

# *AHRQ Healthcare Horizon Scanning System – Potential High Impact Interventions Report*

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## **Priority Area 13: Pulmonary Disease, Including Asthma**

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## **Statement of Funding and Purpose**

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHS290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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## Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High Impact report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to [effectivehealthcare@ahrq.hhs.gov](mailto:effectivehealthcare@ahrq.hhs.gov).

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# Executive Summary

## Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identifying new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, more than 11,000 leads about topics have resulted in identification and tracking of more than 900 topics across the 14 AHRQ priority areas and one cross-cutting area.

## Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest (COI). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight

experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the potential high impact range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as potential high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

## Results

The table below lists the three topics for which (1) preliminary phase III or later data were available for drugs or phase II, III, or later data were available for devices and procedures; (2) information was compiled by April 15, 2012, in this priority area; *and* (3) we received six to eight sets of comments from experts between February 2011 and April 26, 2012. (Thirty-six topics in this priority area were being tracked in the system as of May 2012.) For the Potential High Impact Interventions Report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present two summaries on two topics (indicated below by an asterisk) that emerged as having potential for high impact on the basis of experts’ comments and their assessment of potential impact. The material on interventions in this Executive Summary and report is organized alphabetically by disease state. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

### Priority Area 13: Pulmonary Disease, Including Asthma

Topic	High Impact Potential
1. *Ivacaftor (Kalydeco, VX-770) for treatment of cystic fibrosis in patients with G551D- <i>CFTR</i> mutation	Moderately high
2. *Oral sustained-release prostacyclin (treprostinil UT-15C) for treatment of pulmonary arterial hypertension	Moderately high
3. Roflumilast (Daliresp) for treatment of chronic obstructive pulmonary disease	No high-impact potential at this time

## Discussion

Pulmonary disease is priority area in which relatively few topics have been identified as meeting criteria for the AHRQ Healthcare Horizon Scanning System. The topics that experts deemed as having potential high impact were a new disease-modifying drug targeted at one of the genetic mutations seen in patients with cystic fibrosis (CF) and an oral formulation of a drug for pulmonary arterial hypertension (PAH) that could improve patient adherence to treatment, reduce complications of therapy, and allow patients to initiate therapy sooner, which could slow disease progression. Another drug, roflumilast, failed to meet its primary endpoints in a just-completed phase III trial.

## Ivacaftor (Kalydeco, VX-770) for Treatment of Cystic Fibrosis in Patients with G551D-CFTR Mutation

- **Key Facts:** Current therapies for CF have improved median survival times, but patients with CF still have shorter-than-normal life expectancy and require extensive treatment over a lifetime to maintain their health as well as possible. Thus, an unmet need exists for novel, effective therapies to improve outcomes in this patient population. The oral tablet ivacaftor (Kalydeco™, VX-770, Vertex Pharmaceuticals, Inc., Cambridge, MA) targets the defective CF transmembrane conductance regulator (CFTR) protein that causes CF. The drug is intended as first-line treatment for patients with the G551D-CFTR mutation—about 4% of patients with CF. In clinical trials, ivacaftor is administered in doses of 150 mg every 12 hours. The drug is in several phase III clinical trials cosponsored by the Cystic Fibrosis Foundation. In trials, effects on pulmonary function were reported as early as 2 weeks, and a statistically significant treatment effect was reported to be maintained through week 48. Also through week 48, investigators reported, patients given ivacaftor were 55% less likely to have a pulmonary exacerbation than patients given placebo. Ivacaftor in combination with another experimental CF drug, VX-809, has also been shown to improve lung function in patients with CF who have two copies of the CFTR-F508del mutation, according to recent phase II trial results. The F508del mutation occurs in about 70% of patients with CF, giving ivacaftor the potential for a much broader indication in the future.
- On January 31, 2012, the U.S. Food and Drug Administration (FDA) granted marketing approval for ivacaftor for treating patients aged 6 years and older who have a G551D mutation in the CFTR gene. Ivacaftor costs about \$294,000 per year, and some financial analysts expect that third-party payers would cover it because other effective therapies for CF are lacking. Additionally, the manufacturer is expected to implement stratified pricing terms based on patient insurance status and income. Third-party payers have begun to develop policies; generally, payers are categorizing the drug as a specialty pharmaceutical requiring prior authorization for those who have prescription drug coverage. Co-payments vary according to the terms of a patient's benefits.
- **Key Expert Comments:** Overall, experts commenting on this topic were moderately confident that this drug could meet the need for a novel effective oral treatment for CF, although this view was tempered by the fact that the drug is intended for only the 4% or so of patients with CF who have the mutation. Experts anticipated that this drug would affect current care processes and patient management by offering patients a convenient oral therapy to directly treat CF's cause, which could reduce the need for intravenous treatments, ventilation therapy, and chest therapy, if the drug halts disease progression. The \$294,000 annual cost of ivacaftor therapy was identified as a potentially controversial issue. Even for patients with prescription drug coverage, co-payments are expected to be significant.
- **Potential for High Impact:** Moderately high

## Oral sustained-release prostacyclin (oral treprostinil, UT-15C) for treatment of pulmonary arterial hypertension

- **Key Facts:** PAH is a progressive, life-threatening disorder that is difficult to diagnose and currently has no cure. For patients with PAH, treprostinil is available as an intravenous formulation administered using an indwelling central line catheter or by subcutaneous injection every 3 days (Remodulin<sup>®</sup> injection, United Therapeutics Corp., Silver Spring, MD). An inhaled formulation (Tyvaso<sup>®</sup>, United Therapeutics) is also available, requiring dosing four times daily. The same company is developing an oral treprostinil diethanolamine (UT-15C), which is a synthetic analog of the lipid prostacyclin that is purported to inhibit platelet accumulation and act as a vasodilator. An oral formulation given twice daily might provide an early and convenient option for managing PAH, which might improve outcomes, slow disease progression, and reduce complications from injected forms of treprostinil. In a phase III trial, patients with PAH treated with oral treprostinil (0.25 mg) improved their median 6-minute walk distance compared with placebo. In February 2012, FDA accepted the company's new drug application for review, with a decision date of October 27, 2012. The drug has been granted orphan drug designation. No official cost information for treprostinil diethanolamine is available at this time. However inhaled and injectable prostacyclin treatments from the same manufacturer cost about \$100,000 annually. Third-party payers are expected to cover treprostinil diethanolamine because intravenous treprostinil is considered medically necessary by several third-party payers for patients with World Health Organization Class II–IV symptoms and oral dosing is expected to reduce the cost of care.
- **Key Expert Comments:** Overall, experts commenting on this intervention stated that oral treprostinil presents a more convenient option than injectable and inhaled formulations, which are already available. Experts stated that the oral formulation could reduce the need for routine visits to health care facilities as well as unexpected visits due to complications arising from injections, potentially reducing the cost of care. The experts also assumed that the oral formulation would cost less than the other formulations. These factors could reduce barriers to care and improve health disparities. Experts expect the oral formulation to be widely accepted by clinicians and patients. Although the oral formulation may allow patients to initiate therapy earlier, improving health outcomes, the experts do not expect the oral formulation to be more effective than the currently available options.
- **Potential for High Impact:** Moderately high

# **Pulmonary Disease, Including Asthma, Interventions**

# **Ivacaftor (Kalydeco, VX-770) for Treatment of Cystic Fibrosis in Patients with G551D-CFTR Mutation**

Current therapies for cystic fibrosis (CF) have improved predicted median survival, but patients with CF still have a shorter-than-normal life expectancy and require extensive treatment over a lifetime to maintain good health as much as possible. Thus, an unmet need exists for novel, effective medications to improve outcomes in this patient population. Ivacaftor (Kalydeco™, VX-770, Vertex Pharmaceuticals, Inc., Cambridge, MA) is a small-molecule, cystic fibrosis transmembrane conductance regulator (CFTR) modulator that improves the function of the *CFTR* gene by increasing CFTR activity in transporting ions across the cell membrane to the cell surface, improving hydration and clearing mucus in patients with CF.<sup>1,2</sup> Ivacaftor also promotes functional activity for two other *CFTR* mutations (F508del and R117H) and has some effect on the wild-type *CFTR* gene. Ivacaftor targets the defective protein that causes CF and is intended as a first-line treatment for the 4% of patients with CF who have the G551D mutation.<sup>3</sup> Ivacaftor is administered 150 mg twice daily with fat-containing food in patients 6 years of age and older.<sup>4</sup>

Ivacaftor is being investigated in several phase III clinical trials. In a randomized, double-blind, placebo-controlled, phase III, clinical trial, cosponsored by the Cystic Fibrosis Foundation and the drug's manufacturer, patients (n=161) with at least one copy of CF mutation G551D given ivacaftor had a predicted forced expiratory volume in 1 second measurement that was 10.6 percentage points higher than patients treated with placebo through week 24 (p<0.001).<sup>5</sup> Effects on pulmonary function were observed as early as 2 weeks, and a significant treatment effect was maintained through week 48. Also through week 48, patients given ivacaftor were 55% less likely to have a pulmonary exacerbation than patients given placebo (p<0.001). Patients treated with ivacaftor also demonstrated a significant improvement in quality of life (p<0.001). By 48 weeks, patients treated with ivacaftor had gained significantly more weight and secreted significantly less chloride in sweat samples (a key indicator for *CFTR* activity; p<0.001 for both measures). The incidence of adverse events was similar with ivacaftor and placebo, with a lower proportion of serious adverse events with ivacaftor than with placebo (24% vs. 42%).<sup>5</sup> Ivacaftor in combination with another experimental CF drug, VX-809, has also been shown to improve lung function in patients with CF who have two copies of the *CFTR*-F508del mutation, according to recent, phase II trial results.<sup>6</sup> The F508del mutation is the most common CF mutation, occurring in about 70% of patients with CF.<sup>7</sup> Thus, ivacaftor may gain a broader patient indication in the future.

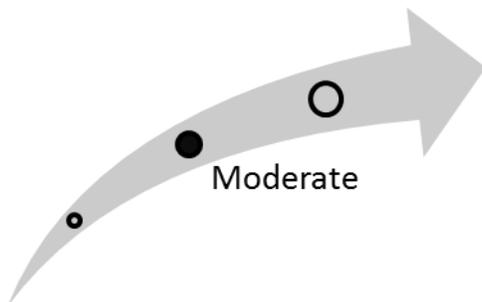
On January 31, 2012, FDA granted marketing approval for ivacaftor for treating patients aged 6 years and older who have a G551D mutation in the *CFTR* gene.<sup>8</sup> Ivacaftor's annual pricing was set at about \$294,000.<sup>9</sup> The manufacturer has implemented stratified pricing terms based on patient insurance status and income.<sup>10</sup> While ivacaftor's annual price is high, pricing was purported to be derived following conversations with patients, physicians, and payers.<sup>11</sup> Third-party payers have begun to develop policies; generally, payers are categorizing the drug as a specialty pharmaceutical requiring prior authorization for those who have prescription drug coverage. Co-payments vary according to the terms of a patient's benefits.

## **Clinical Pathway at Point of This Intervention**

Routine use of inhaled medications and ventilators and/or chest physiotherapy helps to release the thick mucus associated with CF, which damages lung tissue over time. Patients with CF often require chronic use of inhaled, intravenous, or oral antibiotics to prevent or treat acute infections in lungs already weakened by disease. Lung transplantation can reduce the effects of CF for some individuals.<sup>12</sup> As disease progresses, some patients require mechanical breathing support, especially while asleep. Ivacaftor is intended as first-line treatment for patients with CF who have the G551D-

*CFTR* mutation, and it can be used in conjunction with physiotherapy, mechanical devices, and antibiotics as needed.

**Figure 1. Overall High Impact Potential: Ivacaftor (Kalydeco, VX-770) for treatment of cystic fibrosis in patients with G551D-*CFTR* mutation**



Overall, experts commenting on this intervention expressed some confidence that this drug has potential to meet the need for a novel CF treatment that can improve health outcomes, although this view was tempered by the fact that CF is relatively rare and this drug is intended for only the approximate 4% of patients with CF who have this specific mutation. Because the drug is intended to be delivered orally, it could reduce the need for visits to health care facilities for regular oxygen, chest, and intravenous therapies. However, because of the small patient population and the drug’s oral administration, ivacaftor is not expected to have a major impact on health care processes such as staffing or infrastructure requirements; thus, the experts expected it could be easily adopted. The \$294,000 annual cost of ivacaftor therapy was identified as a potentially controversial issue. Forthcoming information regarding third-party payer coverage, patient co-payments, real-world clinical efficacy, and offsets of other health care costs from improved outcomes from the drug will help to elucidate and better define these issues. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

## Results and Discussion of Comments

Six experts, with backgrounds in clinical practice, health systems, or research, offered perspectives on this intervention.<sup>13-18</sup> Experts generally agreed that the unmet need for novel treatments for CF is important, particularly if those treatments are disease-modifying instead of merely palliative. However, experts stated that the importance of this unmet need is tempered by the fact that CF is a rare condition and that within the small population affected by CF, 96% of patients would not be eligible for this treatment.

Based on positive clinical trial results, ivacaftor appears to have a sound theory underlying its mechanism of action and potential to improve patient outcomes, the experts said. However, one health systems expert noted that additional clinical trials evaluating quality of life should be performed to better evaluate the drug’s impact.

One expert representing a clinical perspective stated that the oral administration of ivacaftor could improve health disparities because rural patients and “working families” commonly have barriers to treatment when frequent travel to a care facility for intravenous therapy is required.

Experts anticipated that this drug would affect current care processes and patient management by offering patients a convenient oral therapy to directly treat CF’s cause, which could reduce the need for intravenous fluids, ventilation therapy, and chest therapy, if the drug halts disease progression. However, clinicians will need to spend some time initially to explain to patients the advantages and limitations of the new therapy and how it affects their care.

Because the drug is intended to be administered as an oral treatment and because of CF's rarity, it was not anticipated by experts providing comments to have a major impact on health care operations such as staffing and infrastructure needs. However, some experts suggested that if this drug is proven to be effective, it might reduce frequency of outpatient visits and inpatient care for flares and complications for patients with the affected mutation, requiring significantly less treatment resources.

The experts stated that the current price of the drug is quite high but overall, the price may have limited impact because of the small number of patients eligible for this therapy. Additionally, reductions in oxygen and chest therapy, hospitalizations, and other complications could significantly offset costs in the long term. However, one expert representing a health systems perspective estimated that treating all eligible patients with ivacaftor would cost the health care system about \$400 million annually, which the reviewer regarded as an unsustainable trend for a disease that affects such a small population of patients.

Although one clinical expert stated there will always be some patients hesitant about any new drug, the experts thought patient and clinical acceptance of ivacaftor would be wide and rapid. Possible barriers to acceptance include issues that could arise from coverage and costs such as high patient co-payments. Additionally, if physicians observe limited efficacy in clinical practice they could be hesitant to prescribe such an expensive drug.

## Oral Sustained-Release Prostacyclin (Treprostinil, UT-15C) for Treatment of Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a progressive, life-threatening disorder that currently has no cure.<sup>19</sup> PAH is characterized by hypertension in the pulmonary artery, which carries blood from the heart to the lungs. Small arteries throughout the lungs narrow, increasing resistance to blood flow through the lungs. To overcome the increased resistance, blood pressure increases in the pulmonary artery and the right ventricle. When increased pressure cannot fully overcome the resistance to blood flow, symptoms including shortness of breath during exertion and fainting spells can occur.<sup>19</sup> PAH symptoms overlap with other, more common heart and lung problems; it can take several months of tests before PAH is definitively diagnosed in a patient.<sup>20</sup> In the United States, about 1,000 new PAH cases are diagnosed annually.<sup>19</sup>

Treprostinil is currently available for patients with PAH as an intravenous formulation administered using an indwelling central line catheter or by subcutaneous injection every 3 days (Remodulin<sup>®</sup> injection, United Therapeutics Corp., Silver Spring, MD). An inhaled formulation (Tyvaso<sup>®</sup>, United Therapeutics) is also available that requires four doses daily with 4 hours between each dose.<sup>21-24</sup> Treprostinil is a synthetic analog of the lipid prostacyclin that is purported to inhibit platelet accumulation and act as a vasodilator.<sup>25</sup> Because no cure currently exists for PAH, an oral formulation of treprostinil could provide early and convenient symptom management, which might improve outcomes and slow disease progression.<sup>26</sup> Additionally, an oral formulation of the drug could reduce complications from injections and visits to health care facilities for injections. Oral treprostinil (United Therapeutics) is a novel salt formulation consisting of treprostinil diethanolamine encapsulated in tablets that allow for sustained release of the drug through a small hole drilled into the tablet with a laser, allowing twice daily dosing.<sup>27</sup> In phase III trials, the drug was administered as a tablet (0.25 mg) twice daily.<sup>26</sup> Treprostinil diethanolamine is purported to have a longer duration than inhaled treprostinil and is simpler to administer than the injected drug.<sup>28</sup>

Oral treprostinil was investigated in a randomized phase III clinical trial. Patients (n=228) with PAH receiving oral treprostinil (0.25 mg) demonstrated an improvement in median 6-minute walk distance by about 23 meters compared with placebo (p=0.0125).<sup>27</sup> The median change from baseline to week 12 for patients treated with oral treprostinil was 25 meters compared with 5 meters for patients given placebo.<sup>27</sup>

United Therapeutics is licensed to develop treprostinil diethanolamine by Supernus Pharmaceuticals, Inc. (Rockville, MD), which invented the osmotic delivery system used in the medication.<sup>29</sup> In February 2012, FDA accepted the company's new drug application and set a decision date of October 27, 2012.<sup>30</sup> Oral treprostinil also has been granted orphan drug designation.<sup>27</sup>

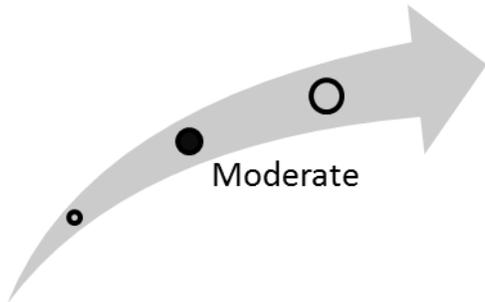
No official cost information for treprostinil diethanolamine is available as of this writing. Inhaled and injectable prostacyclin treatments cost about \$100,000 per year for Tyvaso and Remodulin.<sup>31</sup> Third-party payers are likely to cover treprostinil diethanolamine because intravenous treprostinil is considered medically necessary by at least one major third-party payer in patients with World Health Organization Class II–IV PAH symptoms.<sup>32</sup> Oral dosing is expected to eliminate the cost of intravenous administration and care visits, which should increase payers' willingness to cover treprostinil diethanolamine.

### Clinical Pathway at Point of This Intervention

PAH is typically treated with medication, although surgery may also be considered. Several types of medication can be prescribed to reduce PAH symptoms, including anticoagulants, calcium channel blockers, digoxin, diuretics, endothelin receptor antagonists, inhaled oxygen,

phosphodiesterase type-5 inhibitors, and prostacyclins. Some patients use a combination of these medications. In advanced cases, surgical treatment options including heart or heart-lung transplantation and atrial septostomy (in which a hole is created between the top two chambers of the heart) can be used. No curative therapy currently exists for PAH. The primary treatment goal is to lessen symptoms and slow disease progression. Despite treatment, PAH will continue to worsen over time.<sup>20</sup> Treprostinil diethanolamine is an oral synthetic prostacyclin analog intended to simplify and improve early PAH-symptom management.<sup>25,26</sup>

**Figure 2. Overall High Impact Potential: Oral sustained-release prostacyclin (treprostinil, UT-15C) for treatment of pulmonary arterial hypertension**



Overall, experts commenting on this topic stated that oral treprostinil, a prostacyclin analog, presents a more convenient option compared with injectable and inhaled forms of treprostinil, which are already available. The experts stated that the oral formulation could reduce the need for routine visits to health care facilities as well as unexpected visits due to complications from injections, reducing the cost of care. The experts also thought that the oral formulation would cost less than current formulations. Although the oral formulation could promote earlier initiation of therapy, which could slow disease progression, the experts did not expect the oral formulation to be more effective than the currently available options. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

## Results and Discussion of Comments

Six experts, with backgrounds in clinical practice, research, or health systems, offered their perspectives on this intervention.<sup>33-38</sup> Overall the experts stated that PAH is a life-threatening condition that is difficult to diagnose and manage, while disease progression is certain. Oral treprostinil is expected to facilitate treatment and could allow patients to initiate treatment earlier, which could improve outcomes. Although limited data are available, the reviewers assumed that oral treprostinil would have similar efficacy to the injectable and inhaled formulations of the drug with enhanced ease of administration. The experts stated that oral treprostinil could reduce health disparities by reducing patient visits to health care facilities compared with other modes of administration. Additionally, the experts generally assumed that the oral formulation would cost less than the current formulations, which could reduce health disparities.

The experts stated that oral treprostinil could affect health care infrastructure by moving more care to an outpatient setting and requiring fewer visits to a treatment facility. The experts stated oral treprostinil could be used more frequently than other drugs to treat patients with PAH. One reviewer with a health systems perspective stated that the drug could also be used to treat patients with PAH earlier, providing time to “win support for more intense methods as a patient’s condition progresses.” The oral administration combined with clinician familiarity with other forms of treprostinil led the experts to expect oral treprostinil to be widely accepted by patients and clinicians if side effects can be minimized with the appropriate dosage. One clinical expert also stated concern

that clinician acceptance could result in off-label use for unrelated indications, which has occurred for other PAH treatments.

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