PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

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PCORI HEALTH CARE HORIZON SCANNING SYSTEM VOLUME 3 ISSUE 2

High Potential Disruption Report November 2021

Prepared for:

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

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

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Statement of Funding and Purpose

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

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

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

Financial Disclosure Statement

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

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Preface

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

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

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

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

This edition of the *High Potential Disruption Report* is the second of 2 editions planned for 2021 and includes topics (ie, interventions intended for a specific use within a specific patient population) and trends (ie, high-level disruptions occurring within or across clinical areas from a combination of factors that, taken together, create a paradigm shift). These topics and trends have been identified by stakeholders and the horizon scanning team as having high potential to cause disruption to health care.

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

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Introduction

Background

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

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

System Overview

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

PCORI currently defines its project scope as interventions with high potential for disruption in 6 focus areas: Alzheimer's disease and other dementias, cancer, cardiovascular diseases, COVID-19, 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 focus areas in the future.

From April 2020 to April 2021, under PCORI's direction, we performed a separate scan for COVID-19 (see the Horizon Scanning COVID-19 Supplement) topics and trends. This work used a slightly different process than did the main PCORI HCHSS and produced separate reports highlighting COVID-19 topics and trends. At PCORI's request, in May 2021, we incorporated COVID-19 scanning into the main PCORI HCHSS process and named COVID-19 as a focus area. As of May 2021, COVID-19 content (ie, topics and trends) has been scanned, identified, and selected according to the process as described in this High Potential Disruption Report and in the *PCORI Health Care Horizon Scanning System: Horizon Scanning Protocol and Operations Manual*. The reader should note that some features particular to the COVID-19 Supplement High Impact Reports have not been carried forward into this report. Instead, all COVID-19 content (ie, topics and trends) included in this High Potential Disruption Report has been formatted according to the standards established for PCORI HCHSS High Potential Disruption Reports.

Broad Scanning to Identify Topics and Trends

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

Analysts present potential topics and trends at nomination meetings. After a brief presentation and discussion, HCHSS team members vote in blinded fashion to include or exclude the topic or trend based on the criteria described in the *PCORI Health Care Horizon Scanning System: Horizon Scanning Protocol and Operations Manual*. All included topics and trends may be viewed at the PCORI Horizon Scanning Database website.

Developing Topic and Trend Profiles

Included topics with late-phase clinical data are further developed as topic profiles—reports that rely on focused searches and more robust analysis. Each topic profile is sent to stakeholders for comment with the goal of obtaining at least 5 sets of comments and ratings before a topic is eligible for consideration for this report. Stakeholders provide varied perspectives and/or areas of knowledge in health care (eg, clinical, health systems, research, nursing, patient, caregiver), ideally including at least one patient, patient representative, or caregiver.

Included trends are developed into trend profiles, revised according to comments from the nomination meeting (if needed), and edited before being sent to internal ECRI stakeholders for comment. Each trend profile is posted to an internal ECRI online bulletin board, and a pool of about 50 ECRI internal stakeholders—representing health care business and finance, clinical engineering, health systems, health care generalist, information technology, nursing, physician, physician assistant, and research perspectives—is invited to provide input on each trend. Any stakeholder from the pool may self-select to review a trend, based on his or her expertise and interest. In addition, trends are sent to one or more external stakeholders representing various perspectives (eg, clinical, health systems, research, nursing, patient, caregiver). The horizon scanning project manager monitors the process to ensure that at least 5 stakeholders representing appropriate perspectives review each trend.

For both topics and trends, stakeholder commenters read a written summary of the topic or trend and then complete a brief online survey, which elicits ratings about the topic's or trend's potential to disrupt a number of key areas of health care, its overall disruptive potential, and the expected timing and likelihood of the disruption. Commenters also provide a written explanation for the selected ratings.

ECRI follows strict conflict-of-interest policies and ensures that comments and ratings received from any stakeholder with potential conflicts of interest are balanced by inputs from other neutral parties, including ECRI experts. See the *PCORI Health Care Horizon Scanning System: Horizon Scanning Protocol and Operations Manual* for details about ECRI's conflict-of-interest policy.

Archiving Topics and Trends

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

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

Report Methods

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

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

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

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

High Potential Disruption Report Topic and Trend Selection Meeting

For some topics or trends, consensus in stakeholder ratings is unclear (ie, there is wide variation among stakeholder opinions about whether the topic will be highly disruptive). The horizon scanning team meets to discuss and vote on whether to include these topics or trends in the *High Potential Disruption Report*.

The assigned analyst for each topic or trend presents a summary of stakeholder comments and ratings received for the topic or trend. A brief discussion then takes place, during which team

members may ask questions or provide perspectives regarding the topic's or trend's disruptive potential. After the discussion, a blinded vote determines whether the topic or trend should be included in the *High Potential Disruption Report*. The topic or trend must receive a majority affirmative vote to be included. Topics or trends selected for inclusion are assigned to analysts to draft topic or trend summaries.

Producing the *High Potential Disruption Report*

After topic and trend selection, the PCORI HCHSS project manager creates a production schedule and assigns the selected topics and trends to the appropriate analysts for topic and trend summary drafting. Analysts draft an analysis of each topic, which includes highlights, PICO information, an evidence development summary, manufacturer and regulatory information, cost information (if available), and a summary of key stakeholder perspectives. Likewise, analysts draft an analysis for each trend, which includes a trend description, a list of clinical areas potentially disrupted, lists of potential opportunities (ie, pros) and threats (ie, cons), and a summary of key stakeholder perspectives.

Topic Summaries

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

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

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

Trend Summaries

Potentially disruptive trends can occur across or within clinical areas and arise from a combination of factors that, taken together, create a paradigm shift in health care. Identification of these trends goes beyond the 6 focus areas PCORI initially defined. Each trend summary begins with a brief list highlighting key takeaways for the reader, followed by a description of the nature and importance of the trend, a listing of clinical areas potentially affected by the trend, a brief discussion of opportunities and threats (ie, potential positive and negative disruptions) posed by the trend, and a summary of key stakeholder perspectives.

Report Compilation

Topic and trend summaries are compiled into chapters: 1 for each of the 6 PCORI-defined focus areas and 1 for potentially disruptive trends that do not fit within any of the 6 PCORI-defined focus areas. After a chapter has been compiled, the project manager reviews all content and writes a chapter summary, which provides basic information and statistics about topics or trends included in the chapter and currently monitored or recently archived in the HCHSS. Each chapter is reviewed carefully by the medical copyeditor, senior technical reviewer, and project director before compilation into the final report.

After compilation, the project manager reviews the content and writes the overall reporting period summary, which provides basic information and statistics about topics or trends included in the report and currently monitored or recently archived in the HCHSS.

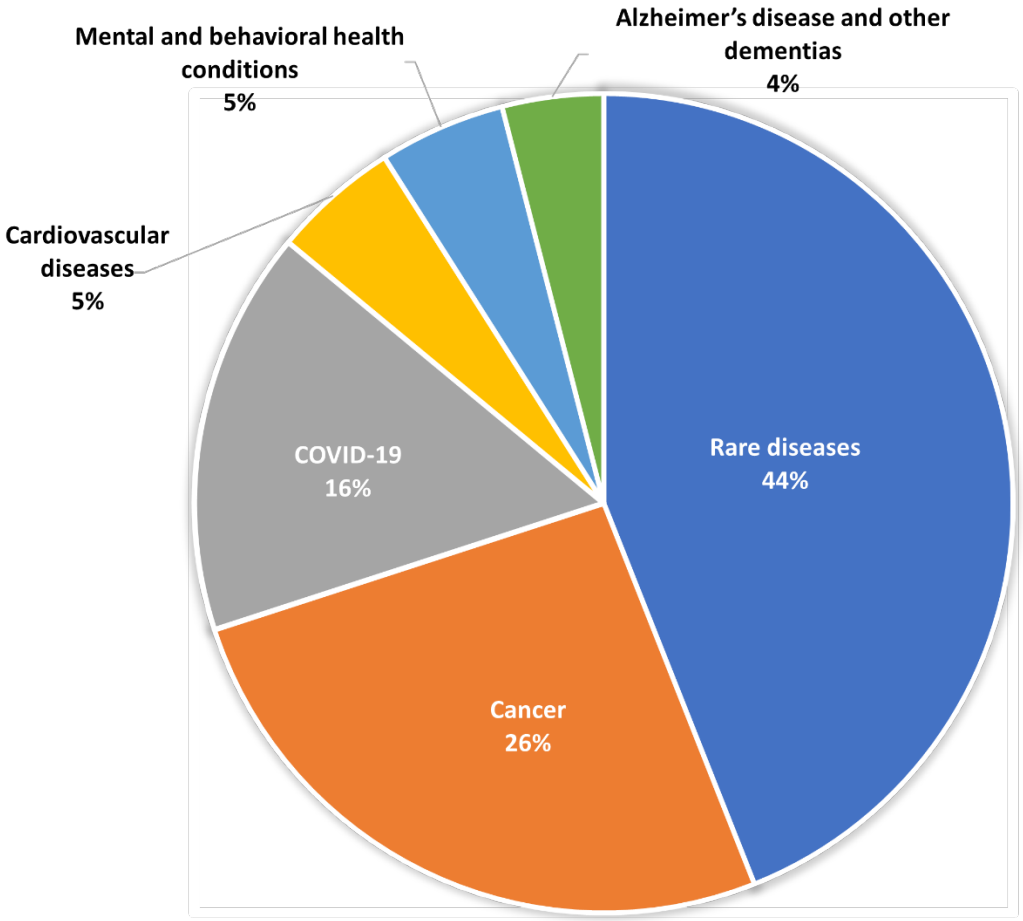
Reporting Period Summary

The PCORI HCHSS began operating in December 2018. Since then, review of about 15 750 information leads has led to the identification of about 730 potential topics across the 6 PCORI focus areas and 195 high-level trends occurring in all areas of health care.

As of September 3, 2021, after subjecting the potential topics to our inclusion criteria and nomination process, 527 have been selected. Of these, 315 topics are being actively monitored in the system; an additional 230 topics have been archived. The 315 actively monitored topics represent 143 diseases and conditions and span the PCORI-defined focus areas as follows (see also Figure 1):

- Alzheimer's disease and other dementias: 12 topics (4%)
- Cancer: 82 topics (26%)
- Cardiovascular diseases: 17 topics (5%)
- COVID-19: 50 topics (16%)
- Mental and behavioral health conditions: 16 topics (5%)
- Rare diseases: 138 topics (44%)

Figure 1. Percentage of All Actively Monitored Topics by Focus Area

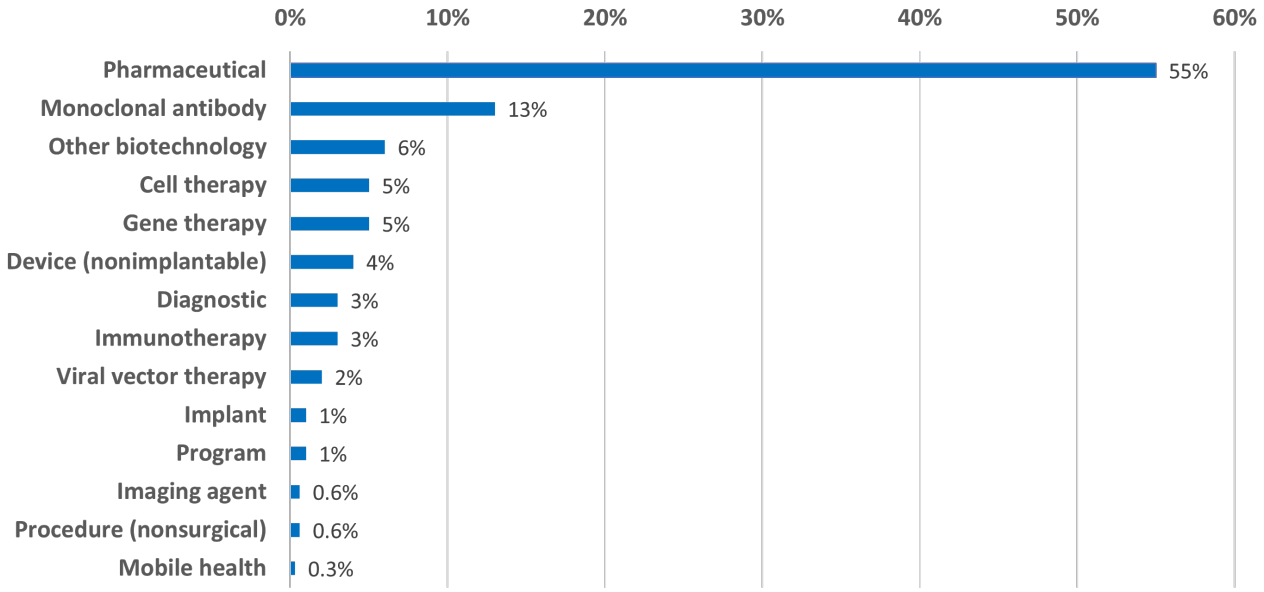


Across all focus areas, the 315 monitored topics represent the following therapeutic classes* (see also Figure 2):

- Cell therapy: 15 topics (5%)
- Device (nonimplantable): 12 topics (4%)
- Diagnostic: 9 topics (3%)
- Gene therapy: 17 topics (5%)
- Imaging agent: 2 topics (0.6%)
- Immunotherapy: 8 topics (3%)
- Implant: 4 topics (1%)
- Mobile health: 1 topic (0.3%)
- Monoclonal antibody: 42 topics (13%)
- Other biotechnology: 20 topics (6%)
- Pharmaceutical: 172 topics (55%)
- Procedure (nonsurgical): 2 topics (0.6%)
- Program: 4 topics (1%)
- Viral vector therapy: 7 topics (2%)

* Total does not equal 100% because of rounding.

Figure 2. Percentage of All Currently Monitored Topics by Therapeutic Class

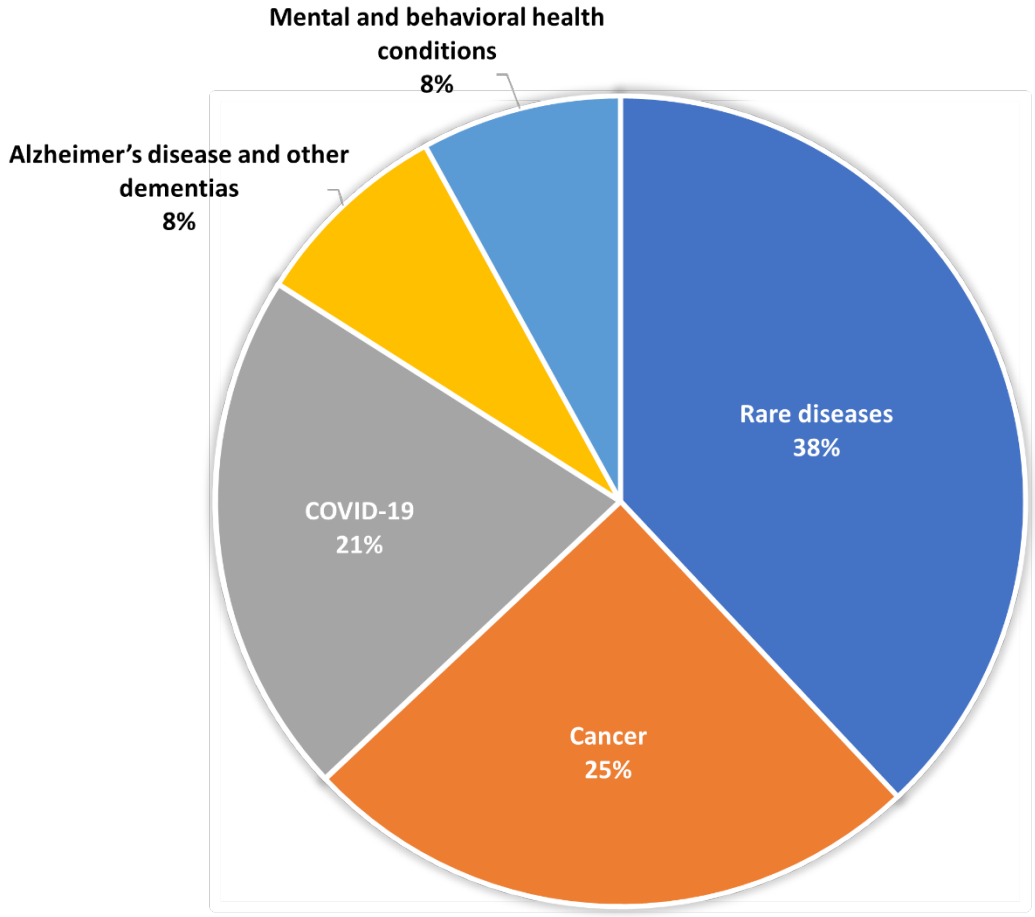


From the 315 actively monitored topics, we have selected—based on the procedures described in Report Methods—24 topics for inclusion in this report, distributed across the PCORI focus areas as follows* (see also Figure 3):

- Alzheimer's disease and other dementias: 2 topics (8%)
- Cancer: 6 topics (25%)
- COVID-19: 5 topics (21%)
- Mental and behavioral health conditions: 2 topics (8%)
- Rare diseases: 9 topics (38%)

* For the focus area of cardiovascular diseases, no topics (0%) met requirements for inclusion in this report.

Figure 3. Percentage of Topics Selected for Report by Focus Area

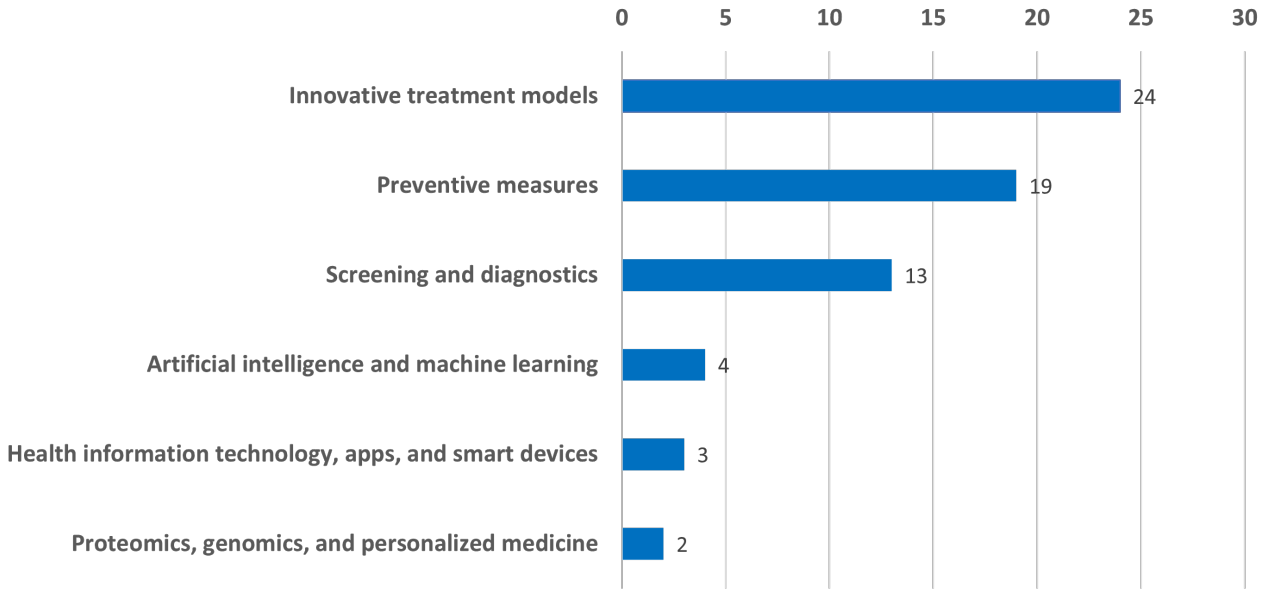


Likewise, as of September 3, 2021, after subjecting potential trends to our inclusion criteria and nomination process, we have selected 136 trends occurring across clinical areas or within a clinical area that can potentially create a paradigm shift in health care (ie, large, high-level disruptions). Of these trends, 50 are being actively monitored in the system and 86 have been archived. Among the 50 actively monitored trends, 6 themes have emerged* (see also Figure 4):

- Artificial intelligence and machine learning: 4 trends
- Health information technology, apps, and smart devices: 3 trends
- Innovative treatment models: 24 trends
- Preventive measures: 19 trends
- Proteomics, genomics, and personalized medicine: 2 trends
- Screening and diagnostics: 13 trends

* Trend number exceeds 50 because some trends fall into multiple theme categories.

Figure 4. All Currently Monitored Trends by Theme



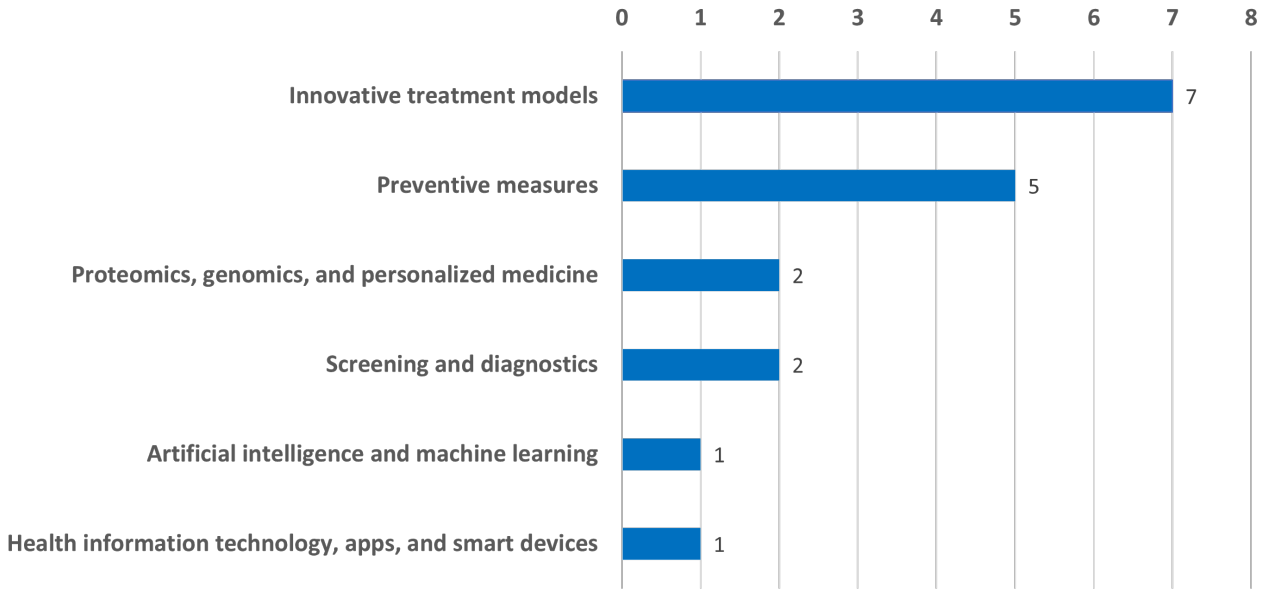
From the 50 actively monitored trends, we have selected—based on the procedure described in Report Methods—15 trends for inclusion in this report, distributed by theme as follows* (see also Figure 5):

- Artificial intelligence and machine learning: 1 trend
- Health information technology, apps, and smart devices: 1 trend
- Innovative treatment models: 7 trends
- Preventive measures: 5 trends
- Proteomics, genomics, and personalized medicine: 2 trends
- Screening and diagnostics: 2 trends

* Trend number exceeds 15 because some trends fall into multiple theme categories.

- Three trends fall into treatment models and preventive measures.
- One trend falls into artificial intelligence, preventive measures, and treatment models.
- One trend falls into health information technology and screening and diagnostics.
- One trend falls into personalized medicine and screening and diagnostics.
- One trend falls into preventive measures and screening and diagnostics.
- One trend falls into screening and diagnostics and treatment models.

Figure 5. Trends Selected for Report by Theme

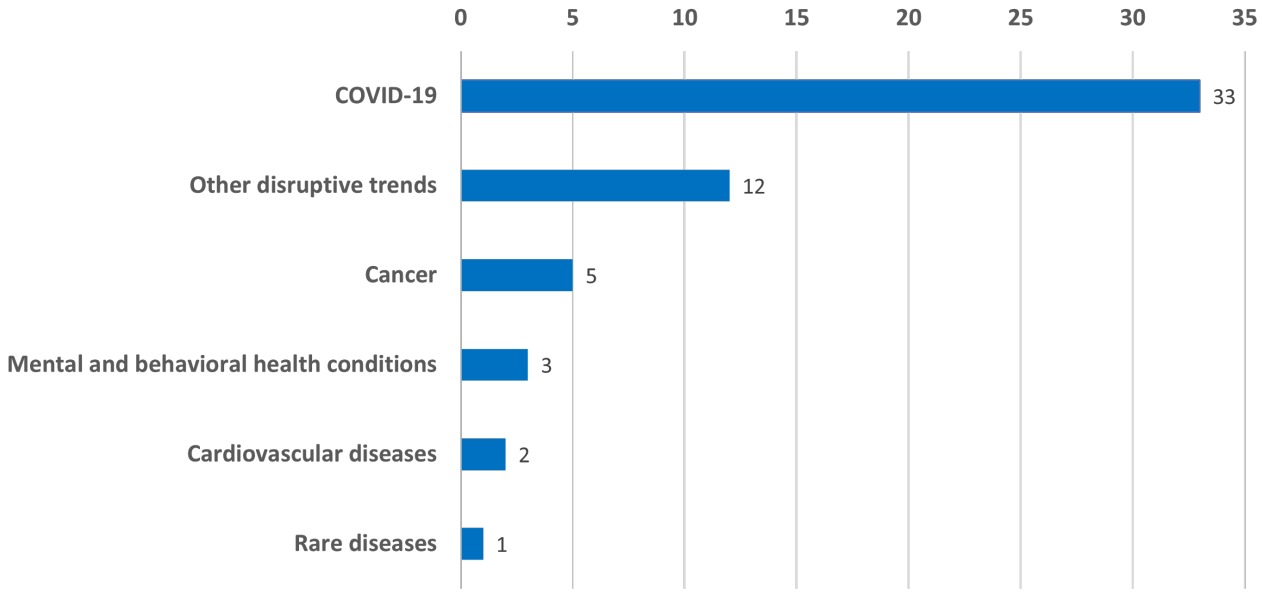


The 50 actively monitored trends span the PCORI-defined focus areas as follows* (see also Figure 6):

- Cancer: 5 trends
- Cardiovascular diseases: 2 trends
- COVID-19: 33 trends
- Mental and behavioral health conditions: 3 trends
- Other disruptive trends: 12 trends
- Rare diseases: 1 trend

* Trend number exceeds 50 because some trends fall into multiple focus areas.

Figure 6. All Currently Monitored Trends by Focus Area

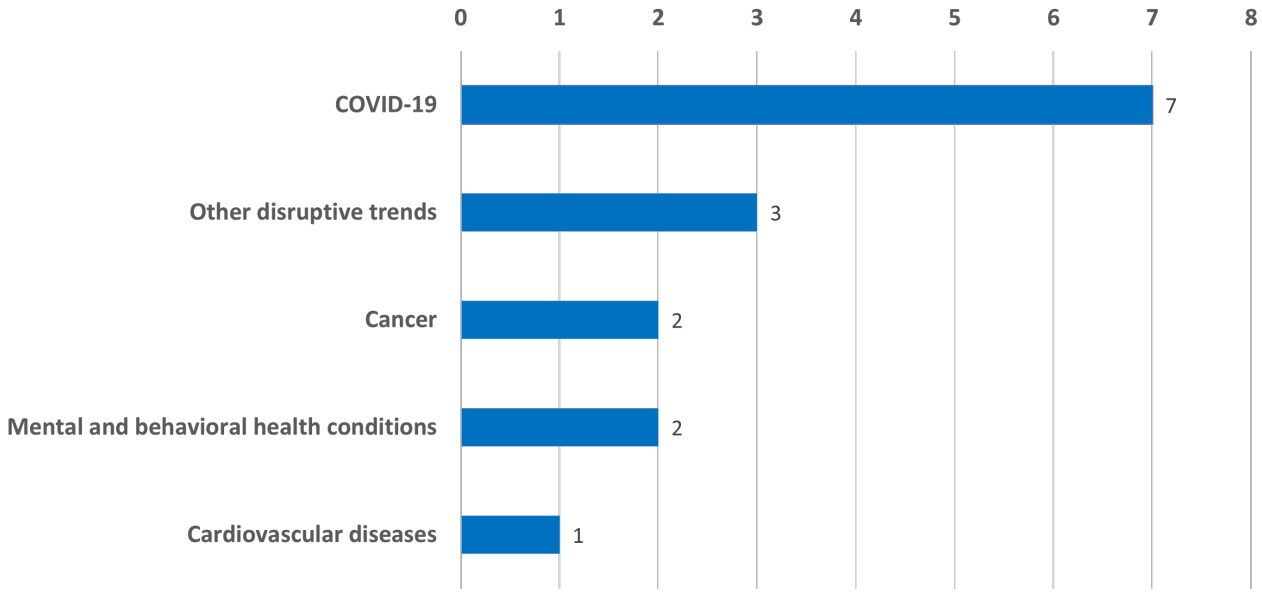


From the 50 actively monitored trends, we have selected—based on the procedure described in Report Methods—15 trends for inclusion in this report, distributed by focus area as follows* (see also Figure 7):

- Cancer: 2 trends
- Cardiovascular diseases: 1 trend
- COVID-19: 7 trends
- Mental and behavioral health conditions: 2 trends
- Other disruptive trends: 3 trends

* For the focus areas of Alzheimer's disease and other dementias and rare diseases, no trends met requirements for inclusion in this report.

Figure 7. Trends Selected for Report by Focus Area



Chapter 1. Alzheimer's Disease and Other Dementias

For the Alzheimer's disease and other dementias focus area, we considered for inclusion 2 topics for which (1) preliminary phase 3 data for drugs, phase 2 (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled and sent for stakeholder comment before September 3, 2021; *and* (3) we received at least 5 sets of comments and ratings from stakeholders between September 18, 2020, and September 17, 2021.

As of September 3, 2021, we were monitoring 12 topics in this focus area, including the 2 topics considered for inclusion in this report. These 12 topics are available—or will soon be available—for viewing on the PCORI Horizon Scanning Database website.

The 12 monitored topics encompass pharmaceuticals and biotechnologies for treating Alzheimer's disease and/or related symptoms (eg, agitation). Of these, 10 topics are too early in development to meet the criteria (as outlined above) for eligibility for this report.

Topics Considered for Inclusion in This Report

Table 1.1 lists the 2 topics selected for inclusion in this report based on stakeholder ratings and comments and available data. Topics are listed and discussed alphabetically by topic title.

Table 1.1. Included Topics for Focus Area: Alzheimer's Disease and Other Dementias

Topic title
Aducanumab-avwa (Aduhelm) to treat early Alzheimer's disease
Periodic therapeutic plasma exchange (Alzheimer's management by albumin replacement protocol) to treat mild to moderate Alzheimer's disease

Trends Considered for Inclusion in This Report

As of September 3, 2021, we had not identified any trends pertaining to the Alzheimer's disease and other dementias focus area that met the criteria for entry into the PCORI Health Care Horizon Scanning System.

Topic Summaries

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

Aducanumab-avwa (Aduhelm) to Treat Early Alzheimer's Disease

Highlights

- Aducanumab-avwa is a recombinant human monoclonal antibody that is intended to reduce cognitive decline and the progression of Alzheimer's disease (AD) in early and mild stages.
- AD affects millions of Americans, particularly adults aged 55 years or older, and a significant unmet need exists for treatments. Aducanumab is the first FDA-approved treatment to target and affect an underlying pathophysiology of AD in the brain: the presence of amyloid beta plaques.

- Stakeholders commenting on this topic thought aducanumab-avwa might improve health outcomes, including quality of life, for patients experiencing memory loss and who fear losing their independence.
- Most stakeholders thought that both the cost (depending on insurance reimbursement) and delivery of the treatment (which occurs in infusion centers) would increase disparities in access and add to the burden of care for patients and caregivers.
- Stakeholders also thought that the repeated intravenous infusions required for this treatment might impact care delivery and staffing.

Patient Population

Aducanumab is intended for patients with AD and evidence of mild cognitive impairment or mild dementia.

Intervention

AD is a neurodegenerative disorder and the most common cause of dementia, accounting for 60% to 80% of dementia cases. In patients, it results in progressive memory loss, confusion, and other cognitive impairments that degrade their ability to perform activities of daily living. AD has no cure and has limited options for effective symptom management. No disease-modifying treatments have been available despite decades of research.[1] The Alzheimer's Association website offers more information on AD.

The amyloid hypothesis of AD pathogenesis suggests that the accumulation of amyloid beta (Aβ) protein fragments in the brain is the primary cause of AD.[2] However, no Aβ-targeted therapy has demonstrated improved outcomes in patients with AD.

Aducanumab is a recombinant human monoclonal antibody that preferentially binds aggregated forms of Aβ (ie, soluble oligomers and insoluble fibrils) that are thought to cause the neurotoxic effects linked with AD.[3,4] The drug is approved by the FDA.

Aducanumab's high degree of selectivity for aggregated forms of Aβ might differentiate it from other Aβ-targeting antibodies that failed to demonstrate clinical improvement in clinical trials.[4] Although aducanumab-avwa's exact mechanism of action is unclear, animal models suggest that the drug binds to aggregated isoforms (different versions) of the Aβ protein fragments, leading to their clearance by microglia.[5] This might reduce cognitive decline in patients with early AD and improve their ability to perform activities of daily living.[6]

According to the FDA-approved label, treatment with aducanumab-avwa should be initiated in patients with early, symptomatic stages of AD (mild cognitive impairment and mild AD dementia) with confirmed presence of amyloid plaques based on magnetic resonance imaging scans of the brain.

A clinician refers a patient to an infusion center to receive aducanumab-avwa. After an initial titration, aducanumab-avwa is given intravenously at a dosage of 10 mg/kg every 4 weeks.[7]

Evidence Development Summary

Ongoing Trials

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

Table 1.2. Ongoing Clinical Trial

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
A Study to Evaluate Safety and Tolerability of aducanumab in participants with AD who had previously participated in the aducanumab studies 221AD103, 221AD301, 221AD302 and 221AD205 EMBARK NCT04241068	Adults aged 50 to 90 years (n = 2400) who have AD and participated in an earlier trial of aducanumab-avwa	Phase 3b, randomized, open-label trial to evaluate the long-term safety and tolerability of aducanumab-avwa in patients with AD who had previously participated in aducanumab-avwa studies Primary outcome measures: • AEs and serious AEs up to week 118 • Number of participants with ARIA up to week 102	Primary and study completion October 2023

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

Recently Completed and Ongoing Trials With Available Results

Our searches identified 2 recently completed late-phase trials with results reported in a company news release.[8]

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

Two Phase 3 Studies, 221AD302 EMERGE and 221AD301 ENGAGE, of Aducanumab (BIIB037) in Early Alzheimer's Disease. NCT02484547, NCT02477800. Biogen, 2020.[8]

- **Patient population/planned enrollment:** Adults aged 50 to 85 years with early AD enrolled in 2 cohorts, receiving either a low or high dose of aducanumab-avwa; EMERGE (n = 1638), ENGAGE (n = 1647)
- **Study design:** Two phase 3, randomized, double-blind, placebo-controlled studies to evaluate the efficacy and safety of aducanumab-avwa in patients with early AD
- **Primary outcome:** Change from baseline in CDR-SB score up to week 78
- **Secondary outcomes:** Change from baseline in MMSE score up to week 78, change from baseline in ADAS-Cog 13 score up to week 78, and change from baseline in ADCS-ADL-MCI score up to week 78
- **Results presented by study authors:** "These studies were discontinued on March 21, 2019, following the results of a pre-specified futility analysis which relied on an earlier and smaller dataset. The futility analysis was based on data available as of December 26, 2018, from 1,748 patients who had the opportunity to complete the 18-month study period and predicted that both studies were unlikely to meet their primary endpoint upon completion. …

  "Following the discontinuation of EMERGE and ENGAGE, additional data from these studies became available resulting in a larger dataset, which included a total of 3,285 patients, 2,066 of whom had the opportunity to complete the full 18 months of treatment. A new extensive analysis of this larger dataset showed a different outcome than the outcome predicted by the futility analysis. Specifically, the new analysis of this larger dataset showed EMERGE to be

statistically significant on the pre-specified primary endpoint (P = 0.01). Biogen believes that data from a subset of ENGAGE support the findings from EMERGE, though ENGAGE did not meet its primary endpoint."

"In EMERGE, which met its pre-specified primary endpoint in the new analysis, patients treated with high dose aducanumab showed a significant reduction of clinical decline from baseline in CDR-SB scores at 78 weeks (23% versus placebo, P = 0.01). In EMERGE, patients treated with high dose aducanumab also showed a consistent reduction of clinical decline as measured by the pre-specified secondary endpoints: the Mini-Mental State Examination (MMSE; 15% versus placebo, P = 0.06), the AD Assessment Scale–Cognitive Subscale 13 Items (ADAS-Cog 13; 27% versus placebo, P=0.01), and the AD Cooperative Study-Activities of Daily Living Inventory Mild Cognitive Impairment Version

(ADCS-ADL-MCI; 40% versus placebo, P = 0.001). Imaging of amyloid plaque deposition in EMERGE demonstrated that amyloid plaque burden was reduced with low and high dose aducanumab compared to placebo at 26 and 78 weeks (P < 0.001). Additional biomarker data of tau levels in the cerebrospinal fluid supported these clinical findings. …

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

See Biogen presentation for additional details on data from the EMERGE and ENGAGE trials.[9]

Manufacturers and Regulatory Status

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

On June 7, 2021, aducanumab-avwa was approved through the FDA's accelerated approval pathway.[10,11] FDA based its approval on results from two phase 3 trials, EMERGE and ENGAGE, that demonstrated statistically significant dose- and time-dependent reductions of Aβ plaques in patients' brains. The FDA judged these outcomes as likely to imply clinical benefit, even though only one of these trials, EMERGE, demonstrated clinical effectiveness. On July 8, 2021, the FDA released updated prescribing information for aducanumab-avwa to specify the initiation of the drug in patients with AD at disease stages exhibiting mild cognitive impairment or mild dementia. This population most closely resembles the patient population evaluated in the clinical trials supporting approval.[7]

Accelerated approval requires a postapproval, randomized controlled trial to verify that the drug provides expected clinical benefit. Biogen has a 9-year period to conduct this trial.[12] The FDA had previously granted aducanumab fast track designation to treat AD.[13]

In March 2019, the developers had discontinued the EMERGE and ENGAGE trials after preliminary results from a futility analysis showed the trials were unlikely to meet their primary end point of reducing cognitive decline.[14] However, in December 2019, the manufacturers' analysis of larger accumulated data sets from the two phase 3 trials, including data that became available after trial discontinuation, indicated significant reductions in cognitive decline for subsets of patients receiving high doses.[3] However, only 1 of 11 members of the FDA's Peripheral and Central Nervous System Drugs Advisory Committee who reviewed the aducanumab data indicated that the EMERGE trial results, when viewed independently, provided strong evidence for clinical effectiveness. And no committee members voted to consider results from EMERGE as the primary evidence for clinical effectiveness.[8,15]

Cost Information

According to Biogen, aducanumab-avwa will cost $4312 per infusion for a patient of average weight (74 kg, or 163 lb). Administration once every 4 weeks at the maintenance dose of 10 mg/kg would result in a yearly cost of about $56 000.[16] This estimate does not include costs of tests to determine treatment eligibility, infusion procedures, or diagnostic magnetic resonance imaging (MRI) scans to monitor for amyloid-related imaging abnormalities, which might include brain edema, microhemorrhages, or superficial siderosis (iron deposition in the brain). Instructions for dosage and administration specify obtaining MRI scans before (within 1 year) treatment is started and before the seventh and 12th infusions.[7] Patients could be eligible for Biogen's payment assistance program to cover out-of-pocket costs.[16]

Key Stakeholder Perspectives

Between July 25 and August 30, 2021, eight stakeholders, reflecting caregiver, clinical, health systems, nursing, patient, and research perspectives, provided comments and ratings on this treatment. The list below provides a summary of key stakeholder perspectives.

- Aducanumab might lower amyloid buildup in the brain, improving patients' cognitive function and their ability to perform activities of daily living.
- Aducanumab would increase immediate costs for patients, payers, and health care facilities, depending on insurance reimbursement and copayments required of patients. However, the treatment could reduce overall costs if it decreases need for inpatient and long-term care facilities.
- Aducanumab might disrupt health care delivery with repeated clinic visits needed during the treatment period and increase the need for caregiver support in the short term. However, it might provide significant relief to caregivers by improving patients' activities ability to perform of daily living over the long term.
- It might be challenging for clinicians to accurately diagnose eligible subjects who have early AD compared with other forms of dementia, which might impact the current paradigm of patient care and staffing needs at neurology clinics.
- If effective, aducanumab-avwa would increase health care disparities, given the large target population needing to visit infusion centers. Patients in rural areas or underserved populations might have difficulty reaching requisite facilities.

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

Highlights

- Periodic therapeutic plasma exchange is an investigational therapy intended to slow cognitive decline and the progression of mild to moderate Alzheimer's disease (AD).
- AD affects millions of Americans, particularly adults aged 55 years or older, and a significant unmet need exists for treatments.
- Although the use of human albumin in plasma exchange has been researched for more than 10 years, results from a recent clinical trial have generated renewed interest in this therapy.

- Stakeholders commenting on this topic thought that this treatment could address the unmet need and improve patient-oriented health outcomes, including ability to perform activities of daily living.
- Most stakeholders thought that the cost and delivery of the treatment (eg, infusion center resources, insurance coverage) would create disparities in access to care and add more burden for patients and caregivers.
- Stakeholders expressed concern about a lack of reporting of the treatment's side effects, of evidence related to long-term effectiveness, and of comparative studies with relation to oral drugs such as donepezil and memantine.

Patient Population

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

Intervention

AD causes up to 80% of dementia cases, has no cure, and has limited effective treatment options.[1] The Alzheimer's Association website offers more information about AD.

AMBAR is a therapeutic approach under study that involves plasma exchange using albumin to replace the plasma volume that is removed.[17] Researchers theorize that such replacement can lead to a shift of the dynamic equilibrium that exists between brain cerebrospinal fluid (CSF) and plasma amyloid beta peptide (Aβ), most of which is bound to albumin. Albumin infused as volume replacement would theoretically bind and capture additional free-circulating Aβ. These processes purportedly reduce levels of free Aβ in plasma, resulting in a diffusion gradient that draws Aβ from the CSF and slows the progression of AD driven by Aβ.[17] This might improve symptoms and delay progression of cognitive decline in the intended population.[17,18]

A clinician refers a patient to an infusion center for the plasma exchange. During a 6-week intensive period, patients undergo weekly total plasma exchange (2.5-3 L plasma removal) and volume replacement with a 5% albumin solution (Albutein). A 12-month maintenance phase follows, during which patients undergo monthly low-volume plasma exchange (650-880 mL plasma removal) and volume replacement with a 20% albumin solution or intravenous immunoglobulin (IVIG).[19]

Three regimens are being tested that use some combination of albumin with or without IVIG as the replacement[19]:

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

Evidence Development Summary

Ongoing Trials

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

Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed late-phase trial with published results.[20] We summarize this most recent study with results as written in the abstract of the peer reviewed, published article.

The following abbreviations are used in this section: AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale—cognitive subscale; ADCS-ADL, Alzheimer's Disease

Cooperative Study—activities of daily living; ADCS-CGIC, Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change; AMBAR, Alzheimer's management by albumin replacement; CDR-sb, Clinical Dementia Rating scale—sum of boxes; MMSE, Mini-Mental State Examination; P, *P* value; PE, plasma exchange.

A Randomized, Controlled Clinical Trial of Plasma Exchange With Albumin Replacement for Alzheimer's Disease: Primary Results of the AMBAR Study. NCT01561053. Boada et al, 2020.[20]

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

Manufacturers and Regulatory Status

The Albutein and IVIG (Flebogamma 5% DIF) treatment protocol (Grifols, SA, Barcelona, Spain) was evaluated in a phase 2/3 clinical trial for treating mild to moderate AD.[21] The FDA has not approved Albutein to treat AD, but it has been commercially available since 1978, and the FDA has approved it for use in several other indications.[22] IVIG also is not labeled for use in AD but is indicated to treat primary (inherited) immunodeficiency in adults and pediatric patients aged 2 years or older.[23] Albutein and IVIG, as used in the AMBAR protocol, could be administered as an off-label treatment for mild to moderate AD.

In a December 6, 2019, news release, the company announced that it would discuss the next steps for the AMBAR clinical development program with the FDA.[24] On May 19, 2021, the manufacturer opened the first AMBAR center to treat patients with AD in Barcelona, Spain, and plans to open several others in Europe, the United States, and China.[25] As of September 2021, the company had not announced any regulatory updates, although positive data from the phase 2/3 clinical trial were published in July 2020.[20]

Cost Information

An online aggregator of US-based prescription drug prices, Drugs.com, reported a retail price of $57.53 for 250 mL of 5% Albutein and $57.53 for 50 mL of 25% Albutein; 5% Flebogamma IVIG was priced at $270.19 for 50 mL as of October 2021.[26,27] The estimated maximum drug cost (for high-dose Albutein and Flebogamma) for 14 months would be about $12 700, although the precise figure will depend on the prescribed dosing regimen, which varies with multiple patient

characteristics.[19,26,27] Note that this estimate excludes the costs of administration and other fees associated with infusion procedures, which are likely to be substantial given the number of required treatments.

Key Stakeholder Perspectives

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

- AMBAR protocol could slow AD progression, thereby improving patient health outcomes, and disrupt the paradigm of care, because it is an infusion-based treatment rather than an oral drug.
- AMBAR might increase costs for payers and health care facilities, depending on insurance reimbursement and copayments required of patients. The treatment would save overall costs because of decreased needs for home health aides or long-term care facilities.
- Concerns exist regarding the lack of reporting on adverse events and long-term effectiveness (beyond 14 months) as well as the efficacy of AMBAR's purported mechanism of action for lowering cerebral amyloid.
- AMBAR might increase disparities for those experiencing hardships due to social determinants of health, who have less access to health care and insurance coverage.
- Given the absence of any other effective treatments addressing slow cognitive decline, this intervention might provide significant relief to caregivers by improving patients' cognition and ability to perform activities of daily living.

Chapter 2. Cancer

For the cancer focus area, we considered for inclusion 18 topics for which (1) preliminary phase 3 data for drugs, phase 2 (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled and sent for stakeholder comment before September 3, 2021; *and* (3) we received at least 5 sets of comments and ratings from stakeholders between September 18, 2020, and September 17, 2021.

As of September 3, 2021, we were monitoring 82 topics in this focus area, including the 18 considered for inclusion in this report. These 18 topics are available—or will soon be available—for viewing on the PCORI Horizon Scanning Database website.

The 82 monitored topics encompass pharmaceuticals, gene and cellular therapies, viral vector therapies, monoclonal antibodies, and devices intended to treat 34 cancers and/or related conditions. Ten topics were developed or were being developed as topic profiles to be sent for stakeholder comment; however, fewer than 5 sets of stakeholder comments were received for these topics before September 3, 2021, so they were not considered for inclusion in this report. The remaining 54 topics are too early in development to meet the criteria (as outlined above) for eligibility for this report.

Topics Considered for Inclusion in This Report

Table 2.1 lists 6 topics selected for inclusion in this report based on stakeholder ratings and comments and available data. Topics are listed and discussed alphabetically by title.

Table 2.1. Included Topics for Focus Area: Cancer

Topic title
^{131}I-omburtamab to treat leptomeningeal metastases from relapsed neuroblastoma
Axicabtagene ciloleucel (Yescarta) to treat indolent B-cell non-Hodgkin lymphomas
Idecabtagene vicleucel (Abecma) to treat relapsed or refractory multiple myeloma
Relugolix (Orgovyx) to treat relapsed, locally advanced, or metastatic androgen-sensitive prostate cancer
Sotorasib (Lumakras) as a second-line treatment for locally advanced or metastatic, *KRAS* G12C mutation–positive non–small cell lung cancer [a]
Tabelecleucel to treat Epstein-Barr virus–associated posttransplant lymphoproliferative disorder[a]

[a] Topic appears for the first time in this edition of the *High Potential Disruption Report*.

Table 2.2 lists 12 topics considered, but not selected, for inclusion during the *High Potential Disruption Report* decision meeting. A majority of the voting team agreed that these topics lacked high potential for disruption, based on stakeholder ratings and comments and available data. Each record contains a note explaining the reasons for exclusion.

Table 2.2. Topics Considered but Not Included for Priority Area: Cancer

Topic title	Exclusion reason(s) and notes based on stakeholder comments
Belumosudil (KD025) to treat chronic graft-vs-host disease	Belumosudil is unlikely to change the current paradigm of care because no major changes will be needed for the patient care infrastructure. Although preliminary data suggest that belumosudil might improve health outcomes in patients, more long-term data are needed to assess safety and side effect profiles.
Brexucabtagene autoleucel (Tecartus) to treat adult B-precursor acute lymphoblastic leukemia	Because patients with this disease are already receiving similar intravenous medications, brexucabtagene autoleucel has limited potential to disrupt the health care delivery system or disrupt the current paradigm of care. Data from the study show potential, but the study lacks a sufficiently large sample size to accurately predict whether the treatment is viable.
Burosumab-twza (Crysvita) to treat FGF23-related hypophosphatemia in tumor-induced osteomalacia	Preliminary data from a small clinical trial suggest that burosumab-twza might improve health outcomes in patients with limited treatment options, but the data are insufficient to assess burosumab-twza's disruptive potential at this time.
Copanlisib (Aliqopa) plus rituximab (Rituxan) to treat indolent non-Hodgkin lymphoma	Similar combination therapies exist, greatly lowering the disruptive potential of this treatment. More data comparing the treatment with other available treatments are needed, to determine whether the combination treatment will benefit patients. The lack of quality-of-life data and the rates of serious adverse events lower the potential benefits and disruption of this treatment.
DCVax-L to treat glioblastoma multiforme (adjuvant setting)	Preliminary data suggest that the DCVax-L vaccine might lead to a slight increase in patients' overall survival. However, long-term results are needed to make a definitive statement about whether DCVax-L has potential to improve health outcomes substantially.
Lifileucel (LN-144) to treat locally advanced or metastatic melanoma (second-line setting)	Results from a single-arm study suggest that lifileucel might improve health outcomes in patients with limited treatment options. However, additional efficacy and safety data are needed to evaluate whether lifileucel's benefits outweigh its risks.
N-803 (Anktiva) to treat bacillus Calmette-Guérin–unresponsive, high-grade, non–muscle invasive bladder cancer	N-803 might improve patient health outcomes because it delays the need for surgical intervention. However, interim data from a small, single-arm study might be insufficient to assess the treatment's effectiveness. Also, because N-803 is given in combination with bacillus Calmette-Guérin over repeated doses, it might add costs and increase access-to-care issues.
Pegloprastide (AVB-620) to prevent repeat breast cancer surgery	Pegloprastide is one of several new modalities used to prevent repeat breast cancer surgery. Current evidence does not suggest that using pegloprastide during surgery will prevent disease recurrence, and any benefit is likely to be incremental.
Pembrolizumab (Keytruda) to treat metastatic esophageal or esophagogastric junction carcinoma (first-line setting)	Results from a clinical trial showed that the benefit pembrolizumab offered to patients was incremental compared with that of standard of care. And even though pembrolizumab will be expensive, its cost is unlikely to be greater than that of available targeted therapies.

Topic title	Exclusion reason(s) and notes based on stakeholder comments
Relatlimab (BMS-986016) to treat locally advanced or metastatic melanoma (first-line setting)	Although relatlimab plus nivolumab extended the progression-free survival of trial participants, some discontinued their treatment because of toxicity. Additionally, there is no clear way to identify patients who are likely to benefit from this combination.
Selinexor (Xpovio) to treat advanced unresectable dedifferentiated liposarcoma (third-line setting)	Results from a clinical trial showed that selinexor offered only a modest improvement to patient health outcomes. Additionally, the reported high-grade adverse events are likely to outweigh the drug's benefits.
Synthetic hypericin (SGX301) to treat cutaneous T-cell lymphoma (first-line setting)	Although preliminary data found that the treatment improved response rates to a modest level, more data are needed to assess the treatment's ability to improve patient-oriented outcomes before the potential for disruption can be determined.

Trends Considered for Inclusion in This Report

For the cancer focus area, we considered for inclusion 6 trends for which (1) information was compiled and sent for stakeholder comment before September 3, 2021; *and* (2) we received at least 5 sets of comments and ratings from stakeholders between September 18, 2020, and September 17, 2021. These 6 trends are available—or will soon be available—for viewing on the PCORI Horizon Scanning Database website.

Table 2.3 lists 2 trends selected for inclusion in this report, based on stakeholder ratings and comments and available data. Trends are listed and discussed alphabetically by title.

Table 2.3. Included Trends for Focus Area: Cancer

Topic title
Proteomic profiling to diagnose cancer and guide personalized, targeted therapy[a]
Somatic genome editing to treat disease

[a] Topic appears for the first time in this edition of the *High Potential Disruption Report*.

Table 2.4 lists 4 trends considered but not selected for inclusion in this report, based on stakeholder ratings and comments and available data. Each record notes the reasons for exclusion.

Table 2.4. Trends Considered but Not Included for Focus Area: Cancer

Trend title	Exclusion reason(s) and notes based on stakeholder comments
Messenger RNA vaccines against cancers	More data are needed supporting the safety and efficacy of messenger RNA vaccines against specific cancers before the disruptive potential can be properly assessed. Because most ongoing trials are in early phases, the treatments might not be widely available for a considerable amount of time.
Optical coherence tomography for evaluating tumor margins during breast cancer surgery	OCT is already being used for breast cancer surgery. Any analysis tool adding OCT is likely to provide only incremental benefit unless shown in a randomized controlled study to improve health outcomes.
Prostate-specific membrane antigen–targeted positron emission tomography imaging agents to diagnose prostate cancer	Early and more accurate diagnosis might improve patient outcomes. However, prostate-specific membrane antigen radiopharmaceuticals rely on positron emission tomography imaging, which is not routinely used and might not be available in clinics. These issues might impact care delivery and increase costs and disparities.

Trend title	Exclusion reason(s) and notes based on stakeholder comments
Tumor-specific conjugated fluorescent imaging agents to help visualize cancers intended for surgical resection	Because this approach will aid the surgical resection of only certain tumors, it might be only an incremental improvement to other surgical imaging modalities.

Abbreviation: OCT, optical coherence tomography.

Topic Summaries

We present below 6 summaries on topics deemed to have high potential for disruption.

^{131}I-omburtamab to Treat Leptomeningeal Metastases From Relapsed Neuroblastoma

Highlights

- ^{131}I-omburtamab is a monoclonal antibody conjugated with radiation-emitting iodine-131 (^{131}I) that specifically targets neuroblastoma cells overexpressing the cell-surface protein B7-H3.
- In about 5% to 10% of cases, neuroblastoma cells migrate to the leptomeninges, the tissues encasing the brain and spinal cord. Because leptomeningeal metastases are difficult to treat, patients who develop the disease survive for only 2 to 6 months.
- Stakeholders commenting on this topic thought that preliminary data suggest that ^{131}I-omburtamab could improve patient survival but will likely be available only at large health centers that have the specialists and resources to offer this treatment.
- Stakeholders also thought that this treatment is not expected to disrupt health care delivery or the paradigm of care. If long-term data confirm the preliminary data findings, ^{131}I-omburtamab might become the standard of care. However, there are also concerns about whether the treatment might cause adverse events over time.

Patient Population

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

Intervention

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

About 5% to 10% of patients with neuroblastoma will develop leptomeningeal metastases, a complication that occurs when the initial disease migrates to the tissues encasing the brain and the spinal cord (ie, leptomeninges). Leptomeningeal metastases are difficult to treat, and the survival of affected patients ranges from 2 to 6 months.[28]

^{131}I-omburtamab (131I-8H9) is a conjugated drug, meaning that it joins a B7-H3–specific monoclonal antibody with radiation-emitting iodine-131.[29,30] B7-H3 is a cell-surface protein involved in immune regulation that is highly expressed in neuroblastoma cells.[30] ^{131}I-omburtamab purportedly binds B7-H3–expressing cells with high affinity and exposes them to radiation emitted by iodine-131.[29,30] Iodine-131 emits mainly short-range beta radiation that does not penetrate deeply into tissue, potentially sparing surrounding healthy tissue from the harmful effects of radiation.[30]

This novel approach to target and kill leptomeningeal metastases has potential to improve health outcomes in patients who have limited treatment options and a poor prognosis.[28-30]

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

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified a single ongoing trial for this topic. We present this phase 2/3 trial in Table 2.5.

Table 2.5. Ongoing Clinical Trial

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
^{131}I-omburtamab radioimmunotherapy for neuroblastoma central nervous system/ leptomeningeal metastases (Study 101) NCT03275402 See preliminary results by Lisby et al, 2020, and Y-mAbs Therapeutics, 2020, under Recently Completed and Ongoing Trials With Available Results	Pediatric patients (n = 32) who have high-risk neuroblastoma with relapse in the leptomeninges	Phase 2/3, single-group assignment, open-label study to evaluate the safety and efficacy of ^{131}I-omburtamab Patients will receive intrathecal ^{131}I-omburtamab at a dose of 50 mCi at week 1. Patients will be evaluated for eligibility for a second dose at week 5. Primary outcome: Overall survival Secondary outcomes: Progression-free survival, objective response rate, and adverse events	Primary completion May 2026 Study completion December 2026

Abbreviation: ^{131}I, iodine-131.

Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed late-phase trial with published results.[31,32] We summarize results as written in a conference abstract and a company news release.

The following abbreviations are used in this section: ^{131}I, iodine-131; MSK or MSKCC, Memorial Sloan Kettering Cancer Center; OLINDA, organ level internal dose assessment; p, *P* value; SAE, severe adverse event; SD, stable disease.

^{131}I-omburtamab Radioimmunotherapy for Neuroblastoma Central Nervous System/Leptomeningeal Metastases (Study 101). NCT03275402. Lisby et al, 2020[31] and Y-mAbs Therapeutics, 2020.[32]

- **Patient population/planned enrollment:** Pediatric patients (n = 32) with high-risk neuroblastoma with relapse in the leptomeninges
- **Study design:** Phase 2/3, single-group assignment, open-label study to evaluate the safety and efficacy of ^{131}I-omburtamab. Patients received intrathecal ^{131}I-omburtamab at a dose of 50 mCi at week 1. Patients were evaluated for eligibility for a second dose at week 5.
- **Primary outcome:** Overall survival at 3-year follow-up
- **Secondary outcomes:** Progression-free survival, objective response rate, and adverse events
- **Results presented by Lisby et al:** "The interim analysis includes 17 patients (10 at MSKCC; 7 at other sites) who received at least one cycle of ^{131}I-omburtamab before 30-Jun-2019 and have been followed for at least six months. 8 patients received 1 cycle; 9 patients received two cycles. The median follow-up time for these patients is 179 days. 15 patients remain alive at the cut-off date. The OLINDA mean absorbed doses were 3.46 mSv/MBq in the brain and 5.97 mSv/MBq in the liver. Dosimetry level estimates in the cerebrospinal fluid at 0.56 Gray/mCi were orders of magnitude higher than those in the blood at 0.008 Gray/mCi. The most common SAEs were related to myelosuppression. Overall, the administration of ^{131}I-Omburtamab was well tolerated."
- **Results presented in a Y-mAbs news release:** "Preliminary Overall Survival ("OS") data for the Company's multicenter Study 101 for the first 18 months appears supportive of the conclusion from an earlier Study 03-133 at MSK on survival improvement for these patients, with 75% of patients surviving after 18 months. Additionally, the preliminary propensity score analysis of Study 03-133 compared to external control subjects, shows a significant difference in three years overall survival ($p<0.001$). Finally, an independent radiographic evaluation of the tumor responses in Study 101, shows that for ten evaluable patients with measureable disease, a total of 40% of the patients responded to omburtamab, 20% with complete response ("CR") and 20% with partial response ("PR"), and another five patients had stable disease ("SD"). All nine patients with response or SD maintained these at six months follow up."

Manufacturers and Regulatory Status

Investigators at Y-mAbs Therapeutics, Inc (New York, New York), are studying ^{131}I-omburtamab in a phase 2/3 clinical trial to treat children who have high-risk neuroblastoma with relapse in the leptomeninges.

Based on results from this study, Y-mAbs completed a rolling submission of a biologics license application (BLA) to the FDA in August 2020.[33] In October 2020, the company announced that it received a refusal-to-file letter from the FDA regarding its BLA.[34] In June 2021, the company announced that it had concluded a type B meeting with the FDA, at which the agency issued guidance to amend the BLA. Y-mAbs planned to resubmit the BLA by the end of 2021.[35] The FDA had previously granted ^{131}I-omburtamab breakthrough therapy designation to treat leptomeningeal metastases from relapsed neuroblastoma.[36]

Cost Information

Cost information is currently unavailable for this topic.

Key Stakeholder Perspectives

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

- Currently, patients with leptomeningeal metastases have very poor outcomes and are in urgent need of effective treatments. Preliminary data suggest that ^{131}I-omburtamab might improve patient survival beyond the typical survival of 2 to 6 months. However, safety and quality-of-life data are needed to evaluate this treatment further.
- ^{131}I-omburtamab is expected to be available only at large medical centers with specialists and resources needed to treat leptomeningeal metastases. Smaller health centers are unlikely to have the required infrastructure and personnel to offer this treatment.
- Even though ^{131}I-omburtamab requires intensive surgical and medical interventions, it is not expected to disrupt the large health centers that would offer treatment. The adoption of ^{131}I-omburtamab is also not expected to disrupt the paradigm of care, because patients already undergo various intensive treatments.
- If long-term data continue to show a clinical benefit for patients, ^{131}I-omburtamab could become the standard of care and have a positive impact for patients and their families. However, there are concerns about whether patients might experience adverse events over time, which, depending on severity, might decrease quality of life.

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

Highlights

- Axicabtagene ciloleucel is an engineered chimeric antigen receptor (CAR) T-cell therapy produced by genetically modifying a patient's own T cells to program them to generate an immune response to their cancer. Given as a single intravenous infusion, the therapy was approved by the FDA in March 2021 to treat patients who have relapsed or refractory follicular lymphoma previously treated with 2 or more lines of systemic therapy.
- Patients with relapsed or refractory B-cell non-Hodgkin lymphoma that has progressed despite multiple treatments have limited treatment options. In particular, patients who experience early relapse after initial treatment have a poor prognosis with available treatments.
- Stakeholders commenting on this topic indicated that the high response rates induced by axicabtagene ciloleucel suggested that the therapy has substantial potential to improve patient health outcomes. However, stakeholders also noted that the treatment was associated with a high burden of adverse events that could negatively impact patient quality of life.
- Stakeholders suggested that adoption of axicabtagene ciloleucel would substantially increase the cost of treating indolent non-Hodgkin lymphoma because of the high cost of both the CAR T-cell therapy and the procedures associated with its preparation, administration, and posttreatment management.
- Stakeholders suggested that the high cost and requirement for administration during an inpatient stay at specialized centers could limit adoption and increase health disparities based on socioeconomic status or access to these centers.

Patient Population

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

Intervention

Indolent B-cell lymphomas account for about 40% of non-Hodgkin lymphomas and are diagnosed in about 30 000 people each year in the United States.[37] The most common forms of indolent B-cell lymphomas are follicular lymphoma and marginal zone lymphoma, which together account for about three-quarters of cases.

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

Axicabtagene ciloleucel (Yescarta) is a CAR T-cell therapy that consists of patient-derived (ie, autologous) T cells that are genetically modified to express a CAR receptor.[38] The CAR receptor in axicabtagene ciloleucel targets CD19, an antigen expressed on the surface of normal and malignant B cells. The CAR protein construct contains an antibody-like region that binds to CD19 linked to an intracellular T-cell signaling domain, which produces activating signals that induce CAR T-cell proliferation and tumor cell killing.[39]

To produce axicabtagene ciloleucel, T cells are obtained from the patient's blood and sent to the manufacturer's facility to be genetically modified with the CAR construct. The cells are grown in number in culture and returned to the patient's treatment facility.[38]

CAR T-cell therapies are available only at specialist centers equipped to handle administration and manage adverse events associated with the treatment. To prepare for administration, patients undergo a cytotoxic chemotherapy-based conditioning regimen to deplete lymphocytes, which purportedly improves expansion, function, and persistence of CAR T cells through multiple mechanisms.[40] After this regimen, patients receive a single infusion of the manufactured CAR T-cell therapy. According to the FDA-approved label, the target dose is about 2×10^6 CAR T cells/kg with a maximum dose of 2×10^8 CAR T cells.[41]

Evidence Development Summary

Ongoing Trials

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

Table 2.6. Ongoing Clinical Trial

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
A phase 2 multicenter study of axicabtagene ciloleucel in subjects with relapsed/refractory indolent non-Hodgkin lymphoma (ZUMA-5) NCT03105336 See preliminary results by Jacobson et al, 2020, under Recently Completed and Ongoing Trials With Available Results	Patients (n = 160) with FL or MZL that has progressed after at least 2 lines of treatment with combination systemic therapy	Single-arm, phase 2 trial of the safety and efficacy of axicabtagene ciloleucel to treat relapsed or refractory indolent non-Hodgkin lymphomas First, patients will undergo leukapheresis to collect white blood cells to manufacture axicabtagene ciloleucel. Next, patients will undergo 3 days of treatment with a conditioning regimen of cyclophosphamide and fludarabine. Finally, patients will receive an infusion of axicabtagene ciloleucel at an unspecified dose. Primary outcome: Objective response rate Selected secondary outcomes: Duration of response, progression-free survival, overall survival, and percentage of patients experiencing adverse events	Primary completion February 2022 Study completion February 2037

Abbreviations: FL, follicular lymphoma; MZL, marginal cell lymphoma.

Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed phase 2 trial with published results. We summarize results as written in a conference abstract.[42]

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

A Phase 2 Multicenter Study of Axicabtagene Ciloleucel in Subjects With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma (ZUMA-5). NCT03105336. Jacobson et al, 2020.[42]

- **Patient population/planned enrollment:** Patients (n = 160) with FL or MZL that had progressed after at least 2 lines of combination systemic therapy
- **Study design:** Single-arm, phase 2 trial of the safety and efficacy of axicabtagene ciloleucel to treat relapsed or refractory indolent non-Hodgkin lymphomas. First, patients underwent

leukapheresis to collect the white blood cells needed to manufacture axicabtagene ciloleucel. Next, patients underwent 3 days of treatment with a conditioning regimen containing cyclophosphamide and fludarabine. Finally, patients received an infusion of axicabtagene ciloleucel at an unspecified dose.

- **Primary outcome:** ORR
- **Secondary outcomes:** DOR, OS, PFS, and percentage of patients experiencing AEs
- **Results presented by study authors:** "As of 3/12/2020, 146 patients with iNHL (124 FL; 22 MZL) received axi-cel;84 patients with FL had ≥ 12-months follow-up. The median age was 61 years (range, 34 – 79); 57% of patients were male. Thirty-eight percent of patients had ECOG 1, 86% had stage III/IV disease, 47% had ≥ 3 FLIPI, and 49% had high tumor bulk (GELF). Patients had a median 3 prior lines of therapy (range, 1 – 10); 64% had ≥ 3 prior lines. Progression < 2 years after initial chemoimmunotherapy (POD24) occurred in 55% of patients, and 68% were refractory to last prior treatment. Axi-cel was successfully manufactured for all enrolled patients.

  "With a median follow-up of 17.5 months (range, 1.4 – 31.6), the ORR was 92% among efficacy-evaluable patients with iNHL (n = 104), with a 76% CR rate. In patients with FL (n = 84), the ORR was 94% (80% CR rate); in those with MZL (n = 20), the ORR was 85% (60% CR rate). ORR was comparable across key risk groups analyzed by FLIPI, POD24, GELF, refractory status, and prior lines of therapy. As of the data cutoff, 62% of all treated patients had ongoing responses (64% for FL). The medians for DOR, PFS, and OS were not reached; 12-month estimated rates were 72% (95% CI, 61 – 80), 74% (95% CI, 63 – 82), and 93% (95% CI, 86 – 97), respectively.

  "AEs of any grade occurred in 99% of all treated patients. Grade ≥ 3 AEs occurred in 86% of patients with iNHL (85% in FL; 95% in MZL), most commonly neutropenia (33%), decreased neutrophil count (27%), and anemia (23%). Grade ≥ 3 cytokine release syndrome (CRS; per Lee, et al, *Blood*. 2014) occurred in 7% of patients with iNHL (6% in FL; 9% in MZL). Grade ≥ 3 neurologic events (NEs; per CTCAE v4.03) occurred in 19% of patients with iNHL (15% in FL; 41% in MZL). Most CRS (118/119) and NEs (81/87) of any grade resolved by data cutoff. Grade 5 AEs occurred in 3 patients: multisystem organ failure in the context of CRS (Day 7; related to axi-cel; n = 1 FL), aortic dissection (Day 399; unrelated to axi-cel; n = 1 FL), and coccidioidomycosis infection (Day 327; unrelated to axi-cel; n = 1 MZL).

  "The median peak CAR T cell level was 38 cells/μL (range, 0 – 1415) in all treated patients with iNHL, with 36 cells/μL (range, 0 – 1415) in those with FL and 53 cells/μL (range, 2 – 453) in those with MZL. The AUC_{0-28} was 448 cells/μL × days (range, 6 – 19,900) in all treated patients with iNHL, with 422 cells/μL × days (range, 6 – 19,900) and 552 cells/μL × days (range, 13 – 6468) in those with FL and MZL, respectively. The median time to peak was 9 days (range, 8 – 371) in all patients, 8 days (range, 8 – 371) in patients with FL, and 15 days (range, 8 – 29) in patients with MZL. In efficacy-evaluable patients with FL, median peak CAR T cell levels were numerically greater in those with ongoing response at 12 months than in those who relapsed (P = .057). In all treated patients with FL, CAR T cell peak was associated with Grade ≥ 3 CRS (P = .031) and NEs (P = .005)."

Manufacturers and Regulatory Status

Kite Pharma, a Gilead Company (South San Francisco, California), is developing axicabtagene ciloleucel. On March 5, 2021, the FDA granted accelerated approval to axicabtagene ciloleucel to treat adult patients with relapsed or refractory follicular lymphoma after 2 or more lines of systemic therapy.[43] This indication was approved based on response rate, and continued approval for this indication may be contingent upon verification and description of clinical benefit in one or more confirmatory trials.

The supplemental biologics license application Kite Pharma submitted had also pursued FDA approval for treating patients who have marginal zone lymphoma[44]; however, the scope of the accelerated approval was limited to treating patients who have follicular lymphoma.

The FDA had granted both indications breakthrough therapy designation.[44] Earlier, I agency approved axicabtagene ciloleucel for a different indication, to treat relapsed or refractory diffuse large B-cell lymphoma.

The prescribing information carries a black box warning regarding the potential for cytokine release syndrome, which labeling indicates occurred in 88% of patients, and neurologic toxicities, which occurred in 81% of patients.[41] Severe instances of these toxicities may be life threatening and require supportive care or immunosuppressive treatment, or both.

To mitigate the risk associated with these toxicities, axicabtagene ciloleucel is available only to facilities enrolled in a risk evaluation and mitigation strategy (REMS).[45] The program requires that facilities enroll and comply with the REMS requirements and have onsite immediate access to a minimum of 2 doses of tocilizumab for each patient for infusion within 2 hours if needed to treat cytokine release syndrome. Certified health care facilities must ensure that providers who prescribe, dispense, or administer the therapy undergo training in managing cytokine release syndrome and neurologic toxicities. Before discharge, patients are given a wallet card listing side effects that can lead to death and are instructed to remain within 2 hours' travel time from the administering facility for at least 4 weeks after they receive their infusion.[45]

Cost Information

According to an online aggregator of US prescription drug prices, Drugs.com, the list price of axicabtagene ciloleucel was $373 000 per treatment regimen as of July 30, 2020.[46] This price excludes additional costs for hospital care while the therapy is prepared and given and side effects managed, which can bring the total cost of treatment to nearly $1 million per patient.[47,48]

Key Stakeholder Perspectives

Between September 1 and September 14, 2021, eight stakeholders, reflecting clinical, health systems, and patient perspectives, provided comments and ratings on axicabtagene ciloleucel to treat indolent non-Hodgkin lymphomas. The list below provides a summary of key stakeholder perspectives.

- Axicabtagene ciloleucel has substantial potential to improve patient health outcomes for patients with relapsed/refractory indolent non-Hodgkin lymphomas, particularly patients who are unlikely to respond to treatment alternatives. However, this potential is based on the high response rates observed in the ZUMA-5 trial and might not translate to improvements in patient survival. Long-term data are required to gauge survival benefit sufficiently.
- Axicabtagene ciloleucel treatment is associated with substantial toxicity, particularly potentially life-threatening adverse events (eg, cytokine release syndrome, neurologic toxicities). These potential toxicities may outweigh the positive effects of the therapy on the disease.
- Administration of axicabtagene is complex and may place substantial burden on health care workers and patients. Health care workers must be trained in CAR T-cell therapy administration and management of adverse events, and the therapy will likely be offered only in specialized centers. Treatment requires an inpatient stay, which may impose a logistical burden on patients and caregivers.
- Axicabtagene ciloleucel will likely increase the cost of care for patients with indolent non-Hodgkin lymphomas, based on both the high direct cost of the drug and the procedural costs associated with the therapy's administration.

- The therapy has the potential to exacerbate existing health disparities because of its high cost and because its distribution is limited to specialty centers.

Idecabtagene Vicleucel (Abecma) to Treat Relapsed or Refractory Multiple Myeloma

Highlights

- Idecabtagene vicleucel (Abecma, or ide-cel) is an engineered chimeric antigen receptor (CAR) T-cell therapy that uses the patient's own T cells to target multiple myeloma cells overexpressing the B-cell maturation antigen (BCMA). It is given as a single intravenous infusion. In March 2021, the FDA approved ide-cel for use in treating relapsed or refractory multiple myeloma (RRMM).
- Most patients with multiple myeloma develop RRMM, which no longer responds to ongoing treatment and is unlikely to respond to subsequent standard treatments.
- Stakeholders commenting on this topic thought that preliminary data suggest that ide-cel has substantial potential to improve outcomes for patients with RRMM because of the lack of effective treatment options for these patients. However, its uptake might be limited by the significant adverse events associated with the treatment and its limited availability through specialized treatment centers.
- Stakeholders thought that these CAR T-cell therapies are expected to be very expensive and costly to administer, with additional costs for monitoring patients and managing complications. These costs might limit the availability of these therapies and increase disparities among patients of low and middle economic status.

Patient Population

Ide-cel is intended to treat adult patients who have RRMM after 4 or more lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and a monoclonal antibody against cluster of differentiation 38 (CD38).

Intervention

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

In the past 15 years, several new therapeutic agents for multiple myeloma have become available and, when used sequentially, have improved patient survival. However, most patients eventually have disease that no longer responds to standard therapies.[49] Patients with heavily treated RRMM need new interventions to address this problem.

BCMA is a receptor expressed preferentially by plasma cells and is highly overexpressed in malignant plasma cells from patients with multiple myeloma. High levels of BCMA are associated with cell proliferation, cell survival, and more progressive disease.[49,50] Therefore, BCMA is a promising target for multiple myeloma therapies.

Ide-cel (idecabtagene vicleucel, or Abecma) is a CAR T-cell therapy that is engineered to target BCMA using the patient's own T cells.[51] T cells collected from a blood sample are sent to a laboratory to be genetically modified using a lentiviral vector encoding an anti-BCMA CAR. The genetically modified T cells that make up this therapy are grown in number and then reintroduced

into the patient.[51,52] The treatment purportedly targets malignant BCMA-expressing plasma cells to promote a robust immune response against these cells.[51]

A clinician prescribes ide-cel to be given at a hospital qualified to provide specialized care required for CAR T-cell administration. A nurse gives the patient a single intravenous infusion of ide-cel at a dose ranging from 300×10^6 to 460×10^6 CAR T cells. After treatment, patients should be monitored for 7 days at the treating facility for signs and symptoms of cytokine release syndrome and neurologic toxicities.[51,53]

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 6 ongoing trials for this topic. We present 4 of these trials in Table 2.7. We excluded a phase 1 trial of ide-cel in RRMM (NCT02658929) and present preliminary results from the ongoing KarMMa trial (NCT03361748) under Recently Completed and Ongoing Trials With Available Results.

Table 2.7. Ongoing Clinical Trials

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
Efficacy and Safety Study of bb2121 Versus Standard Regimens in Subjects with Relapsed and Refractory Multiple Myeloma (KarMMa-3) NCT03651128	Patients (n = 381) who have RRMM that has been treated with 2 to 4 lines of therapy, including treatment with a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody	Phase 3, randomized, controlled, parallel-assignment, open-label trial to evaluate the safety and efficacy of ide-cel in patients with RRMM Patients will be randomly assigned to receive either a single ide-cel infusion at a dose of 150×10^6 to 450×10^6 CAR T cells or investigator's choice of antimyeloma therapy Primary end point: Progression-free survival Secondary end points: Overall survival, event-free survival, overall response rate, complete response rate, duration of response, time to response, time to progression, adverse events, and quality of life	Primary completion May 2022 Study completion November 2025

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
An Efficacy and Safety Study of bb2121 in Subjects With Relapsed and Refractory Multiple Myeloma and in Subjects With High-risk Multiple Myeloma (KarMMa-2) NCT03601078	Patients (n = 181) who have RRMM that has been treated with at least 3 lines of therapy, including treatment with a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody or who have high-risk MM who have received only one line of therapy and experienced progressive disease within 18 months of the start of initial therapy	Phase 2, single-group assignment, open-label trial to evaluate the safety and efficacy of ide-cel in patients with RRMM or high-risk MM Patients will receive a single infusion of ide-cel (150×10^6 to 450×10^6 CAR T cells). Primary end points: Overall response rate and complete response rate Secondary end points: Complete response rate, overall response rate, time to response, duration of response, and progression-free survival	Primary completion August 2022 Study completion February 2027
Safety and Efficacy of bb2121 (ide-cel) Combinations in Multiple Myeloma (KarMMa-7) NCT04855136	Patients (n = 415) who have RRMM	Phase 1/2, multiarm trial of the safety and efficacy of ide-cel in combination with various FDA-approved and investigational MM drugs In Arm A, patients will receive ide-cel in combination with the investigational E3 ligase modulatory compound cereblon. In Arm B, patients will receive ide-cel in combination with the investigational gamma secretase inhibitor BMS-986405. In Arm C, patients will receive ide-cel in combination with established MM therapies, including combination therapy with: • Daratumumab, pomalidomide, and dexamethasone • Bortezomib, pomalidomide, and dexamethasone Primary end points: Dose-limiting toxicity rates and complete response rate Secondary end points: Complete response rate, overall response rate, time to response, duration of response, progression-free survival, and overall survival	Primary completion November 2024 Study completion April 2026

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
A Study to Evaluate the Safety of bb2121 in Subjects With High Risk, Newly Diagnosed Multiple Myeloma (NDMM) (KarMMa-4) NCT04196491	Patients (n = 60) who have newly diagnosed, high-risk MM as defined by IMWG criteria	Phase 1, single-group assignment, open-label trial of the safety and efficacy of ide-cel in patients with newly diagnosed MM Patients will receive a single ide-cel infusion at a dose between 150×10^6 and 800×10^6 CAR T cells, with a planned starting dose of 450×10^6 cells. After adequate bone marrow recovery or 90 days after ide-cel treatment, patients may receive lenalidomide maintenance therapy. Primary end points: Dose-limiting toxicity rates and adverse events Secondary end points: Complete response rate, overall response rate, time to response, and duration of response	Primary and study completion January 2025

Abbreviations: bb2121, idecabtagene vicleucel; CAR, chimeric antigen receptor; CD38, cluster of differentiation 38; ide-cel, idecabtagene vicleucel; IMWG, International Myeloma Working Group; MM, multiple myeloma; RRMM, relapsed and refractory multiple myeloma.

Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed phase 2 trial with published results.[54] We summarize results as written in the abstract of a peer reviewed, published article.

The following abbreviations are used in this section: bb2121, idecabtagene vicleucel; CAR, chimeric antigen receptor; CD38, cluster of differentiation 38; ide-cel, idecabtagene vicleucel; RRMM, relapsed and refractory multiple myeloma.

Efficacy and Safety Study of bb2121 in Subjects With Relapsed and Refractory Multiple Myeloma (KarMMa). NCT03361748. Munshi et al, 2021.[54]

- **Patient population/planned enrollment:** Patients (n = 140) who had RRMM that was treated with at least 3 lines of therapy, including treatment with a protease inhibitor, an immunomodulatory agent, and an anti-CD38 antibody, either sequentially or in the same line
- **Study design:** Phase 2, single-group assignment, open-label trial to evaluate the safety and efficacy of ide-cel in patients with RRMM. Patients received a single ide-cel infusion at a dose of 150×10^6 to 450×10^6 CAR T cells.
- **Primary outcome:** Overall response rate
- **Secondary outcomes:** Progression-free survival, complete response, duration of response, and adverse events
- **Results presented by study authors:** "Of 140 patients enrolled, 128 received ide-cel. At a median follow-up of 13.3 months, 94 of 128 patients (73%) had a response, and 42 of 128 (33%) had a complete response or better. Minimal residual disease (MRD)-negative status ($<10^{-5}$ nucleated cells) was confirmed in 33 patients, representing 26% of all 128 patients who were treated and 79% of the 42 patients who had a complete response or better. The median progression-free survival was 8.8 months (95% confidence interval, 5.6 to 11.6). Common toxic

effects among the 128 treated patients included neutropenia in 117 patients (91%), anemia in 89 (70%), and thrombocytopenia in 81 (63%). Cytokine release syndrome was reported in 107 patients (84%), including 7 (5%) who had events of grade 3 or higher. Neurotoxic effects developed in 23 patients (18%) and were of grade 3 in 4 patients (3%); no neurotoxic effects higher than grade 3 occurred. Cellular kinetic analysis confirmed CAR+ T cells in 29 of 49 patients (59%) at 6 months and 4 of 11 patients (36%) at 12 months after infusion."

Manufacturers and Regulatory Status

Investigators at bluebird bio, Inc (Cambridge, Massachusetts), in collaboration with Bristol Myers Squibb Co (New York, New York), are studying ide-cel. On March 26, 2021, the FDA approved ide-cel to treat adults who have RRMM that has been treated with at least 3 lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody, either sequentially or in the same line.[55] The approval was based on results from the KarMMa trial (NCT03361748). Earlier, the FDA had granted ide-cel orphan drug and breakthrough therapy designations to treat RRMM.[56,57]

The prescribing information carries a black box warning regarding the potential for cytokine release syndrome, which labeling indicates occurred in 85% of patients; neurologic toxicities, which occurred in 28% of patients; and hemophagocytic lymphohistiocytosis/macrophage activation syndrome, which occurred in 4% of patients.[53] Severe instances of these toxicities may be life threatening and require supportive care or immunosuppressive treatment, or both.

To mitigate the risk associated with these toxicities, ide-cel is available only to facilities enrolled in a risk evaluation and mitigation strategy (REMS).[53] The program requires that facilities enroll and comply with the REMS requirements and "ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after Abecma infusion, if needed for treatment of CRS [cytokine release syndrome]. Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense, or administer Abecma are trained about the management of CRS and neurologic toxicities."[53]

A second BCMA-targeting CAR T-cell therapy for RRMM (ciltacabtagene autoleucel, under study by Janssen Pharmaceuticals, Inc, (Titusville, New Jersey) has also reached late stages of development. A new drug application for ciltacabtagene autoleucel has been submitted to the FDA.[58]

Cost Information

According to an online aggregator of US prescription drug prices, Drugs.com, the list price of ide-cel was $438 000 per treatment regimen as of August 4, 2021.[59] This price excludes additional costs for hospital care while the therapy is prepared and given and potential management of side effects, which can bring the total cost of treatment to nearly $1 million per patient.[47]

Key Stakeholder Perspectives

Between September 1 and September 16, 2021, eight stakeholders, reflecting clinical, health systems, nursing, patient, patient representative, and research perspectives, provided comments and ratings on ide-cel. The list below provides a summary of key stakeholder perspectives.

- Ide-cel, as the only currently approved CAR T-cell treatment for RRMM, has substantial potential to improve health outcomes. These patients, who have undergone and exhausted previous treatments, have limited available therapeutic options.
- Reports of significant adverse events (eg, cytokine release syndrome, neurologic toxicity) after treatment of multiple myeloma with ide-cel could limit patient quality of life.

- Ide-cel will likely be available only at specialized centers with staff trained to administer the CAR T-cell therapy and manage potential adverse events. Additionally, treatment and monitoring requires an extended inpatient stay that could be burdensome to patients and caregivers. These factors might limit the accessibility of ide-cel among certain patient populations, particularly those lacking easy access to specialized centers.
- The cost of ide-cel is very high and may limit accessibility of the therapy to certain patients, particularly patients who have already incurred the costs of multiple prior treatment regimens. The high cost of the therapy may also worsen existing disparities based on socioeconomic status.

Relugolix (Orgovyx) to Treat Relapsed, Locally Advanced, or Metastatic Androgen-Sensitive Prostate Cancer

Highlights

- Relugolix is an FDA-approved drug that selectively antagonizes the gonadotropin-releasing hormone (GnRH) receptor by binding with high affinity to pituitary GnRH receptors. Relugolix purportedly reduces testosterone to levels typically achieved with surgical or drug-mediated castration, preventing prostate cancer cells from growing.
- Androgen deprivation therapy (ADT) blocks the production of testosterone, which increases the risk of hormonal flares and cardiovascular events. The only other available GnRH antagonist is an injectable treatment, which is less convenient and carries risk of injection-site reactions. Effective oral treatments are needed.
- Stakeholders commenting on this topic thought that data from the phase 3 trial showed that relugolix could improve patient outcomes while reducing side effects, but the drug will likely be accessible only to those with good health insurance coverage.
- Although stakeholders raised concern that the drug's price of more than $2400 for a 30-day supply might be cost prohibitive for many, some noted that an effective oral therapy will reduce treatment time and transportation costs.

Patient Population

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

Intervention

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

ADT deprives prostate cancer cells of growth-stimulating androgens, either by surgery or by drug therapy. It is considered the standard of care for androgen-sensitive prostate cancer.[60,61] The most commonly used ADT is a GnRH agonist (eg, leuprolide, goserelin). However, GnRH agonists, or activators, have substantial shortcomings, including the need for periodic injections (once every 3 to 6 months) and possible increased risk of adverse cardiovascular events.[60-62] Additionally, after GnRH agonist therapy is started, testosterone surges. To suppress the potential adverse events of this surge, an androgen-receptor antagonist (eg, bicalutamide, flutamide) is typically given at the same time.

GnRH antagonists represent an alternative means of ADT. However, the available GnRH antagonist, degarelix (Firmagon), has not been widely adopted, which might be because of the need for monthly injections and the high incidence of injection-site reactions.[61]

Relugolix (Orgovyx) is a selective GnRH antagonist that binds with high affinity to the pituitary GnRH receptors. This interaction causes the pituitary gland to decrease production of gonadotropin hormones, which are responsible for testosterone production in the testes.[60,63] Relugolix purportedly reduces testosterone to levels typically achieved with surgical or drug-mediated castration, preventing prostate cancer cells from growing.[60,63] Thus, the drug could improve health-related outcomes. Upon ending relugolix therapy, testosterone levels are expected to recover to prevent loss of bone density and cardiac events and to establish glycemic control.[64]

The other GnRH antagonist, degarelix, is given as a monthly under-the-skin injection. In contrast, relugolix is taken by mouth, which might reduce the number of clinic visits and avoid injection-site adverse events.[60,61] Additionally, relugolix is thought to have a lower risk of cardiac events compared with GnRH agonists.

A clinician prescribes relugolix tablets. According to the FDA-approved label, this drug is taken by mouth at a dosage of 120 mg once daily, after a single loading dose of 360 mg on day 1.[64]

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified a single ongoing trial for this patient population and clinical indication. We present this trial in Table 2.8.

Table 2.8. Ongoing Clinical Trial

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
A study to evaluate the safety and efficacy of relugolix in men with advanced prostate cancer (HERO) NCT03085095 See preliminary results by Shore et al, 2020, and Myovant Sciences, 2020, under Recently Completed and Ongoing Trials With Available Results	Men (n = 1134) with prostate cancer that has relapsed after local primary intervention with curative intent (eg, surgery, radiation therapy), locally advanced prostate cancer unlikely to be cured by local primary intervention, or newly diagnosed metastatic androgen-sensitive prostate cancer	Phase 3, randomized, parallel-assignment, open-label trial to evaluate the safety and efficacy of relugolix in men with prostate cancer Patients will be randomly assigned in a 2:1 ratio to receive either oral relugolix at a daily dose of 120 mg (after a loading dose of 360 mg on day 1) or subcutaneous leuprolide at a dosage of 22.5 mg every 3 months. Primary end point: Sustained castration rate Secondary end points: Castration resistance–free survival, quality of life, PSA response rate, and time to PSA progression	Primary completion October 2019 Study completion November 2021

Abbreviation: PSA, prostate-specific antigen.

Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed late-phase trial with published results. We summarize the results as written in an abstract of a peer reviewed, published article[63] and a company news release.[65]

The following abbreviations are used in this section: CI, confidence interval; HR, hazard ratio; P or p, *P* value; PSA, prostate-specific antigen.

A Study to Evaluate the Safety and Efficacy of Relugolix in Men With Advanced Prostate Cancer (HERO). NCT03085095. Shore et al, 2020,[63] and Myovant Sciences, 2020.[65]

- **Patient population/planned enrollment:** Men (n = 930) with prostate cancer that had relapsed after local primary intervention with curative intent (eg, surgery, radiation therapy), locally advanced prostate cancer unlikely to be cured by local primary intervention, or newly diagnosed metastatic androgen-sensitive prostate cancer
- **Study design:** Phase 3, randomized, parallel-assignment, open-label trial to evaluate the safety and efficacy of relugolix in men with prostate cancer. Patients were randomly assigned in a 2:1 ratio to receive either oral relugolix at a daily dose of 120 mg (after a loading dose of 360 mg on day 1) or subcutaneous leuprolide at a dosage of 22.5 mg every 3 months.
- **Primary outcome:** Sustained castration rate
- **Secondary outcomes:** Castration resistance–free survival, quality of life, PSA response rate, and time to PSA progression
- **Results presented by Shore et al:** "A total of 622 patients received relugolix and 308 received leuprolide. Of men who received relugolix, 96.7% (95% confidence interval [CI], 94.9 to 97.9) maintained castration through 48 weeks, as compared with 88.8% (95% CI, 84.6 to 91.8) of men receiving leuprolide. The difference of 7.9 percentage points (95% CI, 4.1 to 11.8) showed noninferiority and superiority of relugolix (P<0.001 for superiority). All other key secondary end points showed superiority of relugolix over leuprolide (P<0.001). The percentage of patients with castrate levels of testosterone on day 4 was 56.0% with relugolix and 0% with leuprolide. In the subgroup of 184 patients followed for testosterone recovery, the mean testosterone levels 90 days after treatment discontinuation were 288.4 ng per deciliter in the relugolix group and 58.6 ng per deciliter in the leuprolide group. Among all the patients, the incidence of major adverse cardiovascular events was 2.9% in the relugolix group and 6.2% in the leuprolide group (hazard ratio, 0.46; 95% CI, 0.24 to 0.88)."
- **Results for the secondary end point of castration resistance–free survival were reported in a Myovant 2020 news release:**

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

Manufacturers and Regulatory Status

Myovant Sciences, Ltd (Basel, Switzerland), manufactures relugolix. On December 18, 2020, Myovant received FDA approval for relugolix to treat adult men who have advanced prostate cancer.[66] This approval was based on results from the phase 3 HERO trial.[67]

Cost Information

An online aggregator of US-based prescription drug prices, Drugs.com, reported a retail price of $2424 for a 30-day supply of relugolix oral tablets as of October 12, 2021.[68] A 1-year supply costs nearly $30 000, when including the day 1 loading dose, which requires 2 additional pills.

Key Stakeholder Perspectives

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

- Relugolix could improve patient outcomes because it reduces the risk of hormone flares associated with ADT, injection errors or trauma at the injection site, and cardiovascular events.
- This drug will likely be partially covered under insurance plans such as Medicare part D but could have substantial copayments compared with other prostate cancer treatments, such as leuprolide acetate injection (Lupron) or degarelix.
- In the absence of effective oral drugs, relugolix could decrease health disparities for many because it is taken by mouth rather than by injection, limiting the number of office visits and, thus eliminating the associated patient transportation issues and sparing caregivers lost wages. However, the cost of $2424 for a 30-day supply is much more than the cost for other prostate cancer treatments, which could be a barrier for many.
- Relugolix will reduce the use of health care resources (eg, infrastructure, staff requirements) because patients would not need repeated clinic visits. However, monitoring is required for medication compliance, which can be done using telehealth.

Sotorasib (Lumakras) as a Second-Line Treatment for Locally Advanced or Metastatic, *KRAS* G12C Mutation–Positive Non–Small Cell Lung Cancer

Highlights

- Sotorasib is an oral small-molecule inhibitor that irreversibly binds to *KRAS* G12C, a mutant form of the Kirsten rat sarcoma (KRAS) protein associated with resistance to targeted therapies and poor health outcomes in patients with non–small cell lung cancer (NSCLC). About 13% of patients with NSCLC harbor the *KRAS* G12C gene mutation.
- Sotorasib was approved by the FDA in May 2021 to treat adults with *KRAS* G12C mutation–positive, locally advanced or metastatic NSCLC who have received previous systemic therapy.
- Sotorasib is very costly, with its price listed at $18 700 for a 30-day supply.
- Most stakeholders commenting on this topic thought that current data suggest considerable potential for sotorasib to improve patient-oriented health outcomes and quality of life. They indicated that patient care might be further disrupted if follow-up studies show safety and efficacy in earlier lines of treatment.
- Stakeholders also thought that, as an oral drug, sotorasib would be widely available to patients regardless of their geographic location. However, sotorasib's high cost might limit its availability for patients who are uninsured or underinsured.

Patient Population

Sotorasib is intended for adults who have locally advanced or metastatic NSCLC harboring the *KRAS* G12C gene mutation and who have received at least one prior systemic therapy.

Intervention

NSCLC is the most common type of lung cancer, accounting for about 80% to 85% of all lung cancers. Its treatment has been transformed over the past 10 years by an increased understanding of the molecular events underlying the disease. In particular, the FDA has approved multiple agents targeting specific molecular drivers in NSCLC (eg, *EGFR* mutations, *ALK* translocations) to treat NSCLC that harbors certain mutations. The American Cancer Society website offers more information on NSCLC.

Mutations in the *KRAS* gene have been reported to occur in about one-third of NSCLC cases.[69] These gene mutations promote cell division, growth, invasiveness, and survival and thus represent a rational candidate for targeted therapy.[70] The *KRAS* G12C mutation is caused by a glycine-to-cytosine substitution at position 12 that results in an active form of the KRAS protein.[69,70] About 13% of patients with NSCLC harbor *KRAS* G12C, which is associated with resistance to targeted therapies and poor outcomes.[70]

Even though gain-of-function mutations in *KRAS* are very common in cancer, development of an effective KRAS inhibitor has been unsuccessful.[69] Therefore, new treatments with the potential to target *KRAS*-mutated malignancies are highly sought.

Sotorasib (Lumakras) is a novel, small-molecule drug that irreversibly binds to the KRAS G12C protein and keeps it in an inactive form.[70-72] Sotorasib-mediated inhibition of KRAS G12C is thought to promote tumor shrinkage and have low potential to cause serious drug-related adverse events because of the drug's high degree of specificity for KRAS.[70]

A clinician prescribes sotorasib. According to the FDA-approved label, this drug is intended to be taken by mouth at a once-daily dose of 960 mg until disease progression or intolerable toxicity.[71]

Evidence Development Summary

Ongoing Trials

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

Table 2.9. Ongoing Clinical Trials

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
Study to Compare AMG510 "Proposed INN Sotorasib" with Docetaxel in Non–small Cell Lung Cancer (NSCLC) (CodeBreaK 200) NCT04303780	Patients (n = 345) who have locally advanced or metastatic, *KRAS* G12C mutation–positive NSCLC who have undergone treatment with at least one systemic therapy	Phase 3, randomized, parallel-assignment, open-label trial to evaluate the safety and efficacy of sotorasib in patients who have NSCLC with the *KRAS* G12C mutation Patients will be randomly assigned to treatment with either oral sotorasib or intravenous docetaxel. Primary end point: Progression-free survival Secondary end points: Overall survival, objective response rate, quality of life, duration of response, and disease control rate	Primary completion November 2021 Study completion April 2026
A Phase 1/2 Study Evaluating the Safety and Tolerability, PK, and Efficacy of AMG510 in Subjects With a Specific *KRAS* Mutation (CodeBreaK 100) NCT03600883 See preliminary results by Skoulidis et al, 2021, and Ramalingam et al, 2021, under Recently Completed and Ongoing Trials With Available Results	Patients (n = 733) who have locally advanced or metastatic, *KRAS* G12C mutation–positive solid tumor cancers, including NSCLC	Phase 1/2, sequential-group assignment, open-label trial to evaluate the safety and efficacy of sotorasib in patients who have solid tumor cancers with the *KRAS* G12C mutation Patients will receive oral sotorasib at increasing once-daily doses beginning with 180 mg. Primary end point: Objective response rate Secondary end points: Progression-free survival, duration of response, and duration of stable disease	Primary and study completion January 2026

Abbreviations: AMG510, sotorasib; INN, international proprietary name; *KRAS* G12C, Kirsten rat sarcoma gene with a glycine-to-cytosine substitution at position 12; NSCLC, non–small cell lung cancer; PK, pharmacokinetics.

Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed late-phase trial with published results. We summarize results as written in a peer reviewed, published article[71] and a conference abstract.[73]

The following abbreviations are used in this section: AMG510, sotorasib; BM, brain metastases; CI, confidence interval; CNS, central nervous system; CR, complete response; *KEAP1*, Kelch-like ECH-associated protein 1 gene; *KRAS* G12C, Kirsten rat sarcoma gene with a glycine-to-cytosine substitution at position 12; NSCLC, non–small cell lung cancer; PD, progressive disease; PD-L1, programmed cell death ligand 1; PK, pharmacokinetics; RANO-BM, Response Assessment in Neuro–Oncology Brain Metastases; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SD, stable disease; *STK11*, serine/threonine kinase 11 gene; *TP53*, tumor protein 53 gene.

A Phase 1/2 Study Evaluating the Safety and Tolerability, PK, and Efficacy of AMG510 in Subjects With a Specific *KRAS* Mutation (CodeBreaK 100). NCT03600883. Skoulidis et al, 2021,[71] and Ramalingam et al, 2021.[73]

- **Patient population/planned enrollment:** Patients (n = 733) who had locally advanced or metastatic, *KRAS* G12C mutation–positive, solid tumor cancers, including NSCLC
- **Study design:** Phase 1/2, sequential-group assignment, open-label study to evaluate the safety and efficacy of sotorasib in patients who have solid tumor cancers with the *KRAS* G12C mutation. Patients received oral sotorasib at a once-daily dose of 960 mg.
- **Primary outcome:** Objective response rate
- **Secondary outcomes:** Overall survival, progression-free survival, duration of response, and adverse events
- **Results presented by Skoulidis et al:** "Among the 126 enrolled patients, the majority (81.0%) had previously received both platinum-based chemotherapy and inhibitors of programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1). According to central review, 124 patients had measurable disease at baseline and were evaluated for response. An objective response was observed in 46 patients (37.1%; 95% confidence interval [CI], 28.6 to 46.2), including in 4 (3.2%) who had a complete response and in 42 (33.9%) who had a partial response. The median duration of response was 11.1 months (95% CI, 6.9 to could not be evaluated). Disease control occurred in 100 patients (80.6%; 95% CI, 72.6 to 87.2). The median progression-free survival was 6.8 months (95% CI, 5.1 to 8.2), and the median overall survival was 12.5 months (95% CI, 10.0 to could not be evaluated). Treatment-related adverse events occurred in 88 of 126 patients (69.8%), including grade 3 events in 25 patients (19.8%) and a grade 4 event in 1 (0.8%). Responses were observed in subgroups defined according to PD-L1 expression, tumor mutational burden, and co-occurring mutations in *STK11*, *KEAP1*, or *TP53*."
- **Results presented by Ramalingam et al:** "174 patients were included: 40 had stable BM (23.0%) while 134 (77.0%) had no BM at baseline. In the BM group, 65% had received prior radiotherapy, and 20% had received prior brain surgery. Systemic efficacy of sotorasib per RECIST 1.1 is shown in the Table [select poster P52]. Per central RANO-BM review, 16 patients had baseline and ≥1 on-treatment evaluable scans: 3 had target and 13 had non-target CNS lesions. 9 patients had 1 lesion, 2 had 4 lesions, and 5 had ≥5 lesions. Of 13 patients with non-target CNS lesions, 2 had CR, 11 had SD. Of 3 patients with target lesions, 1 had SD, and 2 had PD. Overall, intracranial disease control was achieved in 14 of 16 patients (87.5%) with evaluable BM. Safety in the BM group was consistent with previous reports."

Manufacturers and Regulatory Status

Amgen, Inc (Thousand Oaks, California), manufactures sotorasib. On May 28, 2021, the FDA granted accelerated approval to sotorasib to treat adults with locally advanced or metastatic NSCLC whose tumors harbor a *KRAS* G12C mutation as determined by an FDA-approved test and who have received at least one prior systemic therapy.[74] At the same time, the FDA approved the therascreen KRAS RGQ PCR Kit (Qiagen NV, Hilden, Germany)[75] to determine *KRAS* G12C mutation status from a tumor biopsy and the Guardant360 CDx test (Guardant Health, Inc, Redwood City, California)[76] to identify the *KRAS* G12C mutation in a blood sample.

Approval for this indication was based on the objective response rate reported in the phase 1/2 Codebreak 100 trial, and continued approval for this indication may be contingent upon verification and description of clinical benefit in one or more trials, such as the phase 3 Codebreak 200 trial.

The FDA had previously granted sotorasib breakthrough therapy and priority review designations for this indication.[77,78]

Cost Information

An online aggregator of US-based prescription drug prices, Drugs.com, reported a retail price of about $18 700 for a 30-day supply of sotorasib oral tablets as of October 6, 2021.[79] On average, patients in the Codebreak 100 trial received 11 months of treatment.[71] Therefore, treatment, as provided in the trial, would cost about $205 700 per patient.

Key Stakeholder Perspectives

Between March 24 and April 15, 2021, nine stakeholders, reflecting clinical, health systems, patient, and research perspectives, provided comments and ratings on sotorasib. The list below provides a summary of key stakeholder perspectives.

- Data from the Codebreak 100 trial showed that sotorasib improved health outcomes, with manageable adverse events, for adults with *KRAS* G12C mutation–positive NSCLC, a patient population that responds poorly to available therapeutic approaches.
- As an oral drug, sotorasib would be easy to use and could shift care from infusion centers to a home setting, although only for a relatively select patient population. If patients require fewer trips to medical centers for treatment and evaluation, sotorasib might become available to many patients regardless of their geographic location.
- As a novel targeted therapy, sotorasib is expected to be substantially more expensive compared with the standard of care. Although some insured patients might be able to bear some out-of-pocket costs, patients who are uninsured or underinsured will have difficulty affording this drug. Stakeholders noted that the high price of other oncology drugs and the limited patient population and treatment duration for sotorasib might produce a modest to moderate cost impact on the broader system.
- Before sotorasib was developed, the KRAS G12C protein was not considered a target that could be bound tightly by a drug. Each year, between 10 000 and 20 000 patients with NSCLC and *KRAS* G12C mutations might be eligible for treatment with sotorasib. Patient care might be further disrupted if follow-up studies show safety and efficacy of sotorasib in earlier lines of treatment.

Tabelecleucel to Treat Epstein-Barr Virus–Associated Posttransplant Lymphoproliferative Disorder

Highlights

- Tabelecleucel is an off-the-shelf donor-derived cell therapy currently under study for treating patients with rituximab-refractory Epstein-Barr virus (EBV)–associated posttransplant lymphoproliferative disorder (PTLD). This patient population has limited treatment options.
- Tabelecleucel has demonstrated activity against EBV-PTLD in several nonrandomized trials, and its developer intends to submit a biologics license application for tabelecleucel to the FDA in the first quarter of 2022.
- Stakeholders commenting on this topic thought that tabelecleucel has substantial potential to improve health outcomes in a patient population with limited effective treatment options.
- Stakeholders thought that tabelecleucel would have limited effects on patient management, disparities, and costs.

Patient Population

Tabelecleucel is intended to treat children and adults who develop an EBV-associated PTLD after undergoing hematopoietic stem cell transplantation (HSCT) or solid organ transplantation, and who have undergone treatment with rituximab or rituximab-based chemoimmunotherapy.

Intervention

Tabelecleucel is a cell therapy consisting of EBV-specific T cells that are intended to generate an immune response against EBV-associated PTLD.[80,81] Occurring in about 2% to 20% of patients after HSCT or solid organ transplantation, PTLDs are characterized by a substantial increase in the number of lymphoid or plasma cells. Many PTLDs are driven by EBV, which may become active in individuals who have compromised immune systems after these transplant procedures.

Tabelecleucel is prepared from a cell bank of cryopreserved, donor-derived, cytotoxic T lymphocyte (CTL) cell lines.[80,81] This cell bank consists of several hundred individual CTL cell lines that were generated from cells obtained from EBV-seropositive donors. To produce the CTL cell lines, donor cells are cultured in the laboratory in the presence of EBV antigen, which purportedly selects for EBV-specific T cells and eliminates alloreactive T cells that could attack the patient's tissues. Tabelecleucel is available as an off-the-shelf therapy that purportedly requires only partial human leukocyte antigen matching and can be delivered from inventory within 3 days.[82]

In clinical trials, tabelecleucel is given in 5-week cycles. Each cycle consists of intravenous tabelecleucel (2×10^6 cells/kg) on days 1, 8, and 15. Treatment cycles continue until maximal response, unacceptable toxicity, initiation of therapy outside of trial protocol, or treatment failure. In the latter case, a patient's disease may fail to respond to the initially selected CTL line if, for example, the patient is infected with an EBV variant not recognized by the initial EBV-specific CTL line. EBV-PTLD that does not respond to the initially selected cell line may be switched to treatment with other cell lines that might have activity against the patient's EBV variant.[80,83]

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 2 ongoing trials for this topic. We present these trials in Table 2.10.

Table 2.10. Ongoing Clinical Trials

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
Tabelecleucel for Solid Organ or Allogeneic Hematopoietic Cell Transplant Participants with Epstein-Barr Virus-Associated Post-Transplant Lymphoproliferative Disease (EBV+ PTLD) After Failure of Rituximab or Rituximab and Chemotherapy (ALLELE) NCT03394365 See preliminary results by Atara Biotherapeutics, 2021, under Recently Completed and Ongoing Trials With Available Results	Patients (n = 66) who have been diagnosed with an EBV-PTLD after HCT or SOT and have been treated with rituximab or rituximab plus chemotherapy Patients must not have central nervous system PTLD that is untreated or being actively treated.	Phase 3, nonrandomized trial of the safety and efficacy of tabelecleucel to treat EBV-PTLD All patients will receive treatment with tabelecleucel administered in 5-week cycles. Each cycle will consist of intravenous administration of tabelecleucel (2×10^6 cells/kg) on days 1, 8, and 15, followed by no treatment through day 35. Treatment will continue until maximal response, unacceptable toxicity, initiation of therapy outside of trial protocol, or failure to respond to tabelecleucel. Patients with stable or progressive disease after initial treatment may receive treatment with different tabelecleucel cell lines (up to 4 cell lines in the HCT cohort and up to 2 cell lines in the SOT cohort). Primary end point: Objective response rate	Primary completion June 2022 Study completion June 2027
A Study to Evaluate Tabelecleucel in Participants With Epstein-Barr Virus-Associated Diseases NCT04554914	Patients (n = 228) with various EBV-associated diseases whose disease is newly diagnosed, has relapsed, or did not respond to prior treatment, including cohorts of patients with EBV-PTLD, for whom standard first-line therapy (rituximab or chemotherapy) is inappropriate, and with EBV-PTLD involving the central nervous system	Phase 2, nonrandomized trial of the safety and efficacy of tabelecleucel All patients will receive treatment with tabelecleucel administered in 5-week cycles. Each cycle will consist of intravenous administration of tabelecleucel (2×10^6 cells/kg) on days 1, 8, and 15, followed by no treatment through day 35. Treatment will continue until maximal response, unacceptable toxicity, initiation of therapy outside of trial protocol, or failure to respond to tabelecleucel. Patients with stable or progressive disease after initial treatment may receive treatment with up to 4 different tabelecleucel cell lines. Primary end point: Objective response rate	Primary completion June 2027 Study completion May 2029

Abbreviations: EBV-PTLD, Epstein-Barr virus–associated posttransplant lymphoproliferative disorder; HCT, hematopoietic cell transplantation; SOT, solid organ transplantation.

Recently Completed and Ongoing Trials With Available Results

Our searches identified 3 reports covering 4 recently completed late-phase trials.[80,82,83] We summarize the 3 most recent publications with results as written in a corporate slide presentation; the abstract of a peer reviewed, published article; and a conference abstract.

The following abbreviations are used in this section: CNS, central nervous system; CR, complete remission; EAP, expanded access program; EBV, Epstein-Barr virus; EBV-CTLs, Epstein-Barr virus–specific cytotoxic T lymphocytes; EBV-PTLD, Epstein-Barr virus–associated posttransplant lymphoproliferative disorder; ECOG, Eastern Cooperative Oncology Group performance status; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplant; IORA, independent oncologic and radiographic assessment; ORR, objective response rate; OS, overall survival; POD, progression of disease; PR, partial remission; PTLD, posttransplant lymphoproliferative disorder; Q3, third quarter (July-September); SOT, solid organ transplant; tab-cel, tabelecleucel; yr, year.

Tabelecleucel for Solid Organ or Allogeneic Hematopoietic Cell Transplant Participants With Epstein-Barr Virus-Associated Post-transplant Lymphoproliferative Disease (EBV+PTLD) After Failure of Rituximab or Rituximab and Chemotherapy (ALLELE). NCT03394365. Atara Biotherapeutics, 2021.[82]

- **Patient population/planned enrollment:** Patients (n = 66) with a diagnosed EBV-PTLD after HCT or SOT and who had been treated with rituximab or rituximab plus chemotherapy. Patients must not have had central nervous system PTLD that was untreated or being actively treated.
- **Study design:** Phase 3, nonrandomized trial of the safety and efficacy of tabelecleucel for treating EBV-PTLD. All patients received treatment with tabelecleucel given in 5-week cycles. Each cycle consisted of intravenous administration of tabelecleucel (2×10^6 cells/kg) on days 1, 8, and 15, followed by no treatment through day 35. Treatment was to continue until maximal response, unacceptable toxicity, initiation of therapy outside of trial protocol, or failure to respond to tabelecleucel. Patients could receive treatment with multiple different tabelecleucel cell lines (up to 4 cell lines in the HCT cohort and up to 2 cell lines in the SOT cohort).
- **Primary outcome:** Objective response rate
- **Selected secondary outcomes:** Duration of response and overall survival
- **Results presented by study authors:** "Interim Analysis by IORA for Phase 3 Pivotal Study. Conducted in Q3 2020. Included analysis of all patients with 6-month follow up for durability of response. 50% ORR by IORA across HCT and SOT cohorts. Safety: No new safety signals versus prior tab-cel studies."

Therapeutic Effects of Epstein-Barr Virus Immune T-lymphocytes Derived From a Normal HLA-Compatible or Partially-Matched Third-Party Donor in the Treatment of EBV Lymphoproliferative Disorders and EBV-Associated Malignancies. NCT01498484. Biological Therapy in Treating Patients at High-Risk or With Lymphoma, Lymphoproliferative Disease, or Malignancies. NCT00002663. Prockop et al, 2020.[80]

- **Patient population/planned enrollment:** Patients (n = 46) who had undergone HSCT (n = 33) or SOT (n = 13) and developed an EBV-PTLD that failed to respond to rituximab therapy. These trials also enrolled additional patients with other EBV-associated diseases.
- **Study design:** Phase 1/2 (NCT00002663) and phase 2 (NCT01498484) single-arm trials of donor-derived allogeneic EBV-CTLs to treat EBV-PTLD. All patients received treatment with EBV-CTLs in cycles consisting of 3 weekly infusions followed by 3 weeks of no treatment. Patients whose

disease failed to respond to the first EBV-CTL treatment cycle could receive treatment with EBV-CTLs derived from a different donor.

- **Primary outcome:** Response rate
- **Results presented by study authors:** "EBV-CTLs did not induce significant toxicities. One patient developed grade I skin graft-versus-host disease. Complete remission (CR) or sustained partial remission (PR) was achieved in 68% of HCT recipients and 54% of SOT recipients. For patients who achieved CR/PR or stable disease after cycle 1, one year overall survival was 88.9% and 81.8%, respectively. In addition, 3 of 5 recipients with POD after a first cycle who received EBV-CTLs from a different donor achieved CR or durable PR (60%) and survived longer than 1 year. Maximal responses were achieved after a median of 2 cycles."

Expanded Access Protocol for Tabelecleucel for Patients With Epstein-Barr Virus-Associated Viremia or Malignancies. NCT02822495. Prockop et al, 2019.[83]

- **Patient population/planned enrollment:** Patients with EBV-associated diseases and malignancies (including EBV-PTLD) for whom no appropriate therapeutic options existed and who were ineligible to enroll in clinical studies of tabelecleucel. The analysis presented here includes 26 patients with EBV-PTLD who had undergone HSCT (n = 14) or SOT (n = 12).
- **Study design:** Expanded access program to allow patients with EBV-associated diseases, including EBV-PTLD, and no appropriate therapeutic option access to tabelecleucel. All patients received tabelecleucel (1.6×10^6 to 2×10^6 cells/kg) on days 1, 8, and 15 of each 4-week treatment cycle. Patients could receive up to 4 distinct tabelecleucel cell lines with different HLA restrictions.
- **Results presented by study authors:** "All subjects had received prior rituximab and 7/12 SOT subjects received prior chemotherapy. Intermediate/high risk PTLD-prognostic index (PTLD-IPI; Choquet et al, *Ann Hematol* 2007) was noted in 79% and 42% of HCT and SOT subjects, respectively. The results are presented in table 1.

  "While the median follow-up time in HCT subjects is short, 3 subjects were followed for over 12 months including 2 who were followed for more than 24 months.

  "In subjects responding to tabelecleucel, 1-year OS was 85.7% in HCT and 100% in SOT, and no deaths were attributable to PTLD progression. In a subset of study subjects (HCT: n=11; SOT: n=11) with adequate ECOG, no CNS disease, and no PTLD-related ventilatory support, who would have likely been eligible for Atara's ongoing phase-3 trials, the ORR was 55% (HCT) and 82% (SOT), with a 2-yr OS of 79% (HCT) and 81% (SOT). The safety profile of tabelecleucel was consistent with previously published data. At the data snapshot for this abstract, no tabelecleucel-related adverse events led to treatment discontinuation or death. In addition, no cytokine release syndrome, organ rejection or tumor flare adverse events were reported in the PTLD subjects treated with tabelecleucel on this EAP."

Manufacturers and Regulatory Status

Tabelecleucel is being developed by Atara Biotherapeutics, Inc (South San Francisco, California), and is currently in phase 3 development. Atara Bio has indicated that it plans to complete a biologics license application filing for use of tabelecleucel in treating EBV-PTLD to the FDA in the first quarter of 2022.[82] The company states that the application will be based on data from the phase 3 ALLELE trial and supportive data from earlier phase 2 trials and an expanded access program. The FDA had earlier granted tabelecleucel orphan drug status and breakthrough therapy designation for the EBV-PTLD indication.[81,84]

Cost Information

Cost information is currently unavailable for this topic.

Key Stakeholder Perspectives

Between June 11 and July 13, 2021, seven stakeholders, reflecting clinician, health systems, nursing, and research perspectives, provided comments and ratings on tabelecleucel for treating EBV-PTLD. The list below provides a summary of key stakeholder perspectives.

- Tabelecleucel has a moderate to large potential to improve health outcomes for patients with EBV-PTLD whose disease no longer responds to rituximab-based regimens, based on the response rates observed in clinical trials. However, the magnitude of effect of the treatment is difficult to assess because of a lack of a control arm in these trials.
- Tabelecleucel could have disparate effects on health disparities. The highly specialized nature of the treatment could lead to its availability being limited to select centers, which could increase disparities based on access to such centers. Conversely, the off-the-shelf nature of tabelecleucel could make it more accessible than alternatives such as bespoke CTL lines generated by treating facilities.
- Patients with EBV-PTLD are likely already being managed at specialty centers for their posttransplant care; therefore, adoption of tabelecleucel is unlikely to cause a substantial shift in care setting. Additionally, although tabelecleucel represents a novel therapy that could provide a treatment option for patients whose disease no longer responds to rituximab therapy, tabelecleucel is given through standard intravenous administration, which is unlikely to require substantial training or require substantial alterations to patient management.
- Tabelecleucel is likely to be an expensive treatment. However, this cost is likely to represent only an incremental increase, relative to treatments currently employed to treat patients who have EBV-PTLD. Additionally, the small number of patients affected by the condition could limit the overall cost impact of tabelecleucel adoption.

Trend Summaries

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

Proteomic Profiling to Diagnose Cancer and Guide Personalized, Targeted Therapy

Highlights

- Proteomic profiling uses test results from tissue or blood samples to identify proteins that are associated with cancer.
- VeriStrat and Stroma Liquid Biopsy are examples of proteomic profiling tests. They are intended to identify protein biomarkers that can help confirm a diagnosis of cancer and help guide selection of targeted therapies or match patients to clinical trials.
- Stakeholders commenting on this trend thought that proteomic profiling is beginning to diffuse as some proteomic tests are commercially available and other manufacturers have begun to develop new assays. If used properly to detect early-stage cancer and guide targeted therapy selection for patients, proteomic profiling could improve health outcomes.

However, some patients might not benefit from proteomic profiling because their disease develops resistant mutations against the selected targeted therapies.

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

Description

Proteomic profiling involves the systematic separation, identification, and characterization of proteins present in a patient's tumor or blood sample.[85,86] In patients with suspected cancer, clinicians use proteomic profiling to identify a cancer-associated protein that might confirm the presence and origin of a specific cancer type.[86] In addition, proteomic profiling could help identify overexpressed proteins that are known to be therapeutic targets, such as those caused by chromosomal rearrangements. Clinicians could then use this information to select an on-label or off-label targeted therapy that is most likely to benefit a patient who has cancer or help enroll patients in clinical trials of investigational therapies.[85,87]

Proteomic tests, such as VeriStrat (Biodesix, Inc, Boulder, Colorado)[88] and Stroma Liquid Biopsy (Biotech Support Group, LLC, Monmouth Junction, New Jersey),[89] analyze specific protein biomarkers in patients with suspected cancer to determine the tissue origin of a solid tumor and help develop personalized treatment plans.

Clinical Area(s) Potentially Disrupted

Proteomic profiling could disrupt the oncology clinical area by simultaneously confirming a diagnosis of cancer and recommending targeted therapies that are likely to benefit patients.[87] In patients suspected of having cancer (eg, based on clinical features or family history), proteomic profiling might disrupt radiology departments by detecting cancers that have not progressed to a stage that medical imaging can detect.[86]

Opportunities

Proteomic profiling could improve health outcomes by detecting cancer early in patients suspected of having the disease and matching patients with targeted therapies or clinical trials likely to benefit them. If used in routine screening, proteomic profiling might also detect early-stage cancers before they can be identified using medical imaging.[86,87] In tumors that are composed of more than one cell type, proteomic analysis might identify several biomarkers that are involved in cancer growth.[90]

Threats

As a novel testing approach, proteomics might add to clinician burden by requiring physicians to learn about protein signatures for different cancer types and understand which could be drug targets.[87,90] Implementing proteomics into the workflow could increase disparities by being available only to patients who are insured or able to pay for treatment out of pocket.[90]

Key Stakeholder Perspectives

Between September 13 and September 20, 2021, five stakeholders, reflecting health care generalist, health systems, nursing, and research perspectives, provided comments and ratings on this trend. The list below provides a summary of key stakeholder perspectives.

- Proteomic profiling to identify cancer at its early stages and direct clinicians to targeted therapies for patients is beginning to diffuse as some proteomic tests are commercially

available and other manufacturers have begun to develop new assays. Protein expression–based targeted therapies could improve health outcomes and quality of life, but in some cases, the improvements in survival outcomes will be incremental. Optimizing and the therapies' efficacy might be no more effective than systemic chemotherapy.
- Adopting proteomic profiling into clinical use could disrupt health care delivery. Many eligible patients might not have access to health centers that offer proteomic testing. If evidence demonstrates that proteomic profiling will be an important tool for the diagnosis and treatment of cancer, it might be moderately disruptive.
- Proteomic profiling is likely to be very expensive; it is unclear whether insurance companies will cover it. The cost of proteomic profiling is likely to be added to other routine testing (eg, imaging, companion diagnostics). Additionally, health care costs might increase when proteomic profiling is used to prescribe off-label targeted therapies for unapproved indications, used for all circumstances, or not used properly to guide patient management.
- Even with its high cost, if proteomic profiling can inform decisions on targeted therapies that are safe and effective for treating early-stage cancer, it might reduce overall health care costs, especially those associated with treating late-stage disease.

Somatic Genome Editing to Treat Disease

Highlights

- Somatic genome editing is intended to target and repair a mutated gene in non–germ line tissues to restore the gene's regular function and help treat diseases.
- This technology is being evaluated in several clinical trials for genetic disorders in which the patient's DNA is permanently modified to provide a durable treatment effect.
- Stakeholders commenting on this trend generally agreed that this technology would be life-changing for those who lack effective treatments for their genetic conditions; however, its uptake would largely depend on insurance coverage and access.
- Stakeholders were concerned about the risks of unintended long-term consequences to the health of treated patients and subsequent generations.

Description

The Genetic Disease Foundation lists more than 6000 genetic disorders that either are fatal or cause serious illness in humans.[91] Gene-editing technology holds great promise for treating and/or preventing several such diseases and conditions due to the technology's potential to selectively modify, delete, or replace genes for treating genetic diseases in human patients.[92] This technology could create therapies with durable or permanent effects, obviating the need for ongoing treatment (eg, with medications).[93]

Clinical applications of genome editing are being explored to modify somatic (ie, non–germ line) cells using ex vivo or in vivo delivery.[92] In ex vivo applications, cells (eg, lymphocytes, stem cells) taken from the patient or a donor are modified through gene editing and then introduced into the patient (eg, via infusion or grafting). For instance, clinical studies have shown promise for using gene editing to treat HIV-1 infection by blocking the production of the receptor by which the AIDS virus gains access to CD4 lymphocytes. Other trials are exploring this technology to correct the abnormal hemoglobin gene that causes sickle cell anemia.[94]

In contrast, in vivo applications use viral vectors or nanoparticles to directly inject gene editors into the patient, either systemically or into specific locations of interest. For instance, a trial is exploring in vivo gene editing to treat transthyretin amyloidosis, a life-threatening disease caused

by accumulation of misfolded transthyretin (TTR) protein in tissues.[95] According to study results published in June 2021, in vivo treatment with NTLA-2001 was associated with reduction of serum TTR protein concentrations, with only mild adverse events.[96] Another trial is studying in vivo delivery to treat Leber congenital amaurosis 10, a disorder resulting in severe visual impairment early in life and that is often attributable to single-gene mutations.[97]

Clinical Area(s) Potentially Disrupted

Gene-editing technology might disrupt patient health outcomes and influence the delivery of treatment. Gene editing might also improve understanding of various rare genetic disorders. This technology could be costly for patients, and some might not have the resources to pursue these treatments. Although it is unclear whether this technology would be a one-time treatment or require several procedures, the potential for gene-editing approaches to produce long-term disease control might reduce caregiver burden and costs associated with lost wages because of disease burden or repeat clinic visits.

Opportunities

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

Threats

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

Key Stakeholder Perspectives

Between September 22 and October 14, 2021, eleven stakeholders, reflecting clinical, health systems, nursing, and research perspectives, provided comments and ratings on this trend. The list below provides a summary of key stakeholder perspectives.

- If proved safe and effective, somatic gene-editing technology could cure diseases caused by genetic mutations. This could greatly improve patient outcomes, particularly for those who have conditions for which limited effective treatments are available.
- The clinician learning curve and special training associated with gene editing and patient monitoring is likely to disrupt care delivery, staffing, and costs.
- Clinical care with this technology is likely to be very expensive for patients, as well as for health systems, particularly if applied to diseases with higher prevalence. These therapies might be inaccessible to patients who are uninsured and those with limited insurance coverage. However, treating and preventing genetic diseases could reduce long-term costs associated with disease management, such as hospitalizations, repeated treatments, and other care.
- This technology might increase disparities if patients are unable to access gene-editing therapies because of geographic or socioeconomic barriers. However, it might reduce health disparities if cures can be realized for diseases that predominantly affect minority groups.
- Patient and clinician acceptance of this technology might impact the uptake of gene-editing technology because some early gene therapy studies have had adverse outcomes, and there are significant ethical concerns surrounding the technology. The long-term effects of using

this technology are unknown, so long-term monitoring of patients and their offspring will likely be required.

Chapter 3. Cardiovascular Diseases

For the cardiovascular diseases focus area, we considered for inclusion a single topic for which (1) preliminary phase 3 data for drugs, phase 2 (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled and sent for stakeholder comment before September 3, 2021; *and* (3) we received at least 5 sets of comments and ratings from stakeholders between September 18, 2020, and September 17, 2021.

As of September 3, 2021, we were monitoring 17 topics in this focus area, including the topic considered for inclusion in this report. These 17 topics are available—or will soon be available—for viewing on the PCORI Horizon Scanning Database website.

The 17 monitored topics encompass pharmaceuticals, gene and cellular therapies, devices, and implants intended to treat 10 cardiovascular diseases and/or related symptoms. Of these, 16 are too early in development to meet the criteria (as outlined above) for eligibility for this report.

Topic Considered for Inclusion in This Report

Table 3.1 lists the topic considered but not selected for inclusion in this report, based on stakeholder ratings and comments and available data. The record notes the reasons for exclusion.

Table 3.1. Topic Considered but Not Included for Focus Area: Cardiovascular Diseases

Topic title	Exclusion reason(s) and notes based on stakeholder comments
Organ Care System to treat end-stage heart failure requiring transplantation	This topic was included in an earlier edition of the *High Potential Disruption Report*. Stakeholders reviewed an updated version of the topic. The technology is likely to cause only small to moderate disruption to the overall heart transplantation process, including patient selection, transplantation surgery, and follow-up care. Further, the high additional cost might limit widespread adoption without more data demonstrating a significant improvement over the standard of care for donor organ procurement.

Trends Considered for Inclusion in This Report

For the cardiovascular diseases focus area, we considered for inclusion 2 trends for which (1) information was compiled and sent for stakeholder comment before September 3, 2021; *and* (2) we received at least 5 sets of comments and ratings from stakeholders between September 18, 2020, and September 17, 2021. These 2 trends are available—or will soon be available—for viewing on the PCORI Horizon Scanning Database website.

Table 3.2 lists one trend selected for inclusion in this report based on stakeholder ratings and comments and available data.

Table 3.2. Included Trend for Focus Area: Cardiovascular Diseases

Trend title
Artificial intelligence to predict cardiovascular events and health outcomes[a]

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

Table 3.3 lists one trend considered but not selected for inclusion in this report, based on stakeholder ratings and comments and available data. The record notes the reasons for exclusion.

Table 3.3. Trend Considered but Not Included for Focus Area: Cardiovascular Diseases

Trend title	Exclusion reason(s) and notes based on stakeholder comments
Wearable drug delivery systems to better manage chronic conditions	Stakeholders commenting on this trend thought that the shift toward wearable drug delivery systems is already somewhat established for diseases that require multiple daily injections, such as diabetes. Stakeholders did not anticipate further rapid or widespread growth of this trend for conditions that require less frequent administration/injections.

Trend Summaries

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

Artificial Intelligence to Predict Cardiovascular Events and Health Outcomes

Highlights

- Artificial intelligence (AI) technology is increasingly being integrated into cardiovascular care to help clinicians improve outcomes and prevent adverse events by analyzing large volumes of laboratory, imaging, and physiologic data.
- AI analysis could allow clinicians to provide more personalized care without additional testing by leveraging existing data in patient records.
- Specific applications for cardiovascular care include AI systems to detect impending heart failure exacerbations in patients monitored at home and to help screen patients for cardiac arrhythmias at physicians' offices.
- Stakeholders reviewing this trend thought that AI integration into cardiovascular care remains in a developmental phase but is likely to increase in effectiveness and clinical usefulness over time.
- Stakeholders also thought more regulatory oversight of the technology was warranted, to ensure data transparency and prevent negative impacts on populations that might be underrepresented in patient data used to develop and train AI algorithms for cardiovascular care.

Description

AI technology is increasingly being integrated into clinical settings. These technologies are intended to help clinicians improve care by processing and utilizing patient data gathered from multiple laboratory tests, imaging examinations, physiologic monitoring, and other clinical information in electronic health records.[98] In cardiovascular care, goals for using AI to improve outcomes might be helping clinicians better adhere to the latest clinical guidelines[99] or providing more personalized assessment of specific cardiovascular disease risks.[100]

Several AI applications for cardiovascular care have been developed. For example, an international group of AI and cardiovascular specialists developed a machine learning approach to

provide real-time decision support to adults living with heart failure.[101] The system analyzes patient data collected at home (eg, blood pressure, heart rate, oxygen saturation) to identify changes suggesting impending heart failure exacerbations. Depending on its analysis, the system might advise patients to continue normal care, to alter treatment by calling their physician, or to seek emergency treatment.[101] Additionally, EKO Devices (Oakland, California) offers an AI algorithm for a digital stethoscope that allows primary care providers to screen patients for cardiac arrhythmias (eg, atrial fibrillation, murmur).[102]

In more preliminary research, investigators at Harvard University (Boston, Massachusetts) and Rensselaer Polytechnic Institute (Troy, New York) have proposed that AI analysis of chest computed tomography (CT) images taken for lung cancer screening might detect undiagnosed heart conditions.[103]

Clinical Area(s) Potentially Disrupted

If implemented effectively and equitably, AI applied to cardiovascular care has potential to positively affect patient health outcomes. As part of that change, greater AI integration into cardiovascular care could prompt disruptions in care settings, such as allowing more home-based care and remote monitoring with automated review of patient vital signs and other patient data. These changes could, in turn, disrupt patient management by allowing clinicians to intervene sooner (eg, medication adjustments) based on system-generated alerts when abnormal readings or concerning subtle trends are detected.

Opportunities

Wider application of AI into cardiovascular care might improve outcomes by automatically combining relevant patient data from multiple sources to provide a more personalized cardiovascular risk assessment. In some cases, application of AI algorithms might let clinicians leverage existing data in electronic medical records to improve cardiovascular risk assessment without requiring additional testing. AI integration might allow primary care providers to detect subtle arrhythmias or other cardiac problems earlier and refer patients to cardiologists for specialized disease management before more serious complications develop, potentially improving outcomes.

Threats

Applying AI more broadly to the diagnosis and management of cardiovascular disease could lead to possible errors if data sets used to train AI algorithms do not represent all patient populations with the diseases of interest. Increased automation and AI integration might generate concern among physicians, who might view the technology as an encroachment on the doctor and patient relationship. AI-assisted analysis of patient data might increase clinical staff workloads, including additional patient monitoring and follow-up examinations. Applying AI analysis of patient data collected for other clinical indications (eg, chest CT scans for lung cancer screening) could create a risk of cardiovascular disease overdiagnosis, especially in the absence of symptoms or other signs suggestive of cardiovascular disease. Wider acceptance of AI patient data review to predict cardiovascular events and outcomes might raise medicolegal concerns for institutions that have not adopted AI risk assessment tools for cardiovascular disease.

Key Stakeholder Perspectives

Between September 13 and September 17, 2021, six stakeholders, reflecting allied health, clinical engineering, health systems, health care generalist, and research perspectives, provided

comments and ratings on this trend. The list below provides a summary of key stakeholder perspectives.

- Employing the power of AI to combine data from multiple sources has great potential, but AI is still in the developmental phase, and its usefulness and effectiveness to improve care is likely to increase over time.
- AI has the potential to affect patient care both positively and negatively. In particular, AI systems can make incorrect predictions, and overreliance on these systems could lead to adverse outcomes for some patients.
- AI applications could negatively impact care for certain groups, based on ethnicity or socioeconomic status, if these groups are unequally represented in AI system training data. Strong regulatory oversight and data transparency will be needed to mitigate these risks.
- Overriding an AI-generated misdiagnosis might create additional work for trained clinicians who need to demonstrate why their judgment is more accurate than that of an AI system.
- Even with likely improvements in accuracy and clinical usefulness over time, AI assistance in cardiovascular diagnoses and risk assessment will continue to supplement, rather than replace, clinician judgment.

Chapter 4. COVID-19

For the COVID-19 focus area, we considered for inclusion 11 topics for which (1) preliminary phase 3 data for drugs, phase 2 (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled and sent for stakeholder comment before September 3, 2021; and (3) we received at least 5 sets of comments and ratings from stakeholders between September 18, 2020, and September 17, 2021.

As of September 3, 2021, we were monitoring 50 topics in this focus area, including the 11 considered for inclusion in this report. These 50 topics are available—or will soon be available—for viewing on the PCORI Horizon Scanning Database website.

The 50 monitored topics encompass diagnostics, immunotherapies, monoclonal antibodies, pharmaceuticals, and programs intended to diagnose, prevent, treat, or manage COVID-19 and associated issues. Seven topics were developed as topic profiles to be sent for stakeholder comment; however, fewer than 5 sets of stakeholder comments were received for these topics before September 3, 2021, so they were not considered for inclusion in this report. The remaining 32 topics are too early in development to meet the criteria (as outlined above) for eligibility for this report.

Topics Considered for Inclusion in This Report

Table 4.1 lists 5 topics selected for inclusion in this report based on stakeholder ratings and comments and available data. Topics are listed and discussed alphabetically by title.

Table 4.1. Included Topics for Priority Area: COVID-19

Topic title
Aviptadil (Zyesami) to treat critical COVID-19 with respiratory failure
JNJ-78436735 (Ad26.COV2-S) vaccine for preventing coronavirus infection
Moderna COVID-19 vaccine (mRNA-1273) for preventing coronavirus infection
Pfizer-BioNTech COVID-19 vaccine for preventing coronavirus infection
Sabizabulin (VERU-111) to treat COVID-19 at high risk of progressing to acute respiratory distress syndrome[a]

[a] Topic appears for the first time in this edition of the *High Potential Disruption Report*.

Table 4.2 lists 6 topics considered, but not selected, for inclusion during the *High Potential Disruption Report* decision meeting. A majority of the voting team agreed that these topics lacked high potential for disruption, based on stakeholder ratings and comments and available data. Each record contains a note explaining the reasons for exclusion.

Table 4.2. Topics Considered but Not Included for Focus Area: COVID-19

Topic title	Exclusion reason(s) and notes based on stakeholder comments
Casirivimab plus imdevimab (REGEN-COV) to treat patients hospitalized with COVID-19	Because the treatment benefits only a subset of the study population, the stakeholders thought that REGEN-COV would have low to moderate impact. Further data are needed on the ability of the treatment to affect length of stay in the intensive care unit or hospital, to determine whether REGEN-COV can significantly impact recovery.

Topic title	Exclusion reason(s) and notes based on stakeholder comments
CERC-002 to treat COVID-19	Because many monoclonal antibodies have received emergency use authorization from the FDA, CERC-002 has very low potential to disrupt the health care delivery system or treatment models. More data and larger sample sizes are needed before the full disruptive impact of CERC-002 can be determined.
Covaxin (BBV152) to prevent COVID-19	Because other COVID-19 vaccines are already FDA authorized or approved and widely available in the United States and have higher efficacy, Covaxin has a very low disruptive potential.
Inhaled nebulized interferon beta-1a (SNG001) to treat COVID-19	The available data show that only a subgroup benefited from this treatment, lowering its disruptive potential. More data with larger sample sizes and comparisons with other inhaled treatments are needed before SNG001's full disruptive potential can be determined.
NT-300 to treat mild to moderate COVID-19	Preliminary data suggest that NT-300 might prevent progression to severe COVID-19; however, it did not significantly shorten recovery time, and additional data from larger trials are needed to assess disruptive potential.
NVX-CoV2373 to prevent COVID-19	Vaccines with similar efficacy to NVX-CoV2373 are already FDA authorized or approved and widely available in the United States, lowering the disruptive potential of this vaccine. Because the available data for NVX-CoV2373 do not show any significant advantages over the other COVID-19 vaccines, stakeholders believe that it has a very low chance of disruption.

Trends Considered for Inclusion in This Report

For the COVID-19 focus area, we considered for inclusion 23 trends for which (1) information was compiled and sent for stakeholder comment before September 3, 2021; *and* (2) we received at least 5 sets of comments and ratings from stakeholders between September 18, 2020, and September 17, 2021. These 23 trends are available—or will soon be available—for viewing on the PCORI Horizon Scanning Database website.

Table 4.3 lists 7 trends selected for inclusion in this report based on stakeholder ratings and comments and available data. Trends are listed and discussed alphabetically by title.

Table 4.3. Included Trends for Focus Area: COVID-19

Topic title
Aerial drones to deliver COVID-19 vaccines[a]
Digital COVID-19 immunization records for work, school, or travel
Mobile health clinics to increase access to COVID-19 health services
Post-COVID-19 recovery programs
Reinstatement of mask mandates to prevent COVID-19[a]
Surveillance programs to identify and follow the spread of emerging SARS-CoV-2 variants
Vaccines to prevent COVID-19 in children younger than 12 years[a]

[a] Topic appears for the first time in this edition of the *High Potential Disruption Report*.

Table 4.4 lists 16 trends considered, but not selected, for inclusion in this report, based on stakeholder ratings and comments and available data. Each record notes the reasons for exclusion.

Table 4.4. Trends Considered but Not Included for Focus Area: COVID-19

Topic title	Exclusion reason(s) and notes based on stakeholder comments
Artificial intelligence-assisted assessment of clinical data to determine COVID-19 prognosis	AI-assisted algorithms might help plan staff capacity and resource allocation to treat patients who have acute COVID-19. However, assessing the risk of deterioration does not mean their likelihood of survival will be better if treated earlier. These algorithms will augment the assessment and judgment by a clinician, not replace them.
COVID-19 testing impact calculator	The COVID-19 testing impact calculator could help organizations make effective decisions on when to test individuals, but the cost of testing and other efforts recommended by the calculator might be prohibitive.
COVID-19 vaccine allocation planner	Now that the supply of COVID-19 vaccines is easily meeting demand in the United States, an allocation planner is not disruptive or necessary.
Employee SARS-CoV-2 testing programs to reopen businesses	Increasing access to testing will help open businesses, control the spread of COVID-19, and speed return to normalcy. However, with many employers enforcing mask and/or vaccine mandates to return to work, there will be reduced demand for testing. Overall, this trend has diffused, minimizing future disruption.
Home-based care programs to manage patients with COVID-19	A home-based care model would reduce hospitalizations and improve health outcomes for patients with COVID-19 and chronic diseases. However, the need for adequate internet speed, proximity to a monitoring hospital, and nursing staff to visit these homes reduces its potential for disruption.
Hyperimmune immunoglobulin to treat COVID-19	Available data has shown that hyperimmune immunoglobulin does not provide significant clinical benefit to patients and is not as effective as initially hoped, making the treatment unlikely to cause disruption.
Incentive programs to increase COVID-19 vaccine uptake	Incentives like lotteries might increase vaccine uptake for some individuals; however, this effort could be unsustainable over the long term. Individuals who are opposed to getting the vaccine might remain hesitant, thus reducing the disruption potential for such programs.
Indoor air sampling to detect airborne SARS-CoV-2	Indoor air sampling to detect airborne coronavirus would have low disruptive potential because it represents only one component of an effective infection prevention strategy. Further, the long turnaround time for testing results greatly limits the value of local air sampling for real-time risk detection compared with rapid point-of-care testing to detect positive COVID-19 cases.
Lowering testosterone levels to treat coronavirus infection	Although data from clinical trials suggest that antiandrogen therapy might slow disease progression, speed recovery, and reduce the risk of mortality, its use is limited by the high incidence of side effects, concerns about long-term consequences, and negative patient perception of lowering testosterone. The disruption is likely to be incremental now that a number of treatments have been authorized by FDA for COVID-19.
Machine learning to predict the spread of COVID-19	Machine learning could help governments predict geographic outbreaks of COVID-19; however, the impact of machine learning is questionable because of the high variability in how officials respond to these data.
Phone applications to manage COVID-19 vaccine communications and scheduling	Phone applications for COVID-19 vaccine scheduling are largely diffused at this stage of the pandemic. Reminder emails and texts from large pharmacy chains and clinics cater to individuals who remain hesitant to receive the COVID-19 vaccine.

Topic title	Exclusion reason(s) and notes based on stakeholder comments
Populationwide antibody testing to quantify coronavirus infection rates	Populationwide antibody testing is unlikely to directly impact patient health outcomes because it is intended to measure the prevalence of COVID-19. Although it is helpful to understand the spread and severity of the virus, this will not significantly impact population health outcomes now that a large proportion of Americans are vaccinated.
Say Yes! COVID Test Initiative to reduce the spread of COVID-19	More data are needed about the outcomes of this initiative before its disruptive potential can be determined. Political and personal resistance throughout the United States to participate in vaccine initiatives might also prevent the intervention from taking hold.
Smell training to treat olfactory dysfunction after COVID-19 disease course	Olfactory training kits are a currently available, low-cost treatment option that might improve quality of life for the small percentage of patients who experience long-term olfactory dysfunction after COVID-19 infection. However, smell training is unlikely to be highly disruptive to the overall health care system because most cases resolve without intervention and variability in insurance coverage and provider understanding might further limit diffusion.
Vaccine mandates to prevent COVID-19	Because a majority of health care workers and people in high-risk settings are vaccinated, implementation of vaccine mandates in these settings might not increase vaccination rates to a significant amount in the populations. Legal and public barriers might also prevent the diffusion of these mandates.
Variant-specific vaccines to prevent COVID-19	Stakeholders thought that these vaccines would have only low to moderate disruptive potential because booster shots have been approved with the original vaccine formulas and because of the time it will take before variant-specific vaccines are available.

Abbreviation: AI, artificial intelligence.

Topic Summaries

We present below 5 summaries on topics deemed to have high potential for disruption.

Aviptadil (Zyesami) to Treat Critical COVID-19 With Respiratory Failure

Highlights

- Aviptadil is a synthetic form of a naturally occurring hormone involved in oxygen absorption and lung protection; it might also prevent coronavirus replication. It is being developed to treat patients who have critical COVID-19 and respiratory failure.
- Early data suggest aviptadil might offer statistically significant improvement in recovery from respiratory failure compared with standard of care.
- The FDA is reviewing an emergency use authorization application for aviptadil to treat critical COVID-19 with respiratory failure.
- Stakeholders reviewing this topic thought that aviptadil might become a new standard of care for critical COVID-19 with respiratory failure if early data are confirmed in ongoing phase 3 trials, given the lack of effective treatment options for this population.

Patient Population

Aviptadil is intended for patients aged 12 years or older who have critical COVID-19 with respiratory failure.

Intervention

Aviptadil (Zyesami, formerly RLF-100) is a synthetic form of human vasoactive intestinal polypeptide (VIP) under study as a rescue therapy for patients with critical COVID-19. VIP is a naturally occurring hormone with multiple protective functions in alveolar type 2 cells in the lungs. One of these functions is the production of pulmonary surfactant, a mixture of lipids and proteins that line the inner lung, protect lung cells, and help with oxygen absorption.[104-106] VIP also purportedly blocks coronavirus replication and the associated cytokine-mediated inflammatory response (ie, cytokine storm) linked with COVID-19.[107]

Alveolar type 2 cells express high levels of ACE-2 (angiotensin-converting enzyme 2) receptors, a known cellular entry point for the SARS-CoV-2 virus. Entry of SARS-CoV-2 into alveolar type 2 cells results in decreased surfactant production, oxygen insufficiency, and lung injury, thus presenting a plausible hypothesis for COVID-19 disease progression.[104-107] Aviptadil's lung-protective and antiviral effects could improve survival in patients with COVID-19-induced respiratory failure.[107]

In clinical trials, aviptadil is given by intravenous (IV) infusion or as a nebulized inhalant. For IV administration, patients receive 12-hour infusions of aviptadil at ascending doses of 50, 100, or 150 pmol/kg/hr on 3 successive days.[108] As an inhalant, aviptadil (100 µg drug per 1 mL saline per dose) is given over a time span of about 5 minutes every 8 hours for a maximum of 14 days (or 42 doses).

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 3 ongoing trials for this topic. We present these trials in Table 4.5.

Table 4.5. Ongoing Clinical Trials

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
I-SPY COVID-19 TRIAL: An Adaptive Platform Trial for Critically Ill Patients (I-SPY_COVID) NCT04488081	Adults (n = 1500) with confirmed COVID-19 hospitalized and placed on high-flow oxygen (mask or nasal cannula) or intubated	Phase 2, randomized, open-label, parallel-assignment trial to identify agents with strong potential, when added to remdesivir, to reduce the need for and duration of mechanical ventilation and improve survival in critically ill patients with COVID-19 Patients will be assigned to one of multiple arms, one of which will add treatment with aviptadil to remdesivir; other agents being tested include dornase alfa, IC-14, celecoxib, famotidine, narsoplimab, and cyclosporine. Aviptadil will be given as a nebulized inhalant every 8 hours for a maximum of 14 days (or 42 doses), at 100 µg drug per 1 mL saline per dose, given over a time span of about 5 minutes. Primary outcome: Improvement in clinical condition (ordinal level 4 or less for at least 48 hours) through 28 days Secondary outcomes: Improvement in disease severity, ventilator-free days, and frequency of SAEs, all through 60 days, and survival at 28 days	Primary completion July 2022 Study completion November 2022

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
ACTIV-3b: Therapeutics for Severely Ill Inpatients with COVID-19 (TESICO) NCT04843761	Adults (n = 640) hospitalized with confirmed COVID-19 infection and recent respiratory failure (4 days or less since initiation of respiratory support) likely due to SARS-CoV-2 pneumonia	Phase 3, randomized, double-blind, placebo-controlled, parallel-assignment trial comparing safety and efficacy of aviptadil and remdesivir, either alone or together, vs placebo, added to SOC (including corticosteroids) to treat COVID-19-related acute respiratory failure Comparisons will include aviptadil + remdesivir + SOC vs aviptadil placebo + remdesivir + SOC, and aviptadil placebo + remdesivir placebo + SOC vs aviptadil + remdesivir placebo + SOC. Primary outcome: Recovery at 90 days, categorized from 1 (best—at home off oxygen for at least 77 days) to 6 (worst—patient died) Selected secondary outcomes: All-cause mortality, days alive outside acute hospital care, incidence of organ failure, and time to hospital discharge	Primary completion October 2022 Study completion April 2023
ZYESAMI (Aviptadil) Intermediate Population Expanded Access Protocol (SAMICARE) NCT04453839 See data reported by Youssef et al, 2020, and in 2 news releases by NeuroRx, 2021, under Recently Completed and Ongoing Trials With Available Results	Patients with critical COVID-19 and respiratory failure who were ineligible for enrollment in NCT04311697, living more than 50 miles from a collaborating research center, or already hospitalized and unable to be safely transported to another facility	Expanded access protocol for phase 2/3 trials to test efficacy of intravenous aviptadil to treat patients who have critical COVID-19 and respiratory failure Patients will be treated with 12-hour infusions of aviptadil at ascending doses of 50, 100, or 150 pmol/kg/hr on 3 successive days. Primary outcome: Resolution of respiratory failure (day 0 through days 28 and 60) Secondary outcomes: Improvement on NIAID scale, survival, time to ICU discharge, and time on mechanical ventilation (time frame for all outcomes through days 28 and 60)	No trial end date listed Last updated March 2021

Abbreviations: IC-14, anti-CD14 monoclonal antibody; ICU, intensive care unit; NIAID, National Institute of Allergy and Infectious Diseases; pmol/kg/hr, picomoles of drug per kilogram of body weight per hour; SAEs, serious adverse events; SOC, standard of care; µg, micrograms.

Recently Completed and Ongoing Trials With Available Results

Our searches identified 3 recently completed late-phase trials with available results.[107-109] We summarize the 3 most recent and indication-relevant studies with results as written in a non–peer reviewed article and 2 news releases.

The following abbreviations are used in this section: CI, confidence interval; CL, confidence level; EAP, expanded access protocol; ECMO, extracorporeal membrane oxygenation; HFNC,

high-flow nasal cannula; ICU, intensive care unit; P, *P* value; pmol/kg/hr, picomoles of drug per kilogram of body weight per hour; WHO, World Health Organization.

Intravenous Aviptadil for Critical COVID-19 With Respiratory Failure (COVID-AIV). NCT04311697. NRx Pharmaceuticals, 2021.[109]

- **Patient population/planned enrollment:** Adults (n = 196) who had critical COVID-19 with respiratory failure and were receiving maximal conventional medical therapy
- **Study design:** Phase 2/3, randomized, double-blind, parallel-assignment trial comparing the safety and efficacy of 12-hour intravenous administrations of aviptadil at escalating doses, 50, 100, and 150 pmol/kg/hr on 3 successive days with placebo to treat critical COVID-19 with respiratory failure, in addition to standard of care (excluding mechanical ventilation or ECMO)
- **Primary outcome:** Resolution of respiratory failure through days 28 and 60
- **Secondary outcomes:** Time on ventilation and time to ICU discharge
- **Results presented by study authors:** "Across all patients and sites, [aviptadil] met the primary endpoint for successful recovery from respiratory failure at days 28 (P = .014) and 60 (P = .013) and also demonstrated a meaningful benefit in survival (P = < .001) after controlling for ventilation status and treatment site. In addition to the robust overall significance across all 196 treated patients at all 10 clinical sites, the prespecified analysis of recovery from respiratory failure is clinically and statistically significant in the 127 patients treated by High Flow Nasal Cannula (HFNC) (P = .02), compared to those treated with mechanical or non-invasive ventilation at tertiary care hospitals. In this group, [aviptadil] patients had a 71% chance of successful recovery by day 28 vs. 48% in the placebo group (P = .017) and a 75% rate of successful recovery by day 60 vs. 55% in the placebo group (P = .036). Eighty-four percent (84%) of HFNC patients treated at tertiary medical centers with [aviptadil] survived to day 60 compared with 60% of those treated with placebo (P = 007)."

ZYESAMI (Aviptadil) Intermediate Population Expanded Access Protocol (SAMICARE). NCT04453839. NRx Pharmaceuticals, 2021.[107]

- Patient population/planned enrollment: Adults and children aged 12 years or older (n = 240) with critical COVID-19 with respiratory failure who are ineligible for an aviptadil clinical trial, who live more than 50 miles from a participating trial site, or who are already hospitalized but too ill to safely transfer to a trial site
- (Note: Some patients in this report might have contributed results to the publication by Youssef et al108 cited below.)
- Study design: Unphased expanded access protocol to offer aviptadil given as 12-hour intravenous administrations at escalating doses, 50, 100, and 150 pmol/kg/hr on 3 successive days, to patients with critical COVID-19 with respiratory failure who had exhausted all approved COVID-19 therapies. Patients were receiving maximal intensive care (n = 196) or palliative care determined by their families and treating physicians (n = 56). Enrolled patients were already receiving mechanical ventilation (56%) or noninvasive respiratory support, mostly HFNC (44%).
- Primary outcome: Resolution of respiratory failure through day 28
- Secondary outcome: Treatment-related adverse events
- Results presented by study authors: "Among patients receiving maximal intensive (i.e. non-palliative) care, 76% of those treated with HFNC were discharged from the hospital or were alive and in the hospital at day 28, compared to 54% of those treated with mechanical ventilation. These numbers are congruent with the previously reported, topline, randomized, clinical data of

[aviptadil] in Critical COVID-19 patients with respiratory failure. Many of the patients involved in this EAP had prolonged illness or had exclusion factors limiting their access to the randomized clinical trial, and were enrolled as a last resort in this EAP. Treatment related adverse events from this EAP are congruent with those seen in the randomized controlled phase 2b/3 clinical trial of [aviptadil]. Treatment related adverse events included diarrhea (5%) and hypotension (5%). Other adverse events included tachycardia and flushing."

Prospective, Open-Label, Administratively Controlled Trial of Aviptadil for the Treatment of Respiratory Failure, Which May Include Patients From ZYESAMI (Aviptadil) Intermediate Population Expanded Access Protocol (SAMICARE). NCT04453839. Youssef et al, 2020.[108]

- **Patient population/planned enrollment:** Adults (n = 21) with critical COVID-19 and severe comorbidity who were ineligible for phase 3 aviptadil trials and were consecutively admitted to an ICU and treated with intravenous aviptadil, compared with control patients (n = 24) with comparable comorbidity and treated with standard of care by the same ICU clinical team over the same time frame

  (*Note:* Some patients from this report might have contributed data to results described in the NRx Pharmaceuticals news release above.[107])
- **Study design:** Prospective, open-label, controlled study to determine the safety and efficacy of 3 successive 12-hour intravenous infusions of aviptadil at 50, 100, or 150 pmol/kg/hr to treat critical COVID-19 with respiratory failure and severe comorbidity in patients ineligible for phase 3 aviptadil trials
- **Primary outcomes:** Survival, recovery from respiratory failure, and improvement on the WHO 10-point ordinal scale for COVID-19
- **Results presented by study authors:** "Seventeen of 21 patients survived to day 60 in the aviptadil treated group compared to 5 of 24 control patients (81% vs 21%; P < 0.0001). Kaplan-Meier analysis demonstrates a 4 fold advantage in the probability of survival (80% vs. 20%; P < .0006). The Hazard Ratio 0.149 (95% CL:0.050, 0.445). A similar 9 fold advantage was seen in the cumulative probability of Recovery from Respiratory Failure (Hazard ratio: 0.115; 95% CL: 0.0254, 0.5219). Between Day 28 and day 60 a mean 6.1 point difference in the 10 point WHO Ordinal Scale for COVID-19 was seen between aviptadil treated patients, who exhibited a 2.6 point mean improvement from the time of ICU admission vs those treated with standard of care who exhibited a mean 3.5 point mean decrement (Wilcoxon rank-sum: P < 0.001). Improved radiographic appearance was seen in both lungs of 17 patients and in one lung of 2 treated patients. Four of five aviptadil treated patients initially on Extracorporeal Membrane Oxygenation (ECMO) have been decannulated, compared to 3 of 13 ECMO treated controls (80% vs 23%; P = 0.045). A 75% (95% CI ± 3%: P < 0.001) reduction in IL-6 was seen. At day 60, a similar 5.5 fold advantage was seen in the cumulative probability of Recovery from Respiratory Failure (55%vs 10%; P = 0.002) at 60 days. The hazard ratio is 0.115 (95% CL: 0.0254, 0.5219). Patients treated with Aviptadil were 7 times more likely (% WHO 0-1 57.1% (12/21) for aviptadil vs 8.3% (2/24) control, P-value = %0.0008 to achieve resolution of their symptoms."

Manufacturers and Regulatory Status

NRx Pharmaceuticals, Inc (Radnor, Pennsylvania), formerly NeuroRx, Inc,[110] is developing aviptadil in collaboration with Relief Therapeutics, AG (Genève, Switzerland). On June 1, 2021, NRx Pharmaceuticals submitted an emergency use authorization (EUA) application to the FDA for use of aviptadil to treat patients who are critically ill with COVID-19 and have respiratory failure. This application was based on results of the phase 2/3 COVID-AIV trial.[111] As of October 7, 2021, the application was still under review by the FDA.

The EUA for aviptadil was originally sought in September 2020, based on results from a 21-patient case-control study.[106] However, in December 2020, the company announced that the FDA had not granted EUA based on this application.[112] The FDA had granted aviptadil fast track designation in June 2020.[113]

Cost Information

Cost information is currently unavailable for this topic.

Key Stakeholder Perspectives

Between August 17 and September 7, 2021, nine stakeholders, reflecting allied health, clinical, health systems, patient/patient representative, and research/scientific perspectives, provided comments and ratings on aviptadil to treat COVID-19. The list below provides a summary of key stakeholder perspectives.

- Safe and effective treatments are lacking for critical COVID-19 with respiratory failure, so new therapeutics for this population are highly desired.
- In early trials, aviptadil appears to offer a safe and effective new treatment for critical COVID-19 with respiratory failure.
- If aviptadil can help patients with severe disease leave the hospital sooner, it might disrupt the shortage of intensive care unit beds in areas hard hit by surges in COVID-19 cases.
- Aviptadil could become a new standard of care for critical COVID-19 with respiratory failure if additional data from ongoing phase 3 trials confirm the drug's early promise and safety profile.

JNJ-78436735 (Ad26.COV2-S) Vaccine for Preventing Coronavirus Infection

Highlights

- JNJ-78436735 is an investigational vaccine intended to prevent COVID-19, the disease caused by infection with the novel coronavirus, SARS-CoV-2. The FDA granted JNJ-78436735 emergency use authorization (EUA) for preventing COVID-19 in individuals aged 18 years or older. The FDA subsequently amended this EUA to allow for a booster dose of JNJ-78436735 at least 2 months after initial vaccination.
- JNJ-78436735 is in phase 3 development, with full data on efficacy and safety in adults expected in January 2023. Trials investigating use of this vaccine in adolescents are under way.
- Stakeholders commenting on this topic thought JNJ-78436735 might improve patient and population health outcomes by reducing COVID-19 disease incidence and spread, potentially lowering the burden of COVID-19 on the health care system.
- Some stakeholders also thought that, because JNJ-78436735 was developed using a traditional vaccine platform, it might provide a more familiar alternative for individuals hesitant to receive COVID-19 vaccines developed through newer technologies.

Patient Population

JNJ-78436735 is authorized for use in adults aged 18 years or older. Investigations studying its use in adolescents are under way.

Intervention

JNJ-78436735 (Ad26.COV2-S; Johnson & Johnson, New Brunswick, New Jersey) is a recombinant (ie, genetically engineered) adenoviral vector vaccine intended to prevent COVID-19,[114-116] the disease caused by infection with the novel coronavirus, SARS-CoV-2. Common early symptoms of COVID-19 include cough, fatigue, fever, and loss of smell or taste. Most individuals who contract COVID-19 develop mild symptoms. However, for older adults and individuals with certain preexisting medical conditions such as cancer, cardiovascular disease, chronic lung disease, diabetes, and hypertension,[117] disease progression can be severe, causing respiratory distress, organ failure, and death. Vaccination can help limit the transmission of SARS-CoV-2 and decrease COVID-19-caused deaths in hospitalized patients.[118] The Centers for Disease Control and Prevention (CDC) website offers more information about COVID-19.

JNJ-78436735 uses a shortened, weakened form of a common cold virus to carry genetic material into special antigen-presenting cells in the patient's body. The genetic material codes for the expression of the full-length stabilized form of the spike protein of SARS-CoV-2. This protein, present on the surface of the virus, is instrumental in the virus's ability to infect host cells, thus causing COVID-19. JNJ-78436735 is designed to deliver spike protein DNA to the nucleus of immune cells in the vaccinated individual, stimulating the expression of the SARS-CoV-2 spike protein in these cells.[119,120] This initiates the process of antibody production against the spike protein and memory cell formation, which are both necessary for mounting an immune response that can prevent SARS-CoV-2 infection.[114,116,121]

The FDA-authorized label specifies that JNJ-78436735 is administered as a single, 0.5-mL intramuscular injection, containing 5×10^{10} virus particles.[115] The single required dose contrasts with messenger RNA (mRNA)–based vaccines that require a 2-dose regimen, but a clinical trial is investigating use of an initial 2-dose regimen with this vaccine. The FDA has amended the initial EUA to allow for a booster dose of JNJ-78436735 at least 2 months after the initial single dose.[122]

Unpunctured, multidose vials of JNJ-78436735 can be stored between 2 °C and 8 °C (36-46 °F) long term and between 9 °C and 25 °C (47-77 °F) for up to 12 hours.[115]

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 9 ongoing trials for this topic. We present 3 of the most relevant, late-phase trials in Table 4.6. We excluded three phase 2 trials (NCT04535453, NCT04765384, and NCT04436276) and one phase 3 trial (NCT04838795) because they had smaller sample sizes and/or restricted patient populations.

Table 4.6. Ongoing Clinical Trials

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
A Study of Ad26.COV2.S for the Prevention of SARS-CoV-2-Mediated COVID-19 in Adult Participants (ENSEMBLE) NCT04505722	Adults (n = 44 325) with or without underlying health conditions associated with progression to severe COVID-19 and no previous prophylactic treatment for COVID-19	Phase 3, randomized, parallel-assignment, double-blind trial to evaluate the safety and efficacy of Ad26.COV2.S for the prevention of COVID-19 Patients will be randomly assigned to receive either a single intramuscular injection of Ad26.COV2.S (5×10^{10} virus particles) or placebo. Primary end point: Number of participants with first occurrence of moderate to severe/critical COVID-19 (confirmed by molecular testing) Secondary end points: Adverse events, number of participants with first occurrence of symptomatic or asymptomatic COVID-19, number of patients requiring medical intervention, and burden of disease	Primary completion January 2021 Study completion January 2023
A Study to Evaluate Dose Levels of Ad26.COV2.S Administered as a Two-Dose Schedule in Healthy Adults (CR108960) NCT04908722	Adults (n = 1350) aged 18 to 55 years, without underlying health conditions, associated with progression to severe COVID-19	Phase 3, randomized, parallel-assignment, double-blind trial to evaluate the safety and efficacy of 6 dose levels of a 2-dose regimen of Ad26.COV2.S for the prevention of COVID-19 Patients will be randomly assigned to receive 1 of 6 different unspecified dose levels of Ad26.COV2.S to be given in 2 successive intramuscular injections, spaced 56 days apart. Primary end point: Concentration of spike protein–binding antibodies Secondary end point: Adverse events	Primary completion April 2022 Study completion February 2023

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
A study of Ad26.COV2.S for the Prevention of SARS-CoV-2-Mediated COVID-19 in Adults (ENSEMBLE 2) NCT04614948	Adults (n = 31 836) with or without underlying health conditions associated with progression to severe COVID-19	Phase 3, randomized, parallel-assignment, double-blind trial to evaluate the safety and efficacy of Ad26.COV2.S for the prevention of COVID-19 Patients will be randomly assigned to receive 2 successive intramuscular injections of Ad26.COV2.S or placebo, given 56 days apart Primary end point: Number of participants with first occurrence of moderate to severe/critical COVID-19 Secondary end points: Adverse events, number of participants with first occurrence of symptomatic or asymptomatic COVID-19, number of patients requiring medical intervention, and burden of disease	Primary completion May 2022 Study completion May 2023

Abbreviation: Ad26.COV2.S, JNJ-78436735.

Recently Completed and Ongoing Trials With Available Results

Our searches identified 2 late-phase trials with reported results. We summarize the most recent and indication-relevant studies with results as written in the abstract of a peer reviewed, published article[114]; a non–peer reviewed preprint article[123]; and a news release.[124]

The following abbreviations are used in this section: 20H/501Y.V2, Beta variant of SARS-CoV-2; Ad26.COV2.S, JNJ-78436735; CI, confidence interval; VE, vaccine effectiveness.

A Study of Ad26.COV2.S for the Prevention of SARS-CoV-2-Mediated COVID-19 in Adult Participants (ENSEMBLE). NCT04505722. Sadoff et al, 2021.[114]

- **Patient population/planned enrollment:** Adults (n = 44 325) with or without underlying health conditions associated with progression to severe COVID-19
- **Study design:** Phase 3, randomized, parallel-assignment, double-blind trial to evaluate the safety and efficacy of Ad26.COV2.S for the prevention of COVID-19. Patients were randomly assigned to receive either a single intramuscular injection of Ad26.COV2.S (5×10^{10} virus particles) or placebo.
- **Primary outcome:** Number of participants with first occurrence of moderate to severe/critical COVID-19 (confirmation by molecular testing)
- **Secondary outcomes:** Adverse events, number of participants with first occurrence of symptomatic or asymptomatic COVID-19, number of patients requiring medical intervention, and burden of disease
- **Results presented by study authors:** "The per-protocol population included 19,630 SARS-CoV-2-negative participants who received Ad26.COV2.S and 19,691 who received placebo. Ad26.COV2.S protected against moderate to severe-critical Covid-19 with onset at least 14 days after administration (116 cases in the vaccine group vs. 348 in the placebo group; efficacy, 66.9%; adjusted 95% confidence interval [CI], 59.0 to 73.4) and at least 28 days after administration (66 vs. 193 cases; efficacy, 66.1%; adjusted 95% CI, 55.0 to 74.8). Vaccine efficacy

was higher against severe-critical Covid-19 (76.7% [adjusted 95% CI, 54.6 to 89.1] for onset at ≥14 days and 85.4% [adjusted 95% CI, 54.2 to 96.9] for onset at ≥28 days). Despite 86 of 91 cases (94.5%) in South Africa with sequenced virus having the 20H/501Y.V2 variant, vaccine efficacy was 52.0% and 64.0% against moderate to severe-critical Covid-19 with onset at least 14 days and at least 28 days after administration, respectively, and efficacy against severe-critical Covid-19 was 73.1% and 81.7%, respectively. Reactogenicity was higher with Ad26.COV2.S than with placebo but was generally mild to moderate and transient. The incidence of serious adverse events was balanced between the two groups. Three deaths occurred in the vaccine group (none were Covid-19-related), and 16 in the placebo group (5 were Covid-19-related)."

Effectiveness of the Single-Dose Ad26.COV2.S COVID Vaccine. NCT04505722. Polinsky et al, 2021.[123]

- **Patient population/planned enrollment:** 390 517 vaccinated and 1 524 153 matched unvaccinated individuals aged 18 years or older
- **Study design:** Retrospective cohort study of insurance claims data on individuals newly vaccinated with Ad26.COV2.S and up to 10 unvaccinated individuals matched exactly by age, sex, date, location, and comorbidity index plus 17 COVID-19 risk factors via propensity score matching
- **Primary outcome:** Vaccine effectiveness (VE) was determined for observed SARS-CoV-2 infection and COVID-19–related hospitalization. The nationwide data were stratified by age, immunocompromised status, calendar time, and Delta-variant incidence (by state).
- **Results presented by study authors:** "Among 390,517 vaccinated and 1,524,153 matched unvaccinated individuals, VE was 79% (95% CI, 77% to 80%) for COVID-19 and 81% (79% to 84%) for COVID-19-related hospitalizations. VE was stable over calendar time. Among states with high Delta variant incidence, VE during June/July 2021 was 78% (73% to 82%) for infections and 85% (73% to 91%) for hospitalizations. VE for COVID-19 was higher in individuals < 50 years (83%; 81% to 85%) and lower in immunocompromised patients (64%; 57% to 70%). All estimates were corrected for under-recording; uncorrected VE was 69% (67% to 71%) and 73% (69% to 76%), for COVID-19 and COVID-19-related hospitalization, respectively."

A Study of Ad26.COV2.S for the Prevention of SARS-CoV-2-Mediated COVID-19 in Adults (ENSEMBLE 2). NCT04614948. Johnson and Johnson, 2021.[124]

- **Patient population/planned enrollment:** Adults (n = 31 836) with or without underlying health conditions associated with progression to severe COVID-19
- **Study design:** Phase 3, randomized, parallel-assignment, double-blind trial to evaluate the safety and efficacy of Ad26.COV2.S for the prevention of COVID-19. Patients were randomly assigned to receive 2 successive intramuscular injections of Ad26.COV2.S (5×10^{10} virus particles) or placebo, given 56 days apart.
- **Primary outcome:** Number of participants with first occurrence of moderate to severe/critical COVID-19 (confirmation by molecular testing)
- **Secondary outcomes:** Adverse events, number of participants with first occurrence of symptomatic or asymptomatic COVID-19, number of patients requiring medical intervention, and burden of disease
- **Results presented by study authors:** "Compared to the single-dose results, ENSEMBLE 2 also demonstrated increased efficacy of a two-dose schedule against moderate to severe/critical COVID-19 of 75 percent (CI, 55%-87%; n = 14 cases vaccine arm, n = 52 cases placebo arm) and severe/critical COVID-19 of 100 percent (CI, 33%-100%; n = 0 cases vaccine arm, n = 8 cases

placebo arm) at least 14 days following the second vaccination prior to unblinding. In the U.S., efficacy against moderate to severe/critical COVID-19 was 94 percent (CI, 58%-100%; n = 1 case vaccine arm, n = 14 cases placebo arm).

"Median follow-up time in the ENSEMBLE 2 study was 36 days since second vaccination, with 29 percent of participants having at least two months of follow-up after receipt of their second dose.

"The vaccine, when given as a second dose or booster, remained generally well-tolerated."

Manufacturers and Regulatory Status

JNJ-78436735 was developed by Janssen Pharmaceutical, LLC (Titusville, New Jersey), a subsidiary of Johnson & Johnson, Inc (New Brunswick, New Jersey). On February 27, 2021, the FDA issued an EUA for use of JNJ-78436735 for preventing COVID-19 in individuals aged 18 years or older.[115] The EUA was based on data from the phase 3 ENSEMBLE trial (see Table 4.6). Janssen planned to submit a biologics license application to the FDA later in 2021.[125]

On October 20, 2021, the FDA amended the initial EUA to provide for a booster dose of JNJ-78436735 to be given at least 2 months after initial vaccination. This amendment also provides for a heterologous, or mix-and-match, strategy for booster doses, allowing individuals initially receiving JNJ-78436735 to obtain a booster dose with either of the other 2 COVID-19 vaccines with authorization or approval from the FDA.[122]

An ongoing phase 3 trial is continuing evaluation of the safety and efficacy of a 2-dose primary regimen of JNJ-78436735 (see Table 4.6). The vaccine is also being tested in adolescents in 2 trials, one of which is ongoing[126] and one of which is not yet recruiting.[127]

On April 13, 2021, the CDC and the FDA recommended a pause in the use of Ad26.COV2.S after reports of 6 cases of a rare thromboembolic syndrome, cerebral venous sinus thrombosis with thrombocytopenia, were observed in the United States among recipients of this vaccine. After discussion of the benefits and risks of resuming vaccination, on April 23, 2021, the CDC's Advisory Committee on Immunization Practices reaffirmed its interim recommendation for use of the Janssen COVID-19 vaccine in all individuals aged 18 years or older under the FDA's EUA, which now includes a warning that rare clotting events might occur after vaccination, primarily among women aged 18 to 49 years.[115,128] The associated fact sheet for health care providers[129] addresses this risk and also notes increased risk of Guillain-Barré syndrome, a rare neurological disorder, within 42 days after vaccination.

Cost Information

The price of the JNJ-78436735 vaccine has been reported at $10 per dose.[130] However, the American Rescue Plan Act of 2021 provides funding for COVID-19 vaccine activities. Under Subtitle D—Public Health, JNJ-78436735 should be available to adults in the United States at no direct cost.[131]

Key Stakeholder Perspectives

Between August 9 and September 1, 2021, eight stakeholders, reflecting clinical, health systems, nursing/physician assistant, patient/patient representative, and research perspectives, provided comments and ratings on JNJ-78436735. The list below provides a summary of key stakeholder perspectives.

- JNJ-78436735 might improve patient and population health outcomes by reducing COVID-19 incidence and spread, alleviating disease symptoms, reducing hospitalizations and deaths, and helping end the spread of the disease within communities.

- By preventing or lessening the severity of disease, the vaccine might lower the burden of COVID-19 on the health care system and allow resources to be directed toward treating other diseases.
- A single-dose vaccine might also increase overall vaccination rates in the population and improve vaccination compliance, which could help reduce the development of variants of concern. The single-dose regimen of JNJ-78436735, as well as the vaccine's ease of storage requirements, might help mitigate health disparities and production and distribution bottlenecks. Areas with limited access to vaccination might benefit most.
- Unlike the novel technology used for mRNA vaccine developments, JNJ-78436735's traditional mode of production might mitigate vaccine hesitancy seen in individuals unsure about mRNA COVID-19 vaccines.

Moderna COVID-19 Vaccine (mRNA-1273) for Preventing Coronavirus Infection

Highlights

- The Moderna vaccine is an investigational vaccine intended to prevent COVID-19, the respiratory illness caused by infection with the novel coronavirus, SARS-CoV-2.
- The Moderna vaccine is in phase 3 development, with primary completion expected in October 2022. The FDA granted the Moderna vaccine emergency use authorization (EUA) for preventing COVID-19 in individuals aged 18 years or older. The FDA amended this EUA to allow for a single booster dose of the vaccine for older adults or those with health conditions or occupations placing them at risk for serious complications from COVID-19. The company has submitted a biologics license application to the FDA for approval of the vaccine.
- Stakeholders commenting on this topic thought that the Moderna vaccine could improve population health outcomes by reducing the incidence of COVID-19, reducing the need for hospitalizations for severe illness, and mitigating spread of virus variants.
- Stakeholders also expected reductions in the cost of care and overall burden to the health care system associated with treating COVID-19.

Patient Population

The mRNA-1273 vaccine is authorized by the FDA for use in individuals aged 18 years or older. It is under investigation for use in children aged 6 months to 17 years.

Intervention

The mRNA-1273 vaccine (Moderna, Cambridge, Massachusetts) is intended to prevent COVID-19, the respiratory illness caused by infection with the novel coronavirus, SARS-CoV-2. The duration and severity of COVID-19 varies substantially across individuals but is often more serious for people of advanced age, with certain preexisting conditions, or with weakened immune systems.[132] Serious cases might cause acute respiratory distress, requiring hospitalization, and extremely severe cases can result in death.

SARS-CoV-2 spreads through person-to-person contact via aerosolized droplets, and spread can occur even if an infected individual is asymptomatic. Some infected individuals continue to have persistent symptoms and/or organ dysfunction after recovering from acute COVID-19.[133] The Centers for Disease Control and Prevention (CDC) website offers more information on COVID-19.

The mRNA-1273 vaccine uses messenger RNA (mRNA) to encode a portion of the spike protein, which is present on the outer surface of the virus and is responsible for viral fusion and entry into host cells. To manufacture mRNA-1273, mRNA encoding viral spike protein is packaged within lipid nanoparticles. In the body, this allows the mRNA to be delivered more efficiently into the cytosol of host antigen-presenting cells (APCs). Once inside, the mRNA induces APCs to manufacture the viral spike protein and display it on their cell membranes.[133] Recognition of this foreign protein by other immune cells elicits a host immune response that includes production of antibodies targeted against the virus, thus preventing future infection or limiting disease severity.[134] Once viral proteins are made and an immune response is triggered, host cells break down and eliminate the spike protein mRNA from the vaccine.[135]

A health care worker gives the vaccine as an intramuscular injection at a dose of 100 µg in 0.5 mL. Two doses of mRNA-1273 are required for the initial course, with the second dose given 28 days after the first.[136] The FDA also authorized allowance for a single booster shot for individuals aged 65 years or older and for younger adults with health conditions or occupations placing them at high risk for serious complications from COVID-19.[122] The booster dose is recommended to be given at least 6 months after completion of the initial course, and at half the initial dose.[137]

mRNA-1273 must be stored at cold temperatures between –50 and –15 °C (–58 to 5 °F) to remain effective.[138,139] Unpunctured vials can be stored thawed for up to 30 days at refrigerator temperatures between 2 and 8 °C (36 to 46 °F).[139]

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified more than 15 ongoing trials for this topic. Table 4.7 includes 4 trials, of which 3 are the largest and latest-phase trials, and 1 additional trial testing mRNA-1273 in children aged 6 months to 11 years.

Table 4.7. Ongoing Clinical Trials

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
A Study of SARS CoV-2 Infection and Potential Transmission in Individuals Immunized with Moderna COVID-19 Vaccine (CoVPN 3006) NCT04811664	Adults (n = 37 500) aged 18 to 29 years without a self-reported known history of SARS-CoV-2 infection	Phase 3, randomized, open-label, crossover trial to assess SARS-CoV-2 infection, viral shedding, and subsequent potential transmission in individuals immunized with mRNA-1273 Participants are randomly assigned in a 1:1 ratio to treatment with mRNA-1273 (2 intramuscular injections, 28 days apart; 100 µg/injection in 0.5 mL suspension) or standard of care. Additional patients are assigned to a "vaccine declined" group. The standard-of-care and vaccine-declined groups have the option of being vaccinated at months 4 and 5, after the follow-up period for the vaccinated group. Primary outcomes: Efficacy of mRNA-1273 against SARS-CoV-2 infection and effect of mRNA-1273 vaccine on peak viral load (SARS-CoV-2 infection diagnosed by PCR among participants who were SARS-CoV-2 seronegative at enrollment) Secondary outcomes: Impact of mRNA-1273 vaccine on secondary transmission of SARS-CoV-2 infection and its efficacy to prevent serologically confirmed SARS-CoV-2 infection	Primary and study completion December 2021

A Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 Vaccine in Adolescents 12 to <18 Years Old to Prevent COVID-19 (TeenCove)
NCT04649151
See preliminary results by Moderna, 2021, under Recently Completed and Ongoing Trials With Available Results
	Healthy adolescents (n = 3732) aged 12 to 17 years who are not pregnant	Phase 2/3, randomized, quadruple-blind (participants, providers, investigators, outcomes assessor), placebo-controlled study to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 SARS-CoV-2 vaccine in healthy adolescents
		Participants are randomly assigned in a 2:1 ratio to treatment with mRNA-1273 (2 intramuscular injections, 28 days apart; 100 µg/injection) or matching placebo (saline).
		Primary outcomes:
		• Number of participants with:
		  ○ Solicited local and systemic adverse reactions
		  ○ Adverse events
		  ○ Serum antibody levels that meet or exceed the threshold of protection from COVID-19
		• Seroresponse rate of vaccine recipients
		Secondary outcome: Number of participants with SARS-CoV-2 infection regardless of symptomology
			Primary and study completion June 2022

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
A Study to Evaluate Efficacy, Safety, and Immunogenicity of mRNA-1273 Vaccine in Adults Aged 18 Years and Older to Prevent COVID-19 (COVE Study) NCT04470427 See preliminary results by El Sahly et al, 2021 and Baden et al, 2021, under Recently Completed and Ongoing Trials With Available Results	Healthy adults or adults with preexisting medical conditions who are in stable condition (n = 30 420), at high risk of SARS-CoV-2 infection, and not pregnant or breastfeeding	Phase 3, randomized, quadruple-blind (participants, providers, investigators, outcomes assessors), placebo-controlled trial to evaluate the efficacy, safety, and immunogenicity of mRNA-1273 in adults Participants are randomly assigned in a 1:1 ratio to treatment with mRNA-1273 (2 intramuscular injections, 28 days apart; 100 µg/injection) or matching placebo (saline). Primary outcomes: Efficacy of mRNA-1273 in preventing a first occurrence of symptomatic COVID-19 with onset at least 14 days after the second dose, and number of participants with adverse events and with solicited local and systemic adverse reactions Secondary outcome: Number of participants with a first occurrence of COVID-19 and SARS-CoV-2 infection, regardless of symptomology or severity, starting 14 days after second dose of mRNA-1273 or placebo	Primary and study completion October 2022

A Study to Evaluate Safety and Effectiveness of mRNA-1273 COVID-19 Vaccine in Healthy Children Between 6 Months of Age and Less Than 12 Years of Age NCT04796896	Children (n = 6975) aged 6 months to <12 years, born at full term with a minimum birth weight of 2.5 kg, and healthy or with stable chronic disease	Phase 2/3, open-label, randomized, placebo-controlled, blinded study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 SARS-CoV-2 vaccine in healthy children
		Part 1 investigates 3 different dose levels of mRNA-1273 given in 2 injections, 28 days apart. In part 2, participants are randomly assigned in a 1:1 ratio to treatment with mRNA-1273 (2 intramuscular injections, 28 days apart; 100 µg/injection) or matching placebo (saline).
		Primary outcomes:
		• Number of participants with:
		  ○ Solicited local and systemic adverse reactions
		  ○ Adverse events
		  ○ Adverse event of special interest (including MIS-C)
		  ○ Serum antibody levels that meet or exceed the threshold of protection from COVID-19
		• Seroresponse rate of vaccine recipients
		Secondary outcome: Number of participants with SARS-CoV-2 infection regardless of symptomology
			Primary and study completion June 2023

Abbreviations: MIS-C, multisystem inflammatory syndrome in children; PCR, polymerase chain reaction test.

Recently Completed and Ongoing Trials With Available Results

Our searches identified 2 ongoing late-phase trials with published results. We summarize 3 recent and indication-relevant studies associated with ongoing trials sponsored by the manufacturer, with results as written in abstracts of a peer reviewed, published article[140]; a non–peer reviewed preprint article[141]; and a news release.[142]

The following abbreviations are used in this section: CDC, Centers for Disease Control and Prevention; CI, confidence interval; mRNA-1273e, earlier test cohort, vaccinated from July to December 2020; mRNA-1273p, test cohort initially randomly assigned to placebo and then vaccinated from December 2020 to April 2021; NP, nasopharyngeal; RT-PCR, real-time reverse transcription polymerase chain reaction test.

A Study to Evaluate Efficacy, Safety, and Immunogenicity of mRNA-1273 Vaccine in Adults Aged 18 Years and Older to Prevent COVID-19 (COVE Study). NCT04470427. El Sahly et al, 2021,[140] and Baden et al, 2021.[141]

- **Patient population/planned enrollment:** Healthy adults or adults with preexisting medical conditions who were in stable condition (n = 30 415), at high risk of SARS-CoV-2 infection, and not pregnant or breastfeeding
- **Study design:** Phase 3, randomized, observer-blinded, placebo-controlled trial to evaluate the efficacy, safety, and immunogenicity of mRNA-1273 in adults. Participants were randomly assigned in a 1:1 ratio to treatment with mRNA-1273 (2 intramuscular injections, 28 days apart; 100 µg/injection) or matching placebo (saline).
- **Primary outcome:** Prevention of COVID-19 illness with onset at least 14 days after the second injection in participants not previously infected with SARS-CoV-2
- **Secondary outcomes:** Efficacy of the mRNA-1273 vaccine in preventing severe COVID-19, COVID-19 after the first dose, COVID-19 regardless of prior SARS-CoV-2 infection, serologically confirmed SARS-CoV-2 infection, SARS-CoV-2 infection regardless of symptom status, and asymptomatic SARS-CoV-2 infection
- **Results presented by El Sahly et al from the randomized phase of COVE trial:** "The trial enrolled 30,415 participants; 15,209 were assigned to receive the mRNA-1273 vaccine, and 15,206 to receive placebo. More than 96% of participants received both injections, 2.3% had evidence of SARS-CoV-2 infection at baseline, and the median follow-up was 5.3 months in the blinded phase. Vaccine efficacy in preventing Covid-19 illness was 93.2% (95% confidence interval [CI], 91.0 to 94.8), with 55 confirmed cases in the mRNA-1273 group (9.6 per 1000 person-years; 95% CI, 7.2 to 12.5) and 744 in the placebo group (136.6 per 1000 person-years; 95% CI, 127.0 to 146.8). The efficacy in preventing severe disease was 98.2% (95% CI, 92.8 to 99.6), with 2 cases in the mRNA-1273 group and 106 in the placebo group, and the efficacy in preventing asymptomatic infection starting 14 days after the second injection was 63.0% (95% CI, 56.6 to 68.5), with 214 cases in the mRNA-1273 group and 498 in the placebo group. Vaccine efficacy was consistent across ethnic and racial groups, age groups, and participants with coexisting conditions. No safety concerns were identified."
- **Results presented by Baden et al, 2021, from the open-label phase of the COVE trial, examining efficacy against Delta variant:** "There were 14,746 participants in the earlier mRNA-1273 (mRNA-1273e) group and 11,431 in the later placebo-mRNA1273 (mRNA-1273p) group. Covid-19 cases increased from the start of the open-label phase to July-August 2021. During July and August, 162 Covid-19 cases occurred in the mRNA-1273e group and 88 in the mRNA-1273p group. Of the cases sequenced, 144/149 [97%]) in the mRNA-1273 and 86/88 (99%) in the mRNA-1273p groups were attributed to Delta [Delta variant of SARS-CoV-2]. The

incidence rate of Covid-19 was lower for the mRNA-1273p (49.0/1000 person-years) versus mRNA-1273e (77.1/1000 person-years) group [36.4% (95% CI 17.1%-51.5%) reduction]. There were fewer severe Covid-19 cases in the mRNA-1273p (6; 6.2/1000 person-years) than mRNA-1273e (13; 3.3/1000 person-years) [46.0% (95% CI −52.4%-83.2%) reduction]. Three Covid-19 related hospitalizations occurred with two resulting deaths in the mRNA-1273e group."

A Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 Vaccine in Adolescents 12 to <18 Years Old to Prevent COVID-19 (TeenCove). NCT04649151. Moderna, 2021.[142]

- **Patient population/planned enrollment:** Healthy adolescents (n = 3732) aged 12 to 17 years who were not pregnant
- **Study design:** Phase 2/3, randomized, observer-blinded, placebo-controlled study to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 SARS-CoV-2 vaccine in healthy adolescents. Participants were randomly assigned in a 2:1 ratio to treatment with mRNA-1273 (2 intramuscular injections, 28 days apart; 100 µg/injection) or matching placebo (saline).
- **Primary outcome:** Number of participants with adverse reactions and serum antibody levels that met or exceeded the threshold of protection from COVID-19, and seroresponse rate of vaccine recipients
- **Secondary outcome:** Number of participants with SARS-CoV-2 infection regardless of symptomology
- **Results presented by study authors:** "In this Phase 2/3 study, 3,732 adolescent participants ages 12 to less than 18 years were enrolled and randomized 2:1 to two 100 µg doses of mRNA-1273 or placebo. The primary endpoint of non-inferior immunogenicity versus the Phase 3 adult study comparator group was met. After two doses, no cases of COVID-19 were observed in the vaccine group using the case definition from the adult Phase 3 COVE study, compared to 4 cases in the placebo group, resulting in a vaccine efficacy of 100% starting 14 days after the second dose. Because the incidence rate of COVID-19 is lower in adolescents, a secondary case definition based on the CDC definition of COVID-19 was also evaluated to include cases presenting with milder symptoms. Using the CDC definition, which requires only one COVID-19 symptom and a nasopharyngeal (NP) swab or saliva sample positive for SARS-CoV-2 by RT-PCR, a vaccine efficacy of 93% after the first dose was observed.

  "mRNA-1273 was generally well tolerated with a safety and tolerability profile generally consistent with the Phase 3 COVE study in adults. No significant safety concerns have been identified to date. The majority of adverse events were mild or moderate in severity. The most common solicited local adverse event was injection site pain. The most common solicited systemic adverse events after the second dose of mRNA-1273 were headache, fatigue, myalgia and chills."

Manufacturers and Regulatory Status

mRNA-1273 is being developed by Moderna, Inc (Cambridge, Massachusetts). On December 18, 2020, the FDA issued an EUA for the Moderna mRNA-1273 COVID-19 vaccine to prevent COVID-19 in individuals aged 18 years or older.[143] This authorization was based on data from an ongoing phase 3 trial with 30 420 adults that is expected to have full data by October 2022.[144]

On October 20, 2021, the FDA amended its initial EUA to allow for a single booster shot of mRNA-1273 for individuals aged 65 years or older and for younger adults with health conditions or occupations placing them at high risk for serious complications from COVID-19.[122] The booster dose is recommended to be given at least 6 months after completion of the initial course and at half the initial dose (50 µg).[137] This decision was based, in part, on Moderna's submission of an

application to include a booster dose of the vaccine,[145] following positive initial findings from its amended phase 2 trial investigating safety and efficacy of third doses.[146] The FDA has also authorized a heterologous (or mix-and-match) strategy for booster doses, allowing individuals initially receiving mRNA-1273 to obtain a booster dose with either of the other 2 COVID-19 vaccines with FDA EUA or approval.[122]

On June 1, 2021, Moderna announced that it had initiated a rolling submission with the FDA for a biologics license application for use of mRNA-1273 in adults aged 18 years or older.[147] Moderna had been granted the FDA's fast track designation for development of mRNA-1273 in May 2020.[148]

On June 10, 2021, the company filed for an EUA to use mRNA-1273 to vaccinate adolescents, aged 12 to 17 years, based on data from its phase 2/3 trial, which enrolled 3732 participants.[149,150]

Outside of clinical trials, cases of myocarditis and pericarditis have been reported among Moderna mRNA-1273 vaccine recipients, particularly after the second dose and within a few days of vaccine administration. In June 2021, the FDA updated the authorized prescribing information for the vaccine to include a warning about the potential for an increased risk of myocarditis and pericarditis in vaccine recipients.[139]

Cost Information

The pricing for mRNA-1273 has been estimated at $25 to $37 per dose.[138,151] However, the American Rescue Plan Act of 2021 provides funding for COVID-19 vaccines. Under Subtitle D—Public Health, mRNA-1273 should be available to adults in the United States at no direct cost.[131]

Key Stakeholder Perspectives

Between July 30 and August 30, 2021, nine stakeholders, reflecting allied health, clinical, health systems, and research perspectives, provided comments and ratings on mRNA-1273. The list below provides a summary of key stakeholder perspectives.

- The Moderna vaccine might substantially improve population health outcomes by preventing coronavirus infection or reducing case severity in some patients, resulting in decreased morbidity and mortality. The vaccine could also prevent the further spread of the SARS-CoV-2 virus.
- The vaccine might decrease the health care burden, staffing, and costs associated with treatment of COVID-19, freeing up health care resources for patients with other health problems.
- Because the Moderna vaccine does not require extreme refrigeration for 30 days once stock vials are thawed, transport to rural and underserved areas might be more feasible than with other COVID-19 mRNA vaccines. This improved access might help reduce disparities.
- Because the vaccine is free to the public, vaccination should not increase health disparities for underinsured or uninsured patients. The prophylactic effect of the vaccine will alleviate disparities for those who cannot afford hospital care associated with severe COVID-19 illness.

Pfizer-BioNTech COVID-19 Vaccine for Preventing Coronavirus Infection

Highlights

- The Pfizer-BioNTech vaccine is a messenger RNA (mRNA) vaccine intended to prevent COVID-19 by generating a protective immune response against the novel coronavirus, SARS-CoV-2.
- The Pfizer-BioNTech vaccine is being tested in phase 3 trials, with primary completion of the largest pivotal trial expected in May 2023.
- The FDA granted the Pfizer-BioNTech vaccine emergency use authorizations (EUA) for preventing COVID-19 in children aged 5 through 15 years. Full approval has been granted for individuals aged 16 years or older. The FDA also amended the original EUA to provide a third primary series dose for individuals aged 12 years or older who are immunocompromised and a single booster dose of the vaccine, named BNT162b2, for select individuals aged 18 years or older.
- Stakeholders commenting on this topic thought that the Pfizer-BioNTech vaccine might significantly improve population health outcomes by preventing infection with coronavirus, mitigating disease spread, and conferring immunity to much of the population.

Patient Population

BNT162b2 is FDA authorized for healthy children and adults aged 5 years or older. It is under investigation for healthy children younger than 5 years of age.

Intervention

The Pfizer-BioNTech vaccine (Pfizer, New York, New York, and BioNTech, Mainz, Germany) is a lipid nanoparticle–encapsulated mRNA vaccine intended to prevent COVID-19, the respiratory illness caused by infection with the novel coronavirus, SARS-CoV-2. The virus spreads through person-to-person contact via aerosolized droplets, and transmission can occur even from infected individuals who are asymptomatic.

Individuals with COVID-19 often present with symptoms ranging from mild to severe within 5 days after incubation. Severe disease—more common in individuals of advanced age or with certain preexisting conditions such as cancer, cardiovascular disease, chronic lung disease, diabetes, and hypertension[117]—can result in acute respiratory distress, hospitalization, or death.[152] Some individuals experience persistent symptoms and/or organ dysfunction for weeks or months after recovering from acute symptoms.[153] The Centers for Disease Control and Prevention website offers more information on COVID-19.

BNT162b2 mRNA encodes the viral spike protein, which is present on the virus's membrane and is required for viral entry into host cells, which causes infection.[154,155] The vaccine is manufactured by packaging this mRNA within lipid nanoparticles that deliver the mRNA more efficiently into host antigen-presenting cells (APCs).[154,155] Once inside, the mRNA purportedly induces APCs to manufacture the viral spike protein and display it on their cell membranes.[133] Recognition of this foreign protein by other immune cells elicits a host immune response that includes production of antibodies targeted against the virus, thus preventing future infection or limiting disease severity.[134] Once an immune response is triggered, host cells break down and eliminate the spike protein mRNA delivered by the vaccine.[135]

According to the FDA-authorized label, BNT162b2 is given intramuscularly in 2 doses of 0.3 mL each, given 3 weeks apart.[156] The EUA also provides for a third primary dose, given 28 days

after the second dose, for individuals aged 12 years or older who are immunocompromised, and a single booster dose, given at least 6 months after the second dose, for individuals aged 65 years or older or aged 18 to 64 years with high risk for complications of COVID-19.[157] Third doses are provided at the same 0.3 mL volume specified for the initial series.

Vaccine vials should be stored in an ultra-low-temperature freezer between –90 and –60 °C (–130 to –76 °F) until used or expired but could be stored at cold temperatures, –25 to –15 °C (–13 to 5 °F), for up to 2 weeks. Once they have reached room temperature, vials should be diluted and used within 2 hours.[156]

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 8 ongoing trials for this topic. In Table 4.8, we present 3 late-phase trials with greatest relevance to the approvals and authorizations for this vaccine (see section on Manufacturers and Regulatory Status). We excluded earlier-phase trials and those with smaller enrollments.

Table 4.8. Ongoing Clinical Trials

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
Study to Evaluate the Safety and Efficacy of a Booster Dose of BNT162b2 in Participants ≥16 Years of Age NCT04955626	Participants (n = 10 000) aged 16 years or older who are healthy and have received 2 prior doses of BNT162b2 in trial NCT04368728, with the second dose being at least 175 days before the booster dose	Phase 3, randomized, placebo-controlled, parallel-assignment, triple-blind study (participants, care providers, and investigators) evaluating the safety, tolerability, and efficacy of a booster dose (30 µg) of BNT162b2, administered to participants having previously received 2 doses of BNT162b2 at least 6 months before random assignment Primary end points: Confirmed COVID-19 incidence in participants with and without evidence of past SARS-CoV-2 infection and percentage of participants reporting adverse events Secondary end points: Confirmed severe COVID-19 and incidence of asymptomatic SARS-CoV-2 infection	Primary completion February 2022 Study completion August 2022

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
Study to Evaluate the Safety, Tolerability, and Immunogenicity of an RNA Vaccine Candidate Against COVID-19 in Healthy Children <12 Years of Age NCT04816643	Children (n = 4644) aged 6 months to 11 years who are healthy and not pregnant	Phase 1/2/3 study to evaluate the safety, efficacy and immunogenicity of BNT162b2 Phase 1 is an open-label, dose-finding study to evaluate the preferred dose level from 3 different dose levels (10, 20, and 30 µg). Phase 2/3 is a randomized, placebo-controlled, observer-blinded study of safety, tolerability, immunogenicity, and efficacy at the dose level selected from phase 1. Participants in both phases will receive 2 vaccine doses, 21 days apart. Primary end points: Percentage of participants reporting local reactions/adverse events, and geometric mean ratio of SARS-CoV-2 neutralizing titers in participants in each age group at selected dose level to those aged 16 to 25 years in study C4591001 Secondary end points: Geometric mean titers of SARS-CoV-2 serum neutralizing antibody titers and ratio of confirmed COVID-19 illness, in all age groups of phase 2/3 participants with and without evidence of prior SARS-CoV-2 infection for the active vaccine group to the placebo group	Primary completion March 2022 Study completion September 2023

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals NCT04368728	Patients (n = 43 998) aged 12 years or older who are healthy, not pregnant, and at risk for acquiring COVID-19	Phase 1/2/3, randomized, placebo-controlled, observer-blinded, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals Phase 1 is intended to identify a preferred vaccine candidate and dose levels; phase 2/3 is an efficacy and safety study of BNT162b2. In the phase 2/3 portion of the study, participants will be assigned in a 1:1 ratio to receive 2 doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (30 µg per dose). Primary end points: Confirmed COVID-19 in phase 2/3 participants with and without evidence of infection before vaccination, percentage of participants reporting adverse events, and local and systemic reactions Secondary end point: Confirmed COVID-19 or severe COVID-19 in phase 2/3 participants with and without evidence of infection before vaccination	Primary and study completion May 2023

Recently Completed and Ongoing Trials With Available Results

Our searches identified 2 recently completed late-phase trials with published results. We summarize the 2 most recent and indication-relevant studies with results as written in abstracts of 2 peer reviewed, published articles[158,159] and a news release.[160]

The following abbreviations are used in this section: CI, confidence interval; GMT, geometric mean titer.

Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals. NCT04368728. Polack et al, 2020,[158] and Frenck et al, 2021.[159]

- **Patient population/planned enrollment:** Patients (n = 43 548) aged 16 years or older and patients (n = 2260) aged 12 to 15 years. In both groups, patients were healthy, not pregnant, and at risk of acquiring COVID-19.
- **Study design:** Phase 2/3, randomized, placebo-controlled, observer-blinded, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals. Participants were assigned in a 1:1 ratio to receive 2 doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (30 µg per dose).
- **Primary outcomes:** Confirmed COVID-19 in phase 2/3 participants with and without evidence of infection before vaccination and percentage of participants reporting adverse events

- **Secondary outcome:** Confirmed severe COVID-19 in phase 2/3 participants without evidence of infection before vaccination
- **Results presented by study authors Polack et al:** "A total of 43,548 participants underwent randomization, of whom 43,448 received injections: 21,720 with BNT162b2 and 21,728 with placebo. There were 8 cases of Covid-19 with onset at least 7 days after the second dose among participants assigned to receive BNT162b2 and 162 cases among those assigned to placebo; BNT162b2 was 95% effective in preventing Covid-19 (95% credible interval, 90.3 to 97.6). Similar vaccine efficacy (generally 90 to 100%) was observed across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions. Among 10 cases of severe Covid-19 with onset after the first dose, 9 occurred in placebo recipients and 1 in a BNT162b2 recipient. The safety profile of BNT162b2 was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups."
- **Results presented by study authors Frenck et al:** "Overall, 2260 adolescents 12 to 15 years of age received injections; 1131 received BNT162b2, and 1129 received placebo. As has been found in other age groups, BNT162b2 had a favorable safety and side-effect profile, with mainly transient mild-to-moderate reactogenicity (predominantly injection-site pain [in 79 to 86% of participants], fatigue [in 60 to 66%], and headache [in 55 to 65%]); there were no vaccine-related serious adverse events and few overall severe adverse events. The geometric mean ratio of SARS-CoV-2 50% neutralizing titers after dose 2 in 12-to-15-year-old participants relative to 16-to-25-year-old participants was 1.76 (95% confidence interval [CI], 1.47 to 2.10), which met the noninferiority criterion of a lower boundary of the two-sided 95% confidence interval greater than 0.67 and indicated a greater response in the 12-to-15-year-old cohort. Among participants without evidence of previous SARS-CoV-2 infection, no Covid-19 cases with an onset of 7 or more days after dose 2 were noted among BNT162b2 recipients, and 16 cases occurred among placebo recipients. The observed vaccine efficacy was 100% (95% CI, 75.3 to 100)."

Study to Evaluate the Safety, Tolerability, and Immunogenicity of an RNA Vaccine Candidate Against COVID-19 in Healthy Children <12 Years of Age. NCT04816643. Pfizer, Inc, 2021.[160]

- **Patient population/planned enrollment:** Children (n = 4644) aged 6 months to 11 years who were healthy and not pregnant
- **Study design:** Phase 1/2/3 study to evaluate safety, efficacy, and immunogenicity of BNT162b2. Phase 1 is an open-label, dose-finding study to evaluate the preferred dose level from 3 different dose levels (10, 20, and 30 µg). Phase 2/3 is a randomized, placebo-controlled, observer-blinded study of safety, tolerability, immunogenicity, and efficacy at the dose level selected from phase 1. Participants in both phases received 2 vaccine doses, 21 days apart.
- **Primary outcomes:** Percentage of participants reporting local reactions/adverse events, and geometric mean ratio of SARS-CoV-2 neutralizing titers in participants in each age group at selected dose level to those aged 16 to 25 years in study C4591001
- **Secondary outcomes:** GMTs of SARS-CoV-2 serum neutralizing antibody titers and ratio of confirmed COVID-19 illness, in all age groups of phase 2/3 participants with and without evidence of prior SARS-CoV-2 infection, for the active vaccine group to the placebo group
- **Results presented by study authors:** "The data summarized from this Phase 2/3 study, which is enrolling children 6 months to 11 years of age, was for 2,268 participants who were 5 to 11 years of age and received a 10 µg dose level in a two-dose regimen. In the trial, the SARS-CoV-2–neutralizing antibody geometric mean titer (GMT) was 1,197.6 (95% confidence interval [CI, 1106.1, 1296.6]), demonstrating strong immune response in this cohort of children one month after the second dose. This compares well (was non-inferior) to the GMT of 1146.5 (95% CI:

1045.5, 1257.2) from participants ages 16 to 25 years old, used as the control group for this analysis and who were administered a two-dose regimen of 30 µg. Further, the COVID-19 vaccine was well tolerated, with side effects generally comparable to those observed in participants 16 to 25 years of age."

Manufacturers and Regulatory Status

BNT162b2 is being developed by Pfizer, Inc (New York, New York), and BioNTech SE (Mainz, Germany). On December 11, 2020, the FDA granted EUA for use of BNT162b2 in preventing COVID-19 in individuals aged 16 years or older.[161] On May 10, 2021, the EUA was expanded to include adolescents aged 12 to 15 years, based on favorable safety and efficacy data for this population from the ongoing phase 1/2/3 trials.[161]

On August 12, 2021, authorization was expanded, providing for a third primary dose of vaccine to individuals aged 12 years or older who are immunocompromised, to be given at least 28 days after the second dose.[157]

On August 23, 2021, the FDA granted BNT162b2 full approval for the prevention of COVID-19 disease in individuals aged 16 years and older.[162] The EUA was further expanded on October 29, 2021, to include children aged 5 to 11 years, based on ongoing trial data.[163]

On September 22, 2021, the FDA issued an amended EUA for BNT162b2 to allow for a booster dose of BNT162b2 for people aged 65 years or older and those aged 18 to 64 years at high risk of severe COVID-19 or serious complications due to frequent institutional or occupational exposure. The booster dose is to be given at least 6 months after completion of the primary series of 2 injections.[164] On October 20, 2021, the FDA authorized a heterologous (or mix-and-match) strategy for booster doses, allowing individuals initially receiving BNT162b2 to obtain a booster dose with either of the other 2 COVID-19 vaccines with the FDA EUA or approval.[122]

The phase 3 trial in 43 998 children and adults is ongoing at the time of this report's writing, with completed data expected in November 2021.[165] The manufacturer has also begun another phase 1/2/3 trial to evaluate the safety, tolerability, and immunogenicity of BNT162b2 in 4644 children aged 6 months to 11 years.[166] See Table 4.8 for further details about ongoing trials.

The vaccine's associated fact sheet for health care providers notes that reports of adverse events after use of BNT162b2 under EUA suggest increased risks of myocarditis and pericarditis, particularly after the second dose of the vaccine.[157] Symptom onset has typically been within a few days after vaccination. The fact sheet also provides warnings regarding potential for general reactions and adverse events associated with administration of BNT162b2, such as allergic reactions, including anaphylaxis, and hypersensitivity reactions (eg, localized swelling or pain, rash), and fainting.

Cost Information

Pfizer has reportedly charged the US government $19.50 per dose of BNT162b2 for the first 100 million doses.[138] However, the American Rescue Plan Act of 2021 provides funding for COVID-19 vaccines. Under Subtitle D—Public Health, BNT162b2 is available to residents in the United States at no direct cost.[131]

Key Stakeholder Perspectives

Between August 2 and August 30, 2021, ten stakeholders, reflecting clinical, health systems, nursing, research, and systems perspectives, provided comments and ratings on BNT162b2. The list below provides a summary of key stakeholder perspectives.

- An effective vaccine might greatly decrease the burden on the health care delivery system if severe morbidity and mortality are prevented, allowing for resources used for COVID-19 to

be reallocated to other health care needs. Cost burdens might also be lowered if the vaccine prevents inpatient stays and treatments associated with severe COVID-19.

- Because the vaccine is authorized for use in children, it might improve population health by slowing infections, hospitalizations, and death in a substantial portion of the population and by slowing development of new viral variants.
- By preventing the spread of COVID-19, the vaccine might allow for the safe reopening of community activities and increase protection for children as they resume school in person, reducing the social and economic impact of the pandemic.
- Stakeholders raised concern that the Pfizer-BioNTech vaccine's ultra-cold temperature storage requirements might contribute to health disparities in areas where the vaccine cannot be easily stored and administered. However, updated prescription information eases these requirements, permitting the vaccine to be stored temporarily at cold temperatures of a typical freezer, thus facilitating transport and storage.

Sabizabulin (VERU-111) to Treat COVID-19 at High Risk of Progressing to Acute Respiratory Distress Syndrome

Highlights

- Sabizabulin, also known as VERU-111, is a small-molecule alpha and beta (αβ) tubulin inhibitor or microtubule disruptor intended to treat adults hospitalized with COVID-19 who have underlying health conditions that place them at high risk of developing acute respiratory distress syndrome (ARDS).
- It purportedly treats COVID-19 through 2 mechanisms: by decreasing SARS-CoV-2 infectivity and reducing inflammation associated with the disease.
- Stakeholders commenting on this topic thought that phase 2 clinical trial data suggest sabizabulin has significant potential to improve patient health outcomes by reducing mortality and lengths of hospitalization and mechanical ventilation, although additional data in more patients are needed.
- Stakeholders also thought sabizabulin, if approved, has potential to reduce burden on the health care system and staffing and decrease COVID-19 treatment costs by reducing length of hospitalization, mechanical ventilation rates, and staff utilization.

Patient Population

Sabizabulin is intended for adults who are hospitalized with COVID-19 and are at high risk of progressing to ARDS.

Intervention

Sabizabulin, also known as VERU-111, is a small-molecule αβ tubulin inhibitor or microtubule disruptor. It is under study to treat patients hospitalized with COVID-19 who are at high risk of developing ARDS because of underlying health conditions (eg, diabetes, chronic kidney disease, severe obesity), are aged 65 years or older, or have an immunocompromised status.

Sabizabulin might treat COVID-19 by decreasing SARS-CoV-2 infectivity and reducing inflammation. The drug purportedly works by binding to colchicine-binding sites on αβ tubulin, the monomer components of microtubules (structures in the cytoskeleton, the cell's internal scaffolding). Incorporation of sabizabulin-bound tubulin into microtubules prevents microtubule elongation, thereby disrupting the function of the microtubule scaffold. The transport of the SARS-

CoV-2 virus along microtubules is thought to be critical for multiple steps in the viral life cycle, and microtubule disruption might inhibit production of additional virus.[167]

Microtubule disruption might also produce anti-inflammatory effects, because microtubules are thought to initiate leukocyte-mediated inflammatory processes (eg, the release of proinflammatory cytokines). Cytokines are thought to contribute to hyperinflammation in COVID-19, which is associated with increased disease severity and worse outcomes.[167]

In phase 3 clinical trials, sabizabulin is taken by mouth or given through a nasogastric tube at a dosage of 9 mg daily for up to 21 days or until discharge from the hospital.

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified a single ongoing trial for this topic. We present this trial in Table 4.9.

Table 4.9. Ongoing Clinical Trial

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
VERU-111 in the Treatment of SARS-Cov-2 Infection by Assessing Its Effect on the Proportion of Patients Who Die on Study (VERU-111) NCT04842747	Adults (n = 300) who are hospitalized with COVID-19, have low blood oxygen saturation, and have comorbidities or other known factors for being at high risk of developing ARDS (eg, asthma, chronic lung disease, diabetes mellitus, chronic kidney disease requiring dialysis, severe obesity [BMI ≥ 40 kg/m^2], aged 65 years or older, residence in a nursing home or long-term care facility, being immunocompromised)	Phase 3, randomized, double-blind, placebo-controlled study to assess the safety and efficacy of sabizabulin (VERU-111) taken by mouth or given in a nasogastric tube at a dosage of 9 mg daily for up to 21 days or until the patient is discharged from the hospital, in addition to standard-of-care treatment (limited to convalescent plasma, dexamethasone, and remdesivir) Primary outcome: Survival at day 60 Secondary outcomes: Survival without respiratory failure, days in intensive care unit, change in baseline on WHO Ordinal Scale for Clinical Improvement, days on mechanical ventilation, days hospitalized, and viral load	Primary completion January 2022 Study completion March 2022

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; kg/m^2, body weight in kilograms divided by height in meters squared; WHO, World Health Organization.

Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed late-phase trial with published results.[168] We summarize the study with results as written in a news release.

The following abbreviations are used in this section: ARDS, acute respiratory distress syndrome; BMI, body mass index; ICU, intensive care unit; kg/m^2, body weight in kilograms divided by height in meters squared; p, *P* value; WHO, World Health Organization.

COVID-19 Treatment of Severe Acute Respiratory Syndrome With Veru-111. NCT04388826. Veru, Inc, 2021.[168]

- **Patient population/planned enrollment:** Adults (n = 40) who were hospitalized with COVID-19, had low blood oxygen saturation, and had comorbidities or other known factors for being at high risk of developing ARDS, such as asthma, chronic lung disease, diabetes mellitus, chronic kidney disease requiring dialysis, severe obesity (BMI ≥ 40 kg/m^2), age older than 65 years, residence in a nursing home or long-term care facility, or being immunocompromised
- **Study design:** Phase 2, randomized, double-blinded, placebo-controlled study to assess the safety and efficacy of sabizabulin (VERU-111) taken by mouth or through a nasogastric tube at a dosage of 18 mg once daily for 21 days or until hospital discharge in addition to standard-of-care treatment (limited to convalescent plasma and remdesivir)
- **Primary outcome:** Survival without respiratory failure at day 29
- **Secondary outcomes:** WHO Ordinal Scale for Clinical Improvement, resolution of fever and low blood oxygen saturation, hospital discharge, and survival without respiratory failure at days 15 and 22
- **Results presented by study authors:** "For the primary endpoint in hospitalized patients that had > 1 dose of study drug, VERU-111 treatment compared to placebo had a statistically significant and clinically meaningful reduction in the proportion of patients who are treatment failures (dead or alive with respiratory failure) with a 30% treatment failure rate in the placebo group (n = 20) compared to a 5.6% in the VERU-111 treated group (n = 18) at Day 29. This represents an 81% relative reduction in treatment failures and showed statistical significance with p = 0.05.

  "Subgroup analyses of treatment failures (dead or alive with respiratory failure) in patients at high risk for ARDS:

  "Age: older patients, an analysis of > 60 years of age diagnosed with COVID-19 who are at higher risk for death and respiratory failure: Treatment failures were 9% for VERU-111 versus 50% for placebo; p = 0.046.

  "Severity of COVID-19, an analysis of patients with a WHO Score of Disease Severity ≥5 (hospitalized; on oxygen) at baseline: Treatment failures were 11% for VERU-111 versus 54% for placebo; p = 0.04.

  "Secondary Endpoints

  "In the Intent to Treat (ITT) population, VERU-111 reduced the proportion of patients who died on study from 30% (6/20) in the placebo group to 5.3% (1/19) in the VERU-111 treated group (p = 0.044). This is a 82% relative reduction in mortality in the VERU-111 treated group.

  "In patients that received > 1 dose of VERU-111 or placebo, VERU-111 showed a statistically significant and clinically meaningful reduction in days in ICU (VERU-111 patients at 3.00 ± 7.16 days versus placebo 9.55 ± 11.54; p=0.04). Additionally, the proportion of patients in the ICU for ≥ 3 days on study was significantly lower (VERU-111 at 28%, versus placebo, 60%; p = 0.046).

  "VERU-111 reduced the days on mechanical ventilation from an average of 5.4 days in the placebo group to 1.6 days in the VERU-111 treated group.

  "VERU-111 was tolerated with a good safety profile.

  "… The use of remdesivir and dexamethasone did not have a significant effect on patient outcomes in the study. A subgroup analysis of patients that received standard of care was conducted. There were eleven patients in the entire study that did not receive standard of care of either remdesivir or dexamethasone (six in the sabizabulin treated group and five in the placebo group). In patients that did not receive the standard of care, sabizabulin treatment

resulted in a statistically significant reduction in days in ICU (sabizabulin 0 days versus placebo 9.53 ± 12.56 days; p = 0.014) and days on mechanical ventilation (sabizabulin zero days versus placebo 3.93 ± 8.74 days). In the sabizabulin group on standard of care, no patient required ICU admission or mechanical ventilation on study."

Manufacturers and Regulatory Status

Sabizabulin to treat COVID-19 is being developed by Veru, Inc (Miami, Florida), and is in phase 3 clinical development.

Veru stated in February 2021 that it intended to seek funding from The Biomedical Advanced Research and Development Authority of the US Department of Health and Human Services and other agencies to meet commercial drug supply needs if sabizabulin demonstrates positive results and gains FDA approval.[168]

Cost Information

Cost information is currently unavailable for this topic.

Key Stakeholder Perspectives

Between August 9 and September 7, 2021, nine stakeholders, reflecting clinical, health systems, patient representative, and research perspectives, provided comments and ratings on sabizabulin to treat COVID-19 at high risk of progressing to ARDS. The list below provides a summary of key stakeholder perspectives.

- Available phase 2 clinical trial data suggest sabizabulin might significantly improve patient health outcomes by reducing hospitalization length, respiratory failure, time on mechanical ventilation, and mortality in patients at increased risk for progressing to ARDS. However, the study sample size was small, and additional data in more patients are needed to verify sabizabulin's antiviral, anti-inflammatory, and clinically significant effects and to determine its safety.
- If effective, sabizabulin is likely to impact health care delivery by freeing up hospital beds and mechanical ventilators and might reduce staffing shortages and demands.
- Sabizabulin might lower treatment costs by improving patient health outcomes and by reducing length of hospitalization, mechanical ventilation rates, and staff utilization.
- Given the ongoing COVID-19 pandemic, challenges due to the Delta variant, and shortage of intensive care unit beds and staffing, if approved, sabizabulin is likely to disrupt the health care system immediately.

Trend Summaries

We present below 7 summaries on trends deemed to have high potential for disruption.

Aerial Drones to Deliver COVID-19 Vaccines

Highlights

- Aerial drones are being investigated to deliver COVID-19 vaccines in a timely and efficient manner to locations lacking easy access to vaccine supply.
- The first COVID-19 vaccine drone delivery program in the United States was launched in August 2021 by Flight Forward, a subsidiary of United Parcel Service (UPS), intended to supplement ground delivery of messenger RNA (mRNA)-based COVID-19 vaccines.

- Drone companies are forming partnerships with firms that design specialized containers for ultra-cold storage and temperature monitoring to meet the ultra-cold storage requirements of some COVID-19 vaccines.
- Stakeholders commenting on this trend thought that, if drones could successfully deliver vaccines to rural areas and increase the proportion of vaccinated individuals, it might reduce disparities related to access to care, improve population health outcomes, and reduce long-term health care costs.
- Stakeholders also thought that disruption might be limited by the current widespread availability of vaccines in the United States and that this delivery method might be more widely adopted in other nations, in remote locations where access to health care is limited and infrastructure does not support routine ground transportation of medical supplies.

Description

Aerial drones are being investigated to deliver COVID-19 vaccines to locations lacking easy access to vaccine supply, potentially overcoming gaps in current vaccine delivery methods.[169] Technological advancements have allowed aerial drones to deliver medical supplies to remote areas, and this approach might be cheaper and faster than ground transportation or helicopters.[170]

The first COVID-19 vaccine drone delivery program in the United States was launched in August 2021 by Flight Forward, a subsidiary of UPS, intended to supplement ground delivery of mRNA-based COVID-19 vaccines to Atrium Health Wake Forest Baptist's family medicine practices in Winston-Salem, North Carolina.[171,172] Because some COVID-19 vaccines require ultra-cold storage, drone companies are forming partnerships with firms that design specialized containers for ultra-cold storage and temperature monitoring. For example, both Flight Forward and the Canada-based drone company Draganfly have collaborated with Cold Chain Technologies to ensure proper temperature control during shipment.[170,173,174] This technology could support highly specialized cold chain logistics.

The COVID-19 pandemic has also spurred innovative medical supply delivery companies to expand their existing networks. Zipline is a drone delivery company that has shipped lightweight medical supplies, including COVID-19 vaccines and blood for transfusion, in Rwanda and Ghana for years and is working with policymakers to expand delivery drones in the United States.[175] Air Methods, an air medical service provider in Greenwood Village, Colorado, in partnership with Wingcopter, a German drone manufacturer, recently announced the launch of Spright, a drone-based, health care–specific rapid-delivery network across the United States.[176-178] Air Methods is leveraging its existing infrastructure of more than 300 bases, serving hundreds of hospitals in predominantly rural areas, across 48 states. These efforts might provide faster, more flexible distribution of COVID-19 vaccines and other medical supplies.[169]

Clinical Area(s) Potentially Disrupted

Use of aerial drones to deliver COVID-19 vaccines might affect areas related to access to care, patient health outcomes, health care disparities, health care delivery systems, and costs.

Opportunities

The use of aerial drones to deliver COVID-19 vaccines might provide a rapid and flexible delivery option for remote areas, support the medical supply chain, and reduce disparities in access to vaccines. This method might be cost efficient compared with other types of air and ground transportation. Increased access to vaccines might improve vaccination rates and have a positive impact on population health.

Threats

Disparities in access might develop if drone delivery of vaccines to distant, difficult-to-reach locations is restricted because of operating ranges and weight limits. Additionally, weather conditions might delay this mode of vaccine delivery. Vaccine doses might be wasted if the drones are unable to keep the vaccines within a precise temperature range or if staffing resources and infrastructure are not available to receive, store, and administer the doses before expiration.

Key Stakeholder Perspectives

Between September 16 and September 17, 2021, eight stakeholders, reflecting clinician, health care generalist, health systems, and research perspectives, provided comments and ratings on this topic. The list below provides a summary of key stakeholder perspectives.

- Drone delivery of vaccines might reduce disparities in access to care by quickly and efficiently delivering vaccines to rural areas across the United States where health care resources are limited. However, this disruption might be limited by the current US vaccine surplus and other barriers to vaccine uptake such as vaccine hesitancy among a substantial portion of nonvaccinated individuals.
- If drones expand access to COVID-19 vaccines and increase the proportion of vaccinated individuals, population health outcomes might improve by preventing the spread of COVID-19 and reducing mortality rates.
- Using drones to deliver vaccines could increase up-front costs because of the need for technology and infrastructure to facilitate shipping and receiving. However, it might lower long-term costs by preventing vaccine wastage and reducing health care resource use.
- This delivery method might be more widely adopted outside of the United States, in remote locations where access to health care is more limited and infrastructure does not support routine ground transportation of medical supplies.
- Technical and logistical issues related to the use of drones might limit diffusion, including the varied quality, range, and operation of drones, as well as potentially lagging infrastructure to receive and administer the vaccine doses after delivery.

Digital COVID-19 Immunization Records for Work, School, or Travel

Highlights

- Several smartphone applications (apps) have been developed to maintain a digital record of people's vaccination status. These apps could facilitate return to work, school, and travel, while protecting other sensitive information.
- Private companies and state-run efforts have made these apps widely available to help the public maintain a digital record of their vaccination status to facilitate compliance with vaccine mandates.
- By linking vaccination records directly from the provider, some of these apps provide a verifiable source of vaccination status wherever required and allow users to verify their immunization status for third parties (eg, airlines, border services agents).
- Stakeholders commenting on this topic thought that digitized COVID-19 immunization records provide convenient portability of immunization status, which over the long term

could help prevent COVID-19 from spreading in the community, decrease health care costs, and help businesses return to normal.
- Stakeholders were concerned about data privacy and security of users' personal health information because of the potential for the data security measures of these apps to be compromised.

Description

COVID-19 vaccine mandates are increasingly being implemented for individuals who are traveling or returning to work or school, necessitating a means for these individuals to document their vaccination status.[179] Traditionally, vaccinated individuals are issued a written card that includes identifying information, the vaccine product they received, and when the next dose is due. Because paper vaccination cards can be easily damaged, lost, or falsified, private companies and state-run efforts have focused on digital systems that provide secure storage of immunization records to address these issues.[180,181]

For example, digital records of COVID-19 vaccination and testing status are being used for international travel across 27 European Union member nations.[182] Additional examples of digital records include the SMART Health Card for travel to Aruba[183] and ArriveCAN[184] for travel into Canada. In the United States, cell phone apps are available to help the public maintain a digital record of their vaccination status to facilitate compliance with mandates for return to work, school, and travel. Examples include the New York State Department of Health's Excelsior Pass,[185] California's Digital Covid-19 Vaccine Record,[186] and the Colorado State Department's myVaccineRecord, linked to the myColoradoapp,[187] previously used for digital driver's license records.

Some digital vaccination records obtain immunization data directly from the provider, which purportedly provides a verifiable source of vaccination status wherever required and allows users to verify their immunization status with third parties (eg, an airline or border services agent). Such verification might be facilitated through a platform such as CommonPass.[188] Moreover, digital vaccine records could use verifiable credentials aligned with Fast Healthcare Interoperability Resources standards, which might be compatible for uploading to these platforms.[189]

Clinical Area(s) Potentially Disrupted

Digital COVID-19 immunization records might create health care disparities for those who are not technologically savvy or do not use smartphones. They might improve patient and population health outcomes by streamlining vaccination status management for work, school, or travel.

Opportunities

Digital COVID-19 immunization records might improve adherence to public health guidance and reopening procedures. Compliance with public health guidelines could limit the spread of COVID-19. Because paper vaccine cards are easier to falsify, digital apps might provide people with verifiable and convenient immunization credentials.

Threats

Digital COVID-19 immunization records might create socioeconomic disparities by permitting only people with an immunity advantage to return to work, school, and travel. It might also raise privacy concerns about sharing and storing protected health information. Technical problems while using these apps and incompatibility between different platforms for data storage might raise concerns.

Key Stakeholder Perspectives

Between August 10 and August 19, 2021, nine stakeholders, reflecting clinical, health systems, nursing, and research perspectives, provided comments and ratings on this topic. The list below provides a summary of key stakeholder perspectives.

- Smartphone applications that keep a digital record of vaccination status might provide convenient access and sharing of verifiable vaccination records. If effective, this could open up opportunities to use digital health records for other purposes.
- These apps could increase ethnic and socioeconomic disparities for individuals who lack access to a smartphone or who are unwilling to get the COVID-19 vaccine for personal reasons.
- Concerns exist regarding the ways in which these digital systems maintain data privacy. Some tools allow users to simply scan a photo of their vaccination card or use a QR code with a name and driver's license, which could be misused.
- Even with a verifiable credentialing system that allows individuals to manage their health information and control what they share, apps might not permit clinical data sharing because of obstacles involving electronic health record data integration across platforms.

Mobile Health Clinics to Increase Access to COVID-19 Health Services

Highlights

- Mobile health clinics—customized motor vehicles that travel to communities to provide health care—might help meet shortages in COVID-19 health services, including access to testing, vaccinations, and health screenings.
- These vehicles are outfitted with basic medical examination room equipment, COVID-19 test kits, and COVID-19 vaccines and provide space where staff can perform multiple tests per day and/or administer vaccines.
- Ease of movement and setup of mobile health clinics might improve implementation of testing and vaccination initiatives in scattered or harder-to-reach populations.
- Stakeholders commenting on this topic thought that mobile health clinics might benefit rural areas where health facilities are lacking.
- Stakeholders also thought that the use of mobile clinics depends on the availability of health care workers to staff these units, insurance reimbursements, and funding to run the clinics.

Description

As the COVID-19 pandemic continues, many underserved and rural communities in the United States still face challenges surrounding access to testing and vaccination. An estimated 2000 mobile clinics (customized motor vehicles that travel to communities to provide health care) are active and may be able to help meet needs for COVID-19 health services.[190]

In addition to the existing mobile clinic infrastructure, various companies are offering mobile clinics. For example, Aardvark Mobile Tours, LLC (Conshohocken, Pennsylvania), offers mobile health trucks that are equipped with both positive and negative air pressure and the ability to be Certified Laboratory Improvement Amendments of 1988 certified up to biosafety level 2.[191] The vehicles can be used for rapid testing, vaccinations, and health screenings. The trucks offer a self-contained space with air conditioning and heating that takes 15 minutes to set up. The easily sterilized areas and partitions, which separate the nurses conducting the tests from the individuals

receiving them, help maintain safety.[191] Two to 4 testing windows allow nurses to administer up to 400 tests a day, similar to drive-through testing facilities, which can be inaccessible to people who rely on public transportation. The company supplies an experienced driver, maintenance, insurance, logistics management, and a program manager so the clients can maintain focus on delivering care.[191]

Additionally, a mobile vaccination clinic in North Carolina expanded its vaccination efforts to include farmworkers who do not reside in that state.[192] Other pilot programs (eg, Curbside Care) have also begun vaccinating eligible individuals in mobile clinics in rural parts of Michigan.[193]

Clinical Area(s) Potentially Disrupted

By focusing on prevention and providing accessible care, mobile health clinics could improve patient health outcomes and reduce the costs associated with emergency care visits. Resistance to unconventional medical care settings might influence uptake and increase disparities in underserved areas. Making health services more accessible via mobile vans and buses might help boost the economy by reducing missed workdays and the associated lost wages and promoting a return to normalcy.

Opportunities

Mobile health clinics might increase access to COVID-19 testing in underserved areas and rural communities experiencing outbreaks in infections, which would improve patient and population health outcomes while reducing disparities. These clinics might lead to faster implementation of testing initiatives in outbreak areas and rural communities, which would inform future public health guidelines.

Threats

Although the mobile health clinics would benefit harder-to-reach populations, they might lead to long wait times if the mobile testing/vaccination site is overwhelmed.

Key Stakeholder Perspectives

Between August 20 and September 13, 2021, six stakeholders, reflecting health systems and research perspectives, provided comments and ratings on this topic. The list below provides a summary of key stakeholder perspectives.

- Direct-to-consumer services such as mobile health clinics might add convenience and reduce disparities for underserved populations that might not have access to care because of transportation barriers or other factors.
- Mobile health clinics might increase access to COVID-19 health services such as testing and administering vaccines; however, the usability of mobile clinics depends on the availability of health care workers to staff these units.
- Mobile health clinics might help control the spread of COVID-19 by helping patients with their COVID-specific needs; however, operational costs and issues with insurance reimbursement might impact the ability of these clinics to provide care.
- These mobile health centers might be able to supplement the shortfalls of the health care system during the COVID-19 pandemic; however, low acceptance and use of these services could reduce their potential for disruption.

Post-COVID-19 Recovery Programs

Highlights

- Multidisciplinary clinical rehabilitation programs might help facilitate patient recovery from the long-term effects of COVID-19.
- Several hospitals across the country are setting up post-COVID-19 recovery programs to accommodate the growing need for continued care in patients experiencing postacute sequelae of SARS-CoV-2 infection.
- Some programs provide recovery from specific side effects (eg, neurological effects); other programs have multidisciplinary teams of primary care physicians, pulmonologists, neurologists, mental health professionals, and other health care practitioners.
- Stakeholders commenting on this topic thought that these recovery programs, if conducted correctly, might improve patient outcomes and provide data for better managing the growing cases of patients experiencing long-term effects from COVID-19.
- Stakeholders expressed concern that these recovery programs might not be covered by insurance, which might increase financial burden on those patients with long-term effects.

Description

Some individuals who have recovered from COVID-19 have an increased risk of long-term health problems because of damage to their lungs, heart, kidneys, and/or brain that persists beyond the time of acute infection.[194-197] Even with no detectable damage to these organs, some patients still report lingering and debilitating symptoms months after clearing the infection. A recent study suggested that 37% of individuals with confirmed COVID-19 had at least one long COVID symptom in the 3- to 6-month period after infection.[198] The National Institutes of Health has launched an initiative to study postacute sequelae of SARS-CoV-2 infection.[199]

Many hospitals across the United States have set up post-COVID-19 recovery programs to accommodate the growing need for continued care in patients experiencing long-term side effects from COVID-19.[200-202] Ongoing post-COVID-19 medical, psychological, and rehabilitation programs might help ensure more patients experience a full recovery from COVID-19.

Patients who have cleared the viral infection but are still experiencing symptoms can go to postinfection programs with or without a referral, where they will be screened to identify their clinical needs and establish a therapeutic plan. The programs consist of multidisciplinary teams of primary care physicians; pulmonologists; neurologists; mental health professionals; physical, occupational, and speech therapists; and other health care practitioners. Some recovery programs address specific areas, such as neurological effects, long-term symptoms in pediatric populations, or respiratory recovery.[203-205] Some programs have implemented new therapeutic approaches to accommodate the precautions needed to minimize the risk of viral spread, such as negative-pressure rooms for patients in need of inpatient rehabilitation and isolation as well as therapy through telemedicine.[206]

Clinical Area(s) Potentially Disrupted

Since these post-COVID recovery programs need a multidisciplinary clinical team to deliver care in an integrated, efficient manner, they are likely to disrupt the process of care delivery. These programs might improve health outcomes for a large patient population impacted by lingering symptoms of COVID-19, including children and adults, and they might reduce caregiver burden and costs associated with lost wages and repeated clinic visits for patients.

Opportunities

Post-COVID-19 recovery programs might improve management of long-term sequelae from COVID-19 while increasing knowledge about the long-term effects of COVID-19.

Threats

These programs might increase health care costs, including out-of-pocket costs to patients if clinic visits are not covered by insurance. Patients might face long wait times due to the lack of recovery programs and high levels of demand for these services.

Key Stakeholder Perspectives

Between September 10 and September 15, 2021, five stakeholders, reflecting clinical engineering, health care generalist, health systems, nursing, and research perspectives, provided comments and ratings on this topic. The list below provides a summary of key stakeholder perspectives.

- Post-COVID-19 recovery programs might improve health outcomes and quality of life for patients who continue to have persistent symptoms after the main course of COVID-19.
- Insurance coverage might not be available for patients with postacute sequelae of COVID-19, which could significantly increase health care costs for patients.
- Health care disparities might be reduced if the multidisciplinary recovery programs help manage various postacute symptoms in a large proportion of the population; however, disparities might increase because of poor access to these services.
- Patients who do not respond to post-COVID treatments will challenge providers who are still learning about effective patient management strategies for post-COVID patients.
- Although full recovery from COVID-19 is an important goal for those who have had the disease, the large number of post-COVID patients with ongoing health care needs might strain the health system and disrupt the health care needs of non-COVID patients.

Reinstatement of Mask Mandates to Prevent COVID-19

Highlights

- Mask mandates have been reinstated in various states and localities following the rise in infections and hospitalizations attributable to the emergence of the Delta variant, as well as the relaxation of public health measures intended to curb viral transmission.
- Although many state governments are in favor of reinstating these mandates, some state governments are opposing or banning the introduction of mask mandates, particularly for certain settings, such as schools.
- Stakeholders commenting on this trend thought that reinstatement of mask mandates might have a substantial impact on reducing COVID-19 transmission and allow businesses to stay open, if surges of COVID-19 cases are prevented or lessened.
- Stakeholders were concerned that mask mandates that require vaccinated individuals to wear masks might deter some unvaccinated individuals from getting vaccinated.

Description

Mask mandates are a public health intervention that could periodically be implemented in response to increasing COVID-19 case numbers. For example, many states and localities reinstated mask mandates during the rise in COVID-19 cases in the United States in the summer of 2021.[207]

Real-world studies have found that masking can reduce the emission of virus-laden droplets, resulting in a decreased risk of transmission and infection. For example, a study of a COVID-19 outbreak aboard the US Navy ship USS *Theodore Roosevelt* found that masking reduced the risk of acquiring infection by more than 70%.[208] The Centers for Disease Control and Prevention currently recommends the use of multilayer cloth masks for unvaccinated people in public settings and requires masks for all people while on public transportation. Although fully vaccinated people are not required to wear masks, it is still recommended that they do so in indoor public places in areas of high transmission because of the possibility of breakthrough infections and transmission of the virus by vaccinated individuals.[207,209]

Because of a resurgence of cases, many states have made masking a requirement or recommendation. States such as Illinois and Nevada have mandated that all individuals are required to wear a mask in indoor public places, regardless of vaccination status. Other states, such as New York and California, are recommending that vaccinated people wear masks in indoor settings but are requiring it for unvaccinated individuals.[207] Conversely, some states, such as Arizona, Florida, and Texas, have banned the implementation of mask mandates in places like schools.[210]

Clinical Area(s) Potentially Disrupted

Reinstatement of mask mandates is likely to disrupt health care costs and health outcomes. Masking in public, regardless of vaccination status, might significantly impact patient and population health outcomes if the intervention can prevent COVID-19 transmission and infection.

Opportunities

Mask mandates might help increase protection against COVID-19 for individuals in public areas. In particular, highly vulnerable populations, such as people with compromised immune systems or individuals who are unvaccinated, might benefit from reimplementation of mask mandates. Additionally, reduction of viral spread by widespread mask use could lead to a reduction in death rates and the health care costs associated with treating COVID-19. Instead of having to shut down stores, mask mandates might allow businesses to continue more normal operations in areas that are experiencing high levels of infections.

Threats

Reimplementation of mask mandates after their discontinuation might increase societal distrust or resentment of public health officials and measures. Additionally, some individuals may choose to remain unvaccinated if they must still wear a mask irrespective of vaccination status. The mandates might also trigger political backlash that could exacerbate societal distrust if state or local governments are debating the validity of the mandates or deeming them unlawful.

Key Stakeholder Perspectives

Between August 2 and August 30, 2021, fourteen stakeholders, reflecting clinical, clinical engineering, health care generalist, health systems, patient/patient representative, and research perspectives, provided comments and ratings on this trend. The list below provides a summary of key stakeholder perspectives.

- Because many vaccinated individuals who end up contracting COVID-19 are asymptomatic, reinstating mask mandates might help reduce the asymptomatic or presymptomatic transmission of COVID-19 and impact community health outcomes in a positive way.
- Mask mandates, if effective, might decrease the number of people hospitalized with severe COVID-19 and needing access to care, which might ease the burden on the health care delivery system and impact staffing, costs, and availability of health care resources.

- Although mask mandates might not stop the COVID-19 pandemic, they might be an effective tool to decrease the spread of COVID-19; however, the public might first need to be reeducated on the proper use of masks and how to obtain the correct type of masks.
- The general population might not comply with new mask mandates, and reinstatement of mandates might increase distrust in public health guidance regarding masking or other public health issues because the mandates had previously been established and then lifted.
- Mask mandates might discourage those who do not want to wear masks again from spending time in public places, which could affect economic growth for those areas and thus individuals' quality of life.

Surveillance Programs to Identify and Follow the Spread of Emerging SARS-CoV-2 Variants

Highlights

- Multiple genetic variants of SARS-CoV-2 with higher transmissibility have been identified including variants first identified in the United Kingdom (Alpha), South Africa (Beta), Brazil (Gamma), and India (Delta).
- The variants appear to be more transmissible compared with the previously dominant variant, which might lead to an increase in infections and subsequent COVID-19-related deaths. Concerns remain that these or future variants might compromise COVID-19 vaccine efficacy.
- The Centers for Disease Control and Prevention (CDC) is working with clinical and national laboratories, state and local health departments, and genomic sequencing companies to expand the national surveillance infrastructure for detecting and tracking new variants.
- Stakeholders commenting on this topic thought that surveillance programs for emerging variants might help prevent their spread, thus improving population health, reducing health care costs, and decreasing hospitalizations. They might also help predict the performance of diagnostics, treatments, and vaccines.
- Stakeholders also thought that surveillance programs might not be established before novel variants spread, and their usefulness might be limited in communities with a low uptake of preventive measures.

Description

In December 2020, 4 genetic variants of SARS-CoV-2 with higher transmissibility were identified. The variants arose in the United Kingdom (Alpha), South Africa (Beta), Brazil (Gamma), and India (Delta).[211-214] They have subsequently been detected in countries around the world. The higher transmissibility of these variants, as opposed to the previously dominant coronavirus strain, has contributed to more hospitalizations and an increase in COVID-19-related deaths.[213,215-217] Moreover, some variants are more likely to cause breakthrough infections in vaccinated individuals or reinfections in those who have recovered from COVID-19. For instance, variants Beta, Gamma, and Delta have accumulated mutations in a region of the spike protein that serves as a key target for neutralizing antibodies.[212,214,218]

Surveillance programs are needed to support public health responses to these emerging variants. This will require expanded testing and genomic sequencing to identify where the variants are starting to spread, followed by contact tracing and quarantine programs to decrease transmission.[213,216] With support from the CDC, genomic sequencing companies Illumina (San

Diego, California) and Helix (San Mateo, California) will expand the national surveillance infrastructure to track the emergence and prevalence of new variants.[219] The CDC has also formed partnerships with clinical laboratories, national laboratories, state and local health departments, and universities to ramp up sequencing-based surveillance and contact tracing.[213,216]

As of October 2021, the CDC considered only Delta to be a variant of concern.[220] Alpha, Beta, and Gamma have been downgraded to variants being monitored because their prevalence has decreased substantially. However, the CDC expects that these variants, and any other emerging variants, could still threaten public health.[220,221]

Clinical Area(s) Potentially Disrupted

Surveillance programs might anticipate the emergence of variants that are more transmissible than are previous SARS-CoV-2 strains. This has the potential to improve clinician and/or caregiver safety by preventing health systems from becoming overburdened. These programs might also improve patient and population health outcomes because early detection of emerging coronavirus strains might help suppress their spread.[216] Surveillance programs use sequencing methods that are very costly. Unless they have government funding, these programs might be very expensive for companies to maintain and might cause disparities in regions without adequate resources.

Opportunities

The pandemic has put pressure on health care facilities, caused financial hardship, and increased anxiety for patients, providers, and policy makers. The emergence of variants that are more transmissible compared with previous SARS-CoV-2 strains might cause even more burden. Early detection of emerging coronavirus strains in communities might help suppress their spread.[216] Working side by side with public health campaigns, surveillance programs can identify variant outbreaks and direct efforts in surrounding communities to contain the spread of variants.[216,222] Of particular concern is the potential for the emergence of variants that can evade vaccine- or infection-induced immunity.[222] If such variants are identified, mitigation strategies might trigger lockdowns and broader restrictions to contain the spread of these variants and provide data relevant to the production of variant-specific vaccines.

Threats

Surveillance programs might have difficulty detecting and predicting the spread of highly transmissible variants. If variants such as Alpha, Beta, Gamma, and Delta spread rapidly and are responsible for most COVID-19 cases, surveillance programs are unlikely to help suppress their spread.[220,221] Because of their high cost and limited access, surveillance programs might be unavailable in remote rural communities.

Key Stakeholder Perspectives

Between September 13 and September 17, 2021, five stakeholders, reflecting health care generalist, health systems, and research perspectives, provided comments and ratings on this trend. The list below provides a summary of key stakeholder perspectives.

- Surveillance programs might provide officials with data to direct the creation of new public health guidelines that can be applied to prevent the spread of more-infectious variants, which might improve population health, decrease hospitalizations, and reduce health care costs. Additionally, the programs might help make resources more available and make health care more accessible for patients with COVID-19.

- The identification of new mutations can help predict the performance and reliability of diagnostics, treatments, and vaccines. Additionally, stakeholders thought that knowing the sequence of variant spike proteins could help develop new vaccine boosters.
- The success of these programs relies on having reporting systems that share information at a national level among the CDC, its partners, and health officials. However, well-structured systems might not be established before novel variants arise.
- The usefulness of surveillance programs might be limited in communities with a low uptake of preventive measures such as vaccinations, mask wearing, social distancing, and contact tracing.

Vaccines to Prevent COVID-19 in Children Younger Than 12 Years

Highlights

- The Moderna and Pfizer-BioNTech vaccines, authorized or approved by the FDA to prevent COVID-19 in older individuals, are under investigation for use in children younger than 12 years of age.
- The vaccines might be an important preventive that could reduce infection spread and complications among children and their families. The availability of vaccines to children might be of substantial importance considering the increased potential for SARS-CoV-2 transmission and infection caused by circulating variants and the return of children to in-person schooling.
- Both the Moderna and Pfizer-BioNTech vaccines are in phase 3 trials. Data on the Pfizer-BioNTech vaccine in children aged 5 to 11 years have been submitted to the FDA as the manufacturers seek emergency use authorization (EUA). An FDA decision on this application was expected before the end of 2021.
- Stakeholders commenting on the trend generally agreed that vaccinations for children younger than 12 years could improve health outcomes for both children and the community. Stakeholders had concerns about whether the public perception that the full side effect profile of the vaccines in children was not yet known could limit vaccine uptake.

Description

COVID-19 vaccines that have been granted EUA or approved by the FDA are authorized or approved for use only in adults and children older than 12 years of age, leaving a significant portion of the population without a vaccine option. Moderna and Pfizer-BioNTech, makers of FDA-authorized or approved messenger RNA (mRNA) vaccines for COVID-19, are investigating the safety and effectiveness of these products in children younger than 12 years.

The Pfizer-BioNTech vaccine is currently in a phase 2/3 trial in children aged 6 months or older at a range of doses (3, 10, 20, and 30 µg).[223] In September 2021, Pfizer and BioNTech announced that the vaccine elicited robust neutralizing antibody levels in participants aged 5 to 11 years and had side effects similar to those observed in teens and young adults.[160] Based on these results, the companies have applied to the FDA for EUA in this patient population.[224]

The Moderna vaccine is in a phase 2/3 trial in 13 275 children aged 6 months to younger than 12 years and intended to determine the safety and efficacy of 100 µg of its mRNA-1273 vaccine.[223] Moderna expects to have partial trial data by the end of 2021 and, at that time, planned to seek EUA from the FDA for use of its vaccine in children between the ages of 6 years and 11 years.[225]

Based on input from the FDA, both companies had expanded the size of their studies to include at least 3000 children in the 5- to 11-year-old group, to improve the studies' ability to detect rare

side effects in this population. This includes side effects such as heart inflammation, which had been found to occur, albeit at low frequency, in people younger than 30 years receiving mRNA vaccines.[226]

Clinical Area(s) Potentially Disrupted

COVID-19 vaccines for children could disrupt patient and population health outcomes as children go back to school and group activities. Considering the large number of children who would be eligible for vaccination, the process of vaccine administration might affect health care costs. Conversely, increasing the proportion of individuals who have immunity to COVID-19 could lead to reduced costs associated with treating COVID-19 cases. Although vaccines are free for everyone, health disparities might increase for people who are unable to travel to receive them or lack convenient access to vaccination centers.

Opportunities

Vaccines to prevent COVID-19 in children might reduce the incidence of illness, severe illness, and death related to COVID-19, especially in high-risk populations. The vaccines might also improve population health outcomes by reducing the spread of COVID-19 in schools and the community, particularly by young individuals who remain asymptomatic. Reduction of COVID-19 spread might also facilitate a return to social and economic normality. Because variants are more likely to arise in unvaccinated populations, vaccinating children who are younger than 12 years might also reduce the likelihood that newer, more infectious or virulent strains of SARS-CoV-2 will emerge.

Threats

Because of the accelerated approval process, COVID-19 vaccines for children might lead to some adverse events being undetected in the more select population. Because many children infected with SARS-CoV-2 develop only mild COVID-19 symptoms, the risk of adverse events associated with the COVID-19 vaccines could outweigh their benefits in this population.

Key Stakeholder Perspectives

Between August 30 and September 7, 2021, nine stakeholders, reflecting caregiver, clinical, health care generalist, health systems, nursing/physician assistant, and research perspectives, provided comments and ratings on this trend. The list below provides a summary of key stakeholder perspectives.

- COVID-19 vaccines for children younger than 12 years might be important in protecting children as well as their families and other adults with whom they have contact against COVID-19, resulting in fewer individuals getting sick and slowing community spread.
- Many of the concerns that have limited vaccine uptake in currently eligible individuals will likely extend to children younger than 12, because parents might choose not to have their children vaccinated, lowering the uptake and disruptive potential of the vaccines.
- Having children vaccinated might allow less-stringent mitigation efforts at schools, easing anxiety for parents and staff and allowing more focus to be put on education.
- COVID-19 vaccines for children might also ease the burden on the health care system if the vaccines protect recipients against developing severe disease, resulting in fewer hospitalizations and lower health care costs.
- Health disparities could be increased if children from disadvantaged populations have difficulty accessing vaccination sites or if parents are unable to take their children to get vaccinated because of economic hardships associated with taking time off work to do so.

Chapter 5. Mental and Behavioral Health Conditions

For the mental and behavioral health conditions focus area, we considered for inclusion 4 topics for which (1) preliminary phase 3 data for drugs, phase 2 (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled and sent for stakeholder comment before September 3, 2021; *and* (3) we received at least 5 sets of comments and ratings from stakeholders between September 18, 2020, and September 17, 2021.

As of September 3, 2021, we were monitoring 16 topics in this focus area, including the 4 considered for inclusion in this report. These 16 topics are available—or will soon be available—for viewing on the PCORI Horizon Scanning Database website.

The 16 monitored topics encompass pharmaceuticals, devices, and mobile health interventions intended to treat 9 mental and behavioral health conditions. Of these, 12 topics are too early in development to meet the criteria (as outlined above) for eligibility for this report.

Topics Considered for Inclusion in This Report

Table 5.1 lists 2 topics selected for inclusion in this report based on stakeholder ratings and comments and available data. Topics are listed and discussed alphabetically by title.

Table 5.1. Included Topics for Focus Area: Mental and Behavioral Health Conditions

Topic title
MDMA (3,4-Methylenedioxymethamphetamine)-assisted psychotherapy to treat severe posttraumatic stress disorder
Ulotaront (SEP-363856) to treat schizophrenia

Table 5.2 lists 2 topics considered but not selected for inclusion in this report, based on stakeholder ratings and comments and available data. Each record notes the reasons for exclusion.

Table 5.2. Topics Considered but Not Included for Focus Area: Mental and Behavioral Health Conditions

Topic title	Exclusion reason(s) and notes based on stakeholder comments
Zuranolone (SAGE-217) to treat major depressive disorder	The rates of side effects and need for retreatment with zuranolone in clinical trials suggest zuranolone might be incremental for treating major depressive disorder compared with current antidepressants. As an oral drug, its use would not significantly impact current health care delivery or staffing for the treatment of this condition. Zuranolone is likely to be expensive and cost prohibitive to many patients, and its disruption potential is likely to remain small until it is available as a generic drug.
Zuranolone (SAGE-217) to treat postpartum depression	Zuranolone might positively impact patient health for patients' postpartum depression if it is safer and more convenient to use compared with brexanolone; however, more efficacy data are needed to determine its disruptive potential. Currently, discerning the clinical significance of the trial findings and the drug's long-term effects is difficult.

Trends Considered for Inclusion in This Report

For the mental and behavioral health conditions focus area, we considered for inclusion 3 trends for which (1) information was compiled and sent for stakeholder comment before September 3, 2021; *and* (2) we received at least 5 sets of comments and ratings from stakeholders between September 18, 2020, and September 17, 2021. These 3 trends are available—or will soon be available—for viewing on the PCORI Horizon Scanning Database website.

Table 5.3 lists 2 trends selected for inclusion in this report based on stakeholder ratings and comments and available data. Trends are listed and discussed alphabetically by title.

Table 5.3. Included Trends for Focus Area: Mental and Behavioral Health Conditions

Trend title
Mobile crisis-response teams to aid in mental health crises[a]
Psychedelic drugs to treat mental health conditions

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

Table 5.4 lists one trend considered but not selected for inclusion in this report, based on stakeholder ratings and comments and available data. Each record notes the reasons for exclusion.

Table 5.4. Trend Considered but Not Included for Focus Area: Mental and Behavioral Health Conditions

Trend title	Exclusion reason(s) and notes based on stakeholder comments
Artificial intelligence to predict antidepressant treatment response	Using AI is unlikely to become standard of care when choosing antidepressant treatment because of the following: implementing AI-electroencephalogram data widely would require significant infrastructure and staffing changes, it could worsen health outcomes if wait times for this evaluation result in delays in starting treatment, and a number of patients respond to pharmacotherapy as currently prescribed. More data are needed to determine this trend's future potential impact, including whether AI can predict treatment response to other antidepressants and whether it could help predict likelihood of treatment adverse effects.

Abbreviation: AI, artificial intelligence.

Topic Summaries

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

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

Highlights

- MDMA is an oral psychoactive drug being explored for use with psychotherapy to treat patients who have posttraumatic stress disorder (PTSD).
- MDMA is given before an extended psychotherapy session followed by an overnight stay in a clinic. Sessions are conducted by therapists specially trained to establish a therapeutic relationship with patients and increase 2-way communication during the session.
- Stakeholders commenting on this topic thought available data indicated that MDMA-assisted psychotherapy has potential to be a faster acting and more effective treatment for

severe PTSD compared with standard psychotherapy with or without selective serotonin reuptake inhibitor medications. This might improve patient outcomes and decrease long-term treatment costs.

- Stakeholders also thought MDMA-assisted psychotherapy would disrupt the current paradigm of PTSD care, given that treatment requires 8-hour therapy sessions and overnight monitoring.
- Stakeholders identified several potential barriers in access to care: unavailability of treatment in underserved or geographically isolated areas, inability of patients to attend the long sessions and overnight stays, and the potentially high cost of treatment.

Patient Population

This treatment is intended for adults who meet diagnostic criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, for severe PTSD and who have had at least one unsuccessful attempt at either talk therapy or drug treatment.

Intervention

MDMA-assisted psychotherapy is being investigated to treat PTSD, a psychological disorder that can develop after a person experiences or witnesses a traumatic event. PTSD symptoms often include flashbacks, cognitive and mood changes (eg, difficulty concentrating, depression), hyperarousal (eg, feeling on edge, difficulty sleeping), and avoiding experiences that trigger traumatic memories. The National Institutes of Health's National Institute of Mental Health website offers more information on PTSD.

Psychotherapy is the standard of care for treating PTSD but can take months to years to produce effects, and the distress caused by discussing traumatic memories is often uncomfortable for patients and might cause them to avoid seeking help. MDMA is a psychedelic drug that increases availability of monoamine neurotransmitters in the brain and is intended to enhance the tolerability and effectiveness of psychotherapy to treat PTSD. It might work by temporarily altering brain activity associated with emotional memory processing, reducing distress caused by revisiting traumatic memories, increasing empathy and self-compassion, and facilitating extinction of fear responses.[227] MDMA's effects are purportedly mediated mostly through release of the neurotransmitter serotonin,[228] although MDMA also increases levels of other neurotransmitters, such as dopamine and norepinephrine, and the hormones cortisol and oxytocin.[229]

In clinical trials, MDMA is taken by mouth before an 8-hour psychotherapy session at an initial dose of 80 or 120 mg followed by a supplemental half-dose of 40 or 60 mg taken 1.5 to 2 hours later if necessary, totaling 80 to 180 mg per session. Patients undergo 3 sessions, each 1 month apart. Each session is conducted by 2 specially trained therapists who encourage the patient to recall traumatic events with the goal of the patient reexperiencing the intense thoughts and feelings that arise.[230] Patients are monitored overnight at the treatment site and meet with their therapists the next day for a 90-minute follow-up therapy session for further emotional reprocessing.[231]

Evidence Development Summary

Ongoing Trials

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

Table 5.5. Ongoing Clinical Trial

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
A Multi-site Phase 3 Study of MDMA-Assisted Psychotherapy for PTSD (MAPP2) NCT04077437	Adults (n = 100) who meet *DSM-V* criteria for severe PTSD	Phase 3, randomized, double-blind, parallel-assignment trial assessing the efficacy and safety of MDMA-assisted manualized psychotherapy vs manualized psychotherapy with placebo for 3 monthly psychotherapy sessions Primary end point: Clinician-administered PTSD scale (CAPS-5) Secondary end point: Clinician-rated functional impairment disability scale	Primary completion December 2022

Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for *DSM-5*; *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; MDMA, 3,4-methylenedioxymethamphetamine; PTSD, posttraumatic stress disorder.

Recently Completed and Ongoing Trials With Available Results

Our searches identified 8 recently completed late-phase trials. Data from 6 of these trials (NCT01793610, NCT01689740, NCT01211405, NCT01958593, NCT00353938, NCT00090064) were published in 2 pooled analyses, one reporting on results of initial treatment and one reporting on longer-term follow-up.[227,231] Data from 3 of those trials (NCT01793610, NCT01211405, NCT01958593) were published in another pooled analysis.[232] We summarize results from the 4 most recent studies as reported in the peer reviewed, published articles. For brevity, we excluded a completed phase 2, open-label trial (NCT03282123).

The following abbreviations are used in this section: BDI-II, Beck Depression Inventory-II (revised); CAPS-IV, Clinician-Administered PTSD Scale for *DSM-IV*; CAPS-5, Clinician-Administered PTSD Scale for *DSM-5*; CI, confidence interval; *d*, Cohen *d*; *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; *DSM-IV-R*, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, revised; *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; LS, least squares; LTFU, long-term follow-up; MDMA, 3,4-methylenedioxymethamphetamine; MMRM, mixed model for repeated measures; *P* or *p*, *P* value; PTG, posttraumatic growth; PTSD, posttraumatic stress disorder; QT, ventricular depolarization interval from the start of the QRS complex to the end of the T wave; s.d., standard deviation; SDS, Sheehan Disability Scale; SE, standard error.

A Multi-site Phase 3 Study of MDMA-Assisted Psychotherapy for PTSD (MAPP1). NCT03537014. Mitchell et al, 2021.[228]

- **Patient population/planned enrollment:** Adults (n = 100) who meet *DSM-5* criteria for severe PTSD
- **Study design:** Phase 3, randomized, double-blind, parallel-assignment trial assessing the efficacy and safety of MDMA-assisted manualized psychotherapy vs manualized psychotherapy with placebo for 3 monthly psychotherapy sessions. MDMA was dosed 80 to 120 mg at the beginning of an experimental session and was followed 1.5 to 2 hours later with a supplemental dose of 40 or 60 mg.
- **Primary outcomes:** Clinician-administered PTSD scale and CAPS-5
- **Secondary outcome:** Clinician-rated functional impairment disability scale

- **Results presented by study authors:** "MDMA was found to induce significant and robust attenuation in CAPS-5 score compared with placebo ($P < 0.0001$, $d = 0.91$) and to significantly decrease the SDS total score ($P = 0.0116$, $d = 0.43$). The mean change in CAPS-5 scores in participants completing treatment was −24.4 (s.d. 11.6) in the MDMA group and −13.9 (s.d. 11.5) in the placebo group. MDMA did not induce adverse events of abuse potential, suicidality or QT prolongation."

MDMA-Assisted Psychotherapy for Treatment of PTSD. NCT01793610, NCT01689740, NCT01211405, NCT01958593, NCT00353938, NCT00090064. Mithoefer et al, 2019.[231]

- **Patient population/planned enrollment:** Adults (n = 103) who met criteria on the *DSM-IV* for chronic, moderate to severe PTSD; scored at least 50 on the CAPS-IV; and had at least one unsuccessful treatment attempt at or inability to tolerate treatment for PTSD with either talk therapy or drugs
- **Study design:** Six randomized, double-blind, controlled, phase 2 clinical trials at 5 study sites were conducted from April 2004 to February 2017. Active doses of MDMA (75 to 125 mg; n = 72) or placebo or controlled doses (0 to 40 mg; n = 31) were given to individuals with PTSD during manualized psychotherapy sessions consisting of two to three 8-hour sessions spaced 1 month apart. Three nondrug 90-minute therapy sessions preceded the first MDMA exposure, and 3 to 4 followed each experimental session.
- **Primary outcome:** PTSD symptoms (CAPS-IV scores)
- **Secondary outcomes:** Depression symptoms and severity, psychological distress, and quality of life
- **Results presented by study authors:** "After two blinded experimental sessions, the active group had significantly greater reductions in CAPS-IV total scores from baseline than the control group [MMRM estimated mean difference (SE) between groups − 22.0 (5.17), $P < 0.001$]. The between-group Cohen's d effect size was 0.8, indicating a large treatment effect. After two experimental sessions, more participants in the active group (54.2%) did not meet CAPS-IV PTSD diagnostic criteria than the control group (22.6%). Depression symptom improvement on the BDI-II was greatest for the active group compared to the control group, although only trended towards significant group differences [MMRM, estimated mean difference (SE) between groups − 6.0 (3.03), $P = 0.053$]. All doses of MDMA were well tolerated, with some expected reactions occurring at greater frequency for the active MDMA group during experimental sessions and the 7 days following."

Long-Term Follow-up Outcomes of MDMA-Assisted Psychotherapy for Treatment of PTSD: A Longitudinal Pooled Analysis of Six Phase 2 Trials. NCT01793610, NCT01689740, NCT01211405, NCT01958593, NCT00353938, NCT00090064. Jerome et al, 2020.[227]

- **Patient population/planned enrollment:** Adults (n = 105) aged 18 years or older who met criteria on the *DSM-IV* for chronic, moderate to severe PTSD; scored at least 50 on the CAPS-IV; and had at least one unsuccessful treatment attempt at or inability to tolerate treatment for PTSD with either talk therapy or drugs
- **Study design:** Six randomized, double-blind, controlled, phase 2 clinical trials investigated long-term change in PTSD symptoms and additional benefits and harms after MDMA-assisted psychotherapy to treat PTSD. Participants were randomly assigned to either active-group doses of 75, 100, or 125 mg or control-group doses of 25, 30, or 40 mg or placebo at the beginning of 8-hour therapy sessions. An optional supplemental dose of MDMA was given 1.5 to 2.5 hours

after the initial dose. Three nondrug therapy sessions followed the experimental sessions. Control participants received MDMA during an open-label crossover phase.
- **Primary outcome:** PTSD symptoms (CAPS-IV scores)
- **Secondary outcomes:** Suicidal ideation and behavior, relapse of PTSD symptoms, current treatment, and substance use
- **Results presented by study authors:** "There was a significant reduction in CAPS-IV total severity scores from baseline to treatment exit (LS mean (SE) = − 44.8 (2.82), $p < .0001$), with a Cohen's *d* effect size of 1.58 (95% CI = 1.24, 1.91). CAPS-IV scores continued to decrease from treatment exit to LTFU (LS mean (SE) = − 5.2 (2.29), $p < .05$), with a Cohen's *d* effect size of 0.23 (95% CI = 0.04, 0.43). The number of participants who no longer met PTSD criteria increased from treatment exit (56.0%) to LTFU (67.0%). The majority of participants reported benefits, including improved relationships and well-being, and a minority reported harms from study participation."

Posttraumatic Growth After MDMA-assisted Psychotherapy for Posttraumatic Stress Disorder. NCT01793610, NCT01211405, NCT01958593. Gorman et al, 2020.[232]

- **Patient population/planned enrollment:** Adults (n = 60) aged 18 years or older who met criteria on the *DSM-IV-R* for chronic, moderate to severe PTSD; scored higher than 50 on the CAPS-IV; and had at least one unsuccessful treatment attempt at or inability to tolerate treatments for PTSD with psychotherapy and/or drugs
- **Study design:** Three randomized, triple-blind, crossover phase 2 clinical trials investigated 3 different active doses of MDMA to treat PTSD: 75, 100, and 125 mg compared with active control doses of 30 or 40 mg or placebo. Participants were randomly assigned to receive 8 hours of manualized psychotherapy in 2 experimental sessions spaced 3 to 5 weeks apart. An optional supplemental dose of MDMA (equal to half the initial dose) was given 1.5 to 2.5 hours after the initial dose. Three nondrug therapy sessions followed the experimental sessions.
- **Primary outcomes:** PTG and PTSD symptoms
- **Results presented by study authors:** "At primary endpoint, the MDMA group demonstrated more PTG, Hedges' $g = 1.14$, 95% CI [0.49, 1.78], $p < .001$;and a larger reduction in PTSD symptom severity, Hedges' $g = 0.88$, 95% CI [−0.28, 1.50], $p < .001$, relative to the control group. Relative to baseline, at the 12-month follow-up, within-subject PTG was higher, $p < .001$; PTSD symptom severity scores were lower, $p < .001$; and two-thirds of participants (67.2%) no longer met criteria for PTSD. MDMA-assisted psychotherapy for PTSD resulted in PTG and clinical symptom reductions of large-magnitude effect sizes. Results suggest that PTG may provide a new mechanism of action warranting further study."

Manufacturers and Regulatory Status

MDMA-assisted psychotherapy is being investigated by the Multidisciplinary Association for Psychedelic Studies (MAPS; Santa Cruz, California) in phase 3 trials for treating severe PTSD in adults. MAPS announced in May 2021 that MDMA-assisted psychotherapy might be approved by the FDA in 2023, although it did not specify a date for submitting a new drug application (NDA) to the FDA.[233] The FDA granted breakthrough therapy designation to MDMA-assisted psychotherapy for severe PTSD in August 2017.[234]

After MDMA was designated a Schedule I controlled substance in 1985, the developer, MAPS, filed a drug master file application in 1986, followed by an investigational NDA in 2001 for the use of MDMA in combination with psychotherapy.[231]

Cost Information

Cost information is currently unavailable for this topic.

Key Stakeholder Perspectives

Between July 29 and August 29, 2021, ten stakeholders, reflecting allied health, clinical, nursing, patient, and research perspectives, provided comments and ratings on MDMA-assisted psychotherapy to treat PTSD. The list below provides a summary of key stakeholder perspectives.

- Clinical trial data suggest MDMA-assisted psychotherapy might significantly improve patient outcomes and quality of life by relieving PTSD symptoms sooner and more effectively compared with current treatments.
- MDMA-assisted psychotherapy will likely change the current paradigm of care as a unique therapy requiring 8-hour sessions and overnight monitoring, and the therapy will require significant staffing changes to accommodate its delivery (ie, the hiring of additional therapists, nurses, and psychiatrists).
- Access to this intervention might be limited in underresourced and geographically isolated communities by the inability of patients to attend 8-hour sessions and overnight monitoring because of work or home constraints or the cost of treatment. All of these factors might increase health disparities among patients with PTSD.
- MDMA-assisted psychotherapy is likely to be costly up front, especially if reimbursement systems for mental health services do not cover the treatment. However, it might have long-term cost-effectiveness if it works well and results in more durable treatment of PTSD symptoms compared with current treatments.
- Its stigma as a recreational, Schedule I drug (drug with high risk for abuse) might prevent some patients from trying MDMA-assisted psychotherapy to treat their PTSD. But many patients will welcome a new treatment to gain relief from severe PTSD symptoms.

Ulotaront (SEP-363856) to Treat Schizophrenia

Highlights

- Ulotaront, formerly known as SEP-36385, is a novel oral antipsychotic drug intended to treat schizophrenia without blocking dopamine receptors in the brain.
- Standard-of-care antipsychotic drug treatment for schizophrenia affects patients' quality of life and overall health because it can have substantial side effects that can lead to poor medication adherence and outcomes.
- Stakeholders commenting on this topic thought that because it has fewer side effects, ulotaront might significantly improve patient health outcomes and quality of life.
- Stakeholders thought ulotaront might lower long-term costs of patient care, considering that its more favorable side effect profile might improve medication adherence and reduce use of costly health care resources to treat uncontrolled symptoms.

Patient Population

Ulotaront is intended to treat adolescents and adults, aged 13 to 65 years, who have schizophrenia.

Intervention

Schizophrenia is a chronic mental disorder characterized by cognitive, behavioral, and emotional dysfunction that causes significant functional impairment. Patients with schizophrenia

report that undesirable effects from available antipsychotic medications—such as tremors, restlessness, difficulty sleeping, dizziness, sexual side effects, and weight gain—negatively affect their daily activities and quality of life.[235] These negative side effects are a main reason patients stop taking their medication, and nonadherence with recommended antipsychotic medication dosing reportedly occurs in 50% to 75% of patients.[236,237] The National Institutes of Health's National Institute of Mental Health website offers more information about schizophrenia.

Ulotaront is an oral medication intended to treat both positive symptoms (eg, hallucinations, delusions) and negative symptoms (eg, loss of emotion) of schizophrenia, with fewer side effects compared with dopamine-blocking medications. It works differently from available antipsychotics because it does not block the D_2 dopamine or serotonin 2A receptors. The exact way ulotaront produces its antipsychotic effect is unknown, but it is believed to activate trace amine–associated receptor 1 and serotonin 1A receptors.[238] Ulotaront has not been found to cause tremors, involuntary muscle contractions, restlessness, or weight gain.[239]

In clinical trials, ulotaront is taken by mouth at a dosage of 25, 50, 75, or 100 mg once daily.

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 4 ongoing trials for this topic. We present these trials in Table 5.6.

Table 5.6. Ongoing Clinical Trials

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
A Clinical Trial to Study the Efficacy and Safety of an Investigational Drug in Acutely Psychotic People With Schizophrenia (DIAMOND 1) **NCT04072354**	Adolescents and adults (n = 525) aged 13 to 65 years who meet *DSM-5* criteria for schizophrenia	Phase 3, double-blind, randomized, 3-arm, placebo-controlled study to assess the efficacy and safety of 2 doses of SEP-363856, either 50 or 75 mg, taken orally once daily, vs placebo over a period of 6 weeks Primary outcome: Change in schizophrenia symptoms (positive and negative) from baseline Secondary outcome: Change in CGI-S score from baseline	Primary and study completion September 2021
A Clinical Trial That Will Study the Efficacy and Safety of an Investigational Drug in Acutely Psychotic People With Schizophrenia (DIAMOND 2) NCT04092686	Adults (n = 462) aged up to 65 years who meet *DSM-5* criteria for schizophrenia	Phase 3, multiregional, double-blind, parallel-group, long-term trial to assess the safety and tolerability of once-daily SEP-363856 (75 or 100 mg) compared with placebo for 6 weeks Primary outcomes: Change in schizophrenia symptoms (positive and negative) and severity, and adverse events Secondary outcome: Time to relapse	Primary completion October 2021

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
A Study of the Long-term Safety and Tolerability of an Investigational Drug in People With Schizophrenia (DIAMOND 4) NCT04115319	Adults (n = 300) aged 18 to 65 years who meet *DSM-5* criteria for schizophrenia	Phase 3, multiregional, randomized, double-blind, parallel-group, long-term trial to assess the safety and tolerability of once-daily SEP-363856 Patients will be randomly assigned in a 2:1 ratio to receive SEP-363856 (50, 75, or 100 mg/day) or quetiapine XR (400, 600, or 800 mg/day) for 52 weeks. Primary outcome: Adverse events Secondary outcome: Time to relapse	Primary completion March 2022
A Clinical Study to Evaluate the Long-term Safety and Tolerability of an Investigational Drug in People With Schizophrenia (DIAMOND 3) NCT04109950	Adolescents and adults (n = 555) aged 13 to 65 years who meet *DSM-5* criteria for schizophrenia and have completed DIAMOND 1 or DIAMOND 2 trials	Phase 3, multiregional, open-label, long-term trial to assess the safety and tolerability of once-daily SEP-363856 Patients will receive SEP-363856 (25, 50, 75, or 100 mg) for 52 weeks Primary outcome: Adverse events Secondary outcome: Time to relapse	Primary completion November 2022

Abbreviations: CGI-S, Clinical Global Impressions–severity scale; *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; SEP-363856, ulotaront; XR, extended release.

Recently Completed and Ongoing Trials With Available Results

Our searches identified 2 recently completed late-phase trials with published results. We summarize results from these 2 most recent studies as reported in the abstracts of 2 peer reviewed, published articles.[240,241]

The following abbreviations are used in this section: AE or Ae, adverse event; AIMS, Abnormal Involuntary Movement Scale; BNSS, Brief Negative Symptom Scale; CGI-S, Clinical Global Impressions–severity scale; DB, double-blind; *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; LDL, low-density lipoprotein; msec, millisecond; OL, open-label; P, *P* value; PANSS, Positive and Negative Syndrome Scale; QTcF, Fridericia corrected QT interval; SAE, serious adverse event; SAS, Simpson-Angus Scale; SEP-363856, ulotaront.

An Extension Study of Safety and Tolerability of SEP-363856 in Adult Subjects With Schizophrenia. NCT02970929. Correll et al, 2021.[241]

- **Patient population/planned enrollment:** Adults aged 18 to 40 years (n = 157) meeting *DSM-V* criteria for schizophrenia who completed the 4-week double-blind treatment phase of study SEP361-201
- **Study design:** Phase 2, multiregional, open-label extension study to assess the safety and tolerability of once-daily SEP-363856 (25, 50, or 75 mg) for 26 weeks
- **Primary outcome:** AEs
- **Secondary outcomes:** Change in schizophrenia symptoms (positive and negative) and severity, change in depression symptoms and severity, and time to relapse
- **Results presented by study authors:** "A total of 193 patients completed the 4-week DB study, and 156 (80.8%) were dosed in the OL extension study and received at least one dose of SEP-363856 (safety population). Study completer rate was 66.9%; reasons for discontinuation consisted of adverse event (11.5%), withdrawal of consent (10.2%), lack of efficacy (5.1%), and other (6.4%). 15 patients experienced an SAE: schizophrenia (n = 11); acute psychosis (N = 1);

uterine hemorrhage and suicidal ideation (N = 1 each); there were no deaths in the study. Individual AEs with an incidence = 2% were schizophrenia (12.2%), headache (11.5%), insomnia (8.3%), anxiety (5.1%), somnolence (4.5%), nasopharyngitis (4.5%), nausea (3.8%), irritability (3.2%), influenza (3.2%), weight decreased (3.2%), and prolactin increased (2.6%). On movement scales, minimal mean change from OL-baseline to Week 26 occurred on the Barnes total score (−0.1), AIMS total score (0.0) and SAS score (−0.1). Mean month 6 change from DB baseline in weight was −0.3 kg. No clinically meaningful median changes were observed at week 26 in metabolic laboratory parameters (total and LDL cholesterol, triglycerides, hemoglobin A1c) or in prolactin levels. During 6 months of OL treatment, one patient had an increase in QTcF = 60 msec; no patients had a QTcF interval = 480 msec. Treatment with SEP−363856 was associated with significant improvement from OL baseline to week 26 in PANSS total score (−22.6) and BNSS total score (−11.3)."

A Study to Evaluate the Efficacy and Safety of SEP-363856 in Acutely Psychotic Adults With Schizophrenia (SEP361-201). NCT02969382. Koblan et al, 2020.[240]

- **Patient population/planned enrollment:** Hospitalized adults aged 18 to 40 years (n = 245) meeting *DSM-5* criteria for schizophrenia and experiencing acute exacerbation of psychotic symptoms
- **Study design:** Randomized, double-blind, parallel-group, multicenter phase 2 trial comparing the efficacy and safety of flexibly dosed SEP-363856 (50 or 75 mg/day) with placebo
- **Primary outcome:** Change in schizophrenia symptom severity (positive and negative symptoms), using PANSS
- **Secondary outcomes:** Change in depression symptom severity and incidence of AEs
- **Results presented by study authors:** "A total of 120 patients were assigned to the SEP-363856 group and 125 to the placebo group. The mean total score on the PANSS at baseline was 101.4 in the SEP-363856 group and 99.7 in the placebo group, and the mean change at week 4 was −17.2 points and −9.7 points, respectively (least-squares mean difference, −7.5 points; 95% confidence interval, −11.9 to −3.0; P = 0.001). The reductions in the CGI-S and BNSS scores at week 4 were generally in the same direction as those for the primary outcome, but the results were not adjusted for multiple comparisons. Adverse events with SEP-363856 included somnolence and gastrointestinal symptoms; one sudden cardiac death occurred in the SEP-363856 group. The incidence of extrapyramidal symptoms and changes in the levels of lipids, glycated hemoglobin, and prolactin were similar in the trial groups."

Manufacturers and Regulatory Status

Ulotaront is being developed by Sunovion (Marlborough, Massachusetts), a subsidiary of Sumitomo Dainippon Pharma (Osaka, Japan), in collaboration with Otsuka Pharmaceutical Co, Ltd (Tokyo, Japan). It is in phase 3 clinical development. In May 2019, the FDA granted breakthrough therapy designation for SEP-363856 to treat patients with schizophrenia.[242]

Cost Information

Cost information is currently unavailable for this topic.

Key Stakeholder Perspectives

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

- Ulotaront appears effective at improving schizophrenia symptoms, although the magnitude of these effects might be similar to that of current standard-of-care therapies.
- Ulotaront might improve patient health and quality of life by causing fewer side effects (eg, weight gain, movement disorders) compared with standard-of-care therapies.
- A more favorable side effect profile with ulotaront might result in more patients able to take medication to treat schizophrenia, better medication adherence once treatment is initiated, and less use of costly health care resources for uncontrolled symptoms (eg, emergency department visits or hospitalization for acute exacerbations). Results from longer-term studies would validate the developer's preliminary findings and determine ulotaront's duration of effects and cost-effectiveness.

Trend Summaries

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

Mobile Crisis-Response Teams to Aid in Mental Health Crises

Highlights

- Mobile crisis-response teams, consisting of a combination of specially trained mental health workers and emergency medical first responders, respond to mental health crisis calls to deescalate crises and facilitate patient access to appropriate mental health care resources.
- An increase in the number of mobile crisis-response team programs has been observed nationwide in the midst of increased funding for mobile crisis-intervention services and movement toward designating a 3-digit telephone number for mental health emergencies nationwide.
- Stakeholders commenting on this trend thought mobile crisis-response teams have significant potential to improve access to care and health outcomes for individuals experiencing mental health crises compared with current models using law enforcement as the first responders.
- Stakeholders also thought additional mobile crisis-response teams are likely to form, especially in urban areas, given the reported success of existing teams in improving health and community outcomes and saving costs and given the current availability of funding incentives for establishing such teams.

Description

Mobile crisis-response teams, consisting of a combination of specially trained mental health workers, emergency medical technicians (EMTs), and paramedics, are intended to respond to mental health crisis calls to deescalate mental health crises and facilitate patient access to mental health care resources.

Longstanding teams, such as CAHOOTS (Crisis Assistance Helping Out On The Streets),[243] founded in Eugene, Oregon, in 1989, are being joined by an increasing number of new teams nationwide, including STAR (Support Team Assisted Response),[244] founded in Denver, Colorado, in 2020, and upcoming teams in Chicago, Illinois,[245] and Oakland, California.[246]

A database of police-involved shootings maintained by *The Washington Post* indicates that more than 1 in 5 people fatally shot by police officers had "a history of mental health issues, expressed suicidal intentions or was experiencing mental distress at the time of the shooting."[247]

Additionally, a study by the Treatment Advocacy Center suggests people with untreated severe mental illness are 16 times as likely as civilians to be killed during encounters with police.[248] Potential benefits of mobile crisis-response teams include more effective deescalation of mental health crises, reduced risk of fatalities, the facilitation of patient access to appropriate mental health care, and time and cost savings for police departments.[249]

Recent federal initiatives, such as designating the 3-digit phone number 988 for mental health emergencies[250] and increased federal funding for crisis services, including mobile crisis-intervention services,[251] are expected to increase the formation, access, and use of more mobile crisis-response teams nationwide.

Clinical Area(s) Potentially Disrupted

Implementing mobile crisis-response teams to aid in mental health crises might cause a paradigm shift in mental health crisis intervention such that mental health workers and medical personnel responding instead of law enforcement might shift the care setting away from emergency departments and hospitalizations and toward more specific mental health care settings. This trend might affect patient health outcomes, population outcomes, and health disparities. Costs, staffing, and infrastructure might be disrupted in both the short term, to implement the teams, and in the long term, because of the teams' implementation.

Opportunities

Mobile crisis-response teams might improve individual patient health outcomes by deescalating mental health crises more effectively compared with law enforcement intervention, improving patient access to timely and appropriate mental health care, and decreasing the risk of physical injury during crisis intervention. The teams might reduce outcome disparities for individuals facing disproportionate deaths from encounters with law enforcement, such as those with untreated mental health conditions.[247]

Mobile crisis-response teams might reduce the burden on law enforcement, emergency departments, and hospitals, therefore freeing up these resources to address crime and other medical emergencies, and thus potentially improving community safety and population health. During the ongoing COVID-19 pandemic, the teams might help reduce community SARS-CoV-2 transmission by limiting the volume of patients in emergency departments.

Cost savings might result from reducing emergency department visits and hospitalizations, eliminating delays in patient access to mental health care, and decreasing burden on law enforcement.

Threats

Mobile crisis-response teams could lead to physical harm to mental health care workers, EMTs, paramedics, and/or civilian bystanders if law enforcement is not engaged during calls that would necessitate police involvement or in instances in which tensions quickly escalate.

Some communities might have more resources to dedicate to forming mobile crisis-response teams, thus potentially causing mental health care disparities between communities.

Dedicating crisis-response mental health workers and medical responders to work on mobile crisis-response teams might put a strain on local outpatient behavioral health and emergency medical services staffing and services.

Key Stakeholder Perspectives

Between July 13 and July 23, 2021, seven stakeholders, reflecting health care generalist, nursing, and research perspectives, provided comments and ratings on this trend. The list below provides a summary of key stakeholder perspectives.

- By shifting mental health crisis intervention from law enforcement to mental health specialists and medical first responders, mobile crisis-response teams are likely to improve patient health outcomes significantly. The teams might better diffuse mental health crises, encourage more individuals to call for help (especially if there is hesitancy to have law enforcement involved), ensure that individuals get appropriate mental health care and resources, and decrease incarceration and/or physical harm because of escalated encounters with law enforcement.
- Mobile crisis-response teams also have substantial potential to benefit first responders and patient family members and friends. They might keep first responders safer and afford them more time to focus on other job duties (eg, crime, other medical emergencies), and they might provide support and assistance to family members and friends. Additionally, the community at large could benefit from improved safety and community development by allocating first responder resources more efficiently and generating cost savings.
- More communities are likely to implement similar crisis-response teams because existing mobile crisis-response teams have reported improved individual health and community outcomes and cost savings. Existing teams might serve as scalable models for new teams to adopt, and there are currently funding incentives for establishing them.
- Heavily populated urban areas are more likely to implement mobile crisis-response teams, which might increase health disparities for individuals in more rural areas, which are already experiencing a shortage of mental health resources.
- Implementing mobile crisis-response teams could shift mental health personnel away from traditional settings (eg, behavioral health clinics, physician offices), potentially reducing outpatient mental health care resources.

Psychedelic Drugs to Treat Mental Health Conditions

Highlights

- Psychedelic drugs (ie, psychedelics) are being investigated as a novel drug class to treat a variety of mental health conditions, including depression and anxiety disorders.
- Psychedelics are thought to work by altering mood states, changing perception, and facilitating life-altering perspectives.
- Various psychedelics are being studied in clinical trials (including late-phase trials) in pursuit of FDA approval.
- Stakeholders commenting on this trend thought that psychedelics could improve patient health outcomes, especially for those who have found other treatments to be ineffective, and that they might play an important role in mitigating the prevalence of mental health conditions in the United States.
- Stakeholders also thought that psychedelics might significantly impact health care delivery because of changes needed in infrastructure, staffing, and training to facilitate their clinical use.

Description

Psychedelic drugs (eg, psilocybin, lysergic acid diethylamide [LSD], N,N-dimethyltryptamine [DMT], 3,4-methylenedioxymethamphetamine [MDMA], ketamine) alter one's state of consciousness, purportedly by altering certain neurotransmitters in the brain. Their use might provide a patient with altered perception, increased introspection, feelings of closeness with others, and positive mood states. These experiences are often reported as deeply profound and life altering.

Although most psychedelics are designated as Schedule I drugs in the United States, researchers are investigating their potential to treat a variety of mental and behavioral health disorders that have not responded to conventional treatments. Multiple psychedelics to treat mental health conditions are in clinical trials and might diffuse clinically in the United States in the next 2 to 3 years.

Psilocybin is in clinical trials to investigate treatment for depression, anorexia nervosa, obsessive-compulsive disorder, alcohol use disorder, nicotine dependence, cocaine use disorder, and cancer-related anxiety.[252-257] LSD is being explored to treat anxiety associated with life-threatening illness, other anxiety disorders, and depression.[258-260] DMT, a drug present in a psychoactive brew called ayahuasca, is being researched to treat depression.[261,262] MDMA is in phase 3 clinical trials for use during psychotherapy to treat posttraumatic stress disorder (PTSD) and is being investigated as therapy for social anxiety in adults with autism.[263,264]

Ketamine, although not traditionally considered a psychedelic drug, has some psychedelic properties and is being explored off-label to treat PTSD.[265] A closely related molecule, esketamine (Spravato), is FDA approved to treat depression.[266]

In clinical trials, patients are given psychedelics and monitored under medical supervision.

Clinical Area(s) Potentially Disrupted

The use of psychedelics for treating mental health conditions could disrupt treatment models for practitioners of psychiatry and other mental health disciplines. The use of these drugs requires a learning curve; different approaches to prescribing, administering, and monitoring their effects; and changes in the duration and setting of psychotherapy and counseling sessions.

Opportunities

Psychedelics, as a novel approach to treat mental health conditions, might improve patient health outcomes and quality of life by providing new and quicker mechanisms for emotional and cognitive reframing compared with traditional drug treatments and psychotherapy. Psychedelics might be an important additional treatment as demand for mental health care grows in the wake of the COVID-19 pandemic.[267,268]

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

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

Threats

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

Disparities in access to care might increase if clinicians hesitate to prescribe psychedelics (for reasons such as stigma), making the treatment option less readily available to those who might benefit. Disparities might also increase for patients with underlying psychiatric illnesses (eg, schizophrenia, bipolar disorder), who are generally advised not to take psychedelics because of increased risk of negative adverse events (eg, acute psychosis, exacerbation of underlying illness).

Psychedelic treatment could be costly in the short term to build the infrastructure needed to deliver the treatments (eg, areas for patient monitoring, increased clinician training).

Key Stakeholder Perspectives

Between September 13 and September 15, 2021, six stakeholders, reflecting clinical, clinical engineering, health care generalist, health systems, and research perspectives, provided comments and ratings on this trend. The list below summarizes stakeholder perspectives.

- Psychedelics are promising alternatives to conventional treatments for mental health conditions, especially for patients who have hard-to-treat conditions or have not had success with conventional treatments (eg, patients with PTSD or treatment-resistant depression). They could play an instrumental role in mitigating the opioid epidemic and growing mental health concerns in the United States.
- Psychedelics are likely to disrupt current mental health care delivery in many ways; they will require additional security for their storage, a care setting that enables patient monitoring for many hours, longer therapy sessions for both providers and patients, and additional staff and training for their use.
- Patient access to psychedelic treatment is likely to be limited by the factors listed above, patient proximity to treatment facilities and ability to travel, and an already existing shortage of mental health providers. Reduced access for some patients might result in increased health disparities among patients with mental health conditions.
- The initial cost of treatment is likely to be higher for psychedelics than for conventional treatments because of the likely high cost of the drugs, patients needing longer appointment times, and facility and staffing changes to accommodate treatment administration. These factors increasing costs could be outweighed by achieving better treatment success, compared with conventional treatments, in less time and in fewer sessions.

Chapter 6. Rare Diseases

For the rare diseases focus area, we considered for inclusion 15 topics for which (1) preliminary phase 3 data for drugs, phase 2 (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled and sent for stakeholder comment before September 3, 2021; *and* (3) we received at least 5 sets of comments and ratings from stakeholders between September 18, 2020, and September 17, 2021.

As of September 3, 2021, we were monitoring 138 topics in this focus area, including the 15 considered for inclusion in this report. These 138 topics are available—or will soon be available—for viewing on the PCORI Horizon Scanning Database website.

These 138 monitored topics encompass pharmaceuticals, gene and cellular therapies, monoclonal antibodies, viral vector therapies, RNA interference therapies, surgical procedures, and implantable devices intended to treat or prevent 91 rare diseases and/or related conditions. Fourteen topics were developed as topic profiles to be sent for stakeholder comment; however, fewer than 5 sets of stakeholder comments were received for these topics before September 3, 2021, so they were not considered for inclusion in this report. The remaining 109 topics are too early in development to meet the criteria (as outlined above) for eligibility for this report.

Topics Considered for Inclusion in This Report

Table 6.1 lists 9 topics selected for inclusion in this report based on stakeholder ratings and comments and available data. Topics are listed and discussed alphabetically by title.

Table 6.1. Included Topics for Focus Area: Rare Diseases

Topic title
Arimoclomol (BRX-345) to treat Niemann-Pick disease type C
CAP-1002 to treat Duchenne muscular dystrophy
Elivaldogene autotemcel (eli-cel, Lenti-D) to treat cerebral adrenoleukodystrophy[a]
Etranacogene dezaparvovec (AMT-061) to treat hemophilia B[a]
Fosdenopterin (Nulibry) to treat molybdenum cofactor deficiency type A
Human plasminogen (Ryplazim) to treat congenital plasminogen deficiency
Lumasiran (Oxlumo) to treat primary hyperoxaluria type 1
MT1621 to treat thymidine kinase 2 deficiency
Pegcetacoplan (Empaveli) to treat paroxysmal nocturnal hemoglobinuria[a]

[a] Topic appears for the first time in this edition of the *High Potential Disruption Report*.

Table 6.2 lists 6 topics considered but not selected for inclusion in this report, based on stakeholder ratings and comments and available data. Each record notes the reasons for exclusion.

Table 6.2. Topics Considered but Not Included for Focus Area: Rare Diseases

Topic title	Exclusion reason(s) and notes based on stakeholder comments
Avacopan (Tavneos, formerly CCX168) to treat antineutrophil cytoplasmic antibody–associated vasculitis	Stakeholders thought that because the treatment does not eliminate the need for infusion therapies, avacopan lacks high potential to cause disruption. Further, it is replacing another drug that has similar effectiveness and is also taken orally. More data are needed to determine whether avacopan will disrupt the current standard of care.

Topic title	Exclusion reason(s) and notes based on stakeholder comments
Casimersen (Amondys 45) to treat Duchenne muscular dystrophy	Casimersen could cause only moderate disruption because of a potential increase in disparities caused by the high cost of the treatment, varied access to the treatment, and the time and resources needed for weekly infusions. Long-term data are lacking, as is evidence showing that increased dystrophin production improves functional outcomes in patients with Duchenne muscular dystrophy. Other stakeholders cited the small patient population, a fraction of the total DMD population, as limiting disruptive potential.
Fenfluramine hydrochloride low-dose (Fintepla) to treat Lennox-Gastaut syndrome	This treatment might reduce the overall burden of the disease for patients and caregivers. However, the data quality is concerning as it relates to subjective and intermediate outcome measures, small sample sizes, varied efficacy between subgroups, and the lack of long-term follow-up.
Maralixibat (LUM001) to treat Alagille syndrome	The limited available data, with multiple dose levels studied, do not consistently demonstrate a significant improvement from maralixibat compared with the standard of care. Further, the relatively high rates of adverse events during clinical trials and patient withdrawals from trials raise concerns about efficacy and safety.
Olipudase alfa (GZ402665) to treat acid sphingomyelinase deficiency	This enzyme-replacement therapy might improve lung function and reduce the volume of other organs, potentially leading to better quality of life and longer life expectancy for patients who currently have no FDA-approved treatment. However, data are lacking on patient-important outcomes (need for supportive care, activities of daily living, quality of life, and survival), there is no evidence that the treatment improves neurological deterioration, and olipudase alfa is not intended to treat Niemann-Pick disease type A, the most severe form of acid sphingomyelinase deficiency with significant neurologic involvement. Also of concern is the development of inhibiting antibodies or antibody inactivation after long-term enzyme-replacement therapy.
Pridopidine to treat Huntington disease	Although pridopidine might improve patient quality of life and function, it is likely to have only a small effect on symptoms and disease progression and would not modify the underlying disease, making its effect incremental to other available treatments. Safety of the drug is also a concern.

Abbreviation: DMD, Duchenne muscular dystrophy.

Trends Considered for Inclusion in This Report

As of September 3, 2021, we had not identified any trends pertaining to the rare diseases focus area that met criteria for entry into the PCORI Health Care Horizon Scanning System.

Topic Summaries

We present below 9 summaries on topics deemed to have high potential for disruption.

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

Highlights

- Arimoclomol is an oral, small-molecule drug intended to treat Niemann-Pick disease type C (NPC). The therapy is meant to amplify the production of heat shock proteins (HSPs) that purportedly rescue misfolded proteins and clear abnormal protein collections, which would improve liposome function and slow disease progression.

- A new drug application for arimoclomol was submitted to the FDA; however, in June 2021, the FDA issued a complete response letter citing the need for additional evidence to substantiate the validity and interpretation of the phase 2/3 trial's primary outcome measure and to support the application's risk-benefit assessment. The developer is assessing a regulatory path forward for arimoclomol in the United States.
- Stakeholders commenting on this topic thought that, as a disease-modifying drug, arimoclomol might improve patient health outcomes and improve quality of life for patients with NPC.
- Stakeholders thought that arimoclomol might become the standard of care if it becomes the first FDA-approved treatment for NPC.
- Stakeholders also thought that arimoclomol is likely to be expensive—although it is not clear how its price might compare with that of off-label miglustat—but that the cost of the drug might be offset by less use of health care resources because of slowed disease progression (eg, fewer hospitalizations or follow-up visits).

Patient Population

Arimoclomol is intended for children and young adults aged 2 to 18 years with NPC subtypes NPC1 or NPC2.

Intervention

NPC is a rare, genetic, progressive disease characterized by abnormal accumulations of fats (cholesterol and other lipids) in the liver, spleen, lungs, or brain that can eventually cause cell death in these tissues. NPC is caused by variations in the *NPC1* or *NPC2* genes. These variant genes produce proteins that impair normal trafficking of fats related to lysosomes and endosomes in cells.[269]

Signs and symptoms of NPC include difficulty with walking, motor coordination, swallowing, and eating; excessive muscle contractions or eye movements; recurrent pneumonia; and sleep disturbances.[270] Age of onset spans infancy to adulthood. Symptoms vary widely and can be fatal. Because no known cure is available or approved for NPC, novel effective therapies are needed.[269] The Mayo Clinic website offers more information about NPC.

Arimoclomol (BRX-345) is a small-molecule amine intended to treat NPC. It purportedly acts by amplifying and stabilizing heat shock factor 1, a transcription factor that regulates the production of HSPs in physiologically stressed cells. HSPs are thought to correct and promote recycling of misfolded or inappropriately aggregated proteins in cells.

In NPC, abnormally folded and aggregated proteins contribute to abnormal lipid accumulation in affected cells. Arimoclomol purportedly decreases the presence of abnormal proteins in NPC, ultimately decreasing the cellular stress and cell death that contribute to NPC disease progression.[271]

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

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified a single ongoing trial for this topic. We present this trial in Table 6.3.

Table 6.3. Ongoing Clinical Trial

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
Arimoclomol Prospective Study in Patients Diagnosed With Niemann-Pick disease type C NCT02612129 See results by Mengel et al, 2021, and Orphazyme, 2021, under Recently Completed and Ongoing Trials With Available Results	Children and adults aged 2 to 18 years (n = 50) with diagnosed NPC due to variants in the *NPC1* or *NPC2* genes with at least one active neurological symptom	Phase 2/3, randomized, parallel-assignment, placebo-controlled study to assess the efficacy and safety of arimoclomol as an add-on therapy to standard care Participants are randomly assigned to receive arimoclomol capsules orally 3 times daily at a dose of 150 to 600 mg/day (weight based) or matching placebo capsules. Participants had the option of continuing into a 4-year open-label extension study, for a total treatment period of 60 months. Primary outcome: Change in NPC disease severity score at 12 months • Secondary outcomes: Changes in score from baseline at 6, 18, and every 6 months thereafter in NPC-cdb, NPCCSS, NPCCSS individual domains, EQ-5D-Y quality-of-life scale, SARA, 9HPT, CGI-I, and CGI-S • Adverse events	Primary completion June 2018 Study completion May 2022

Abbreviations: 9HPT, 9-hole peg test; CGI-I, Clinical Global Impression—Improvement; CGI-S, Clinical Global Impression—Severity; EQ-5D-Y, EQ-5D for children and adolescents aged 4 to 15 years; NPC, Niemann-Pick disease type C; NPC-cdb, Niemann-Pick disease type C clinical database; *NPC1*, NPC1 like intracellular cholesterol transporter 1 gene; *NPC2*, NPC intracellular cholesterol transporter 2 gene; NPCCSS, Niemann-Pick disease Type C Clinical Severity Scale; SARA, scale for the assessment and rating of ataxia.

Recently Completed and Ongoing Trials With Available Results

Our searches identified a single phase 2/3 trial with published and reported results.[272] We summarize this study with results as written in the abstract of a peer reviewed, published article (full data set from the initial 12-month portion) and a news release (interim data from the open-label extension portion).

The following abbreviations are used in this section: 5D-NPCCSS, 5-domain NPC Clinical Severity Scale; 9HPT, 9-hole peg test; CGI-I, Clinical Global Impression—Improvement; CGI-S, Clinical Global Impression—Severity; EQ-5D-Y, EQ-5D for children and adolescents aged 4 to 15 years; NPC, Niemann-Pick disease type C; NPC-cdb, Niemann-Pick disease type C clinical database; *NPC1*, NPC1 like intracellular cholesterol transporter 1 gene; *NPC2*, NPC intracellular cholesterol transporter 2 gene; NPCCSS, Niemann-Pick Disease Type C Clinical Severity Scale; OLE, open-label extension; P, *P* value; SARA, scale for the assessment and rating of ataxia.

Arimoclomol Prospective Study in Patients Diagnosed With Niemann-Pick Disease Type C. NCT02612129. Mengel et al, 2021,[272] and Orphazyme, 2021.[273]

- **Patient population/planned enrollment:** Children and adults aged 2 to 18 years (n = 50) with diagnosed NPC due to variants in the *NPC1* or *NPC2* genes with at least one active neurological symptom
- **Study design:** Phase 2/3, randomized, parallel-assignment, placebo-controlled study to assess the efficacy and safety of arimoclomol as an add-on therapy to the standard of care. Patients

were randomly assigned in a 2:1 ratio to receive arimoclomol capsules orally 3 times daily at a dosage of 150 to 600 mg/day (weight based) or matching placebo capsules for a double-blinded treatment period of 12 months. Participants had the option of continuing into a 4-year OLE study, for a total treatment period of 60 months.

- **Primary outcome:** Disease severity from baseline to 12 months, as measured by the NPCCSS
- **Secondary outcomes:** Changes in score from baseline at 6, 18, and every 6 months thereafter in NPC-cdb, NPCCSS, NPCCSS individual domains, EQ-5D-Y quality-of-life scale, SARA, 9HPT, CGI-I, and CGI-S; and adverse events
- **Results presented by study authors:**

  Mengel et al reported data from the 12-month randomized portion of the trial:

  "Fifty patients enrolled; 42 completed. At month 12, the mean progression from baseline in the 5-domain NPCCSS was 0.76 with arimoclomol vs 2.15 with placebo. A statistically significant treatment difference in favour of arimoclomol of −1.40 (95% confidence interval: −2.76, −0.03; P = .046) was observed, corresponding to a 65% reduction in annual disease progression. In the prespecified subgroup of patients receiving miglustat as routine care, arimoclomol resulted in stabilisation of disease severity over 12 months with a treatment difference of −2.06 in favour of arimoclomol (P = .006). Adverse events occurred in 30/34 patients (88.2%) receiving arimoclomol and 12/16 (75.0%) receiving placebo. Fewer patients had serious adverse events with arimoclomol (5/34, 14.7%) vs placebo (5/16, 31.3%). Treatment-related serious adverse events (n = 2) included urticaria and angioedema. Arimoclomol provided a significant and clinically meaningful treatment effect in NPC and was well tolerated."[272]

  An Orphazyme news release reported data from the open-label extension portion of the trial:

  "The results demonstrate that arimoclomol provided a sustained benefit to study participants by reducing NPC progression as measured by the 5-domain NPC Clinical Severity Scale (5D-NPCCSS). A slowing of progression from baseline was observed through 36 months in participants who received arimoclomol from the start of the double-blind phase (mean change, 3.5 points). By comparison, disease progression among NPC patients receiving routine clinical care was estimated to be a mean increase of 5.2 points after three years, based on a statistical model combining placebo data from the NPC-002 double-blind study and prospective data from the observational NPC-001 study. The effect was consistent across pre-specified subgroups, including among participants more than four years of age and those treated with miglustat. Also, slowing of progression through 24 months was observed in those participants who initiated arimoclomol treatment upon entering the open-label period (mean change, 0.9 points).

  "Arimoclomol demonstrated a consistent safety profile throughout the 36-month treatment period. Adverse events observed during the open label extension phase were similar to those observed in the double-blind phase. A total of 41 patients joined the OLE following the double-blind period; 33 have now completed up to 36 months of treatment."[273]

Manufacturers and Regulatory Status

Orphazyme A/S (Copenhagen, Denmark), which licensed rights from developer CytRx Corporation (Los Angeles, California), is evaluating arimoclomol for NPC. The drug is in phase 2/3 development. In January 2020, arimoclomol became available to patients in the United States who have NPC through an early access program.[274]

Orphazyme announced in July 2020 that it had completed a rolling new drug application (NDA) to the FDA for arimoclomol to treat NPC.[275] However, on June 18, 2021, the company announced it had received a complete response letter (CRL) from the FDA denying approval, "based on needing additional qualitative and quantitative evidence to further substantiate the validity and interpretation

of the 5-domain NPC Clinical Severity Scale (NPCCSS) and, in particular, the swallow domain," and that "additional data are needed to bolster confirmatory evidence beyond the single phase 2/3 trial to support the benefit-risk assessment of the NDA."[276] Orphazyme has indicated that it is committed to "assessing a path forward for arimoclomol in the U.S."[277] A postaction type A meeting with the FDA to discuss the CRL was scheduled for mid-October 2021.[278]

Arimoclomol for treating NPC received FDA breakthrough therapy designation in December 2019,[279] rare pediatric disease designation in January 2018,[280] fast track designation in June 2016,[281] and orphan drug designation in January 2015.[282]

Cost Information

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

Key Stakeholder Perspectives

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

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

CAP-1002 to Treat Duchenne Muscular Dystrophy

Highlights

- CAP-1002 is an allogeneic cell therapy derived from donor human heart tissue given intravenously every 3 months. The therapy is thought to modulate the immune system to decrease inflammation and muscle degeneration and promote muscle regeneration in patients with Duchenne muscular dystrophy (DMD). It is in phase 2 development.
- CAP-1002 is intended for all patients with DMD, whereas 2 disease-modifying therapies for DMD approved by the FDA in recent years are available only to subsets of patients with specific genetic variants in the *DMD* gene.
- Stakeholders commenting on this topic thought that CAP-1002 might disrupt the care paradigm by shifting care from supportive therapy that primarily treats symptoms to the first disease-modifying therapy that might alter the natural history of DMD.

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

Patient Population

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

Intervention

CAP-1002 is a cell-based therapy intended for DMD, an inherited, X chromosome–linked genetic disorder caused by point mutations or deletions in the dystrophin gene, *DMD*. The *DMD* gene encodes the dystrophin protein, which helps promote muscle function. In patients, the absence of naturally produced (ie, wild-type) dystrophin protein causes progressive muscle fiber cell death (necrosis) and eventual widespread muscle weakness.[283] The Muscular Dystrophy Association website offers more information about DMD.

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

CAP-1002 consists of cardiosphere-derived cells (CDCs), stem cells derived from donor heart tissue. The CDCs in CAP-1002 purportedly secrete growth factors and exosomes that promote cellular regeneration by altering immune system activity.[284]

Data from a completed phase 1/2 trial (ie, HOPE, NCT02485938), which enrolled patients with DMD-associated heart disease, suggest that a solution of CAP-1002 containing 75 million CDCs delivered directly into the heart improves both cardiac muscle and skeletal muscle function.[285,286] Based on the systemic (ie, noncardiac) effects observed in this trial, further studies are delivering CAP-1002 by a more usual route, standard intravenous infusion.

In the completed phase 2 HOPE-2 clinical trial, a solution of CAP-1002 containing 150 million CDCs was given intravenously once every 3 months, 4 times.

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified a single ongoing trial for this topic. We present this trial in Table 6.4.1.

Table 6.4.1. Ongoing Clinical Trial

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
Open-label Extension of the HOPE-2 Trial (HOPE-2-OLE) NCT04428476	Male children aged 10 years or older and adults (n = 14) who have genetically confirmed DMD, were enrolled in the HOPE-2 trial, and completed 12 months of follow-up	Phase 2, open-label, single-arm extension study to assess continued safety and efficacy of an additional 4 intravenous infusions of CAP-1002 (150 million CDCs) given every 3 months to treat DMD Primary outcomes: • Safety (incidence and severity of treatment-emergent AEs) • Efficacy (change in functional capacity measured on full PUL 2.0 clinical scale, from baseline to 12 months) Secondary outcomes: • Changes in midlevel (elbow) dimensions of the PUL 2.0 clinical scale from baseline to 12 months • Changes in distal-level (wrist/hand) dimensions of the PUL 2.0 clinical scale from baseline to 12 months	Primary and study completion October 2021

Abbreviations: AEs, adverse events; CDCs, cardiosphere-derived cells; DMD, Duchenne muscular dystrophy; PUL, Performance of the Upper Limb.

Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed phase 2 trial with reported results.[287] We summarize this study with results as written in a company news release.

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

A Study of CAP-1002 in Ambulatory and Non-ambulatory Patients With Duchenne Muscular Dystrophy (HOPE-2). NCT03406780. Capricor Therapeutics, 2021.[287]

- **Patient population/planned enrollment:** Male children aged 10 years or older and adults (n = 20) who had genetically confirmed DMD, were either ambulatory or nonambulatory, and were receiving stable doses of systemic glucocorticoids
- **Study design:** Phase 2, randomized, double-blind, parallel-assignment study to evaluate the efficacy of CAP-1002 vs placebo. Patients were randomly assigned in a 1:1 ratio to receive CAP-1002 (150 million CDCs) or matching placebo via intravenous infusion every 3 months for a total of 4 doses.
- **Primary outcome:** Change in the midlevel (elbow) dimension of the PUL 2.0 clinical scale, from baseline to month 12
- **Secondary outcomes:** Change in the midlevel (elbow) dimension of the PUL 2.0 clinical scale, from baseline to months 3, 6, and 9; and change in regional systolic left ventricular wall thickening, as assessed by cardiac MRI, from baseline to months 6 and 12
- **Results presented by study authors**: Final efficacy data reported in a news release are shown in Table 6.4.2 and Table 6.4.3.

Table 6.4.2. Upper Limb Function Results (Mean Change From Baseline at 12 Months)[a]

Outcome measure	Δ[b], CAP-1002 (n = 8)[c] vs placebo (n = 12)[c]	*P* value
Midlevel PUL (version 1.2)	2.6	0.01
Shoulder + mid + distal PUL (version 1.2)	3.2	0.02
Shoulder + mid + distal PUL (version 2.0)	1.8	0.04

Abbreviations: Δ, change; PUL, Performance of the Upper Limb.

[a] Nonparametric mixed model repeated measures analysis with percentile ranked baseline, treatment, visit, visit-by-treatment interaction, PUL entry-item score at stratification, and site as model effects.

[b] Mean difference in change from baseline to 12 months.

[c] Intent-to-treat population.

Table 6.4.3. Cardiac Function Results (Mean Change From Baseline at 12 Months)[a]

Outcome measure	Δ[b], CAP-1002 (n = 8)[c] vs placebo (n = 12)[c]	*P* value
LV ejection fraction, %	4.0	0.002
LV end-diastolic volume, indexed mL/m^2	–12.4[d]	0.03
LV end-systolic volume, indexed mL/m^2	–4.2[d]	0.01
Creatine kinase-MB (% of total CK)	–2.2[d]	0.02

Abbreviations: Δ, change; CK, creatine kinase; LV, left ventricular; MB, myocardial.

[a] Nonparametric mixed model repeated measures analysis.

[b] Mean difference in change from baseline to 12 months.

[c] Intent-to-treat population.

[d] Negative value favors CAP-1002.

Manufacturers and Regulatory Status

CAP-1002 is being developed by Capricor Therapeutics, Inc (Beverly Hills, California), and is in phase 2 clinical development for treating DMD. A pivotal phase 3 trial is planned.[288] For this indication, the FDA granted the drug orphan drug designation in April 2015,[289] rare pediatric disease designation in July 2017,[290] and regenerative medicine advanced therapy designation in February 2018.[291]

In December 2018, Capricor placed a voluntary dosing hold on the then-ongoing HOPE-2 trial (NCT03406780) after an enrolled patient experienced a severe allergic reaction during drug infusion.[292] The patient recovered fully from the event, and the HOPE-2 trial dosing resumed in February 2019.[293]

Cost Information

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

Key Stakeholder Perspectives

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

- CAP-1002 has moderate to large potential to improve patient health outcomes and quality of life by preserving upper body strength and reducing heart muscle damage. However,

additional data are needed to demonstrate that these improvements can be maintained over a longer term.
- In one respect, CAP-1002 could reduce disparities in access because it might offer an effective therapeutic option to patients with more advanced DMD (ie, nonambulatory), a traditionally underserved group with limited options.
- Conversely, CAP-1002 could increase disparities based on a patient's insurance coverage, given the anticipated high treatment cost and possible limited geographic availability only at specialty DMD programs.
- CAP-1002 could disrupt the care paradigm by moving beyond treating signs and symptoms to offer the first approach that could change the natural history of DMD.
- CAP-1002 widens the treatment scope to all patients with DMD compared with exon-skipping therapies targeted only to population subsets with specific genetic mutations.

Elivaldogene Autotemcel (eli-cel, Lenti-D) to Treat Cerebral Adrenoleukodystrophy

Highlights

- Elivaldogene autotemcel (eli-cel, Lenti-D) is a one-time gene therapy in phase 3 trials to treat male children with cerebral adrenoleukodystrophy (CALD), a disease caused by loss-of-function variants in the *ABCD1* gene.
- The treatment consists of a single infusion of patient-derived CD34-positive hematopoietic stem cells into which a functional copy of the *ABCD1* gene has been introduced. It is intended to permanently enhance a patient's ability to produce the adrenoleukodystrophy protein, which might slow the progression of CALD.
- In September 2021, the FDA placed a clinical hold on studies of elivaldogene autotemcel for CALD after the company reported a suspected, unexpected, serious adverse reaction of myelodysplastic syndrome in one patient. However, the developer still planned to submit a biologics license application to the FDA by the end of 2021, pending resolution of the clinical hold.
- Stakeholders commenting on this topic thought that elivaldogene autotemcel might be a safer and more effective treatment compared with allogeneic hematopoietic stem cell transplantation (allo-HSCT), improving patient health outcomes, quality of life, and life expectancy, without the risks and limitations associated with allo-HSCT.
- Stakeholders also thought that elivaldogene autotemcel's expected high cost and the likelihood that a limited number of specialized facilities were likely to offer this treatment might increase health disparities and could cause a significant financial burden on caregivers.

Patient Population

Elivaldogene autotemcel is intended for male children aged up to 17 years with active CALD.

Intervention

Elivaldogene autotemcel is a one-time gene therapy intended to treat CALD, the most severe subtype of the rare genetic disorder adrenoleukodystrophy. The disease is caused by loss-of-function variants in the *ABCD1* gene located on the X chromosome and, therefore, occurs predominately in males.[294] Loss-of-function variants in this gene cause accumulation of very-long-

chain fatty acids, which leads to the inflammatory demyelination and progressive neurodegeneration characteristic of CALD.[295]

Neurologic symptoms of CALD typically appear within the first 2 decades of life. After symptom onset, the disease progresses rapidly and, without treatment, patients frequently become bedridden or die within several years. The United Leukodystrophy Foundation website offers more information on CALD.

Although the FDA has approved no treatments for CALD, allo-HSCT has been shown to be effective when given early in the course of the disease.[294] However, the utility of allo-HSCT is limited by the need to identify a suitably matched donor in a timely manner and the substantial risks associated with the procedure, including transplant-related toxicity, graft-vs-host disease, graft failure or rejection, and opportunistic infections.[296] Therefore, novel effective treatments for CALD are sought.

Elivaldogene autotemcel is a single infusion of patient-derived (ie, autologous) CD34-positive hematopoietic stem cells into which a functional copy of the *ABCD1* gene has been introduced.[297] First, CD34-positive cells are isolated in the laboratory from the patient's blood stem cells, and viruses carrying a functional *ABCD1* gene are used to deliver the functional gene into the cell genomes. Next, to prepare for transplantation, the patient undergoes a myoablative chemotherapy conditioning regimen to reduce the volume of stem cells with the nonfunctional gene. Finally, the patient is given a single infusion of an unspecified dose of the CD34-positive cells carrying a functional *ABCD1* gene.[298]

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 2 ongoing trials for this topic. We present these trials in Table 6.5.

Table 6.5. Ongoing Clinical Trials

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
A Clinical Study to Assess the Efficacy and Safety of Gene Therapy for the Treatment of Cerebral Adrenoleukodystrophy (CALD) ALD-104 NCT03852498 See preliminary results by Kühl et al, 2021, under Recently Completed and Ongoing Trials With Available Results	Male children (n = 35) from newborn to 17 years of age with active CALD	Phase 3, single-arm trial to evaluate the safety and efficacy of elivaldogene autotemcel to treat patients who have CALD After stem cell mobilization using granulocyte colony-stimulating factor, all patients will undergo apheresis collection of blood cells from which the elivaldogene autotemcel product will be generated. Next, patients will receive a busulfan/fludarabine conditioning regimen. Finally, patients will receive a single infusion (dose not specified) of elivaldogene autotemcel. Primary outcomes: • Percentage of patients who are alive and have none of 6 major functional disabilities (ie, loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, and complete loss of voluntary movement) at month 24 • Percentage of patients with neutrophil engraftment after drug product infusion at day 42 Selected secondary outcomes, at 24 months: • Change in neurologic function from baseline • Major functional disability-free survival • Rate of graft-vs-host disease • Overall survival • ICU stays • Adverse events	Primary and study completion February 2024

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
Long-Term Follow-up of Participants With Cerebral Adrenoleukodystrophy Who Were Treated With Lenti-D Drug Product LTF-304 NCT02698579 See preliminary results by Kühl et al, 2021, under Recently Completed and Ongoing Trials With Available Results	Male patients (n = 60) with CALD previously treated with elivaldogene autotemcel in the ALD-102 or ALD-104 trials	Unphased, long-term follow-up study to evaluate the safety and efficacy of elivaldogene autotemcel for treating patients who have CALD. All patients received treatment with elivaldogene autotemcel in an earlier clinical trial. Primary outcomes, at 15 years: • Major functional disability-free survival (ie, loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, and complete loss of voluntary movement) • Graft-vs-host disease • Subsequent stem cell transplantation • Drug product–related adverse events • Serious or nonserious immune-related adverse events • Vector-derived replication-competent lentivirus • Insertional oncogenesis • Clonal predominance Selected secondary outcomes, at 15 years: • Overall survival • Change from baseline in neurologic function • Gadolinium enhancement status	Primary and study completion May 2037

Abbreviations: CALD, cerebral adrenoleukodystrophy; ICU, intensive care unit; Lenti-D, elivaldogene autotemcel.

Recently Completed and Ongoing Trials With Available Results

Our searches identified 2 reports on data from 3 trials of elivaldogene autotemcel for CALD.[297,299] We summarize results of these studies as written in the abstract of a peer reviewed, published article and a conference abstract.

The following abbreviations are used in this section: Aes, adverse events; ALD, adrenoleukodystrophy protein; BK, BK polyomavirus; eli-cel, elivaldogene autotemcel; Lenti-D, Lentigene-D (ie, elivaldogene autotemcel); MFD, major functional disability; MRI, magnetic resonance imaging; PE, platelet engraftment; SAE, serious adverse event.

A Study of the Efficacy and Safety of Hematopoietic Stem Cells Transduced With Lenti-D Lentiviral Vector for the Treatment of Cerebral Adrenoleukodystrophy (CALD) (Starbeam/ALD-102). NCT01896102. Eichler et al, 2017,[297] and Kühl et al, 2021.[299]

- **Patient population/planned enrollment:** Male children (n = 32) from newborn to 17 years of age with active cerebral adrenoleukodystrophy
- **Study design:** Phase 2/3, open-label, single-arm study to evaluate the efficacy and safety of hematopoietic stem cells transduced with the elivaldogene autotemcel lentiviral vector. After receiving stem cell mobilization using granulocyte colony-stimulating factor, all patients underwent apheresis collection of blood cells, from which the elivaldogene autotemcel product was generated. Next, patients received a busulfan/cyclophosphamide conditioning regimen. Finally, patients received a single infusion (dose unspecified) of elivaldogene autotemcel.

- **Primary outcomes:** Overall survival, major functional disability (ie, loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, and complete loss of voluntary movement) at month 24, and acute or chronic graft-vs-host disease by month 24
- **Secondary outcomes:** Change in neurologic function from baseline at 24 months, major functional disability-free survival, overall survival, adverse events, severe adverse events, change in laboratory parameters, and emergency department visits and hospitalizations up to 24 months
- **Results presented by study authors:**
  Eichler et al published initial results from study ALD-102 in 2017:
  "A total of 17 boys received Lenti-D gene therapy. At the time of the interim analysis, the median follow-up was 29.4 months (range, 21.6 to 42.0). All the patients had gene-marked cells after engraftment, with no evidence of preferential integration near known oncogenes or clonal outgrowth. Measurable ALD protein was observed in all the patients. No treatment-related death or graft-versus-host disease had been reported; 15 of the 17 patients (88%) were alive and free of major functional disability, with minimal clinical symptoms. One patient, who had had rapid neurologic deterioration, had died from disease progression. Another patient, who had had evidence of disease progression on MRI, had withdrawn from the study to undergo allogeneic stem-cell transplantation and later died from transplantation-related complications."

  Kühl et al presented updated safety and efficacy results from ALD-102/LTF-304 and initial safety results from ALD-104 in 2021 (see Table 6.5 for details of trials ALD-104 and LTF-304):

  "As of January 2020, follow-up for 32 patients in ALD-102/LTF-304 was 30.0 (9.1–70.7) months. Twenty patients completed ALD-102 and enrolled in LTF-304, and 9 additional patients (maximum follow-up 22.1 months) were still in ALD-102; all without MFDs. The primary efficacy endpoint was met in 20/23 (87%) evaluable patients; 2 were withdrawn and 1 died after rapid disease progression and multiple MFDs.

  "As of February 2020, 13 additional patients received eli-cel in ALD-104 with 6.1 (2.2–10.3) months follow-up. Neutrophil engraftment occurred at 13 (11–41) days in ALD-102 (n=32) and 13 (12–31) days in ALD-104 (n=13). Platelet engraftment (PE) occurred at 32 (16–60) days in ALD-102 (n=32) and 27 (18–108) days in ALD-104 (n=12). Two clinically stable ALD-104 patients had an ongoing pancytopenia SAE (considered possibly eli-cel-related), one with PE on Day 108 and the other with available platelet values indicative of PE on Day 104; neither pancytopenia met criteria for failed engraftment. An additional ongoing SAE in ALD-104 was transverse myelitis (eli-cel-unrelated, partially responsive to steroids/plasmapheresis). In ALD-102, 3 Aes were possibly eli-cel-related: BK viral cystitis (n=1) and vomiting (n=2).

  "The safety/tolerability profile of eli-cel treatment regimen was primarily reflective of the known effects of mobilization/apheresis and conditioning. There was no graft failure, graft-versus-host disease, replication competent lentivirus, or insertional oncogenesis. Benign clonal expansion determined by insertional site analysis was observed in one ALD-102 patient, who was clinically well at last available visit (Month 62)."

Manufacturers and Regulatory Status

Elivaldogene autotemcel is in phase 3 development by bluebird bio, Inc (Cambridge, Massachusetts), for treating CALD. The company intended to file a biologics license application (BLA) to the FDA in mid-2021.[300] The FDA had previously granted elivaldogene autotemcel orphan drug status, rare pediatric disease designation, and breakthrough therapy designation for the treatment of CALD.[300]

On September 9, 2021, the FDA placed a clinical hold on studies of elivaldogene autotemcel for CALD after the company reported a suspected, unexpected, serious adverse reaction of myelodysplastic syndrome in one patient who was treated in the phase 3 ALD-104 study. Available evidence suggests that this adverse event was likely brought on by elivaldogene autotemcel

lentiviral vector insertion.[301] The company indicated that it was still on track to submit a BLA by the end of 2021, pending the resolution of the clinical hold.[301]

Cost Information

Cost information is currently unavailable for this topic.

Key Stakeholder Perspectives

Between June 11 and June 29, 2021, nine stakeholders, reflecting health systems, nursing, patient advocate, physician, and research perspectives, provided comments and ratings on elivaldogene autotemcel. The list below summarizes key stakeholder perspectives.

- Elivaldogene autotemcel has moderate to high potential to improve health outcomes for patients with CALD and might disrupt the current standard of care. Novel effective therapies are needed, especially for patients who cannot receive allo-HSCT because a matched donor is unavailable early in the disease course.
- Initial data suggest that elivaldogene autotemcel might be a safer and more effective treatment compared with allo-HSCT, improving functional outcomes, quality of life, and life expectancy, without the limitations and risks associated with allo-HSCT, such as graft-vs-host disease and infection.
- Elivaldogene autotemcel's expected high cost, combined with the likelihood that this treatment would be offered only at certain specialized facilities, might increase health disparities. It also could cause a significant financial burden on caregivers, depending on their insurance coverage, economic status, and geographic location.
- Additional longer-term data are needed to further evaluate the treatment's efficacy, sustainability of effects, and long-term safety.

Etranacogene Dezaparvovec (AMT-061) to Treat Hemophilia B

Highlights

- Etranacogene dezaparvovec (AMT-061) is a one-time gene therapy intended to treat moderately severe to severe hemophilia B. This rare and potentially fatal blood disorder is caused by *FIX* gene variants that impair normal production or function of factor IX, a protein involved in blood clotting.
- Etranacogene dezaparvovec consists of a viral vector that delivers a copy of the *FIX* gene to the patient's cells. The developers plan to submit a biologics license application to the FDA in the first half of 2022.
- Stakeholders commenting on this topic thought that results from the HOPE-B trial suggest that etranacogene dezaparvovec could improve health outcomes and quality of life in patients with hemophilia B. However, its availability might be limited to specialized health centers that are able to offer gene therapies with the appropriate follow-up.
- Stakeholders also thought that the therapy's high cost might limit its availability to patients. However, the high cost of the one-time treatment could be offset by a reduction in the lifetime costs of treating and managing patients who have hemophilia B.

Patient Population

Etranacogene dezaparvovec is intended for adult males who have severe congenital hemophilia B and are receiving prophylactic factor IX replacement therapy.

Intervention

Etranacogene dezaparvovec (AMT-061) is a gene therapy in development to treat severe hemophilia B, a rare, potentially fatal blood disorder.

In hemophilia B, loss-of-function variants in the *FIX* (or *F9*) gene on the X chromosome impair normal production of a protein that plays a role in the blood clotting cascade, factor IX. Deficiency in factor IX results in spontaneous bleeding episodes that might occur in muscles and joints, causing pain and restricted movement, or in organs such as the kidneys, stomach, intestines, or even the brain, which could be serious or fatal.[302] Most cases of hemophilia B are inherited, and the disease disproportionately affects males. The website of the Genetic and Rare Diseases Information Center of the National Institutes of Health website offers more information about hemophilia B.

Standard treatment for hemophilia B requires regular intravenous infusions of replacement factor IX to restore blood clotting capacity.[302-304] Etranacogene dezaparvovec is intended to be given as a one-time treatment and could, therefore, eliminate the need for repeated administration of factor IX by providing a functional *FIX* gene and allowing the body to produce this critical clotting protein.

Etranacogene dezaparvovec consists of a viral vector (adeno-associated viral serotype 5, AAV5) that delivers a copy of the Padua variant of the *FIX* gene to the patient's cells, under control of a liver-specific promoter (limiting transgene activity to liver cells). The Padua variant is known to produce FIX protein with enhanced activity compared with the wild-type factor IX variant (ie, the normally functioning gene variant that predominates in the natural population). This heightened activity is meant to provide sustained coagulation.[303,305,306] The transgene is maintained as an episome, a separate functional genetic element within the nucleus of the patient's cells, and is not intended to integrate into the patient's genome. It is not transferred to offspring.[307-309]

In clinical trials, etranacogene dezaparvovec is given as a single intravenous infusion at a dose of 2×10^{13} genome copies/kg.[310]

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 2 ongoing trials for this topic. We present these trials in Table 6.6.

Table 6.6. Ongoing Clinical Trials

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
Dose Confirmation Trial of AAV5-hFIXco-Padua (CT-AMT-061-01) NCT03489291 See preliminary results by von Drygalski et al, 2021, under Recently Completed and Ongoing Trials With Available Results	Adult males (n = 3) with moderately severe to severe hemophilia B and at least 20 days' exposure to FIX replacement therapy	Phase 2, single-group assignment, open-label study to confirm the efficacy and continued safety of etranacogene dezaparvovec in patients with hemophilia B Patients will receive a single intravenous infusion of etranacogene dezaparvovec at a dose of 2×10^{13} gc/kg Primary outcome: FIX activity levels at 6 weeks Secondary outcomes: • Use of FIX replacement therapy • Annualized bleeding rate • AEs	Primary completion October 2018 Study completion September 2023
HOPE-B: Trial of AMT-061 in Severe or Moderately Severe Hemophilia B Patients NCT03569891 See preliminary results by uniQure, 2021, under Recently Completed and Ongoing Trials With Available Results	Adult males (n = 56) with moderately severe to severe hemophilia B on FIX replacement therapy for at least 150 exposure days	Phase 3, single-group assignment, open-label study to assess the efficacy and continued safety of etranacogene dezaparvovec in patients with hemophilia B Patients will receive a single intravenous infusion of etranacogene dezaparvovec at a dose of 2×10^{13} gc/kg Primary outcome: Annualized bleeding rate Secondary outcomes: • FIX activity levels at 26, 52, and 78 weeks • Use of FIX replacement therapy • AEs	Primary completion September 2021 Study completion March 2025

Abbreviations: AEs, adverse events; FIX, factor IX; gc/kg, geneome copies per kilogram of body weight.

Recently Completed and Ongoing Trials With Available Results

Our searches identified 2 recently completed trials with available results.[306,307] We summarize these results as written in a conference abstract and a company news release.

The following abbreviations are used in this section: AAV5, adeno-associated virus serotype 5; AEs or Aes, adverse events; CRP, C-reactive protein; FIX, factor IX; gc/kg, genome copies per kilogram of body weight; IU, international unit; Nabs, neutralizing antibodies.

Dose Confirmation Trial of AAV5-hFIXco-Padua (CT-AMT-061-01). NCT03489291. von Drygalski et al, 2021.[306]

- **Patient population/planned enrollment:** Adult males (n = 3) who had moderately severe to severe hemophilia B and at least 20 days' exposure to FIX replacement therapy
- **Study design:** Phase 2, single-group assignment, open-label study to confirm the efficacy and continued safety of etranacogene dezaparvovec in patients who have hemophilia B. Patients received a single intravenous infusion of etranacogene dezaparvovec at a dose of 2×10^{13} gc/kg.
- **Primary outcome:** FIX activity levels at 6 weeks
- **Secondary outcomes:** Use of FIX replacement therapy, annualized bleeding rate, and AEs

- **Results presented by study authors:** "All participants had FIX ≤ 1% (severe or moderately-severe FIX deficiency), required routine FIX prophylaxis, and had neutralizing activity to AAV5 at baseline. Following AMT-061 treatment, FIX activity increased rapidly to a mean of 31% at Week 6. At Week 52, mean FIX activity increased further to 41% with FIX activity levels of 50%, 31% and 41% in participants 1-3 respectively. There was no relationship between the presence of anti-AAV5 Nabs and response to etranacogene dezaparvovec. As of 52 weeks, there were no bleeds post-treatment and no requirement for FIX replacement aside from protocol-specified use for perioperative management in participant 3. There were no clinically significant elevations in liver enzymes and no participants required steroids related to the treatment. One participant experienced 2 mild Aes possibly related to treatment shortly after dosing (self-limiting headache and slightly elevated CRP). One patient had hip surgery due to worsening of pre-existing avascular necrosis deemed unrelated by investigator to etranacogene dezaparvovec and received FIX per protocol according to standard clinical practice. No participant developed inhibitors to FIX."

HOPE-B: Trial of AMT-061 in Severe or Moderately Severe Hemophilia B Patients. NCT03569891. uniQure, 2021.[307]

- **Patient population/planned enrollment:** Adult males (n = 56) who had moderately severe to severe hemophilia B on FIX replacement therapy for at least 150 exposure days
- **Study design:** Phase 3, single-group assignment, open-label study to confirm the safety and efficacy of etranacogene dezaparvovec in patients who had hemophilia B. Patients received a single intravenous infusion of etranacogene dezaparvovec at a dose of 2×10^{13} gc/kg.
- **Primary outcome:** Annualized bleeding rate
- **Secondary outcomes:** FIX activity levels at 26, 52, and 78 weeks; use of FIX replacement therapy; and AEs
- **Results presented by study authors:** "During the 52-week period, a single dose of etranacogene dezaparvovec significantly reduced the annualized rate of bleeding requiring treatment by 80 percent from a prospectively collected 3.39 at baseline to 0.68 bleeding episodes per year (p-value < 0.0001). The annualized rate of spontaneous bleeding requiring treatment was also significantly reduced by 85 percent from a prospectively collected 1.16 at baseline to 0.18 bleeds per year during the 52-week period (p-value < 0.0001). Usage of FIX replacement therapy (IU/year and infusions/year) in all patients declined 96 percent during the 52-week period, with 52 of 54 patients (96 percent) successfully discontinuing their prophylactic infusions. As previously announced, of the two non-responders, one patient only received a partial dose (less than 10 percent of the dosage) due to an infusion reaction and a second patient had an unusually high pre-existing Nab titer of 3,212, which is expected in less than 1 percent of the general population. Etranacogene dezaparvovec continues to be generally well-tolerated with no treatment-related serious adverse events. No inhibitors to FIX have been reported and no consistent relationship between safety and pre-existing Nab titers has been observed."

Manufacturers and Regulatory Status

Etranacogene dezaparvovec is being developed by uniQure NV (Amsterdam, the Netherlands) and CSL Behring (King of Prussia, Pennsylvania). It is under evaluation to treat hemophilia B in the phase 2 CT-AMT-061-01 trial and the phase 3 HOPE-B trial. The developers anticipated having 78-week follow-up, phase 3 data on etranacogene dezaparvovec in the second half of 2021, followed by a planned biologics license application submission to the FDA in the first quarter of 2022.[307] The

FDA had previously granted etranacogene dezaparvovec breakthrough therapy designation for this indication.[303]

In December 2020, the FDA placed a clinical hold on the HOPE-B trial after receiving a safety report of a preliminary diagnosis of hepatocellular carcinoma (HCC) in a trial patient treated with etranacogene dezaparvovec. The patient reportedly had multiple risk factors for liver cancer, including advanced age, nonalcoholic fatty liver disease, and a 25-year history of infection with the hepatitis B and C viruses.[311] In April 2021, the FDA removed the clinical hold on the HOPE-B trial after concluding that this patient's liver cancer was unlikely related to the AAV5 vector component of the gene therapy product. The FDA indicated that this patient might have been predisposed to HCC based on genetic analysis of the liver tumor and surrounding tissue, which suggested a precancerous state.[312]

Cost Information

Cost information is currently unavailable for this topic.

Key Stakeholder Perspectives

Between August 22 and September 2, 2021, nine stakeholders, reflecting clinical, health systems, nursing, patient advocate, and research perspectives, provided comments and ratings on etranacogene dezaparvovec. The list below provides a summary of key stakeholder perspectives.

- Data from the HOPE-B trial suggest that a single dose of etranacogene dezaparvovec might lead to durable expression of factor IX. This has the potential to improve health and quality of life in patients with hemophilia B by reducing the number of spontaneous bleeding episodes and the need for prophylactic factor IX infusions.
- As a one-time treatment, etranacogene dezaparvovec could remove the need for frequent clinic visits to treat spontaneous bleeding or receive prophylactic factor IX infusions. However, this treatment is likely to be available only in specialized health centers with the necessary resources, staff, and infrastructure to administer gene therapies and monitor patients for adverse events.
- If approved, etranacogene dezaparvovec is expected to be too costly for patients of low socioeconomic status and for those who lack health insurance or are underinsured. The gene therapy's cost might also place a financial burden on insured patients if their copayments are based on a percentage of the treatment's total cost.
- The lifetime health care costs for treating and managing patients with hemophilia B are already extremely high. As a one-time treatment that could reduce the treatment and management needs of patients with hemophilia B, etranacogene dezaparvovec might decrease the overall health care costs for this patient population.

Fosdenopterin (Nulibry) to Treat Molybdenum Cofactor Deficiency Type A

Highlights

- Molybdenum cofactor deficiency (MoCD) type A is an ultrarare, life-threatening genetic metabolic disorder characterized by loss of molybdenum cofactor.
- MoCD causes catastrophic and irreversible neurologic damage within the first weeks of life, and no effective treatments exist for MoCD type A. Care is mostly supportive.

- Fosdenopterin is a substrate replacement therapy that restores levels of a compound absent in patients with MoCD type A that is an essential precursor in molybdenum cofactor biosynthesis.
- In February 2021, the FDA approved fosdenopterin to reduce the risk of death in patients who have MoCD type A.
- Stakeholders commenting on this topic thought that, as the first disease-modifying therapy for MoCD type A, fosdenopterin has substantial potential to improve patient outcomes and disrupt the current paradigm of care.
- Stakeholders also thought that clinical trial results reported on only a small number of patients and that results from ongoing trials would be needed to confirm the results observed in this small patient population.

Patient Population

Fosdenopterin is intended for patients with MoCD type A.

Intervention

MoCD type A is caused by loss-of-function variants in a gene called the molybdenum cofactor synthesis 1 gene, *MOCS1*. These genetic variants prevent the conversion of guanosine triphosphate to cyclic pyranopterin monophosphate (cPMP), an essential metabolic intermediate needed to produce sufficient levels of molybdenum cofactor.[313,314]

Molybdenum cofactor is a major component of the enzyme sulfite oxidase, which normally helps clear sulfite, a potent neurotoxin, from the body. Buildup of sulfite is believed to cause the rapid, severe damage to the central nervous system seen in patients with MoCD type A.[313-315] The National Library of Medicine's MedlinePlus Genetics website offers more information about MoCD.

Fosdenopterin (Nulibry, formerly ORGN001 or BBP-870) is a synthetic cPMP intended for use as a substrate replacement therapy. By restoring cPMP levels, fosdenopterin is thought to increase molybdenum cofactor biosynthesis that, in turn, restores sulfite oxidase activity to allow sulfite removal and prevent neurotoxicity.[316,317]

According to the FDA-approved prescribing information, fosdenopterin is given daily, intravenously, at an initial dose of 0.4 mg/kg for preterm neonates and 0.55 mg/kg for term neonates.[318] Daily fosdenopterin dose is increased at months 1 and 3 to a maximum dose of 0.9 mg/kg once daily.

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 2 ongoing trials for this topic. We present these trials in Table 6.7.

Table 6.7. Ongoing Clinical Trials

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
Safety & Efficacy Study of ORGN001 (Formerly ALXN1101) in Pediatric Patients With MoCD type A Currently Treated With rcPMP NCT02047461 See results summarized from the Nulibry prescribing information under Recently Completed and Ongoing Trials With Available Results	Children (ages not specified; n = 7) with a genetically confirmed diagnosis of MoCD type A being treated with rcPMP infusions at time of enrollment (rcPMP was an investigational cPMP replacement therapy available to a small number of patients on a named-patient basis)[319]	Phase 2, open-label, single-arm, dose-escalation study to assess the safety and efficacy of fosdenopterin to treat MoCD type A Primary outcomes, at 6 months: • Safety, measured by type, number, and frequency of AEs and SAEs • Change from baseline in laboratory measurements, physical examination findings, vital signs, and EEG results Selected secondary outcomes, at 72 months: • Change from baseline on urine and blood biomarkers • Motor and cognitive function • Safety measures	Primary and study completion December 2021
Study of ORGN001 (Formerly ALXN1101) in Neonates With Molybdenum Cofactor Deficiency (MoCD) Type A NCT02629393 See results summarized from the Nulibry prescribing information under Recently Completed and Ongoing Trials With Available Results	Children aged up to 5 years (n = 5) with a diagnosis of MoCD type A	Phase 2/3, open-label, single-arm study evaluating the safety and efficacy of fosdenopterin to treat MoCD type A Primary outcome: Overall survival at 36 months Selected secondary outcomes, at 12 months: • Growth • Development • Disability • Gross motor function • Feeding pattern	Primary completion December 2021 Study completion December 2022

Abbreviations: AE, adverse event; cPMP, cyclic pyranopterin monophosphate; EEG, electroencephalography; MoCD, molybdenum cofactor deficiency; rcPMP, recombinant *Escherichia coli*–derived cyclic pyranopterin monophosphate; SAE, serious adverse event.

Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed late-phase trial with published results.[319] We summarize this most recent study with results as written in an abstract of a peer reviewed, published article. We also present data from 2 additional trials as summarized in the fosdenopterin prescribing information.[318]

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

Safety & Efficacy Study of ORGN001 (Formerly ALXN1101) in Pediatric Patients With MoCD Type A Currently Treated With rcPMP. NCT02047461; Study of ORGN001 (Formerly ALXN1101) in Neonates With Molybdenum Cofactor Deficiency (MOCD) Type A. NCT02629393. Origin Biosciences, Inc, 2021.[318]

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

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

Efficacy and Safety of Cyclic Pyranopterin Monophosphate Substitution in Severe Molybdenum Cofactor Deficiency Type A: A Prospective Cohort Study. Schwahn et al, 2015.[319]

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

near-normal long-term development. We detected no biochemical or clinical response in patients with type B disease."

Manufacturers and Regulatory Status

Origin Biosciences, Inc (Palo Alto, California), an affiliate of BridgeBio Pharma, Inc (Palo Alto, California), manufactures fosdenopterin. On February 26, 2021, the FDA approved fosdenopterin, under the trade name Nulibry, for injection to reduce the risk of death due to MoCD type A.[320] The new drug application for fosdenopterin was reviewed under the FDA's priority review program.[321] The agency had previously granted fosdenopterin orphan drug, breakthrough therapy, and rare pediatric disease designations for this indication.[322]

Cost Information

According to a media report, fosdenopterin costs about $500 000 per patient per year of treatment.[323]

Key Stakeholder Perspectives

Between June 25 and July 13, 2021, six stakeholders, reflecting health systems, nursing, physician, and research perspectives, provided comments and ratings on fosdenopterin to treat MoCD type A. The list below provides a summary of key stakeholder perspectives.

- Fosdenopterin represents a promising disease-modifying treatment for a disease with no such therapy. As such, fosdenopterin has substantial potential to reduce death rates and improve patient health outcomes.
- Although promising, results are available for only a small number of cPMP-treated patients because of the rarity of the disease. For fosdenopterin to be adopted, the 2 ongoing studies of fosdenopterin (synthetic cPMP) would need to confirm the results observed for recombinant cPMP in earlier trials. Additional safety data may be needed to allay concerns regarding treatment complications reported in trials, including the potential for phototoxicity.
- As a disease-modifying therapy, fosdenopterin might cause substantial disruption of MoCD type A treatment paradigms. In addition, the requirement for daily intravenous dosing and ultracold storage might place a substantial treatment burden on patients and caregivers.
- Fosdenopterin is very costly, which could increase existing disparities based on socioeconomic status, provider access, and insurance coverage. However, if effective, it could reduce costs associated with supportive care and hospital admissions and decrease disparities in access to care, if caregivers could administer the treatment at home. Effects of fosdenopterin adoption on the health care system overall would be minimized by the small number of patients affected by MoCD type A.

Human Plasminogen (Ryplazim) to Treat Congenital Plasminogen Deficiency

Highlights

- Ryplazim is an intravenously administered, purified plasminogen concentrate under study for treating patients with congenital plasminogen deficiency.
- A rare disease, congenital plasminogen deficiency is caused by genetic variants in the plasminogen gene and characterized by the formation of fibrin-rich lesions in mucous membranes throughout the body.

- Ryplazim was approved by the FDA on June 4, 2021, to treat patients who have plasminogen deficiency type 1, making it the first FDA-approved treatment option for patients with the disease.
- Stakeholders commenting on this topic thought that the available clinical data on human plasminogen suggest that it has substantial potential to improve outcomes in patients with congenital plasminogen deficiency, basing their opinions on the observed improvement in plasminogen levels and effect on congenital plasminogen deficiency–related lesions.
- Stakeholders also thought that human plasminogen would substantially disrupt the treatment of patients with congenital plasminogen deficiency because it is the first FDA-approved treatment and because of its requirement for frequent, ongoing intravenous infusions.

Patient Population

Human plasminogen is intended patients with plasminogen deficiency type 1 (hypoplasminogenemia).

Intervention

Congenital plasminogen deficiency is a genetic disease caused by loss-of-function variants in the plasminogen gene, *PLG*.[324] A rare disease, congenital plasminogen deficiency occurs in an estimated 1.6 cases per 1 million population. The website of the Genetic and Rare Diseases Information Center of the National Institutes of Health website offers more information on plasminogen deficiency type 1.

The disease leads to a deficiency in plasminogen, a zymogen (an inactive form of an enzyme) whose active form is plasmin. Plasmin serves a key role in lysis of the protein fibrin. The main clinical manifestation of this deficiency is the formation of fibrin-rich, woody extravascular lesions in mucous membranes throughout the body.[325,326]

Patients with congenital plasminogen deficiency can develop lesions in the conjunctival membranes of the eye and eyelid, which can lead to vision impairment or blindness if left untreated. Lesions can also form in the respiratory tract, possibly leading to respiratory failure, and in the central nervous system, potentially leading to occlusive hydrocephalus. Other affected tissues include mucous membranes in the ears, nasopharynx, oral cavity, gastrointestinal tract, and genitourinary tract.[327]

Human plasminogen replacement therapy (Ryplazim) is under study for treating patients who have congenital plasminogen deficiency. It consists of a purified Glu-plasminogen concentrate isolated from human plasma.[327] The replacement therapy is intended to restore adequate levels of plasminogen activity in these patients, correcting symptoms of the disease. Glu-plasminogen, characterized by a glutamate residue at its amino terminus, is the predominant form of circulating plasminogen and is rapidly converted to the more easily cleaved Lys-plasminogen upon binding to a fibrin clot.

According to the FDA-approved labeling, Ryplazim is given as an intravenous infusion at a dose of 6.6 mg/kg. Dosing frequency is once every 2 to 4 days.[328]

Evidence Development Summary

Ongoing Trials

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

Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed phase 2/3 trial with published results.[327] We summarize results as written in the abstract of a peer reviewed, published article.

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

A Study of Prometic Plasminogen IV Infusion in Subjects With Hypoplasminogenemia. NCT02690714. Shapiro et al, 2018.[327]

- **Patient population/planned enrollment:** Children and adults (n = 15) aged 2 to 80 years with a diagnosis of congenital plasminogen deficiency and a plasminogen activity level ≤ 45%
- **Study design:** Phase 2/3, single-arm, open-label trial of the safety and efficacy of IV plasminogen divided into 3 segments. In segment 1, patients received a single IV infusion of plasminogen (6.6 mg/kg) to determine the individual's pharmacokinetic profile. In segment 2, patients received repeated doses of IV plasminogen every second, third, or fourth day for 12 weeks. In segment 3, patients continued receiving repeat doses of plasminogen at established dosing.
- **Primary outcomes:** Trough plasminogen activity levels during segment 2, number of lesions after 48 weeks of treatment, size of lesions after 48 weeks, and spirometry results after 48 weeks in patients with bronchial lesions
- **Results presented by study authors:** "Reported here are data on 14 patients who completed at least 12 weeks of treatment. The primary end point was an increase in trough plasminogen activity levels by at least an absolute 10% above baseline. The secondary end point was clinical success, defined as ≥50% improvement in lesion number/size or functionality impact from baseline. All patients achieved at least an absolute 10% increase in trough plasminogen activity above baseline. Clinical success was observed in all patients with clinically visible (conjunctiva and gingiva), nonvisible (nasopharynx, bronchus, colon, kidney, cervix, and vagina), and wound-healing manifestations of the disease. Therapeutic effects were rapid, as all but 2 lesions resolved or improved after 4 weeks of treatment. Human Glu-plasminogen was well tolerated in both children and adults."

Manufacturers and Regulatory Status

Liminal BioSciences, Inc (Laval, Québec, Canada), previously known as Prometic Life Sciences, developed Ryplazim. On June 4, 2021, the FDA approved a biologics license application (BLA) for Ryplazim to treat patients who have plasminogen deficiency type 1.[329] Ryplazim is intended to be delivered by a health care practitioner.[328]

The BLA was originally submitted in 2017 and received a complete response letter from the FDA that reportedly identified the need for changes to the chemistry, manufacturing, and controls section of the application.[330,331] The FDA accepted a resubmission of the BLA in September 2020.[332] The agency had previously granted Ryplazim orphan drug and rare pediatric disease designations to treat congenital plasminogen deficiency.[331]

On October 15, 2021, Liminal BioSciences closed the sale of its remaining plasma-derived therapeutics business to Kedrion SpA, (Castelvecchio Pascoli [Lucca], Italy). The sale included Ryplazim, for which Kedrion assumed all development, manufacturing, and marketing activities.[333,334]

Cost Information

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

Key Stakeholder Perspectives

Between February 5 and March 4, 2021, eight stakeholders, reflecting clinical, health systems, nursing, and research perspectives, provided comments and ratings on human plasminogen to treat

congenital plasminogen deficiency. Stakeholders commented before the FDA approval of Ryplazim. The list below provides a summary of key stakeholder perspectives.

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

Lumasiran (Oxlumo) to Treat Hyperoxaluria Type 1

Highlights

- Lumasiran is an RNA interference (RNAi) therapeutic intended to prevent kidney stone formation, kidney damage, and eventual dialysis by reducing accumulation of harmful oxalate crystals.
- In November 2020, the FDA approved lumasiran for reducing urinary oxalate levels in children and adults. A health care provider delivers the drug as an injection under the skin every 1 to 3 months, according to weight-based dosing recommendations.
- Treatment with lumasiran is very expensive. For instance, the first year of treatment would cost more than $1 million for an individual weighing 80 kg (176 lb). However, this must be weighed against the very high cost of ongoing procedures for managing kidney dysfunction, including lithotripsy, surgery, or dialysis, and the impact of these procedures on quality of life.
- Stakeholders commenting on this topic thought that lumasiran could largely shift hyperoxaluria type 1 (PH1) management to a disease prevention model and away from managing complications from progressive stone formation and kidney damage.

Patient Population

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

Intervention

PH1 is a rare, inherited disorder characterized by development of kidney and bladder stones from the buildup of excessive oxalate crystals. As the disease progresses, kidney function declines, and the excessive oxalate buildup in plasma becomes life threatening.[335,336] Before lumasiran's FDA approval, no drug treatments were available for PH1, and disease management included treatment of symptoms and organ transplantation.[335,337,338] The website of the Genetic and Rare Diseases Information Center of the National Institutes of Health website offers more information about PH1.

Lumasiran (Oxlumo) is an RNAi therapeutic intended to reduce glycolate oxidase (GO) expression.[339] GO is a key enzyme in the oxalate metabolic pathway that catalyzes oxalate formation from its precursor glyoxylate. Lumasiran purportedly targets the messenger RNA of the hydroxyacid oxidase 1 gene, *HAO1*, which encodes GO in the liver, thereby reducing oxalate production and buildup. Lumasiran is intended to improve health outcomes and reduce disease burden in patients with PH1 who have oxalate accumulation in the kidneys and the urinary tract.[335,338]

According to the FDA-approved labeling, lumasiran is given by a health care professional as an injection under the skin. Dose and frequency depend on patient weight. The loading dose is 3 or 6 mg/kg once monthly for the first 3 months. Thereafter, maintenance doses (starting 1 month after the final loading dose) are 3 mg/kg once every month for patients weighing less than 10 kg (22 lb) and 3 or 6 mg/kg once every 3 months for patients weighing more than 10 kg.[340]

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 4 ongoing trials for this topic. We present three phase 3 trials in Table 6.8. We excluded a phase 2 trial (NCT03350451) because the later-phase trials examine patients of all ages and different severities of condition.

Table 6.8. Ongoing Clinical Trials

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
A Study to Evaluate Lumasiran in Children and Adults With Primary Hyperoxaluria Type 1 (ILLUMINATE-A) NCT03681184 See preliminary results by Garrelfs et al, 2021, and Assimos et al, 2021, under Recently Completed and Ongoing Trials With Available Results	Patients (n = 39) aged 6 years or older who have a diagnosis of PH1 and an eGFR < 30 mL/min/1.73 m^2	Phase 3, randomized, parallel-assignment, double-blind trial to evaluate the safety and efficacy of lumasiran in patients who have PH1 Patients will be randomly assigned to receive either lumasiran or placebo injected under the skin. Primary end point: Percentage change in 24-hour Uox excretion corrected for BSA up to 6 months Secondary end points: • Percentage change in 24-hour Uox to creatinine ratio from baseline up to 6 months • Percentage of patients with 24-hour Uox corrected for BSA at or below ULN or at or below 1.5 times ULN up to 6 months • Change in eGFR up to 6 months • Change in plasma oxalate up to 6 months • Rate of kidney stone events	Primary completion November 2019 Study completion January 2024

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
A Study of Lumasiran in Infants and Young Children With Primary Hyperoxaluria Type 1 (ILLUMINATE-B) NCT03905694 See preliminary results by Michael et al, 2020, under Recently Completed and Ongoing Trials With Available Results	Infants and children aged up to 5 years (n = 18) with a diagnosis of PH1	Phase 3, single-group, open-label study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran in infants and young children with PH1 Patients will receive lumasiran by injection under the skin. Primary outcome: Percentage change in Uox excretion up to 6 months Selected secondary outcomes, up to 60 months: • Percentage change in Uox excretion • Percentage of patients with Uox excretion at or below the ULN and at or below 1.5 times the ULN • Change in eGFR • Frequency of AEs	Primary completion June 2020 Study completion August 2024
A Study to Evaluate Lumasiran in Patients With Advanced Primary Hyperoxaluria Type 1 (ILLUMINATE-C) NCT04152200 See preliminary results by Alnylam Pharmaceuticals, 2021, under Recently Completed and Ongoing Trials With Available Results	Patients of all ages (n = 21) with a diagnosis of PH1 and eGFR ≤ 45 mL/min/1.73 m^2 for patients 12 months of age or older. Patients younger than 12 months must have serum creatinine considered elevated for their age.	Phase 3, single-group, open-label study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran in patients with PH1 Patients will receive lumasiran by injection under the skin Primary outcomes: • Percentage change in plasma oxalate up to 6 months • Percentage change in predialysis plasma oxalate up to 6 months Selected secondary outcomes: • Absolute change in plasma oxalate up to 60 months • Change in frequency of dialysis up to 60 months • Change in eGFR up to 60 months • Change in quality of life eGFR assessed on PedsQL and KDQOL up to 60 months	Primary completion May 2021 Study completion July 2025

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

Recently Completed and Ongoing Trials With Available Results

Our searches identified 3 recently completed late-phase trials with published results. We summarize these results as written in the abstracts of a peer reviewed, published article[338]; 2 conference abstracts[341,342]; and a company news release.[343]

The following abbreviations are used in this section: AE or Ae, adverse event; BSA, body surface area; CI, confidence interval; Cr, creatinine; DBP, double-blind period; eGFR, estimated

glomerular filtration rate; EP, extension period; ISR, injection-site reaction; KSE, kidney stone event; L/L, patient group initially receiving lumasiran; M, months; P, *P* value; PH1, primary hyperoxaluria type 1; P/L, patient group initially receiving placebo; SAE, serious adverse event; ULN, upper limit of normal; Uox, urinary oxalate.

A Study to Evaluate Lumasiran in Children and Adults With Primary Hyperoxaluria Type 1 (ILLUMINATE-A). NCT03681184. Garrelfs et al, 2021,[338] and Assimos et al, 2021.[341]

- **Patient population/planned enrollment:** Patients (n = 39) aged 6 years or older with PH1 randomly assigned to lumasiran injection (n = 26) or placebo (n = 13)
- **Study design:** Phase 3, randomized, parallel-assignment, double-blind trial to evaluate the safety and efficacy of lumasiran in patients who have PH1. Patients in the lumasiran group received lumasiran (3.0 mg/kg) injected under the skin at day 1 and months 1, 2, 3, and 6; they then received placebo injected under the skin at months 7 and 8, followed by subcutaneous lumasiran (3.0 mg/kg) at month 9 and then every 3 months. Patients in the placebo group received lumasiran-matching placebo injected under the skin at day 1 and months 1, 2, and 3; they then received lumasiran (3.0 mg/kg) injected under the skin at months 6, 7, and 8, followed by subcutaneous lumasiran at month 9 and then every 3 months.
- **Primary outcome:** Percentage change in 24-hour Uox excretion corrected for BSA up to 6 months
- **Secondary outcomes:** Percentage change in 24-hour Uox to creatinine ratio from baseline up to 6 months, percentage of patients with 24-hour Uox corrected for BSA at or below ULN or below 1.5 times ULN up to 6 months, change in eGFR up to 6 months, change in plasma oxalate up to 6 months, and rate of KSEs
- **Results presented by Garrelfs et al:** "The least-squares mean difference in the change in 24-hour urinary oxalate excretion (lumasiran minus placebo) was −53.5 percentage points (P < 0.001), with a reduction in the lumasiran group of 65.4% and an effect seen as early as month 1. The between-group differences for all hierarchically tested secondary end points were significant. The difference in the percent change in the plasma oxalate level (lumasiran minus placebo) was −39.5 percentage points (P < 0.001). In the lumasiran group, 84% of patients had 24-hour urinary oxalate excretion no higher than 1.5 times the upper limit of the normal range at month 6, as compared with 0% in the placebo group (P < 0.001). Mild, transient injection-site reactions were reported in 38% of lumasiran-treated patients."
- **Results presented by Assimos:** "During the DBP, the least square mean treatment difference in 24hr urinary oxalate (Uox) excretion for lumasiran compared to placebo was –53.5% ($p=1.7\times10^{-14}$), and 84% of lumasiran treated patients achieved near-normalization or normalization (≤1.5 x upper limit of normal) of 24hr Uox excretion at M6 (vs 0% placebo-treated patients). In the EP, the 13 patients initially randomized to placebo crossed over to lumasiran (P/L), demonstrating a similar time course and magnitude of Uox reduction. After 6M of treatment, their 24hr Uox mean percent reduction was 57.3% and a comparable proportion (77%) achieved near-normalization or normalization of 24hr Uox excretion. In patients initially randomized to lumasiran (L/L), the reduction in 24hr Uox was sustained through 12M. The calculated rate (per 100 person-days) of kidney stone events (KSE) in the L/L group decreased from a reported rate of 0.87 (95% CI: 0.70, 1.08) over the 12M prior to consent, to observed rates of 0.30 (95% CI: 0.17, 0.51) for the 6M DBP, to 0.23 (95% CI: 0.13, 0.43) with an additional 6M of lumasiran. In the P/L group, KSE rates remained stable from a reported rate of 0.15 (95% CI: 0.07, 0.31) over the 12M prior to consent, to 0.18 (95% CI: 0.07, 0.48) during the 6M DBP, followed by a decrease to 0.05 (95% CI: 0.01, 0.32) during the first 6M of lumasiran treatment. Consistent with the DBP, the most common adverse events related to lumasiran in the EP were mild, transient injection site reactions."

A Study of Lumasiran in Infants and Young Children With Primary Hyperoxaluria Type 1 (ILLUMINATE-B). NCT03905694. Michael et al, 2020.[342]

- **Patient population/planned enrollment:** Infants and children younger than 6 years (n = 18) with a diagnosis of PH1
- **Study design:** Phase 3, single-group, open-label study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran injection in young children
- **Primary outcome:** Percentage change in Uox excretion up to 6 months
- **Selected secondary outcomes:** Percentage change in Uox excretion up to 60 months, percentage of patients with Uox excretion at or below the ULN and at or below 1.5 times the ULN up to 60 months, change in eGFR up to 60 months, and frequency of AEs up to 60 months
- **Results presented by Michael et al:** "Eighteen patients enrolled, including 4 patients <2 years; median age at first dose 4.3 years (range: 0.3-6). The baseline mean spot urinary oxalate:creatinine (Uox:Cr) was 0.63 mmol/mmol (range: 0.17-1.71), equivalent to 5.8×ULN for age. As of March 2020, there were no lumasiran-related serious adverse events; no deaths, severe adverse events, or treatment discontinuations. The most common adverse events related to lumasiran were mild, transient injection site reactions in 3/18 patients."

A Study to Evaluate Lumasiran in Patients With Advanced Primary Hyperoxaluria Type 1 (ILLUMINATE-C). NCT04152200. Alnylam Pharmaceuticals, 2021.[343]

- **Patient population/planned enrollment:** Patients of all ages (n = 21) with a diagnosis of PH1 and eGFR ≤ 45 mL/min/1.73 m^2 for patients 12 months of age or older. Patients younger than 12 months must have had serum creatinine considered elevated for their age.
- **Study design:** Phase 3, single-group, open-label study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran in patients with PH1
- **Primary outcomes:** Percentage change in plasma oxalate up to 6 months and percentage change in predialysis plasma oxalate up to 6 months
- **Selected secondary outcomes:** Absolute change in plasma oxalate up to 60 months, change in frequency of dialysis up to 60 months, change in eGFR up to 60 months, and change in quality of life to 60 months
- **Results presented in an Alnylam news release:** "At six months, treatment with lumasiran resulted in a substantial reduction in plasma oxalate from baseline in both dialysis-independent and -dependent patients. Lumasiran also demonstrated positive results across key secondary endpoints, including measures of urinary oxalate (for patients in Cohort A) and additional measures of plasma oxalate. There were no deaths and no drug related SAEs among enrolled patients. There were two treatment discontinuations due to adverse events in the extension period of the study, neither of which was drug related. The most common drug related Aes (occurring in 10 percent or more of patients) were ISRs reported in five patients (23.8 percent), all of which were mild."

Manufacturers and Regulatory Status

Alnylam Pharmaceuticals (Cambridge, Massachusetts) manufactures lumasiran. On November 23, 2020, the FDA approved the new drug application for lumasiran injection, under the trade name Oxlumo, to lower urinary oxalate levels in children (aged from birth or older) and adults who have PH1.[344] The FDA previously granted lumasiran breakthrough therapy, orphan drug, priority review, and rare pediatric disease designations for treating patients who have PH1.[339]

Cost Information

An online aggregator of US-based prescription drug prices, Drugs.com, reported a retail price of $57 430 for 1 single-use vial of 94.5 mg of lumasiran (as of October 11, 2021).[345] Adult patients with an average weight of 80 kg (176 lb) would receive 240 mg of lumasiran once monthly for 3 months and then once every 3 months. Therefore, the first year of treatment would cost about $1 million ($172 290 per injection). The cost every year thereafter, for the same individual, would be about $689 000.

The company has announced it would work with several health plans and pharmacy benefit managers to create value-based agreements for lumasiran therapy. Under these agreements, the manufacturer will receive certain payments if patients respond to therapy and achieve predefined treatment success targets. Also under such agreements, payers are eligible for rebates if more PH1 diagnoses and requests for lumasiran treatment occur than expected, based on epidemiologic estimates. Further, payers may receive rebates if a patient exceeds an established volume of lumasiran vials over time for the weight-based dosing therapy.[346,347]

Key Stakeholder Perspectives

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

- Lumasiran use has demonstrated substantial reductions in urine oxalate levels that should correlate with reduced kidney stone formation and less kidney injury over the longer term.
- Lumasiran injections could disrupt PH1 treatment by shifting to disease prevention and away from managing complications after stone formation and long-term renal injury requiring more invasive procedures.
- Treatment costs with lumasiran are likely to be high but could translate into reduced long-term treatment costs if the drug prevents kidney stone formation, kidney injury, and eventual need for dialysis and kidney transplantation.
- Improvements in patient outcomes and quality of life could be greatest for younger patients who currently face a longer duration of illness from increased oxalate levels.

MT1621 to Treat Thymidine Kinase 2 Deficiency

Highlights

- MT1621 is an oral combination drug of deoxycytidine and deoxythymidine nucleosides, molecules that are precursors to nucleotides, the building blocks of genetic material.
- The drug is in phase 3 development and is intended to correct the underlying cause of thymidine kinase 2 deficiency (TK2d), a rare, inherited, mitochondrial DNA depletion disorder. It addresses the cause of TK2d by making DNA building blocks (ie, nucleotides) available for normal DNA synthesis.
- The current standard of care for TK2d is supportive, and the FDA has not approved any treatments for the disorder.
- Stakeholders commenting on this topic thought that MT1621 might significantly improve patient health outcomes and quality of life by increasing survival, stabilizing or restoring motor function, and reducing the need for supportive care. If approved, stakeholders believed, it would likely become the standard of care for TK2d.

- Because MT1621 is taken by mouth, stakeholders thought it would be convenient and easy for patients to use. However, disparities in treatment access may arise because of treatment cost and insurance coverage variability.

Patient Population

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

Intervention

TK2d is an ultrarare, inherited, genetic disorder resulting in progressive muscle weakness (myopathy). TK2d has no approved treatments.[348] This mitochondrial DNA depletion disorder is caused by a genetic variation in the *TK2* gene. The *TK2* gene normally produces the protein TK2, a metabolic enzyme that is necessary for generating and maintaining a balanced pool of DNA building blocks (ie, nucleotides) in mitochondria, the specialized structures (ie, organelles) within cells that provide usable energy for the body.[349,350]

Loss of TK2 protein function induces a nucleotide imbalance that impairs DNA synthesis in mitochondria, which, in turn, impairs mitochondrial function. This lowers production of adenosine triphosphate, the molecule that stores and provides energy for body functions.[349,350] This leads to progressive and often severe muscle weakness that impairs movement, eating, and breathing and that can be fatal, most often from respiratory failure.[349-351] The National Library of Medicine's Genetics Home Reference website offers more information about TK2d.

MT1621 is intended to treat the underlying cause of TK2d, purportedly halting disease progression and improving motor and respiratory function.[352,353] MT1621 is an orally administered treatment containing a combination of the nucleosides deoxycytidine and deoxythymidine, precursors of 2 nucleotides that are incorporated into DNA.[352] By providing an external source of nucleosides, MT1621 purportedly restores balance to the nucleotide pool, thus restoring mitochondrial DNA synthesis and mitochondrial function.[354]

In clinical trials, MT1621 is dissolved in solution and taken by mouth at a dosage up to 400 mg/kg daily.[355]

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified 4 ongoing trials for this topic. We present these trials in Table 6.9.

Table 6.9. Ongoing Clinical Trials

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
A Retrospective Study of Subjects With Thymidine Kinase 2 Deficiency NCT05017818	Children and adults of unspecified age (n = 50) with a confirmed genetic mutation in the *TK2* gene	Noninterventional, retrospective chart review to assess survival of patients with TK2d treated with MT1621 compared with in an untreated control group Patients in the intervention group were treated with chemical-grade dCMP/dTMP, dC/dT, or MT1621 outside of a clinical trial. Primary outcomes: Vital status and survival Selected secondary outcomes: • Motor function • Clinician Global Impression of Improvement • Need for nutritional or respiratory support • Adverse events	Primary completion October 2021 Study completion December 2021
An Open-Label Study of Continuation Treatment With Combination Pyrimidine Nucleosides in Patients With TK2 NCT03845712	Children and adults of unspecified age (n = 49) with a confirmed genetic mutation in the *TK2* gene, without other genetic or polygenic disease	Phase 2, open-label, single-arm study to assess the safety and efficacy of MT1621 to treat TK2d All patients will receive MT1621 taken by mouth 3 times daily at a total dosage of up to 400 mg/kg daily for up to 36 months. Annual assessments of safety and efficacy will continue annually after the 36-month treatment period. Primary outcome: Safety, measured by adverse events, laboratory measurements, and electrocardiograms Selected secondary outcomes: • Efficacy, measured by lung and motor function tests, growth, and need for nutritional support • Clinician and caregiver global impression of improvement	Primary and study completion January 2022

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
Treatment of TK2 Deficiency With Thymidine and Deoxycytidine NCT03639701	Children and adults of unspecified age (n = 20) with a confirmed genetic mutation in the *TK2* gene, without other genetic or polygenic disease	Phase 1/2, open-label, single-arm study to assess the safety and efficacy of MT1621 to treat TK2d All patients will receive MT1621 taken by mouth 3 times daily at a total dosage of up to 400 mg/kg daily for up to 60 months. Primary outcome: Safety, measured by adverse events, laboratory measurements, electrocardiograms, and diarrhea incidence Selected secondary outcomes: • Event-free survival • Motor function • Lung function	Primary and study completion April 2024
A Study of the Efficacy and Safety of MT1621 in Thymidine Kinase 2 (TK2) Deficiency (Treatment Naïve) NCT04581733	Children and adolescents younger than 18 years (n = 16) with a confirmed genetic mutation in the *TK2* gene, with onset of disease at ≤ 12 years of age, and who have never received nucleoside treatment for TK2d	Phase 3b, open-label, single-arm study to assess the safety and efficacy of MT1621 for treating TK2d All patients will receive MT1621 taken by mouth 3 times daily at a total dosage of up to 400 mg/kg for up to 12 months. Primary outcome: Acquisition of a motor milestone not present at baseline Secondary outcomes: Time to acquisition of a motor milestone and survival	Primary completion March 2025 Study completion April 2025

Abbreviations: dC/dT, deoxycytidine and deoxythymidine; dCMP/dTMP, deoxycytidine monophosphate and thymidine monophosphate; TK2, thymidine kinase 2; *TK2*, thymidine kinase 2 gene; TK2d, thymidine kinase 2 deficiency.

Recently Completed and Ongoing Trials With Available Results

Our searches identified a single recently completed late-phase trial. We summarize results from this study as presented in a company news release[356] and a poster presentation.[353]

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

A Retrospective Study of Patients With TK2d (RETRO). NCT03701568. Zogenix, 2019,[356] and Quan et al, 2019.[353]

- **Patient population/planned enrollment:** Children and adults (n = 38) with TK2d and who were previously treated with deoxycytidine and deoxythymidine
- **Study design:** Retrospective, observational study to review data from patients previously treated with deoxycytidine and deoxythymidine. Participants were given a fixed combination of deoxycytidine and deoxythymidine at an unknown dose for a median of 77 weeks.
- **Primary outcomes:** Safety and tolerability of deoxycytidine and deoxythymidine therapy for TK2d

- **Secondary outcomes:** BMI, clinical course (achievement, loss, or regain of developmental motor milestones), motor function, and ambulatory assessments
- **Results presented by study authors:** "All treated patients remain alive. A survival analysis using a time-dependent Cox regression model showed that the difference in probability of survival between treated patients and untreated natural history control patients was highly statistically significant ($p<0.0006$) . . . the vast majority of treated patients (94.7%) had either improved (68%) or stabilized (26%) responses in major functional domains."[356]

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

  "Ambulation: 3 subjects who had lost ambulation prior to treatment regained ambulation; 1 subject who had never walked gained ambulation.

  "Respiratory function: 1 subject receiving 24 hours/day of invasive mechanical ventilation prior to treatment discontinued all respiratory support following treatment.

  "Feeding Support: 3 subjects had their feeding tubes removed, out of a total of 8 subjects on feeding tubes at study start."[353]

Manufacturers and Regulatory Status

MT1621 is being developed by Zogenix (Emeryville, California). It is in phase 3 development for treating TK2d. Zogenix announced in August 2020, after meeting with the FDA about a regulatory pathway forward, that it anticipated having all necessary clinical trial data by 2021 and submitting a new drug application in the first half of 2022.[357,358] MT1621 received FDA breakthrough therapy designation in February 2019 and orphan drug designation in July 2016 for this indication.[359,360]

Cost Information

Cost information is currently unavailable for this topic.

Key Stakeholder Perspectives

Between September 3 and September 17, 2021, nine stakeholders, reflecting caregiver, clinical, nursing, health systems, and research perspectives, provided comments and ratings on MT1621 to treat TK2d. The list below provides a summary of key stakeholder perspectives.

- Clinical trial data suggest that MT1621 has significant potential to treat TK2d, moving beyond supportive care. This could improve patient survival and enhance quality of life by stabilizing or restoring motor function and reducing the need for supportive care. However, numerous stakeholders commented that the data are preliminary and limited in quantity, and that ongoing trials are needed to provide additional evidence for evaluating this therapy.
- MT1621 is likely to become the standard of care for TK2d if the FDA approves it, considering that the current standard of care is supportive and a large unmet need exists for treatments.
- The oral delivery route of MT1621 would be convenient and ease care delivery for many patients. However, the drug's cost is, at present, unknown, and if the cost is high, disparities may arise because of insurance coverage variability. However, stakeholders felt the rarity of the disease made large-scale cost disruptions unlikely.
- MT1621 could shift the paradigm of care from supportive to preventive and, therefore, impact the treatment goals and management of patients with TK2d. But because of the rarity of the condition, it is not likely to disrupt population health outcomes or the overall health care system.

- A reduction in the need for supportive care (eg, ambulatory devices, respiratory support, feeding support) is likely to result in a reduction in resource use and significant health care cost savings.

Pegcetacoplan (Empaveli) to Treat Paroxysmal Nocturnal Hemoglobinuria

Highlights

- Pegcetacoplan is a synthetic cyclic peptide that targets the complement pathway that could address the shortcomings of existing complement inhibitors, potentially improving health outcomes for patients with paroxysmal nocturnal hemoglobinuria (PNH).
- FDA-approved treatment with complement component 5 (C5) inhibitors requires ongoing intravenous infusions every 2 weeks to 2 months, and many patients continue to experience anemia and its associated symptoms. In contrast, pegcetacoplan, also FDA approved, is infused under the skin, avoiding the need for repeated intravenous infusions.
- Stakeholders commenting on this topic thought that initial data show pegcetacoplan has better efficacy and safety compared with the C5 inhibitor eculizumab, including sustained improvements in hemoglobin levels and reduced need for blood transfusions, which might prevent disease progression and improve patient health outcomes.
- Stakeholders also thought that the potential for the pegcetacoplan subcutaneous infusion to be given at home could shift the care setting, increase access to care, decrease medical resource use, and improve patient quality of life.

Patient Population

Pegcetacoplan is intended for adults who have a confirmed diagnosis of PNH.

Intervention

PNH is a rare, acquired disease characterized by red blood cell destruction (hemolytic anemia), blood clots (thrombosis), and bone marrow failure (ie, decreased production of one or more major blood cell lineages).[361,362] The Aplastic Anemia and MDS International Foundation website provides more information about PNH.

Dysregulation of the complement pathway is a central cause of PNH, and C5 inhibitors (eculizumab and ravulizumab-cwvz) have been approved by the FDA to treat these patients.[363] However, the C5 inhibitors have substantial shortcomings: many patients treated with C5 inhibitors continue to experience anemia and its associated symptoms,[364] and C5 inhibitors require ongoing intravenous infusions every 2 weeks to 2 months.

Pegcetacoplan (Empaveli, formerly APL-2) is an immune complement system inhibitor approved by the FDA in May 2021 to treat patients who have PNH. The new drug could address the shortcomings of existing complement inhibitors, potentially improving patient health outcomes.

Pegcetacoplan is a synthetic cyclic peptide that targets the complement component 3 (C3), which operates earlier in the complement cascade than does C5. C3 helps regulate opsonization (ie, tagging cell surfaces for immune system targeting), inflammation, and formation of the membrane attack complex on cell surfaces. By targeting C3, pegcetacoplan is thought to offer broader inhibition of the complement cascade compared with existing complement inhibitors that target C5.[364,365] Additionally, pegcetacoplan is given by subcutaneous infusion and, therefore, could avoid the need for repeated intravenous infusions.

According to the FDA-approved label, the drug is given by subcutaneous infusion over 30 to 60 minutes at a dosage of 1080 mg twice weekly.[363]

Evidence Development Summary

Ongoing Trials

Our searches of the National Clinical Trials database identified a single ongoing trial for this topic. We present this trial in Table 6.10.

Table 6.10. Ongoing Clinical Trial

Study name and National Clinical Trials identifier	Patient population and planned enrollment	Study design and outcomes	Estimated date of completion
Pegcetacoplan long term safety and efficacy extension study NCT03531255	Adults (n = 160) with PNH who were previously enrolled in another pegcetacoplan clinical trial	Phase 3, open-label, single-arm extension study to assess the long-term safety and efficacy of twice-weekly pegcetacoplan injections to treat PNH Primary outcome: Incidence and severity of treatment-emergent adverse events through 2 years	Primary and study completion August 2022

Abbreviation: PNH, paroxysmal nocturnal hemoglobinuria.

Recently Completed and Ongoing Trials With Available Results

Our searches identified 2 recently completed late-phase trials with published results.[366,367] We summarize the results as written in an abstract of a peer reviewed, published article and a company news release.

The following abbreviations are used in this section: AEs, adverse events; EMPAVELI, pegcetacoplan; LDH, lactate dehydrogenase; p, *P* value; PNH, paroxysmal nocturnal hemoglobinuria; ULN, upper limit of normal.

A Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients With PNH (PRINCE). NCT04085601. Apellis Pharmaceuticals, 2021.[366]

- **Patient population/planned enrollment:** Adults (n = 53) with PNH who have not received complement-inhibitor treatment within 3 months of enrollment (ie, are treatment naïve)
- **Study design:** Phase 3, randomized, open-label, parallel-assignment trial to assess pegcetacoplan with standard-of-care therapy excluding complement inhibitors to treat PNH in patients not receiving complement inhibitors
- **Primary outcomes:** Hemoglobin stabilization, defined as avoidance of a more than 1-g/dL decrease in hemoglobin without transfusions, and reduction in LDH level, both through week 26
- **Results presented by study authors:** "EMPAVELI demonstrated statistical superiority on the co-primary endpoints of hemoglobin stabilization and reduction in lactate dehydrogenase (LDH) compared to standard of care, which did not include complement inhibitors, at Week 26.
  "86% of EMPAVELI-treated patients achieved hemoglobin stabilization compared to 0% of patients on standard of care (p<0.0001). Hemoglobin stabilization was defined as an avoidance of a >1 g/dL decrease in hemoglobin levels in the absence of transfusions.
  "Mean LDH in the EMPAVELI group decreased by 90% from a baseline of 2151 U/L [9.5x upper limit of normal (ULN)] to 211 U/L, which is within the normal range, compared to a 14% reduction on standard of care from a baseline of 1946 U/L (8.6x ULN) to 1681 U/L (7.4x ULN) (p<0.0001)."
  "EMPAVELI also achieved statistical superiority on several secondary endpoints, including improvements in hemoglobin levels and transfusion avoidance, compared to standard of care, which did not include complement inhibitors.
  "Mean hemoglobin levels in the EMPAVELI group increased from 9.4 g/dL to 12.1 g/dL compared to an increase from a baseline of 8.7 g/dL to 9.4 g/dL on standard of care (p=0.0019).

"91% of patients on EMPAVELI were transfusion free compared to 22% on standard of care (p<0.0001).
"The safety profile of EMPAVELI was consistent with previous studies. At Week 26, 9% of patients in the EMPAVELI group experienced a serious adverse event (SAE) compared to 17% on standard of care. One death was reported in each group, and neither were related to treatment. No cases of meningitis or thrombosis were reported in either group. The most common adverse events reported during the study in the EMPAVELI and standard of care groups, respectively, were injection site reaction (30% vs. 0%), hypokalemia (13% vs.11%), and fever (9% vs. 0%)."

A Study to Evaluate the Efficacy and Safety of APL-2 in Patients With Paroxysmal Nocturnal Hemoglobinuria (PEGASUS). NCT03500549. Hillmen et al, 2021.[367]

- **Patient population/planned enrollment:** Adults (n = 80) with a primary diagnosis of PNH and hemoglobin levels less than 10.5 g/dL despite stable eculizumab therapy for at least 3 months
- **Study design:** Phase 3, randomized, open-label, crossover-assignment trial to compare the safety and efficacy of pegcetacoplan vs eculizumab to treat PNH. All patients received pegcetacoplan plus eculizumab during a 4 week run-in period before random assignment to monotherapy with pegcetacoplan (n = 41) or eculizumab (n = 39) from week 5 to week 16. From week 16 to week 48, all patients received pegcetacoplan.
- **Primary outcome:** Change in hemoglobin level from baseline to week 16
- **Secondary outcomes:** Hemoglobin normalization, defined as a hemoglobin level at or above the lower limit of the reference range without transfusions; transfusion avoidance; absolute reticulocyte count; LDH level, Functional Assessment of Chronic Illness Therapy—fatigue score; and AEs
- **Results presented by study authors: "**Pegcetacoplan was superior to eculizumab with respect to the change in hemoglobin level from baseline to week 16, with an adjusted (least squares) mean difference of 3.84 g per deciliter (P<0.001). A total of 35 patients (85%) receiving pegcetacoplan as compared with 6 patients (15%) receiving eculizumab no longer required transfusions. Noninferiority of pegcetacoplan to eculizumab was shown for the change in absolute reticulocyte count but not for the change in lactate dehydrogenase level. Functional Assessment of Chronic Illness Therapy-Fatigue scores improved from baseline in the pegcetacoplan group. The most common adverse events that occurred during treatment in the pegcetacoplan and eculizumab groups were injection site reactions (37% vs. 3%), diarrhea (22% vs. 3%), breakthrough hemolysis (10% vs. 23%), headache (7% vs. 23%), and fatigue (5% vs. 15%). There were no cases of meningitis in either group."

Manufacturers and Regulatory Status

Apellis Pharmaceuticals, Inc (Waltham, Massachusetts), manufactures pegcetacoplan. On May 14, 2021, Apellis received FDA approval for pegcetacoplan for adults with PNH.[368] This approval was based on results from the phase 3 PEGASUS study evaluating the efficacy and safety of pegcetacoplan compared vs eculizumab in adults with PNH who were treatment naïve.[368] The prescribing information for pegcetacoplan carries a black box warning regarding the potential for serious infections caused by encapsulated bacteria, and the treatment is available only through a restricted program under a risk evaluation and mitigation strategy.[363]

Pegcetacoplan is also in phase 2 development to treat pediatric patients, aged 12 to 17 years, with PNH.[369] That study (NCT04901936) has a primary completion date of April 2024.

Cost Information

An online aggregator of US-based prescription drug prices, Drugs.com, reported a retail price of $36 790 for eight 20-mL vials (160 mL) of pegcetacoplan subcutaneous solution (as of October 14, 2021).[370] Patients would receive one 20-mL dose of pegcetacoplan twice weekly. At those prices, the estimated cost of a 1-year supply is $478 270.

Key Stakeholder Perspectives

Between March 25 and April 20, 2021, nine stakeholders, reflecting clinical, health systems, nursing, patient representative, and research perspectives, provided comments and ratings on pegcetacoplan. The list below provides a summary of key stakeholder perspectives.

- Initial data show better efficacy and safety for pegcetacoplan compared with the C5 inhibitor eculizumab, including sustained improvements in hemoglobin levels and the reduced need for blood transfusions. These improvements might prevent disease progression and improve patient health outcomes. However, longer-term data and comparative data against the other available C5 inhibitor (ravulizumab-cwvz) are needed to confirm these findings.
- The convenient self-administration of the subcutaneous infusion at home could shift the care setting, increase access, and improve quality of life compared with C5 inhibitors, which are given by intravenous infusion. Training would be required to teach patients and caregivers how to perform the subcutaneous infusion.
- Pegcetacoplan might decrease medical visits and hospital admissions, reducing burdens on patients and caregivers, as well as on the health care system.
- Although rates of adverse events with pegcetacoplan were comparable to or relatively fewer compared with eculizumab, the high rate of adverse events seen in trials is a concern, and it is important that patients are vaccinated and monitored to decrease the risk of adverse events related to infections.
- The high cost of pegcetacoplan might increase health disparities for patients who are uninsured or underinsured. However, the current standard of care is also costly, and the high cost might be mitigated by the savings associated with reduced health care resource use.

Chapter 7. Potentially Disruptive Trends

For trends not fitting into one of PCORI's defined focus areas, we considered for inclusion 9 trends for which (1) information was compiled and sent for stakeholder comment before September 3, 2021; *and* (2) we received at least 5 sets of comments and ratings from stakeholders between September 18, 2020, and September 17, 2021. These 9 trends are available—or will soon be available—for viewing on the PCORI Horizon Scanning Database website.

Trends Considered for Inclusion in This Report

Table 7.1 lists 3 trends selected for inclusion in this report based on stakeholder ratings and comments and available data. Trends are listed and discussed alphabetically by title.

Table 7.1. Included Potentially Disruptive Trends

Trend title
Direct-to-consumer genetic-testing collaborations with pharmaceutical companies to facilitate drug development and treatment
Messenger RNA vaccines against infectious diseases[a]
Normothermic machine perfusion to preserve donor organs for transplantation[a]

[a] Topic appears for the first time in this edition of the *High Potential Disruption Report*.

Table 7.2 lists 6 trends considered but not selected for inclusion in this report, based on stakeholder ratings and comments and available data. Each record notes the reasons for exclusion.

Table 7.2. Potentially Disruptive Trends Considered but Not Included

Trend title	Exclusion reason(s) and notes based on stakeholder comments
Artificial intelligence to identify personalized treatment options for traumatic brain injury	This trend remains in the early research phase without identifying specific clinical applications to assess at this point. Thus, this trend has little immediate potential for disruption to clinical care for TBI, although it might hold promise that has yet to be clearly defined.
Closed-loop glucose monitoring (artificial pancreas) systems for type 1 diabetes mellitus	A shift toward automated glucose monitoring is already in progress, and it will likely continue gradually. Low to moderate disruption to diabetes management is likely as the technology improves and costs are potentially reduced to permit wider patient adoption.
N-of-1 trials to research patient-centered outcomes	N-of-1 trials have the potential to disrupt patient outcomes in the future. However, the systems needed for this purpose (eg, development of AI algorithms, updates to insurance coverage policies, research methodology shift away from traditional randomized controlled trials) might be cost prohibitive and labor-intensive and accessible only through academic research centers.
Novel antimicrobial environmental surface coatings to prevent health care–acquired infections	Antimicrobial surface implementation might require special considerations and attention at contact times, and because it would not replace other infection prevention protocol, the intervention is likely to have only an incremental effect and have low potential for disruption. More development might be necessary to maximize its effectiveness along with more data showing that it has a significant improvement in microbial transmission reduction.

Trend title	Exclusion reason(s) and notes based on stakeholder comments
Populationwide antibody testing to quantify coronavirus infection rates	Populationwide antibody testing is unlikely to directly impact patient health outcomes because it is intended to measure the prevalence of COVID-19. Although it is helpful to understand the spread and severity of the virus, this type of testing will not significantly impact population health outcomes now that most Americans are vaccinated.
Smart technology to enhance prosthetic control	This trend has great theoretical potential to disrupt the standard of care for patients with prosthetics. However, implementation of this technology trend for the vast majority of prosthetics users might never be realized because of high costs and coverage restrictions from payers and limited availability of specialists to deploy and maintain these devices to allow widespread patient access.

Abbreviations: TBI, traumatic brain injury.

Trend Summaries

We present below 3 summaries on trends deemed to have high potential for disruption. Trends are ordered alphabetically by trend title.

Direct-to-Consumer Genetic-Testing Collaborations With Pharmaceutical Companies to Facilitate Drug Development and Treatment

Highlights

- Laboratories offering direct-to-consumer (DTC) genetic-testing services are establishing collaborations with drug manufacturers to share patients' genetic data and volunteered genetic-testing questionnaire data.
- Large data sets from DTC genetic testing might enhance drug development and, ultimately, patient access to targeted therapies.
- The first new experimental treatments created through some of these collaborations have entered early testing.
- Stakeholders commenting on this trend thought that collaborations between DTC genetic-testing companies and pharmaceutical companies had the potential to accelerate the availability of novel drugs through the identification of molecular targets and the acceleration of clinical trial enrollment.
- Stakeholders expressed concern about privacy issues surrounding sharing of genetic data, potential self-selection bias from DTC genetic test users who might not represent the broader population, and potentially long lead times in availability of therapeutics from these collaborations.

Description

Laboratories that offer DTC genetic-testing services are using deidentified patient genetic data and data that patients volunteer on questionnaires to drive drug development and treatment.[371] By forming partnerships with pharmaceutical companies, DTC genetic-testing companies can provide large data sets that might identify new disease targets worth pursuing. Once candidate drugs are developed, these collaborations might also facilitate enrollment in clinical trials by identifying

eligible genetic-testing users.[371,372] In particular, these large data sets might identify potential trial participants with rare genetic diseases or genetic predispositions who might be difficult to enroll through traditional recruitment methods.

Multiple DTC testing companies are forming research collaborations to treat chronic conditions with unmet medical needs that might substantially disrupt clinical care in the next 3 years. For example, the genetic-testing company 23andMe (Sunnyvale, California) has established a collaboration with GlaxoSmithKline (Brentford, United Kingdom) to develop treatments for conditions such as cancer, Parkinson disease, and inflammatory conditions.[373] Another genetic-testing company, Nebula Genomics (San Francisco, California), is collaborating with EMD Serono (Rockland, Maryland) to use consumer data to drive the drug development process.[373,374]

Further DTC genetic-testing service collaborations with drug developers have been announced in recent years. In January 2020, 23andMe reported it granted Almirall, SA (Barcelona, Spain), worldwide rights to develop a 23andMe-designed monoclonal antibody targeting the interleukin-36 cytokine subfamily for dermatologic indications.[375] In July 2020, GlaxoSmithKline announced the start of a phase 1 trial of its first-in-class monoclonal antibody targeting the CD96 immune checkpoint receptor, codeveloped with 23andMe, to treat advanced solid tumor cancers.[376,377] The website of 23andMe also lists collaborations with Pfizer, Inc (New York, New York), to treat inflammatory bowel disease and systemic lupus erythematosus; with Celmatix, Inc (New York, New York), to treat infertility in females; and with H Lundbeck A/S (Copenhagen, Denmark) to treat major depressive disorder and bipolar disorder.[378-381]

Clinical Area(s) Potentially Disrupted

Collaborations between companies offering DTC genetic tests and drug developers could shift paradigms for drug target identification and clinical trial recruitment, and these collaborations might expedite drug development processes. Among the clinical areas potentially affected are medical genetics, neurology, cardiology, oncology, and rare and orphan diseases.

Opportunities

These collaborations might provide insight into the most promising targets for drug development and decrease the cost and time needed to develop new agents. Such collaborations might also help investigators with faster and more cost-effective recruitment of patients and asymptomatic carriers for rare diseases into clinical trials. In turn, this might result in additional, new, targeted therapies that address unmet needs and improve patient outcomes.

Threats

Poorly managed collaborations between DTC genetic test companies and drug developers might threaten patient health data privacy. Well-managed collaborations might put competing firms at a competitive disadvantage, jeopardizing further innovation. Consumers who consent to having their genetic test data used might not realize how companies profit from using their data: DTC companies can profit by selling user data and drug companies can profit from the medications created with use of those data.

Key Stakeholder Perspectives

Between September 13 and September 17, 2021, seven stakeholders, reflecting business and finance, health systems, and research perspectives, provided comments and ratings on this topic. The list below provides a summary of key stakeholder perspectives.

- Effective collaborations between DTC genetic-testing companies and drug developers could facilitate discovery of novel therapeutics, potentially decreasing their time to market and making more treatments available to patients.
- However, users of DTC genetic testing might not be representative of the US population as a whole. This risk for selection bias in the data underlying these collaborations could result in conclusions that are not applicable in all patient populations. Additionally, clinical trial enrollment that focuses on DTC users could exclude patients without access to DTC testing from enrolling in these trials.
- Several factors could dissuade DTC users from volunteering their genetic data for these collaborations. For example, some DTC users might be reluctant to provide consent to drug developers to use their genetic data. Additionally, some DTC users might have concerns regarding privacy of personal genetic data. These factors could reduce the pool from which genetic data could be drawn.
- Conversely, some DTC users are likely to volunteer their data, particularly patients with rare genetic diseases that might lack visibility in the drug development landscape. This could facilitate drug development and subsequent treatments for these conditions.
- The time needed to analyze the DTC genetic data and perform this research could significantly delay the availability of drugs discovered through these collaborations.

Messenger RNA Vaccines Against Infectious Diseases

Highlights

- Messenger RNA (mRNA) vaccines, which are the technology used in 2 of the available COVID-19 vaccines, are being developed as prophylactics for multiple additional infectious diseases.
- These vaccines use mRNA that encodes pathogen-specific proteins, which, when expressed in the body, generate a protective immune response against those proteins and the pathogens that express them.
- Multiple companies are pursuing mRNA vaccines, and about 40 prophylactic mRNA vaccine programs for non-COVID-19 infectious diseases are active.
- Stakeholders commenting on this trend thought that because mRNA vaccines have been shown to be safe and effective against COVID-19, mRNA technology might have substantial impact in preventing other infectious diseases; however, stakeholders had concerns that mRNA vaccines might increase disparities, especially in areas where storage and transportation issues could pose a challenge for vaccine access.

Description

Technological advances and innovations in the area of mRNA vaccines made in recent years and accelerated by the use of mRNA vaccines in the COVID-19 pandemic have led to the creation of multiple vaccine platforms against infectious diseases. These vaccines use lipid nanoparticles to deliver genetic information to human cells, producing expression of certain pathogen-specific proteins that can elicit an immune response.[382] The mRNA is degraded by the body after being translated into protein and does not alter human genes. Real-world data from mRNA vaccines used against COVID-19 have shown that they can be efficacious as well as safe and well tolerated.[383,384]

A recently published overview of the mRNA technology market identified 31 companies developing mRNA technologies, including 40 prophylactic vaccine programs for non-COVID-19 infectious diseases.[385] For example, Moderna (Cambridge, MA) has announced development

programs for a wide range of viruses, including Chikungunya, Epstein-Barr, HIV, influenza, Nipah, and Zika.[386] BioNTech (Mainz, Germany) is developing mRNA vaccines for HIV, influenza, and tuberculosis.[387]

Some of the more advanced mRNA vaccine programs to prevent infectious diseases are targeting HIV. The complexity of HIV, as well as its genetic diversity, has been a major challenge and barrier in the creation of an effective preventive vaccine. mRNA-1644 is an HIV vaccine being evaluated by Moderna in a phase 1 trial of 56 healthy adults, set to be completed in April 2023.[388] Preclinical data from VRC01, another mRNA vaccine developed by the University of Pennsylvania (Philadelphia), found that the vaccine was able to protect humanized mice against HIV infection.[389]

Clinical Area(s) Potentially Disrupted

The use of mRNA vaccines against infectious diseases is likely to disrupt health care costs and change the way that patients are managed. The prevention of infection, as well as transmission, might significantly impact patient and population health outcomes. The cost and accessibility of these vaccines might impact disparities in certain populations.

Opportunities

Vaccines might decrease the overall costs related to the treatment of infectious diseases and improve patient health outcomes if they can prevent infection. Since the platform is relatively new compared with other vaccine platforms, the study and use of mRNA vaccines might also improve the understanding of mRNA-based technologies to treat a wide array of infections and diseases.

Threats

Because of the lack of long-term data, mRNA vaccines against infectious diseases might have long-term consequences that were not seen during development and testing. The costs associated with vaccine storage might also be increased because of mRNA vaccines' low-temperature storage requirements. Additionally, the need for proper storage and high costs might also increase disparities if certain populations are unable to access the vaccines because of location or price.

Key Stakeholder Perspectives

Between April 19 and May 3, 2021, seven stakeholders, reflecting health care generalist, health systems, nursing, and research perspectives, provided comments and ratings on this trend. The list below provides a summary of key stakeholder perspectives.

- Using mRNA vaccines against infectious diseases might improve patient outcomes by preventing patients from contracting the targeted virus while also reducing viral transmission by vaccinated individuals to others.
- If the vaccines are effective and uptake is high, they might be able to reduce the burden of certain diseases endemic to the United States, such as AIDS. The vaccines might also be able to disrupt the disease burden of infections globally. In particular, diseases such as malaria, which is moving farther north because of climate change, might be appropriate targets for prophylactic mRNA vaccines.
- Cold chain requirements for vaccine storage could limit access to certain populations, especially in remote areas. However, the quick mass production that is possible with these vaccines might allow for the disruption of population health outcomes in areas that are less developed or lack proper health care.
- The impact of mRNA vaccines might be limited or might take a longer time to achieve if the targeted viruses mutate in a way that would require variant-specific vaccines to be made.

- mRNA vaccines might be cost saving because they could eliminate the need for patients to undergo treatment for disease if the infection is prevented.

Normothermic Machine Perfusion to Preserve Donor Organs for Transplantation

Highlights

- Normothermic machine perfusion attempts to support donor organs during storage and transport in an environment that mimics a living body.
- Systems for preserving donor lungs, hearts, and livers have received FDA premarket approval. Additional systems intended to support donated kidneys are in development.
- The technology might increase the donor organ supply by allowing use of organs deemed ineligible for transplant under current selection criteria.
- Stakeholders commenting on this trend thought the technology has potential to improve outcomes for transplant candidates if it can effectively increase the number of organs transplanted by decreasing the rate at which potential donor organs go unused.
- Stakeholders also thought normothermic machine perfusion might increase disparities if it is not implemented widely among organ transplant centers, limiting some patients' access to a potentially larger, expanded access pool of donor organs.

Description

Preservation of donated organs intended for transplantation has traditionally relied on static cold storage. However, static cold storage has limitations, including a 4- to 6-hour storage window.[390] Additionally, static cold storage poses a risk of organ cold injury and ischemia/reperfusion injury, which could impair organ function. Such limitations might thwart efforts to expand the potential donor pool. To overcome the challenges of static cold storage, manufacturers have been developing systems that preserve organs donated for transplantation in a manner closer to their native environment within a living body. The portable systems perfuse the organs with proprietary solutions to replenish oxygen and essential nutrients and maintain a typical body temperature (ie, normothermic).[390,391]

The systems purportedly allow longer out-of-body times with less organ damage compared with static cold storage, potentially expanding the supply of organs for transplantation. The systems also allow physicians to better assess the clinical status of donor organs, potentially expanding the number of organs considered eligible for transplant.[390,392] The systems could disrupt the cost and technical complexity of organ preservation and transport compared with standard cold storage.

The FDA has granted premarket approval to systems for preserving donor lungs, hearts, and livers.[393-396] Similar systems for preserving donor kidneys are also in development.[391,397] Leading developers include TransMedics, Inc (Andover, Massachusetts),[398] and XVIVO (Goteborg, Sweden).[399]

Clinical Area(s) Potentially Disrupted

The use of normothermic machine preservation could create new learning curves for transplant teams that operate the systems used to transport donated organs to hospitals that perform transplantation surgeries. The technology could alter patient outcomes and treatment models for those patients able to move from organ waiting lists to posttransplant recovery. Normothermic machine preservation could decrease disparities in care if it permits more transplant candidates to

undergo transplantation; however, disparities in access to transplantation could also increase if the technology is not universally adopted at organ transplant programs, preventing wider use of expanded criteria donor organs.

Opportunities

Normothermic machine perfusion has potential to improve patient outcomes for patients awaiting organ transplantation. If the technology can increase donor organ supply through expanded donor criteria, more patients could receive a new organ sooner and leave the transplant waiting list. If more transplant candidates can undergo transplantation and leave waiting lists sooner, their long-term treatment costs might be reduced, in large part from fewer hospitalizations needed to treat serious complications from end-stage organ failure.

Threats

Implementing normothermic machine preservation to collect and transport donor organs could substantially increase procedural costs for transplantation surgery. Additionally, the technology would likely increase the technical complexity of organ harvesting and transport for transplant teams. Hospitals would also face additional capital equipment and supply requirements to offer this service.

Key Stakeholder Perspectives

Between September 13 and September 17, 2021, six stakeholders, reflecting health care generalist, health systems, and research perspectives, provided comments and ratings on this trend. The list below provides a summary of key stakeholder perspectives.

- Normothermic machine preservation might have a positive impact on patient outcomes by increasing the number of organs deemed acceptable for transplant by expanding current organ acceptance criteria.
- The technology could improve access to care by allowing more patients to receive an organ through an expanded access supply of donor organs.
- Conversely, normothermic machine preservation could increase disparities in access if the substantially higher cost and complexity of graft storage and transport limits its availability to only the largest, high-volume transplant centers with greater resources.
- More transplant centers could implement normothermic machine perfusion if additional studies substantiate the technology's promise of expanding the pool of potential donor organs.
- Additionally, diffusion to a greater number of transplant programs could occur if commercially available preservation systems evolve to support multiple organ types, reducing capital costs and learning curves.

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