76.5% and the remission rate was 58.2% at the endpoint.

Discontinuation rates due to adverse events were 6.7% during induction phase and 4.1% during maintenance phases; 6.9% of patients experienced serious treatment-related adverse events. The most common treatment-related adverse events were dizziness (33.0%), nausea (25.1%), headache (24.9%), dissociation (22.4%), somnolence (16.7%), dysgeusia (11.8%), hypnoanesthesia (11.8%), vertigo (10.8%), vomiting (10.8%), and viral upper respiratory tract infection (10.2%).

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

Manufacturers and Regulatory Status

Esketamine HCL is manufactured by Janssen Research & Development, LLC, a unit of Johnson & Johnson (New Brunswick, New Jersey). FDA approved esketamine HCL on March 5, 2019, for treatment-resistant depression in adults. The approval required a REMS plan that specifies it be administered in a “certified doctor’s office or clinic,” that patients’ blood pressure be monitored, and guidance be given on food and liquid intake. Clinicians must also provide guidance for patients who may also be using other nasally administered medications for other conditions, such as corticosteroids or decongestants, on the day of esketamine administration.

FDA had granted esketamine Breakthrough Therapy designation in November 2013.

Cost Information

Johnson & Johnson set esketamine’s wholesale acquisition cost (WAC) at $295 per 28-mg device. The Institute for Clinical and Economic Review’s draft evidence report evaluated the cost-effectiveness of esketamine plus a new oral antidepressant compared with cost-effectiveness of a new oral antidepressant alone (no additional therapy). For esketamine, the lifetime incremental cost-effectiveness ratio was about $198 000 per quality-adjusted life year (QALY) gained, compared with no additional treatment, falling above the oft-cited cost-effectiveness threshold of $150 000 per QALY. Cost per life-year gained was $2.6 million for esketamine compared with no additional therapy, and cost per depression-free day was about $330. The average 5-year annualized potential budgetary impact of using esketamine plus a new oral antidepressant at esketamine’s WAC was an additional per-patient cost of about $12 700.

The report also evaluated the 1-year treatment costs associated with esketamine compared with the cost of intravenous ketamine, including administration costs, and found the costs of esketamine are substantially higher than those of intravenous ketamine. The annual direct cost of esketamine treatment for year one is $36 500, compared with $3600 for ketamine treatment. For year two and future years, the annual direct cost is about $30 800 and $2500, for esketamine and intravenous ketamine, respectively.

Janssen offers copayment assistance for commercially or privately insured patients, including those insured through state and federal health exchanges, who pay $10 per treatment for esketamine medication, up to $7150 annually. The savings program does not cover the cost of administration. The program is unavailable to individuals who use any state or federal government-funded health care program to cover medication costs. Esketamine is not currently covered by insurance.
Results and Discussion of Stakeholder Comments

Five stakeholder commenters, reflecting clinical, systems, and research perspectives, provided comments and ratings on esketamine. We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Commenters offered mixed opinions on the potential for esketamine to improve patient outcomes. Several commenters thought that, based on the study results, esketamine might improve patient outcomes, particularly with regard to the rapid delivery mechanism. However, one commenter with a research perspective expressed concern about the mixed results across studies and several commenters wanted to see more clinical studies that directly compare esketamine to other treatments such as IV ketamine, repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), and augmentation with second-generation antipsychotics or lithium. One commenter with a clinical perspective, who runs a ketamine clinic, noted from experience that ketamine continues to work for years as a maintenance therapy and reduces hospitalization rate and suicidal ideation. Another commenter, with a research perspective, was concerned that the adverse effects of esketamine, including dizziness, vertigo, and dissociation, could have a negative impact on quality-of-life outcomes.

Three commenters with research and systems perspectives thought that stringent regulatory requirements, including administration in a certified facility, the 2-hour posttreatment monitoring period, and driving restrictions might discourage patients from trying this treatment and thus limit its uptake. Three commenters also cited the cost of the drug and lifetime cost-effectiveness ratio as potential limiters to widespread diffusion, thereby reducing potential impact on long-term effectiveness and patient outcomes.

**Health disparities:** Most commenters thought that esketamine would have minimal positive effects and potential negative effects on health disparities because of the method of supervised administration at certified health care facilities, lack of access to local certified facilities, length of posttreatment monitoring and restrictions, high cost, and limited willingness of providers to prescribe nontraditional treatments. However, one commenter with a clinical perspective noted that obtaining insurance coverage would greatly improve access to the treatment and the approval of this intervention might contribute to reducing the stigma surrounding depression treatment.

**Health care delivery system:** Overall, commenters thought that esketamine would have a moderate impact on the health care delivery system. Three commenters, 1 with a health systems perspective and 2 with clinical perspectives, remarked that the requirements for certified facilities, medically supervised administration, and posttreatment monitoring may require additional medical facilities or specialty clinics, additional space at existing facilities, and an increase in staff to monitor patients. Two other commenters with research perspectives thought that the requirements, along with the cost, could limit access in rural areas, lead to poor compliance, and potentially reduce the overall impact of this intervention.

**Current paradigm of patient care:** Commenters generally agreed that esketamine will have a low to moderate impact on the current care paradigm. Three commenters with clinical, research, and systems perspectives noted that the intranasal device is easy to use and less invasive than IV ketamine and ECT. However, all commenters thought that the current
administration and monitoring requirements are inconvenient for the physician and the patient, specifically with regard to the need for additional physician training, time and resource expenses, and the burden on the patient in terms of the weekly or biweekly dosing schedule, time off work, postadministration monitoring, and driving restrictions.

A commenter with a research perspective wanted more information about coverage, copayments, and the need for preauthorization, well as treatment duration, tolerance risk, dependence, and long-term side effects to effectively assess the drug’s potential to shift the current care paradigm.\textsuperscript{94} Another commenter with a research perspective thought that this treatment would have a high impact only if efficacy is proven for patients with MDD who have not improved using other treatment regimens.\textsuperscript{93}

**Health care costs:** Most commenters thought that esketamine has a moderate potential to disrupt costs; however, some views conflicted. Three commenters, 2 with a clinical perspective and 1 with a research perspective, thought that the treatment is expensive compared with the cost of other options for treatment-resistant MDD, including off-label IV ketamine.\textsuperscript{94-96} One commenter with a clinical perspective wanted more information about insurance coverage and highlighted that the patients’ costs include weekly loss of work time.\textsuperscript{94} One commenter with a health systems perspective thought that the treatment was inexpensive, considering the potential to decrease visits to crisis centers and admissions to mental health facilities.\textsuperscript{92} One commenter with a clinical perspective thought that a generic formulation could be administered and covered by payers for a fraction of the cost.\textsuperscript{94}

**Overall disruption potential:** Most commenters thought esketamine has low potential overall to disrupt the health care system. Some thought it might cause a negative disruption. For example, several commenters remarked that esketamine is less cost-effective, more intrusive to patients, and would likely impose a higher burden on clinicians, compared with off-label IV ketamine.\textsuperscript{92,93,95,96} The need to provide certified facilities for administration, the 2-hour postadministration monitoring period, and restrictions on driving and operating machinery would likely limit physicians’ willingness to prescribe and patients’ willingness to accept this treatment, commenters with systems and research perspectives thought.\textsuperscript{92,93} Two commenters with research perspectives stressed the need for additional controlled studies to further assess the efficacy and safety of intranasal esketamine.\textsuperscript{93,96} However, one commenter with a clinical perspective noted that esketamine is a novel paradigm to treat depression; has a rapid, positive effect in an emergency; and might help patients who are not helped by currently approved treatments.\textsuperscript{94} The same commenter strongly advocated for insurers to pay for IV ketamine.\textsuperscript{94}
Chapter 5. Rare Diseases

Chapter Summary

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

As of May 1, 2019, we were monitoring 51 topics in this priority area, including those considered for inclusion in this report. The topics encompass pharmaceuticals, biotechnologies, and implants intended to treat or prevent 40 rare diseases and/or related symptoms. Of the 51 topics we are monitoring, 44 topics are early in development and have not yet met criteria (as outlined above) to be considered for inclusion in this report. We archived one additional topic, Alpha AMS Subretinal Implant for Treating Retinitis Pigmentosa-Mediated Blindness, in this priority area on April 23, 2019. This was done because the developer (Retina Implant AG, Reutlingen, Germany, in collaboration with Wills Eye Hospital, Philadelphia, Pennsylvania) announced that it had ceased business operations, citing an innovation-hostile regulatory climate and unimpressive clinical results. These 52 topics will be described briefly in the June 2019 PCORI Health Care Horizon Scanning System: Horizon Scanning Status Report.

Topics Considered for Inclusion in this Report

Table 1 lists 4 topics selected for inclusion during the High Potential Disruption Report decision meeting. Included topics are those that a majority of the voting team agreed had high potential for disruption, based on stakeholder ratings and comments and available data. Topics are listed alphabetically by topic title. The report below follows the same organization.

Table 1. Included Topics for Priority Area Rare Diseases

<table>
<thead>
<tr>
<th>Topic Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apremilast (Otezla) for Treating Behçet's Disease</td>
</tr>
<tr>
<td>Idebenone for Treating Duchenne Muscular Dystrophy</td>
</tr>
<tr>
<td>Caplacizumab (Cablivi) for Treating Acquired Thrombotic Thrombocytopenic Purpura</td>
</tr>
<tr>
<td>Crizanlizumab (SEG101) for Preventing Recurrent Vaso-Occlusive Crisis in Patients with Sickle Cell Disease</td>
</tr>
</tbody>
</table>
Table 2 lists 3 topics considered but not selected for inclusion during the High Potential Disruption Report decision meeting. Topics considered but not included are those that a majority of the voting team agreed did not have high potential for disruption, based on stakeholder ratings and comments and available data. Each record contains a note explaining the reasons for exclusion. Topics are listed alphabetically by topic title.

Table 2. Topics Considered but Not Included for Priority Area Rare Diseases

<table>
<thead>
<tr>
<th>Topic Title</th>
<th>Exclusion Reason(s) and Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PXT3003 for Treating Charcot-Marie-Tooth Disease Type 1A</td>
<td>Stakeholder commenters thought the potential for disruption was small, citing the drug's questionable mechanism of action, small clinical effect, and dosing-related issues. More data are needed. We continue to actively monitor this topic.</td>
</tr>
<tr>
<td>Triheptanoin (UX007) for Treating Long-Chain Fatty Acid Oxidation Disorders</td>
<td>Stakeholder commenters noted that the clinical trial results for triheptanoin did not show marked differences in efficacy or adverse events compared with traditional trioctanoin oil treatment. This topic has been archived.</td>
</tr>
<tr>
<td>Siponimod (Mayzent) for Treating Multiple Sclerosis</td>
<td>Most stakeholder commenters agreed that siponimod has low disruption potential because of its relative expense (compared with other, approved disease-modifying drugs) and no significant reduction in adverse events based on results from the EXPAND study. We continue to actively monitor this topic for future head-to-head studies.</td>
</tr>
</tbody>
</table>

**Topic Summaries**

We present below 4 summaries on topics deemed to have high potential for disruption. Topics are ordered alphabetically by topic title.

**Apremilast (Otezla) for Treating Behçet’s Disease**

**Highlights**

Blood vessel inflammation is a characteristic of Behçet’s disease, a rare disorder that causes canker mouth sores, genital ulcers, and eye inflammation. Apremilast (Otezla) targets the inflammation process. The drug was considered a safe, effective, and convenient oral therapy for treating symptoms, such as oral ulcers, arising from Behçet’s disease, according to the 5 stakeholders commenting on this topic. They thought the drug had comparable efficacy and better tolerability than the current standard-of-care treatment, tumor necrosis factor (TNF) inhibitors, which could reduce burden on patients and the system from follow-up appointments with multiple specialists. However, the targeted therapy’s high cost combined with copayment assistance programs for patients with private insurance might lead to health disparities. Commenters thought that apremilast might become standard care for Behçet’s disease, but its overall disruption potential could hinge on whether long-term, comparative data become available to further validate its efficacy for this indication.

**Patient Population**

Apremilast is intended for adults aged 18 years or older with active Behçet’s disease.
Intervention

Apremilast is a small-molecule inhibitor of phosphodiesterase type 4 that promotes increases in intracellular cyclic adenosine monophosphate, leading to decreased expression of proinflammatory mediators, such as TNF-α, interleukin (IL)-17, and IL-23. Blood vessel inflammation is a characteristic of Behçet’s disease, which investigators suspect is linked to overactive Th17 cells and increased IL-17 production, suggesting that apremilast might alleviate Behçet’s disease symptoms. For more information on the disease, see National Organization for Rare Disorders. In clinical trials, apremilast is taken orally as 30-mg tablets, twice daily.

Evidence Development Summary

Preliminary data are available for the phase III, randomized, crossover, RELIEF trial (NCT02307513). Trial subjects were adults (n = 207) aged 18 years or older with active Behçet’s disease with at least 3 oral ulcers at the time of random assignment or at least 2 oral ulcers at screening. At the time of random assignment, subjects were given apremilast 30 mg, twice daily, or a placebo, for 12 weeks. Then all patients crossed over to treatment with apremilast through 64 weeks.

Patients given apremilast achieved the primary endpoint of reduced oral ulcer burden over 12 weeks (area under the curve from weeks 0 through 12 [AUC\text{Wk0-12}], which measures the number of oral ulcers over time, accounting for their recurring-remitting pattern), compared with patients given placebo ($P < .0001$). Patients taking apremilast also had reductions in the number of oral ulcers ($P = .0015$) and oral ulcer pain ($P = .0035$) from weeks 1 through 12. Patients also achieved a 62% complete response of oral ulcers, as well as a 70% relative reduction in oral ulcer pain at week 28. Patients initially given placebo who subsequently received apremilast at week 12 gained benefits comparable to those attained by the initial active treatment group.

Adverse event rates were similar between groups during the controlled period (78.8% for the apremilast group versus 71.8% for the placebo group). The most common adverse events reported by patients taking the drug included diarrhea, headache, nausea, and upper respiratory tract infection.

Manufacturers and Regulatory Status

Apremilast is manufactured by Celgene Corp. (Summit, New Jersey), which was acquired by Bristol-Myers Squibb (New York, New York) in January 2019. Apremilast is in phase III development for treating Behçet’s disease. FDA approved it for treating psoriatic arthritis in March 2014, and in September 2014, expanded the indication to include treating plaque psoriasis. Celgene has submitted regulatory filings to further expand apremilast’s indications to include Behçet’s disease; the Prescription Drug User Fee Act decision date is July 21, 2019.

Cost Information

According to the online retail pharmacy price aggregator, GoodRx, a 30-day supply of 60 apremilast 30-mg tablets costs about $3370.
Results and Discussion of Stakeholder Comments

Five stakeholder commenters, reflecting clinical, health systems, and research perspectives, provided comments and ratings on apremilast.\textsuperscript{106-110} We have organized the following discussion of stakeholder comments by the parameters on which they commented.

\textbf{Patient outcomes, quality of life, and overall health:} Overall, commenters considered apremilast to be effective and well tolerated for treating oral ulcers and pain due to Behçet’s disease. This rare disease has limited treatment options and can complicate eating and drinking as well as other health outcomes and quality-of-life parameters. However, one commenter with a research perspective thought that apremilast resulted in health improvements similar to TNF inhibitors.\textsuperscript{109}

\textbf{Health disparities:} Most commenters thought that the high cost of apremilast combined with copayment assistance programs for patients with private insurance would likely lead to health disparities in patients with government insurance or those who are uninsured. However, one commenter with a research perspective noted that the oral administration of apremilast might reduce health disparities in patients with low health literacy who would not need to learn to self-inject TNF inhibitors.\textsuperscript{109} However, these patients would need to remember to take pills twice daily.\textsuperscript{109}

\textbf{Health care delivery system:} Commenters agreed that apremilast would have a minimal impact on the health care delivery system due to the simple oral administration of the drug combined with the small number of patients with Behçet’s disease.

\textbf{Current paradigm of patient care:} Overall, commenters thought that apremilast could disrupt care paradigms due to its enhanced convenience and improved tolerability, which might improve adherence, reduce the need for patient monitoring, and reduce complications such as infections and drug toxicity, thereby reducing overall burden to the health care system. One commenter with a clinical perspective noted that current treatment options for Behçet’s disease are limited by poor efficacy and substantial toxicity.\textsuperscript{107} Another commenter with a clinical perspective thought that the safety and efficacy would likely make it standard of care.\textsuperscript{107} However, one commenter with a research perspective thought that apremilast should be considered only in people who have not responded to other agents first, which might limit apremilast’s potential to disrupt the current standard of care. This commenter also thought that patient outcomes were similar to those reported for TNF inhibitors, somewhat limiting disruptions to care, and thought that comparative trials are needed to determine apremilast’s role in Behçet’s disease management.\textsuperscript{109}

\textbf{Health care costs:} Commenters agreed that that apremilast would substantially add to treatment costs in patients treated with traditional anti-inflammatory agents such as colchicine. However, costs to the system might be similar to those of TNF inhibitors. Reduced complications from toxicity and infections might reduce costs to the system. Commenters agreed that costs to the patient would largely depend on their insurance status.

\textbf{Overall disruption potential:} Overall, commenters thought that apremilast has potential to moderately disrupt treatment paradigms for oral ulcers associated with Behçet’s disease. One commenter with a clinical perspective thought that apremilast could become the first-line standard of care because of its safety and efficacy in treating Behçet’s disease and lack of FDA-approved treatments.\textsuperscript{107} A commenter with a health systems perspective thought that apremilast...
could disrupt care by decreasing the number of providers that a single patient requires for care, which currently includes dentists, dermatologists, pulmonologists, dermatologists, and gynecologists. However, another commenter with a health systems perspective thought cost would be the single biggest factor affecting the diffusion and downstream disruption potential of apremilast. One commenter with a research perspective noted the importance of examining additional disease outcomes, such as visual symptoms, disease progression, and quality of life. Two commenters with research perspectives agreed that although apremilast seems effective in reducing oral ulcer frequency and pain, long-term comparative efficacy trials with standard of care options (including concomitant steroids) are needed to better understand the role of apremilast in managing Behçet’s disease.

Idebenone for Treating Duchenne Muscular Dystrophy

Highlights

Idebenone purportedly protects cell viability and function to preserve cellular energy in patients with Duchenne muscular dystrophy (DMD). The drug appears to improve short-term (1-year) respiratory function in patients with DMD who are not taking corticosteroids, according to data from a phase III trial. The 6 stakeholders commenting on this topic agreed that idebenone has potential to decrease hospitalization rates and ventilator use due to respiratory complications, as well as associated costs, but longer-term data are needed. In addition, idebenone’s long-term disruption potential might be limited if its cost is substantially higher than that of corticosteroids, the standard-of-care treatment for managing respiratory symptoms in patients with DMD.

Patient Population

Idebenone is intended for treating patients with DMD (severe dystrophinopathy) aged 10 years or older with declining lung function. These patients are usually male, because DMD is X chromosome-linked.

Intervention

DMD-causing mutations lead to a loss in dystrophin protein production in muscle cells. Dystrophin loss causes cell damage, dysregulated calcium influx, subsequent mitochondrial dysfunction, and reduced energy production. This manifests clinically as progressive muscle loss and weakness, including a decline in pulmonary function (dyspnea) and related complications.

Idebenone is a small-molecule, synthetic, short-chain benzoquinone with similarity to coenzyme Q-10 that purportedly facilitates electron transport within mitochondria. The developer asserts that maintaining correct electron balance is essential for normal energy metabolism—particularly in nerve and muscle cells, which demand more energy, making them more prone to rapid cell damage or death from mitochondrial dysfunction. Additionally, idebenone might protect cells from oxidative-stress signaling pathways that induce cell death (apoptosis), preserving mitochondrial function and cellular viability. These effects could increase energy production within impaired nerve and muscle tissue in patients with DMD.

Results from a phase II trial suggested that idebenone improved respiratory function, but not cardiac function (defined as peak systolic radial strain values in the left ventricular inferolateral wall). This informed the selection of phase III respiratory function endpoints. In clinical trials,
idebenone was administered orally, 900 mg daily, as two 150-mg tablets taken 3 times a day with meals.

The Muscular Dystrophy Association provides [more information on DMD](#).

### Evidence Development Summary

The international phase III DELOS trial investigated the comparative efficacy of long-term daily idebenone versus placebo across multiple measures of respiratory function in patients aged 10 to 18 years with DMD (n = 64) who were not taking corticosteroids during the trial. The trial’s primary endpoint was the percentage change from baseline in predicted peak expiratory flow rate (PEFR), a respiratory measure with known decline rates that are associated with DMD progression.

Two publications reported results from the DELOS trial. Buyse et al\(^{115}\) 2015 reported that the percentage of predicted PEFR declined significantly (-9.01% predicted; 95% confidence interval [CI], -13.2 to -4.8; \(P < .0001\)) in the placebo group after 52 treatment weeks. But the percentage of predicted PEFR did not decline in patients administered idebenone over the same period (-3.05% predicted; 95% CI, -7.1 to 0.97; \(P = .134\)). A between-group comparison of the predicted PEFR percentage was also statistically significant (5.96% predicted; 95% CI, 0.16 to 11.8; \(P = .044\)).

Idebenone administration was associated with a 66% reduction in loss of predicted PEFR percentage over the trial at week 52; interim measures at 26 (\(P = .007\)) and 39 (\(P = .034\)) treatment weeks also demonstrated efficacy. Of note, the investigators based their sample size calculations on a 10.3% between-group difference in percentage of predicted PEFR, which presumably is a clinically important difference. On 4 additional measures of respiratory function, patients receiving daily idebenone showed improvements compared with the placebo group. Fewer respiratory tract infection–related adverse events were noted among patients receiving idebenone than among patients receiving placebo.\(^{115}\)

Rummey et al\(^{116}\) 2017 reported data from the same trial. They indicated that more patients in the placebo group than the treatment group fell below the thresholds for clinically relevant percentage predicted forced vital capacity (placebo 57%, idebenone 34%) or experienced a bronchopulmonary adverse event, resulting in a hazard ratio of 0.50 (95% CI, 0.26 to 0.97; \(P = .039\)) favoring idebenone.

The ongoing phase III SIDEROS trial ([NCT02814019](#)) is intended to assess the efficacy and safety of idebenone versus placebo. Primary and secondary outcomes include several measures of respiratory function, measured at baseline and week 78. The trial plans to enroll 266 patients with DMD who are receiving corticosteroids, and the primary completion date is August 2019.

SIDEROS-E ([NCT03603288](#)) is an open-label extension study enrolling patients who completed the SIDEROS trial; primary and secondary outcomes include adverse event incidence and several measures of respiratory function, also measured at baseline and week 78. The extension study’s primary completion date is January 2022.

### Manufacturers and Regulatory Status

Santhera Pharmaceuticals (USA), Inc. (Burlington, Massachusetts), is developing idebenone for treating DMD. The drug is in phase III clinical development for this indication. In December 2018, the manufacturer disclosed regulatory work in preparation for filings with FDA.\(^{117}\) These
filings are expected between July 2019 and April 2020 and are likely to include data from the DMD SIDEROS trial.\textsuperscript{118} FDA has granted several designations to idebenone for treating DMD: Orphan Drug designation in August 2016,\textsuperscript{119} Rare Pediatric Disease designation in August 2015,\textsuperscript{120} and Fast Track designation in April 2015.\textsuperscript{112}

Results and Discussion of Stakeholder Comments

Six stakeholder commenters, reflecting caregiver, clinical, nursing, research, and systems perspectives, provided comments and ratings on idebenone for treating DMD.\textsuperscript{121-126} We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Overall, commenters agreed that idebenone improves respiratory function and quality of life without causing severe side effects in patients with DMD who are not taking corticosteroids. But one commenter with a research perspective\textsuperscript{126} questioned the drug’s long-term efficacy, and another with a research perspective\textsuperscript{125} questioned the DELOS study’s small sample size.

**Health disparities:** Because this drug is administered orally, most commenters did not expect idebenone to significantly disrupt health disparities, as patients with DMD often receive oral corticosteroids. However, 2 commenters with nursing\textsuperscript{124} and systems\textsuperscript{121} perspectives noted that the cost of the drug for treating DMD is unknown.

**Health care delivery system:** Commenters unanimously agreed that, as an oral drug that patients take themselves, idebenone could potentially reduce hospitalizations due to respiratory complications for patients with DMD.

**Current paradigm of patient care:** All commenters thought that idebenone has the potential to be easily adopted by patients and caregivers as part of a convenient, less-invasive care paradigm because it may improve 1-year respiratory outcomes and prevent the need for ventilator support. However, one commenter with a clinical perspective\textsuperscript{123} was uncertain about whether the drug would affect long-term outcomes and whether patients taking the drug might eventually require additional support. Additionally, a commenter with a caregiver perspective\textsuperscript{122} noted that some patients with DMD might have difficulty adhering to the treatment regimen, which requires taking 2 pills 3 times a day, with food.

**Health care costs:** Although some commenters noted that idebenone’s cost was unavailable, all thought that the drug would reduce costs associated with respiratory complications, such as hospitalizations and ventilator support. One commenter with a caregiver perspective\textsuperscript{122} also noted that idebenone could potentially reduce costs associated with “side effects and secondary illnesses caused by corticosteroid use, such as hypertension, bone weakness and behavioral changes.”

**Overall disruption potential:** Overall, commenters thought that idebenone has moderately high potential for disruption because of its positive effect on respiratory function in patients with DMD, although the commenter with a clinical perspective\textsuperscript{123} again questioned its effects on long-term patient health outcomes. Two commenters with caregiver\textsuperscript{122} and nursing\textsuperscript{124} perspectives noted that the drug’s diffusion might be limited if its cost were significantly higher than that of corticosteroids.
Caplacizumab (Cablivi) for Treating Acquired Thrombotic Thrombocytopenic Purpura

Highlights

Caplacizumab is the first FDA-approved therapeutic agent indicated for treating acquired thrombotic thrombocytopenic purpura (aTTP), a rare, potentially fatal autoimmune disease estimated to affect fewer than 2000 US adults each year. Pivotal trial results suggest caplacizumab might reduce the time to achieve a normalized blood platelet count. The biologic also reduced the composite rate of aTTP-related death, aTTP recurrence, or thromboembolic events by 74%. Caplacizumab has a list price of $270 000 for a course of treatment; the manufacturer reportedly has a financial assistance program to help eligible patients gain access to the treatment. The 5 stakeholders commenting on this topic agreed that caplacizumab might have a positive impact on patient outcomes compared with the standard of care for aTTP.

Patient Population

Caplacizumab (Cablivi) is intended for treating adults aged 18 years or older with a diagnosis of aTTP.

Intervention

Caplacizumab is a selective, bivalent antibody fragment intended to treat aTTP by targeting von Willebrand factor. A rare autoimmune disease, aTTP develops when the body produces autoantibodies against the ADAMTS13 enzyme (ie, von Willebrand factor–cleaving protease), which is involved in regulating the blood clotting protein, von Willebrand factor. Caplacizumab purportedly inhibits the interaction between von Willebrand factor and platelets by targeting the von Willebrand factor A1 domain, potentially blocking ultra-large von Willebrand factor–mediated platelet interactions and formation of the string-like blood clots that are characteristic of aTTP.

Caplacizumab is intended for use in patients who are also receiving plasma exchange and immunosuppressive therapies (eg, rituximab). The recommended first dose of caplacizumab is an 11-mg bolus intravenous injection at least 15 minutes before initial plasma exchange in a clinic or hospital setting, with an 11-mg subcutaneous caplacizumab injection after the first plasma exchange treatment.

After each daily plasma exchange treatment, a subcutaneous caplacizumab injection (11 mg) is administered. Subcutaneous caplacizumab injections (11 mg) are administered for another 30 days after the last of the plasma exchange sessions. Patients give themselves the subcutaneous injections at home or family caregivers administer them, as appropriate. If signs of aTTP persist (eg, suppressed ADAMTS13 activity) after the initial treatment course, physicians may prescribe an additional 28 days of daily caplacizumab subcutaneous injections.

Caplacizumab therapy may increase risk of bleeding or bruising. Patients are advised to discontinue caplacizumab use if they experience more than 2 aTTP recurrences while taking it.

The National Institutes of Health’s Genetic and Rare Diseases Information Center provides detailed information about aTTP.
Evidence Development Summary

The randomized, phase III HERCULES trial (NCT02553317) compared caplacizumab administered after daily plasma exchange and for 30 days after completing plasma exchange therapy with placebo for treating aTTP in 145 adults aged 18 years or older. The caplacizumab group had a shorter median time to platelet count normalization (primary outcome) than did the placebo group, at 2.69 days (95% CI, 1.89 to 2.83) versus 2.88 days (95% CI, 2.68 to 3.56; \( P = .01 \)). After 6 months, caplacizumab group patients were 1.55 times as likely as placebo group patients to experience a platelet count normalization.

The composite measure of aTTP-related death, aTTP recurrence, or a thromboembolic event, a key secondary outcome, was 74% lower in the caplacizumab group than in the placebo group (12% versus 49%, \( P < .001 \)). Recurrence of aTTP during the trial was 67% lower in the caplacizumab group than in the placebo group (12% versus 38%, \( P < .001 \)). Caplacizumab group patients needed fewer plasma exchanges and had shorter hospitalizations than placebo group patients. No caplacizumab group patients developed refractory disease, compared with 3 patients in the placebo group.

Mucocutaneous bleeding (ie, in the junction between skin and mucous membranes), the most common adverse event, occurred in 65% of the caplacizumab group and 48% of the placebo group. One caplacizumab group patient died from cerebral ischemia after the treatment period, and 3 placebo group patients died during the trial treatment period.

The ongoing open-label, single-arm, phase III Post-HERCULES study (NCT02878603) is intended to assess the long-term safety and efficacy of caplacizumab therapy administered as initial intravenous infusion followed by daily subcutaneous injections for 6 months. The study is designed with multiple primary endpoints—including mortality rate, proportion of patients with aTTP-related events and disease recurrence, number of and time to aTTP-related events, number of and time to disease recurrences, proportion of patients with reported major thromboembolic events, number of and time to major thromboembolic events, change from baseline in cognitive function and quality of life, number of patients with antidrug antibodies, and incidence of adverse events—all through the 36-month follow-up visit or until 7 days after end of treatment (whichever is latest). The trial is enrolling about 104 adults aged 18 years or older with aTTP who completed the HERCULES trial. The follow-up study’s primary completion date is October 2020.

Manufacturers and Regulatory Status

Ablynx NV (Ghent, Belgium), a Sanofi S.A. (Paris, France) company, manufactures caplacizumab. On February 6, 2019, FDA approved Ablynx’s Biologics License Application for caplacizumab-yhdp, under the trade name Cablivi, to treat aTTP in adults in combination with plasma exchange and immunosuppressive therapy. FDA previously granted caplacizumab Orphan Drug, Fast Track, and Priority Review designations.

Cost Information

According to Sanofi, caplacizumab has a wholesale acquisition cost of $270 000 for treating a typical aTTP episode. The company reportedly has launched a patient assistance program to provide financial support to eligible patients to access caplacizumab therapy.
Results and Discussion of Stakeholder Comments

Five stakeholder commenters, reflecting clinical, research, and systems perspectives, provided comments and ratings on caplacizumab for treating aTTP.134-138 We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Overall, commenters thought caplacizumab could have a moderate to large positive disruption on patient outcomes compared with the standard of care for aTTP, especially because it is the first FDA-approved therapy with an indication to treat aTTP. Two commenters with clinical perspectives noted that the secondary outcomes in the HERCULES trial, including a 74% reduction in the composite of death, major thrombosis, or disease recurrence, appeared more impressive than the primary outcome (shortened time to platelet recovery) and may be more clinically meaningful for patients.135,136 One of these commenters (with a clinical perspective) stated, “The difference in early recurrence will be the major benefit of caplacizumab” and should help prevent aTTP exacerbations.136 But one commenter with a research perspective predicted a smaller disruptive potential due to the likely small number of patients who might receive caplacizumab to treat aTTP.138

**Health disparities:** Commenters generally agreed that the availability of caplacizumab is unlikely to reduce health care disparities but could increase them, based on the drug’s high cost and the quality of patients’ insurance coverage. One commenter with a clinical perspective suggested that health care administrators would be disinclined to use caplacizumab in patients without insurance coverage for the drug, given the small mortality benefit and the general effectiveness of standard therapy in the majority of patients with aTTP.136 One commenter with a research perspective anticipated that disparities could increase because caplacizumab, as an expensive, perishable immunochemical targeting a rare disease, might be stocked only at large tertiary centers, thus limiting rural patients’ access to this treatment.138

**Health care delivery system:** Commenters thought use of caplacizumab therapy would be unlikely to cause substantial disruption to the health care delivery system because it is additive to plasma exchange therapy for a rare condition. One commenter with a clinical perspective expected that the addition of caplacizumab would reduce the need for inpatient treatment of acute aTTP episodes and shift more of that care to the outpatient setting.136 This commenter also expected a learning curve for clinicians, especially those with less experience treating aTTP.136

**Current paradigm of patient care:** Three commenters with clinical135,136 and systems137 perspectives expected caplacizumab to create moderate to large disruptions to current treatment protocols for aTTP, especially when drug cost and insurance coverage availability are added into consideration. One commenter with a clinical perspective noted the most compelling argument for its use will likely be its ability to reduce aTTP exacerbations and refractory disease.136 This commenter also anticipated controversies surrounding caplacizumab use that would likely affect how widely it is integrated into care for aTTP. One likely controversy involves appropriate patient selection and cost-effectiveness in different subgroups with varying disease severity (eg, severe aTTP with neurologic or cardiac involvement). This commenter also expected a continued debate on how long caplacizumab therapy should be continued to achieve maximal clinical benefit, especially in conjunction with intensive immunosuppression (with rituximab).136 Two commenters with research138 and systems134 perspectives anticipated a small disruption to current treatment protocols for aTTP, given that caplacizumab is adjunctive therapy.
**Health care costs:** Three commenters with clinical\textsuperscript{135,136} and systems\textsuperscript{137} perspectives thought caplacizumab, at about $270,000 wholesale acquisition cost per treatment regimen, would cause large disruption in treatment costs for aTTP, at least initially. One commenter with a clinical perspective stated, “The increased cost to payers and patients may lead to controversy. Some payers are already reluctant to pay for rituximab, which reduces relapses, and [caplacizumab] arguably has more long-term benefit than rituximab.”\textsuperscript{136} Another commenter with a clinical perspective anticipated that cost disruption could be minimized in the long term if additional evidence were to demonstrate that caplacizumab could substantially reduce frequency of plasma exchange, aTTP-related hospitalizations, and lengths of stay.\textsuperscript{135} Two commenters with research\textsuperscript{138} and systems\textsuperscript{134} perspectives did not expect caplacizumab to cause much disruption to health care costs, generally due to the rarity of aTTP.

**Overall disruption potential:** Commenters were divided on caplacizumab’s overall disruptive potential, largely given the expected small number of patients likely to receive it. Three commenters with clinical\textsuperscript{135,136} and systems\textsuperscript{137} perspectives expected caplacizumab to cause at least moderate disruption overall. One commenter with a clinical perspective noted, “The interplay among safety, efficacy, and cost will be the final determining factors for the use of Cablivi.”\textsuperscript{135} Another commenter with a clinical perspective noted, “Though there is a considerable reduction in the rate of recurrence, particularly early recurrence, which is the most compelling argument for use, this might be offset by earlier use of rituximab. In summary, [caplacizumab] would be nice to have for all patients, but cost may limit use.”\textsuperscript{136} One commenter with a systems perspective noted the lack of existing clinical guidelines for aTTP treatment from US-based guideline developers; this commenter proposed that new guidelines could be developed with the recent availability of caplacizumab as the first FDA-approved treatment for aTTP.\textsuperscript{137}

Crizanlizumab (SEG101) for Preventing Vaso-Occlusive Crises From Sickle Cell Disease

**Highlights**

Crizanlizumab is a humanized monoclonal antibody that blocks P-selectin’s interaction with glycoprotein ligand 1 to inhibit the inflammatory and adhesion processes thought to be involved in vaso-occlusive crises (VOCs). The 7 stakeholders commenting on this topic were generally optimistic about crizanlizumab’s potential to improve health outcomes and quality of life by reducing the number of and increasing the time between hospitalizations from sickle cell disease (SCD) crises. However, monthly infusions required for administering crizanlizumab would likely disrupt current treatment paradigms and increase costs, because the standard-of-care treatment, hydroxyurea, is an oral therapy. This could increase disparities. However, if crizanlizumab leads to fewer hospitalizations, this could reduce the acute care burden on the system and opioid management, potentially saving costs (contingent on final pricing and reimbursement).

**Patient Population**

Crizanlizumab is intended for preventing VOC in patients with SCD aged 16 years or older with a history of VOCs.
Intervention

Inherited SCD-inducing mutations alter the shape of hemoglobin molecules, resulting in sickled red blood cells that are more susceptible to oxidative damage, inappropriate adhesion, and vascular obstruction, which can lead to severely painful VOCs, requiring hospitalization. For more information on SCD, see the National Heart, Lung, and Blood Institute. VOCs are thought to be associated with several processes, including chronic inflammation, erythrocyte microvascular occlusion, impaired oxygen supply, and infarction-reperfusion injury. SCD progresses with age, manifesting with increased complications, frequency of VOC, and increased risk of morbidity and mortality. Patients may progress to thromboembolic events, stroke, organ failure, or early death. The only FDA-approved treatment for SCD, hydroxyurea, can reduce VOC incidence, but it is ineffective in about one-third of adult patients.

Crizanlizumab (SEG101) is a humanized monoclonal antibody against P-selectin, blocking P-selectin’s interaction with glycoprotein ligand 1. P-selectin is expressed on the surface of endothelial cells and platelets and is thought to promote the inflammatory and adhesion processes involved in VOC. In clinical trials, crizanlizumab is administered by intravenous infusion at a dosage of 5 mg/kg, once every 4 weeks.

Evidence Development Summary

The phase II SUSTAIN trial (NCT01895361) involved patients (n = 198) aged 16 to 65 years with SCD who had had 2 to 10 VOCs in the prior 12 months and might also have been receiving hydroxyurea. Patients were randomly assigned 1:1:1 to intravenous treatment with crizanlizumab 2.5 mg/kg (n = 66) or 5.0 mg/kg (n = 67), or placebo (n = 65) 4 times over 52 weeks.

Patients given crizanlizumab achieved the primary endpoint of a reduced median rate of crises per year in the high-dose crizanlizumab group versus placebo (1.63 versus 2.98; 45.3% VOC reduction; P = .01). High-dose crizanlizumab also increased the median time to first crisis (4.07 versus 1.38 months, P = .001) and second crisis (10.32 versus 5.09 months; P = .02) compared with placebo. High-dose crizanlizumab also lowered the median rate of uncomplicated crises per year by 62.9% (P = 0.02). The most common adverse events in patients taking crizanlizumab included arthralgia, chest pain, diarrhea, pruritus, and vomiting.

Manufacturers and Regulatory Status

Crizanlizumab is manufactured by Novartis AG (Basel, Switzerland) and is in phase III development for preventing VOC. In January 2019, the manufacturer disclosed plans for submitting regulatory filings to FDA for this indication within the first half of 2019. FDA granted crizanlizumab Breakthrough Therapy designation for preventing VOC in patients with SCD in January 2019.

Results and Discussion of Stakeholder Comments

Seven stakeholder commenters, reflecting caregiver, clinical, health systems, nursing, and research perspectives provided comments and ratings on crizanlizumab. We have organized the following discussion of stakeholder comments by the parameters on which they commented.

Patient outcomes, quality of life, and overall health: Most commenters considered crizanlizumab effective for preventing VOCs and increasing the time between VOCs in patients
in whom hydroxyurea is ineffective or intolerable. Clinical and caregiver commenters also thought that crizanlizumab would have a greater impact on improving health outcomes if effective for various SCD variants (such as HbSS, HbSC, HbSβ⁰-thalassemia, or HbSβ⁺-thalassemia). One commenter with a clinical perspective stated that crizanlizumab might become the first drug indicated for patients with the HbSC form of the disease. One commenter with a research perspective stated concern for whether the clinical response to crizanlizumab was sustainable and whether long-term adverse events or adherence would become an issue.

**Health disparities:** A commenter with a caregiver perspective noted that if crizanlizumab can effectively treat patients, it could reduce disparities by offering a new treatment option for patients with limited options. Also, one commenter with a nursing perspective noted that, because patients with SCD have few treatment options (including hydroxyurea and opioids), they can sometimes be portrayed as drug seekers because there is no objective way to manage pain. Reduced crises and pain would reduce demands on the system as well as mitigate opioid abuse in this patient population.

Commenters with research, nursing, and health systems perspectives thought that disparities in rural areas or other areas with transportation barriers might occur because of the requirement for 14 infusion visits annually to administer crizanlizumab. Commenters with clinical, nursing, health systems, and caregiver perspectives estimated that about 75% of patients with SCD have public insurance (50% Medicaid, 25% Medicare), which might not cover crizanlizumab, and patients with private insurance might have high copayments for infusion visits, potentially creating disparities. However, one commenter with a clinical perspective noted that the increased development of new SCD treatments is a positive trend for decreasing disparities.

One commenter with a clinical perspective noted that people with SCD have difficulty finding providers in the community setting who want to take care of them—this reluctance being because of typically low reimbursement rates combined with high resource use for social work, opioid management, etc. A new intravenous therapy might gain favorable reimbursement, thereby encouraging providers to accept these patients.

**Health care delivery system:** Most commenters agreed that reducing VOCs would reduce the burden on the health system in terms of acute care, but monthly administration of crizanlizumab would increase demands on infusion centers. Some commenters thought that lack of reimbursement might be a barrier to diffusion, thereby limiting its overall disruption to the health care system.

**Current paradigm of patient care:** One commenter with a clinical perspective thought hydroxyurea should remain first-line therapy because it increases hemoglobin count and potentially offers a survival benefit, which crizanlizumab has not demonstrated. Shifting care from oral hydroxyurea to infused crizanlizumab would also change the treatment paradigm, thought one commenter with a research perspective. Commenters with health systems and clinical perspectives also agreed that crizanlizumab might be used in a select group of patients with SCD because of financial or clinical reasons, including people with the HbSC variant genotypes who receive limited benefit from hydroxyurea (L-glutamine is available for HbSS disease). One commenter with a clinical perspective warned that many patients with SCD have poor venous access, although that could be overcome by using ports and catheters.
Health care costs: Overall, commenters agreed that crizanlizumab, even if costly, might save money by reducing hospitalizations. However, this is highly contingent on the final price of the biologic, which would also highly influence diffusion because of reimbursement and copayments per infusion. One commenter with a clinical perspective noted, for benchmarking purposes, that intravenously administered L-glutamine was approved in 2017 for treating SCD and costs about $3000 per month, and crizanlizumab would likely be priced similarly or be more costly.\(^{147}\)

Overall disruption potential: Commenters generally agreed that crizanlizumab demonstrated potential to decrease the number of SCD hospitalizations and increase the time between hospitalizations due to VOCs, which could change the current standard of care for patients seeking better VOC management. Commenters also agreed that larger, longer-term studies are needed to better understand the full disruptive potential of crizanlizumab and which patients would benefit most from its use.
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