

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

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## **Priority Area 08: Functional Limitations and Disability Potential High Impact Interventions Report**

Prepared for:  
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**Contract No. HHS A290201000006C**

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**January 2012**

## **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. HHS A290201000006C). 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 closer to diffusion into practice in the United States. Drafts of 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 those interventions that experts deem, 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 six 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 the horizon scanning, assessing the leads for topics, or provide opinions regarding potential impact of interventions.

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## **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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**Suggested citation:** ECRI Institute. AHRQ Healthcare Horizon Scanning System Potential High Impact Interventions: Priority Area 08: Functional Limitations and Disability. (Prepared by ECRI Institute under Contract No. HHS A290201000006C.) Rockville, MD: Agency for Healthcare Research and Quality. January 2012. <http://www.effectivehealthcare.ahrq.gov/reports/final.cfm>.

## 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 target technologies and innovations in health care and to create an inventory of target technologies 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 the identification and monitoring of 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 the analysis of 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 utilization 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 identification of 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 7,000 leads about topics have resulted in identification and tracking of more than 900 topics across the 14 AHRQ priority areas.

### 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 to 4 years of potential diffusion (e.g., in phase III trials for pharmaceuticals or biotechnologies or in phase II or a trial with some preliminary efficacy data on the target population for devices and programs) 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 a profile on topics and issuing topic profile 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 high impact potential designation. 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 38 topics for which (1) preliminary phase III data were available for drugs being developed for labeled indications or phase II data for off-label drugs and devices; (2) information was compiled by November 2011 in this priority area; *and* (3) we received six to eight sets of comments from experts between February 2011 and November 1, 2011. (A total of 144 topics in this priority area were being tracked in the system as of November 2011.) For the purposes of the Potential High Impact Interventions Report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present 14 summaries on 14 topics (indicated below by an asterisk) that emerged as potential high impact on the basis of experts’ comments and their assessment of potential impact.

Priority Area 08: Functional Limitations and Disability	
1.	Aflibercept for treatment of wet, age-related macular degeneration
2.	Bupivacaine extended-release liposome injection (Exparel) for treatment of postsurgical pain
3.	*Computerized walking systems (ReWalk and eLegs) for patients with paraplegia
4.	DNA chip to detect lipoprotein lipase (LPL) gene mutations
5.	Ear implant for treatment of Ménière’s disease
6.	*Ezogabine (Potiga) for treatment of epilepsy
7.	*Fingolimod (Gilenya) for treatment of relapsing-remitting multiple sclerosis
8.	Gene-transduced autologous hematopoietic stem cell therapy for severe combined immunodeficiency
9.	Glutamate receptor antagonist (perampanel) for treatment of partial onset epilepsy
10.	High-intensity focused ultrasound for treatment of primary hyperparathyroidism
11.	*Icatibant (Firazyr) for treatment of acute hereditary angioedema
12.	Image-guided interventional endovascular management of multiple sclerosis
13.	*Implantable miniature telescope for treatment of end-stage, age-related macular degeneration
14.	Laquinomod for treatment of relapsing-remitting multiple sclerosis
15.	*Magnetic pierced-tongue aid for management of spinal cord injury

<b>Priority Area 08: Functional Limitations and Disability</b>	
16.	Methacetin breath test for (BreathID) to monitor liver function in patients awaiting liver transplantation
17.	Micro-bypass implant (iStent) for treatment of glaucoma
18.	*Neurostimulation (remedē System) for treatment of central sleep apnea associated with heart failure
19.	Neurostimulation (aura6000) for treatment of obstructive sleep apnea
20.	Neurostimulation (Inspire) for treatment of obstructive sleep apnea
21.	Nitroglycerin for prevention of osteoporosis
22.	NX-001 for prevention of delayed graft function after renal transplantation
23.	*OBI-1 (recombinant B-domain deleted porcine coagulation factor VIII) for treatment of acquired hemophilia
24.	*Off-label propranolol for treatment of life-threatening infantile hemangiomas
25.	*Off-label teriparatide (Forteo) for treatment of hard-to-heal bone fractures
26.	*Orally inhaled dihydroergotamine (Levadex) for treatment of migraine headache
27.	*PTH (1-84) for treatment of hypoparathyroidism
28.	*Ranibizumab (Lucentis) for treatment of diabetic macular edema
29.	Real-time functional magnetic resonance imaging (fMRI) with cognitive training to treat chronic pain
30.	*Recombinant human microplasmin injection (Ocriplasmin) for treatment of focal vitromacular adhesion
31.	Sumatriptan iontophoretic patch (Zelrix) for treatment of acute migraine headache
32.	Synthetic bone grafts for use in foot and ankle fusion surgery
33.	Taliglucerase alfa for treatment of Gaucher's disease
34.	Telcagepant for treatment of migraine headache
35.	Teriflunomide for treatment of relapsing remitting multiple sclerosis
36.	Terlipressin for reversal of hepatorenal syndrome type 1
37.	UroLift system for treatment of lower urinary tract symptoms caused by benign prostatic hyperplasia
38.	Video game therapy for rehabilitation of stroke survivors

## Discussion

Functional limitations encompasses a wide range of disease states and conditions that affect the ability to function normally including, but not limited to, autoimmune diseases, hematologic diseases, conditions causing chronic pain, degenerative diseases, central and peripheral nervous system disorders, physical limitations incurred because of spinal cord injury, sensory conditions (sight, hearing, touch, taste, smell), sleep disorders, organ failure (other than heart), and certain genetic disorders that are outside of the other AHRQ priority areas. The material on interventions in this Executive Summary and the whole report is organized according alphabetically by disease state, and then interventions. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.



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## Central Nervous System Disorder Intervention

### Fingolimod (Gilenya) for Treatment of Relapsing-Remitting Multiple Sclerosis

- **Key Facts:** Multiple sclerosis (MS) is a progressive autoimmune disorder directed against the central nervous system. Even with current treatments, inflammation and subsequent damage to the spinal cord and brain interfere with a variety of functions, which can eventually lead to the need for assisted living conditions. Relapsing-remitting multiple sclerosis (RRMS) is the most common form of MS that is diagnosed. Current first-line therapies consist of injectable immunomodulators that dampen autoimmune responses against the central nervous system (CNS) and include interferon beta-1b, interferon beta-1a, and glatiramer acetate. Fingolimod (Gilenya™, Novartis AG, Basel, Switzerland and Mitsubishi Tanabe Pharma, Osaka, Japan) is a first-in-class new drug in the class called sphingosine 1-phosphate receptor (S1PR) modulators. Investigators from the trials of fingolimod reported that the drug dampens activity of autoreactive lymphocytes by keeping them localized to the lymph nodes, thereby reducing the number lymphocytes with access to the central nervous system and reducing the frequency of relapses compared to interferon beta-1a. The most common adverse events reported in these studies included headache, flu, diarrhea, back pain, abnormal liver tests and cough. Other less common fingolimod-related side effects included transient, generally asymptomatic heart-rate reduction and atrioventricular block upon treatment initiation, mild blood pressure increase, macular edema, and mild bronchoconstriction. In September 2010, the U.S. Food and Drug Administration (FDA) approved fingolimod (0.5 mg) as the first orally administered first-line treatment for RRMS.
- **Key Expert Comments:** As the first oral agent approved to treat RRMS Experts providing comments on this drug expected the oral administration and improved efficacy to result in wide acceptance among clinicians and patients, although costs (estimated at \$48,000 per patient per year) and the adverse event profile might pose some barriers to diffusion and sources of controversy for the drug. Reported sales figures in early 2011 indicated good acceptance thus far, despite its \$48,000 annual per-patient cost. The horizon scanning system is tracking two other orally administered MS drugs in phase III development (teriflunomide, Sanofi-Aventis Paris, France, and laquinimod (Teva Pharmaceutical Industries, Ltd., Jerusalem, Israel). Even though their mechanisms of action differ from that of fingolimod, experts commenting on these other drugs in development did not view them as having potential for high impact because experts viewed the unmet need as having been addressed by fingolimod. Dimethyl fumarate (Biogen Idec, Weston, MA) is another oral agent being tracked in the system in phase III development for treatment of RRMS. However this drug has not yet completed the horizon scanning expert comment process.
- **Potential for High Impact:** High

## Endocrine Disorder Intervention

### PTH (1-84) for Treatment of Hypoparathyroidism

- **Key Facts:** Currently, no approved pharmacotherapy exists for treatment of hypoparathyroidism (very low calcium levels), signaling a need for more effective therapy. Current treatment options for regulation of calcium and phosphorus in the body include supplemental calcium carbonate and vitamin D, although these supplements may lead to

long-term complications. In life-threatening hypoparathyroidism (extremely low calcium levels), intravenous calcium may be administered. Recombinant human (Rh) parathyroid hormone (PTH) (1-84) (NPS Pharmaceuticals, Bedminster, NJ), is a synthetic PTH produced in *Escherichia coli* as a single, nonglycosylated, polypeptide chain containing 84 amino acids, and it is purified by proprietary chromatographic techniques. The manufacturer purports that by replicating the actions of natural PTH, rhPTH can help the body maintain near-normal serum calcium levels without much dependence on supplemental calcium or vitamin D. RhPTH (1-84) was granted orphan drug status by FDA in 2007, and based on preliminary results from the REPLACE trial in November 2011, the company anticipated submitting a new drug application (NDA) to FDA in early 2012.

- **Key Expert Comments:** Experts providing comments thought this drug's potential to treat hypoparathyroidism might reduce overall lifetime treatment costs by reducing lifetime use of supplemental calcium carbonate and vitamin D, and significantly improving patient health outcomes in this patient population.
- **Potential for High Impact:** Moderately high

## Epilepsy Intervention

### Ezogabine (Potiga) for Treatment-Resistant, Partial-Onset Epilepsy

- **Key Facts:** Partial-onset seizures are the most commonly occurring type of seizure in patients with epilepsy. According to the Epilepsy Foundation, about 20% of patients with epilepsy do not respond to currently available pharmacotherapy, and these patients might have to undergo invasive surgical resection or implantation of a vagus nerve stimulator. Therefore, a novel, effective pharmacotherapy would address an important unmet need for these patients. Ezogabine (also known as retigabine, Valeant Pharmaceuticals International, Inc., Mississauga, Ontario, Canada, and GlaxoSmithKline, Middlesex, UK) is a new oral drug with a new mechanism of action. It has been investigated as adjunctive therapy for treatment-resistant epilepsy characterized by partial-onset seizures. After more than 18 months of consideration by FDA, including FDA's issuance of a complete response letter in 2010 to the manufacturers, citing nonclinical reasons for not approving the drug, FDA approved the drug June 10, 2011, as an add-on medication to treat seizures associated with epilepsy in adults. As a condition of approval, FDA recommended the drug be listed on the Controlled Substances Act, which was expected to delay its availability for several months. The FDA approval, however, also required a Risk Evaluation and Mitigation Strategy to inform health care professionals who prescribe the drug of the risk of urinary retention and the symptoms of acute urinary retention. In addition, FDA published information warning patients about risks of neuropsychiatric symptoms, including confusion, hallucinations, psychotic symptoms, and suicidal thoughts. At the time of this report, retail or wholesale costs for the drug in the U.S. were not yet available.
- **Key Expert Comments:** Overall, experts providing comments on this topic (immediately prior to its FDA approval) were optimistic about the drug's potential to meet the need for an effective new pharmacotherapy for this patient population because of its novel mechanism of action and clinical trial data thus far. As an oral drug, it could be incorporated easily into existing care model for epilepsy; if the drug obviates the need for invasive interventions, most experts thought, it could impact several health system parameters, especially care setting, patient management, and treatment costs.
- **Potential for High Impact:** Moderately high

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## Genetic Disorder Intervention

### Icatibant (Firazyr) for Acute Hereditary Angioedemas

- **Key Facts:** Acute hereditary angioedemas (HAEs) result from a genetic disorder caused by dysfunction or deficiency of C1 esterase inhibitor (C1INH), an inhibitor of the C1 protease that is responsible for activating the complement pathway of the innate immune system. If C1INH is deficient, an acute inflammatory response occurs that leads to swelling. Attacks involving the larynx can be fatal; serious attacks are associated with a mortality rate of 15% to 33%. Abdominal attacks can also cause severe pain and disfigurement. Each bout of edema can last 3 to 5 days; the trigger for attacks is unknown. Icatibant (Firazyr®, Shire, plc, Dublin, Ireland) is an injectable drug that was approved in 37 countries outside the U.S. for treatment of type I or type II HAE. In phase III trials, it provided significant relief of symptoms within about 2 hours. Shire submitted an NDA 2 years ago that FDA rejected, after which the company began a new phase III trial that demonstrated positive results in patients who self-administered icatibant to treat acute attacks of HAE. Shire received a recommendation for approval of icatibant from an FDA advisory committee, and FDA approved the drug on August 25, 2011. Shire quickly initiated a program to promote access. The average wholesale cost of this drug in the U.S. was expected to be about \$6,800 per syringe. The company's Quick Start program and extended OnePath Access Program were created to offer product-related services and support to patients. After a health care provider prescribes the drug, patients can enroll to be eligible to receive two syringes of the drug at no cost.
- **Key Expert Comments:** Overall, experts commenting on this drug saw icatibant as having significant potential to shorten the duration of symptoms and improve clinical outcomes in the small number of patients with HAE, a potentially life-threatening condition. Experts noted that while other new treatments have just become available for HAE, icatibant has a different mechanism of action and may be self-administered on an outpatient basis, potentially minimizing hospitalizations and the role emergency personnel play in the management of HAE in a subset of patients.
- **Potential for High Impact:** High.

## Hematologic Disorder Intervention

### OBI-1 for Treatment of Acquired Hemophilia A

- **Key Facts:** Acquired hemophilia is a rare disorder affecting an estimated 20,000 to 25,000 individuals (primarily middle-aged individuals) in the U.S. Current therapies, specifically human factor VIIa (NovoSeven) and FEIBA, work by bypassing the coagulation cascade, producing extremely higher-than-normal levels of factor VIIa to induce coagulation. However, no available therapies address the underlying pathogenesis of acquired hemophilia, in which autoantibodies produced against the body's coagulation factors result in excessive bleeding episodes. OBI-1 therapy is an intravenous recombinant porcine factor VIII product that serves as factor VIII replacement therapy by activating the natural coagulation cascade. OBI-1 was given orphan drug status by FDA in March 2004. The European Commission also granted orphan drug status for OBI-1 for the treatment of hemophilia. Regulatory submission for marketing approval in the European Union is

expected in 2012. Pivotal studies were underway as of late 2011, and the company anticipates submitting an NDA to FDA in 2014.

- **Key Expert Comments:** Overall, experts commenting on this intervention were generally optimistic about OBI-1 therapy's potential to meet the need of patients who suffer complications from acquired hemophilia, highlighting its apparently sound mechanism of action and limited side effects. Experts commenting on this drug generally believe that if efficacy is confirmed in the pivotal trials, OBI-1 therapy has the potential to serve as first-line therapy for patients receiving a diagnosis of acquired hemophilia and may subsequently alter treatment models.
- **Potential for High Impact:** High

## Orthopedic Intervention

### Off-Label Teriparatide for Treatment of Hard-to-Heal Bone Fractures

- **Key Facts:** Pelvic fractures, proximal humeral fractures, and Jones fractures (fifth metatarsal) are known to be very difficult to heal because of their locations, and they are associated with high rates of delayed union and nonhealing. Pelvic fractures have typically been treated through prolonged recumbency after mobilization as fracture healing occurs and symptoms subside. Other methods used to treat pelvic fractures include closed reduction under general anesthesia, traction, spica casts, pelvic slings, and turnbuckles. Surgery has become more common in recent years because of improved treatment for patients who have experienced massive trauma that includes pelvic fracture, improved operative conditions (i.e., blood salvage, anesthesia), improved imaging modalities, better pelvic implant systems, and better understanding of these types of fractures. A pharmacologic treatment to aid healing of such fractures would address an important unmet need. Investigators are studying off-label use of a drug labeled for osteoporosis treatment, teriparatide (Forteo®, Eli Lilly and Co., Indianapolis, IN), for expediting bone healing of delayed union or nonhealing bone fractures. As an osteoporosis treatment in the United States, the average retail price of teriparatide is approximately \$950 for a 28-day supply of 20 mcg daily injections using an injectable pen and cartridge device. The unit cost of teriparatide to treat nonhealing fractures is likely to be comparable; however, the total treatment cost would be lower since long-term use of teriparatide as a maintenance drug is unlikely for the treatment of nonhealing fractures.
- **Key Expert Comments:** Experts thought this drug's potential to treat some types of hard-to-heal or delayed union fractures (e.g., pelvic) could reduce overall treatment costs by shortening hospital stays or avoiding surgery; they also thought it could improve quality of life, independence, and health outcomes and possibly change how treatment is currently provided for some cases of nonhealing fractures. However, this drug is administered by subcutaneous injection by patients (or nonclinical caregivers), which could be a barrier for some patients.
- **Potential for High Impact:** Moderately high

## Pain Intervention

### Inhaled Dihydroergotamine (Levadex) for Treatment of Migraine Headache

- **Key Facts:** Migraine headache, a condition often associated with chronic pain, affects an estimated 28 million people each year in the U.S. Many patients are dissatisfied with their

current migraine medication because of an inconsistent response to the medication, high migraine recurrence rates after treatment, and/or slow onset of action of medication in relieving pain. Therefore, new treatments for migraine headache are highly desired. One currently employed migraine treatment is the ergot alkaloid dihydroergotamine (DHE). DHE is currently available as an injectable solution and nasal spray. Levadex® (MAP Pharmaceuticals, Inc., Mountain View, CA) is a novel, orally inhaled formulation of DHE that is delivered by its developer's proprietary Tempo™ breath-activated metered dose inhaler. Compared to available injectable DHE, Levadex is purported to be more convenient, faster-acting, and is purported to have fewer side effects than other DHE formulations in patients who respond to DHE. It may also avoid the local nasal irritation and inconsistent absorption that has been observed with nasal spray delivery. In August 2011, MAP Pharmaceuticals filed an NDA for Levadex for treatment of migraine headache, and the filing was accepted by FDA. A decision was expected to be made in March 2012. Cost information was not available.

- **Key Expert Comments:** Overall, experts providing comment on the DHE formulation thought a significant unmet need exists for improved treatment for migraine and that an inhaled formulation of DHE that could allow fast, easy, and effective self-administration could address that need. However, this improvement is perceived as largely incremental and experts were unsure whether Levadex would truly improve outcomes more than that achieved by current DHE formulations.
- **Potential for High Impact:** Lower range of high impact

## Sensory Disorder Interventions

### Implantable Miniature Telescope for Age-Related Macular Degeneration

- **Key Facts:** Currently, no treatments are available for end-stage age-related macular degeneration (AMD), and patients experience increasingly diminished vision. The implantable miniature telescope (IMT) (VisionCare Ophthalmic Technologies, Inc., Saratoga, CA) approved by FDA in July 2010 is intended to improve vision in patients 75 years of age or older with stable, severe to profound vision impairment caused by end-stage AMD. FDA, as a condition of approval, requires that patients and their surgeons sign a detailed "acceptance of risk agreement" before surgery, to acknowledge the risks, which include testing to determine candidacy, and the risk of corneal damage and worsened vision after the implantation. The first implantation of the device post-approval was announced by the company in November 2011, and implantation involves the procedure and rehabilitation services delivered as a package the company calls "CentraSight." The reported device cost is about \$15,000, which does not include the costs of implantation and rehabilitation. In October 2011, the Centers for Medicare and Medicaid determined that the device met criteria for pass-through payment, making reimbursement possible. Medicare has no national coverage decision, and coverage is left to the discretion of local Medicare carriers. The implantation of an IMT does not cure macular degeneration; rather, it is intended as an aid to improve vision. Surgically implanted in one eye, the IMT replaces the natural lens and provides an image that has been magnified more than two times.
- **Key Expert Comments:** Experts who commented on this intervention thought the IMT could offer a new option to restore some degree of vision for a condition with no options. Some experts expected the age ceiling for use would lower after initial diffusion and with longer-term data. Demand for specialists in retinal surgery is expected to increase as the

technology diffuses. Significant costs (device and surgery) are anticipated, and it would change treatment paradigms for AMD. Retina specialists will also require training in the implantation procedure.

- **Potential for High Impact:** Moderately high

### **Ranibizumab (Lucentis) for Treatment of Diabetic Macular Edema**

- **Key Facts:** According to the World Health Organization people with diabetes who do not receive appropriate eye care have a 25% to 30% chance of developing clinically significant diabetic macular edema (DME) with moderate or greater vision loss. Currently, the main treatment modality is macular focal/grid laser photocoagulation, because no pharmacotherapies are approved by FDA for treatment of DME. Ranibizumab (Lucentis®, Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland) is an anti-VEGF vascular endothelial growth factor) humanized monoclonal antibody fragment, initially FDA approved for treatment of wet, age-related macular degeneration. It is also FDA-approved for macular edema with retinal vein occlusion. Ranibizumab's mechanism of action allows it to bind to multiple subtypes of VEGF-A. This binding action causes an inhibiting effect, which prevents the growth of new blood vessels under the macula. Because growth of new blood vessels is prevented, the likelihood of vascular leakage and neovascularization is reduced; thus, vision loss as a result of fluid and protein buildup under the macula may be slowed. Investigators in two phase III trials (RISE and RIDE trials) tested ranibizumab in DME patients and reported positive results in June 2011. Genentech planned to file a supplemental biologics license application with FDA for approval for this indication by the end of 2011.
- **Key Expert Comments:** Experts thought that the existence and off-label use of other less costly anti-VEGF drugs might pose a barrier to use of on-label anti-VEGF. However, this intervention has potential as an on-label alternative that might be reimbursed by third-party payers for this indication when off-label use might not be. Availability for on-label DME treatment however could significantly increase per-patient costs compared with off-label use of other anti-VEGF drugs. Also, recent publicity about adverse events occurring as a result of preparation methods of existing anti-VEGFs for ophthalmologic uses may make on-label use more appealing.
- **Potential for High Impact:** Moderately high

### **Recombinant Human Microplasmin (Ocriplasmin) Injection for Treatment of Focal Vitreomacular Adhesion**

- **Key Facts:** Currently, surgical intervention is the primary therapy for patients experiencing significant visual impairment from focal vitreomacular adhesion (VMA), involving posterior vitreous detachment to remove blood, eye debris, and scar tissue in addition to correcting retinal traction. Microplasmin is a recombinant protein produced in *Pichia pastoris*, a species of yeast. Recombinant microplasmin therapy (ThromboGenics NV, Heverlee, Belgium) involves intravitreal injection of recombinant microplasmin, a truncated molecule that retains the catalytic characteristics of human plasmin. ThromboGenics manufactures the microplasmin intravitreal injection and planned to submit a biologics license application to FDA by the end of 2011 for treatment for symptomatic VMA including macular hole; the company submitted an application to the European Medicines Agency in October 2011. Investigators reported that results from two phase III

trials of 652 patients at 90 centers in Europe and the U.S. showed that the trials met their primary endpoints.

- **Key Expert Comments:** Experts thought recombinant microplasmin injection therapy could offer an alternative to surgical intervention for patients most affected by focal vitreomacular adhesion. Overall, while they had reservations regarding the actual number of patients requiring this intervention, most experts thought that microplasmin injection therapy might provide an effective and cost-saving alternative to current standards of treatment.
- **Potential for High Impact:** Moderately high

## Sleep Disorder Intervention

### Neurostimulation (remedē System) for Treatment of Heart-Failure-Associated Central Sleep Apnea

- **Key Facts:** Many patients with heart failure (HF) have a comorbid condition called Cheyne-Stokes respiration, a type of central sleep apnea (CSA) that affects up to two-thirds of HF patients and is associated with increased mortality. Currently, treatment for CSA in these patients is suboptimal. Pharmacotherapy is sometimes used, but is often ineffective or predisposes a patient to other cardiac conditions, prompting some clinicians to suggest the use of continuous positive airway pressure (CPAP), which is associated with low patient adherence. Therefore, effective treatment for CSA is needed. The remedē™ System (Respicardia, Inc., Minnetonka, MN) is an implantable stimulator being investigated for treatment of CSA in these patients. A phase II trial is ongoing in the U.S., and the device is approved in Europe.
- **Key Expert Comments:** Overall, experts who commented on this intervention thought it could have an important impact on many parameters of the health care system, particularly treatment and care models, by offering a very different treatment approach, requiring a different staffing model from usual treatment to implant the device, and requiring infrastructure to accommodate a new surgical procedure for this patient population. In addition, stimulation parameters of the device would need programming and adjusting. While experts wanted to see more data to determine whether this intervention is safe and effective, they were nonetheless optimistic about the technology's potential to address this unmet need.
- **Potential for High Impact:** High

## Spinal Cord Injury Interventions

### Computerized Walking Systems (ReWalk and eLegs) for Paraplegia from Spinal Cord Injury

- **Key Facts:** Currently, conventional manual and powered wheelchairs are the primary assistive devices to restore some degree of mobility in people with paraplegia. However, these devices do not assist users in walking or climbing stairs. Two reciprocating gait orthosis systems in development, the ReWalk-I™ system (Argo Medical Technologies, Ltd., Yokneam Illit, Israel) and the eLegs™ system (Ekso Bionics, Berkeley, CA), could provide greater mobility and freedom to persons with paraplegia from spinal cord injury. The ReWalk system comprises a set of computer-controlled, motorized leg braces that

restore the ability to walk with crutches to patients with paraplegia who retain the ability to use their hands and shoulders to walk with crutches and who have good bone density and cardiovascular health. The eLegs system incorporates technology similar to that in the ReWalk system. FDA classifies the ReWalk system as powered exercise equipment used for medical purposes (e.g., physical therapy), thus making the technology exempt from 510(k) premarket notification and premarket application procedures. The ReWalk-I (institutional use) system is currently FDA-listed for institutional use only, and reported costs are about \$100,000 per system. The company expected to register the ReWalk-P system for personal use with FDA by the end of 2011 and make it available to patients in mid-2012. The company has been quoted in lay press articles as stating that the personal system will cost one-third to one-half the cost of an institutional system. Costs for eLegs are expected to be similar.

- **Key Expert Comments:** Experts thought that the high cost and complexity of this technology could limit its introduction and diffusion into the mainstream of rehabilitative services and centers treating patients with paraplegia from spinal cord injury. Staffing models would be affected by the need for clinical and software engineers and technicians to maintain and adjust the equipment. Also, the equipment would likely be appropriate only for patients whose health was robust enough to use it. Experts indicated that lessons learned from users of this type of intervention might pave the way for future similar interventions capable of addressing the needs of many more patients with this condition.
- **Potential for High Impact:** Moderately high

### **Magnetic Pierced-Tongue Aid for Management of Spinal Cord Injury**

- **Key Facts:** While conventional manual and powered-assisted devices exist that attempt to improve quality of life for individuals with paraplegia, efficacy and safety issues remain a primary concern. The Tongue Drive System (TDS, Georgia Institute of Technology, Atlanta, GA) is a tongue-operated, assistive neurotechnology that consists of a lentil-sized magnetic tracer/stud that is affixed to the tongue, most commonly by piercing. This magnetic tracer communicates synergistically with a headset, magnetic sensors, and a smartphone device to increase patient mobility and allow patients to participate in daily activities. Use of the system would represent a way to purportedly enhance patient mobility and allow patients to perform more daily tasks in a safer, less invasive, and more effective manner than afforded by existing devices. Patients must undergo computer training with the TDS for the computer program to appropriately interpret and calibrate tongue movement, allowing for proper control of the patient wheelchair and computer device. As of November 2011, the TDS has not been approved by FDA and no additional information has been identified from the manufacturer about its status.
- **Key Expert Comments:** Experts commenting on this intervention had diverse perspectives about some aspects, though most thought that the magnetic tongue-directed aid could be a viable alternative to existing technologies. Some experts thought the unmet need was not significant, but others who have worked directly with patients in need of assistive devices to control powered wheelchairs believe this intervention could significantly improve patient health outcomes and QOL, allowing patients to perform daily activities in a quicker and less exhaustive manner than existing technologies such as puff-straws, joysticks, and head-paddles. Several experts thought safety concerns could be a barrier to clinician acceptance, because device malfunction could introduce harm to this patient population. Overall, this device's perceived complex nature, the existence of comparators, and limited safety and



efficacy data thus far have made some experts question device's true impact potential. However, other experts believe this device has the ability to significantly improve patient mobility and QOL when compared with standard mobility devices.

- **Potential for High Impact:** Moderately high

## Vascular Abnormality Intervention

### Off-label Propranolol for Treatment of Infantile Hemangiomas

- **Key Facts:** Currently, no FDA-approved pharmacotherapies are available for treatment of infantile hemangiomas (IHs). Although corticosteroids, interferon alpha, and vincristine are treatment measures used for IHs, limited efficacy, safety concerns, and intolerable adverse events associated with these therapies have prompted investigation for novel therapies with a more efficacious and safer profile. Propranolol (original manufacturer AstraZeneca London, UK, investigator Johns Hopkins University School of Medicine, Baltimore, MD, and Cambridge University Hospital, Cambridge, UK) is a nonselective beta adrenergic receptor antagonist (beta blocker) that exerts its cardiovascular effects by blocking the action of endogenous catecholamines (e.g., epinephrine and norepinephrine) on beta-adrenergic receptors and is being studied for treatment of IHs. Propranolol is not labeled as treatment for IHs, and its intended use by current institutions for this purpose would be considered off-label. A recent retrospective study published August 2011 in *Online First Archives of Dermatology* (Price et al., University of Miami) compared propranolol to oral corticosteroids for treatment of IHs, and investigators reported that propranolol therapy was more effective in treating IHs, with minimal side effects and a cost of about \$205 per treatment, about half the cost of corticosteroids.
- **Key Expert Comments:** Experts expressed optimism about propranolol's ability to meet the need of patients who suffer complications from IHs, and contingent on results from ongoing clinical trials, propranolol has the potential to replace corticosteroids as first-line therapy for treatment of IHs.
- **Potential for High Impact:** High

## **Central Nervous System Disorder Intervention**

## Intervention

### Fingolimod (Gilenya) for treatment of relapsing-remitting multiple sclerosis

Multiple sclerosis (MS) is a common cause of physical disability in the United States.<sup>1</sup> Inflammation damages myelin surrounding nerves, impeding the electrical impulses that travel along the nerves. As the disease progresses, it affects more and more areas, eventually causing interference with vision, speech, walking, writing, memory, sexual function, and bowel and bladder control.<sup>2,3</sup> Relapsing-remitting multiple sclerosis (RRMS) is the most common form of multiple sclerosis and is usually the earliest form to be diagnosed.<sup>4</sup> Current first line-therapies consist of injectable immunomodulators that dampen autoimmune responses against the CNS. However, there are no effective treatments to stop the long-term progression of the disease.<sup>4,5</sup> Fingolimod (Gilenya®, Novartis AG, Basel, Switzerland, and Mitsubishi Tanabe Pharma Corp., Osaka, Japan) is the first oral drug approved (September 2010) by the U.S. Food and Drug Administration (FDA) as first-line therapy for RRMS.

Fingolimod is a synthetic derivative of myriocin, and is the first in a new class of drugs called sphingosine 1-phosphate receptor (S1PR) modulators. It is a cannabinoid antagonist and sphingosine-1-phosphate (S1P) agonist. By modulating the sphingosine 1-phosphate receptor pathway, fingolimod is purported to dampen the activity of autoreactive lymphocytes by keeping them localized to the lymph nodes. In this way, fingolimod is thought to reduce the number lymphocytes with access to the central nervous system and limit damage to the myelin sheath. An inverse relationship was observed between the fingolimod dose and efficacy in MS, whereby the lowest dose showed comparable or increased efficacy, as well as improved safety, compared to the highest drug dose.<sup>6,7</sup> Fingolimod is administered once daily, in a 0.5 mg capsule, with or without food.<sup>8</sup>

In two randomized, multicenter, phase III trials, the effects of fingolimod were evaluated in patients with RRMS. In one trial, the investigators reported patients (n = 1,272) who received either 0.5 or 1.25 mg of fingolimod or placebo once daily for 24 months had annualized relapse rates of 0.18, 0.16, and 0.40, respectively (p <0.001 for either dose vs. placebo).<sup>9</sup> The cumulative probability of disability progression (confirmed after 3 months) was 17.7%, 16.6%, and 24.1%, respectively. Fingolimod at both doses significantly reduced the risk of disability progression during the study (p = 0.02 vs. placebo, for both comparisons). At 24 months, both doses of fingolimod were superior to placebo with regard to magnetic resonance imaging (MRI)-related measures (number of new or enlarged lesions on T(2)-weighted images, gadolinium-enhancing lesions, and brain-volume loss; p <0.001 for all comparisons).<sup>9</sup>

In the second study, the investigators reported patients (n = 1,292) who received either 0.5 or 1.25 mg of fingolimod or intramuscular injection of 30 mcg interferon beta-1a weekly for 12 months. The annualized relapse rate was significantly lower in both groups receiving fingolimod 0.16 (95% confidence interval [CI], 0.12 to 0.21) and 0.20 (95% CI, 0.16 to 0.26) in the 0.5- and 1.25-mg groups respectively compared with the interferon group (0.33; 95% CI, 0.26 to 0.42; p <0.001 for both comparisons).<sup>10</sup> No significant differences were seen among the study groups with respect to progression of disability.<sup>10</sup> The most common adverse events reported in these studies included headache, flu, diarrhea, back pain, abnormal liver tests and cough. Other fingolimod-related side effects included transient, generally asymptomatic heart-rate reduction and atrioventricular block upon treatment initiation, mild blood pressure increase, macular edema, and mild bronchoconstriction.

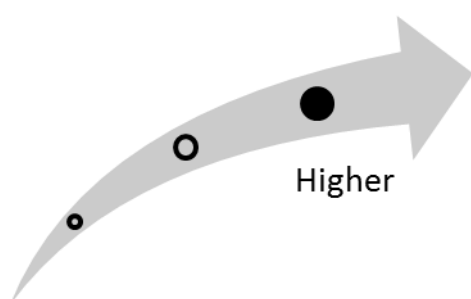
In June 2010, The U.S. Food and Drug Administration's Peripheral and Central Nervous System Drugs Advisory Committee recommended approval of fingolimod, and in September 2010, FDA approved fingolimod (0.5 mg) for the first-line treatment of RRMS. In early October 2010, it was

launched in the United States.<sup>11</sup> Reported sales figures in March 2011 indicated broad acceptance by the MS clinical and patient communities thus far, despite its \$48,000 annual per patient cost.<sup>12</sup>

## Clinical Pathway at Point of This Intervention

First-line treatments to reduce the frequency and severity of relapses for RRMS include the injectable medications interferon beta-1b (Betaseron®, Bayer AG, Leverkusen, Germany), interferon beta-1a (Avonex®, Biogen Idec, Research Triangle Park, NC; Rebif®, EMD Serono, Inc., Rockland, MD; and Pfizer, Inc., New York, NY), and glatiramer acetate (Copaxone®, Teva Pharmaceutical Industries, Ltd., Jerusalem, Israel).<sup>4,5</sup> Fingolimod represents the first oral agent approved in the U.S to treat RRMS.

**Figure 1. Overall High Impact Potential: Fingolimod (Gilenya) for treatment of relapsing-remitting multiple sclerosis**



Fingolimod is the first oral agent approved in the U.S. to treat RRMS. Investigators of phase III trials reported that fingolimod reduced the frequency of relapse compared with interferon beta-1a injection. Experts providing comments on this drug expected the oral administration and improved efficacy to result in wide acceptance among clinicians and patients. However, costs (estimated at \$48,000 per patient per year), coverage by payers, and the adverse event profile of fingolimod may be barriers to diffusion and sources of controversy for the drug. Based on this input, our overall assessment is that this intervention is in the higher end of the high potential impact range.

## Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this intervention.<sup>13-19</sup> Overall, the experts stated that MS is a debilitating disease that results in significant morbidity and disability. There remains a large unmet need for new treatments with improved efficacy and ease of administration. The experts stated that fingolimod may address this unmet need and improve patient health outcomes by increasing the time between relapses and delaying the accumulation of physical disability. As an agent with a new mechanism, fingolimod might improve outcomes in patients who did not respond to previous first-line therapies one expert representing a clinical perspective stated. However, one expert representing a research perspective stated that particularly in the case of RRMS, large, randomized, controlled, triple-blinded studies will be needed to accurately assess how well fingolimod can address the unmet need. Additionally, there was no consensus regarding how fingolimod might affect the frequency and severity of adverse events compared with injectable therapies.

Although several experts thought the high price of fingolimod might increase health disparities for patients without prescription coverage from a third party payer, one expert representing a research perspective stated that patients with poor access to care are now able to take a pill at home instead of requiring routine visits for injections. As an oral therapy potentially slowing disease progression in some patients, fingolimod could reduce infrastructure and staffing needs at treatment facilities as well as assisted living facilities. However, two experts representing a clinical perspective stated that upon initiating treatment, additional monitoring for cardiovascular and ophthalmologic adverse events could add to demands on infrastructure and staffing at treatment centers.

Although physicians might be hesitant to use fingolimod because of its adverse event profile, some experts stated that the increased efficacy of the drug and ease of administration are likely to increase acceptance of the drug. Many of the experts also expect patients to be highly receptive to an oral therapy

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that might slow disease progression. Fingolimod and injectables have roughly similar costs. Some experts stated that if patients are already taking injectable therapy and their insurance covers fingolimod, cost would provide a minimal barrier to diffusion because fingolimod is expected to be used as monotherapy. However one expert representing a health systems perspective stated that controversy could arise if the benefits of treatment with fingolimod are not cost-effective relative to other RRMS therapies, which may affect coverage.

## **Endocrine Disorder Intervention**

## Intervention

### PTH (1-84) for treatment of hypoparathyroidism

Hypoparathyroidism is an endocrine disorder characterized by abnormally low levels of parathyroid hormone (PTH), which can lead to low calcium levels in blood and bones and an increased amount of phosphorus.<sup>20</sup> Symptoms include anxiety, depression, fatigue, headaches, memory problems, muscle cramps and/or tingling of the extremities, muscle spasms, painful menstruation, brittle nails, dry skin, and patchy hair loss.<sup>21</sup> Hypoparathyroidism (low levels of PTH) affects approximately 4 of every 100,000 persons in the United States.<sup>22</sup> Current treatment options for regulation of calcium and phosphorus in the body include supplemental calcium carbonate and vitamin D, although these supplements may lead to long-term complications. In life-threatening hypoparathyroidism (extremely low calcium levels), intravenous calcium may be administered. Currently, no pharmacotherapy is approved for treatment of hypoparathyroidism, signaling a need for more effective therapy.<sup>23</sup>

Recombinant human (rh)PTH (1-84) (NPS Pharmaceuticals, Bedminster, NJ), is a synthetic PTH produced in the bacterium *Escherichia coli* as a single, nonglycosylated, polypeptide chain containing 84 amino acids, and it is purified by proprietary chromatographic techniques.<sup>24</sup> In the human body, PTH, or parathormone, is secreted by the parathyroid glands as a polypeptide containing 84 amino acids. PTH increases the concentration of calcium in the blood by acting upon PTH receptors in three parts of the body: bones, kidney, and intestine. The manufacturer purports that by replicating the actions of natural PTH, rhPTH can help the body maintain near-normal serum calcium levels without much dependence on supplemental calcium or Vitamin D.<sup>25</sup> RhPTH (1-84) has been considered as a potential antiosteoporotic agent and as a bone formation stimulant that may stimulate osteoblasts and reduce both vertebral and nonvertebral fractures. In clinical trials, rhPTH (1-84) is being given by subcutaneous injection at doses of 50, 70, or 100 mcg per day for the treatment of hypoparathyroidism.<sup>26-28</sup>

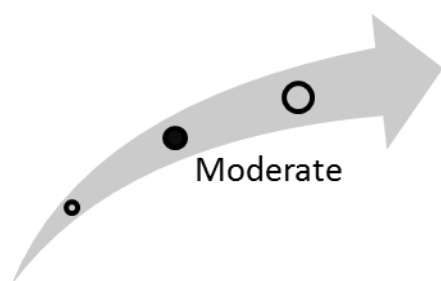
In 2011, Bilezikian and colleagues reported results from the recent phase III REPLACE trial, a 28-week, double-blind, placebo-controlled study evaluating rhPTH for treatment of hypoparathyroidism. In this study, “53 percent (48/90) of NPSP558 [rhPTH]-treated patients achieved the primary endpoint versus 2 percent (1/44) of placebo-treated patients ( $p < 0.0001$ ). At week 24, 43 percent (36/84) of patients treated with NPSP558 were able to achieve independence from active vitamin D therapy and a calcium supplementation dose of 500 mg/day or less, as compared to five percent (2/37) for patients treated with placebo ( $p < 0.0001$ ). Thirteen of the 134 randomized subjects discontinued the study early, of which seven were placebo-treated and six were NPSP558-treated.”<sup>25</sup> RhPTH (1-84) was granted orphan drug status by FDA in 2007 and based on preliminary results from the REPLACE trial in November 2011, the company anticipates submitting a new drug application to the U.S. Food and Drug Administration (FDA) in early 2012.<sup>25,29</sup>

### Clinical Pathway at Point of This Intervention

Once a diagnosis of hypoparathyroidism is made, treatment options to restore the body's calcium and phosphorus to normal levels include calcium carbonate and vitamin D supplements, which usually must be taken for a lifetime. Blood levels are measured regularly to ensure appropriate dosages are being taken, because overtreatment with vitamin D and calcium can cause hypercalcemia, which can adversely affect kidney function.<sup>30</sup> A high-calcium, low-phosphorous diet is recommended, and in cases of life-threatening attacks of low calcium levels or prolonged muscle contractions, calcium is given intravenously in the emergency department. In these cases, cardiac monitoring for abnormal rhythms is also conducted.<sup>30</sup> A dietitian is part of the multidisciplinary team to manage this condition

in stable patients.<sup>20</sup> Currently, there is no approved prescription therapy for hypoparathyroidism.<sup>23</sup> RhPTH (1-84) is a synthetic PTH under study as a daily injection for treatment of hypoparathyroidism to reduce or replace calcium and vitamin D supplementation.

**Figure 2. Overall High Impact Potential: PTH (1-84) for treatment of hypoparathyroidism**



Experts commenting on this intervention thought the drug's potential to treat parathyroidism could reduce overall treatment costs accumulated by lifetime use of supplemental calcium carbonate and Vitamin D, in addition to treatment of hypervitaminosis associated with excessive use of these supplements. They also thought this intervention could significantly improve quality of life and patient health outcomes, because rhPTH (1-84) might decrease incidence of vertebra fractures and other complications of disease in addition to reducing or eliminating the need for supplemental

calcium and Vitamin D. Experts opined that while lack of safety and efficacy studies and increase in per-patient costs might serve as barriers to adoption, this intervention has the potential to significantly affect this patient population. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

## Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, commented on this intervention.<sup>31-37</sup> Experts were mixed regarding importance on pharmacologic agents needed for treatment of hypoparathyroidism. Several experts argued there are several treatment options available for the treatment of this disease, and current treatment modalities are typically effective in managing hypothyroidism. These experts indicated there may not be much of an unmet need for this patient population considering there is a small subset of patients receiving a diagnosis of hypoparathyroidism whose disease is not currently managed by supplemental calcium carbonate and Vitamin D. However, experts who agreed there is an unmet need for this intervention argued that rhPTH (1-84) might significantly improve patient health outcomes and quality of life, potentially reducing or eliminating the need for supplemental calcium and Vitamin D, currently needed for duration of life.

Experts generally agreed this intervention's underlying theory is sound, although more studies need to be conducted to further evaluate rhPTH (1-84)'s efficacy and safety. One research expert indicated that rhPTH (1-84) dose levels and frequency of administration need to be determined for proper evaluation of efficacy and safety. One clinical expert cautioned that while this intervention's theory appears logical, "[hormone] replacement is never truly physiologic and thus outcomes may not be as desired."<sup>36</sup> Opinions regarding this intervention's potential to improve patient health outcomes were mixed. Four experts believe this synthetic hormone could treat the underlying cause of disease rather than managing complications of disease with current treatment modalities. One clinical expert explained that "potentially reducing or [eliminating] the need for other supplements and dietary restrictions would have a large positive outcome for patients, allowing them to live more normal lives."<sup>37</sup> A health systems expert noted that the potential reduction in vertebrae fractures and other bone-related issues would significantly improve patient outcomes and quality of life. Other experts remained uncertain of this therapy's ability to improve patient outcomes, citing the need for long-term efficacy studies to make a proper determination.

The majority of experts agreed that the intervention would not significantly affect the current patient care model or health care delivery infrastructure, indicating self-administration with an



injectable therapy would require minimal adjustment for this patient population. All experts cautioned that patient and clinician acceptance of this intervention might be difficult given the treatment transition to daily self-administered injections of rhPTH (1-84). Experts indicated clinicians might not adopt a therapy that poses regimen-adherence issues for their patients. In terms of patient acceptance, however, one clinical expert explained that patients might be willing to comply with this therapy, considering that adhering to dietary restrictions could be more difficult than adhering to this therapy.

Expert opinions regarding per-patient costs for this intervention were mixed. Several experts opined while initial per-patient costs could increase, potential reduction and elimination of supplemental therapies might decrease these costs long term. One expert indicated that there is not yet enough information regarding this therapy's effect on costs in terms of decreased hospitalizations, reduction in therapy, and other associated financial factors. Two experts strongly indicated that per-patient costs might increase significantly with adoption of this therapy. One research expert stated, "depending on the optimal dose and drug costs, if a patient needs 100 micrograms daily based on cost estimated in the report, this could add about \$200.00/day to treatment costs."<sup>33</sup> Another research expert echoed this sentiment, but added that self-administration of this therapy in the home setting may obviate the need for inpatient hospitalizations for intravenous calcium supplementation, potentially mitigating substantial per-patient costs.

Overall, questions surrounding this therapy's efficacy and safety when compared with existing treatment options and overall costs left several experts skeptical of rhPTH (1-84)'s potential to have high impact for patients in whom hypoparathyroidism has been diagnosed. However, several experts believe that given initial study results, there is potential for this therapy to significantly improve outcomes in patients for this indication where traditional therapies have failed and where there is currently no FDA-approved pharmacologic therapy.

## **Epilepsy Intervention**

## Intervention

### Ezogabine (Potiga) for treatment-resistant, partial-onset epilepsy

Partial-onset seizures are the most common form of epileptic seizures. According to the Epilepsy Foundation, about 20% of patients with epilepsy do not respond to currently available pharmacotherapy, and these patients may have to undergo invasive surgical resection or implantation of a vagus nerve stimulator. Therefore, a novel, effective pharmacotherapy would address an important unmet need for these patients.

Ezogabine (Potiga<sup>TM</sup>, Valeant Pharmaceuticals International, Inc., Mississauga, Ontario, Canada, and GlaxoSmithKline, Middlesex, UK) is an anticonvulsant that has been investigated as an adjunctive therapy for treatment-resistant epilepsy characterized by partial-onset seizures.<sup>38</sup> The compound acts both as a potassium-channel opener and as a potentiator of gamma aminobutyric acid (GABA), representing a new mechanism of action for this indication.<sup>38</sup> In its role as a potassium channel opener, ezogabine is designed to stabilize potassium channels in the open position, thereby increasing the stabilizing membrane current and preventing action potential bursts during the sustained depolarization (i.e., reducing cellular excitability) associated with seizures.<sup>39</sup> Researchers have also suggested that ezogabine increases the concentration of GABA, the major inhibitory neurotransmitter in the brain, which has long been associated with epilepsy.<sup>39</sup> In controlled and open-label clinical trials, ezogabine was administered as an oral tablet (50, 100, or 300 mg tablets), dosed three times per day for a total of 600 to 1,200 mg per day for patients who were on background pharmacotherapy for epilepsy.

In results of a phase III trial of 539 patients with treatment-refractory, partial-onset epilepsy who received ezogabine, investigators reported, “The median reduction in 28-day total partial seizure frequency was 27.9% and 39.9% in patients receiving 600 and 900 mg of retigabine, respectively, compared with only 15.9% patients on placebo, meeting the FDA endpoint.”<sup>39</sup> The company also reported that in its three phase III trials, “Ezogabine caused urinary retention in clinical trials. Urinary retention was reported as an adverse event in 29 out of 1,365 (approximately 2%) patients treated with ezogabine. In all studies of patients with partial-onset seizures, including open-label studies, five patients required catheterization (four on ezogabine and one on placebo). In three controlled clinical studies, 25% of patients receiving ezogabine (199/813) and 11% of patients receiving placebo (45/427) discontinued treatment because of treatment-emergent adverse reactions.”<sup>40</sup>

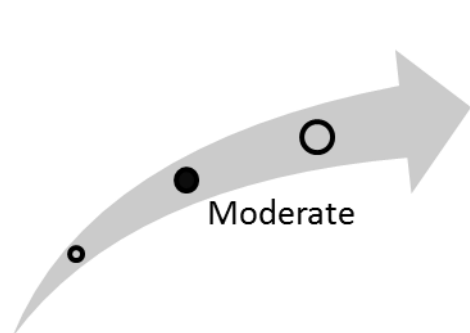
The manufacturers submitted a new drug application to the U.S. Food and Drug Administration (FDA) in October 2009. In August 2010, an FDA advisory panel voted to recommend approval of ezogabine. In December 2010, FDA issued a complete response letter to the manufacturers citing nonclinical reasons for not approving the drug<sup>39</sup> and the company responded in April 2011. On June 10, 2011, GlaxoSmithKline and Valeant Pharmaceuticals announced that ezogabine had been approved for the treatment of partial-onset seizures in adults (18 years and older) by FDA.<sup>40</sup> The FDA approval, however, also required a Risk Evaluation and Mitigation Strategy (REMS) to inform health care professionals who prescribe the drug of the risk of urinary retention and the symptoms of acute urinary retention. Additionally, FDA published consumer information alerting patients to risks of neuropsychiatric symptoms, including confusion, hallucinations, psychotic symptoms, and suicidal thoughts. At the time of this report, retail or wholesale costs for the drug in the U.S. were not yet available.

### Clinical Pathway at Point of This Intervention

According to the Epilepsy Foundation, current treatment for this disease state includes pharmacotherapy (e.g., carbamazepine, gabapentin, phenobarbital, valproate) and, for some patients unresponsive to these agents, surgical resection or vagus nerve stimulation may be indicated.

Ezogabine is being investigated as an adjunct therapy to current antiepileptic medications and would, therefore, likely be used in concert with these medications. If ezogabine is found to be safe and effective for this indication, it would likely displace some of the need for the surgical resection of vagus nerve stimulation. Thus, ezogabine is expected to compete with these interventions as an option for patients whose epilepsy is refractory to existing pharmacotherapy.

**Figure 3. Overall High Impact Potential: Ezogabine (Potiga) for treatment-resistant, partial-onset epilepsy**



Overall, experts commenting on this topic (prior to its FDA approval) were generally optimistic about this drug's potential to meet the need for effective pharmacotherapy for adults with treatment-resistant, partial-onset epilepsy because of its promising mechanism of action and clinical trial data. As an oral drug, experts thought, it could be incorporated easily into the existing care model for epilepsy. However, if ezogabine is proven to obviate the need for invasive interventions for epilepsy, it would affect several health system parameters, especially a change in care setting (medical management rather than surgery), patient management, and treatment costs, most experts opined. 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 clinical, research, health systems, and health administration perspectives, commented on this intervention.<sup>41-46</sup> These experts agreed that an unmet need exists for effective, noninvasive therapies for patients with epilepsy that is refractory to pharmacotherapy. One clinical expert commented that surgical interventions have limited efficacy, thus highlighting the importance of the unmet need for new, more effective options.

Experts expressed strong opinions about the theory underlying the intended mechanism of action of ezogabine, with one expert stating that this mechanism "has the effect of stabilizing the electrical current in the brain and prevents the sudden bursts of activity that occur with seizures."<sup>46</sup> One clinical expert thought that the underlying mechanism is "actually one of the best one could imagine," because "potassium channels have been studied for their role in epilepsy and many drug therapies for epilepsy focus on increasing GABA levels."<sup>41</sup> Another expert, however, tempered this viewpoint, stating, "The overall decrease in neuronal responsiveness may have unintended consequences."<sup>45</sup> Experts were cautiously optimistic about the drug's potential to improve health outcomes, stating that although additional studies are needed to confirm efficacy and side-effects data, results so far suggest improvements in seizure rate. One expert with a health systems perspective believes that potential success of ezogabine could improve patient adherence, which in turn would positively affect patient health outcomes.

Because the drug is characterized by a novel mechanism of action, experts thought, ezogabine has the potential to have an impact on "basic research and our current understanding of the mechanism of the disease,"<sup>41</sup> as one expert put it. They also stated that the drug may obviate the need for surgical resection or electrical stimulation, leading most experts who commented to believe that it has potential to shift current treatment models. Similarly, by potentially reducing the need for invasive interventions, the drug has potential to shift the care setting for treatment-resistant epilepsy from an inpatient to

outpatient setting, they thought, which would, in turn, “reduce hospital stays for surgical treatment of epilepsy, increase patient throughput by not requiring surgery, and decrease the amount of staff required to treat epilepsy.”<sup>45</sup> However, some experts thought that treatment models would remain the same, because the drug is intended to be used as an oral adjunct to current pharmacotherapies.

Experts were divided on whether this intervention would increase or decrease the cost of care. Some experts claimed that costs would be reduced, because drugs are typically less expensive than surgical interventions, while others believe that, as one expert put it, “Surgery is a one-time deal, and [medications are taken for] a lifetime.”<sup>44</sup> That expert thought a long-term increase in care costs would be seen, particularly because ezogabine would be added to current oral medication regimens.

Most experts believe that both patients and clinicians would accept this intervention readily, particularly if it is shown to obviate the need for invasive procedures. One expert with a health systems perspective expressed optimism that this intervention might improve the physician-patient relationship by giving physicians another option to offer in their armamentarium.

## **Genetic Disorder Intervention**

## Intervention

### Icatibant (Firazyr) for treatment of acute hereditary angioedema

Hereditary angioedema (HAE) is a genetic disorder caused by dysfunction or deficiency of C1 esterase inhibitor (C1INH), an inhibitor of the C1 protease that is responsible for activating the complement pathway of the innate immune system. If C1INH is deficient, C1 proteases set off the complement pathway, causing an acute inflammatory response that leads to swelling. Part of the inflammatory response is the release of uncontrolled levels of bradykinin (BK), a potent vasodilator that acts much like a histamine.<sup>47</sup> During a serious attack, the throat may swell and cause the airway to close, resulting in asphyxiation; this is associated with a mortality rate of 15% to 33%.<sup>48</sup> Abdominal attacks can also cause severe pain and disfigurement. Bouts of edema can last 3 to 5 days; the trigger for attacks is unknown.<sup>47</sup>

Icatibant (Firazyr®, Shire, plc, Dublin, Ireland) is a selective and specific synthetic polypeptide bradykinin receptor-2 (BR2) antagonist. Unlike bradykinin receptor-1, BR2 receptors do not appear to be involved in chronic inflammatory diseases but may mediate acute inflammatory processes.<sup>49</sup> Icatibant's affinity for BR2 is similar to BK itself,<sup>49</sup> suggesting it may inhibit or attenuate the biologic activity of BK during acute cases of inflammation and edema. Icatibant is currently available as a subcutaneous injection in a number of countries outside the United States for treatment of patients with type 1 HAE (characterized by insufficient levels of C1INH). In phase III trials, icatibant was administered as three 30 mg subcutaneous injections per day or eight injections of 30 mg over 4 weeks as needed. Development is under way of inhalable and intravenous formulations. Because icatibant is a synthetic peptide, it will not be available as an oral formulation.<sup>49</sup>

In two double-blind, randomized, multicenter trials, the effects of icatibant were evaluated in patients with HAE presenting with cutaneous or abdominal attacks.<sup>50</sup> In results of one trial (n = 56), researchers reported that the primary endpoint of median time to clinically significant relief of symptoms was 2.5 hours compared with 4.6 hours with placebo, although the result did not reach statistical significance (p = 0.14). In the second trial (n = 74), researchers reported that the primary endpoint of median time to clinically significant relief of symptoms was 2 hours with icatibant versus 12 hours with tranexamic acid (p < 0.001). No icatibant-related serious adverse events were reported.<sup>50</sup> An interim analysis from a phase IIIb trial evaluating patients who self-administered icatibant (n = 56) in response to acute HAE attacks was also reported.<sup>51</sup> Icatibant provided symptom relief for 96.2% of self-treated attacks. The median time to onset of at least 30 % primary symptom relief was 2.0 hours; the median time to onset of at least 50% symptom relief was 2.6 hours. For icatibant naïve patients (n = 8), median times to onset of symptom relief were similar between first and second attacks. No serious adverse events were reported. Ninety-five percent of patients reported self-injection of icatibant “preferable” or “very preferable” to administration in the clinic, and 88% of patients were “satisfied” or “very satisfied” with symptom relief following the self-administration of icatibant.<sup>51</sup>

**From 2008 to 2010, icatibant was approved for marketing by regulatory bodies in 37 countries for the subcutaneous symptomatic treatment of acute attacks of HAE in adults with C1INH deficiency. Shire filed a new drug application (NDA) with the U.S. Food and Drug Administration (FDA) in 2007. However, FDA issued a nonapprovable letter in April 2008, and the company began a new program of phase III trials in 2009 in response to FDA's concerns. Initial positive results from these clinical trials were reported in December 2010, and Shire resubmitted its NDA for icatibant in early 2011.<sup>49,52</sup> On June 23, 2011, the Pulmonary-Allergy Drugs Advisory Committee to FDA recommended approval of icatibant, and FDA approved the drug on August 25, 2011. Shire quickly initiated a program to promote access. Its Quick Start**

**program and extended OnePath Access Program were created to offer product-related services and support to patients. After a health care provider prescribes the drug, patients can enroll to be eligible to receive two syringes of the drug at no cost.**

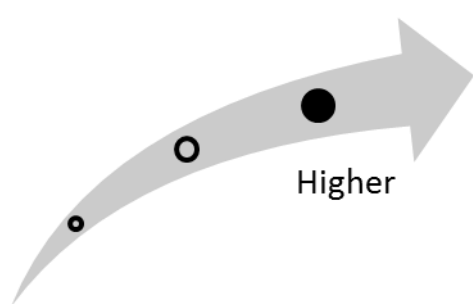
The average wholesale cost of this drug in the U.S. was expected to be about \$6,800 per syringe. The retail cost of one 30 mg dose of ecallantide (Kalbitor®), a recently approved competitor to icatibant, was listed at about \$9,500.<sup>53</sup>

Icatibant is currently under development for treatment of type I or type II HAE. It may not be suitable for patients with other types of HAE, congestive heart failure, or other types of coronary artery disease.<sup>54,55</sup> Thus far, icatibant has proven to be well tolerated in clinical trials. Because of its highly selective affinity for BR2, only minimal side effects have been reported.<sup>49</sup>

## Clinical Pathway at Point of This Intervention

A patient who has HAE typically experiences swelling in the airway and/or extremities and intestines causing repeat episodes of abdominal cramping without apparent cause. Treatment options are currently limited to symptomatic relief and include antiinflammatory medications such as antihistamines; epinephrine and corticosteroids for symptom relief; attenuated androgenic steroids such as danazol, stanozolol, oxymetholone, fluoxymesterone, and methyltestosterone (which are associated with serious side effects) to suppress production of plasma protein C1INH in the liver<sup>47</sup>; and prophylactic administration of antifibrinolytic agents such as tranexamic acid to reduce frequency of attacks. Three new drugs have been approved in the U.S. for treatment of HAE: Cinryze® (Viropharma, Inc., Exton, PA) and Berinert (CSL Behring, King of Prussia, PA) are given intravenously and are plasma-derived C1INH concentrates purified from human plasma for short-term prophylaxis and acute HAE attacks; ecallantide (Kalbitor, Dyax Corp., Cambridge, MA) is a plasma kallikrein inhibitor administered by subcutaneous injection for acute HAE attacks.<sup>47</sup> Icatibant represents a novel mechanism for HAE treatment to reduce inflammation during acute HAE.

**Figure 4. Overall High Impact Potential: Icatibant (Firazyr) for treatment of acute hereditary angioedema**



Overall, experts commenting on this intervention saw icatibant as having significant potential to shorten the duration of symptoms and improve clinical outcomes in the small number of patients who experience HAE, a potentially life-threatening condition. They noted that while other new treatments have just become available for HAE, icatibant has a different mechanism of action and may be self-administered on an outpatient basis, potentially minimizing hospitalizations and the role emergency personnel in the management of HAE in a subset of patients. Thus, experts saw the overall impact as high. Based on this input, our overall assessment is that this intervention is in the higher end of the high potential impact range.

## Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered comments on this intervention.<sup>56-62</sup> Overall, experts agreed that current treatment options for HAE are much less effective than desired, and a strong unmet need exists for new therapies for the disease. All experts offering comments agreed that the theory behind the mechanism of icatibant action is sound, and the available data from clinical trials showed promising results that icatibant appeared efficacious at relieving HAE symptoms within a relatively short duration of time. Two experts with clinical perspectives and two experts with research perspectives believe the findings associated with



icatibant could increase our understanding of targeting pathways involved in immunologic acute-phase responses.

Two experts with clinical perspectives, one with a research perspective, and one with a health systems perspective believe that icatibant could shift care, treatment, and management models and the treatment setting if the drug were to be administered on an outpatient basis in a physician's office or at a patient's home via self-administered subcutaneous injections. Additionally, an expert stated that the ability of patients to self-inject icatibant on an outpatient basis to treat acute HAE attacks was one of the main unmet needs that this drug may address.

Cost was also identified as an area that may be affected by the use of icatibant; however, experts were generally unsure as to the magnitude and direction of the impact on cost, given the unavailability of cost information at this time. One clinical expert and one health systems expert stated that cost savings could be realized if emergency department visits could be avoided; however, another clinical expert stated that costs may increase if icatibant is used for mild cases of HAE, while cost savings may be realized if icatibant is used on an outpatient basis for more serious cases of HAE. The lack of sufficiently effective therapies and the severity of the disease inclined all experts to state that they expected few barriers to acceptance of icatibant by patients and physicians. One clinical expert stated that the high anticipated cost of the intervention and the small population of patients with HAE would prevent providers from stocking a potentially effective therapy, thereby providing a source of controversy. One clinical expert and one research expert also stated that self-injection might present a barrier to patient acceptance. Two research experts and one health systems expert also identified concerns regarding ischemia and stroke, which may be associated with the use of icatibant, as sources of controversy.

Overall, experts viewed icatibant as having significant potential to shorten the duration of symptoms and improve clinical outcomes in the small number of patients affected by HAE.

## **Hematologic Disorder Intervention**

## Intervention

### **OBI-1 (recombinant B-domain deleted porcine coagulation factor VIII) for treatment of acquired hemophilia**

Acquired hemophilia is a rare disease occurring mostly in middle-aged individuals and rarely in children. Currently, the number of individuals with all types of hemophilia in the United States is an estimated 20,000 to 25,000 individuals.<sup>63,64</sup> Acquired hemophilia is rare and affects approximately 1 to 4 individuals per 1 million population.<sup>64</sup> Current therapies, specifically human factor VIIa (NovoSeven®, Novo Nordisk AS (Bagsvaerd, Denmark), and factor VII Inhibitor Bypassing Activity (Feiba™, Baxter International, Inc., Deerfield, IL) work by bypassing the coagulation cascade, producing extremely higher-than-normal levels of factor VIIa to induce coagulation.<sup>65</sup> However, an increase in novel therapies is needed to more effectively address the underlying pathogenesis of acquired hemophilia, in which autoantibodies produced against the body's coagulation factors result in excessive bleeding episodes. OBI-1 (Inspiration Biopharmaceuticals, Inc., Laguna Niguel, CA) therapy is purported to address the unmet need of patients receiving a diagnosis of acquired hemophilia A.

OBI-1 is an intravenous recombinant porcine factor VIII product that serves as factor VIII replacement therapy by activating the natural coagulation cascade.<sup>65</sup> In acquired hemophilia, the production of autoantibodies in adult life inactivates factor VIII, causing hemophilia type A. This therapy purportedly has low cross reactivity with autoantibodies against factor VIII, therefore significantly reducing immunogenicity of the antigen to recombinant porcine factor VIII. In a previous study, OBI-1 was evaluated in patients with congenital hemophilia A. Results from this study demonstrated that OBI-1 had the capacity to stop the bleeding in all study participants, which paved the way for investigation of its efficacy for acquired hemophilia A.<sup>66</sup> In the ongoing trial, OBI-1 is being given by intravenous infusion over a period of 2 to 3 hours in the trial for patients with acquired hemophilia A. In the phase II trial on congenital hemophilia A, OBI-1 was administered a loading dose followed by 50 to 150 U/kg of body weight infused every 6 hours for up to eight doses until bleeding cessation with a dose limit of 1,000 U/kg in 24 hours.<sup>67</sup>

In July 2011, Inspiration Biopharmaceuticals announced results from its pivotal trial in the OBI-1 Accur8 clinical trial program. OBI-1 treatment was given to three patients with acquired hemophilia who had experienced severe bleeds uncontrolled by other therapeutic agents. Bleeding stopped in all three patients treated with OBI-1 therapy. A larger phase III trial was planned to begin in 2011.<sup>68</sup>

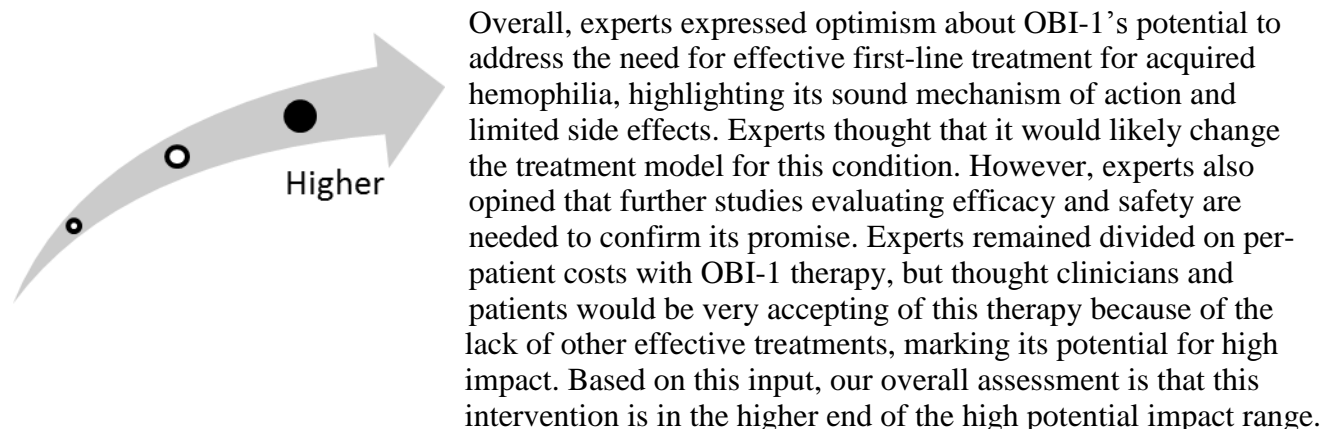
FDA granted OBI-1 orphan drug status in March 2004. The European Commission also granted orphan drug status.<sup>66</sup> A regulatory submission for marketing approval in the European Union is expected in 2012.<sup>69</sup> A U.S. regulatory submission is not expected until 2014.

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

Patients with acquired hemophilia A present a different pattern of bleeding (extensive purpura) when compared with common congenital forms of the disease (bleeding into joints).<sup>64</sup> Primary care providers may be the first to encounter the patient, who is then referred for a hematology consultation, ideally at a comprehensive hemophilia treatment center. These centers provide a multidisciplinary approach that includes a team consisting of hematologists, nurses, social workers, physical therapists, and other health care providers.<sup>63</sup> According to the U.S. Centers for Disease Control and Prevention, treatment involves replacing the missing clotting factor through plasma-derived concentrate or genetically engineered recombinant factors (i.e., not from plasma) of the missing factor, cryoprecipitate for acute bleeding episodes, or other medications intended to induce clotting, such as DDAVP (desmopressin acetate) and Amicar® (epsilon aminocaproic acid).<sup>63</sup> For acquired hemophilia,

treatment also targets production of the antibody inhibitors.<sup>64</sup> OBI-1 is proposed as a treatment for acute bleeding episodes in patients with acquired hemophilia A who have developed inhibitors to human factor VIII.

**Figure 5. Overall High Impact Potential: OBI-1 (recombinant B-domain deleted porcine coagulation factor VIII) for treatment of acquired hemophilia**



## Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.<sup>70-76</sup> Experts agreed that an unmet need exists for more effective therapy aimed at stimulating the natural coagulation cascade and counteracting inhibition of clotting factors by autoantibodies. One expert with a clinical perspective indicated that recombinant porcine factor VIII therapy may be a significant upgrade over current therapies, most notably human factor VIIa, which may induce problems related to hypercoagulation.

Experts agreed that the underlying mechanism of action of OBI-1 therapy is quite sound. One expert with a research background stated, "Recombinant factor VIII is supplied to counter the effects of antibodies to endogenous factor VIII. Since the recombinant factor VIII is porcine based, the antibodies that are interfering with endogenous human factor VIII will not attack the porcine factor VIII."<sup>73</sup> Another expert with a research perspective believes the underlying mechanism shows "great potential to work on acquired hemophilia A" based on results from a previous clinical study.<sup>70</sup> Another expert indicated that the underlying mechanism for OBI-1 therapy seems sound and appears to offer a low risk of adverse events to this patient population. Experts were cautiously optimistic about OBI-1's potential to improve health outcomes, stating that additional studies are needed to confirm efficacy. One clinical expert remained highly optimistic about this therapy's potential to improve several components of a patient's life. This expert stated that with early intervention with OBI-1, "the patient's life can be improved dramatically by decreasing the time and money currently spent on existing infusion treatments that stand a marginal chance of treating this disorder." This same expert also described how a patient's quality of life can be increased by avoiding the complications seen with existing treatments, such as hypercoagulation effects seen with use of human factor VIIa.

Experts' comments were generally mixed regarding whether OBI-1 therapy has the potential to inform current understanding of acquired hemophilia. One expert with a health systems perspective indicated that increased understanding of this therapy's mechanism of action "could change the direction by which other factors could be used for activating the normal hemostatic pathways."<sup>70</sup> An expert with a clinical perspective wrote, "Clinical focus has always been on arresting the bleeding by initiating any intrinsic means available," which results in numerous transfusions and resultant hypercoagulation.<sup>76</sup> This expert added "OBI-1 infusions deliver precisely [factor VIII], which acquired

hemophilia type A patients are missing, and this allows us to study and treat this disorder with increased specificity.”<sup>76</sup> Most experts believe that this therapy has potential to significantly disrupt current care models for this patient population, indicating that OBI-1 may serve as first-line therapy for treatment of acquired hemophilia. These experts claimed that not only does OBI-1 therapy incorporation into the current care model have the potential to replace existing therapies, but it may also offer a new perspective on future treatment modalities for treatment of acquired hemophilia. However, two experts believe that the current care system would not be disrupted by incorporation of OBI-1 therapy and that it might be used as an adjunctive therapy.

Four of seven experts believe that per-patient cost of care with OBI-1 therapy would rise. The other three contended that per-patient costs would decrease, with one expert citing that there might be the potential to shift care for hemophilia A from the inpatient to outpatient setting. Another expert believes that this shift from inpatient to outpatient could also reduce costs to third-party payers. Experts generally agreed that patient acceptance for OBI-1 therapy would be high and that if proven efficacious, this recombinant porcine coagulation factor VIII product has the potential for high impact.

## **Orthopedic Intervention**

## Intervention

### Off-label teriparatide (Forteo) for treatment of hard-to-heal bone fractures

Pelvic fractures, proximal humeral fractures, and Jones fractures (fifth metatarsal) are notoriously difficult to heal because of their locations, the myriad ways the fractures occur, and the varying positions of bone and bone fragments. Pelvic fractures have typically been treated through prolonged recumbency after mobilization as fracture healing occurs and symptoms subside. Other methods used to treat pelvic fractures include closed reduction under general anesthesia, traction, spica casts, pelvic slings, and turnbuckles. Surgery has become more common in recent years because of improved treatment for patients who have experienced massive trauma that includes pelvic fracture, improved operative conditions (i.e., blood salvage and anesthesia), improved imaging modalities, pelvic implant systems, and better understanding of these types of fractures. A significant unmet need exists for a pharmacologic treatment to aid healing of such fractures.

Investigators are studying off-label use of teriparatide (Forteo®, Eli Lilly and Co., Indianapolis, IN) a drug approved for treatment of osteoporosis, to expedite bone healing of delayed union or nonhealing bone fractures. The drug is a recombinant form of human parathyroid hormone (1-34) (rhPTH [1-34]) that targets the parathyroid hormone receptor and functions as a bone metabolism modulator and a parathyroid hormone receptor agonist. In the United States, teriparatide has been commercially available since 2002 for treatment of osteoporosis. As an osteoporosis treatment, patients self-administer teriparatide daily via subcutaneous injections using an injectable pen device with prefilled cartridges.<sup>77,78</sup>

In 2009, Bukata and colleagues<sup>79</sup> reported results from a study of 145 patients (men and women) with fractures who received daily injections of 20 mcg teriparatide as standard treatment for severe osteoporosis or who received the drug off-label as short course of therapy for healing difficult-to-heal fracture. The most common fracture sites of patients in the study were spine, pelvis, hip femur, tibia, and humerus. In this study, “135/145 patients (93%) were determined to have radiographic and clinical union of their fractures, 6/145 patients (4%) demonstrated partial radiographic union of their fractures, but clinically functioned as a healed fracture, and 4/145 patients (3%) failed to see an improvement in pain or experience radiographic fracture union.”

The labeled indications for teriparatide in the U.S. are for treatment of osteoporosis-associated fracture risk in postmenopausal women, men with hypogonadism, and men and women with osteoporosis associated with long-term glucocorticoid therapy. The drug is not labeled as treatment for nonhealing/nonunion fractures or to promote expedited fracture healing,<sup>78</sup> and its use for this purpose would be off-label. As an osteoporosis treatment in the United States, the average retail price of teriparatide is approximately \$950 for a 28-day supply of 20 mcg daily injections using an injectable pen and cartridge device. The unit cost of teriparatide to treat nonhealing fractures is likely to be comparable; however, the total treatment cost would be lower since long-term use of teriparatide as a maintenance drug is unlikely for the treatment of nonhealing fractures.

### Clinical Pathway at Point of This Intervention

Pelvic fractures, proximal humeral fractures, and Jones fractures (fifth metatarsal) are notoriously difficult to heal because of their location, the myriad ways the fractures occur, and the varying positions of bone and bone fragments. Pelvic fractures have typically been treated through prolonged recumbency after mobilization as fracture healing occurs and symptoms subside. Other methods used to treat pelvic fractures include closed reduction under general anesthesia, traction, spica casts, pelvic

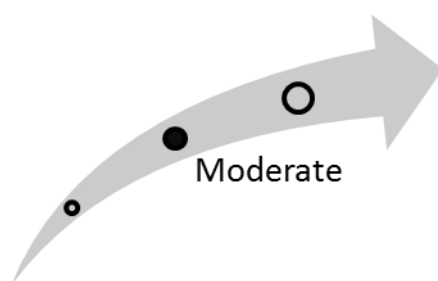
slings, and turnbuckles. Surgery has become more common in recent years because of improved treatment for patients who have experienced massive trauma that includes pelvic fracture, improved operative conditions (i.e., blood salvage, anesthesia), improved imaging modalities, pelvic implant systems, and better understanding of these types of fractures.<sup>80</sup>

Jones fractures are associated with a 50% to 66% nonunion rate and whether to treat conservatively with simple immobilization or to use surgery has been a matter of some controversy.<sup>81</sup>

Proximal humerus fractures are typically treated conservatively using immobilization with a sling or other type of immobilizer device and early motion. If the fracture is stable, gentle range-of-motion exercises are typically prescribed after a week or so. However, an unstable fracture can lead to displacement and increased pain and may require stabilization through surgery.<sup>82</sup>

Teriparatide is being proposed as an adjunctive treatment to aid healing of these challenging fractures.

**Figure 6. Overall High Impact Potential: Off-label teriparatide (Forteo) for treatment of hard-to-heal bone fractures**



Experts commenting on this intervention thought the drug's potential to treat some types of hard-to-heal or delayed union fractures (e.g., pelvic) could reduce overall treatment costs by shortening hospital stay or avoiding surgery. They also thought it could improve quality of life, independence, health outcomes, and possibly change how treatment is provided for some cases of nonhealing fractures. However, this drug is administered by subcutaneous injection by patients (or nonclinical caregivers), which could be a barrier for some patients. 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 clinical, research, health systems, and health administration backgrounds, offered comments on this intervention.<sup>83-88</sup> All experts agreed there is an important need for pharmacologic agents that can accelerate healing of hard-to-heal fractures. An expert from a health system administrator perspective suggested this type of intervention might be cost effective because it could avert the need for surgery in some cases of nonhealing fractures. The expert also indicated that this intervention might offer an alternative to patients who are not surgical candidates because of age and health-related risks.

Opinions regarding this intervention's underlying theory were diverse. One expert with a research perspective commented that teriparatide is already in use for similar indications and that while the underlying mechanism may be sound, it is not novel. An expert with a clinical perspective expressed concern about the difference between osteoporosis treatment and that for fracture care. A similar opinion was given by an expert with a research perspective, who stated that for nonunion or delayed union fractures, the biochemistry is different and could potentially reduce the effectiveness of teriparatide for this purpose. Another expert with a research perspective noted that osteoclasts are stimulated by the parathyroid hormone, and this drug might enhance the parathyroid hormone role in other fracture-healing processes through osteoclast stimulation or some other metabolic process within the bone.

Most experts agreed this drug has potential to improve health outcomes. An expert with a health systems perspective suggested that the potential of this drug to relieve pain, heal fractures, and increase



patients' functional capacity could improve health outcomes. Several experts with a clinical perspective indicated that healing of fractures could reduce severe, prolonged disability and associated economic impact.

Experts indicated that the drug also offers the potential to change patient management models, by possibly allowing more care at home rather than in a rehabilitation facility or hospital. An expert with a health administration perspective indicated that the reduction of pain associated with bone fractures could decrease hospital length of stay and acute-care costs. An expert with a clinical perspective also echoed a similar sentiment. Two experts with a research perspective suggested the drug would be an add-on to current therapy approaches and as such, would offer no change to patient management. Most experts indicated that any potential change in staffing patterns linked to this drug would depend on how well patients learn to self-administer subcutaneous injections. Experts were concerned about elderly patients' capacity to self-administer subcutaneous injections and therefore accept and comply with this medication's dosage requirements.

## **Pain Intervention**

## Intervention

### Orally inhaled dihydroergotamine (Levadex) treatment for migraine headache

Migraine headache is one of the most common chronic pain disorders, affecting an estimated 28 million people each year in the United States.<sup>89</sup> Many patients are not satisfied with their current migraine treatment because of inconsistent response to the medication, high migraine recurrence rates after treatment, and/or slow onset of action of the medication.<sup>90</sup> Therefore, new treatments for migraine headache are highly desired.

One currently employed migraine treatment is the ergot alkaloid dihydroergotamine mesylate (DHE), which has been used for acute treatment of migraine headache since it was introduced in the U.S. in 1946.<sup>91</sup> While the exact mechanism of action of DHE is unclear, it is proposed to act as an agonist of various 5-hydroxytryptamine 1 (5-HT<sub>1</sub> [serotonin]) receptors, which may relieve migraine symptoms by causing meningeal vasoconstriction and trigeminal inhibition of proinflammatory neuropeptide release.<sup>92</sup> DHE is currently available as an injectable solution and as a nasal spray.<sup>91</sup>

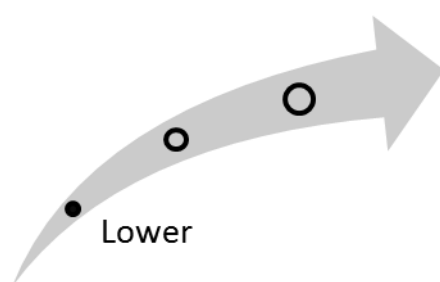
Levadex® (MAP-004, MAP Pharmaceuticals, Inc., Mountain View, CA) is a novel, orally inhaled formulation of DHE that is delivered by its developer's proprietary Tempo™ breath-activated metered dose inhaler.<sup>91,93</sup> Compared with currently available injectable DHE, Levadex is purported to be more convenient and faster-acting with fewer side effects for patients who are known to respond to DHE.<sup>94</sup> Preliminary data suggest that patients treated with Levadex might not experience nausea and vomiting as often as patients treated with intravenous DHE.<sup>94</sup> The developer claims that, compared with the currently available nasal spray DHE, inhaled Levadex would avoid nasal irritation and inconsistent absorption often observed with nasal spray delivery.<sup>90</sup>

In April 2011, results from a randomized, double-blind, phase III trial comparing Levadex to placebo for treatment of 903 patients who experience migraines were published.<sup>95</sup> Of the 903 patients, 792 had a qualifying migraine during the trial (395 patients in the Levadex arm and 397 patients in the placebo arm), and researchers reported that Levadex met its primary endpoints of superiority to placebo in the percentage of patients who reported pain relief (58.7% vs. 34.5%;  $p < 0.0001$ ); freedom from heightened auditory sensitivity (52.9% vs. 33.8%;  $p < 0.0001$ ); freedom from heightened light sensitivity (46.6% vs. 27.2%;  $p < 0.0001$ ); and no nausea (67.1% vs. 58.7%;  $p = 0.0210$ ).<sup>95</sup> In August 2011, MAP Pharmaceuticals filed a new drug application for Levadex for treatment of migraine headache and the U.S. Food and Drug Administration accepted the submission for review; a decision is expected in March 2012.<sup>96</sup>

### Clinical Pathway at Point of This Intervention

Patients with mild to moderate migraine headaches are typically treated with nonsteroidal antiinflammatory drugs (NSAIDs). Patients experiencing more severe symptoms and those who do not respond to NSAIDs may be treated with migraine-specific drugs such as triptans or DHE. Several existing formulations are available for triptans and DHE, and patients' use of one treatment over another is based mainly on delivery method preference and response to treatment. Levadex would represent another delivery option for DHE treatment of acute migraine headache.

**Figure 7. Overall High Impact Potential: Orally inhaled dihydroergotamine (Levadex) treatment for migraine headache**



Overall, experts providing comments on this topic believe that a significant unmet need exists for an improved formulation of DHE that could allow fast, easy, and effective self-administration. However, this improvement is largely incremental and experts were unsure whether Levadex would truly improve outcomes compared with current DHE formulations. Based on this input, our overall assessment is that this intervention is in the lower end of the high potential impact range.

## Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered comments on this intervention.<sup>97-103</sup> Experts were divided on the significance of an orally inhaled DHE formulation to address the unmet need of better migraine treatments noting that Levadex provides only an alternative delivery method for an existing drug. Some experts suggested that this was significant; one expert with a clinical background expressed the opinion that DHE was the best available treatment for acute chronic migraine and that an orally inhaled delivery method had the potential for more consistent dosing than the nasal spray formulation and offered more convenience than injected formulations. Conversely, one expert with a research perspective noted that, given the availability of a nasal spray formulation of DHE that could be used in the home setting, Levadex does not really address a gap in treatment.

Most experts agreed that the scientific rationale behind the treatment is sound, largely based on successful historical use of DHE to treat migraine and the successful creation of orally inhaled medications for other conditions. However, one expert with a clinical perspective argued that patients might experience some degree of variability in intraoral absorption, ultimately decreasing efficacy. This expert also questioned whether mucosal irritation in the lower airway might occur, because studies involving intranasal DHE have reported irritation to the nasal mucosa. Additionally, several experts had concerns regarding the delivery method and suggested that patient training would be needed to ensure accurate dosing. However, one clinical expert who had observed use of the device suggested that it seemed easy to master and convenient. While multiple experts noted that clinical trial results demonstrated efficacy of Levadex, two experts offering research and clinical perspectives suggested that a head-to-head comparison with an alternate DHE formulation would be more meaningful than comparison with placebo and noted the lack of data supporting increased patient satisfaction relative to use of the nasal spray formulation.

As a formulation change to an existing treatment, Levadex would not cause significant changes to migraine treatment models, health care staffing, or health care infrastructure, experts believe. However, multiple experts noted that Levadex has the potential to reduce visits to the emergency department for migraine treatment where intravenous infusion would likely be administered. The change from emergency department intravenous infusion to at-home self-administration figured prominently experts' estimates of Levadex's impact on health care costs. One clinical expert noted that if Levadex replaces intravenous administration of DHE, it has the potential to reduce costs; however, if patients currently using established alternatives such as oral triptans switch to use of Levadex, it could increase costs.

Aside from the concerns regarding the need to train patients in the use of the Levadex inhaler to ensure proper dosing, most of the experts thought there would not be barriers to acceptance of Levadex

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by patients or physicians. However, one expert with a clinical perspective noted that potential side effects of intraoral DHE, when compared with triptans, could affect patient acceptance. Several experts noted that the ability to easily treat oneself on location wherever the migraine occurred would allow patients who respond to DHE increased access to rapid migraine treatment and likely spur rapid adoption.

## **Sensory Disorder Interventions**

## Intervention

### **Implantable Miniature Telescope (IMT) for treatment of end-stage, age-related macular degeneration**

No treatments are currently available for end-stage, dry, age-related macular degeneration (AMD).<sup>104</sup> As approved by the U.S. Food and Drug Administration (FDA) in July 2010, the implantable miniature telescope (IMT) is intended to improve vision in patients 75 years of age or older with stable, severe to profound vision impairment caused by end-stage AMD. The implantation of an IMT does not cure macular degeneration, rather, it is intended as an aid to improve vision.<sup>105</sup> Surgically implanted in one eye, the IMT replaces the natural lens and provides an image that has been magnified more than 2 times.<sup>106</sup> The IMT combines a wide-angle micro-optic with the optics of the cornea. Its telephoto system magnifies images in front of the eye approximately 2.2 or 2.7 times their normal size. The magnification is projected onto perimacular areas of the retina instead of the macula alone, where breakdown of photoreceptors and loss of vision may have occurred as a result of wet AMD.<sup>107</sup> The intraocular telescope is surgically implanted in the capsular bag (containing the lens) and is held in place by two loops.<sup>108</sup> Implantation is performed via limbal or scleral tunneling procedures. Topical antibiotics and nonsteroidal antiinflammatory medications are usually given for at least 2 days after surgery. Postsurgery steroid treatment lasting approximately 3 months was given in a clinical trial conducted for premarket approval.<sup>108</sup> The first implantation of the device post-approval was announced by the company in November 2011, and implantation involves the procedure and rehabilitation services delivered as a package the company calls “CentraSight.” The reported cost of the device itself is about \$15,000 (i.e., exclusive of surgery and rehabilitation costs). In October 2011, the Centers for Medicare and Medicaid determined that the device met criteria for pass-through payment, making reimbursement possible. Medicare has no national coverage decision, and coverage is left to the discretion of local Medicare carriers.

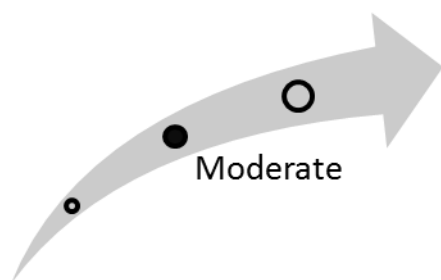
VisionCare Ophthalmic Technologies, Inc. (Saratoga, CA), manufactures the IMT. The device has been Conformité Européenne (CE) marked for distribution in Europe and also has received Israel Ministry of Health approval.<sup>107</sup>

Researchers reported<sup>109</sup> that in a trial of IMT in patients with end-stage AMD, 103 of 173 (59.5%) telescope-implanted eyes gained three lines or more (doubling of visual angle) of best-corrected visual acuity (BCVA) compared with 18 (10.3%) of 174 fellow control eyes ( $p < 0.0001$ ). The most common complication reported was inflammatory deposits. Hudson and colleagues (2006)<sup>110</sup> reported that in a study in patients with bilateral, end-stage AMD, at 1 year, 67% of eyes receiving an implant achieved a three-line or more improvement in BCVA versus 13% of fellow eye controls ( $p < 0.0001$ ).

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

After a diagnosis of AMD, treatment typically involves laser surgery to destroy abnormal blood vessels in some cases.<sup>111</sup> First-line medications usually prescribed to arrest growth of abnormal blood vessels may include bevacizumab (Avastin®, Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland), ranibizumab (Lucentis®, also Genentech) and pegaptanib (Macugen®, Eyetech, Inc., Palm Beach Gardens, FL). The IMT is intended to be used when first-line medications are no longer effective in patients with severe to profound vision impairment due to end-stage AMD. A retina specialist is required to perform the surgical implantation of the IMT.<sup>112</sup>

**Figure 8. Overall High Impact Potential: Implantable Miniature Telescope (IMT) for treatment of end-stage, age-related macular degeneration**



Experts thought the IMT could offer an alternative for a condition for which no current treatment is available to restore some degree of vision. Experts thought the demand for specialists in retinal surgery would increase as the technology diffuses; however, its applicability is limited to individuals of a specific age cohort at this time. Experts expected significant costs to be associated with the device and surgery, because it has no competing intervention and would be a new addition to the care paradigm for AMD.

Experts thought that third-party coverage would be likely if the device provides significant benefits in terms of independence and quality of life and has a low rate of complications. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

## Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered comments on this intervention.<sup>113-119</sup> Most experts agreed that treatment options for end-stage AMD are limited, and available medications do not provide improvement for some patients at all or for others after a time. Experts also agreed that no treatments are available to improve vision in these patients. The IMT concept of sending images to areas in the retina not affected by AMD was considered novel by most experts. One expert with a clinical perspective agreed with the IMT concept provided it is deemed compatible with the cornea and intraocular pressure. One expert with a health administration perspective questioned how the brain will adapt to and interpret the IMT's sending of images to the retina. Another expert with research experience thought this benefit was unsatisfactory because it does not address the underlying cause of AMD.

Concerning IMT's impact on health outcomes (i.e., improved visual acuity), experts agreed that IMT has potential to improve visual acuity, although its impact over the long term is not yet known. An expert with research perspective indicated that the different photoreceptors on the retina (primarily rods at the periphery and primarily cones at the center) process images differently, and this could affect quality of vision in some patients. However, the same expert also thought that these detriments would likely be outweighed by the benefits of having a larger portion of the visual field available for sight. An expert with a health administration perspective suggested the age of the intervention's targeted population (persons aged 75 years and older) might decrease as IMT technology is diffused and more data on its real-world effectiveness emerge. However, this expert also indicated that low risk for complications and payer acceptance would affect how quickly the target age for the intervention would be lowered. An expert with a clinical perspective expressed concern over a patient's difficulty to adapt to an IMT given previous inability to adjust to wearable telescopes. This may ultimately lead to removal of the IMT for that patient population.

All experts agreed that the IMT would increase per-patient costs and would increase the demand for retinal specialists. Patient acceptance, excluding costs, was not perceived as a detriment to adoption according to most experts commenting on this parameter. An expert with a clinical perspective noted the potential for unequal refractive power (anisometropia) if the IMT is implanted in one eye, leading to decrease in patient acceptance in a small number of this patient population. Most experts thought the IMT would have little impact on improving health disparities.



## Intervention

### Ranibizumab (Lucentis) for treatment of diabetic macular edema

Diabetic macular edema (DME) is a thickening or swelling of the retina caused by leaking fluid from blood vessels within the macula in patients with diabetes mellitus.<sup>120</sup> The swelling that occurs as a result of fluid build-up distorts central vision, mainly affecting an individual's ability to see form, color, and detail. Patients gradually lose their ability to focus on objects in their central field of vision over a period of months or years as the disease progresses.<sup>120</sup> According to the World Health Organization, people with diabetes who go untreated for eye care have a 25% to 30% chance of developing clinically significant macular edema (CSME) with moderate vision loss.<sup>121</sup> Currently, the main treatment modality is macular focal/grid laser photocoagulation, because there are no pharmacotherapies approved by FDA for the treatment of DME.

Ranibizumab (Lucentis, Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland) is an anti-VEGF (vascular endothelial growth factor) humanized monoclonal antibody fragment, initially developed and approved by FDA for the treatment of wet AMD.<sup>122</sup> It is also FDA-approved for macular edema with retinal vein occlusion. Ranibizumab's mechanism of action allows it to bind to multiple subtypes of VEGF-A. This binding action causes an inhibiting effect, which prevents the growth of new blood vessels under the macula. By preventing the growth of new blood vessels, the likelihood of vascular leakage and neovascularization is reduced; thus, vision loss as a result of fluid and protein buildup under the macula is also reduced.<sup>123</sup> In pivotal phase III clinical trials, ranibizumab is administered as a 0.5, 1.0, or 2.0 mg intravitreal injection given once every 4 to 5 weeks. Treatment is often required indefinitely.<sup>123</sup>

Boyer and colleagues (2011) presented results from the combined RIDE and RISE clinical trials evaluating ranibizumab in 759 patients receiving a diagnosis of DME with baseline visual acuity of 20/40 to 20/320. Results showed 62.2% to 63.2% of patients receiving intravitreal ranibizumab improved visual acuity to the 20/40 baseline for driving. In terms of achieving the primary endpoint of a gain of at least 15 letters on the Early Treatment Diabetic Retinopathy Study scale over baseline, 33.6% and 44.8% of patients receiving a 0.3 mg dose of ranibizumab and 45.7% and 39.2% of patients receiving a 0.5 mg dose of ranibizumab achieved endpoints compared with 12.3% and 18.1% treated with sham.<sup>124</sup> The percentage of patients receiving a 0.5 mg dose of ranibizumab who gained at least 10 letters (two lines on the eye chart) was 65.6%. In terms of eyesight deterioration (loss of three lines on the eye chart), less than 4% of patients treated with ranibizumab were reported compared with 8.5% to 10.2% of patients treated with sham.<sup>124</sup>

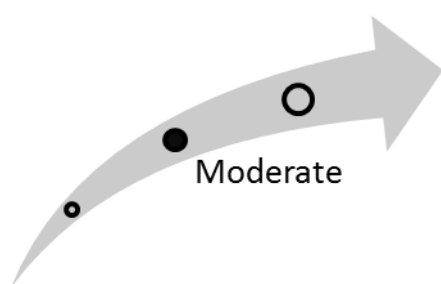
Ranibizumab has been approved by FDA since 2006 for wet AMD.<sup>123</sup> In June 2010, ranibizumab was approved in the United States for patients with macular degeneration following retinal vein occlusion.<sup>123</sup> Investigators from phase III trials (RISE and RIDE trials) reported positive preliminary results in June 2011, and Genentech planned to file for approval by the end of 2011.

### Clinical Pathway at Point of This Intervention

A patient who presents with DME receives a history and physical including an assessment of the individual's history of vision and eye disease, and risk factors for DME including diabetic history (type 1 at higher risk), older age, poor glucose control, pregnancy, hypertension, and increased lipid levels.<sup>121</sup> Using a high magnification ophthalmoscope, the ophthalmologist can identify the retinal thickening that indicates macular edema. Yellow exudates and poor visual acuity may also be detected. Treatment for DME is focused on glycemic control, optimal blood pressure control, and macular focal/grid laser photocoagulation. Laser photocoagulation reduces the risk of moderate visual loss but

some patients suffer permanent visual loss even after intensive treatment. New advances in pharmacotherapy and surgical techniques have shown promise in the treatment of DME.<sup>121</sup>

**Figure 9. Overall High Impact Potential: Ranibizumab (Lucentis) for treatment of diabetic macular edema**



Experts thought ranibizumab could offer an alternative to laser photocoagulation for treatment of DME, for which no FDA approved pharmacotherapy exists to restore vision. Some experts thought that the frequency of intravitreal administration of ranibizumab might pose a barrier to patient adherence, therefore limiting its ability to significantly improve patient outcomes and potentially affecting patient acceptance. Experts expected significant costs to be associated with this intervention, particularly if it is used as an adjunctive therapy to laser

photocoagulation. Experts thought that the existence and off-label use of other anti-VEGF agents, significant per-patient costs, and potential patient nonadherence because of intravitreal injection frequency may serve as barriers to ranibizumab's impact. However, its potential to significantly restore vision or slow progression of disease suggests that this intervention has moderate potential impact. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

## Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered comments on this intervention.<sup>125-131</sup> All experts agreed that treatment options for DME are limited, with laser photocoagulation being an invasive intervention with a variable degree of efficacy. One research expert stated that with regards to photocoagulation, "some treated patients experience permanent vision loss after laser treatment."<sup>131</sup> This expert also believes the increasing number of people being diagnosed with diabetes will warrant more effective therapy for the treatment of DME. Experts also agreed that no FDA-approved treatments are available to improve vision in these patients. Regarding ranibizumab's potential to fulfill the unmet need in this patient population, one clinical expert stated, "The burden of loss of vision to the individual has far reaching consequences and thus any therapy that improves vision or slows down vision loss [is] important and addresses an important unmet need."<sup>129</sup>

Experts also agreed that ranibizumab for treatment of DME has the potential to significantly improve patient health outcomes, with one clinical expert stating that ranibizumab has been shown to improve visual acuity more effectively than laser photocoagulation and steroids. Some experts believe in the potential of ranibizumab to improve patient outcomes, but would like more published clinical results to more competently evaluate this therapy's efficacy and safety. In terms of this intervention's potential to impact health disparities, opinions were mixed among experts, with several experts arguing the frequency of physician visits needed for intravitreal injection would increase nonadherence among patients in rural and low socioeconomic areas, increasing disparities. One research expert thought the pricing of ranibizumab in terms of dollars per quality-adjusted life-year would be significantly more expensive compared with laser photocoagulation, therefore widening the barrier for the economically disadvantaged. One expert believes ranibizumab has the ability to improve health disparities on the basis that African Americans and Hispanics are most affected by DME, with access still likely to remain a barrier.

Experts remained mixed on this intervention's potential to disrupt the current health care delivery infrastructure, with some experts suggesting that an effective intravitreal drug would not significantly affect current settings, while other experts argued repeated physician visits for intravitreal injection compared with the outpatient procedure with standard laser photocoagulation could significantly change the current infrastructure. One research expert stated that this intervention's potential to disrupt the current delivery infrastructure "would depend on whether [ranibizumab] emerges as a monotherapy or an adjunct to laser therapy."<sup>131</sup> Expert opinions were also mixed regarding the potential for ranibizumab to disrupt how patients are currently managed, with some experts believing the change from laser therapy to intravitreal injection is significantly disruptive. One research expert stated, "Current standard of treatment with laser has longer lasting effect and requires an extended interval between treatments (4 months). With ranibizumab, patients will require more frequent follow-up visits and more frequent injections/treatments (monthly)."<sup>129</sup> One clinical expert did not expect much disruption, since "retina specialists already use anti-VEGF therapy for DME (Avastin)."<sup>125</sup>

All experts agreed that this intervention's potential for clinician and patient acceptance is high, because the need for more effective therapy to treat DME is acknowledged. In terms of per-patient costs for ranibizumab, experts opined that costs would significantly increase, with one research expert stating "costs have been calculated for quality adjusted life year as \$5862 for Laser, \$23000 for Ranibizumab and approximately \$3000 for Avastin (which has recently been shown to be as effective as Ranibizumab for AMD in a head-to-head CATT trial)."<sup>129</sup> This research expert also believes that there is controversy surrounding the cost of ranibizumab and the financial burden it may place on patients and the health care provider, with benefits of this intervention having to be exceptional to justify the financial responsibility. Overall, experts believe that while financial implications for this therapy may serve as a barrier to widespread diffusion, the potential efficacy and safety of ranibizumab for the treatment of DME has them thinking this is an intervention of high potential impact.

## Intervention

### Recombinant human microplasmin (Ocriplasmin) injection for treatment of focal vitreomacular adhesion

Focal vitreomacular adhesions are characterized by a vitreous gel with an abnormally strong bond to the retina; they have an effect on the development and progression of numerous back-of-the-eye conditions and have been associated with a poor prognosis in diabetic retinopathy and AMD.<sup>132,133</sup> Patients experiencing significant visual impairment undergo surgical intervention such as posterior vitreous detachment in order to remove blood, eye debris, and scar tissue in addition to correcting retinal traction. Vitreoretinal surgeons are responsible for the performance of this procedure. Microplasmin is a recombinant protein produced in *Pichia pastoris*, a species of yeast.<sup>134</sup> Recombinant microplasmin is a truncated molecule that retains the catalytic characteristics of human plasmin.<sup>135,136</sup> Results from recent clinical trials indicate that microplasmin is a potential nonsurgical approach for the resolution of focal vitreomacular adhesion. This result was achieved 1 month after a single intravitreal injection of microplasmin. Intravitreal injections require a local anesthetic (eye drops) to minimize discomfort to the patient and an antiseptic solution to prevent contamination when injecting the solution into the eye.<sup>135,137,138</sup>

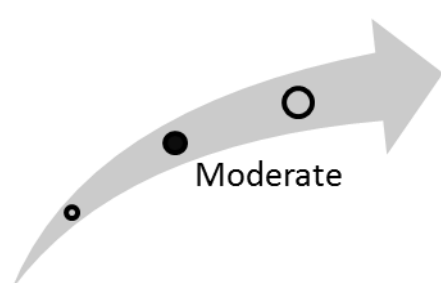
ThromboGenics NV (Heverlee, Belgium), is studying Ocriplasmin in phase III trials, and in August 2011, the company stated intentions of submitting a biologics license application to FDA before the end of 2011.<sup>133,135,139,140</sup>

Stalmans and colleagues (2010) reported pooled results from TG-MV-006 and TG-MV-007 phase III trials conducted on 652 patients at 48 centers in Europe and the U.S.<sup>141</sup> They reported that both the trials met the primary endpoints with 26.4% of the 465 Ocriplasmin-treated patients achieving resolution of their vitreomacular adhesions at 28 days, compared with 10.2% of 182 patients who received a placebo injection ( $p = 0.000002$ ). In patients without epiretinal membrane, 37.4% of 270 patients given Ocriplasmin injections achieved nonsurgical resolution of their vitreomacular adhesions at 28 days compared with 14.3% of 119 placebo treated patients ( $p = 0.000003$ ). The pooled results, stated the investigators, confirmed that microplasmin was generally safe and well tolerated. There was no evidence of an increased risk of retinal tear or detachment.<sup>141</sup>

### Clinical Pathway at Point of This Intervention

In patients with significant visual impairment, a surgical procedure called posterior vitreous detachment is typically recommended to clear blood and debris from the eye, remove scar tissue, and alleviate traction on the retina. This procedure is performed by vitreoretinal surgeons.<sup>135</sup> The developer proposes vitreal injection with recombinant human microplasmin (a proteolytic enzyme) as a nonsurgical method to perform vitreolysis.<sup>137,142</sup>

**Figure 10. Overall High Impact Potential: Recombinant human microplasmin (Ocriplasmin) injection for treatment of focal vitreomacular adhesion**



Experts commenting on this intervention thought recombinant microplasmin injection therapy could offer an alternative for a condition in which invasive surgical intervention is the primary standard of treatment for those patients most affected by focal vitreomacular adhesion. Some experts believe that microplasmin injection could potentially serve as first-line therapy for patients, while other experts thought that surgical intervention might

ultimately be needed for some patients, particularly in the case of the intervention's ineffectiveness. A potential shift in care setting and management could occur, transitioning to more outpatient care with care potentially being provided by a retinal specialist. In general, experts believe that an alternative therapy to surgical intervention would decrease cost of treatment, although an expert expressed concern that costs of injection might offset surgical costs. 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 clinical, research, health systems, and health administration backgrounds, offered comments on this intervention.<sup>143-148</sup> Most of the experts agreed that treatment options for focal vitreomacular adhesion are primarily limited to surgery, and effective and safe noninvasive treatment is necessary for this population. One expert with a clinical perspective expressed that surgical interventions present risk, including "optic disk, foveal, and extra-foveal damage" and that "less invasive or pharmacological approaches will reduce these risks."<sup>148</sup> However, one expert with a research perspective questioned the significance of the unmet need, believing that only a small percentage of the patient population continues to require surgery, regardless of intervention with microplasmin injection.

All experts agreed that the underlying mechanism for recombinant microplasmin injection appears sound and promising, with several experts citing efficacy in clinical studies as quantitative proof of the intervention's concept. Concerning microplasmin injection's impact on patient health outcomes, experts agreed that the intervention has potential to eliminate surgical intervention and reduce associated adverse events in this disease population. An expert with a research perspective indicated that the elimination of surgical intervention would not only improve patient health outcomes, but also quality of life.<sup>144</sup> However, one expert with a research perspective would like to see more data in order to determine to what degree the resolution of focal vitreomacular adhesions improves the patients' quality of life.

There were mixed comments regarding the intervention's potential to disrupt the current care model for this patient population. Several experts believe that integration of microplasmin injection therapy would affect the current intervention model for patients suffering from focal vitreomacular adhesion, with one clinical expert stating that "this intervention has the potential to be a first-line non-invasive approach for the treatment of vitreomacular adhesion and may eliminate the need for vitreomacular surgery."<sup>148</sup> Other experts believe that the current model of care would be minimally impacted, stating that existing interventions would not be completely eliminated and that surgery would ultimately be available for patients not responding to microplasmin injection therapy. Regarding potential shift in patient management, most experts believed recombinant human microplasmin injection may reduce or eliminate the need for vitreomacular surgery. One expert believes this treatment could shift patient management to outpatient care "by a retinal specialist."<sup>148</sup> One expert with a health systems perspective believes that there would not be any change to patient management for this disease.

Most experts agreed that per-patient cost would decrease with reduction of surgical interventions for this patient population. However, one clinical expert believes that while "less surgical costs" may be incurred, "total cost may be offset by the cost of the medicine."<sup>147</sup> Most of the experts agreed that patients would accept this intervention, because microplasmin injection can provide an effective alternative to surgical intervention. One clinical expert thought that while success of this intervention might lead to patient acceptance and physician adoption, there are concerns regarding "percent success rate and potential side-effects" of microplasmin injection therapy.<sup>148</sup> Overall, while one expert had reservations regarding how many patients would actually need this intervention, the remainder believe that the therapy has potential for high impact to provide a sound alternative to current treatment for patients in whom focal vitreomacular adhesion has been diagnosed.

## **Sleep Disorder Intervention**

## Intervention

### **Neurostimulation (remedē system) for treatment of central sleep apnea in patients with heart failure**

Many patients with heart failure have a comorbid condition called Cheyne-Stokes respiration, a type of central sleep apnea (CSA) that affects up to two thirds of heart failure patients and is associated with increased mortality. The cascade of events from this disordered breathing can trigger many types of events, including atrial fibrillation, inflammation, intrathoracic pressure changes, myocardial ischemia, and release of oxygen radicals. Currently, there are no commonly accepted treatments for CSA in these patients. Pharmacotherapy is sometimes used, but is often ineffective or predisposes a patient to cardiac conditions, prompting some clinicians to suggest the use of continuous positive airway pressure (CPAP), which is associated with low patient adherence. Therefore, effective treatments for CSA are needed.

The remedē System™ (Respicardia, Inc., Minnetonka, MN) is an implantable stimulator being investigated for treatment of CSA in patients with heart failure. According to the manufacturer, the system is intended to deliver electrical pulses via a transvenous stimulator lead positioned within a vein, near one of the phrenic nerves. The phrenic nerve stimulation is intended to restore natural breathing to enable better oxygenation, less activation of the sympathetic nervous system, and improved sleep. According to the manufacturer, the system consists of three implantable components: a pulse generator comprising electronic circuitry and a battery, which are hermetically sealed in a titanium case; a stimulation lead; and a sensing lead that detects respiration. The system also includes an external programmer, which is used to change the pulse generator settings or to review diagnostic data via telemetry. The pulse generator, which appears to be similar to a pacemaker, is implanted under the skin below the collarbone. The manufacturer has not released the details of the implantation procedure.

According to the company, the device is being studied under an investigational device exemption phase II trial approved by FDA, and the device was Conformité Européenne (CE) marked in Europe in August 2010.<sup>149</sup> Ponikowski and colleagues reported results from a multicenter (five centers in the U.S. and Europe), 2-night, 13-patient feasibility study at the European Society of Cardiology Heart Failure meeting in May 2010.<sup>150</sup>

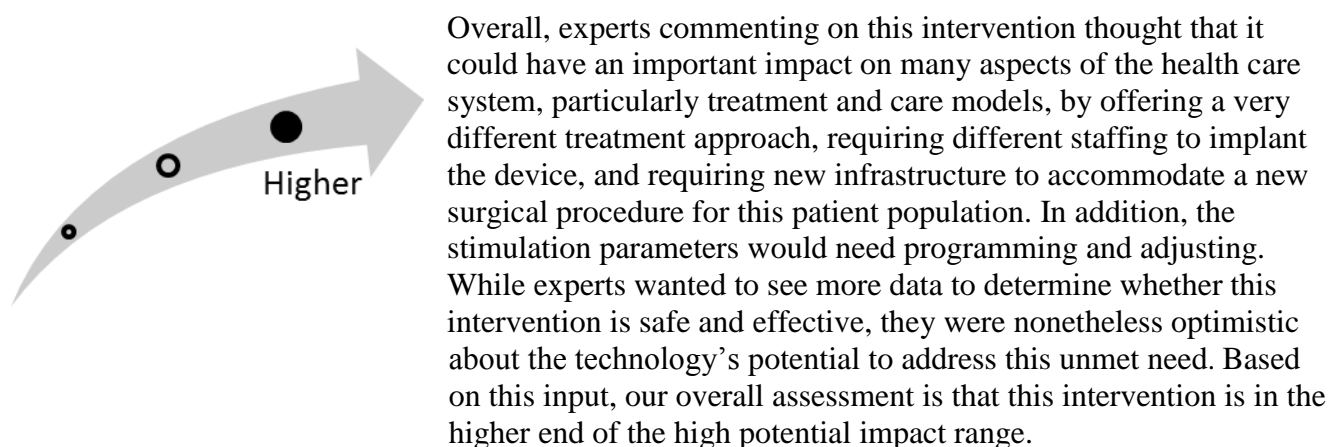
Patients served as their own controls with 1 night of no intervention and 1 night of unilateral phrenic nerve stimulation. The endpoint was a 50% reduction in CSA. The authors reported “no deleterious effect on sleep or airway tone, no stimulation-related arrhythmias, and one thrombus in azygos vein on review of the cine: lead was removed after anticoagulation without sequelae.” On sleep apnea indices, the authors reported a “49% ( $p = 0.0006$ ) decrease on the apnea-hypopnea index,” a “91% decrease on the central apnea index ( $p < 0.0001$ ),” and a “51% ( $p = 0.0005$ ) decrease in arousals.”

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

According to the American Heart Association, first-line treatment for CSA can include diuretics to lower cardiac-filling pressure and angiotensin-converting enzyme inhibitors and beta blockers to lessen CSA severity. In some patients, however, these agents can actually predispose a patient to CSA. If CSA persists, clinicians may prescribe nighttime supplemental oxygen, although its effectiveness in improving heart function, mortality, and quality of life has also been questioned. CPAP and other kinds of pressure support intended to improve breathing are sometimes used. The respiratory stimulant theophylline is not typically used long term because of its potential adverse consequences in heart

failure patients (i.e., inotropic and arrhythmia-inducing effects). If the remedē system is approved for marketing, it would likely displace the use of CPAP, which is associated with low patient adherence.

**Figure 11. Overall High Impact Potential: Neurostimulation (remedē system) for treatment of central sleep apnea in patients with heart failure**



## Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered their perspectives on this intervention.<sup>151-156</sup> Experts generally agreed that there is an important unmet need for effective CSA treatment for heart failure patients, based on the current lack of available therapies, the prevalence of the condition, and the negative outcomes associated with CSA secondary to heart failure.

Most experts stated that it was difficult to determine whether this intervention has the potential to improve health outcomes, given the very preliminary data, although they believe that the underlying theory of the technology is sound. One expert with a clinical perspective stated, “Whether this would improve heart failure outcomes is much less certain. The question remains as to where on the causal pathway of adverse outcomes in CHF [congestive heart failure] sleep disordered breathing lies.”<sup>155</sup> One expert with a research perspective stated, “Phrenic nerve stimulation as a means to restore normal breathing and improve sleep has a reasonable theoretical basis, but the degree of improvement that could be expected is unclear.”<sup>156</sup>

Experts generally agreed that this intervention has the potential to impact the current care model and patient management and to shift care setting. This intervention will shift the focus from oxygen-based therapies to neurostimulation. If this treatment is proven effective, it has the potential to “become the de facto treatment for patients with CSA and heart failure,” which represents an important change, because optimal medical care for CSA is so highly debated and largely ineffective.<sup>153</sup> The intervention would also shift care from the outpatient setting of at-home medical therapy or CPAP therapy to inpatient surgery and cardioelectrophysiology laboratories.

Because the intervention requires surgery, it would require a moderate learning curve on the part of physicians, and would have a notable impact on costs, experts thought. Although clinicians are already familiar with placement of similar technology such as implantable cardioverter-defibrillators and pacemakers, surgeons would need to learn how to place this particular device. One expert with a clinical perspective pointed out that there are “not too many cardiac electrophysiologists available for such a large patient population,” which might prove to be an obstacle for diffusion.<sup>151</sup>

Experts were divided on how this intervention would impact costs. Most experts suggested that the device and the surgical procedure to implant it would be expensive, especially when compared with current CSA interventions. However, some experts also suggested that if the intervention is shown to



improve patient outcomes, it would ultimately reduce the long-term costs associated with CSA and heart failure. Experts were divided on whether third-party payers would reimburse the use of the device, stating on one hand that the device would “likely be covered,” but on the other hand that “reimbursement will be limited until the intervention analytics can be established and public and private payers understand the increased costs of this intervention and its patient benefits.”<sup>154</sup>

Experts anticipated high patient and clinical acceptance of this intervention, citing that “similar available technologies have gained support and wide acceptability.”<sup>151</sup> Although a couple of experts noted that the invasiveness of the implantation procedure might cause some reluctance to accept it, one expert noted that the invasiveness of other devices on the market to which CHF patients have already been exposed limits this as a barrier.

## **Spinal Cord Injury Rehabilitation Interventions**

## **Intervention**

### **Computerized walking systems (ReWalk and eLegs) for patients with paraplegia from spinal cord injury**

Currently, conventional manual and powered wheelchairs are the primary assistive devices to restore some degree of mobility in people with paraplegia. However, these devices do not assist users in walking or climbing stairs. Two reciprocating gait orthosis systems in development, the ReWalk system (Argo Medical Technologies, Ltd., Yokneam Illit, Israel) and the eLegs system (Ekso Bionics, Berkeley, CA) may provide greater mobility and freedom to persons with paraplegia from spinal cord injury.

The ReWalk system comprises a set of computer-controlled, motorized leg braces that restore the ability to walk with crutches to patients with paraplegia who retain the ability to use their hands and shoulders to walk with crutches and who have good bone density and cardiovascular health. The wearable support system uses an array of sensors and proprietary computer algorithms to analyze body movements and manipulate the motorized leg braces to help users maintain proper gait with the use of crutches for walking, climbing stairs, and other movements. The onboard computer, sensor array, and rechargeable batteries that power the wearable exoskeleton are contained in a backpack that users wear in addition to the leg braces. The ReWalk system weighs approximately 35 lb.<sup>157</sup>

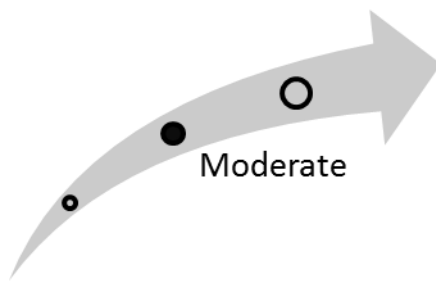
The eLegs system incorporates technology similar to that in the ReWalk system. The 45-lb eLegs system is based on the HULC (human universal load carrier), a motorized exoskeleton designed to allow users to carry up to 200 lb continuously for several hours over any terrain, currently in use by the U.S. military. The manufacturer anticipates clinical testing of the eLegs system in rehabilitation hospitals in the United States by the end of 2011.<sup>158</sup>

The U.S. Food and Drug Administration (FDA) classifies the ReWalk reciprocating gait orthosis as powered exercise equipment (product code BXB) used for medical purposes (e.g., physical therapy), thus making the technology exempt from 510(k) premarket notification or premarketing approval application procedures.<sup>159</sup> Such products require only FDA device registration and listing. As of November 2011, the ReWalk-I system was FDA-listed for institutional use only, and reported costs are about \$100,000 per system. The company expects to register ReWalk-P, for personal use for those who qualify for its use upon medical examination and rehabilitation training, by the end of 2011, and to make it available to patients mid-2012.<sup>157,160</sup> The company has been quoted in various lay press articles as stating that the personal system will cost one-third to one-half the cost of a ReWalk institutional system. Costs for eLegs are expected to be similar.

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

Occupational and physical therapists work with patients after acute treatment of spinal cord injury to evaluate their functional abilities, determine what type of rehabilitation is appropriate for individual patients, implement specific exercises and routines, and determine the type of assistive devices that could help them become more independent with daily living skills.<sup>161</sup> Currently, conventional manual and powered wheelchairs are the primary assistive devices used to restore mobility to people with paraplegia. The ReWalk and eLegs reciprocating gait orthosis systems would be used to assist patients with paraplegia to stand and move, improving their quality of life by increasing their mobility and independence.

**Figure 12. Overall High Impact Potential: Computerized walking systems (ReWalk and eLegs) for patients with paraplegia from spinal cord injury**



Experts thought that the high cost and complexity of this technology could limit its introduction and diffusion into the mainstream of rehabilitative services and centers treating patients with paraplegia from spinal cord injury. They expected that staffing models would be affected by the need for clinical and software engineers and technicians to maintain and adjust the equipment. Also, they thought that equipment would likely be appropriate only for patients whose health was robust enough to use it. Experts indicated that lessons learned from users of this type of intervention may pave the way for future similar interventions capable of addressing the needs of many more patients with this condition. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

## Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, commented on this intervention.<sup>162-168</sup> Two of seven experts thought that a major benefit of this intervention would be psychological, allowing patients to have improved social interactions. Three experts (clinical and nonclinical) reported that this intervention could increase the time of rehabilitation because more sessions would be needed to train patients use these new devices. Clinical experts also indicated that muscle atrophy, muscle tone and spasms, especially during the first year after spinal cord injury, could affect the response to these devices and require constant adjustments.

Cost was a limiting factor mentioned by the experts in terms of access and diffusion, especially to populations affected by health disparities and by limited access to rehabilitative services. The device cost is an estimated \$85,000, plus the cost of software programing and adjustments.

Two experts with research perspectives indicated that this type of device would work only in patients with significant upper body strength. For example, those who retain use of their hands and shoulders, can stand with the aid of crutches, and have good bone density and good cardiovascular health might be the appropriate population that could benefit from these devices.

Six experts reported that staffing patterns in rehabilitation centers would likely change with introduction of these devices. Three experts thought there would be a need for additional technical staff (clinical and software engineers) to address computer hardware and software issues needed to maintain the equipment.

## Intervention

### Magnetic pierced-tongue aid for management of spinal cord injury

While conventional manual and powered-assisted devices exist that attempt to improve quality of life (QOL) for individuals with paraplegia, efficacy and safety issues remain a primary concern. Specifically, regarding neuroassistive technology for this patient population, surgical invasiveness and risk of adverse events remain factors that may decrease patient acceptance and overall QOL. Use of the magnetic pierced-tongue aid system, a tongue-operated assistive neurotechnology for managing spinal cord paralysis, would represent a novel device that might enhance patient mobility and allow patients to perform more daily tasks in a safer, less invasive, and more effective manner.

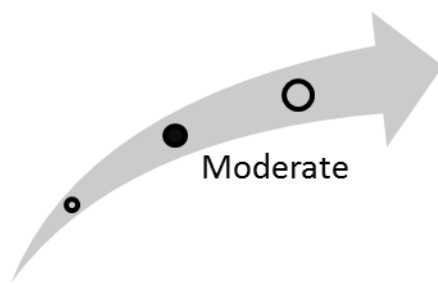
The Tongue Drive System (TDS, Georgia Institute of Technology, Atlanta, GA) is a tongue operated assistive neurotechnology that consists of a lentil-sized magnetic tracer/stud that is affixed to the tongue, most commonly by piercing.<sup>169</sup> The magnetic tracer/stud creates a magnetic field around the pierced glossal area, where magnetic sensors located on wireless headset/headphones communicate with a wheelchair. Since the tongue is a durable muscle that does not tire easily and is generally spared in spinal cord injuries and neuromuscular diseases, it was designated an ideal target for this neuroassistive technology.<sup>170</sup> The change in magnetic field (prompted by tongue movement) in the mouth is detected by the magnetic sensors on the headset, transmitting information wirelessly to a smartphone carried by the patient. The smartphone can then transmit information to a wheelchair or computer, commanding these devices to perform tasks such as wheelchair movement or daily computer tasks (e.g., email).<sup>170</sup> This system can be recharged via USB after 2 days of continuous use. There is a standby mechanism for the TDS, allowing patients to perform daily tasks, such as eating, sleeping, and conversing, without unnecessary use of the TDS.<sup>170</sup> Patients must undergo computer training with the TDS for the computer program to appropriately interpret and calibrate tongue movement, to allow for proper control of the patient wheelchair and computer device.<sup>169</sup>

Ghovanloo and colleagues (2009) reported results from a trial of five patients with tetraplegia to determine the usability of the TDS for patients with spinal cord injury. “Each subject completed the course at least twice using each strategy while the researchers recorded the navigation time and number of collisions. Using discrete control, the average speed for the five subjects was 5.2 meters per minute and the average number of collisions was 1.8. Using continuous control, the average speed was 7.7 meters per minute and the average number of collisions was 2.5.” As of November 2011, the TDS had not been approved by FDA, and no additional manufacturer or regulatory status information was available.<sup>171</sup> No cost information about the device was identified.

### Clinical Pathway at Point of This Intervention

After patients receive acute treatment for spinal cord injuries, they work with occupational therapists who evaluate their functional abilities and determine what type of individual rehabilitation is appropriate and who work with patients to implement specific exercises and routines and determine what type of assistive devices could help patients become more independent with daily living skills.<sup>161</sup> Conventional manual and powered wheelchairs currently used have considerable limitations in restoring mobility and improving QOL for patients who have spinal cord injuries. The magnetic pierced-tongue aid would provide patients with the ability to perform tasks, such as wheelchair movement or daily computer/phone tasks, through synergistic communication between a tongue-mounted magnetic tracer, magnetic sensors, smartphones, computers, and wheelchairs.

**Figure 13. Overall High Impact Potential: Magnetic pierced-tongue aid for management of spinal cord injury**



Experts commenting on this intervention thought that the magnetic tongue-directed aid could be a viable alternative to existing technologies. Some experts thought the unmet need was not significant, but others who have worked directly with patients in need of assistive devices to control powered wheelchairs believe this intervention could significantly improve patient health outcomes and QOL, allowing patients to perform daily activities in a quicker and less exhaustive manner. Several experts thought safety concerns could be a barrier to clinician acceptance, because

device malfunction could introduce harm to this patient population. Overall, this device's perceived complex nature, the existence of comparators, and limited safety and efficacy data thus far have made some experts question device's true impact potential. However, other experts believe this device has the ability to significantly improve patient mobility and QOL when compared with standard mobility devices. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

## Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, provided comments on this intervention.<sup>172-178</sup> Generally, experts opined that there is a significant need to introduce new assistive technology aimed at restoring mobility in patients with spinal cord injury. Several experts reported the magnetic tongue-directed neuroassistive device could become a viable alternative technology to conventional manual and powered devices for this patient population. One research expert mentioned the potential efficiency of this device in terms of control and communication, stating, "I've worked with people using puff-straws, joysticks, and head-paddles, but this looks appropriate for patients with a much higher degree of impairment than [use of] head paddles and joysticks. Also, unlike air puff, this system is more sensitive and can speed up communication and control tasks. Air puff systems take forever to get anything done and I've seen users get frustrated."<sup>172</sup> Another research expert believes the TDS has the ability to replace currently available assistive devices, stating, "it is relatively discreet, quick to respond to commands, unobstructive to one's senses, and can be used for long periods of time without excessive strain."<sup>177</sup> A health systems expert reported this device would serve as a particularly good alternative for patients with compromised lung function who might struggle to operate sip-and-puff assistive devices. This same expert also suggested this device may be positively adopted as a neuroassistive device not requiring invasive neurosurgery for proper device function. However, several experts thought this device might not significantly impact this patient population, suggesting the availability of numerous comparators believed to effectively restore mobility, including sip-and-puff, chin-control, head-control, and speech-control assistive devices.

Experts expressed concerns over limited efficacy and safety studies available for this device. A research expert stated patient mobility and QOL improvement "were not measured" in a recent study and "it is also unclear how usable this technology is compared to other available assistive mobility technologies."<sup>176</sup> Several experts shared this opinion, affirming the need for comparative studies with currently available assistive devices to determine whether a clear benefit to using the TDS exists. A health systems expert questioned the device's ability to safely and effectively improve patient outcomes, particularly if the device presents difficulties in learning, training, and maintenance. However, one expert opined the technology seems usable based on available studies, and would allow

patients to communicate at “normal or near-normal” speed in addition to providing significant mobility improvement over conventional assistive devices, allowing for more patient participation in daily societal activities.<sup>173</sup>

Experts generally agreed this neuroassistive device would not significantly impact health disparities, although one clinical expert opined the anticipated cost of this device could increase health disparities. Five experts shared opinions that this device would not significantly disrupt the current health care delivery infrastructure or how patients are managed, stating the current system in place is readily equipped for this device’s implementation and adoption. Several experts conceded adoption of this device might require an increase in hiring of rehabilitation specialists, computer specialists, and biomedical hardware specialists, in order to properly train patients and ensure proper functioning of this device. One expert believes that the anticipated increase in specialists for this device in combination with the device’s potential complexities may increase time in patient management.

Experts were split on the TDS’s potential acceptance by both clinicians and patients. Four experts generally agreed that provided this device proves safe and effective, the TDS would be easily accepted by clinicians and physical therapists. Three of these experts believe the potential of this device to improve patient dependence would increase patient acceptance. One clinical expert stated this device would pose minimal health risks to this patient population while increasing patients’ accessibility and communication with society, significantly improving patient outcomes. Several experts mentioned several barriers to physician acceptance, including the uncertainty of degree to which this device significantly improves patient health outcomes combined with the potential change in infrastructure needed to ensure successful operation of the device, both by the patient and training staff. In terms of patient acceptance, a health systems expert asked, “How does having the stud in your tongue affect your clarity of speech? What about elderly patients, or those who culturally or religiously reject body piercings? How sure is the manufacturer that the stud will not set off alarms in department stores, since magnetic devices are used for anti-theft tags on products?”<sup>178</sup> Negative perceptions regarding the required tongue piercing for this device seems to be a predominating issue for elderly patient adoption, according to several experts. One research expert opined that elderly patients may have more reservation than the younger patient population, stating “the elderly patients had already been trained to use other assistive devices and did not want theirs to be replaced.”<sup>177</sup>

Overall, experts believe this novel neuroassistive device has potential to fulfill the unmet need of this patient population, as long as further studies evaluating the technology’s efficacy and safety are provided. Several experts doubt this device’s ability to have high impact for this patient population, considering the currently available assistive devices available, combined with the potential complex nature of the device. However, a research expert summarized the opinions of those experts believing in this device’s ability for high impact, stating the TDS “could be a cost-effective way to help improve the quality of life, mobility, and degree of interaction with electronic devices for patients with high-level spinal cord injuries with limited effects on current healthcare infrastructure.”<sup>177</sup>

## **Vascular Abnormality Intervention**



## Intervention

### Off-label propranolol for treatment of life-threatening infantile hemangiomas

Infantile hemangiomas (IHs) are vascular anomalies that manifest as benign soft tissue tumors, affecting up to 10% of the infant population.<sup>179</sup> Although 85% to 90% of IHs regress on their own without treatment, the remainder may become problematic if they “ulcerate, have massive growth, cause disfigurement, or impact normal function or cosmetic development.”<sup>179,180</sup> These problematic IHs are commonly located in the face, ear, orbit, and airway, and complications may include obstruction of airways and vision, cardiac insufficiency, hypothyroidism, painful ulcerations, and hemorrhage.<sup>179,180</sup> Currently, there are no U.S. Food and Drug Administration (FDA)-approved pharmacotherapies for treatment of IHs. Although corticosteroids, interferon alfa, and vincristine are treatment measures used for IHs, limited efficacy, safety concerns, and intolerable adverse events associated with these therapies have prompted investigation for novel therapies with a more efficacious and safer profile. Propranolol is a beta blocker that may replace or serve as an adjunct therapy to corticosteroids for treatment of life-threatening IHs.

Propranolol (original manufacturer AstraZeneca London, UK, investigator Johns Hopkins University School of Medicine, Baltimore, MD, and Cambridge University Hospital, Cambridge, UK) is a nonselective beta adrenergic receptor antagonist (beta blocker) that has been widely used for cardiovascular indications (e.g., hypertension, angina pectoris).<sup>181,182</sup> The drug exerts its cardiovascular effects by blocking the action of endogenous catecholamines (e.g., epinephrine and norepinephrine) on beta-adrenergic receptors.<sup>182</sup> Researchers have suggested that propranolol’s early, intermediate, and long-term effects on IHs are the result of three different mechanisms of action.<sup>180</sup> Specifically, the early effects, which manifest as a “brightening” of the IH’s surface, can be attributed to propranolol’s vasoconstrictive qualities.<sup>180</sup> Intermediate effects (i.e., growth arrest) are thought to be a result of propranolol’s blocking of proangiogenic signals (e.g., vascular endothelial growth factor, basic fibroblast growth factor, and matrix metalloproteinase 2/9).<sup>180</sup> Finally, long-term effects are characterized by IH regression, due to apoptosis (programmed cell death) in proliferating endothelial cells.<sup>180</sup> Several clinical trials report varying administration doses for propranolol. Addenbrooke’s Hospital (Cambridge, UK) has identified a protocol for administering propranolol: administer 1 mg of propranolol orally (in suspension form; divided in three doses) per kilogram of body weight per day in week 1, double the dose in week 2, and adjust propranolol dose according to patient weight gain thereafter. Some protocols recommend initial hospitalization for dose titration.

Balma-Mena and colleagues (2010) reported results from a clinical trial evaluating lesion dimensions in 48 patients with “significant” IHs.<sup>183</sup> Volumetric analysis was used to determine that 95.6% of hemangiomas had improved to near complete resolution. Adverse events experienced in this clinical trial included sleep disturbance (4.2%), treatment taste intolerance (4.2%), wheezing resulting from a respiratory infection treated with inhaled salbutamol. Upon discontinuation of propranolol, four patients experienced tumor regrowth, of which three patients experienced tumor size reduction once treatment was again initiated.<sup>183</sup>

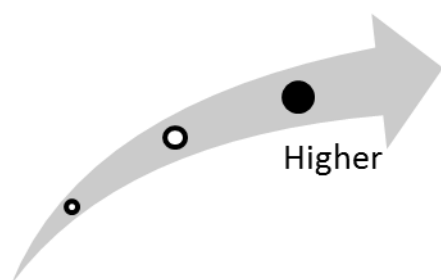
Propranolol is not labeled as treatment for IHs under any circumstances, and its intended use by current institutions for this purpose would be considered off-label. A recent retrospective study published August 2011 in *Online First Archives of Dermatology* (Price et al., University of Miami) compared propranolol to oral corticosteroids, and investigators reported that propranolol therapy was more effective in treating IHs with minimal side effects and cost about \$205 per treatment, about half the cost of corticosteroids.

The Pierre Fabre Group (Paris, France) is currently investigating propranolol specifically for this indication in an ongoing phase II/phase III clinical trial, with an estimated primary completion date in November 2011 and estimated study completion date in May 2013.<sup>184</sup>

## Clinical Pathway at Point of This Intervention

Currently, no well-defined or FDA-approved treatments for life-threatening IH exist.<sup>185</sup> Although corticosteroids (e.g., prednisone) are typically used as first-line treatment, these systemic drugs are associated with variable efficacy and safety concerns, including growth disturbances, immune system dysfunction, and severe tissue loss.<sup>181</sup> Second-line therapeutic options include interferon alfa and vincristine, which are not labeled for IH and are associated with undesirable side effects and toxicity.<sup>181</sup> Surgical intervention is typically reserved for IHs that have disfiguring or life threatening potential.<sup>186</sup> Because these treatments are all associated with limitations, clinicians have investigated propranolol for treatment of IHs.

**Figure 14. Overall High Impact Potential: Off-label propranolol for treatment of life-threatening infantile hemangiomas**



Experts expressed optimism about propranolol's ability to meet the need of patients who experience complications from infantile hemangiomas, highlighting promising results from early efficacy studies. Experts generally indicated that both patient and clinician acceptance would be high for this intervention, because providing a more efficacious and safe therapy for the treatment of IHs is of critical importance. However, experts opined that frequency of treatment and potential increase in hospital stays might serve as barriers to acceptance for some clinicians and parents of patients.

Experts also opined that further studies evaluating efficacy and safety must be performed. Overall, experts agreed that contingent on results of ongoing clinical trials, propranolol has the potential to replace corticosteroids as first-line therapy for treatment of IHs, marking its potential for high impact. Based on this input, our overall assessment is that this intervention is in the higher end of the high potential impact range.

## Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered their perspectives on this intervention.<sup>187-193</sup> Experts agreed that an unmet need exists for more effective therapy aimed to reduce and treat life-threatening infantile hemangiomas. One clinical expert stated, "Existing treatment regimens have an unsatisfactory balance between treatment efficacy (low) and treatment side effects (high) that are potentially serious. The use of propranolol to treat IH has the potential to change that balance, creating high rates of treatment success with a low risk of serious adverse treatment side effects."<sup>191</sup>

Five experts agreed that propranolol has the ability to improve patient outcomes, with one research expert indicating results from early efficacy studies are "promising, with over 95% of patients in two separate studies responding positively to the therapy."<sup>193</sup> One clinical expert thought the existing data and literature combined with general belief among various clinicians support propranolol's ability to effectively and safely treat IHs when compared with current standards of therapy. Two experts were skeptical of propranolol's ability to improve patient health outcomes, citing insufficient evidence displaying efficacy of propranolol in addition to a lack of understanding of this therapy's underlying mechanism in treating IHs. One research expert stated, "The three initial studies have mixed

results...good, but not overwhelming (regrowth, side effects, etc.).”<sup>188</sup> Most of the experts did not expect this therapy to impact health disparities, although one clinical expert opined that this therapy might be more accessible to economically disparate populations than other available treatment options.

Experts generally agreed this therapy would not significantly disrupt the current health care delivery infrastructure for this patient population. Three experts noted this therapy would require inpatient hospitalization for the very first treatment, leading to slightly increased inpatient volume. Most experts also agreed this therapy would minimally affect the manner with which patients who have IHs would be managed, with one clinical expert noting propranolol administration would most likely require “more inpatient stays from the beginning of the therapy. There will be a switch from surgical to medical service management.”<sup>192</sup> One research expert cited propranolol’s potential to mitigate management of this disease’s complications including “hemangiomas that affect the airways, vision, cardiovascular system, thyroid, or [IHs] that hemorrhage or are painful.”<sup>193</sup> Experts agreed on propranolol’s potential acceptance by clinicians and families of this patient population, indicating that clinicians would readily adopt a more efficacious and safe therapy for treatment of IHs, while parents would be ready to adopt a therapy that would improve their child’s patient health outcomes and quality of life. One research expert opined that frequency of administration may serve as a barrier to parent acceptance, given the therapy may be applied three times daily for a six-to-nine month span in certain propranolol protocols. One expert opined that parents may have a negative perception about the use of “off-label” products, and may be more willing to accept this therapy if it has FDA approval. Most experts believe that given propranolol’s current low cost and purported high efficacy with minimal adverse events, it has potential to significantly reduce the per-patient cost of care overall for this patient population. One clinical expert cautions that initial costs of care might increase, given the in-hospitalization for initial treatment, and frequency of physician visits to monitor progress over the treatment period. However, this expert opines that this therapy’s efficacy, reduction in surgical intervention, and lessened need for treatment for adverse events from current standards of therapy will significantly reduce long-term costs of care.

Overall, experts indicated that propranolol has potential to significantly fulfill the unmet need for this patient population, citing propranolol’s potential to effectively treat IHs while reducing risk of adverse events at a significantly lower cost when compared with other treatment modalities. Provided further efficacy and safety studies validate the use of propranolol for the treatment of IHs, experts believe this therapy could replace corticosteroids as first-line therapy.

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