AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 08: Functional Limitations and Disability

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. HHSA290-2010-00006-C

Prepared by:
ECRI Institute
5200 Butler Pike
Plymouth Meeting, PA 19462

December 2015

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. HHSA290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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

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

Disclaimer Regarding 508-Compliance

Individuals using assistive technology may not be able to fully access information in this report. For assistance contact info@ahrq.gov.

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.

Public Domain Notice

Suggested citation: ECRI Institute. AHRQ Healthcare Horizon Scanning System Potential High-Impact Interventions: Priority Area 08: Functional Limitations. (Prepared by ECRI Institute under Contract No. HHSA290-2010-00006-C.) Rockville, MD: Agency for Healthcare Research and Quality. December 2015. http://effectivehealthcare.ahrq.gov/index.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 emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

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

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

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to: effectivehealthcare@ahrq.hhs.gov.

Richard Kronick, Ph.D.
Director
Agency for Healthcare Research and Quality

Arlene S. Bierman, M.D., M.S.
Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director, Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Contents

Figures

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 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 24,500 leads about potential topics has resulted in identification and tracking of about 2,400 topics across the 14 AHRQ priority areas and 1 cross-cutting area; more than 750 topics are being actively tracked in the system.

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 a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

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

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 195 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

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

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the high-impact-potential 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 having potentially 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 22 topics for which (1) preliminary phase III data for drugs or pivotal data for devices were available; (2) information was compiled and sent for expert comment before November 6, 2015, in this priority area; and (3) we received five to eight sets of comments from experts between January 1, 2014, and November 16, 2015. (In this priority area, 202 topics were being tracked in the system as of November 6, 2015.) We present 16 summaries on 17 topics (indicated below by an asterisk) that emerged as having high-impact potential on the basis of experts' comments. The material in this Executive Summary and report is organized alphabetically by disease state and then by intervention. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 08: Functional Limitations and Disability

Topic	High-Impact Potential
1. * Asfotase alfa (Strensiq) for treatment of hypophosphatasia in infants and children	High
2. Cholbam for treatment of bile acid synthesis and peroxisomal disorders	No high-impact potential at this time; archived November 2015 on the basis of experts' comments
3. * Conestat alfa (Ruconest) for treatment of acute hereditary angioedema	Lower end of the high-impact-potential range
4. * Daclizumab (Zinbryta) for treatment of relapsing-remitting multiple sclerosis	Lower end of the high-impact-potential range
5. Deflazacort for treatment of Duchenne muscular dystrophy	No high-impact potential at this time; continuing to track new developments
6. * Drisapersen for treatment of Duchenne muscular dystrophy	Moderately high
7. * Eliglustat tartrate (Cerdelga) for treatment of Gaucher's disease type 1	Lower end of the high-impact-potential range
8. * Elosulfase alfa (Vimizim) for treatment of Morquio A syndrome	Moderately high
9. * Eltrombopag (Promacta) for treatment of severe or very severe aplastic anemia	Moderately high
10. * Eteplirsen for treatment of Duchenne muscular dystrophy	Moderately high

Topic	High-Impact Potential
11. * Idebenone (Raxone/Catena) for treatment of Duchenne muscular dystrophy	Lower end of the high-impact-potential range
12. Intraoral tongue-drive computerized system to maneuver electric wheelchairs	Prior high impact topic (June 2015); archived September 2015 after 2 years with no development
13. * L-glutamine for prevention of vaso-occlusive sickle cell crises	Moderately high
14. * Migalastat hydrochloride (Galafold) for treatment of Fabry disease	Moderately high
15. * Obeticholic acid for treatment of primary biliary cirrhosis	Moderately high
16. Patiromer (Veltassa) for treatment of hyperkalemia	No high-impact potential at this time; archived November 2015 on the basis of experts' comments
17. * Pediatric Vision Scanner screening for strabismus and amblyopia	Moderately high
18. * Prosthetic arm with body-machine interface (DEKA Arm System) to restore natural-like arm functions after amputation	Moderately high
19. * Sebelipase alfa (Kanuma) for treatment of lysosomal acid lipase deficiency	High
20. Sodium zirconium cyclosilicate for treatment of hyperkalemia	No high-impact potential at this time; archived November 2015 on the basis of experts' comments
21. * Tasimelteon (Hetlioz) for treatment of non–24-hour sleep-wake disorder	Lower end of the high-impact-potential range
22. * Wearable battery-powered exoskeleton (ReWalk Personal) to enable mobility in community or home settings for patients with paraplegia	Moderately high

Discussion

The AHRQ priority area of functional limitations encompasses a wide range of disease states and conditions. For purposes of horizon scanning, AHRQ defines this area using the U.S. Department of Health and Human Services definition of disability: "In general, disabilities are characteristics of the body, mind, or senses that, to a greater or lesser extent, affect a person's ability to engage independently in some or all aspects of day-to-day life." The horizon scanning team put this definition into operation by considering interventions in the context of conditions that impair activities of daily living (e.g., feeding, bathing, toileting/continence, transfers, such as those from bed to chair or wheelchair) or ambulation, dressing, or other independent activities of daily living (e.g., medication management, telephone use, leaving home without assistance, making meals, housekeeping).

Prior High-Impact Topics Archived Since June 2015 Report

One potential high-impact topic from the June 2015 report has been archived.

- **Intraoral tongue-drive computerized system to maneuver electric wheelchairs:** In the June 2015 AHRQ Potential High-Impact Interventions Report and previous reports, this topic was deemed by expert comments to have high-impact potential. The intraoral tongue-drive system, developed at the Georgia Institute of Technology (Atlanta), is a computerized, tongue-operated device intended to enable individuals with quadriplegia maneuver an electric wheelchair. The tongue-drive system addresses an unmet need for improved tools (over sip and puff methods) to maneuver an electric wheel chair, communicate, and function independently, experts previously commented. However, the developer has not found a manufacturing partner, and no apparent developments have occurred since completion of a

study more than 2 years ago. Thus, we archived this topic in September 2015. Should development and evidence development recommence, we will consider tracking it again.

Eligible Topics Deemed Not High-Impact

We archived three topics deemed by experts' comments to have no potential for high-impact and moved one topic back to passive tracking to await more data and notice of regulatory filing. These topics are described briefly below.

- **Cholbam for treatment of bile acid synthesis and peroxisomal disorders:** Cholbam is an oral capsule formulation of cholic acid, a primary biliary acid whose absence or underproduction is a severe symptom of bile acid synthesis disorders and several peroxisomal disorders. In March 2015, the U.S. Food and Drug Administration (FDA) approved Cholbam as a bile acid replacement therapy for treating pediatric and adult patients who have bile acid synthesis disorders due to single-enzyme defects and for patients with peroxisomal disorders. Despite Cholbam's status as the first approved drug for these indications, several reservations remain regarding the drug's treatment efficacy, adverse event profile, and relative superiority, if any, to other treatment options for these patient populations. Consulted experts echoed these concerns, with several comments noting the poor quality of the manufacturer's supporting clinical trials and Cholbam's apparent lack of quality of life benefits. As a result, we archived this topic in November 2015, while noting its regulatory status.
- **Deflazacort for treatment of Duchenne muscular dystrophy:** Deflazacort is a glucocorticoid widely used internationally as an immunosuppressant and treatment for Duchenne muscular dystrophy (DMD). In international clinical trials, as well as anecdotal reports from American patients and caregivers, chronic deflazacort therapy reportedly improved patients' muscle strength and mobility, reduced overall weakness, and delayed or prevented scoliosis and cardiac and pulmonary functional declines in some patients. To date, FDA has not approved deflazacort for any indication, but Marathon Pharmaceuticals, LLC (Northbrook, IL), is investigating the drug for American market use, and its oral tablet formulation was granted fast-track, orphan drug, and rare pediatric disease statuses for treating DMD. Researchers at the University of Rochester (Rochester, NY) are also independently studying deflazacort open-label in a phase III trial for the same indication. This topic was originally eligible for high-impact potential consideration because available late-phase clinical trial data were available and Marathon stated intentions to complete a regulatory submission in 2015. However, Marathon announced that deflazacort's filing timeline is delayed until at least early 2016, and expert comments were divided in their opinion of the drug's potential for impact. Thus, we will continue to track this topic and monitor deflazacort's clinical and regulatory developments and resend for expert comment if new information warrants.
- **Two potassium binders (patiromer and sodium zirconium cyclosilicate) for treatment of hyperkalemia:** The potassium binders patiromer (Veltassa®; Relypsa, Inc., Redwood City, CA) and sodium zirconium cyclosilicate (ZS Pharma, Inc., Coppell, TX) are intended to lower serum potassium levels in patients with chronic kidney disease, especially those whose hyperkalemia is caused by renin-angiotensin-aldosterone-system inhibitors. Despite some side effects from standard treatment, sodium polystyrene sulfonate, experts commenting on this topic did not think a substantial unmet need was apparent. The experts also thought that even though some data show that the drugs lower serum potassium levels, the available evidence did not indicate that the drugs would have clinically significant

patient health outcomes. Thus, these topics were archived in the horizon scanning system in November 2015 because of lack of high-impact potential.

Potential High-Impact Interventions

Below are 16 summaries on 17 interventions that, according to experts' comments, have high-impact potential. The conditions addressed by these interventions are a bone marrow disorder, severe aplastic anemia (SAA); a central nervous system disorder, multiple sclerosis (MS); the genetic disorders hereditary angioedema, Duchenne muscular dystrophy (DMD), Fabry disease, Gaucher's disease, hypophosphatasia, lysosomal acid lipase deficiency (LALD), Morquio A syndrome, and sickle cell disease (SCD); a liver disorder, primary biliary cirrhosis (PBC); sensory disorders related to vision in children and sleep in blind people; and spinal cord injury and upper limb amputation. The drugs are a monoclonal antibody, two enzyme inhibitors, three enzyme replacement therapies, and a molecular chaperone that ensures an enzyme is folded properly for physiologic action; exon-skipping molecules that modify gene expression; a short-chain benzoquinone, structurally similar to coenzyme Q_{10}; a pharmaceutical-grade amino acid; and farnesoid-X-receptor (FXR), melatonin-receptor, and thrombopoietin-receptor agonists. A screening tool checks vision alignment in young children. The devices discussed are an exoskeleton to enable people with paraplegia to stand, turn, and walk and an advanced prosthetic arm.

Bone Marrow Disorder

Eltrombopag (Promacta) for Treatment of Severe Aplastic Anemia

- **Key Facts:** SAA is treated with immunosuppressive therapy in older patients or those who do not have a matched sibling donor for a hematopoietic stem cell transplant (HSCT). Immunosuppressive therapy is ineffective for 20% to 40% of patients, and about one-third of patients who do respond experience a relapse. An unmet need exists for treatments for SAA in patients who have an insufficient response to immunosuppressive therapy. Eltrombopag (Promacta®) is a thrombopoietin receptor agonist that increases production of all types of blood cells by inducing proliferation and differentiation of bone marrow stem cells. According to the manufacturer's labeling, eltrombopag is administered at an initial dose of 50 mg as an oral tablet, once daily. The dose may be adjusted every 2 weeks to achieve a target platelet count of 50×10^9/L or more. The maximum dose is 150 mg daily. The medication comes in 12.5, 25, 50, 75, and 100 mg tablets or in an oral suspension formulation of 25 mg.
- In August 2014, FDA approved eltrombopag for treating SAA in patients who have had an insufficient response to immunosuppressive therapy. The drug had received FDA's breakthrough therapy designation in January 2014. Eltrombopag reportedly costs about $70,000 per patient per year, depending on the pharmacy. The drug is included in most payer formularies as a specialty pharmaceutical requiring prior authorization.
- According to the manufacturer's labeling, eltrombopag may cause hepatic decompensation, liver enzyme elevation, thrombotic or thromboembolic events, or cataracts. Common adverse events reported in patients with SAA treated with eltrombopag include nausea, fatigue, cough, diarrhea, and headache. In a phase II clinical trial, Desmond et al. (2014) reported that 8 of 43 patients had new cytogenetic abnormalities seen in bone marrow aspirates, including 5 with chromosome loss or partial deletion of chromosome 7. They also reported that 40% of patients had trilineage or bilineage responses at 3–4 months. In an extension study, 5 of these patients were able to discontinue treatment and maintain stable

blood counts for an average of 13 months without eltrombopag. Phase II and III trials are ongoing.

- **Key Expert Comments:** Experts commenting on this intervention agreed that alternative SAA treatments are needed because this disease greatly affects those who have it. Clinicians and patients will mostly favor the easy administration and demonstrated effectiveness of eltrombopag, experts said, even if some clinicians are reluctant to prescribe it based on the surrogate outcomes reported from clinical trials. Experts suggested that patient management may be largely simplified with eltrombopag use compared to immunosuppressive therapy or HSCT. Although the cost may be high, health disparities for some minority ethnic groups may improve if they have access to eltrombopag, experts thought.
- **High-Impact Potential:** Moderately high

Central Nervous System Disorder

Daclizumab (Zinbryta) for Treatment of Relapsing-Remitting Multiple Sclerosis

- **Key Facts:** FDA has approved several pharmacotherapies for treating relapsing forms of MS, but a need remains for additional effective medications, because many patients are unable to achieve adequate, sustained symptom remission. Daclizumab is a multifaceted monoclonal antibody and immunomodulator in late-phase development for treating relapsing forms of MS. Researchers hypothesize that daclizumab competitively inhibits interleukin-2 receptor subunit CD25 activation, leading to selective inhibition of T-cell activation and subsequently curbing MS-related neuroinflammation. Daclizumab is manufactured as a high-yield process formulation (HYP; DAC HYP) and is administered via monthly 150 or 300 mg subcutaneous injections. Clinical trial results suggest daclizumab may be superior to both placebo and an active comparator medication for reducing annualized relapse rates and active brain lesions in patients with relapsing-remitting MS. Ongoing late-phase clinical trials are examining daclizumab's long-term safety and efficacy for this patient population.

  Based on positive data from two pivotal trials (DECIDE and SELECT), daclizumab's co-manufacturers submitted a biologics license application to FDA. In April 2015 these development partners announced that FDA had accepted their application for daclizumab (Zinbryta™). Pricing is unknown, but experts anticipate that the drug will be competitively priced with other MS therapies on the market.
- **Key Expert Comments:** Although available data support daclizumab's utility for treating relapsing-remitting MS, experts thought that the drug has potential for high impact, but on the lower end of the range because of the number of other effective competing pharmacotherapies. They also noted that daclizumab lacks long-term efficacy data at this time, which might affect diffusion. Experts also thought that patients may prefer available oral MS medications as long as possible before having to switch to an injectable drug, such as daclizumab.
- **High-Impact Potential:** Lower end of the high-impact potential range

Genetic Disorders

Asfotase Alfa (Strensiq) for Treatment of Hypophosphatasia in Infants and Children

- **Key Facts:** Hypophosphatasia (HPP) is a rare autosomally inherited metabolic bone disorder, with a range of bone development–related symptoms whose severities depend on the patient's age at disorder onset. HPP is caused by various mutations to the alkaline phosphatase, liver/bone/kidney (*ALPL*) gene; these mutations result in abnormally low systemic levels of alkaline phosphatase, a key bone mineralization enzyme. Although adult-onset HPP has relatively mild symptoms such as premature tooth loss, infant- and juvenile-onset HPP are marked by more severe symptoms including cranial hypomineralization, pneumonia, and abnormal bone development. Regrettably, these early-onset HPP forms have mortality rates as high as 50%.

  Asfotase alfa (Strensiq™) is a recombinant enzyme replacement therapy (ERT) designed to target underlying genetic causes of HPP. The drug is the first medication approved by FDA for treating pediatric forms of HPP and may become a new standard of care for severe pediatric HPP while also holding promise as a therapy for older patients. As approved, asfotase alfa is injected subcutaneously for treating perinatal-, infant-, and juvenile-onset HPP, at thrice-weekly bodyweight-dependent doses up to 3 mg/kg. In clinical trials enrolling pediatric and adolescent HPP patients, asfotase alfa was well tolerated and is associated with improved strength and functional mobility and reduced mortality rates. This drug's long-term efficacy and adverse event profile are under investigation in ongoing trials, and the manufacturer is also studying treatment efficacy for adult patients with HPP.

  After asfotase alfa's October 2015 FDA approval, the drug's manufacturer announced that it would be priced at about $285,000 per patient annually. We anticipate that asfotase alfa will be added to third-party payer policies in 2016, with coverage as a specialty drug, and should diffuse widely among patients and clinicians.
- **Key Expert Comments:** Consensus expert opinion held that asfotase alfa addresses a significant unmet need for effective therapies for patients with HPP. Experts viewed the drug's efficacy and safety profile favorably, anticipating that these factors, along with expected third-party payer coverage and manufacturer financial assistance programs, would promote broad acceptance and adoption by patients, caregivers, and clinicians. As the first approved disease-modifying therapy for HPP, asfotase alfa could dramatically improve patient health outcomes and will likely become a new standard of care for early-onset HPP, experts also thought.
- **High-Impact Potential:** High

Conestat Alfa (Ruconest) for Treatment of Acute Hereditary Angioedema

- **Key Facts:** Hereditary angioedema (HAE) is life-threatening. Available treatments are associated with significant side effects, such as thrombosis, and the most effective treatment, a human C1 esterase inhibitor (C1INH, also called C1 inhibitor) concentrated from donated blood, is not always available. Thus, an unmet need exists for a treatment for acute HAE attacks that has fewer side effects. Conestat alfa (Ruconest®) is a plasma-free, recombinant, human C1INH that FDA approved in July 2014. It can be self-administered when patients experience an acute attack. Conestat alfa is produced in the milk of transgenic rabbits. Because it is not isolated from human blood, it does not carry a risk of transmission of human infectious agents. However, since it is produced by rabbits, patients who have an

allergy to rabbits cannot use the drug. Conestat alfa is given by intravenous (IV) infusion over 5 minutes. A clinician experienced in treating HAE supervises the first dose; then, patients may be trained to self-administer the drug. For patients who weigh less than 84 kg, the dose is 50 IU per kg. For patients who weigh 84 kg or more, the dose is 4,200 IU (2 vials). In a clinical trial, most patients experienced mild to moderate treatment-emergent adverse events. The most common adverse events were headache, nausea, and diarrhea. A serious but uncommon adverse event is anaphylaxis. No reports of thromboembolic events or increased risk of deep vein thrombosis have been associated with conestat alfa, unlike with alternative treatments. In a phase III, randomized trial of conestat alfa against placebo, Riedl and coauthors (2014) reported reduced median time to the onset of symptom relief (90 vs. 152 minutes) and reduced median time to minimal symptoms (303 vs. 483 minutes). Moldovan and coworkers (2012) reported that 87% of patients with acute HAE achieved symptom relief within 4 hours. One observational study is ongoing.

In July 2014, FDA approved the drug for treating HAE attacks in adult and adolescent patients. The wholesale acquisition cost of conestat alfa is $9,500 for 2 vials, the maximum single dose. The U.S. Centers for Medicare & Medicaid Services has no national coverage determination for conestat alfa. Thus, coverage is left to the discretion of local Medicare prescription drug plans. Our search of representative third-party payers found seven (i.e., Aetna, Anthem, HealthPartners, Humana, Regence, United Healthcare, Wellmark) with policies that outline coverage criteria for conestat alfa. Additionally, Blue Cross/Blue Shield Massachusetts denies coverage.

- **Key Expert Comments:** Experts commenting on this intervention agreed that conestat alfa may improve patient health, although they differed over how important the unmet need is. Clinical experts stressed that supply issues with alternative treatments make this intervention more crucial in emergency scenarios. Conestat alfa may be readily accepted by clinicians and patients because of its good safety profile, easy administration, and effectiveness, experts commented. Health care infrastructure, patient management, and health disparities are not likely to be greatly affected by use of conestat alfa, experts said.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Eliglustat Tartrate (Cerdelga) for Treatment of Gaucher's Disease Type 1

- **Key Facts:** Gaucher's disease, an orphan disease affecting an estimated 6,000 patients in the United States, has long been treated using IV ERT; no oral therapy had been available until eliglustat tartrate was developed. ERT costs between $300,000 and $350,000 per patient per year (depending on the brand used) and is inconvenient for patients because it requires IV infusions every 2–3 weeks lifelong. Eliglustat tartrate purportedly partially inhibits the enzyme glucosylceramide synthase, resulting in reduced glucosylceramide. Four phase III trials of eliglustat tartrate are ongoing. Mistry and colleagues (2015) and Cox and coauthors (2015) reported positive data from two of these trials, showing significant reduction in spleen volume and noninferiority to an IV ERT comparator, respectively.

  FDA approved eliglustat tartrate (Cerdelga™) in August 2014 as an orally administered, alternative first-line treatment for Gaucher's disease type 1. The drug is administered as 84 mg tablets, once or twice daily depending on the patient's CYP2D6 metabolism rate. The drug costs about $316,000 per patient per year, comparable to IV ERT. The manufacturer offers a copayment assistance program for patients with private insurance; several third-party payers cover the drug but require prior authorization and impose quantity limits.

- **Key Expert Comments:** Patients need a more convenient treatment for Gaucher's disease, and experts suggested this oral compound could increase patient adherence to treatment recommendations. The effect of this on health outcomes and quality of life remains to be seen, experts said. Experts anticipated modest adoption of eliglustat tartrate because of its convenience and use in the home setting. Adoption may be limited by competing therapies that are more familiar to clinicians. Experts noted its impact would be contingent on eliglustat tartrate being proved to be as effective as the standard of care.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Elosulfase Alfa (Vimizim) for Treatment of Morquio A Syndrome

- **Key Facts:** Morquio A syndrome (mucopolysaccharidosis type IV) is a rare, heritable metabolic disorder caused by mutations to *GALNS*, a gene that normally encodes the glycosaminoglycan-degrading enzyme *N*-acetylgalactosamine-6-sulfatase. Patients with Morquio A syndrome have deficient *N*-acetylgalactosamine-6-sulfatase levels that lead to dangerous systemic accumulations of the glycosaminoglycan keratan sulfate. Excess keratan sulfate often causes potentially fatal symptoms such as heart valve abnormalities, hydrocephalus, skeletal dysplasia (dwarfism), and spinal cord compression. Severely affected patients may survive only to late childhood or adolescence.

  Elosulfase alfa (Vimizim®) is an FDA-approved *GALNS* ERT, intended to check or ameliorate Morquio A syndrome symptoms. Elosulfase alfa is delivered as a weekly 2 mg/kg intravenous infusion over a minimum of 3.5–4.5 hours. In clinical trials, elosulfase alfa infusions provided limited functional mobility improvements in pediatric patients; treatment-related side effects include fever, headache, nausea and vomiting, and abdominal pain. Elosulfase alfa's long-term efficacy and safety are under investigation in ongoing trials.

  Elosulfase alfa continues to diffuse broadly among American and international patients with Morquio A syndrome. Annually, elosulfase alfa costs about $380,000 per patient in the United States. The drug is widely covered by third-party payers, often classified as a specialty pharmaceutical with prior authorization required.
- **Key Expert Comments:** Experts concluded that elosulfase alfa addresses an unmet need among patients with Morquio A syndrome, although its impact was dampened by its noncurative nature. Experts also remarked that the drug's treatment efficacy was limited, with no response observed among several clinical trial patients. However, as an approved nonsurgical intervention, experts foresaw elosulfase alfa's continued high use, regardless of its cost.
- **High-Impact Potential:** Moderately high

Exon-Skipping Therapies (Drisapersen, Eteplirsen) for Treatment of Duchenne Muscular Dystrophy

- **Key Facts:** DMD is a progressively debilitating muscle-wasting disorder caused by dystrophin gene mutations. The dystrophin gene normally encodes a protein, dystrophin, central to muscle cell structural integrity; however, in DMD, mutated dystrophin genes produce nonfunctioning dystrophin protein, broadly impacting patient's muscle cell tissue. As DMD advances, patients may experience heart defects, general muscle weakness and fatigue, and respiratory and motor difficulties. No cure exists, and disorder-related complications are eventually fatal; patients rarely survive to age 50.

Standard of care is palliative, focusing on minimizing the effects of patients' most acute motor and respiratory symptoms. An unmet need exists for DMD treatments that can increase patients' functional independence and delay the need for assistive palliative interventions such as wheelchairs. Drisapersen (Kyndrisa™) and eteplirsen are investigational injectable therapies that induce skipping of errant sections of mutated dystrophin gene during RNA transcription; developers hypothesize that this "exon-skipping" activity will enable creation of functional dystrophin protein and consequently prevent or delay functional decline in patients with DMD. Both medications are intended to treat a patient subpopulation—representing about 13% of adolescent male DMD patients—with exon 51–associated dystrophin gene mutations.

In completed and ongoing clinical trials, drisapersen and eteplirsen administrations increased systemic and functioning dystrophin levels in patients with DMD and demonstrated efficacy for improving patients' ambulatory and respiratory function and delaying typical functional decline rates. Both drugs are also relatively well tolerated, although drisapersen administration has been inconclusively associated with some potentially severe side effects. Long-term safety and efficacy results were inconsistent, but ongoing studies are attempting to provide support for these drugs' durable use.

- **Key Expert Comments:** Assessing exon-skipping interventions, experts agreed that an unmet need exists for effective, novel DMD treatments. Experts also anticipated that these drugs would be widely accepted by patients and clinicians, if approved. However, experts acknowledged that, because only a subgroup of DMD patients are eligible for these therapies, exon-skipping medications' potential impact on the overall DMD patient population is somewhat limited. However, experts concluded that both drisapersen and eteplirsen have moderate high-impact potential to positively affect patient health outcomes.
- **High-Impact Potential:** Moderately high

Idebenone (Raxone/Catena) for Treatment of Duchenne Muscular Dystrophy

- **Key Facts:** Respiratory decline is a common, severe symptom in patients with DMD. As DMD progresses, respiratory function declines precipitously, compelling many older patients to use assisted-breathing devices or high-dose corticosteroids. An unmet need exists for effective therapies that recover respiratory function and functional independence in patients with DMD.

  Idebenone (Raxone®/Catena®) is an oral short-chain benzoquinone with potent antioxidant and cytoprotective properties. Both properties purportedly improve sustained intracellular energy transfer via adenosine triphosphate (ATP) production. Researchers also hypothesize that this biochemical activity circumvents pathways affected by DMD and may ameliorate the disorder's associated muscle-wasting symptoms. Late-phase clinical trial data supports the tolerability of 450–900 mg daily idebenone administration and the drug's efficacy for relieving patients' respiratory symptoms.

  To date, idebenone is the only investigational DMD medication to successfully complete a phase III clinical trial. Investigators published peer-reviewed results from this study in 2015. Idebenone's developer announced that it had initiated meetings with FDA and the European Medicines Agency and plans to complete concurrent American and European regulatory filings in the first quarter of 2016.
- **Key Expert Comments:** Overall, experts agreed that a significant need exists for effective DMD medications and thought that idebenone could address this need. Despite clinical data indicating some efficacy for improving patient health outcomes, experts acknowledged that

idebenone will not replace present standards of care because it does not modify the disease itself. Accordingly, they concluded that idebenone would have high-impact potential in the lower end of the range and, if approved, would most likely be an adjunct therapy to traditional palliative care.

- **High-Impact Potential:** Lower end of the high-impact-potential range

L-Glutamine for Prevention of Vaso-Occlusive Sickle Cell Crises

- **Key Facts:** Standard prophylactic and acute treatment for vaso-occlusive crises (VOCs) in SCD is a myelosuppressive chemotherapeutic agent called hydroxyurea; however, the drug is effective for only two-thirds of affected adults and increases the infection risk. Researchers are investigating whether pharmaceutical-grade L-glutamine taken prophylactically might prevent VOCs, reduce pain, reduce hospitalizations, shorten hospital stays, and fulfill the unmet need for a therapy without side effects. Researchers speculate that oxidative stress, adhesive leukocytes, and chronic inflammation play roles in VOCs. L-glutamine is a nonessential amino acid that acts as a precursor to nicotinamide adenine dinucleotide (NAD), an electron acceptor that reduces oxidative stress in cells. Supplementing L-glutamine levels may increase the NAD concentration, potentially altering the redox state of red blood cells and preventing VOCs. In clinical trials, pharmaceutical-grade L-glutamine is administered twice daily at a dose of 0.3–0.6 g/kg. Doses are rounded to 5- or 10-g increments with an upper limit of 30 g per day. L-glutamine is a powder that can be mixed with water or unheated beverages and foods (e.g., yogurt, applesauce, cereal).

  In a phase III, randomized, placebo-controlled trial, Niihara and colleagues (2014) reported statistically significant decreases in VOC incidence, hospitalization incidence, cumulative hospital days, acute chest syndrome incidence, and median time to first VOC for patients who took L-glutamine. No clinical trials are ongoing. The manufacturer expected to initiate a phase III trial and submit a new drug application to FDA by the end of 2015, although no further information has been released. FDA granted the intervention orphan drug and fast-track statuses for treating SCD. No cost, coverage, or payment information is available yet. If pharmaceutical-grade L-glutamine gains approval for this indication, we anticipate third-party payers would cover it as a specialty pharmaceutical.
- **Key Expert Comments:** Experts commenting on this intervention agreed that a substantial unmet need exists to reduce pain, VOCs, and hospitalizations. Clinicians and patients may readily adopt L-glutamine because it appears safe, is an oral amino acid, and will likely be of low cost, experts said. Experts noted that it is unlikely to affect health care delivery infrastructure or patient management except by potentially reducing hospital use.
- **High-Impact Potential:** Moderately high

Migalastat Hydrochloride (Galafold) for Treatment of Fabry Disease

- **Key Facts:** Treatment for Fabry disease is ERT using recombinant alpha-galactosidase A (alpha-GAL) enzyme; however, ERT has variable tissue distribution, a requirement for weekly or biweekly IV infusions, and a high cost. Migalastat (Galafold™) is a small-molecule modulator of alpha-GAL activity intended to activate endogenous residual alpha-GAL as a monotherapy or potentiate the activity of exogenously provided alpha-GAL activity as a combination therapy with ERT. Migalastat is intended to function as a pharmacologic chaperone for alpha-GAL to promote the proper folding of endogenous alpha-GAL for appropriate trafficking and function. Restored enzymatic activity of alpha-GAL reduces the levels of globotriaosylceramide (GL-3) and prevents its damaging

accumulation. Migalastat may also work as a combination therapy with ERT by binding to and stabilizing exogenous alpha-GAL and increasing uptake in affected organs. Based on an enzymatic assay, the manufacturer estimates 30% to 50% of patients with Fabry disease have mutations that are suited to migalastat monotherapy. Migalastat is administered orally; the optimal dose is still under study. In clinical trials, it is administered at a dosage of 150 mg every other day or 250 mg in cycles of 3 days on and 4 days off. The most commonly reported adverse events include headache, arthralgia, diarrhea, back pain, pain in an extremity, and fatigue.

Migalastat is administered as either a monotherapy or combination therapy with ERT for treating Fabry disease. In February 2004, FDA granted migalastat orphan drug status. Three phase III clinical trials are ongoing. The drug's manufacturer will not seek regulatory approval in 2015 as originally intended, but after meeting with FDA, it has indicated it may conduct additional trials on migalastat's effect on gastrointestinal symptoms. In a clinical trial (n=67) of migalastat's effect on levels of GL-3, inclusions in interstitial capillaries of the kidneys, the primary endpoint, was not met. However, in a post-hoc analysis including only patients with amenable mutations (n=42), Barlow and coauthors (2014) showed a statistically significant reduction of GL-3. In a followup study, glomerular filtration rate remained steady over an average of 32 months for patients with amenable mutations, according to Bichet and colleagues (2014). Two other studies (Giugliani and coworkers, 2013; Germain and coauthors, 2012) also supported the analysis that only patients with amenable mutations responded to migalastat.

Pricing, coverage, and payment information for migalastat is not available. Treatments for a rare condition such as Fabry disease are likely to be costly, and it is unclear whether the manufacturer will price migalastat lower than ERT. If migalastat is approved, its use is likely to be reimbursed by third-party payers as a specialty pharmaceutical because of the limited treatment options for patients with Fabry disease.

- **Key Expert Comments:** Experts commenting on this intervention agreed that a large unmet need exists for effective and convenient treatment. Migalastat may be readily accepted by clinicians and patients because of its oral administration and good tolerability, experts suggested. As an oral drug, it is unlikely to have a significant impact on health care delivery infrastructure or patient management, experts thought, but it could add to overall costs.
- **High-Impact Potential:** Moderately high

Sebelipase Alfa (Kanuma) for Treatment of Lysosomal Acid Lipase Deficiency

- **Key Facts:** Lysosomal Acid Lipase Deficiency (LALD) is associated with significant morbidity including hypercholesterolemia, cardiovascular disease, and liver damage. It may lead to liver failure and, in the most severe form, death. Treatments for LALD address symptoms but do not target the underlying deficiency. Sebelipase alfa (Kanuma®) is a recombinant form of the human lysosomal acid lipase enzyme, intended to prevent accumulation of cholesterol esters and triglycerides and maintain adequate lipid metabolism. It is administered by IV infusion 1 mg/kg, every other week. In clinical trials, about 10% of patients experienced infusion-related reactions (i.e., fever, vomiting).

  In a clinical trial of patients with early-onset LALD, Jones and coworkers (2015) reported improved 12-month survival for 9 patients who received sebelipase alfa compared to a historical cohort (67% vs. 0%, respectively). In another clinical trial of patients with late-onset LALD (n=66), Burton and colleagues (2015) reported that 31% of patients had normal levels of alanine aminotransferase after 20 weeks of sebelipase alfa treatment

compared with 7% of patients in the placebo group. Two phase III trials and an expanded access protocol are ongoing. The manufacturer is studying sebelipase alfa for treating infants, children, and adults who have LALD. FDA approved sebelipase alfa for LALD in December 2015; FDA previously granted orphan drug status to the therapy and fast-track and breakthrough therapy statuses for treating infants. No cost, coverage, or payment information is available because sebelipase alfa was just approved by FDA, but it is likely to be expensive. Now approved, its use is likely to be reimbursed by third-party payers because of the limited treatment options for patients with LALD.

- **Key Expert Comments:** Experts commenting on this intervention agreed that patients with the most severe disease need a treatment to prolong survival and avoid liver or stem cell transplants. As an ERT, sebelipase alfa targets the underlying cause of the disease, not just symptoms, experts noted; as such, acceptance from clinicians and patients is likely to be high. Although health care delivery infrastructure will be minimally affected, regular infusions will change the care setting for patient management and potentially reduce the number of surgeries needed, experts thought. Experts expect a high cost comparable to other ERTs for rare diseases, with third-party payers and patients bearing these costs.
- **High-Impact Potential:** High

Liver Disorder

Obeticholic Acid for Treatment of Primary Biliary Cirrhosis

- **Key Facts:** PBC is a chronic and progressive liver disease that eventually requires a liver transplant and may still recur. The standard of care for earlier-stage disease is to delay progression by using ursodiol (also known as ursodeoxycholic acid), which is ineffective in up to 40% of patients. Obeticholic acid is a first-in-class, bile acid–analogue agonist of the farnesoid X receptor (FXR), which is a negative feedback regulator of bile acid levels. The drug purportedly increases bile flow and prevents toxic buildup of bile acids in hepatocytes, preventing further fibrosis, using a mechanism of action distinct from ursodiol. It is administered at a dosage of 5 or 10 mg or titrated up from 5 mg to 10 mg over 6 months; it is taken orally once daily. The most common adverse event reported has been pruritus, and it may also decrease high-density lipoprotein levels (potentially increasing risk for cardiovascular disease).

  In the phase III POISE trial (n=217), which evaluated obeticholic acid's effects on liver function, Nevens and coauthors (2014) reported that 46% and 47% of patients who received obeticholic acid, 5 mg and 10 mg, respectively, met the primary endpoint of improved alkaline phosphatase and bilirubin levels, compared with 10% of patients who received placebo. In a phase II trial, Hirschfield and coworkers (2014) reported that average levels of alkaline phosphatase decreased 21% to 25% from baseline in patients who received obeticholic acid compared with a 3% average reduction in the placebo group. An ongoing phase II trial is investigating obeticholic acid's effect on high-density lipoprotein levels. The manufacturer has submitted a new drug application and expects a decision in February 2016 under FDA's accelerated approval pathway. FDA granted orphan drug and fast-track statuses for the drug. Pricing, coverage, and payment information for obeticholic acid is not available yet. If obeticholic acid is approved by FDA, third-party payers would likely cover it as a specialty pharmaceutical requiring prior authorization if it shows sufficient efficacy and safety.

- **Key Expert Comments:** Experts commenting on this intervention agreed that patients who do not respond to ursodiol need an additional safe and effective treatment option, and obeticholic acid might provide that. Although published data rely on surrogate markers to support obeticholic acid's benefits to patient health, most experts agreed that clinicians will accept the link between the markers and disease progression and survival and will prescribe the drug. Obeticholic acid's effects on patient management and cost will largely depend on its effectiveness because, as experts pointed out, the drug is likely to cost more than ursodiol but may reduce the need for liver transplants. Overall, experts thought that an additional option with few major side effects would be welcome in patients who do not respond to ursodiol.
- **High-Impact Potential:** Moderately high

Sensory Disorders

Pediatric Vision Scanner Screening for Strabismus and Amblyopia

- **Key Facts:** The leading cause of preventable monocular vision loss in children is amblyopia, which is most often caused by strabismus. Early amblyopia detection by pediatricians and other primary care clinicians can be difficult because standard screening methods lack sufficient sensitivity and specificity and require infants, toddlers, and young children to sit still for several minutes, making the screening impractical for many infants and toddlers. Thus, common screening technologies miss detection in very young children who should be referred to an ophthalmologist for further evaluation and possible treatment. Treatment success declines as age at identification increases.

  The Pediatric Vision Scanner (PVS) is intended for use as a screening tool to enable earlier and more accurate amblyopia or strabismus detection so that patients can be more appropriately referred to specialist care. The system uses proprietary technology called retinal birefringence scanning to screen for amblyopia and strabismus. The PVS simultaneously assesses both eyes during a 2- to 5-second scan to detect both binocular alignment and the eyes' ability to focus on a target. The system's software indicates (with a "pass" or passing grade) whether the patient's eyes accurately fixated on the target. If the eyes did not fixate, a pediatrician refers the patient for further evaluation. Five clinical trials evaluated the sensitivity and specificity of the PVS compared with other screening devices. Investigators from the largest and most recently reported PVS trial (Jost and colleagues 2014), in children aged 2–6 years, reported that, "The sensitivity of the PVS to detect strabismus and amblyopia (0.97; 95% CI [confidence interval], 0.94-1.00) was significantly higher than that of the SureSight Autorefractor (0.74; 95% CI, 0.66-0.83). Specificity… (0.87; 95% CI, 0.80-0.95) was significantly higher than that of the SureSight Autorefractor (0.62; 95% CI, 0.50-0.73)." FDA has determined the PVS to be a nonsignificant risk device. This means the PVS has abbreviated requirements for labeling; institutional review board approval is all that is needed to conduct trials (i.e., no prior FDA approval needed for trials); and reporting rules are streamlined for the regulatory approval pathway. The PVS is not yet cleared for marketing.

  The device's cost is not yet available but is expected to be in line with costs of existing scanning vision screening equipment. Third-party reimbursement for pediatric vision screening has been long established and the payment is about $30 per screening. The company indicated it expects its screening exam cost to fall within the reimbursed amount. The manufacturer is collaborating with VisionQuest 20/20, a nonprofit organization that

addresses preventable vision loss in children, to establish a nationwide vision screening and tracking program in pediatric offices and preschools. The company has also established a crowd-funding site to raise funds to complete its development to meet regulatory requirements.

- **Key Expert Comments:** PVS use in very young populations is a significant factor in its potential to fulfill the unmet need for early diagnostic tools for amblyopia and strabismus, experts commenting on this intervention agreed. Experts thought that the capabilities of the PVS to screen younger children and identify possible problems earlier could contribute to improved patient health outcomes. Experts especially liked the ease of use, quick scan time, low risks, and minimal training needed to successfully operate the device in a primary care setting. Experts believe that these factors will contribute to wide acceptance and adoption, which may improve the accuracy of referrals to specialists.
- **High-Impact Potential:** Moderately high

Tasimelteon (Hetlioz) for Treatment of Non–24-Hour Sleep-Wake Disorder

- **Key Facts:** About half of all blind people are believed to be affected by non–24-hour sleep-wake disorder (non-24) because of a lack of light receptors to reset the circadian rhythm. Patients with non-24 may experience reduced quality of life and debilitation due to poor sleep quality and excessive daytime sleepiness. Stimulants and sedatives may provide temporary or partial relief of symptoms, but patients need treatment that addresses the underlying cause of the disease. Tasimelteon is a dual melatonin receptor agonist that, according to the manufacturer, resets the circadian rhythm by acting in the hypothalamus. It is taken orally at a dosage of 20 mg, 1 hour before bedtime, at the same time every night. According to Lockley and coauthors (2013), in a clinical trial of 20 patients, total nighttime sleep in the worst quartile of nights improved by 67.2 minutes and daytime sleep shortened by 59.4 minutes. One phase III trial is ongoing.

  FDA granted orphan drug status and priority review for the manufacturer's new drug application; FDA approved the drug in January 2014 as Hetlioz™. Tasimelteon reportedly costs about $135,000 per patient per year. Several third-party payers cover the drug as a specialty pharmaceutical requiring prior authorization and imposing quantity limits.
- **Key Expert Comments:** Overall, tasimelteon's biggest impact on the health care system will likely be its cost, experts agreed. Clinicians and patients are likely to adopt tasimelteon because of its good safety profile and low abuse potential, experts agreed. In terms of improving patient health or altering patient management, experts noted the small amount of data and very modest improvements in sleep and waking times.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Spinal Cord Injury

Wearable, Battery-Powered Exoskeleton (ReWalk Personal) to Enable Mobility in Community or Home Settings for Patients with Paraplegia

- **Key Facts:** Wheelchair users with paraplegia can experience pressure ulcers, osteoporosis, depression, and cardiovascular, respiratory, urinary, and gastrointestinal adverse events associated with confinement to power-assisted devices. The ReWalk Personal system is a wearable, battery-powered exoskeleton with motorized leg braces and crutches for support, which are meant to provide mobility and independence in community and home settings. The 35 lb device uses a tilt sensor, onboard computer, and rechargeable battery to propel the

motorized leg braces when patients shift their body weight. It is designed to mimic a natural walking gait and functional speed while allowing users to sit, stand, walk, and turn for about 4 hours at a time. It is customized to fit the patient, although height and weight restrictions apply. Patients with sufficient bone density, flexibility, and cardiovascular health, as determined by a physician's exam, complete device training at a rehabilitation center. Although patients control the exoskeleton, trained caregivers must be present to assist patients while they use the device, even during home use.

Two studies are ongoing to evaluate the ReWalk Personal in community and home settings. Esquenazi and colleagues (2012) reported that all patients (n=12) were able to transfer to the exoskeleton and walk with it independently for 5–10 minutes. All patients made positive comments about emotional and psychosocial benefits, and some patients reported improvements in pain, bowel and bladder function, and spasticity. In contrast, Benson and coauthors (2015) reported (after we had already received experts' comments on this intervention) that about two-thirds of candidates for their study of the ReWalk did not meet criteria or were not interested in committing to a 10-week training program. Further, enrolled patients (n=10) reported that the exoskeleton did not reach their high expectations for benefits.

FDA cleared the ReWalk Personal in June 2014 under the de novo pathway. The device is also available for use in a rehabilitation setting, and that use preceded the ReWalk Personal version clearance. Physician approval and training certification are required to use the assistive device. The manufacturer stated that diffusion has been limited because of the time it takes to evaluate and train patients and process reimbursement claims. The ReWalk Personal costs about $70,000. Medicare Part B may cover exoskeletons as durable medical equipment for beneficiaries whose physician has prescribed it for home use, although the decision is left to the discretion of local carriers. Patients must pay 20% of the Medicare-approved amount. Our searches found eight policies from third-party payers that deny coverage of the ReWalk Personal on the basis that it is experimental.

- **Key Expert Comments:** Experts commenting on this intervention agreed that an unmet need exists for a mobility and upright standing device. An exoskeleton for community or home use may prevent complications associated with prolonged wheelchair use, experts agreed. They suggested the high cost will have the greatest effect on patient acceptance and access, possibly contributing to health disparities.
- **High-Impact Potential:** Moderately high

Upper Limb Amputation

Prosthetic Arm with Body-Machine Interface (DEKA Arm System) To Restore Natural Arm Function After Amputation

- **Key Facts:** Prosthetic arms that provide natural movements, intuitive control, and fine motor function are not available to patients who have had an arm amputated, leaving many with limited function. The DEKA Arm System combines a body-machine interface with other inputs to control a prosthetic hand and arm with up to 10 powered degrees of freedom. According to Resnik and coworkers (2013), more than 90% of users in a clinical study (n=37) reported being able to perform functions with the DEKA Arm that could not be performed with their own prosthesis. Resnik and Borgia (2014) reported that about 80% of patients said they would want to or might want to receive the device.

The developer received FDA clearance for the prosthetic arm in June 2014 but has not found a manufacturing partner for commercial distribution. Thus, the prosthesis is not yet commercially available. The developer has stated that it will manufacture the DEKA Arm if a partner is not found, but no timeline has been given. Cost is unclear but reportedly will be tens of thousands of dollars. Prosthetic arms are covered under Medicare Part B as durable medical equipment; coverage from private third-party payers is restricted to medically necessary uses.

- **Key Expert Comments:** A significant unmet need exists for restoring natural arm function to patients with upper limb amputations, and this device provides functionality beyond any available prostheses, experts agreed. They thought that clinician and patient enthusiasm, likely to be high, might be tempered by high costs and complex training, potentially increasing health disparities because of unequal access. Experts suggested that its overall impact would be mitigated by the small population likely to use the DEKA Arm.
- **High-Impact Potential:** Moderately high

Bone Marrow Disorder Intervention

Eltrombopag (Promacta) for Treatment of Severe Aplastic Anemia

Unmet need: Severe aplastic anemia (SAA) is treated with immunosuppressive therapy (IST) in older patients or those who do not have a matched sibling donor for a hematopoietic stem cell transplant (HSCT). IST is ineffective for 20% to 40% of patients, and about one-third of patients who do respond experience a relapse.[1,2] An unmet need exists for treatments for patients with SAA who have an insufficient response to IST. Eltrombopag (Promacta®) is a thrombopoietin receptor agonist intended to stimulate production of blood cells that was recently approved by the U.S. Food and Drug Administration (FDA) for treating SAA in patients who have had an insufficient response to IST.[3]

Intervention: Eltrombopag is a thrombopoietin-receptor agonist that increases production of all types of blood cells by inducing proliferation and differentiation of bone marrow stem cells.[3] According to the manufacturer's labeling, eltrombopag is administered at an initial dose of 50 mg once daily. The dose may be adjusted every 2 weeks to achieve a target platelet count of 50×10^9/L or more. The maximum dose is 150 mg daily. The medication comes in 12.5, 25, 50, 75, and 100 mg tablets or in an oral suspension formulation of 25 mg.

Patients who achieve a trilineage response (i.e., red blood cells, neutrophils, and platelets) may be tapered off of eltrombopag as long as blood counts remain sufficient.[4]

According to the manufacturer's labeling, eltrombopag may cause hepatic decompensation (typically in patients being treated for thrombocytopenia associated with hepatitis C virus infection), liver enzyme elevation, thrombotic or thromboembolic events, or cataracts. Clinicians should monitor liver function and ocular health during therapy. Common adverse events reported in patients with SAA treated with eltrombopag include nausea, fatigue, cough, diarrhea, and headache.[4] In a phase II clinical trial, 8 of 43 patients had new cytogenetic abnormalities seen in bone marrow aspirates, including 5 with chromosome loss or partial deletion of chromosome 7.[5]

Clinical trials: In a phase II trial (n=43), patients with an insufficient response to IST and a low platelet count were treated with eltrombopag and monitored for clinically significant changes in blood counts and transfusion dependence. Desmond and colleagues (2014) reported that 40% of patients had trilineage or bilineage responses at 3–4 months. In an extension study, 5 of these patients were able to discontinue treatment and maintain stable blood counts for an average of 13 months without eltrombopag.[5] Phase II and III trials are ongoing.

Manufacturer and regulatory status: GlaxoSmithKline, plc (GSK; Middlesex, UK), developed eltrombopag under the trade name Promacta in the United States. In August 2014, FDA approved eltrombopag for treating "patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy."[4] The drug had received FDA's breakthrough therapy designation in January 2014, and the supplemental new drug application for this indication had been granted priority review in April 2014. Earlier, FDA had approved eltrombopag for treating thrombocytopenia due to chronic immune thrombocytopenia or hepatitis C virus infection.[3] GSK is also studying eltrombopag for treating moderate aplastic anemia and as first-line therapy for SAA in combination with IST.[6,7]

Cost: As of November 2015, eltrombopag reportedly cost about $70,000 per patient per year, depending on the pharmacy.[8] The U.S. Centers for Medicare & Medicaid Services (CMS) has no national coverage determination for eltrombopag. Thus, coverage is left to the discretion of local Medicare Part D prescription drug plans whether to include the drug on their formularies. To identify coverage policies, ECRI Institute routinely searches 11 representative, private, third-party payers that publish their coverage policies and formularies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners,

Humana, Medica, Regence, United Healthcare, Wellmark).[9-17] The drug is listed in these payer formularies as a specialty pharmaceutical for treating SAA, and it requires prior authorization.

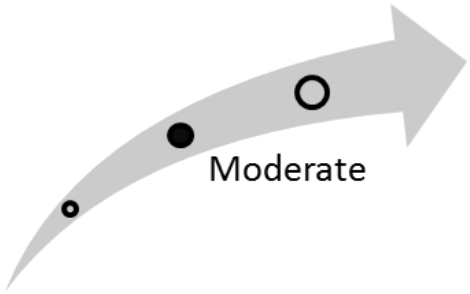
Clinical Pathway at Point of This Intervention

HSCT is the preferred treatment for children or young adults with SAA who have a matched sibling donor. If successful, HSCT is curative. Complications of HSCT include graft rejection, acute and chronic graft-versus-host disease, and infections. Medical therapy may compete with HSCT for older patients or those without a matched sibling donor, because complications of HSCT are more common in those groups. However, patients for whom HSCT is not an option are prescribed IST before eltrombopag.[1]

IST for SAA typically consists of horse antithymocyte globulin (ATG) and cyclosporine. IST is intended to inhibit the destruction of bone marrow stem cells by the immune system. Horse ATG is administered by intravenous (IV) infusion, and cyclosporine is administered as an oral solution.[1] The standard medical treatment for SAA, IST is effective in 60% to 80% of patients.[1,2] However, about one-third of responders experience a relapse. Patients may need blood transfusions if they have persistent cytopenias. Patients may develop cytogenetic abnormalities, most commonly on chromosome 7, that are associated with high-grade myelodysplasia and leukemia. These patients are likely to have disease that is refractory to IST.[1] Eltrombopag is intended for patients with an insufficient response to IST. It is also under study for use with IST as first-line therapy.[1]

Alternative ISTs are alemtuzumab and rabbit ATG, which may be tried in patients whose disease does not respond to standard IST or who experience relapse. Both options have a 30% to 40% response rate for refractory SAA.[1] Eltrombopag is expected to compete with these options.

Figure 1. Overall high-impact potential: eltrombopag (Promacta) for treatment of severe aplastic anemia



Experts commenting on this intervention agreed that alternative SAA treatments are needed for patients, who are greatly affected by this disease. Clinicians and patients will favor the easy administration and effectiveness of eltrombopag shown thus far, experts said, even if some clinicians raised concerns about use of surrogate outcomes in the clinical trials. Experts suggested that patient management may be largely simplified with eltrombopag use compared to IST or HSCT. Although the cost may be high, health disparities for some minority ethnic groups may improve if they have access to eltrombopag, experts thought. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this intervention.[18-23] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: SAA has a large disease burden, and patients need an alternative to IST and HSCT, experts agreed. The extent to which eltrombopag can improve patient health would be clearer with longer-term data, experts said; however, most thought the initial trial results showed promising improvements in blood counts and transfusion independence. One clinical expert noted that hematopoiesis continued in some patients even after stopping the drug, which is a boon to patient health.[22]

Acceptance and adoption: Clinicians and patient prefer oral drugs over more invasive (i.e., HSCT) or resource-intensive (i.e., IST infusion) treatment options, experts agreed. Experts were split over the severity of eltrombopag's side effect profile, noting that more severe side effects might dampen patient acceptance.[19,20,22]

Health care delivery infrastructure and patient management: Health care delivery infrastructure will be little affected by eltrombopag adoption because it is an oral drug that patients take at home, experts explained. Two experts noted that patients who improve with eltrombopag may not need a HSCT or may avoid IST complications, which would significantly alter the way their disease is managed.[18,23]

The cost of eltrombopag may be burdensome for some patients but the overall system impact may be small because of the small population affected by SAA, experts commented. Clinical experts suggested that long-term cost savings may be realized if eltrombopag is effective, especially if sufficient hematopoiesis continues when patients stop taking the drug.[22,23]

Health disparities: Health disparities in SAA are related to economic means and disproportionate prevalence in some age and ethnic groups (e.g., eastern Asian), experts noted. The high cost of eltrombopag is likely to exacerbate health disparities among patients who do not have insurance coverage or cannot afford the drug, experts agreed. This may be more common among young people, who are also more likely to receive a diagnosis of SAA than older adults. A clinical expert thought that minority ethnic groups that are underrepresented in HSCT donor pools may benefit from access to an oral medication and see reduced health disparities compared with groups that are more likely to find a donor match.[23]

Central Nervous System Disorder Intervention

Daclizumab (Zinbryta) for Treatment of Relapsing-Remitting Multiple Sclerosis

Unmet need: Clinical specialists rank multiple sclerosis (MS) as the most common central nervous system autoimmune disease among adults.[24] Although patient diagnoses can vary over the course of the disorder, the initial diagnosis in more than 80% of patients are relapsing forms of MS, marked by alternating periods of worsening neurologic function and full or partial recovery.[25] Of the four recognized forms of MS, three are relapsing—progressive-relapsing, relapsing-remitting, and secondary-progressive. As relapsing MS progresses, damage to myelin and nerves causes declines in cognitive, motor, sensory, and sexual function. Patients' disease-free periods differ in length, but are consistently followed by relapse intervals with equivalent or exacerbated symptoms.[26] FDA has approved multiple noncurative, injectable and oral medications for first- and second-line MS therapy.[27] However, these drugs are not universally effective, and some patients cannot tolerate them.[24,27,28] Additional treatment options are needed for managing symptoms in patients with relapsing MS.

Intervention: Daclizumab is a humanized, IgG1 subtype, monoclonal antibody that binds to alpha subunit (CD25) of T-cell interleukin-2 (IL-2) receptors.[29,30] Daclizumab binding competitively inhibits normal IL-2 signaling, preventing antigen-specific T-cell activation hypothesized to underlie autoimmune disease pathologies, including that of MS.[30-32] Researchers also propose that daclizumab may effectively treat relapsing forms of MS by expanding and activating $CD56^{bright}$ NK (natural killer) cells, which can travel into the space under the myelin sheath to kill activated T cells, and by mediating innate lymphoid cell development, a process thought to elicit autoimmune disease states when dysregulated.[33]

Daclizumab has been investigated as both an intravenously and subcutaneously injected therapy for relapsing forms of MS. However, in late-phase clinical trials and its proposed formulation for the market, daclizumab is composed as a high-yield process formulation, injected monthly at a dose of 150 or 300 mg.[34,35] The high-yield process formulation of the drug has a different glycosylation profile that is purported to result in decreased antibody-dependent cellular cytotoxicity.[34]

Clinical trials: Two large completed phase III trials, the SELECT and DECIDE studies, examined daclizumab's efficacy and safety for treating relapsing forms of MS. In the SELECT study, adult patients (n=621) were randomly assigned in a 1:1:1 ratio to receive monthly placebo, 150 mg daclizumab, or 300 mg daclizumab, with more than 92% of patients in each group completing the trial.[34] After 52 treatment weeks, investigators observed that annualized relapse rates (ARR) were lower for patients administered daclizumab (150 mg daclizumab ARR, 0.21 [54% reduction]; 95% confidence interval [CI], 0.16 to 0.29; $p<0.0001$; 300 mg daclizumab ARR, 0.23 [50% reduction]; 95% CI, 0.17 to 0.31; $p<0.0001$) than for patients receiving placebo (ARR, 0.46; 95% CI, 0.37 to 0.57). Statistically, higher numbers of patients given daclizumab were relapse-free than patients receiving placebo after the same treatment period (daclizumab 150 mg, 81% relapse-free; daclizumab 300 mg, 80% relapse-free; placebo, 64% relapse-free; $p<0.0003$). Treatment-related adverse event rates were comparable across study groups.[34]

The DECIDE study (n=1,841) compared 150 mg monthly daclizumab injections to weekly intramuscularly injected interferon beta-1a for treating relapsing MS.[36] Measured after 144 treatment weeks, patients receiving daclizumab exhibited a 45% reduction in ARR when compared to a patient group given interferon beta-1a ($p<0.0001$).[37] Neurologically, daclizumab therapy was also associated with fewer new or newly enlarging T2-hyperintense lesions after 96 weeks (54% comparative reduction; $p<0.0001$). Also, after 96 weeks, 73% of patients given daclizumab were relapse-free, compared with 59% of patients administered interferon beta-1a (nominal $p<0.0001$).[36]

Subcutaneous daclizumab treatment was associated with increased susceptibility to infections and skin reactions and a heightened risk for elevated liver function tests and systemic immune-mediated adverse events.[38,39] Seven patients in these trials experienced serious adverse events affecting vital organs; several other patients withdrew from a trial or discontinued treatment because they could not tolerate the drug or had emerging clinical symptoms.[38,39] Previously, intravenously infused daclizumab was also associated with headache, hypertension, impaired wound healing, tremor, and vomiting;[40] ongoing extension studies are examining subcutaneously injected daclizumab's long-term safety and efficacy.

Manufacturer and regulatory status: AbbVie (North Chicago, IL) and Biogen (Cambridge, MA) are partners and cosponsors for American clinical trials investigating daclizumab for treating relapsing forms of MS. In April 2015, the companies announced that FDA had accepted their biologics license application for high-yield process daclizumab, branded as Zinbryta™, supported by data from the DECIDE and SELECT trials.[41]

FDA first approved daclizumab in 1997, branded as Zenapax®, for use in immunosuppressive regimens to prevent organ transplant rejection.[42] However, daclizumab's former manufacturer, F. Hoffman-La Roche, Ltd. (Basel, Switzerland), withdrew the drug from major commercial markets in 2009 because of "diminishing market demand."[43]

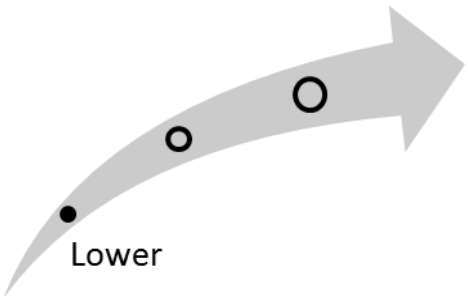
Diffusion and costs: FDA has not approved daclizumab for treating relapsing MS and to date, the drug has not diffused beyond clinical trials for this indication. Neither AbbVie nor Biogen have announced potential per-dose or per-patient retail pricing for daclizumab, although industry analysts project that the drug will competitively align with available second-line MS pharmacotherapies.

Clinical Pathway at Point of This Intervention

Relapsing forms of MS are characterized by exacerbations (also known as attacks, flareups, or relapses), episodes of inflammation and scarring that cause demyelination of neurons and broadly affect nerve signaling and functioning. Symptoms vary and can include cognitive impairment, dizziness, general fatigue, pain, peripheral numbness or weakness, slurred speech, tremor or unsteady gait, and visual deficits.[44,45] The severity and location of neural damage at symptom onset determine which symptoms manifest.[46]

Three of the four recognized forms of MS are relapsing.[47,48] Available MS medications attempt to reduce inflammation frequency and symptom severity to delay disease progression and minimize corresponding functional limitations.[44] No cure exists, and approved medications have inconsistent efficacy across patients.[46] As a potential second-line MS medication, daclizumab could compete with approved oral and injectable pharmacotherapies such as dimethyl fumarate (Tecfidera®), natalizumab (Tysabri®), and fingolimod (Gilenya®).[28,49-51]

Figure 2. Overall high-impact potential: daclizumab (Zinbryta) for treatment of relapsing-remitting multiple sclerosis



Experts acknowledged a sizable need for additional therapies for relapsing forms of MS and thought that daclizumab could address this need. Experts anticipated that patients with poor responses to other approved drugs would widely accept daclizumab because it is injected as are other MS treatments. However, experts also anticipated that factors including daclizumab's unresolved safety profile and other available MS pharmacotherapy options might limit the drug's overall impact for treating MS, although it could be important to patients whose disease does not respond to other therapies. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided feedback on this intervention.[52-57] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: All consulted experts agreed that MS significantly affects patient and health care resources and that an unmet need exists for new, effective treatments for patients with inadequate responses to available drugs. However, the MS therapy market competition and lack of universal efficacy led most experts to think that this drug's potential to broadly improve patient health outcomes for all MS patients was somewhat limited.

Acceptance and adoption: Experts anticipated that daclizumab would be widely accepted among patients unresponsive to approved MS drugs. Similarly, clinicians would welcome this drug as a new option after other options failed, with two clinical experts specifically noting that daclizumab would be adopted as a second- or third-line therapy.[52,57]

Health care delivery infrastructure and patient management: Experts acknowledged that if approved, daclizumab would be one of several injectable MS treatments. As such, experts did not foresee daclizumab substantially affecting health care delivery infrastructure or patient management.

Health disparities: In general, experts thought that daclizumab would have little to no impact on health disparities. Several experts remarked that available third-party payer coverage and manufacturer copayment assistance programs mitigate the high cost of MS drugs for patients; experts predicted that daclizumab costs would be similarly managed.[52,54,57] However, one research expert concluded that the anticipated cost of daclizumab might increase health disparities for certain economically disadvantaged patients.[55]

Genetic Disorder Interventions

Asfotase Alfa (Strensiq) for Treatment of Hypophosphatasia in Infants and Children

Unmet need: Hypophosphatasia (HPP) is a rare metabolic disorder that causes decreased bone mineralization—a phenomenon known clinically as hypomineralization and colloquially as "soft bones"—and bone instability in pediatric and adult patients.[58,59] The disorder results from any of 200 or more possible mutations to the alkaline phosphatase, liver/bone/kidney (*ALPL*) gene.[59,60] *ALPL* normally encodes alkaline phosphatase, an enzyme involved in mineralization. Mutations to *ALPL* lead to alkaline phosphatase deficiencies (also known as tissue nonspecific alkaline phosphatase, or TNSALP, deficiencies), which allow atypical accumulation of compounds, including inorganic pyrophosphate, characteristic of HPP.[61] Although milder, autosomal dominant forms of HPP may manifest only as rickets and premature loss of primary ("baby") teeth or early loss of adult teeth, autosomal recessive inherited HPP cases are more severe and can result in cranial hypomineralization, hypercalcemia or hypercalcinuria (elevated calcium levels in blood or urine), respiratory compromise, and pneumonia.[62] In the most extreme cases of infantile HPP, hypomineralization leads to caput membranaceum (incomplete ossification of skull bones), malformed limbs during prenatal development and at birth, and stillbirth or rapid death caused by respiratory failure.[58,63] Perinatal-, infant-, and juvenile-onset HPP have estimated mortality rates as high as 50%.[58,62]

Asfotase alfa was developed to address this need. Before its recent approval, recommended HPP standard of care was initial treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), possibly followed by surgical procedures to address severe HPP symptoms.[64,65]

Intervention: Asfotase alfa is a first-in-class enzyme replacement therapy (ERT) developed to treat HPP. The drug is a human recombinant fusion protein that includes the constant region of the human IgG1 Fc domain, a human TNSALP catalytic domain, and a terminal deca-aspartate peptide domain that gives the protein high affinity for bone.[66] Purportedly, this composition enables asfotase alfa to effectively and efficiently provide supplemental TNSALP to treat underlying symptoms of HPP, with limited systemic effects.

Asfotase alfa is injected subcutaneously for treating perinatal-, infant-, and juvenile-onset HPP. The recommended dosages are 2 mg/kg administered 3 times per week, or 1 mg/kg administered 6 times per week, depending on patients' injection-site tolerance. In some cases, patients may receive 3 mg/kg thrice weekly injections if they fail to respond to lower doses.[67]

Clinical trials: In clinical trials, asfotase alfa was investigated at its approved dosage, up to a maximum single-injection dose of 40 mg.[68,69]

Pivotal data were generated from phase II North American clinical trials enrolling adolescents with HPP (n=13). These patients, aged 5–13 years, were administered either thrice-weekly 2 mg/kg or twice-weekly 3 mg/kg asfotase alfa for at least 12 months; 12 of these patients received continuous asfotase alfa therapy for more than 3 years.[70] Trial investigators reported that over the treatment period, patients improved functional strength and mobility across multiple standard measures, including the following:[70]

- Bruininks-Oseretsky Test of Motor Proficiency Second Edition (BOT-2) Strength scaled score (baseline median [min, max]=4 [1, 13]; last assessment median [min, max]=15 [10, 24]; $p<0.0001$)
- Median running speed/agility scaled scores (baseline median [min, max]=3 [1, 9; equivalent to 2 standard deviations below age norms]; last assessment median [min, max]=12 [7, 19]; ($p<0.0001$)

- Shuttle run (baseline median [min, max]=21.6 seconds [12.4, 33.1]; last assessment median [min, max]=9.1 seconds [8.1, 10.6])

In a separate analysis, these patients also reported significant improvements in qualitative measures of functional ability and perceived disability (for all measures, $p<0.014$); patients' caregivers also described perceived improvements in their children's global function, mobility, and real-world task ability (for all measures, $p<0.05$).[71]

In pediatric patients aged 3 years or younger, asfotase alfa treatment has reportedly improved rickets, respiratory and motor function, and cognitive symptoms commonly associated with HPP. Patients treated with asfotase alfa also exhibited improved survival rates compared with historical controls; decreased mortality is hypothesized to be primarily driven by improved respiratory function and reduced respiratory failure events.[72] Researchers have reported sustained or additional treatment efficacy when patients are treated with asfotase alfa for up to 1 year.[72,73]

Overall, asfotase alfa has been well tolerated by patients in clinical trials, with only minimal injection-related adverse events observed. In a recently reported study that enrolled 11 patients, 3 reported severe adverse events were classified as possibly treatment-related: chronic hepatitis, conductive deafness, and craniosynostosis.[74] The latter two events were observed in the same patient, and investigators noted that both are common complications of HPP. Chronic hepatitis was observed in another patient who was concurrently treated for asthma.[74]

Ongoing phase II and II/III trials are investigating asfotase alfa's long-term efficacy and safety.[71,75]

Manufacturer and regulatory status: Asfotase alfa was developed and is manufactured by Alexion Pharmaceuticals, Inc. (Cheshire, CT), following Alexion's acquisition of the drug's original developer, Enobia Pharma Corp.[76] In October 2015, FDA approved asfotase alfa, branded as Strensiq™, for treating perinatal-, infantile- and juvenile-onset HPP.[77]

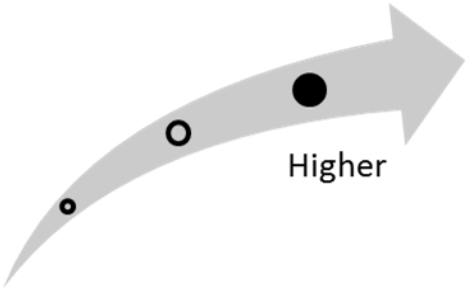
Diffusion and costs: Because of its recent approval, commercial asfotase alfa diffusion data are not available; however, fewer than 100 patients have received the drug across various clinical trials.[72,73,75] We expect Alexion to provide updated diffusion information in 2016, as larger ongoing trial readouts and quarterly sales data are reported.

After FDA approval, Alexion announced that Strensiq would be priced at about $285,000 per patient per year; this figure, while high, is lower than industry observers' speculations that projected the ERT would cost closer to $400,000 per patient per year.[78] Additionally, Alexion established a patient resource program, OneSource, that includes a financial assistance component; with this mechanism and presumed third-party payer coverage, direct patient costs will likely be much lower.[79]

Clinical Pathway at Point of This Intervention

Before asfotase alfa's approval, clinical experts recommended that pediatric patients with HPP receive initial treatment with NSAIDs to manage inflammatory symptoms.[80] Neurosurgery, osteotomy, and dental surgery are palliative options used to address abnormal bone development, fractures, and tooth loss in pediatric, adolescent, and adult patients.[64,65] In the absence of competing interventions, we believe that asfotase alfa will become the new standard of care for treating HPP.

Figure 3. Overall high-impact potential: asfotase alfa (Strensiq) for treatment of hypophosphatasia in infants and children



We received expert comments on asfotase alfa during the 3 months before the drug's approval. Experts were universally enthusiastic about the data on the drug's efficacy, safety, and potential to positively affect health outcomes in this patient population. Although some experts noted that available efficacy data were based on clinical trials with small sample sizes, they were impressed with the reported efficacy and agreed that asfotase alfa could effectively address a significant unmet need. Experts stated that the ERT's expected price could negatively affect health care disparities, but acknowledged that anticipated manufacturer and third-party payer assistance could minimize this effect. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, assessed this intervention.[81-86] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Experts unanimously agreed that severe HPP is a disorder with a significant unmet need for effective nonsurgical treatment options. Similarly, these experts also concluded that asfotase alfa ERT has high potential to positively address this need and improve patient health outcomes

Acceptance and adoption: All commenting experts remarked that asfotase alfa would be widely accepted and adopted by clinicians and eligible patients and caregivers as a treatment option for a disorder with a high mortality rate and no other disease-modifying therapeutic options.

Health care delivery infrastructure and patient management: Several experts compared asfotase alfa's anticipated impact on this parameter to that of standard palliative care, including various surgical interventions and their attendant infrastructure and patient management implications. Experts' consensus opinion was that asfotase alfa's availability would positively impact health care delivery infrastructure and patient management, both by reducing present burdens and by shifting treatment from surgery to long-term pharmacotherapy.

Health disparities: Experts acknowledged that asfotase alfa's projected cost could negatively impact health disparities, as a therapy with no immediate competitors and an anticipated price point in line with recent rare disease drugs. However, several expert comments indicated that these disparities could be mitigated by financial assistance programs and third-party coverage.[82,85,86] Overall, experts concluded that the drug would have little impact in this regard.

Conestat Alfa (Ruconest) for Treatment of Acute Hereditary Angioedema

Unmet need: Hereditary angioedema (HAE) is a life-threatening condition characterized by sudden and painful angioedema attacks, in which a patient's skin and other organs swell. It affects an estimated 6,000–10,000 individuals in the United States. Although several treatments are available, many patients experience significant side effects from them. The most effective treatment, a human C1 esterase inhibitor (C1INH, also called C1 inhibitor) concentrate from donated blood, replaces the protein that is deficient in HAE, but it is not always available.[87] The World Allergy Organization recommends that patients with HAE carry on-demand treatment for two attacks and know how to self-administer the drug.[88] An unmet need exists for a treatment with fewer side effects for acute attacks. Conestat alfa (Ruconest®) is a plasma-free, recombinant, human C1INH, recently approved for treating acute HAE attacks.[89,90]

Intervention: Conestat alfa is a recombinant human C1 esterase inhibitor (rhC1INH) for treating acute angioedema attacks in patients with HAE. It is produced in the milk of transgenic rabbits. Because it is not isolated from human blood, it does not carry a risk of transmitting human infectious agents. However, since it is derived from rabbits, patients who have a rabbit allergy cannot use the drug. The drug's manufacturer states that patients must have a negative immunoglobulin E test for rabbit allergy every year or every 10 treatments, whichever comes first.[89]

Conestat alfa is taken by IV infusion over 5 minutes. For the first dose, a clinician experienced in treating HAE supervises. Patients may be trained to recognize the onset of an acute attack and self-administer the drug. For patients who weigh less than 84 kg, the dose is 50 IU per kg. For patients who weigh 84 kg or more, the dose is 4,200 IU (2 vials). If symptoms persist, a second dose can be given, but no more than 2 doses are to be given in 24 hours, according to the manufacturer.[91] In a clinical trial, most patients reported mild to moderate treatment-emergent adverse events.[92] The most common adverse events reported were headache, nausea, and diarrhea. A serious but uncommon reported adverse event was anaphylaxis.[91-93] Although thromboembolic events have been reported with plasma-derived C1INH, none were reported with rhC1INH. Additionally, researchers did not identify any risk of deep vein thrombosis.[94]

Clinical trials: One observational study is ongoing.[95] In a phase III RCT, authors reported the following:[93]

> Median (95% confidence interval) time to beginning of symptom relief at the primary attack location was 90 minutes (61-150) in rhC1INH-treated patients vs 152 minutes (93, not estimable) in placebo-treated patients (p =.031) based on the [Treatment Effect Questionnaire] and 75 minutes (60-105) vs 303 minutes (81-720, P =.003) based on a [visual analog scale] decrease of at least 20 mm. Median time to minimal symptoms was 303 minutes (240-720) in rhC1INH-treated patients vs 483 minutes (300-1,440) in placebo-treated patients based on the [Treatment Effect Questionnaire] (p =.078) and 240 minutes (177-270) vs 362 minutes (240, not estimable; p =.005), based on an overall [visual analog scale] less than 20 mm.

Reports from other studies state similar median times to onset of symptom relief and to minimal symptoms.[92,96,97] Moldovan and coauthors (2012) reported that 87% of patients with acute HAE achieved symptom relief within 4 hours.[98]

Manufacturer and regulatory status: Pharming Group NV (Leiden, the Netherlands) and Santarus, Inc., a wholly owned subsidiary of Valeant Pharmaceuticals International, Inc. (Laval, Canada), jointly developed conestat alfa under the trade name Ruconest.[89] In July 2014, FDA approved conestat alfa ERT for acute angioedema attacks in adults and adolescents with HAE.[90]

Before the approval, FDA had granted conestat alfa orphan drug status. Conestat alfa is contraindicated in patients who have a rabbit allergy or who have a history of immediate, life-threatening hypersensitivity reactions to C1INH preparations.[91]

The manufacturers are also studying conestat alfa in phase II trials for preventing acute attacks. Patients administer the drug once or twice weekly for prophylaxis.[99] Conestat alfa has not been proved effective for a potentially fatal manifestation, laryngeal angioedema.[99]

Diffusion and cost: The wholesale acquisition cost of conestat alfa is $9,500 for 2 vials, the maximum single dose.[100] Dosing is weight dependent.[91] For comparison, the cost of one kit of a human plasma-derived C1INH concentrate, Berinert®, is reportedly about $2,500 per kit.[101] A financial analyst reported results of a survey of physicians with direct experience prescribing conestat alfa.The physicians reported that about 10% of their patients are using conestat alfa; its IV administration was cited as a barrier to diffusion.[102]

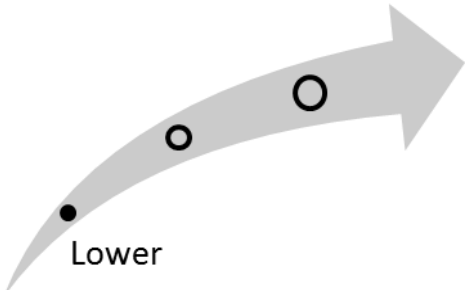
CMS has no national coverage determination for conestat alfa. Thus, coverage decisions are left to the discretion of local Medicare Part D prescription drug plans whether to include the drug on their formularies. To identify coverage policies, ECRI Institute routinely searches 11 representative, private, third-party payers that publish their coverage policies online. Our search found eight payers with policies that outline coverage criteria for conestat alfa.[103-109] Blue Cross/Blue Shield Massachusetts denies coverage.[110]

Clinical Pathway at Point of This Intervention

Epinephrine is used to treat HAE in life-threatening reactions. The most efficacious treatment is a plasma-derived C1INH concentrate such as Berinert,[111] but supply can fluctuate.[87] Berinert is self-administered during acute angioedema and competes with conestat alfa.[112] Berinert may cause significant adverse events including subsequent angioedema attacks, pain, muscle spasms, diarrhea, and vomiting.[112] Frozen plasma that contains C1INH will help during an episode as well. It is available to patients who seek hospital care for acute attacks; in rare cases, it may worsen swelling.[87,111] During an attack, treatment involves pain relief and IV fluid administration.[111]

Ecallantide (Kalbitor®) and icatibant (Firazyr®) are available for treating acute attacks by subcutaneous injection but may be less effective than C1INH concentrates. Although the drugs have different targets, both inhibit the effects of bradykinin, which is thought to be involved in HAE, and decrease the rate of C1INH catabolism. Ecallantide may cause anaphylaxis and cannot be self-administered.[88] Icatibant can be self-administered, but may cause injection-site reactions, fever, increased liver enzymes, and rash.[112] Both drugs compete with conestat alfa.

Figure 4. Overall high-impact potential: conestat alfa (Ruconest) for treatment of acute hereditary angioedema



Experts commenting on this intervention agreed that conestat alfa may improve patient health, although they differed over how important the unmet need is. Clinical experts stressed that supply issues with alternative treatments make this intervention more crucial in emergency scenarios.

Conestat alfa may be readily accepted by clinicians and patients because of its good safety profile, easy administration, and effectiveness, experts commented. Health care infrastructure, patient management, and health disparities are not likely to be greatly affected by use of conestat alfa, experts said. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this intervention.[113-118] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Although experts were split over the importance of the unmet need, two clinical experts noted a need for emergency treatment for HAE because of supply issues with plasma-derived C1INH concentrate and lack of response in some patients for other options.[117,118] Compared with alternative treatments, conestat alfa may improve patient health, experts agreed, because it may decrease time to onset of symptom relief, have fewer side effects, and be administered more easily at home.

Acceptance and adoption: Clinicians and patients are likely to accept conestat alfa because of its low side-effect profile, ease of administration, and effectiveness, experts said. Two experts suggested that supply issues with alternatives may increase adoption of conestat alfa.[115,117] If comparative studies were performed that demonstrated effectiveness compared with Berinert, adoption could increase, two other experts noted.[115,118]

Health care delivery infrastructure and patient management: Because conestat alfa is self-administered, experts expect little or no impact on health care delivery infrastructure. Patient management may be mildly disrupted because patients must be trained on administering the drug and be observed for allergic reactions for the first dose, experts said.[113,118] Care may also be shifted to the home setting if conestat alfa effectively prevents patients from needing emergency care, experts said; however, any reduction in hospital resource use will be limited because of the small patient population.

Costs for patients and third-party payers may increase with use of conestat alfa, because of its high list price, experts said. However, additional treatment costs may be offset if conestat alfa use reduces hospital visits, experts speculated.

Health disparities: Impact on health disparities may be limited, with most impact due to cost of the new drug, experts agreed.

Eliglustat Tartrate (Cerdelga) for Treatment of Gaucher's Disease Type 1

Unmet need: Gaucher's disease is caused by a hereditary deficiency of glucocerebrosidase that leads to enlarged and malfunctioning organs, skeletal disorders, and painful neurologic complications because of glucosylceramide accumulation in these tissues. About 6,000 U.S. patients are affected by the disease, although not all experience symptoms.[119] The only oral drug approved for the disorder (miglustat; Zavesca®) is not available as first-line treatment; IV ERT is approved as first-line therapy and is the standard of care.[120] Eliglustat tartrate (Cerdelga™) is the first oral therapy approved by FDA as first-line therapy.[121] It is intended to have fewer side effects than miglustat, which is known to cause diarrhea, abdominal swelling, tremor, and weight loss.

Intervention: Eliglustat tartrate reportedly partially inhibits the enzyme glucosylceramide synthase to reduce glucosylceramide production (i.e., substrate reduction).[122,123] Dosing depends on a patient's rate of CYP2D6 metabolism, determined by an approved genotype test. Patients with Gaucher's disease who are extensive or intermediate metabolizers take 84 mg, twice daily. Patients who are poor metabolizers take 84 mg, once daily. Patients who are ultra-rapid metabolizers cannot use eliglustat tartrate because they may not achieve adequate concentrations for therapeutic effect. A specific dose cannot be recommended for patients who are indeterminate metabolizers.[121]

Clinical trials: Four phase III trials are ongoing.[124-127] The ENCORE trial, which is evaluating the percentage of patients whose disease remains stable during eliglustat tartrate treatment, reported in the per-protocol population that 85% (84/99) patients who completed eliglustat treatment and 94% (44/47) of 47 patients who completed IV ERT with imiglucerase met the composite primary endpoint for noninferiority. The between-group difference was -8.8% (95% CI, -17.6 to 4.2).[128]

Another phase III trial (ENGAGE trial, n=40) is assessing improvement (i.e., reduction) in spleen size. Researchers reported that the mean spleen volume decreased by about 28% (95% CI, -33% to -23%) in the eliglustat group and increased about 2% (95% CI, -3% to 7%) in the placebo group.[129] (We rounded reported figures to the nearest whole number.)

Manufacturer and regulatory status: Genzyme Corp., a subsidiary of Sanofi (Paris, France), developed eliglustat tartrate for treating type 1 Gaucher's disease.[123] FDA approved eliglustat tartrate in August 2014 "…for the long-term treatment of adult patients with Gaucher['s] disease type 1 who are CYP2D6 extensive metabolizers (EM), intermediate metabolizer (IM), or poor metabolizers (PM) as detected by an FDA-cleared test."[121] Eliglustat tartrate is available through specialty pharmacies.[130]

As conditions of FDA approval, Genzyme must complete two postmarketing clinical trials to evaluate the effects of renal and hepatic impairment on eliglustat tartrate pharmacokinetics, to be completed in 2017. Genzyme has further committed to developing 21 and 42 mg dose strengths to accommodate dose adjustments.[121]

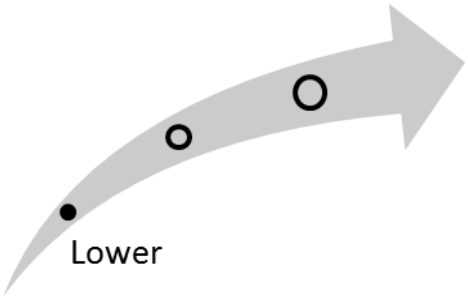
Diffusion and cost: The company reported about $17.3 million in U.S. Cerdelga net sales in the third quarter of 2015.[131] As of December 2015, eliglustat tartrate reportedly cost about $308,000 per patient per year (when taken twice daily, based on costs for 56 capsules of 84 mg each),[130] compared with $300,000 to $350,000 per patient per year for IV ERT.[132-134] Genzyme offers a copayment assistance program for U.S. patients who have commercial insurance and prescription drug coverage. The program covers 100% of out-of-pocket expenses including copayments, co-insurance, and deductibles up to the program maximum, regardless of financial status. Patients are ineligible if they have insurance or prescription coverage in part or in full from any State or Federal health care program (e.g., Medicare, Medicaid, Veterans Affairs).[135]

Our searches of 11 representative, private, third-party payers that publish their policies online found 7 formularies listing eliglustat tartrate;[11,13,16,136-139] 3 payers have policies that may cover eliglustat tartrate with prior approval.[140-142]

Clinical Pathway at Point of This Intervention

Approaches to treating Gaucher's disease have taken two routes: ERT or drugs that inhibit upstream components of the glucosylceramide biosynthetic pathway (i.e., substrate reduction). ERT (e.g., imiglucerase, taliglucerase alfa) is the standard first-line treatment.[143] ERT is expensive and requires lifelong IV infusions every 2–3 weeks.[144] A temporary break from ERT because of personal issues or lifestyle changes can lead to disease progression. Eliglustat tartrate competes with ERT as first-line treatment. Another oral drug used for substrate reduction, miglustat, is approved for use only by patients who are ineligible for ERT.[145] Miglustat frequently causes side effects, such as diarrhea, abdominal swelling, tremor, and weight loss that affect patient acceptance. Further, clinical improvements with miglustat are reportedly less effective and slower than with ERT.[143]

Figure 5. Overall high-impact potential: eliglustat tartrate (Cerdelga) for treatment of Gaucher's disease type 1



Overall, experts commenting on this intervention suggested that patients need a more convenient treatment for Gaucher's disease, and eliglustat tartrate might increase patient adherence to treatment recommendations. In doing so, they thought, it could lead to improved health outcomes and quality of life but agreed that additional data are necessary. Experts anticipated modest adoption because the drug is taken orally. However, they also noted that patients have several treatment options. Experts suggested that this oral drug could simplify patient management by shifting the care setting to home care, although the small patient population will limit its impact on infusion centers. Experts noted that the drug's impact potential is contingent on eliglustat tartrate being proved as effective as or more effective than the standard of care. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this intervention.[146-151] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: An unmet need exists for a treatment with easier administration than IV ERT, experts agreed. An oral drug might improve outcomes by increasing patient compliance with treatment and improving quality of life, experts also agreed. A clinical expert called for more trials comparing eliglustat tartrate to standard treatment and studying its long-term efficacy.[147]

Acceptance and adoption: Clinicians are likely to welcome an additional option for patients, especially an oral drug, but may need additional safety and efficacy data before fully embracing eliglustat tartrate, experts noted. Patients are likely to prefer oral administration over IV ERT, experts concurred. A health systems expert said, "This will simplify patient care in the home and be welcomed by patients and their families."[151]

Health care delivery infrastructure and patient management: Health care delivery infrastructure is unlikely to experience a large disruption, experts agreed. Although infusion centers that serve patients with Gaucher's disease might see a decrease in demand, the patient population is small enough that the change would not be disruptive, experts explained. Patient management may be simplified because patients will not need to visit an infusion center for regular treatment, most experts speculated. Experts agreed eliglustat tartrate is expensive and is a lifelong cost; it is likely to be covered by third-party payers, although some patients may face high copayments, experts said.

Health disparities: The high cost of the drug might prevent some patients from accessing it, especially those who are insured through State or Federal agencies (because they are ineligible for the manufacturer's assistance program) or those without insurance, a research expert noted.[146] Conversely, a health systems expert thought that competition for market share between eliglustat tartrate and IV ERT may decrease costs.[151] Ease of administration might improve access for patients who find it difficult to get IV infusions once every 2–3 weeks, one expert with a research perspective thought.[148] Two experts pointed out that populations that are disproportionately affected by Gaucher's disease (e.g., Ashkenazi Jews) would benefit from this treatment option.[149,150]

Elosulfase Alfa (Vimizim) for Treatment of Morquio A Syndrome

Unmet need: Mucopolysaccharidosis type IV A, commonly known as Morquio A syndrome or MPS IV, is a rare, autosomal recessive inherited metabolic disorder resulting from deficiencies in the *N*-acetylgalactosamine-6-sulfatase enzyme. Normally, *N*-acetylgalactosamine-6-sulfatase degrades glycosaminoglycans such as keratan sulfate (KS).[152,153] Mutations to the *N*-acetylgalactosamine-6-sulfate sulfatase (*GALNS*) gene lead to *N*-acetylgalactosamine-6-sulfatase deficiencies and subsequent abnormal KS accumulation in bone, cornea, synovial fluid, connective tissue, tendons, and urine.[153-155] Excess KS can cause potentially fatal cardiovascular, locomotor, postural, and sensory symptoms such as conductive or sensorineural hearing loss, hydrocephalus, spinal cord compression, and systemic skeletal dysplasia (dwarfism).[154,156]

Before elosulfase alfa's approval, standard of care for Morquio A syndrome was palliative treatment only, including orthopedic surgeries and assistive devices to address sensory and motor symptoms.[154,157,158] Disease progression may dictate multiple surgical interventions, especially when patients' respiratory function declines significantly. Pediatric patients with severe signs and symptoms may survive only to late adolescence. A need exists for treatments that target underlying causes of Morquio A syndrome and improve or relieve the disorder's most incapacitating symptoms.

Intervention: Elosulfase alfa is a purified synthetic human form of *N*-acetylgalactosamine-6-sulfatase, composed to mediate cellular uptake to lysosomes and hydrolyze sulfate from nonreducing ends of glycosaminoglycans.[159,160] This ERT is intended to address *GALNS* deficiencies and stimulate catabolism of excess KS.[156,159,161] Theoretically, elosulfase alfa therapy can prevent or treat certain reversible functional symptoms of Morquio A syndrome and may also supplement traditional palliative care.

In its approved formulation, elosulfase alfa is intravenously infused in a weekly dosage of 2 mg/kg, delivered over a minimum of 3.5–4.5 hours.[159]

Clinical trials: In an ongoing phase III trial, adolescent patients with Morquio A syndrome (n=176) are administered placebo, weekly 2 mg/kg elosulfase alfa infusions, or biweekly 2 mg/kg elosulfase alfa infusions.[162] Weekly elosulfase alfa administration improved patient ambulation compared to placebo, measured on the 6-minute walk test at 24 treatment weeks (estimated mean effect, 22.5 meters; 95% CI, 4.0 to 40.9; p=0.017); however, investigators reported no significant treatment-based improvements in the 3-minute stair climb test. Weekly and biweekly elosulfase alfa treatments were also associated with normalized urine KS levels compared with placebo.[162] Infusion-related adverse events were observed in 22.4% of patients (1.3% of all infusions), but no patients discontinued treatment due to adverse events.[162] Researchers reported similar results from multiple smaller studies.[163,164]

A smaller phase II trial (n=15) published preliminary pediatric patient treatment efficacy data in 2013. In a group of patients younger than 5 years old, researchers noted that 8 patients receiving weekly 2 mg/kg elosulfase alfa infusions demonstrated statistically significantly decreased normalized urine KS levels after 26 treatment weeks. Treatment-related functional ambulatory data were not reported.[165]

In clinical trials conducted for the new drug application to FDA, elosulfase alfa administration was associated with several adverse effects, including potentially fatal anaphylactic and hypersensitivity reactions and precipitating symptoms. Elosulfase alfa treatment does not reduce patients' risk of spinal or cervical cord compression, which can be life threatening if not appropriately monitored.[166]

Researchers continue to investigate elosulfase alfa's treatment efficacy and adverse event profiles in American and international studies.[167-169]

Manufacturer and regulatory status: BioMarin Pharmaceutical, Inc. (San Rafael, CA), manufacturers elosulfase alfa, branded in all markets as Vimizim™.[159] FDA approved the drug in February 2014 as the first medication for treating Morquio A syndrome; to date, no competing pharmacotherapies have FDA approval.[170]

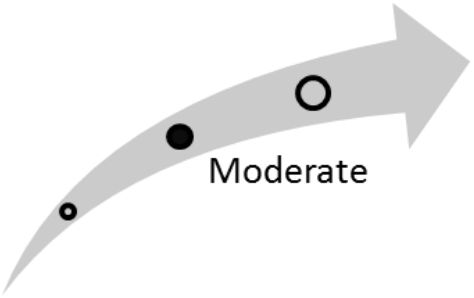
Diffusion and costs: U.S.-specific market data are unavailable, but BioMarin announced that third-quarter 2015 Vimizim sales from 32 countries totaled $65.1 million, with full-year worldwide, projected sales of $220 to $235 million. These figures represent continued diffusion, with third-quarter sales increased 158% and 9-month sales up 320% year-over-year from 2014 to 2015.[171] More than 1,700 patients are receiving Vimizim, and the company estimates a total market of 3,000 patients worldwide, although it did not disclose country-by-country figures.[172]

BioMarin initially priced elosulfase alfa at $1,069 per 5 mg, with estimated annual per-patient treatment costs of $380,000, assuming a pediatric patient weighing about 22.5 kg.[173] As a bodyweight-dependent medication, costs vary among patients, mainly based on age.[159]

Clinical Pathway at Point of This Intervention

Palliative treatments, including surgeries to relieve associated cardiovascular, respiratory, and sensory symptoms, are the standard of care for Morquio A syndrome.[158,174] Upper cervical spinal fusion is among the most common surgical procedures for this disorder, often performed during childhood to prevent spinal cord compression due to subluxation of the first cervical vertebra on the second.[156,174] Elosulfase alfa is the only ERT for treating Morquio A syndrome and is also the only FDA-approved medication for this indication. As a noncurative medication for treating Morquio A syndrome, elosulfase alfa can be used, in complement with other interventions, to improve patients' ambulation.[166]

Figure 6. Overall high-impact potential: elosulfase alfa (Vimizim) for treatment of Morquio A syndrome



Because elosulfase alfa is the only approved medication for treating Morquio A syndrome, experts reasoned that it could address an unmet need for some patients. But experts also noted that available clinical trial data did not adequately support the drug's broader treatment efficacy. Additionally, experts thought that elosulfase alfa's high retail price and potentially limited third-party payer coverage could temper its diffusion. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered comments on this intervention.[175-181] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: All experts agreed that elosulfase alfa has significant potential to address an unmet need. However, experts noted the drug's limited clinical efficacy and safety profile in concluding that elosulfase alfa might have comparably modest potential to improve patient health outcomes.[176,177,181]

Acceptance and adoption: Consensus expert opinion held that, as the first approved nonsurgical intervention for Morquio A syndrome, elosulfase alfa would continue to be widely adopted by clinicians and patients.

Health care delivery infrastructure and patient management: Overall, experts anticipated that elosulfase alfa use would minimally impact health care delivery infrastructure and patient management, despite requiring a shift from palliative care standards to regular outpatient infusion therapy. Two experts thought that elosulfase alfa–related patient health outcome improvements would actually reduce patient management burdens, and they anticipated that continued elosulfase alfa use would better reveal these potential patterns.[178,180] However, one expert with a research background contrastingly foresaw further elosulfase alfa diffusion increasing clinical staff requirements and subsequent patient management resource use.[176]

Health disparities: Most experts stated that elosulfase alfa would have little effect on health disparities. Two experts, however, noted that elosulfase alfa's pricing could increase health disparities for eligible economically disadvantaged patients.[176,181]

Exon-Skipping Therapies (Drisapersen, Eteplirsen) for Treatment of Duchenne Muscular Dystrophy

Unmet need: Duchenne muscular dystrophy (DMD) is a rare, X-linked recessive disorder caused by mutations in the dystrophin gene. As an X-linked disorder, DMD primarily affects males.[182,183] Normally, the dystrophin gene encodes the dystrophin protein, which is important for muscle tissue strength. Dystrophin gene mutations result in a lack of functional dystrophin protein, compromising muscle cell structural integrity and heightening these cells' susceptibility to damage.[183] These muscle deficiencies result in potentially fatal symptoms including heart defects, muscle weakness, and motor-skill and respiratory-function deficits.[184,185]

DMD symptoms are commonly observed by age 6 and may be apparent during infancy.[182,186] Standard treatment is palliative, concentrating on managing patients' most prominent symptoms using assistive devices and various medications.[182,183] Unfortunately, DMD symptoms are often fatal by age 40.[183,187] An unmet need exists for effective, potentially disease-modifying interventions that can both address patients' severe symptoms and enhance patients' quality of life.

Intervention: Drisapersen is an investigational 2′-O-methyl phosphorothioate oligonucleotide, synthesized as a single-strand RNA sequence complimentary to the 79-exon dystrophin gene.[188-190] Eteplirsen, in comparison, is an experimental phosphorodiamidate morpholino oligomer (PMO), a member of a class of synthetic molecules expressly developed to modify expression of various genes.[191] Biochemically, both drugs function as antisense oligomer therapeutics, altering the splicing activity of the dystrophin RNA transcript.[190,191]

Several dystrophin gene loci are susceptible to mutations resulting in malfunctioning dystrophin genes and subsequent dystrophy disorders. Drisapersen and eteplirsen are intended to treat patients with DMD caused by dystrophin exon 51 mutations.[189,190] These two drugs purportedly induce skipping of this defective exon, facilitating production of functioning dystrophin protein, addressing an underlying biochemical cause of severe DMD symptoms and hypothetically delaying disease progression.[188,192] Experts estimate that about 13% of all adolescent male patients with DMD have exon 51-associated dystrophin gene mutations amenable to drisapersen or eteplirsen therapies.[193]

In clinical trials, drisapersen has been administered in weekly injectable formulations at doses up to 9 mg/kg; the drug is under regulatory review as a subcutaneous injection.[188,192,194,195] Eteplirsen is intravenously infused; the manufacturer has tested 30 and 50 mg/kg weekly doses in clinical trials.[196,197]

Clinical trials: The DEMAND trial series is the largest drisapersen efficacy study to date. It enrolled adolescent male DMD patients aged 5 years or older (n=186).[198,199] Patients were randomly assigned to receive placebo, 3 mg/kg drisapersen weekly, 6 mg/kg drisapersen weekly, or alternating weekly and biweekly 3 mg/kg drisapersen cycles with a washout period.[198] Investigators reported "clinically significant" differences in ambulation between patients receiving drisapersen and those receiving placebo after 48 treatment weeks;[198] assays also demonstrated that patients administered drisapersen had higher systemic levels of functional dystrophin protein.[200] Subsequent analyses of these patients' data, however, showed no statistically significant treatment-related improvement in 6-minute walk test performance, a standard measure of patient ambulation.[199]

Reported safety analyses from phase II and III trials note that drisapersen was relatively well tolerated. However, potentially severe treatment-related adverse events, including hematuria, myocarditis, and renal events, were observed in patients administered 6 mg/kg drisaspersen.[199]

Eteplirsen's focal clinical trial has continuously studied a small cohort of adolescent male patients (n=12) for more than 3 years. In this ongoing study, patients receive either 30 or 50 mg/kg eteplirsen, intravenously infused weekly; investigators regularly monitor ambulation and respiratory measures.[201,202] The drug's efficacy appears inconsistent when observed at various manufacturer-

reported time points. Although eteplirsen treatment was associated with delayed ambulatory declines and improved stability of respiratory function at 24 and 120 treatment weeks,[202,203] after 168 weeks, ambulatory function in patients receiving eteplirsen had begun to decline at a rate comparable to that observed in untreated patients.[201] Similarly, analysis of long-term respiratory measures demonstrated limited and inconsistent benefit for sustained eteplirsen treatment compared with untreated patients with DMD across measured time points.[201,203,204] Eteplirsen is, however, well tolerated in clinical trials, with no serious adverse events observed.[202] A phase II trial and an open-label phase III trial (PROMOVI) are also recruiting patients to confirm these findings across 96-week treatment cycles.[205]

Manufacturer and regulatory status: Drisapersen was originally manufactured and developed by Prosensa Therapeutics (Leiden, the Netherlands). During drisapersen's development, FDA granted breakthrough therapy, fast-track, and orphan drug statuses.[193] As Prosensa began filing a rolling new drug application (NDA) for drisapersen in October 2014, the company was acquired by BioMarin Pharmaceutical, which completed the NDA submission in April 2015.[206,207]

FDA set a decision date of December 27, 2015, for drisapersen, branded as Kyndrisa™.[208] Members of an FDA advisory panel that met in November 2015 reviewed drisapersen relatively unfavorably, noting issues with the drug's available efficacy and safety data.[208-210] We note, though, that panel decisions are not binding on FDA's final decision.

Sarepta Therapeutics, Inc. (Cambridge, MA; formerly AVI BioPharma, Bothell, WA), is developing eteplirsen for treating DMD. In 2007, FDA granted fast-track and orphan drug statuses to eteplirsen for this indication. Sarepta initially announced intentions to pursue early FDA approval for eteplirsen in fall 2014, but delayed those plans after meetings between company executives and FDA regulators.[211] Sarepta's rolling NDA was completed in 2015 with an announced FDA decision date of February 26, 2016.[212]

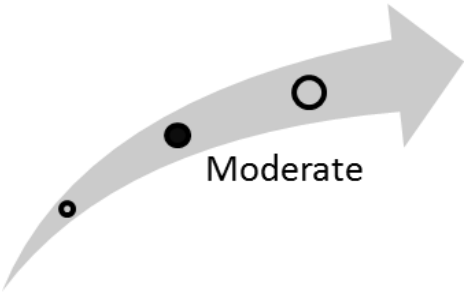
Diffusion and costs: Use of these drugs is limited to clinical trials until FDA approval. Based on reported clinical trial data, more than 300 patients have received drisapersen or eteplirsen in clinical trials, with the majority of patients administered drisapersen.[202,213]

As of December 2015, no pricing projections were available for drisapersen or eteplirsen. BioMarin has multiple recently approved, chronically administered therapies for genetic diseases with significantly lower incidence rates than DMD; these drugs are priced at up to $1,200 per patient per day.[173] Drisapersen might be priced similarly to or lower than available BioMarin products due to factors including patient demand and potential direct market competition from eteplirsen. Eteplirsen, conversely, is Sarepta's lead clinical candidate and could either be competitively priced against drisapersen or marketed at a premium because of pressure to serve as a corporate tent pole.

Clinical Pathway at Point of This Intervention

Palliative interventions are standard of care for DMD and focus on patients' most acute symptoms. Assistive orthopedics, corticosteroids, facilitated respiratory devices, and supportive cognitive therapy respectively address DMD-related functional ambulatory issues, cardiac and general muscle declines, deteriorating respiratory function, and learning disabilities.[182,214,215] Exon-skipping therapies may be prescribed before or as an adjunct to palliative care, in an attempt slow progression and maintain limited functional independence.

Figure 7. Overall high-impact potential: exon-skipping therapies (eteplirsen and drisapersen) for treatment of Duchenne muscular dystrophy



Consulted experts concurred that a significant unmet need exists for effective, nonpalliative therapies for treating DMD. Despite these drugs' underwhelming clinical efficacy, most experts still agreed that exon-skipping therapies, if approved, offer valuable new options that might improve patient health outcomes. Accordingly, experts also anticipated that these two drugs would be widely accepted by patients and adopted by clinicians. Based on this input, our overall assessment is that these interventions are in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical and research backgrounds, offered perspectives on drisapersen for treating DMD,[216-221] and six experts, with similar backgrounds, commented on eteplirsen for treating the same indication.[222-227] Among consulted experts, three clinical respondents offered opinions on both interventions.[216,220,221,223,227,228] We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: All experts agreed that, with a dearth of treatment options for DMD, an important unmet need exists for novel nonpalliative therapies for this indication. Experts concluded that drisapersen and eteplirsen have solid potential to address this unmet need and improve patient health outcomes, at least among an eligible patient subset. Several experts, however, thought that the limited patient pool also constrains the two drugs' potential impact.[216,217,227]

Acceptance and adoption: Experts universally stated that both drugs would be widely accepted and adopted, with clinician and patient support driven by a lack of competing nonpalliative DMD treatments, regardless of any concerns surrounding treatment efficacy.

Health care delivery infrastructure and patient management: Given the significant resource and patient management demands required to serve patients with DMD, most commenting experts considered drisapersen and eteplirsen to have minimal potential impact in these domains. However, one research expert evaluating drisapersen stated that if the drug were to be widely used long-term, it could potentially lead to significant disruptions in patient management compared with present standards.[220]

Health disparities: Experts opinions were split on exon-skipping therapies' potential health disparity impact. Although multiple experts predicted no or minimal impact, others commented that drisapersen and eteplirsen could moderately or significantly intensify health disparities, primarily based on the drugs' high anticipated costs.[217,218,222,224]

Idebenone (Raxone/Catena) for Treatment of Duchenne Muscular Dystrophy

Unmet need: In addition to ambulatory symptoms, DMD is commonly marked by progressively declining respiratory function.[184] Respiratory issues are fatal in nearly 75% of DMD patients.[183,187] Palliative interventions are standard for treating DMD but have limited efficacy, particularly among older patients.[182] An unmet need exists for effective therapies that address respiratory dysfunction and delay or halt respiratory declines, improving patients' quality of life and theoretically reducing respiratory dysfunction–related morbidity, extending patients' lifespans.

Intervention: Idebenone is being developed to address the respiratory symptoms of DMD. It is a short-chain benzoquinone with structural similarity to coenzyme Q_{10} but with significantly higher therapeutic potential due to its strong antioxidant and cytoprotective properties.[229,230] Researchers have linked DMD to excessive, mitochondrial defect–driven oxidative cell damage in patients and clinical models, supporting the potential therapeutic efficacy of idebenone and similarly cytoprotective compounds.[229]

Biochemists hypothesize that idebenone acts as a transporter molecule, moving electrons directly from the cytoplasm to complex III of the mitochondrial respiratory chain.[229,231] This direct transit would bypass pathways affected by mitochondrial defects, facilitating sustained adenosine triphosphate (ATP) production and offsetting muscle-wasting symptoms frequently associated with DMD.[229,232]

Idebenone is administered as 150 mg oral tablets at dosages between 450 mg and 900 mg daily. Investigators note that all tested dosages have been well tolerated.[233,234]

Clinical trials: The international phase III DELOS trial investigated the comparative efficacy of long-term daily idebenone versus placebo across multiple measures of respiratory function in corticosteroid-free adolescent patients with DMD (n=64). The trial's primary endpoint was percentage change from baseline in predicted peak expiratory flow rate (PEFR), a respiratory measure with known decline rates associated with DMD progression.

Investigators published DELOS results in the April 2015 issue of The Lancet.[235] Overall, they reported that the percentage of predicted PEFR declined significantly (-9.01% predicted; 95% CI, -13.2 to -4.8; $p<0.001$) in the placebo group after 52 treatment weeks, while percentage of predicted PEFR did not decline significantly in patients administered idebenone over the same period (-3.05% predicted; 95% CI, -7.1 to 0.97; $p=0.134$). A between-group comparison of predicted PEFR was also statistically significant (5.96% predicted; 95% CI, 0.16 to 11.8; $p=0.044$). Idebenone administration was associated with a 66% reduction in loss of percentage predicted PEFR over the trial week at 52; interim measures at 26 ($p=0.007$) and 39 ($p=0.034$) treatment weeks also demonstrated treatment efficacy. Of note, the investigators based their sample size calculations on a 10.3% between-group difference in percentage predicted PEFR, which presumably is a clinically important difference.

On seven additional measures of respiratory function, patients receiving daily idebenone showed improvements compared to the placebo group.[234,235] Fewer respiratory tract infection–related adverse events were noted among patients receiving idebenone than among patients receiving placebo.[235]

Manufacturer and regulatory status: Takeda Pharmaceutical Co., Ltd. (Osaka, Japan), initially developed idebenone as an investigational Alzheimer's disease therapy. Now, Santhera Pharmaceuticals Holding AG (Liestal, Switzerland) is developing and manufacturing idebenone for treating DMD and other diseases. In February 2007, FDA granted orphan drug status to idebenone for treating DMD and in April 2015 granted it fast-track status.[236,237] Santhera announced that it was preparing an NDA for idebenone and had started pre-NDA meetings with FDA.[237,238] In November

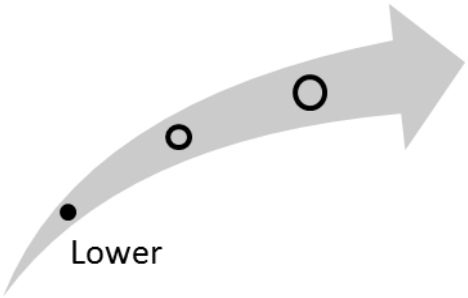
2015, Santhera announced that it had completed new comparative analyses and was including that data, along with DELOS primary and secondary endpoint results, in its American and European regulatory filings.[239]

Diffusion: Idebenone has not been approved for treating DMD. With optimistic NDA submission and approval timelines, idebenone's earliest prospective commercial availability is mid-2016. Through December 2015, the drug had not diffused beyond clinical trial patients for this indication.

Clinical Pathway at Point of This Intervention

No approved disease-modifying therapies exist for treating DMD; standard of care includes palliative options for the disorder's more severe symptoms. If approved, idebenone would likely be prescribed as an adjunct to palliative therapies, particularly for patients displaying disease-related declining respiratory functions. We also note that, if approved, previously discussed exon-skipping therapies could compete with or complement idebenone.

Figure 8. Overall high-impact potential: idebenone (Raxone/Catena) for treatment of Duchenne muscular dystrophy



Consulted experts commenting agreed that a significant need exists for additional, effective DMD therapies and concluded that idebenone could address this need. Given its demonstrated efficacy and tolerability, idebenone would be broadly supported by clinicians and patients, experts thought. If approved, idebenone was also anticipated to have little impact on health disparities, patient management, or health care delivery infrastructure. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical and research backgrounds, provided perspectives on this intervention.[240-245] We have organized the following discussion according to the parameters on which they commented.

Unmet need and health outcomes: Unanimously, experts concurred that a substantial unmet need exists for interventions that effectively treat severe DMD symptoms. Based on available data, experts also determined that idebenone has demonstrated efficacy for improving respiratory function and has substantial potential to improve patient health outcomes.[240,242,245]

Acceptance and adoption: As an oral medication with established clinical efficacy and a solid safety profile, idebenone could be widely accepted by clinicians and patients, the experts thought. Projecting regulatory approval, experts also stated that a sparse market of competing approved DMD therapies could also foster idebenone acceptance and adoption.

Health care delivery infrastructure and patient management: Experts' overall opinion was that idebenone would not heavily impact health care delivery infrastructure or patient management,

because it is an oral medication that requires no immediate clinical oversight. Optimally, some experts foresaw idebenone use reducing patient management demands, but indicated that additional long-term efficacy data were needed to bolster these predictions.[240,241,244]

Health disparities: Experts thought that idebenone, with its relatively small intended patient population, would not significantly impact health disparities. Although the drug's potential cost could exacerbate health disparities, experts expected third-party payer coverage and various financial support programs would minimize patients' direct financial burden.

L-Glutamine for Prevention of Vaso-Occlusive Crises in Sickle Cell Disease

Unmet need: Sickle cell disease (SCD) is characterized by painful vaso-occlusive crises (VOCs) caused by an accumulation of sickled red blood cells that block blood vessels and can lead to death. Standard prophylactic and acute treatment is a myelosuppressive chemotherapeutic agent called hydroxyurea; however, the drug is effective for only two-thirds of affected adults and increases the risk of infection.[246] Therefore, an unmet need exists for better treatments for SCD. Researchers are investigating whether pharmaceutical-grade L-glutamine taken prophylactically might prevent VOCs, reducing pain and hospitalizations for patients with SCD.

Intervention: Although the exact mechanisms leading to VOCs are unclear, researchers speculate that oxidative stress, adhesive leukocytes, and chronic inflammation play roles. When sickled red blood cells start to accumulate in blood vessels, they activate a feedback loop that exacerbates inflammation and produces reactive oxygen species. Ischemia caused by the blockage contributes to the feedback loop. Together, these dynamic events may lead to a VOC.[247]

L-glutamine is a nonessential amino acid naturally produced by the body. Among its many roles, L-glutamine acts as a precursor to nicotinamide adenine dinucleotide (NAD), an electron acceptor that reduces oxidative stress in cells. Supplementing L-glutamine levels may increase the NAD concentration, potentially altering the redox state of red blood cells. This mechanism potentially interrupts the feedback loop involving reactive oxygen species and could prevent VOCs.[248] Pharmaceutical-grade L-glutamine differs from L-glutamine over-the-counter dietary supplement because it is manufactured according to FDA standards regarding purity, stability, concentration, batch-to-batch consistency, and reliability.[249] In clinical trials, it is administered twice daily at a dose of 0.3–0.6 g/kg. Doses are rounded to 5 or 10 g increments with an upper limit of 30 g per day. L-glutamine comes as a powder that can be mixed with water or unheated beverages and foods (e.g., yogurt, applesauce, cereal). Instructions advise against mixing it with alcohol, soda, or highly acidic juices.[248,250] In one clinical trial, adverse events for patients taking L-glutamine were similar to those observed in patients taking placebo.[248]

Clinical trials: No ongoing trials are registered at the National Clinical Trials database (ClinicalTrials.gov). A phase III, randomized, placebo-controlled trial (n=230) was conducted to evaluate the effect of L-glutamine on reducing the incidence of VOCs. Patients in the trial were stratified by hydroxyurea use and assigned to treatment with L-glutamine or placebo in a 2:1 ratio. The drug was administered daily for 48 weeks and tapered off over 3 weeks before the final evaluation was made 2 weeks later. Niihara and coworkers (2014) reported that the median incidence of VOC was lower in the treatment group than the placebo group (3 events vs. 4 respectively; p=0.008). The median incidence of hospitalization was also lower in the treatment group than placebo group (2 events vs. 3 events respectively; p=0.005), and median cumulative hospital days were reported to be lower by 41% (6.5 days treatment group vs. 11 days placebo group, p=0.022). Acute chest syndrome occurred in 11.9 % of the L-glutamine group and 26.9% of the placebo group (p=0.006). The median time-to-first crisis was 54 days in placebo group and 87 days in treatment group (p=0.010).[248]

Manufacturer and regulatory status: Emmaus Life Sciences, Inc. (Torrance, CA), is developing pharmaceutical-grade L-glutamine for preventing VOCs in patients with SCD. FDA has granted the intervention orphan drug and fast-track statuses for treating SCD.[246] Emmaus completed a phase III trial in March 2014. After meetings with FDA in June and October 2014, Emmaus indicated that it intended to submit an NDA to FDA sometime in 2015 while simultaneously

initiating a confirmatory phase III trial;[251] however, as of December 2015, Emmaus had not released any information regarding progress toward these milestones.

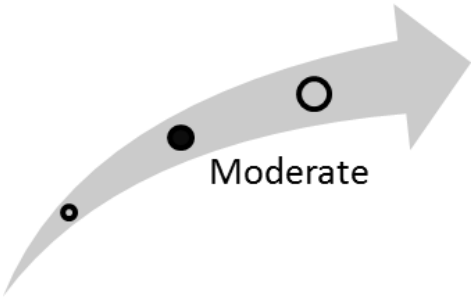
Diffusion and cost: No cost information is available because FDA has not approved L-glutamine for preventing VOCs in patients with SCD. However, Emmaus Life Sciences produces a powdered form of L-glutamine, Nutrestore®, approved for nutritional support in patients with short bowel syndrome; it costs about $300 for 84 packets of 5 g each.[252] For patients with SCD taking the maximum daily dose (30 g), this is a 2-week supply.

No coverage, coding, or payment information is available yet; if the drug gains approval, we anticipate third-party payers would reimburse for the drug, although copayments may be high.

Clinical Pathway at Point of This Intervention

The only possible cure for SCD is bone marrow or stem cell transplant. Because of the high risks associated with these procedures, they are usually done only in severe cases in children with minimal organ damage.[253] Treatment primarily focuses on pain management and symptom control.[254,255] Antibiotics prevent infections, which patients with SCD are vulnerable to, while pain relievers help during a VOC.[254] An expert-panel report issued by the National Institutes of Health in 2014 also recommends the use of hydroxyurea,[255,256] which stimulates the production of fetal blood cells, but this has potential risks of cytopenias (decrease in number of any of the cellular blood components) and increased infection.[254] If approved, L-glutamine could be used as first- or second-line therapy in patients who cannot tolerate hydroxyurea.

Figure 9. Overall high-impact potential: L-glutamine for prevention of vaso-occlusive crises in sickle cell anemia



Experts commenting on this intervention agreed that a substantial unmet need exists for reducing pain, VOCs, and hospitalizations. Clinicians and patients may readily adopt L-glutamine because it appears safe, is an oral drug, and its cost is not expected to be high, experts said. Experts noted that it is unlikely to affect health care delivery infrastructure or patient management. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this intervention.[257-262] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A substantial unmet need exists for an SCD therapy that prevents VOCs, hospitalizations, and pain, without intolerable side effects, experts agreed. L-glutamine may improve patient health by reducing the incidence of VOCs and the total days spent in the hospital, experts thought, basing their opinions on the limited data available. One clinical

expert suggested L-glutamine is suited for second-line therapy in patients who do not tolerate hydroxyurea, a drug that lowers mortality risk associated with VOC.[261]

Acceptance and adoption: Acceptance from clinicians and patients is likely to be high, experts agreed. Positive features of the drug that experts cited to support their opinions include its oral, at-home administration, good safety profile, and likely acceptable cost.

Health care delivery infrastructure and patient management: As an oral drug, L-glutamine is unlikely to have an impact on health care delivery infrastructure, experts said. Most experts noted that the drug's use may decrease the frequency and duration of hospital visits. Patient management may involve less clinician monitoring for side effects and fewer hospitalizations with use of L-glutamine, experts thought. The cost of the drug is unlikely to significantly increase overall health care costs and may offset some costs by reducing hospital use, experts noted.

Health disparities: Health disparities among minority ethnic groups disproportionately affected by SCD (e.g., African Americans, Asians) may improve with use of an oral drug that is not likely to be expensive and can be taken at home, experts thought.

Migalastat Hydrochloride (Galafold) for Treatment of Fabry Disease

Unmet need: Fabry disease is a genetic disorder characterized by cellular buildup of globotriaosylceramide, a type of fat that causes a wide range of symptoms and can lead to heart attack, stroke, and kidney damage. Treatment for Fabry disease is ERT using recombinant alpha-galactosidase A (alpha-GAL) enzyme; however, ERT has multiple shortcomings, including variable tissue distribution, a requirement for weekly or biweekly IV infusions, and the high cost and complexity of recombinant protein manufacturing.[263] Migalastat (Galafold™) is an orally administered, small-molecule modulator of alpha-GAL activity intended to potentiate the activity of endogenous residual alpha-GAL as a monotherapy or potentiate the activity of exogenously provided alpha-GAL activity as a combination therapy with ERT.[264]

Intervention: Migalastat is intended to function as a pharmacologic chaperone for alpha-GAL, which is deficient in Fabry disease. Chaperones ensure proper folding of target proteins, an essential process for full enzymatic activity and proper trafficking within the cell.[265] Many of the mutations that cause Fabry disease are missense mutations (in which one amino acid is changed), causing misfolded proteins to be prematurely degraded in the endoplasmic reticulum instead of moved to the lysosome to carry out their function. Migalastat is intended to promote the proper folding of endogenous alpha-GAL for proper trafficking and function.[264] Restored enzymatic activity of alpha-GAL reduces the levels of globotriaosylceramide (GL-3) and prevents its damaging accumulation. Migalastat may also work as a combination therapy with ERT by binding to and stabilizing the exogenous alpha-GAL and increasing uptake in affected organs.[266]

To test a patient's potential response to migalastat, the manufacturer has developed a cell-based in vitro assay with a third party to test the enzymatic activity of each patient's alpha-GAL when exposed to migalastat.[267,268] Based on this test, the manufacturer estimates 30% to 50% of patients with Fabry disease have mutations that are suited to migalastat monotherapy.[267] Migalastat is administered orally; the optimal dosage is still under study. In clinical trials, it is administered at a dosage of 150 mg every other day or 250 mg in cycles of 3 days on and 4 days off.[269] The manufacturer reported that migalastat was generally well tolerated in phase II and III clinical trials. No severe adverse events have been reported. The most commonly reported adverse events include headache, arthralgia, diarrhea, back pain, pain in an extremity, and fatigue.[269-271]

Clinical trials: Three phase III clinical trials are ongoing.[272-274] In a clinical study (n=67) of migalastat's effect on levels of GL-3 inclusions in interstitial capillaries of the kidneys, the primary endpoint was not met. However, a post-hoc analysis including only patients with amenable mutations (n=42) showed a statistically significant reduction of GL-3.[275] In a followup study, glomerular filtration rate remained steady over an average of 32 months for patients with amenable mutations.[271] Two earlier studies supported the analysis that only patients with amenable mutations responded to migalastat.[276,277]

Manufacturer and regulatory status: Amicus Therapeutics, Inc. (Cranbury, NJ), is developing migalastat as a monotherapy and a combination therapy with ERT for treating Fabry disease. In February 2004, FDA granted orphan drug status to Amicus for migalastat. Phase III trials are under way with some data already reported, and an open-label extension trial is ongoing. The company intended to seek accelerated drug approval by the end of 2015;[264] however, after meeting with FDA, Amicus has indicated that it will further evaluate existing data and possibly collect more data on migalastat's effect on gastrointestinal symptoms before pursuing regulatory approval.[278]

Cost: Pricing information for migalastat is not available because it is not yet approved by FDA. ERT for Fabry disease costs more than $200,000 per patient per year.[279] Although a small-molecule

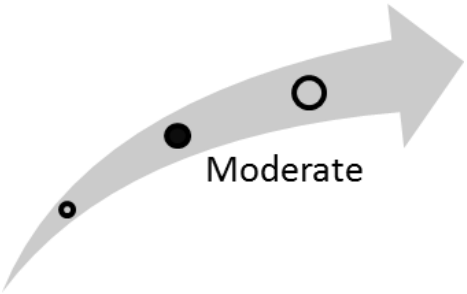
drug such as migalastat has the potential to be manufactured at a lower cost than recombinant protein therapy, treatments for a rare condition such as Fabry disease are likely to be of high cost. Whether Amicus will price migalastat lower than ERT is unclear.[279] If migalastat is approved, its use is likely to be reimbursed by third-party payers because of the limited treatment options for patients with Fabry disease.

Clinical Pathway at Point of This Intervention

No cure exists for Fabry disease. Because of the disease's systemic nature, the patient's primary treatment requires a multidisciplinary team to manage symptoms.[263,280] Analgesics are required for pain management, but NSAIDs are ineffective. Lifestyle changes may be recommended to reduce some symptoms, such as pain and gastrointestinal and kidney problems.[263,281] Cardiac symptoms are managed with medication, pacemakers, or surgery.[281] ERT using agalsidase beta, a recombinant form of alpha-GAL, is available to target the buildup of globotriaosylceramide. ERT breaks down the lipid deposits in many cells and improves overall symptoms.[263,281]

Patients on migalastat may experience fewer symptoms of Fabry disease and, therefore, require less symptom management. However, any pain or other manifestations would still need treatment as they arise.

Figure 10. Overall high-impact potential: migalastat hydrochloride for treatment of Fabry disease



Experts commenting on this intervention agreed that a large unmet need exists for effective and convenient treatment. Migalastat may be readily accepted by clinicians and patients to meet that need because of its oral administration and good tolerability, experts suggested. As an oral drug, it can be easily integrated into a care pathway and is unlikely to have a major effect on health care delivery infrastructure or patient management, experts thought, but it would add to overall costs. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this intervention.[282-287] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A large unmet need exists for convenient and effective treatment of Fabry disease, experts agreed. Migalastat may improve quality of life for patients by providing an oral option that can be taken at home with few adverse events, the experts thought. It may decrease symptoms of Fabry disease if its convenience and safety profile improve patient adherence to treatment, but more studies focused on patient-oriented outcomes are needed, experts said. One clinical expert suggested that it could become the standard of care if used in combination with ERT.[287]

Acceptance and adoption: Clinicians and patients are likely to favor a well-tolerated, oral option over ERT given by IV infusion, most experts agreed. However, an expert with a research perspective thought that clinicians may be less likely to accept migalastat without additional data from clinical trials.[283] The same expert also thought cost, especially if migalastat is used in combination with ERT, may hinder patient adoption.[283]

Health care delivery infrastructure and patient management: A small decrease in demand on health care delivery infrastructure and patient management may result from use of migalastat because it is an oral drug taken at home that may replace IV infusion of ERT for some patients, two experts thought.[282,287] However, experts agreed that any impact would be minimal because the patient population is small.

Cost impacts may depend on whether migalastat replaces or complements ERT. When migalastat is used as a solo treatment, overall health care costs may decrease slightly by removing costs associated with IV infusion. If used in combination with ERT, costs to patients and third-party payers may be substantial, experts thought.[283,286]

Health disparities: Health disparities may increase because migalastat is likely to be an expensive drug, some experts thought. An expert with a research perspective stated that adherence issues may be less likely than with ERT, which may reduce health disparities.[282]

Sebelipase Alfa (Kanuma) for Treatment of Lysosomal Acid Lipase Deficiency

Unmet need: Lysosomal acid lipase deficiency (LALD) is associated with significant morbidity including hypercholesterolemia, cardiovascular disease, and liver damage. Early-onset LALD, also called Wolman's disease, is often fatal in the first year of life. Late-onset LALD, also called cholesteryl ester storage disease (CESD), occurs in older children and adults and may cause liver failure. Treatments for LALD address symptoms but do not target the underlying deficiency.[288] Sebelipase alfa (Kanuma®) is an ERT that is the first treatment to restore functional lysosomal acid lipase (LAL) levels.[289]

Intervention: Sebelipase alfa is a recombinant form of the human LAL enzyme. It is intended to replace the deficient enzyme to prevent accumulation of cholesterol esters and triglycerides in cells and tissues and to maintain adequate lipid metabolism.[290] Sebelipase alfa is administered by IV infusion at a dosage of 1 mg/kg, weekly or every other week.[290,291]

In clinical trials, about 10% of patients experienced infusion-related reactions (i.e., fever, vomiting) including severe reactions in two patients. Other adverse events reported were mild to moderate and mostly unrelated to sebelipase alfa.[292-294] In one clinical trial, 6% of patients had antidrug antibodies at more than one time point, but no subjects developed neutralizing antibodies.[294]

Clinical trials: In a clinical trial of patients with early-onset LALD (Wolman's disease), survival over 12 months and growth, liver, and hematologic effects were reported for 9 patients who received sebelipase alfa; they were compared to a historical cohort that received the standard of care. Jones and coauthors reported, "In addition to improved survival to 12 months of age relative to the historical cohort (n=21) (67% versus 0%, respectively), all subjects demonstrated improved weight gain, improvement of GI [gastrointestinal] symptoms, and reductions in hepatosplenomegaly."[292] In another clinical trial of patients with late-onset LALD (CESD; n=66), Burton and coworkers reported that 31% of patients had normal levels of alanine aminotransferase after 20 weeks of sebelipase alfa treatment compared with 7% of patients in the placebo group. Patients treated with sebelipase alfa also had improved lipid levels and reduced hepatic fat content compared with those outcomes in patients treated with placebo.[295] Two phase III trials and an expanded access protocol are ongoing.[296-298]

Manufacturer and regulatory status: Synageva Biopharma Corp., owned by Alexion Pharmaceuticals (Cheshire, CT), is developing sebelipase alfa under the trade name Kanuma for treating LALD. The manufacturer is studying sebelipase alfa for treating infants, children, and adults who have LALD, which includes patients with Wolman's disease and CESD. FDA approved sebelipase alfa for LALD in December 2015.[291] FDA previously granted orphan drug status to the therapy and fast-track and breakthrough therapy statuses for treating infants.[289]

Cost: No cost information is available because sebelipase alfa was just recently approved by FDA. Sebelipase alfa is intended to treat a rare disease and is likely to be expensive.

No coverage, coding, or payment information is available. After evaluating coverage decisions in the wake of FDA approval, third-party payers are likely to reimburse its use because of the limited treatment options for patients with LALD.

Clinical Pathway at Point of This Intervention

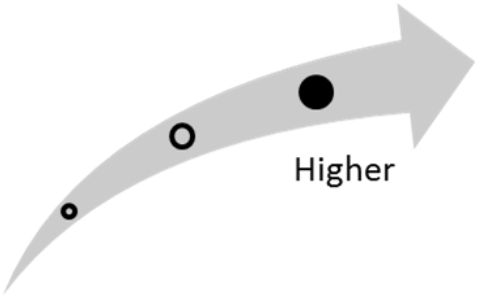
Patients with Wolman's disease may be successfully treated with a hematopoietic stem cell transplant from an umbilical cord donor or bone marrow donor.[288] However, risk of significant morbidity and mortality are associated with stem cell transplants. Sebelipase alfa may provide a

treatment option for patients who do not have a matched donor or are not healthy enough to undergo a stem cell transplant. Nutritional support and hormone supplements may be used in conjunction with sebelipase alfa in patients who are experiencing gastrointestinal symptoms and loss of adrenal function.

Patients with CESD may receive statin therapy (e.g., lovastatin, simvastatin) to decrease total serum cholesterol and increase high-density lipoprotein cholesterol. The goal of statin therapy is to lower the risk of cardiovascular disease associated with CESD. Statin therapy may lower liver volume and lipid content and resolve hepatomegaly. However, statins do not lower liver lipid levels to a normal range, and the risk of cirrhosis and liver failure remains. Statins may be used with other cholesterol-lowering medications that prevent absorption of cholesterol in the intestines (e.g., ezetimibe) or that aid conversion of cholesterol to bile acids (e.g., cholestyramine).[288] Sebelipase alfa may compete with or complement cholesterol-lowering therapy in patients with CESD.

Patients with CESD who progress to cirrhosis and liver failure may need a liver transplant.[288] Sebelipase alfa may slow progression of CESD and delay or prevent the need for a liver transplant.

Figure 11. Overall high-impact potential: sebelipase alfa (Kanuma) for treatment of lysosomal acid lipase deficiency



Experts commenting on this intervention, before FDA approval, agreed that patients with the most severe disease need treatment options that prolong survival and avoid liver or stem cell transplants. As an ERT, sebelipase alfa targets the underlying cause of the disease, not just symptoms, experts noted; as such, acceptance from clinicians and patients is likely to be high. Although health care delivery infrastructure will be minimally affected, regular infusions will change the care setting for patient management and potentially reduce the number of surgeries needed, experts thought. Experts expect a high cost comparable to other ERTs for rare diseases, with third-party payers and patients bearing these costs. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this intervention.[299-304] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: For patients with early onset or severe LALD, experts agreed a substantial unmet need exists for treatment that improves survival and abrogates the need for liver or stem cell transplants. A less important unmet need exists for patients with milder LALD who manage symptoms through diet and statin therapy, experts said. Likewise, patients with the most severe disease are the most likely to benefit from sebelipase alfa as demonstrated by improved survival for patients with Wolman's disease seen in a clinical trial, experts concurred. Experts also noted that trials with more patients and longer term outcomes (i.e., more than 1 year) are needed to support the preliminary results seen in smaller trials.

Acceptance and adoption: Strong clinician acceptance is likely, experts concluded, because sebelipase alfa would be the only treatment that targets the cause of the disease instead of symptoms. Clinician enthusiasm may be tempered by the route of administration (i.e., IV infusion), two experts thought.[299,303] Patients are also likely to accept the treatment, especially those with more severe disease, experts said. Additional studies to elucidate long-term benefits and side effects may influence patient adoption in the future, two clinical experts suggested.[303,304] Experts again noted that the likely high cost may be a barrier for some patients.

Health care delivery infrastructure and patient management: Institutions with infusion therapy services will likely be able to absorb the additional demand for services from the small number of patients affected, experts thought. Patient management may be moderately affected on several dimensions. A clinical expert noted that regular infusions of sebelipase alfa would be a big change for patients, especially if they need to travel to an infusion center or to have permanent venous access established.[304] An expert with a research perspective stated that improved cholesterol levels and reduced hepatic complications, possible benefits of sebelipase alfa, may decrease the need for stem cell or liver transplants.[302] Another research expert questioned whether the therapy could be tapered when patients improved; if not, the burden of continuous infusions may significantly impact patient management, the expert suggested.[300]

Despite the lack of cost information, experts agreed that the cost of sebelipase alfa is likely to be high and on par with other ERTs for rare diseases. (Such ERTs have been typically priced at about $300,000 per patient per year.) Experts also said that third-party payers and patients are likely to share these costs.

Health disparities: Most experts suggested that the presumed high cost of sebelipase alfa may exacerbate economically based health disparities and preclude some patients from receiving treatment, especially those with high deductibles and copayments or without insurance coverage.[300,302-304]

Liver Disease Intervention

Obeticholic Acid for Treatment of Primary Biliary Cirrhosis

Unmet need: Primary biliary cirrhosis (PBC) is a chronic and progressive liver disease characterized by impaired bile flow (i.e., cholestasis), resulting from destruction of small-to-medium bile ducts. Although the disease may slowly progress over two decades, cirrhosis develops and will eventually result in death unless a patient receives a liver transplant. Even after transplantation, PBC has a high recurrence rate. The standard care for earlier disease stages is to delay progression by using ursodiol (also known as ursodeoxycholic acid), which is ineffective in up to 40% of patients.[305] Obeticholic acid may delay PBC progression in patients whose disease does not respond to ursodiol by activating the farnesoid X receptor (FXR), a negative feedback regulator of bile acid synthesis.[306]

Intervention: Obeticholic acid is a bile acid analogue and first-in-class FXR agonist. FXR is a nuclear receptor expressed in the liver, intestine, kidney, and adipose tissue that regulates bile acid synthesis and transport. As an FXR agonist, obeticholic acid purportedly induces the bile acid signaling pathway to limit bile acid production, increase bile flow (i.e., choleresis), and prevent toxic buildup in hepatocytes.[306,307] By preventing hepatocyte damage, obeticholic acid may also prevent further fibrosis.[307]

Ursodiol, the standard treatment for PBC, is an isomer of the bile acid chenodeoxycholic acid. Despite structural similarities to obeticholic acid, ursodiol has not been shown to bind to FXR (or any other intracellular receptor). Ursodiol's mechanism of action is unclear, but it may enhance choleresis by reducing bile acid hydrophobicity and reduce fibrosis by competitively replacing endogenous cytotoxic bile acids.[308,309] Obeticholic acid's different mechanism of action may improve outcomes for patients who respond inadequately or who do not respond to ursodiol.

In clinical trials, obeticholic acid is administered at a dosage of 5 or 10 mg, once daily, orally. Researchers are also studying an initial dose of 5 mg that is titrated up to 10 mg after 6 months.[310,311]

The most common adverse event is pruritus, which occurs in more than 56% of patients treated with obeticholic acid, compared with 38% for placebo. Pruritus associated with obeticholic acid is dose dependent, but its incidence and severity generally decrease over time for patients who continue taking the drug.[312,313] In one clinical trial, patients who started at 5 mg of obeticholic acid and were titrated up to 10 mg experienced pruritus less severely and less often than did patients who initiated treatment at 10 mg.[312] One clinical trial reported mean decreases of 16% to 26% in high-density lipoprotein (HDL) levels,[314] which may increase a patient's risk for cardiovascular disease. An ongoing phase II trial is investigating obeticholic acid's effect on HDL levels.

Clinical trials: The phase III POISE trial (n=217), which evaluated obeticholic acid's effects on liver function, reported that 47% of patients who received 10 mg of obeticholic acid and 46% of patients who received 5 mg met the primary endpoint compared with 10% of patients who received placebo. The composite primary end point was defined as alkaline phosphatase levels reduced by 15% or more to less than 1.67 times the upper limit of normal and bilirubin levels within normal limits.[314] In a phase II trial, levels of alkaline phosphatase decreased 21% to 25% on average from baseline in patients who received obeticholic acid compared with a 3% average reduction in the placebo group.[315] Two phase III trials are ongoing.[316,317]

Manufacturer and regulatory status: Intercept Pharmaceuticals, Inc. (New York, NY), is developing obeticholic acid for treating primary biliary cirrhosis in patients who do not respond to or cannot tolerate long-term ursodiol treatment. FDA granted orphan drug and fast-track statuses to the manufacturer.[318] Intercept submitted an NDA under FDA's accelerated approval pathway in June 2015 and expects a decision in February 2016.[319] The NDA was supported by data on the surrogate endpoints of alkaline phosphatase and bilirubin levels, which were established as

noninvasive long-term indicators of disease progression and treatment effectiveness by the Global PBC Study Group. The Group, an international and multicenter collaboration of medical centers performing PBC research, performed a meta-analysis of patient data from cohort studies and reported that alkaline phosphatase and bilirubin levels can predict liver transplant or mortality outcomes.[320]

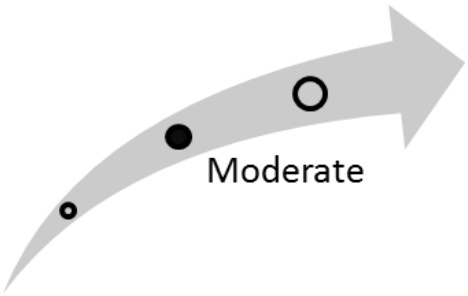
Cost: No cost information is available because FDA has not yet approved obeticholic acid. As of December 2015, the bile acid derivative Actigall® (i.e., ursodiol) reportedly cost about $235 for 30 capsules; generic versions cost as little as $35 for a month's supply.[321,322]

No coverage, coding, or payment information is available, because obeticholic acid is not yet approved by FDA. If obeticholic acid is approved, and third-party payers deem the evidence to be sufficient to support its use, it will likely be added to formularies.

Clinical Pathway at Point of This Intervention

The first-line treatment for PBC is a bile acid, ursodiol, that improves liver function in about 60% of patients. It is not a cure, but can improve survival to normal life expectancy and reduce the risk of liver failure if started early in the course of disease.[305] For patients who do not respond to ursodiol, obeticholic acid may become a second-line or adjunct treatment. Most patients receive a diagnosis of PBC when it is at an advanced stage, at which point a liver transplant may be recommended even though PBC may still recur.[305,323-325] Treatments for disease symptoms, such as nutritional and fat supplements, may also be used to improve quality of life and may complement obeticholic acid use.[323]

Figure 12. Overall high-impact potential: obeticholic acid for treatment of primary biliary cirrhosis



Experts commenting on this intervention agreed that patients who do not respond to ursodiol need a safe and effective treatment option such as obeticholic acid. Although published data rely on surrogate markers to support obeticholic acid's benefits to patient health, most experts agreed that clinicians would accept the link between the markers and disease progression and survival and would prescribe the drug. Obeticholic acid's effects on patient management and costs will largely depend on its effectiveness, as experts pointed out that the drug is likely to cost more than ursodiol but may reduce the need for liver transplants. Overall, experts thought that an additional option with few major side effects would be welcome in patients who do not respond to ursodiol. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this intervention.[326-331] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Ursodiol is not effective for up to 40% of patients with PBC, experts said, demonstrating a need for alternatives. Although some experts were too skeptical to proclaim a large benefit to patient health on the basis of surrogate marker data,[328,330] others were more convinced. One research expert said "the preliminary results are very good and since the surrogate outcomes seem to be directly linked to disease progression, the outlook for this drug is very high."[331]

Acceptance and adoption: Few options are available for patients who do not respond to ursodiol, which makes obeticholic acid an attractive second-line choice, experts explained. They also said that its lack of major side effects will strengthen demand for it. Although one expert with a research perspective noted that additional data may be needed to convince clinicians to prescribe obeticholic acid,[327] another health systems expert pointed out that the surrogate markers used to indicate effectiveness in clinical trials are widely accepted within the PBC research community as indicators of disease remission or progression.[328]

Health care delivery infrastructure and patient management: Obeticholic acid is administered similarly to ursodiol, which will limit any impact on health care delivery infrastructure and patient management, experts agreed. Experts said that obeticholic acid may reduce the need for liver transplants, a major change in patient management and costs.[328-331] Obeticholic acid is likely to be more expensive than ursodiol, which is available in a generic formulation, experts thought.

Health disparities: Health disparities in PBC may be related to its higher prevalence among women than men, two health systems experts said. One suggested disparities may decrease slightly with the availability of a new treatment,[329] and the other said that disparities may increase because women generally earn less money and may be less able to afford treatment than men.[328]

Sensory Disorder Interventions

Pediatric Vision Scanner Screening for Strabismus and Amblyopia

Unmet need: The leading cause of preventable monocular vision loss in children is amblyopia (lazy eye), which is most often caused by strabismus (misaligned eyes).[332] Early amblyopia detection can be difficult because standard screening methods identify only risk factors for amblyopia and lack sufficient sensitivity and specificity. They either miss cases that should be referred for further evaluation and possible treatment or over-refer cases.[333] Standard screening methods cannot be effectively used on children younger than about 4 years old. If found early, amblyopia and strabismus are fully treatable; however, as many as half of affected children are not identified until school age, when treatment may not be as effective. A need exists for improved screening for these conditions to identify children who should be referred to a specialist for further evaluation.

Intervention: The Pediatric Vision Scanner (PVS) is intended for use as a screening tool for early amblyopia or strabismus detection so that patients can be more appropriately referred to specialist care. The device can be used either as a portable, handheld device or mounted on a table.[334]

According to the manufacturer, the device uses proprietary technology called retinal birefringence scanning, which measures polarized light reflected by the retina. It can distinguish between light reflected by the fovea and light reflected by the paracentral retina. The PVS simultaneously assesses both eyes to detect both binocular alignment and whether the eyes are focused on a target.[335] The screening device performs a 2.5-second scan of the eyes to automatically detect the presence of amblyopia, strabismus, or other serious eye conditions.[334] Testing with the PVS requires minimal cooperation and no verbal response from the individual being screened. During the scan, the patient looks at a fixed target within the device as a focal point. The device is designed to determine when the patient looks away from the target during the scan, which allows for these measurements to be discarded and for measurements to continue until a requisite minimum of five scans has been obtained. The software then provides a result as to whether the patient's eyes were accurately fixating on the target, indicating a "pass" or passing grade, or if one or both eyes were not properly fixating, indicating the need to refer the patient to a specialist for further testing.[334]

The PVS is designed for use in a pediatric office as an early detection screening tool to promote preventive care and reduce false referrals for ophthalmic specialist care.[334]

Clinical trials: Five registered trials evaluated the sensitivity and specificity of the PVS, with positive results (sensitivity 94% to 98%; specificity 74% to 88%).[336-340] The most recent trial of the PVS (compared with the SureSight Vision Screener test) enrolled 300 patients 2–6 years of age. Study investigators reported the following:[339]

> The sensitivity of the PVS to detect strabismus and amblyopia (0.97; 95%CI, 0.94-1.00) was significantly higher than that of the SureSight Autorefractor (0.74; 95%CI, 0.66-0.83). Specificity of the PVS for strabismus and amblyopia (0.87; 95%CI, 0.80-0.95) was significantly higher than that of the SureSight Autorefractor (0.62; 95%CI, 0.50-0.73).

As with any screening tool, the potential for false-positive or false-negative tests results exists with the PVS. False-negative results could lead to a delay in care for amblyopia or strabismus; false-positive results could lead to unnecessary specialty referrals. However, the PVS purportedly will reduce the rate of false-positive results associated with other screening methods.[334]

Manufacturer and regulatory status: The PVS has been developed by REBIScan, Inc. (Cambridge, MA). FDA has determined the PVS to be a nonsignificant risk investigational device,[334] meaning it has abbreviated requirements for labeling, institutional review board (IRB) approval for trials, and streamlined trial and reporting rules. The IRB serves as FDA's surrogate for review, approval, and ongoing review of nonsignificant-risk device studies.[341] Some in the ophthalmology field expected the device to be on the market before the end of 2014;[333] however, as of December 2015, the device had not been approved.

Diffusion and cost: Reimbursement for pediatric vision screening has been long established; the company indicated it expects its screening exam cost to fall within the reimbursed amount. Thus, PVS testing may be reimbursed by public and private third-party payers in a manner similar to that of other instrumented pediatric vision screening tests that use photoscreening devices, which insurance companies cover under the procedural terminology code (CPT; published by the American Medical Association) for "ocular photoscreening with interpretation and report, bilateral."[333] The reported reimbursement rate is about $25 to $30 per screening. Reported prices for photoscreening devices range from about $4,200 to $7,500.[333]

REBIScan is collaborating with VisionQuest 20/20 (Phoenix, AZ), a nonprofit organization that addresses preventable vision loss in children, to establish a nationwide vision screening program. Pediatric offices and preschools are expected to use the PVS to screen for amblyopia and strabismus. A tracking system will monitor children referred to specialists to ensure they receive proper followup care.[342]

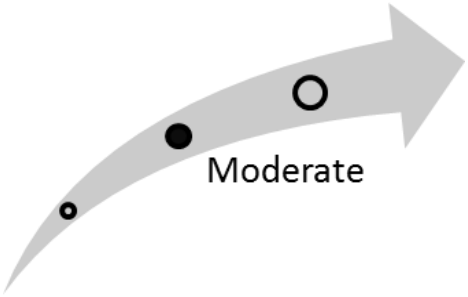
The company has established a crowd-funding site to raise funds to complete its development to meet regulatory requirements.[343]

Clinical Pathway at Point of This Intervention

Amblyopia-associated refractive error is treated with corrective lenses. Patches and eye drops are used to force the child to use the nondominant eye, allowing the weaker eye to become stronger.[344] Children younger than 5 years of age who receive treatment typically recover to almost completely normal vision; however, delaying treatment can result in permanent vision problems, and after the age of 10 years, only partial vision recovery can be expected.[332]

The REBIScan PVS is intended to enable more appropriate referrals and referrals of children at younger ages to an ophthalmologist for further evaluation so that treatment can start when the disorder is at a more correctable stage.[334] Detection methods include annual visual acuity testing at well-child checkups; however, such screening cannot be performed until a child is 4–5 years old (i.e., can follow directions and respond). Automated photoscreening devices are also used.[332] Visual acuity testing and photoscreening devices lead to both missed diagnoses and false positives that lead to unnecessary referrals.[334] The REBIScan manufacturer has indicated that the PVS, if used during annual well-child visits, can reduce health care expenditures by detecting amblyopia and strabismus at earlier stages and reducing false-positive referrals to specialist care.

Figure 13. Overall high-impact potential: Pediatric Vision Scanner screening for strabismus and amblyopia



Overall, experts commenting on this intervention thought use of the PVS in very young children is a significant factor in its potential for fulfilling the unmet need for early screening tools for amblyopia and improving patient outcomes for affected patients. The quick, noninvasive screening procedure, low associated risks, and minimal training requirements to use the device could aid in wide acceptance and adoption, experts anticipated. They suggested widespread use would improve the accuracy of referrals to specialists. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this intervention.[345-350] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: An unmet need exists for earlier screening, diagnosis, and treatment of amblyopia and strabismus, most experts agreed. Experts speculated that patients would achieve better outcomes with earlier treatment and clinicians would make more accurate referrals to specialists. However, some experts expressed skepticism that a more accurate screening device necessarily translates to improved patient health.[346,348,350]

Acceptance and adoption: Acceptance among clinicians, young patients, and their parents is likely to be high, experts agreed. The PVS is easy to use, noninvasive, and allows earlier diagnosis of amblyopia and strabismus, experts said, which will contribute to clinician adoption. One expert with a research perspective thought that the cost may be prohibitive for some clinicians if it is more expensive than other screening tools, as expected.[346]

Health care delivery infrastructure and patient management: Providers who replace their current screening modalities with the PVS, necessitating purchase or leasing of the device and training of staff, will experience an initial small disruption in care delivery, experts agreed. Any disruptions in patient management will likely be related to specialist referrals—improved screening accuracy could increase referrals if more cases are detected earlier while some false positives are avoided—the experts thought.

Initials costs may increase as providers purchase or lease the PVS and train staff. Lifetime vision care costs may decrease if children receive earlier and more effective treatment, experts noted. Likewise, overall health care system costs might decrease if fewer false positive referrals are made to specialists, one expert with a research perspective pointed out.[347] Costs for screening and referrals to specialists are likely to be covered by third-party payers, two experts said.[348,350]

Health disparities: If the PVS is used in low-cost clinics or preschools, health disparities might decrease for children who do not have insurance, experts said. However, as one clinical expert noted, early screening will have a limited effect on disparities unless it is followed by corrective vision care for those who have the condition.[350] If the PVS is primarily used in pediatrician offices, disparities are unlikely to be affected for patients who do not have insurance or do not attend well-child visits, another clinical expert thought.[349]

Tasimelteon (Hetlioz) for Treatment of Non–24-Hour Sleep-Wake Disorder

Unmet need: The National Sleep Disorders Foundation estimates that, of people who are totally blind in the United States, 65,000–95,000 experience a disorder called non–24-hour sleep-wake disorder (non-24). The disorder arises from a lack of light receptors to reset the circadian rhythm.[351] Besides having difficulties associated with blindness, patients with non-24 often experience reduced quality of life and debilitation due to poor sleep quality and excessive daytime sleepiness. Patients may attempt to relieve symptoms of non-24 using sleep aids such as melatonin and stimulants during the day, but these do not address the underlying cause. In January 2014, FDA approved tasimelteon (Hetlioz™) as the first drug approved for treating non-24.[352]

Intervention: Tasimelteon is a dual melatonin-receptor agonist with selective activity mediated through receptors MT1 and MT2. It reportedly resets the circadian rhythm by acting on the suprachiasmatic nucleus of the hypothalamus to synchronize melatonin and cortisol release with the 24-hour, day-night cycle.[353] Tasimelteon is intended to improve nighttime sleep and reduce daytime sleep by maintaining a 24-hour sleep-wake cycle.

According to the manufacturer, tasimelteon is taken orally at a dosage of 20 mg, 1 hour before bedtime, at the same time every night. Tasimelteon may cause drowsiness or affect mental alertness, so patients are advised to limit activity after taking it.[354] Patients might not notice its effects for weeks to months after initiating treatment, according to a discussion held between FDA and the manufacturer.[355]

Clinical trials: A clinical trial (n=84) assessed circadian rhythm by measuring urinary 6-sulphatoxymelatonin (aMT6s) and cortisol. Clinical responders were defined as patients whose circadian rhythm was entrained (adjusted) by tasimelteon who scored 3 or higher on the Non-24 Clinical Response Scale. In results of this study, Lockley and colleagues reported that the proportion of patients entrained by tasimelteon was greater than placebo, as measured by urinary aMT6s and cortisol timing ($p=0.0171$ and $p=0.0313$, respectively). They also reported that the number of clinical responders was greater for tasimelteon than placebo, and greater improvement was seen in the Clinical Global Impression of Change and measures of total nighttime sleep, daytime nap duration, and mid-point of sleep timing (MoST) than in the placebo group ($p<0.05$).[356] In an extension of the clinical trial (n=20), Lockley and coworkers reported that patients receiving the drug maintained their circadian rhythms (as measured by aMT6s and cortisol levels) better than those taking placebo (aMT6s: tasimelteon, 90%; placebo, 20%; $p=0.0026$; cortisol: tasimelteon, 80%; placebo, 20%; $p=0.0118$). Total nighttime sleep was 67.2 minutes longer in the worst quartile of nights and total daytime sleep duration was 59.4 minutes shorter in tasimelteon-treated patients ($p<0.05$). The MoST from both nighttime and daytime sleep increased 36 minutes in tasimelteon-treated patients ($p=0.0108$).[357] In both trials, tasimelteon was reported to be safe and well tolerated. One phase III trial is ongoing to evaluate tasimelteon's safety.[358]

Manufacturer and regulatory status: Vanda Pharmaceuticals, Inc. (Washington, DC), manufactures tasimelteon under the brand name Hetlioz.[359] FDA approved tasimelteon in January 2014 as an orphan drug[352] that is indicated for treating non-24. It is contraindicated in women of child-bearing potential and individuals with severe liver impairment.[354] The manufacturer's label warns that tasimelteon may impair mental alertness and thus, should be taken only before bedtime. Patients taking strong CYP1A2 inhibitors (e.g., fluvoxamine) or strong CYP3A4 inducers (e.g., rifampin) should not use tasimelteon.

According to a medical review from FDA, common adverse events associated with tasimelteon included headache, increased alanine aminotransferase levels, abnormal dreams or nightmares, cardiac conduction disorder, sleep disorder, upper respiratory tract infection, somnolence, and urinary tract infection. The most common serious adverse event was gastroenteritis.[360]

Diffusion and cost: Tasimelteon is a specialty pharmaceutical that is available through a small network of pharmacies.[361] As an orally administered pharmaceutical used in an outpatient setting, tasimelteon is not expected to require significant changes to health care staffing or infrastructure.

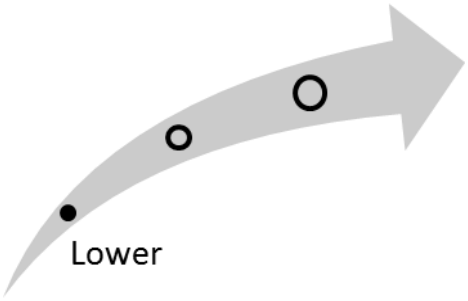
As of November 2015, tasimelteon reportedly cost about $135,000 per patient per year, an increase of about $50,000 per year over the previous year's cost.[361,362] According to the manufacturer, the number of patients on tasimelteon rose by 22% in the first quarter of 2015 compared with the last quarter of 2014.[363] If half (about 35,000 patients) the estimated population with non-24 opted to take the drug, the cost to the health system would be about $4.7 billion annually.

Our search of 11 representative, private, third-party payers that publish their policies online found 10 policies for tasimelteon that require prior authorization;[364-373] several policies list tasimelteon as a nonpreferred drug,[365,367-369,373] subject to quantity limits,[364,365,370,373] and approved only after failure of over-the-counter melatonin therapy.[364,367,372]

Clinical Pathway at Point of This Intervention

Other drugs that may have an effect on regulating the circadian rhythm are melatonin and ramelteon, although neither is FDA approved for non-24. Benzodiazepines or nonbenzodiazepine hypnotics have also been prescribed to improve nighttime sleep quality; to limit daytime sleep, patients have been prescribed caffeine in various forms.[374,375] Nonpharmacologic treatments include chronotherapy and lifestyle changes.[374] Tasimelteon is likely to be used in place of other drugs, but potentially in combination with nonpharmacologic treatments.

Figure 14. Overall high-impact potential: tasimelteon (Hetlioz) for treatment of non–24-hour sleep-wake disorder



Overall, tasimelteon's cost will likely be the biggest impact on the health care system, experts agreed. Clinicians and patients are likely to adopt tasimelteon because of its good safety profile and low abuse potential, experts agreed. In terms of improving patient health or altering patient management, experts noted the small amount of data and modest improvements in sleep and waking times when suggesting the drug is likely to have a lesser impact. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this intervention.[376-381] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A modest unmet need exists for improving productivity and quality of life for patients with non-24, experts agreed. Studies report that the majority of patients respond well to tasimelteon, experiencing improved entrainment and willingness to continue using the drug, experts noted. Several experts suggested comparative studies are needed with other

therapies (e.g., melatonin, sleep hygiene) to determine whether tasimelteon sufficiently improves patient health, especially relative to its high cost.

Acceptance and adoption: Because tasimelteon is the only drug approved to treat non-24, clinicians are likely to accept it, experts thought. Its positive safety profile and low potential for abuse may contribute to clinicians' acceptance, experts said. One research expert thought clinician acceptance may be limited because of the length of time (i.e., weeks to months) it may take for patients to experience an effect.[378] For patients who have third-party payer coverage for tasimelteon, acceptance is likely to be high, experts stated.

Health care delivery infrastructure and patient management: Little to no impact will be evident in health care delivery infrastructure and patient management, experts agreed, because tasimelteon is an oral drug taken at home. A research expert noted that the additional monitoring for weeks or months to see an effect may have a small impact on patient management.[378] The high cost of tasimelteon is likely to be the largest impact factor, experts concurred, especially among third-party payers that are providing coverage. One clinical expert suggested that limited total health care resources mean that payers that weigh the overall societal benefit could limit drug coverage to more severe cases.[381]

Health disparities: Health disparities may increase due to the drug's high cost and uneven coverage from third-party payers, experts agreed, which may limit access for some patients, especially the economically disadvantaged. Patients who use tasimelteon may experience reduced disparities related to quality of life, a health systems expert speculated.[380]

Spinal Cord Injury Intervention

Wearable, Battery-Powered Exoskeleton (ReWalk Personal) To Enable Mobility in Community or Home Settings in Patients With Paraplegia

Unmet need: Conventional manual and powered wheelchairs improve quality of life for individuals with paraplegia; however, mobility, independence, and safety issues remain a primary concern. Wheelchair users can experience pressure ulcers, osteoporosis, depression, and cardiovascular, respiratory, urinary, and gastrointestinal adverse events associated with confinement to power-assisted devices. To address these issues in a home or community setting, a wearable, battery-powered exoskeleton has been developed to enable select patients with paraplegia to "walk" upright.

Intervention: The ReWalk Personal exoskeleton is a wearable, battery-powered exoskeleton with motorized leg braces and crutches for support. The device uses a tilt sensor near the chest to propel the motorized leg braces when patients shift their body weight. The onboard computer and rechargeable batteries are contained in a waist pack; the most recent version (6.0) no longer requires a backpack for these components.[382,383] The waistband provides additional support and holds the leg braces together. Heel plates fit into the user's shoes.[384] The ReWalk system weighs about 35 lb and is activated by a controller on a wrist band.[384,385]

The ReWalk system is designed to mimic a natural walking gait and functional speed (up to 1.6 mph).[383] Patients using the device can sit, stand, walk, and turn.[382] Although the manufacturer claims the exoskeleton can be used on stairs, FDA has not approved it for this use.[386,387] The system can be used on multiple surfaces and terrains for indoor and outdoor use. It can be used for 4 hours of continuous walking (generally one day of use) and recharged overnight.[384,386]

The ReWalk Personal exoskeleton is customized to fit the patient. However, patients must be 160–190 cm tall (5 feet, 3 inches to 6 feet, 3 inches) and weigh less than 100 kg (220 lb).[386] Patients must have sufficient bone density, flexibility, and cardiovascular health, as determined by a physician's exam. Although patients control the exoskeleton, trained caregivers must be present to assist during use of the device, even during home use.[382] It is intended for daily, personal use by patients with paraplegia who complete device training at a rehabilitation or training center.[385]

A significant potential safety issue with wearable exoskeletons is a computer problem or other device malfunction that puts the user at risk of harm in certain environments or situations (e.g., device failure while crossing a street, traversing a ramp, or in crowds). However, a trained caregiver must be with a patient using the exoskeleton and could aid in these scenarios.[382] Patients are also at risk for pressure sores, bruising or abrasions, falls and associated injuries, and diastolic hypertension during use.[387] No safety issues for clinical staff are anticipated with the exoskeleton.

Clinical trials: Two studies are ongoing to evaluate the ReWalk Personal in community and home settings.[388,389] One study reported in 2012 that all patients (n=12) were able to transfer to the exoskeleton and walk with it independently for 5–10 minutes. All patients made positive comments about emotional and psychosocial benefits, and some patients reported improvements in pain, bowel and bladder function, and spasticity.[390] Another study of 6 patients from 2012 reported that no adverse safety events occurred and that the system was well tolerated.[391]

A study published in 2015, after experts commented on this intervention, reported that 10 of 60 candidates (17%) were enrolled and 5 (8%) completed the training program. Primary reasons that candidates were not enrolled included ineligibility (24) and lack of interest in a 10-week training program (16). Five of 10 enrolled subjects experienced grade I/II skin aberrations. Walking speeds were faster and walking distances were longer in all exoskeleton users than in individuals not using

the device; subjects indicated the exoskeleton did not generally meet their high expectations in terms of hoped-for benefits.[392]

Manufacturer and regulatory status: ReWalk Robotics, Ltd. (Yokneam Ilit, Israel; formerly Argo Medical, Inc.), has developed the ReWalk Personal system. FDA cleared the ReWalk Personal in June 2014 under the de novo pathway, which is for first-of-a-kind devices of low to moderate risk.[387] Wearable exoskeletons are expected to be used by patients with paraplegia who retain use of their hands and shoulders, can stand using crutches, have good bone density, and have good cardiovascular health. Patients using the equipment need to be comfortable using a computer-controlled device and undergoing extensive training in a rehabilitation facility. Physician approval and training certification are required to use the assistive device. The technology is contraindicated for people who have a history of neurologic injuries other than spinal cord injury, severe spasticity, significant contractures, unstable spine, unhealed limb or pelvic fractures, or other severe concurrent medical issues.[387]

Patients using the systems require extensive training on a ReWalk Rehabilitation unit with rehabilitation specialists before they can purchase a ReWalk Personal. Patients must also be trained how to troubleshoot or compensate for possible malfunctions that occur while using the device. A trained caregiver, such as a family member or home health aide, assists when patients use the device.[387]

Diffusion and cost: The manufacturer states that it sold 25 ReWalk systems (both ReWalk Rehabilitation for institutional use and ReWalk Personal systems) in the first half of 2015 and 31 in the last quarter of 2014;[393,394] it is unclear how many were ReWalk Personal systems. The manufacturer stated that diffusion is limited by the time it takes to evaluate and train patients and process reimbursement claims.[393] The ReWalk Personal costs about $70,000.[395] Medicare Part B may cover exoskeletons as durable medical equipment for beneficiaries whose physician has prescribed it for home use. Patients must pay 20% of the Medicare-approved amount. If a durable medical equipment supplier does not accept direct Medicare reimbursement, Medicare cannot limit the amount a supplier can charge. In certain geographic areas, Medicare's competitive bidding program may be in effect, which means that Medicare pays for the equipment and related supplies only if they are obtained from contracted suppliers. These suppliers cannot charge patients more than 20% coinsurance and any unmet yearly deductible for any equipment or supplies included in the competitive bidding program.[396]

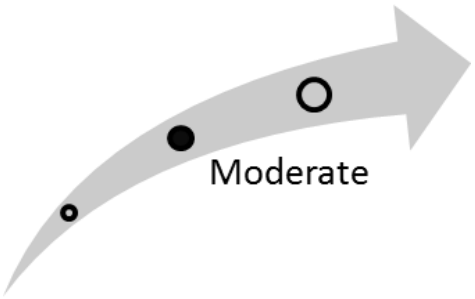
Our searches of 11 representative, private, third-party payers that publish their coverage policies online found 8 policies pertaining to the ReWalk Personal exoskeleton. Those payers—Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, and Regence—consider use of exoskeletons to be experimental and do not cover them.[397-404]

Clinical Pathway at Point of This Intervention

Acute spinal cord injury requires immediate medical attention. A physician completes a physical exam, including neurologic exam, to identify the location of the injury. Magnetic resonance imaging, computerized tomography, or spine radiography may be ordered.[405] Emergency treatment of a spinal cord injury involves immobilizing the spine as gently and quickly as possible. Acute treatment includes maintaining breathing, preventing shock, immobilizing the neck, and avoiding possible complications. Medications, prolonged immobilization, or surgery may be required.[405] Ongoing treatment such as physical therapy, occupational therapy, or other rehabilitation therapies, as well as muscle spasticity medications may be needed.[406]

Conventional manual and powered wheelchairs are the primary assistive devices for mobility in many patients with paraplegia and compete with exoskeletons to provide mobility. Powered wheelchairs for patients with paraplegia can be controlled with a joystick. Other devices that provide upright support, such as stationary standers, compete with exoskeletons to provide benefits associated with upright weight-bearing postures.

Figure 15. Overall high-impact potential: wearable, battery-powered exoskeleton (ReWalk Personal) to enable mobility in community or home settings in patients with paraplegia



Overall, experts commenting on this intervention agreed that an unmet need exists for a mobility and upright-standing device. An exoskeleton for community or home use may prevent complications associated with prolonged wheelchair use, the experts agreed. They suggested the high cost will have the most effect on patient acceptance and access, possibly contributing to health disparities. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this intervention.[407-412] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: An alternative to prolonged wheelchair use, associated with functional limitations and health complications, is an important unmet need for patients with paraplegia, the experts agreed. The exoskeleton may potentially improve mobility; independence; pain, bowel and bladder function; spasticity; bone density; and skin integrity, experts speculated, although they also conceded that more studies are needed.

Acceptance and adoption: Experts were split over how readily clinicians may accept the exoskeleton for patients with paraplegia. Clinicians who are slow to adopt may point to other options, fall risks, costs, and the amount of training required by staff and patients as reasons for abstaining, experts said. Alternatively, some clinicians may believe the benefits of improved mobility, independence, and quality of life outweigh the risks and recommend consideration of the device, experts suggested. Patients are likely to be guided by their physicians' views of the exoskeleton and are initially limited to using it in a rehabilitation setting, thus requiring clinician buy-in for training before using the exoskeleton in a home setting, two clinical experts stated.[411,412] Patients who are highly motivated to walk, who can commit to intensive training, and who can afford the device may readily adopt the exoskeleton, experts noted.

Health care delivery infrastructure and patient management: Health care delivery infrastructure is likely to be minimally impacted by use of the exoskeleton, experts agreed. The biggest impact will be in the additional training needed for physical therapists, biomedical engineers, and other staff, experts noted. Patient management may also be impacted by the amount of training needed for patients and caregivers in rehabilitation and home settings, experts concurred.

Rehabilitation centers need to purchase an exoskeleton for patient training and may need additional staff to provide it, factors that will impact cost to the centers, experts said. Patients and third-party payers may face substantial costs because of the high price of the exoskeleton and a need to replace it every 5 years, experts stated. A clinical expert suggested any overall effects would be limited because the patient population is small.[411] An expert with a research perspective speculated that any controversies over costs may be minimal because many in the affected population are likely combat veterans.[410]

Health disparities: Health disparities may increase because of the high cost of the exoskeleton, all experts agreed. A clinical expert noted that patients must pay for 20% of the cost of durable medical equipment that is covered by Medicare, which may be prohibitive for some.[412] Two experts mentioned that additional training and maintenance of the device may be required, adding to costs that may affect access.[407,410]

Upper Limb Amputation Intervention

Prosthetic Arm with Body-Machine Interface (DEKA Arm System) to Restore Arm Function After Amputation

Unmet need: Patients in whom an upper limb has been amputated have options for prostheses, but prosthesis function is generally limited to sequential movements that require deliberate effort to control. Patients do not have options that provide natural movement, intuitive controls, or tactile sensations.[413] As a result, many patients with an arm prosthesis are still functionally limited. Advances incorporating miniaturized computer components, lightweight but strong materials, and body-machine interfaces combined into a prosthetic hand and arm have resulted in the DEKA Arm System, a device that has up to 10 powered degrees of freedom and multiple unique features.[414]

Intervention: The following information is based on descriptions of the Gen 3 DEKA Arm System used in clinical studies. Whether the features of this arm will be available in a commercially produced prosthesis is unclear.[414,415] DEKA arm features movable joints, a wrist, and independently movable fingers. The device has a metallic external structure with no exposed mechanics, does not require a fabric sleeve, and is dust and water resistant. The entire arm is resistant to light rain, and the fingers up to the base can be immersed in water.[415]

An embedded LED wrist display alerts the user to grip, mode, power, battery charge, and system faults. An audible vibration indicates when the mode changes between hand and arm, when it moves in or out of standby, and when grip mode or grip pressure is changed.[414]

The DEKA arm is designed for three configurations: shoulder, humeral, and radial.[414] It can be used only by patients who have limb loss at the shoulder joint, mid-upper arm, or mid-lower arm—not at the elbow or wrist.[416] The humeral and shoulder configurations can accommodate an internal battery while all configurations can use an external battery worn on a belt or harness.[414,415] The internal battery has a run time of about 1 hour and the external battery, about 6 hours.[415] The shoulder configuration weighs 9.8 lb, the humeral configuration weighs 6.8 lb, and the radial configuration weighs 2.8 lb.[415]

The shoulder configuration has 10 powered degrees of freedom and additional passive degrees of freedom that allow for simultaneous, coordinated movement at the shoulder, humeral rotator, elbow, forearm, wrist, thumb, index finger, or fingers three to five.[414] Although several movements can be performed at once by combining foot controls, myoelectrodes, pneumatic bladders, manual switches, and other common input devices, the DEKA arm must switch between hand and arm modes to accomplish many tasks.[414,415] A limited number of hand movements can be performed when in arm mode.[415] The hand mode has six programmed grips for objects of various sizes and shapes.[415] The detent feature allows users to manipulate an object in the hand without losing the grip on it (e.g., holding and using a spray bottle).[415] The wrist has four powered movements.[415] The shoulder configuration has an endpoint control system that uses software to coordinate joint movements to bring the end of the prosthesis into a desired position from one command instead of a series of commands.[415] A dynamic socket controller regulates inflatable bladders inside transhumeral sockets to stabilize the device and provide pressure relief. Patients control this function using buttons.[414]

Patients using the DEKA arm can perform several tasks that are reportedly too complex for other prosthetic devices, including using keys and zippers.[416] Several features have been incorporated into the DEKA arm to prevent accidents and user errors. For example, the device is able to recognize when it is moving toward the head and reduce its speed to avoid a collision. It can distinguish between intentional foot controls and walking, trips, or stumbles.[415]

Before using a DEKA arm, patients may need targeted muscle reinnervation to expand the number of distinct electromyographic signal sites available for surface myoelectrodes. In targeted muscle reinnervation, surgeons transfer nerve connections that once controlled a patient's hand or

arm to remaining muscles. The procedure offers more intuitive control of a prosthesis because the nerves that once controlled the amputated limb control the reinnervated muscles. Signals from the transferred nerves are amplified by the reinnervated muscle and are more easily detected by surface electrodes.[413]

Clinical trials: In one study of 37 patients using second- and third-generation DEKA Arm System, researchers reported that 79% of Gen 2 and 85% of Gen 3 users indicated they wanted to receive or might want to receive a DEKA arm; 95% of Gen 2 and 91% of Gen 3 prior prosthesis users reported that they were able to perform new activities that were beyond the capabilities of their own prosthetic devices.[417] Researchers further reported that patients rated satisfaction and usability higher for the third-generation device than the second-generation device.[418] A prospective, observational cohort study with 75 patients is ongoing to evaluate the change in quality of life while using the device at home for 13 weeks.[419]

Manufacturer and regulatory status: The DEKA Arm System was developed by DEKA Integrated Solutions (Manchester, NH) in conjunction with prosthetic engineers from Next Step Bionics and Prosthetics, Inc. (Manchester, NH), and Biodesigns, Inc. (Westlake Village, CA).[420,421] The U.S. Defense Advanced Research Projects Agency's (DARPA) "Revolutionizing Prosthetics" program provided funding to DEKA with the goal of developing a prosthetic arm with natural control.[421] In May 2014, FDA cleared the DEKA Arm System through its de novo classification process.[416,422]

The system is not yet commercially available because the developer is seeking a partner to manufacture and commercialize the prosthesis. The developer stated that if a manufacturing partner is not found, DEKA Integrated Solutions will manufacture and sell the DEKA arm, although no timetable was given.[423] The developer has received another grant from DARPA for developing a prosthesis with a sense of touch.[424]

Diffusion and cost: DEKA Integrated Solutions does not yet have a manufacturing partner, so no cost information is available.[416] In an interview with the Boston Business Journal, the developer said the cost will depend on the number made, but would ideally be in the range of tens of thousands of dollars.[425]

Medicare Part B covers artificial limbs as durable medical equipment for beneficiaries whose physician has prescribed it for home use. Patients must pay 20% of the Medicare-approved amount. If a durable medical equipment supplier does not accept direct Medicare reimbursement, Medicare cannot limit the amount a supplier can charge. In certain geographic areas, Medicare's competitive bidding program may be in effect, which means that Medicare pays for the equipment and related supplies only if they are obtained from contracted suppliers. These suppliers cannot charge patients more than 20% coinsurance and any unmet yearly deductible for any equipment or supplies included in the competitive bidding program.[426]

Our searches of 11 representative, private, third-party payers that publish their policies online found 9 policies related to upper arm prostheses that employ myoelectric control. The policies outline specific criteria for providing coverage of these devices when medically necessary.[427-435] Although the DEKA arm presumably falls under these policies, only two, Blue Cross/Blue Shield Alabama and Regence, specifically reference the DEKA arm as an example of a myoelectric prosthesis.[429,434]

Clinical Pathway at Point of This Intervention

After a patient's amputation site has completed primary healing, long-term care is often provided by physical medicine and rehabilitation physicians, who focus on pain management, medications, and occupational and physical therapy.[436] They coordinate care for emotional health,

prosthetic treatment, occupational and physical therapy, social services, and return-to-work issues.[436] Occupational therapists also address pain control, self-care strategies, work needs, and prosthetic training.[437]

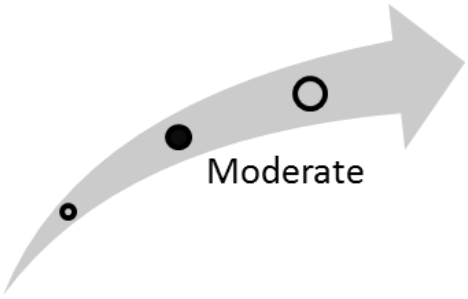
Prosthesis options for patients depend on the degree of amputation and remaining function. Amputations on the limb closer to the trunk need prostheses that have more functions to control more joints. Four types of prostheses are commonly available, as follows:[437,438]

- Passive: requires use of another limb to reposition it; may be functional or cosmetic
- Body-powered: operated by moving a cable often connected to opposite shoulder or by a switch often controlled by the chin
- Myoelectric: composed of an external battery, electric motor, and microprocessing unit that responds to transcutaneous electric signals sent by remaining muscles
- Hybrid: combines body-powered and myoelectric mechanisms for controlling prostheses

Tasks using a prosthesis are performed in sequential steps. Some myoelectric devices use pattern recognition to improve response speed and decrease operation burdens.[413]

Patients choose a prosthesis based on factors including function, weight, aesthetics, cost, and ease of use. Not all prostheses can be configured for all degrees of amputation and many prostheses have no fine motor control and cannot use multiple joints at once. They may look unnatural, can be heavy or uncomfortable, may not be waterproof, and have no tactile sensation.[439] Patients commonly use prostheses for only a portion of the day or specific tasks because of these disadvantages.[438]

Figure 16. Overall high-impact potential: prosthetic arm with body-machine interface (DEKA Arm System) to restore natural arm function after amputation



Overall, experts commenting on this intervention thought a significant unmet need exists for restoring natural arm function to patients with upper limb amputations, and this device provides functionality well beyond any available prostheses. Experts thought that clinician and patient enthusiasm might be tempered by high costs and complex training, potentially increasing health disparities due to unequal access. Experts suggested that the prosthesis' overall impact would be mitigated by the small population likely to use the DEKA arm. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this intervention.[440-445] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: An unmet need exists for a prosthetic arm that restores natural arm functions to individuals who have had an amputation, experts agreed. The DEKA Arm System has more degrees of freedom, better coordinated gross and fine motor functions, and greater

potential to improve quality of life than available prostheses, experts concurred. Some experts tempered their enthusiasm by noting that this device lacks sensory perception and is not suitable for all patients who have had an arm amputated.

Acceptance and adoption: Acceptance among clinicians may vary, as indicated by contrasting expert comments. The experts thought that clinicians focusing on improved quality of life and function for patients will readily accept the device, but other clinicians may be reluctant because of the cost and complexity of the prosthesis. One expert with a research perspective suggested that doctors might not want to invest time and effort in training themselves on the device if only a small number of their patients would benefit.[442]

Cost and complexity may be barriers to patient adoption, experts agreed. "…Patients with reduced mental capacity, brain injury, etc[.,] may have significant difficulty with the use of this device and thus would not accept it," a clinical expert said.[444] Highly motivated patients who desire the increased function of the device will overcome these barriers, some experts said.

Health care delivery infrastructure and patient management: No infrastructure changes are necessary because the DEKA arm will be offered in the same setting as other limb prostheses, the experts noted. Increased staffing and training will be necessary for providing initial and ongoing care to patients who use the device, experts said. Patients will need device-specific surgery to use the device and extensive device maintenance provided by biomedical engineers, the experts thought. Small community hospitals may face large barriers to implementing processes for using the DEKA arm because of its complexity and the limited demand, but larger hospitals may be more capable of handling the changes, a research expert suggested.[442]

Initial costs for the device, surgery, and complex training will be high, experts agreed. Ongoing maintenance will also be expensive because of the complexity of the prosthesis, experts said. One clinical expert suggested that improved function will reduce costs associated with long-term and home care for completing activities of daily living and community involvement.[444]

Health disparities: Health disparities may be increased because of the high cost and complexity of the device, the experts agreed. Patients without any insurance or inadequate insurance may have difficulty paying for the device; even patients who have 80% of the cost covered by Medicare Part B as durable medical equipment might not be able to afford the remainder, one expert with a research perspective noted.[443] The complexity of the device means patients will need access to maintenance and technical-support experts, which may be a barrier for rural patients, another research expert pointed out.[442] Experts commented that patients with low literacy or mental capacity may be unable to learn how to use the device.

References

1. Shin SH, Lee JW. The optimal immunosuppressive therapy for aplastic anemia. Int J Hematol. 2013 May;97(5):564-72. Also available: http://dx.doi.org/10.1007/s12185-013-1331-y. PMID: 23605367.
2. Aplastic anemia: treatment. [internet]. Rockville (MD): The Aplastic Anemia and MDS International Foundation; 2014 Dec 2 [accessed 2015 Mar 13]. [2 p]. Available: http://www.aamds.org/about/aplastic-anemia/treatment.
3. GSK receives FDA approval of an additional Promacta (eltrombopag) indication for use in patients with severe aplastic anaemia (SAA) who have had an insufficient response to immunosuppressive therapy (IST). [internet]. Middlesex (UK): GlaxoSmithKline plc.; 2014 Aug 26 [accessed 2014 Nov 24]. [10 p]. Available: http://www.gsk.com/en-gb/media/press-releases/2014/gsks-promacta-eltrombopag-receives-fda-approval-of-an-additional-indication/.
4. GlaxoSmithKline. Highlights of prescribing information: Promacta (eltrombopag) tablets, for oral use. Research Triangle Park (NC): GlaxoSmithKline; 2014 Aug. 35 p.
5. Desmond R, Townsley DM, Dumitriu B, et al. Eltrombopag restores trilineage hematopoiesis in refractory severe aplastic anemia that can be sustained on discontinuation of drug. Blood. 2014 Mar 20;123(12):1818-25. Also available: http://dx.doi.org/10.1182/blood-2013-10-534743. PMID: 24345753.
6. National Heart, Lung, and Blood Institute (NHLBI). Eltrombopag for moderate aplastic anemia. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2014 Nov 24]. [4 p]. Available: https://www.clinicaltrials.gov/ct2/show/NCT01328587 NLM Identifier: NCT01328587.
7. European Group for Blood and Marrow Transplantation. hATG+CsA vs hATG+CsA+eltrombopag for SAA (RACE). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Nov 24]. [5 p]. Available: https://www.clinicaltrials.gov/ct2/show/NCT02099747 NLM Identifier: NCT02099747.
8. Promacta pricing info. [internet]. Santa Monica (CA): GoodRx, Inc. [accessed 2014 Nov 25]. [8 p]. Available: http://www.goodrx.com/promacta/price.
9. OmedaRx. Promacta, eltrombopag. Policy No: dru180. [internet]. Portland (WA): OmedaRx; 2015 May 1 [accessed 2015 Dec 17]. [12 p]. Available: http://blue.regence.com/trgmedpol/drugs/dru180.pdf.
10. Aetna, Inc. 2015 Aetna specialty pharmacy drug list. [internet]. Hartford (CT): Aetna, Inc.; 2015 Jul [accessed 2015 Sep 16]. [9 p]. Available: https://www.aetna.com/content/dam/aetna/pdfs/formulary/2015_Value_Specialty.pdf.
11. Blue Cross and Blue Shield of Alabama. Specialty pharmacy drug management list. East Birmingham (AL): Blue Cross and Blue Shield of Alabama; 2015 Dec 1. 2 p. Also available: https://www.myprime.com/content/dam/prime/memberportal/forms/2014/FullyQualified/Other/ALL/BCBSAL/COMMERCIAL/ALL/AL_Specialty_Drug_List.pdf.
12. Blue Cross and Blue Shield of Massachusetts. Your pharmacy program. Rockland (MA): Blue Cross and Blue Shield of Massachusetts; 2015 Jan 1. 45 p.
13. CIGNA Corporation. Drug list search results. [internet]. Bloomfield (CT): CIGNA Corporation [accessed 2015 Oct 27]. [144 p]. Available: http://www.cigna.com.
14. HealthPartners. Specialty drug list. [internet]. Minneapolis (MN): HealthPartners; 2015 Oct 1 [accessed 2015 Oct 27]. [3 p]. Available: http://www.healthpartners.com.
15. Humana, Inc. Provider drug list search - Promacta. [internet]. Louisville (KY): Humana, Inc. [accessed 2015 Dec 07]. [2 p]. Available: http://apps.humana.com/UnsecuredDrugListSearch/ProviderSearchResults.aspx.
16. Medica. Medica 2015 comprehensive preferred drug list (PDL). Minnetonka (MN): Medica; 2015 Dec 1. 171 p. Also available: http://www.medica.com.
17. Wellmark, Inc. Wellmark specialty drug list. Des Moines (IA): Wellmark, Inc.; 2015 Jul 31. 1 p. Also available: http://www.wellmark.com.

18. Expert Commenter 1573. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS2048 - Eltrombopag (Promacta) for treatment of severe or very severe aplastic anemia. 2015 Jul 22 [review date].

19. Expert Commenter 1546. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS2048 - Eltrombopag (Promacta) for treatment of severe or very severe aplastic anemia. 2015 Jul 17 [review date].

20. Expert Commenter 1192. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2048 - Eltrombopag (Promacta) for treatment of severe or very severe aplastic anemia. 2015 Jul 23 [review date].

21. Expert Commenter 420. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2048 - Eltrombopag (Promacta) for treatment of severe or very severe aplastic anemia. 2015 Jul 20 [review date].

22. Expert Commenter 663. (External, Clinical). Horizon Scanning Structured Comment Form. HS2048 - Eltrombopag (Promacta) for treatment of severe or very severe aplastic anemia. 2015 Aug 3 [review date].

23. Expert Commenter 1437. (External, Clinical). Horizon Scanning Structured Comment Form. HS2048 - Eltrombopag (Promacta) for treatment of severe or very severe aplastic anemia. 2015 Aug 10 [review date].

24. National Institute of Neurological Disorders and Stroke (NINDS). Multiple sclerosis: hope through research. [internet]. Bethesda (MD): National Institutes of Health (NIH); 2012 Jun 01 [updated 2014 May 21] [accessed 2014 Jun 05]. [11 p]. Available: http://www.ninds.nih.gov/disorders/multiple_sclerosis/detail_multiple_sclerosis.htm.

25. Relapsing-remitting MS (RRMS). [internet]. New York (NY): National Multiple Sclerosis Society [accessed 2014 Jun 05]. [5 p]. Available: http://www.nationalmssociety.org/What-is-MS/Types-of-MS/Relapsing-remitting-MS.

26. Rabasseda X. Highlights from the 25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). Drugs Today. 2010;46(1):49-67.

27. Gilenya (fingolimod) capsules prescribing information. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2012 May. 22 p. Also available: http://www.pharma.us.novartis.com/product/pi/pdf/gilenya.pdf.

28. How relapsing-remitting MS (RRMS) is diagnosed. [internet]. New York (NY): National Multiple Sclerosis Society [accessed 2011 Mar 11]. [2 p]. Available: http://www.nationalmssociety.org/about-multiple-sclerosis/relapsing-ms/relapsing-remitting-ms-rrms/how-rrms-is-diagnosed/index.aspx.

29. Giovannoni G, Mikulskis A, McNeil M, et al. Evaluation of immunogenicity in multiple sclerosis patients continuously treated with daclizumab-HYP during the SELECT and SELECTION clinical trials. Mult Scler. 2013 Oct;19(11). Also available: http://dx.doi.org/10.1177/1352458513502429.

30. Bielekova B. Daclizumab therapy for multiple sclerosis. Neurotherapeutics. 2013;10(1):55-67. Also available: http://dx.doi.org/10.1007/s13311-012-0147-4. PMID: 23055048.

31. Pfender N, Martin R. Daclizumab (anti-CD25) in multiple sclerosis. Exp Neurol. 2014 Dec;262PA:44-51. Also available: http://dx.doi.org/10.1016/j.expneurol.2014.04.015. PMID: 24768797.

32. Huss DJ, Mehta DS, You X, et al. IL-2R(beta)(gamma)-signaling contributes to regulatory T cell maintenance and stability in daclizumab HYP-treated RRMS patients. Mult Scler. 2014 Sep;20(1) Also available: http://dx.doi.org/10.1177/1352458514547846.

33. Wuest SC, Mexhitaj I, Chai NR, et al. A complex role of herpes viruses in the disease process of multiple sclerosis. PLoS ONE. 2014;9(8):e105434. Also available: http://dx.doi.org/10.1371/journal.pone.0105434. PMID: 25148387.

34. Gold R, Giovannoni G, Selmaj K, et al. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): A randomised, double-blind, placebo-controlled trial. Lancet. 2013;381(9884):2167-75. Also available: http://dx.doi.org/10.1016/S0140-6736(12)62190-4. PMID: 23562009.

35. Giovannoni G, Gold R, Selmaj K, et al. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECTION): A multicentre, randomised, double-blind extension trial. Lancet Neurol. 2014 May;13(5):472-81. Also available: http://dx.doi.org/10.1016/S1474-4422(14)70039-0. PMID: 24656609.

36. Detailed results from Biogen Idec and Abbvie's pivotal phase 3 decide study further define the efficacy and safety profile of Zinbryta (daclizumab high-yield process). [internet]. Cambridge (MA): Biogen Idec; 2014 Sep 12 [accessed 2014 Dec 04]. [5 p]. Available: http://www.biogenidec.com/press_release_details.aspx?ID=14712&Action=1&NewsId=2377&currentPage=2&M=NewsV2&PID=61997.

37. Kappos L, Wiendl H, Selmaj K, et al. Daclizumab HYP versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med. 2015 Oct 8;373(15):1418-28. Also available: http://dx.doi.org/10.1056/NEJMoa1501481. PMID: 26444729.

38. Selmaj K, Kappos L, Arnold DL, et al. Safety and tolerability of daclizumab HYP treatment in relapsing-remitting multiple sclerosis: Results of the DECIDE study. Mult Scler. 2014 Sep;20(1) Also available: http://dx.doi.org/10.1177/1352458514546077.

39. Milo R. The efficacy and safety of daclizumab and its potential role in the treatment of multiple sclerosis. Ther Adv Neurol Disord. 2014 Jan;7(1):7-21. Also available: http://dx.doi.org/10.1177/1756285613504021.

40. Review of safety for Zenapax (daclizumab). Rockville (MD): U.S Food and Drug Administration (FDA), Center for Biologics Evaluation and Research; 1997 Dec 12. 16 p. Also available: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113478.pdf.

41. FDA accepts Biologics license application for Zinbryta (daclizumab high-yield process) for treatment of MS. [internet]. Cambridge (MA): Biogen; 2015 Apr 29 [accessed 2015 Jun 11]. [5 p]. Available: http://media.biogen.com/press-release/corporate/fda-accepts-biologics-license-application-zinbryta-daclizumab-high-yield-pro.

42. Hoffman-La Roche, Inc. Zenapax (daclizumab) sterile concentration for injection - drug label. Nutley (NJ): Hoffman-La Roche, Inc.; 1997 Dec. 2 p. Also available: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113468.pdf.

43. Birgerson LE. Zenapax discontinuation notice. Nutley (NJ): Hoffmann-La Roche Inc.; 2009 Sep. 2 p. Also available: http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM194907.pdf.

44. Mayo Clinic staff. Multiple sclerosis.Rochester (MN): Mayo Foundation for Medical Education and Research (MFMER); 2012 Dec 15 [accessed 2013 Apr 12]. [9 p]. Available: http://www.mayoclinic.com/health/multiple-sclerosis/DS00188/.

45. National Institutes of Health (NIH). Multiple sclerosis. In: PubMed Health [internet]. Bethesda (MD): National Library of Medicine (U.S.); 2013 Sep 25 [accessed 2014 Jun 05]. [8 p]. Available: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001747/.

46. National Institute of Neurological Disorders and Stroke (NINDS). NINDS multiple sclerosis information page. [internet]. Bethesda (MD): National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH); 2012 Aug 14 [accessed 2013 Apr 12]. [3 p]. Available: http://www.ninds.nih.gov/disorders/multiple_sclerosis/multiple_sclerosis.htm.

47. For people with relapsing MS. [internet]. New York (NY): National Multiple Sclerosis Society [accessed 2012 Mar 06]. [2 p]. Available: http://www.nationalmssociety.org/about-multiple-sclerosis/relapsing-ms/index.aspx.

48. What we know about progressive-relapsing MS (PRMS). [internet]. New York (NY): National Multiple Sclerosis Society [accessed 2013 Jun 03]. [2 p]. Available: http://www.nationalmssociety.org/about-multiple-sclerosis/progressive-ms/progressive-relapsing-ms/index.aspx.

49. FDA approves first oral drug to reduce MS relapses. [internet]. Rockville (MD): U.S. Food and Drug Administration (FDA); 2010 Sep 22 [accessed 2011 Mar 11]. [1 p]. Available: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm226755.htm.

50. FDA approves new multiple sclerosis treatment Aubagio. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2012 Sep 12 [accessed 2012 Sep 25]. [2 p]. Available: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm319277.htm.

51. Oral laquinimod for multiple sclerosis granted fast track status by FDA. In: Medical News Today [internet]. Bexhill-on-Sea (UK): MediLexicon International Ltd.; 2009 Feb 16 [accessed 2012 Nov 27]. [6 p]. Available: http://www.medicalnewstoday.com/releases/139148.php.

52. Expert Commenter 1530. (External, Clinical). Horizon Scanning Structured Comment Form. HS1223 - Daclizumab (Zinbryta) for treatment of multiple sclerosis. 2015 Mar 17 [review date].

53. Expert Commenter 1383. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS1223 - Daclizumab (Zinbryta) for treatment of multiple sclerosis. 2015 Feb 17 [review date].

54. Expert Commenter 394. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS1223 - Daclizumab (Zinbryta) for treatment of multiple sclerosis. 2015 Feb 13 [review date].

55. Expert Commenter 1192. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1223 - Daclizumab (Zinbryta) for treatment of multiple sclerosis. 2015 Feb 13 [review date].

56. Expert Commenter 1219. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1223 - Daclizumab (Zinbryta) for treatment of multiple sclerosis. 2015 Feb 12 [review date].

57. Expert Commenter 1488. (External, Clinical). Horizon Scanning Structured Comment Form. HS1223 - Daclizumab (Zinbryta) for treatment of multiple sclerosis. 2015 Mar 17 [review date].

58. Rockman-Greenberg C. Hypophosphatasia. Pediatr Endocrinol Rev. 2013 Jun;10 Suppl 2:380-8. PMID: 23858621.

59. Hypophosphatasia. In: Genetics Home Reference [internet]. Bethesda (MD): National Library of Medicine (U.S.); 2015 Apr 6 [accessed 2015 Apr 13]. [4 p]. Available: http://ghr.nlm.nih.gov/condition=hypophosphatasia.

60. American Academy of Pediatrics (AAP), American College of Obstetricians and Gynecologists (ACOG). Guidelines for perinatal care. 7th ed. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2012. 580 p. Also available: http://reader.aappublications.org/guidelines-for-perinatal-care-7th-edition/598.

61. Millan JL, Plotkin H. Hypophosphatasia - pathophysiology and treatment. Actualizaciones en Osteologia. 2012 Sep 1;8(3):164-82. PMID: 25254037.

62. Hypophosphatasia. Boonton (NJ): Soft Bones Foundation. 4 p. Also available: http://softbones.org/resources/SoftBones_Foundation_Brochure-01.2013.pdf.

63. Mornet E. Hypophosphatasia. Best Pract Res Clin Rheumatol. 2008 Mar;22(1):113-27. Also available: http://dx.doi.org/10.1016/j.berh.2007.11.003. PMID: 18328985.

64. Plotkin H. Hypophosphatasia treatment & management. In: Medscape Reference [internet]. New York (NY): WebMD, LLC; 2010 May 06 [accessed 2012 Feb 23]. [3 p]. Available: http://emedicine.medscape.com/article/945375-treatment.

65. FAQs. [internet]. Boonton (NJ): Soft Bones Foundation [accessed 2015 Apr 13]. [2 p]. Available: http://softbones.org/content.php?146.

66. Whyte MP, Greenberg CR, Salman NJ, et al. Enzyme-replacement therapy in life-threatening hypophosphatasia. New Eng J Med. 2012 Mar 8;366(10):904-13. Also available: http://dx.doi.org/10.1056/NEJMoa1106173. PMID: 22397652.

67. Strensiq (asfotase alfa) injection, for subcutaneous use prescribing information. Cheshire (CT): Alexion Pharmaceuticals, Inc.; 2015 Oct. 8 p. Also available: http://www.strensiq.com/images/pi.pdf.

68. Enobia Canada Limited Partnership. Extension study of protocol ENB-002-08 - ENB-0040 treatment in severly affected infants and young children with hypophosphatasia (HPP). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2012 Apr 10]. [4 p]. Available: http://www.clinicaltrials.gov/ct2/show/NCT01205152 NLM Identifier: NCT01205152.

69. Enobia Canada Limited Partnership. Open-label study of ENB-0040 in infants and children <_ 5 years of age with hypophosphatasia (HPP). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2012 Apr 10]. [5 p]. Available: http://www.clinicaltrials.gov/ct2/show/NCT01176266 NLM Identifier: NCT01176266.

70. Phillips D, Hamilton K, Moseley S, et al. OR29-4 Significantly improved muscle strength, running speed, and agility in children with hypophosphatasia treated with asfotase alfa. [internet]. Washington (DC): Endocrine Society; 2015 Mar 7 [accessed 2015 Apr 07]. [1 p]. Available: https://endo.confex.com/endo/2015endo/webprogram/Paper20906.html.

71. Phillips D, Hamilton K, Moseley S, et al. Improved activities of daily living and physical function, with decreased pain, in children with hypophosphatasia treated for three years with asfotase alfa: results from the childhood health assessment questionnaire and the pediatric outcomes data collection instrument. [internet]. Washington (DC): Endocrine Society; 2015 Mar 6 [accessed 2015 Apr 07]. [1 p]. Available: https://endo.confex.com/endo/2015endo/webprogram/Paper21021.html.

72. Greenberg CR, Landy H, Taylor J, et al. Hypophosphatasia: one year of treatment of life-threatening disease using bone-targeted human recombinant tissue non-specific alkaline phosphatase. Bethesda (MD): American College of Medical Genetics and Genomics (ACMG); 2010. 1 p. Also available: http://acmg.omnibooksonline.com/2010/data/papers/004.pdf.

73. Rodriguez E, Bober MB, Davey L, et al. Respiratory mechanics in an infant with perinatal lethal hypophosphatasia treated with human recombinant enzyme replacement therapy. Pediatr Pulmonol. 2012 Sep;47(9):917-22. Also available: http://dx.doi.org/10.1002/ppul.22527. PMID: 22328548.

74. Whyte M, Simmons J, Lutz R, et al. Sustained efficacy and tolerability in infants and young children with life-threatening hypophosphatasia treated with asfotase alfa. Presesented at the European Calcified Tissue Society Congress 2014, Czech Republic, Prague. In: Bone Abstracts [internet]. Bristol (UK): European Calcified Tissue Society (ECTS); 2014 May 17 [accessed 2015 May 05]. [2 p]. Available: http://www.bone-abstracts.org/ba/0003/ba0003PP363.htm.

75. Kishnani P, Rockman-Greenberb C, Whyte M, et al. Hypophosphatasia: enzyme replacement therapy (ENB-0040) decreases TNSALP substrate accumulation and improves functional outcome in affected adolescents and adults. Endocr Abstracts. 2012;29:OC8.1. Also available: http://www.endocrine-abstracts.org/ea/0029/ea0029oc8.1.htm.

76. Alexion completes rolling BLA submission to U.S. FDA for asfotase alfa as a treatment for patients with hypophosphatasia. [internet]. Cheshire (CT): Alexion Pharmaceuticals, Inc.; 2014 Dec 30 [accessed 2015 May 05]. [4 p]. Available: http://news.alexionpharma.com/press-release/company-news/alexion-completes-rolling-bla-submission-us-fda-asfotase-alfa-treatment-p.

77. FDA approves new treatment for rare metabolic disorder. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2015 Oct 23 [updated 2015 Oct 26]; [accessed 2015 Dec 04]. [5 p]. Available: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm468836.htm.

78. Carroll J. UPDATED: Alexion wins FDA OK on Strensiq, but startles analysts on price. [internet]. Washington (DC): FierceMarkets; 2015 Oct 23 [accessed 2015 Dec 04]. [4 p]. Available: http://www.fiercebiotech.com/story/alexion-wins-priority-review-voucher-fda-ok-strensiq/2015-10-23.

79. Welcome to OneSource. [internet]. Cheshire (CT): Alexion Pharmaceuticals, Inc. [accessed 2015 Dec 04]. [4 p]. Available: http://www.strensiq.com/onesource.

80. Mornet E. Hypophosphatasia. Orphanet J Rare Dis. 2007;2:40. PMID: 17916236.

81. Expert Commenter 396. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS1335 - Asfotase alfa (Strensiq) for treatment of hypophosphatasia in infants and children. 2015 Jul 29 [review date].

82. Expert Commenter 1384. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS1335 - Asfotase alfa (Strensiq) for treatment of hypophosphatasia in infants and children. 2015 Jul 22 [review date].

83. Expert Commenter 1192. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1335 - Asfotase alfa (Strensiq) for treatment of hypophosphatasia in infants and children. 2015 Jul 20 [review date].

84. Expert Commenter 1576. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1335 - Asfotase alfa (Strensiq) for treatment of hypophosphatasia in infants and children. 2015 Jul 28 [review date].

85. Expert Commenter 1516. (External, Clinical). Horizon Scanning Structured Comment Form. HS1335 - Asfotase alfa (Strensiq) for treatment of hypophosphatasia in infants and children. 2015 Aug 25 [review date].

86. Expert Commenter 756. (External, Clinical). Horizon Scanning Structured Comment Form. HS1335 - Asfotase alfa (Strensiq) for treatment of hypophosphatasia in infants and children. 2015 Sep 15 [review date].

87. Hereditary angioedema. In: MedlinePlus [internet]. Bethesda (MD): National Library of Medicine (U.S.); 2014 May 12 [accessed 2014 Nov 20]. [2 p]. Available: http://www.nlm.nih.gov/medlineplus/ency/article/001456.htm.

88. Frank MM. Hereditary angioedema. In: Medscape Reference [internet]. New York (NY): WebMD, LLC; 2015 Feb 25 [accessed 2015 Mar 02]. [6 p]. Available: http://emedicine.medscape.com/article/135604-overview.

89. Ruconest. [internet]. Leiden (The Netherlands): Pharming Group NV [accessed 2014 Oct 27]. [4 p]. Available: http://www.pharming.com/products/ruconest.

90. FDA approves new product to treat rare genetic disease. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2014 Jul 17 [accessed 2014 Oct 28]. [4 p]. Available: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm405526.htm.

91. Ruconest (C1 esterase inhibitor [recombinant]) for intravenous use, lyophilized powder for reconstitution product information. Leiden (The Netherlands): Pharming Group NV; 2014 Jul. 22 p.

92. Riedl MA, Levy RJ, Suez D, et al. Efficacy and safety of recombinant C1 inhibitor for the treatment of hereditary angioedema attacks: A North American open-label study. Ann Allergy Asthma Immunol. 2013 Apr;110(4):295-9. Also available: http://dx.doi.org/10.1016/j.anai.2013.02.007. PMID: 23535096.

93. Riedl MA, Bernstein JA, Li H, et al. Recombinant human C1-esterase inhibitor relieves symptoms of hereditary angioedema attacks: phase 3, randomized, placebo-controlled trial. Ann Allergy Asthma Immunol. 2014 Feb;112(2):163-69. Epub 2014 Jan 7. Also available: http://dx.doi.org/10.1016/j.anai.2013.12.004. PMID: 24468257.

94. Reshef A, Zanichelli A, Longhurst H, et al. Recombinant human C1 inhibitor treatment does not affect d-dimer levels and is not associated with thromboembolic events in hae patients [abstract 130]. J Allergy Clin Immunol. 2014 Feb;133(2):AB36. Also available: http://dx.doi.org/10.1016/j.jaci.2013.12.154.

95. Pharming Technologies B.V. C1 inhibitor registry in the treatment of hereditary angioedema (HAE) attacks. In: ClinicalTrials.gov [database online]. Bethesda (MD): U.S. National Library of Medicine (NLM); 2000- [accessed 2015 Jun 08]. [3 p]. Available: https://clinicaltrials.gov/ct2/show/NCT01397864 NLM Identifier: NCT01397864.

96. Li HH, Moldovan D, Bernstein JA, et al. Recombinant human-C1 Inhibitor is effective and safe for repeat hereditary angioedema attacks. J Allergy Clin Immunol Pract. 2015 May-Jun;3(3):417-23. Epub 2015 Feb 10. Also available: http://dx.doi.org/10.1016/j.jaip.2014.12.013. PMID: 25680925.

97. Zuraw B, Cicardi M, Levy RJ, et al. Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema. J Allergy Clin Immunol. 2010 Oct;126(4):821-7.e14. Also available: http://dx.doi.org/10.1016/j.jaci.2010.07.021. PMID: 20920772.

98. Moldovan D, Reshef A, Fabiani J, et al. Efficacy and safety of recombinant human C1-inhibitor for the treatment of attacks of hereditary angioedema: European open-label extension study. Clin Exp Allergy. 2012 Jun;42(6):929-35. Also available: http://dx.doi.org/10.1111/j.1365-2222.2012.03984.x. PMID: 22909164.

99. Pharming and Salix announce initiation of clinical study of Ruconest for prophylaxis of hereditary angioedema. [internet]. Leiden (The Netherlands): Pharming Group NV; 2014 Aug 28 [accessed 2014 Oct 27]. [4 p]. Available: http://www.pharming.com/archives/2086.

100. Priority Health. Pharmacy prior authorization form: Ruconest (recombinant c1 esterase inhibitor). Grand Rapids (MI): Priority Health; 2014 Nov. 1 p. Also available: https://www.priorityhealth.com/provider/forms/~/media/documents/drug-auth-forms/o-s/ruconest-pa-commercial-medicaid-michild.pdf.

101. Berinert pricing info. [internet]. Santa Monica (CA): GoodRx, Inc. [accessed 2015 Mar 02]. [8 p]. Available: http://www.goodrx.com/berinert.

102. Ruconest: Feedback from physician interviews and sales update. London (UK): Stifel; 2015. 6 p. Also available: http://www.pharming.com/archives/2580.

103. Aetna, Inc. Clinical policy bulletin: hereditary angioedema. Number: 0782. [internet]. Hartford (CT): Aetna, Inc.; 2015 May 22 [accessed 2015 Jun 11]. [38 p]. Available: http://www.aetna.com/cpb/medical/data/700_799/0782.html.

104. Anthem Insurance Companies. Pharmacotherapy for hereditary angioedema (HAE) [policy #DRUG.00058]. [internet]. North Haven (CT): Anthem Insurance Companies, Inc.; 2014 Oct 14 [accessed 2014 Oct 28]. [10 p]. Available: http://www.anthem.com/medicalpolicies/policies/mp_pw_c164427.htm.

105. United HealthCare Services, Inc. Hereditary angioedema (HAE), treatment and prophylaxis. Policy number 2013D0044C. Edina (MN): United HealthCare Services, Inc.; 2014 Nov 1. 13 p. Also available: http://www.unitedhealthcare.com.

106. Wellmark, Inc. Hereditary angioedema therapies. Medical policy: 05.01.23. [internet]. Des Moines (IA): Wellmark, Inc.; 2014 Oct 01 [accessed 2014 Oct 28]. [4 p]. Available: https://www.wellmark.com/Provider/MedPoliciesAndAuthorizations/MedicalPolicies/policies/Cinryze.aspx?pf=true.

107. Humana, Inc. Provider drug list search - ruconest. [internet]. Louisville (KY): Humana, Inc. [accessed 2015 Jun 11]. [1 p]. Available: http://apps.humana.com/UnsecuredDrugListSearch/Search.aspx.

108. Regence Group. Ruconest, recombinant human C1 esterase inhibitor. Policy no. dru373. [internet]. Portland (OR): Regence Group; 2015 Mar 13 [accessed 2015 Jun 11]. [6 p]. Available: http://blue.regence.com/trgmedpol/drugs/dru373.pdf.

109. HealthPartners. Hereditary angioedema (HAE) drug therapy. Policy number H004-03. Minneapolis (MN): HealthPartners; 2014 Nov 14. 3 p. Also available: https://www.healthpartners.com/public/coverage-criteria/hae/.

110. Blue Cross and Blue Shield of Massachusetts. Medication look up: Ruconest. [internet]. Rockland (MA): Blue Cross and Blue Shield of Massachusetts [accessed 2015 Nov 25]. [1 p]. Available: http://www.bcbsma.com.

111. Hereditary angioedema. [internet]. Bethesda (MD): National Library of Medicine (U.S.); 2014 May 12 [accessed 2014 Nov 20]. [4 p]. Available: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002427/.

112. Clinical policy bulletin: hereditary angioedema. Number: 0782. [internet]. Hartford (CT): Aetna, Inc.; 2014 Oct 10 [accessed 2014 Oct 28]. [15 p]. Available: http://www.aetna.com/cpb/medical/data/700_799/0782.html.

113. Expert Commenter 1489. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS2145 - Conestat alfa (Ruconest) for treatment of acute hereditary angioedema. 2015 Apr 3 [review date].

114. Expert Commenter 1192. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2145 - Conestat alfa (Ruconest) for treatment of acute hereditary angioedema. 2015 Apr 7 [review date].

115. Expert Commenter 1320. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2145 - Conestat alfa (Ruconest) for treatment of acute hereditary angioedema. 2015 Apr 3 [review date].

116. Expert Commenter 1546. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS2145 - Conestat alfa (Ruconest) for treatment of acute hereditary angioedema. 2015 Apr 8 [review date].

117. Expert Commenter 1493. (External, Clinical). Horizon Scanning Structured Comment Form. HS2145 - Conestat alfa (Ruconest) for treatment of acute hereditary angioedema. 2015 Apr 17 [review date].

118. Expert Commenter 1259. (External, Clinical). Horizon Scanning Structured Comment Form. HS2145 - Conestat alfa (Ruconest) for treatment of acute hereditary angioedema. 2015 Apr 27 [review date].

119. FDA approves new drug to treat a form of Gaucher disease. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2014 Aug 19 [accessed 2014 Sep 02]. [5 p]. Available: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm410585.htm.

120. The physician's guide to Gaucher disease. Danbury (CT): National Organization for Rare Disorders (NORD); 2013. 17 p. Also available: http://nordphysicianguides.org/gaucher-disease/.

121. Egan AG. NDA approval for Cerdelga (eliglustat). NDA 205494. 2014 Aug 19.

122. Genzyme announces positive new data from two phase 3 studies for oral eliglustat tartrate for Gaucher disease. [internet]. Cambridge (MA): Genzyme; 2013 Feb 15 [accessed 2013 Jul 25]. [7 p]. Available: http://news.genzyme.com/press-release/genzyme-announces-positive-new-data-two-phase-3-studies-oral-eliglustat-tartrate-gauch.

123. Genzyme Corporation: eliglustat tartate (Genz-112638). [internet]. Tucker (GA): National Gaucher Foundation [accessed 2013 Jul 25]. [2 p]. Available: http://www.gaucherdisease.org/genzyme_drug_information2.php.

124. Genzyme. A study of eliglustat tartrate (Genz-112638) in patients with Gaucher disease (ENGAGE). In: ClinicalTrials.gov [internet]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2013 Jul 25]. [4 p]. Available: http://www.clinicaltrials.gov/ct2/show/NCT00891202 NLM Identifier: NCT00891202.

125. Genzyme. A study of eliglustat tartrate (Genz-112638) in patients with Gaucher disease to evaluate once daily versus twice daily dosing (EDGE). In: ClinicalTrials.gov [internet]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2013 Jul 25]. [4 p]. Available: http://www.clinicaltrials.gov/ct2/show/NCT01074944 NLM Identifier: NCT01074944.

126. Genzyme. A study of eliglustat tartrate (Genz-112638) in patients with Gaucher disease who have reached therapeutic goals with enzyme replacement therapy (ENCORE). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2013 Jul 25]. [4 p]. Available: http://www.clinicaltrials.gov/ct2/show/NCT00943111 NLM Identifier: NCT00943111.

127. Genzyme. Skeletal response to Eliglustat in patients with Gaucher disease (EXOSKEL). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2014 Apr 11]. [4 p].

128. Cox TM, Drelichman G, Cravo R, et al. Eliglustat compared with imiglucerase in patients with Gaucher's disease type 1 stabilised on enzyme replacement therapy: a phase 3, randomised, open-label, non-inferiority trial. Lancet. 2015 Jun 13;385(9985):2355-62. Epub 2015 Mar 25. Also available: http://dx.doi.org/10.1016/S0140-6736(14)61841-9. PMID: 25819691.

129. Mistry PK, Lukina E, Ben Turkia H, et al. Effect of oral eliglustat on splenomegaly in patients with Gaucher disease type 1: the ENGAGE randomized clinical trial. JAMA. 2015 Feb 17;313(7):695-706. Also available: http://dx.doi.org/10.1001/jama.2015.459. PMID: 25688781.

130. Cerdelga (eliglustat) pricing info. [internet]. Santa Monica (CA): GoodRx, Inc. [accessed 2015 Dec 03]. [10 p]. Available: http://www.goodrx.com/cerdelga.

131. Sanofi grew sales and business EPS in Q3 2015. [internet]. Paris (France): Sanofi; 2015 Oct 29 [accessed 2015 Dec 03]. [26]. Available: http://en.sanofi.com/NasdaQ_OMX/local/press_releases/sanofi_grew_sales_and_business_1962157_29-10-2015!07_30_00.aspx.

132. Elelyso pricing info. [internet]. Santa Monica (CA): GoodRx, Inc. [accessed 2014 Sep 02]. [2 p]. Available: http://www.goodrx.com/elelyso.

133. Vpriv pricing info. [internet]. Santa Monica (CA): GoodRx, Inc. [accessed 2014 Sep 02]. [3 p]. Available: http://www.goodrx.com/vpriv.

134. Cerezyme pricing info. [internet]. Santa Monica (CA): GoodRx, Inc. [accessed 2014 Sep 02]. [3 p]. Available: http://www.goodrx.com/cerezyme.

135. About CYP2D6 metabolizer status. [internet]. Boston (MA): Genzyme Corporation; 2014 Sep 26 [accessed 2014 Oct 06]. [3 p]. Available: http://www.cerdelga.com/genotyping.html.

136. Anthem Insurance Companies. Exclusive specialty drug list. [internet]. North Haven (CT): Anthem Insurance Companies, Inc.; 2015 Jul [accessed 2015 Dec 03]. [3 p]. Available: http://file.anthem.com/44150MUMENABS.pdf.

137. Blue Cross and Blue Shield of Massachusetts. Formulary: Cerdelga. [internet]. Rockland (MA): Blue Cross and Blue Shield of Massachusetts [accessed 2015 Jun 02]. [1 p]. Available: http://www.bcbsma.com.

138. HealthPartners. Type I Gaucher disease enzyme replacement therapy: imiglucerase (Cerezyme), velaglucerase (Vpriv) and telaglucerase (Elelyso). Policy #: T005-03. [internet]. Minneapolis (MN): HealthPartners; 2014 Dec 22 [accessed 2015 Jul 17]. [3 p]. Available: https://www.healthpartners.com/public/coverage-criteria/type-i-gaucher-disease-enzyme-replacement-therapy/.

139. Wellmark, Inc. Wellmark preferred drug list. [internet]. Des Moines (IA): Wellmark, Inc.; 2015 Jul 31 [accessed 2015 Nov 24]. [13 p]. Available: http://www.wellmark.com.

140. Aetna, Inc. Clinical policy bulletin: lysosomal storage disorders: treatments. Number: 0442. [internet]. Hartford (CT): Aetna, Inc.; 2015 Oct 23 [accessed 2015 Dec 03]. [50 p]. Available: http://www.aetna.com/cpb/medical/data/400_499/0442.html.

141. Humana, Inc. Cerdelga (eliglustat). Louisville (KY): Humana, Inc.; 2015 Aug 27. 4 p. Also available: http://www.humana.com.

142. United HealthCare Services, Inc. Prior authorization/notification program: Cerdelga (eliglustat). Edina (MN): United HealthCare Services, Inc.; 2015 Mar 1. 2 p. Also available: https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Pharmacy%20Resources/Clinical%20Programs/PA_Notification_Cerdelga.pdf.

143. Gaucher disease - eliglustat tartrate. Manuf Chem. 2011 Mar;82(3):20.

144. Pastores GM, Weinreb NJ, Aerts H, et al. Therapeutic goals in the treatment of Gaucher disease. Semin Hematol. 2004 Oct;41(4 Suppl 5):4-14. PMID: 15468045.

145. Zavesca home page. [internet]. Cambridge (MA): Genzyme [accessed 2013 Jul 25]. [2 p]. Available: http://www.zavesca.com/.

146. Expert Commenter 1546. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS1870 - Eliglustat tartrate (Cerdelga) for treatment of Gaucher's disease type 1. 2015 Aug 7 [review date].

147. Expert Commenter 1026. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1870 - Eliglustat tartrate (Cerdelga) for treatment of Gaucher's disease type 1. 2015 Aug 25 [review date].

148. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1870 - Eliglustat tartrate (Cerdelga) for treatment of Gaucher's disease type 1. 2015 Aug 13 [review date].

149. Expert Commenter 1015. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS1870 - Eliglustat tartrate (Cerdelga) for treatment of Gaucher's disease type 1. 2015 Aug 5 [review date].

150. Expert Commenter 663. (External, Clinical). Horizon Scanning Structured Comment Form. HS1870 - Eliglustat tartrate (Cerdelga) for treatment of Gaucher's disease type 1. 2015 Sep 8 [review date].

151. Expert Commenter 1582. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS1870 - Eliglustat tartrate (Cerdelga) for treatment of Gaucher's disease type 1. 2015 Oct 9 [review date].

152. Yutaka T, Okada S, Kato T, et al. Galactose 6-sulfate sulfatase activity in Morquio syndrome. Clin Chim Acta. 1982 Jul 1;122(2):169-80. PMID: 6809361.

153. GALNS. In: Genetics Home Reference [internet]. Bethesda (MD): National Library of Medicine (U.S.); 2010 Jul 01 [accessed 2014 Apr 03]. [4 p]. Available: http://ghr.nlm.nih.gov/gene/GALNS.

154. Hendriksz CJ, Harmatz P, Beck M, et al. Review of clinical presentation and diagnosis of mucopolysaccharidosis IVA. Mol Genet Metab. 2013 Sep-Oct;110(1-2):54-64. Also available: http://dx.doi.org/10.1016/j.ymgme.2013.04.002. PMID: 23665161.

155. Hendriksz CJ, Al-Jawad M, Berger KI, et al. Clinical overview and treatment options for non-skeletal manifestations of mucopolysaccharidosis type IVA. J Inherit Metab Dis. 2013 Mar;36(2):309-22. Also available: http://dx.doi.org/10.1007/s10545-012-9459-0. PMID: 22358740.

156. Tomatsu S, Montano AM, Oikawa H, et al. Mucopolysaccharidosis type IVA (Morquio A disease): clinical review and current treatment. Curr Pharm Biotechnol. 2011 Jun;12(6):931-45. PMID: 21506915.

157. Montano AM, Tomatsu S, Gottesman GS, et al. International Morquio A Registry: clinical manifestation and natural course of Morquio A disease. J Inherit Metab Dis. 2007 Apr;30(2):165-74. Also available: http://dx.doi.org/10.1007/s10545-007-0529-7. PMID: 17347914.

158. Regier DS, Oetgen M, Tanpaiboon P. Mucopolysaccharidosis type IVA. In: GeneReviews [internet]. Seattle (WA): University of Washington, Seattle; 2014 Mar 13 [accessed 2014 Dec 12]. [29 p]. Available: http://www.ncbi.nlm.nih.gov/pubmed/23844448 .

159. Vimizim (elosulfase alfa) injection, solution, concentrate prescribing information. In: DailyMed [internet]. Bethesda (MD): National Library of Medicine (U.S.); 2014 Feb 01 [accessed 2014 Apr 11]. [12 p]. Available: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=0caa2565-12b2-0ad0-1f9a-273e81c3d4cc.

160. BioMarin. Briefing document for the Endocrinologic and Metabolic Drugs Advisory Committee: Vimizim (elosulfase alfa) for the treatment of mucopolysaccharidosis type IVA (Morquio A syndrome). Rockville (MD): U.S. Food and Drug Administration (FDA); 2013 Nov 19. 210 p. Also available: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm375127.pdf.

161. European Medicines Agency (EMA). Summary of opinion (initial authorisation): Vimizim (elosulfase alfa). London: European Medicines Agency (EMA); 2014 Feb 20. 2 p. Also available: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002779/WC500161935.pdf.

162. Hendriksz CJ, Burton B, Fleming TR, et al. Efficacy and safety of enzyme replacement therapy with BMN 110 (elosulfase alfa) for Morquio A syndrome (mucopolysaccharidosis IVA): a phase 3 randomised placebo-controlled study. J Inherit Metab Dis. 2014 Nov;37(6):979-90. Epub 2014 May 9. Also available: http://dx.doi.org/10.1007/s10545-014-9715-6. PMID: 24810369.

163. Hendriksz CJ, Vellodi A, Jones S, et al. A multicenter, open-label, extension study to evaluate the long-term efficacy and safety of BMN110 in patients with mucopolysaccharidosis IVA (MPS IVA, Morquio A syndrome). J Inherit Metab Dis. 2013 Sep;36(2 suppl 1):S303.

164. Hendriksz C, Vellodi A, Jones S, et al. Long term outcomes of a phase 1/2, multicenter, open-label, dose-escalation study to evaluate the safety, tolerability, and efficacy of BMN 110 in patients with mucopolysaccharidosis IVA (Morquio A syndrome). Mol Genet Metab. 2012 Feb;105(2):S35.

165. Jones S, Harmatz P, Bialer M, et al. Preliminary findings evaluating safety and efficacy of recombinant human Nacetylgalactosamine-6-sulfatase (rhGALNS) in pediatric patients less than 5 years of age with Mucopolysaccharidosis IVA (Morquio A syndrome, MPSIVA). J Inherit Metab Dis. 2013 Sep;36(2 suppl 1):S304.

166. BioMarin Pharmaceutical Inc. Highlights of prescribing information: Vimizim. Novato (CA): BioMarin Pharmaceutical Inc.; 2014 Feb. 11 p. Also available: http://www.vimizim.com/pdf-download/?file_name=Prescribing-Information.pdf.

167. BioMarin Pharmaceutical. Long-term efficacy and safety extension study of BMN 110 in patients with Mucopolysaccharidosis IVA (Morquio A Syndrome). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2014 Jun 04]. [5 p]. Available: http://clinicaltrials.gov/ct2/show/NCT01415427 NLM Identifier: NCT01415427.

168. BioMarin Pharmaceutical. Efficacy and safety study of BMN 110 for Morquio A Syndrome patients who have limited ambulation. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2014 Jun 05]. [5 p]. Available: http://clinicaltrials.gov/ct2/show/NCT01697319 NLM Identifier: NCT01697319.

169. BioMarin Pharmaceutical. Study of BMN 110 in pediatric patients < 5 years of age with Mucopolysaccharidosis IVA (Morquio A Syndrome). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2014 Jun 05]. [4 p]. Available: http://clinicaltrials.gov/ct2/show/NCT01515956 NLM Identifier: NCT01515956.

170. FDA approves Vimizim to treat rare congenital enzyme disorder. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2014 Feb 14 [accessed 2014 Jun 05]. [1 p]. Available: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm386008.htm.

171. BioMarin announces third quarter 2015 financial results and company update. [internet]. San Rafael (CA): BioMarin Pharmaceutical Inc.; 2015 Oct 29 [accessed 2015 Nov 11]. [14 p]. Available: http://investors.bmrn.com/releasedetail.cfm?ReleaseID=939338.

172. BioMarin Pharmaceutical. BioMarin Pharmaceutical's (BMRN) CEO Jean-Jacques Bienaime on Q1 2015 results - earnings call transcript. [internet]. New York (NY): Seeking Alpha; 2015 Apr 30 [accessed 2015 Jun 11]. [30 p]. Available: http://seekingalpha.com/article/3126256-biomarin-pharmaceuticals-bmrn-ceo-jean-jacques-bienaime-on-q1-2015-results-earnings-call-transcript.

173. BioMarin's newly approved orphan drug Vimizim priced at USD380,000 per year. Englewood (CO): IHS Global Insight; 2014 Feb 19. 1 p.

174. Solanki GA, Martin KW, Theroux MC, et al. Spinal involvement in mucopolysaccharidosis IVA (Morquio-Brailsford or Morquio A syndrome): presentation, diagnosis and management. J Inherit Metab Dis. 2013 Mar;36(2):339-55. PMID: 23385297.

175. Expert Commenter 410. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS871 - Elosulfase alfa (Vimizim) for treatment of Morquio A syndrome. 2015 Feb 4 [review date].

176. Expert Commenter 429. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS871 - Elosulfase alfa (Vimizim) for treatment of Morquio A syndrome. 2015 Feb 3 [review date].

177. Expert Commenter 529. (External, Research/Scientific/Technical). Horizon Scanning Structured Comment Form. HS871 - Elosulfase alfa (Vimizim) for treatment of Morquio A syndrome. 2015 Feb 18 [review date].

178. Expert Commenter 1015. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS871 - Elosulfase alfa (Vimizim) for treatment of Morquio A syndrome. 2015 Feb 18 [review date].

179. Expert Commenter 1192. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS871 - Elosulfase alfa (Vimizim) for treatment of Morquio A syndrome. 2015 Jan 30 [review date].

180. Expert Commenter 1259. (External, Clinical). Horizon Scanning Structured Comment Form. HS871 - Elosulfase alfa (Vimizim) for treatment of Morquio A syndrome. 2015 Feb 18 [review date].

181. Expert Commenter 1516. (External, Clinical). Horizon Scanning Structured Comment Form. HS871 - Elosulfase alfa (Vimizim) for treatment of Morquio A syndrome. 2015 Feb 23 [review date].

182. Duchenne muscular dystrophy. In: Pubmed Health [internet]. Bethesda (MD): National Library of Medicine (U.S.); 2014 Feb 03 [accessed 2014 Oct 17]. [5 p]. Available: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001724/.

183. Duchenne muscular dystrophy (DMD) - overview. [internet]. Chicago (IL): Muscular Dystrophy Association [accessed 2014 Oct 17]. [3 p]. Available: http://mda.org/disease/duchenne-muscular-dystrophy/overview.

184. Duchenne muscular dystrophy (DMD) - signs and symptoms. [internet]. Chicago (IL): Muscular Dystrophy Association [accessed 2014 Oct 17]. [3 p]. Available: http://mda.org/disease/duchenne-muscular-dystrophy/signs-and-symptoms.

185. Mayo clinic staff. Muscular dystrophy. [internet]. Rochester (MN): Mayo Foundation for Medical Education and Research (MFMER); 2012 Jan 18 [accessed 2014 Oct 17]. [6 p]. Available: http://www.mayoclinic.org/diseases-conditions/muscular-dystrophy/basics/definition/con-20021240?p=1.

186. Muscular dystrophy: diagnostic tools. [internet]. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2014 Sep 18 [accessed 2014 Oct 17]. [4 p]. Available: http://www.cdc.gov/ncbddd/musculardystrophy/diagnostic-tool.html.

187. Centers for Disease Control and Prevention (CDC). Muscular dystrophy: data & statistics. [internet]. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2014 Sep 18 [accessed 2014 Oct 17]. [3 p]. Available: http://www.cdc.gov/ncbddd/musculardystrophy/data.html.

188. Siva K, Covello G, Denti MA. Exon-skipping antisense oligonucleotides to correct missplicing in neurogenetic diseases. Nucl Acid Ther. 2014 Feb;24(1):69-86. Also available: http://dx.doi.org/10.1089/nat.2013.0461. PMID: 24506781.

189. Wu B, Cloer C, Lu P, et al. Exon skipping restores dystrophin expression, but fails to prevent disease progression in later stage dystrophic dko mice. Gene Ther. 2014 Sep;21(9):785-93. Also available: http://dx.doi.org/10.1038/gt.2014.53. PMID: 24942628.

190. Flanigan KM, Voit T, Rosales XQ, et al. Pharmacokinetics and safety of single doses of drisapersen in non-ambulant subjects with Duchenne muscular dystrophy: results of a double-blind randomized clinical trial. Neuromuscul Disord. 2014 Jan;24(1):16-24. Also available: http://dx.doi.org/10.1016/j.nmd.2013.09.004. PMID: 24321374.

191. Wilton SD, Fletcher S. Novel compounds for the treatment of Duchenne muscular dystrophy: emerging therapeutic agents. Appl Clin Gen. 2011;4:29-44.

192. Aoki Y, Yokota T, Wood MJ. Development of multiexon skipping antisense oligonucleotide therapy for Duchenne muscular dystrophy. Biomed Res Int. 2013;2013:402369. Also available: http://dx.doi.org/10.1155/2013/402369. PMID: 23984357.

193. GlaxoSmithKline's drisapersen (previously GSK2402968/PRO051) to receive Food and Drug Administration breakthrough therapy designation for potential treatment of patients with Duchenne muscular dystrophy. [internet]. Middlesex (UK): GlaxoSmithKline plc.; 2013 Jun 27 [accessed 2015 Jan 23]. [7 p]. Available: http://www.gsk.com/en-gb/media/press-releases/2013/glaxosmithkline-s-drisapersen-previously-gsk2402968pro051-to-receive-food-and-drug-administration-breakthrough-therapy-designation/.

194. Prosensa Therapeutics. A study of the safety, tolerability & efficacy of long-term administration of drisapersen in US & Canadian subjects. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Jan 23]. [6 p]. Available: https://www.clinicaltrials.gov/ct2/show/NCT01803412 NLM Identifier: NCT01803412.

195. Prosensa Therapeutics. A phase I/II, open-label, escalating dose, pilot study to assess effect, safety, tolerability and PK of multiple SC doses of drisapersen in patients with Duchenne muscular dystrophy and to assess the potential for IV dosing as an alternative route of administration. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Jan 23]. [4 p]. Available: https://www.clinicaltrials.gov/ct2/show/NCT01910649 NLM Identifier: NCT01910649.

196. Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. Ann Neurol. 2013 Nov;74(5):637-47. Also available: http://dx.doi.org/10.1002/ana.23982. PMID: 23907995.

197. Sarepta Therapeutics. Realizing the potential of RNA-targeted technology - Barclays global healthcare conference [slide set]. Cambridge (MA): Sarepta Therapeutics; 2015 Mar 12. 31 p.

198. Goemans N, Voit T, McDonald C, et al. Drisapersen treatment for Duchenne muscular dystrophy: Results of a 96-week follow-up of an open-label extension study following two placebo-controlled trials. Neurology. 2014 Jul 8;83(2).

199. Voit T, Topaloglu H, Straub V, et al. Safety and efficacy of drisapersen for the treatment of Duchenne muscular dystrophy (DEMAND II): an exploratory, randomised, placebo-controlled phase 2 study. Lancet Neurol. 2014 Oct;13(10):987-96. Epub 2014 Sep 7. Also available: http://dx.doi.org/10.1016/S1474-4422(14)70195-4.

200. Goemans NM, Tulinius M, Van Den Akker JT, et al. Systemic administration of PRO051 in Duchenne's muscular dystrophy. New Eng J Med. 2011 Apr 21;364(16):1513-22. Also available: http://dx.doi.org/10.1056/NEJMoa1011367. PMID: 21428760.

201. Sarepta Therapeutics reports long-term outcomes through 168 weeks from phase IIb study of eteplirsen in Duchenne muscular dsytrophy. [internet]. Cambridge (MA): Sarepta Therapeutics; 2015 Jan 12 [accessed 2015 Mar 24]. [9 p]. Available: http://investorrelations.sarepta.com/phoenix.zhtml?c=64231&p=irol-newsArticle&ID=2006709.

202. Mendell JR, Goemans N, Lowes LP, et al. Longitudinal effect of eteplirsen vs. historical control on ambulation in DMD. Ann Neurol. 2015 Nov 17:Epub ahead of print. Also available: http://dx.doi.org/10.1002/ana.24555. PMID: 26573217.

203. Sarepta Therapeutics announces eteplirsen demonstrates stability on pulmonary function tests through 120 weeks in phase IIb study in Duchenne muscular dystrophy. [internet]. Cambridge (MA): Sarepta Therapeutics; 2014 Feb 5 [accessed 2015 Mar 24]. [6 p]. Available: http://investorrelations.sarepta.com/phoenix.zhtml?c=64231&p=irol-newsArticle&ID=1897116.

204. Sarepta Therapeutics reports long-term outcomes through 144 weeks from phase IIb study of eteplirsen in Duchenne muscular dsytrophy. [internet]. Cambridge (MA): Sarepta Therapeutics; 2014 Jul 10 [accessed 2015 Mar 24]. [8 p]. Available: http://investorrelations.sarepta.com/phoenix.zhtml?c=64231&p=irol-newsArticle&ID=1946426.

205. Sarepta Therapeutics. Confirmatory study of eteplirsen in DMD patients (PROMOVI). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Dec 04]. [4 p]. Available: http://www.clinicaltrials.gov/ct2/show/NCT02255552 NLM Identifier: NCT02255552.

206. BioMarin announces completion of tender offer for Prosensa's shares and commences subsequent offering period. [internet]. San Rafael (CA): BioMarin Pharmaceutical Inc.; 2015 Jan 15 [accessed 2015 Jan 23]. [2 p]. Available: http://investors.bmrn.com/releasedetail.cfm?ReleaseID=891441.

207. BioMarin completes rolling NDA submission to FDA for drisapersen for treatment of Duchenne muscular dystrophy amenable to Exon 51 skipping. [internet]. Novato (CA): BioMarin Pharmaceutical Inc.; 2015 Apr 27 [accessed 2015 Jun 11]. [2 p]. Available: http://investors.bmrn.com/releasedetail.cfm?ReleaseID=908731.

208. FDA advisory committee discusses clinical data package for BioMarin's Kyndrisa (drisapersen) for the treatment of Duchenne muscular dystrophy amenable to exon 51 skipping. [internet]. San Rafael (CA): BioMarin Pharmaceutical Inc.; 2015 Nov 24 [accessed 2015 Dec 01]. [3 p]. Available: http://investors.bmrn.com/releasedetail.cfm?ReleaseID=944400.

209. Burton TM. FDA panel: BioMarin muscular dystrophy drug trials didn't prove effectiveness. [internet]. New York (NY): Wall Street Journal; 2015 Nov 24 [accessed 2015 Dec 01]. [7 p]. Available: http://www.wsj.com/articles/fda-panel-biomarin-muscular-dystrophy-drug-trials-didnt-prove-effectiveness-1448409019.

210. Feurstein A. BioMarin's Duchenne drug is done, Sarepta survives but faces challenge. [internet]. New York (NY): The Street; 2015 Nov 25 [accessed 2015 Dec 01]. [7 p]. Available: http://www.thestreet.com/story/13378278/1/biomarin-s-duchenne-drug-is-done-sarepta-survives-but-faces-challenge.html?puc=yahoo&cm_ven=YAHOO.

211. Sarepta Therapeutics announces plans to submit new drug application to FDA for eteplirsen for the treatment of Duchenne muscular dystrophy by year end 2014. [internet]. Cambridge (MA): Sarepta Therapeutics; 2014 Apr 21 [accessed 2015 Mar 24]. [6 p]. Available: http://investorrelations.sarepta.com/phoenix.zhtml?c=64231&p=irol-newsArticle&ID=1920025.

212. Sarepta Therapeutics announces tentative FDA advisory committee meeting to review eteplirsen as a treatment for Duchenne muscular dystrophy. Cambridge (MA): Sarepta Therapeutics, Inc.; 2015 Oct 14. 3 p. Also available: http://investorrelations.sarepta.com/phoenix.zhtml?c=64231&p=irol-newsArticle&ID=2097104.

213. BioMarin presentation at FDA advisory committee meeting. San Rafael (CA): BioMarin Pharmaceutical Inc.; 2015 Nov 24. 104 p. Also available: http://files.shareholder.com/downloads/ABEA-3W276N/1090888955x0x863346/AEF00248-5747-4ACF-8C2F-39F5B1D7FCC3/BMRN_AdCom_with_safe_harbor_112415.pdf.

214. Duchenne muscular dystrophy (DMD) - medical management. [internet]. Chicago (IL): Muscular Dystrophy Association [accessed 2014 Oct 17]. [5 p]. Available: http://mda.org/disease/duchenne-muscular-dystrophy/medical-management.

215. Muscular dystrophy: treatment and care. [internet]. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2014 Aug 19 [accessed 2014 Oct 17]. [5 p]. Available: http://www.cdc.gov/ncbddd/musculardystrophy/treatments.html.

216. Expert Commenter 1261. (External, Research/Scientific/Technical). Horizon Scanning Structured Comment Form. HS795 - Drisapersen for treatment of Duchenne muscular dystrophy. 2015 Apr 24 [review date].

217. Expert Commenter 394. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS795 - Drisapersen for treatment of Duchenne muscular dystrophy. 2015 Feb 13 [review date].

218. Expert Commenter 404. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS795 - Drisapersen for treatment of Duchenne muscular dystrophy. 2015 Feb 10 [review date].

219. Expert Commenter 1192. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS795 - Drisapersen for treatment of Duchenne muscular dystrophy. 2015 Feb 17 [review date].

220. Expert Commenter 1219. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS795 - Drisapersen for treatment of Duchenne muscular dystrophy. 2015 Feb 18 [review date].

221. Expert Commenter 1488. (External, Clinical). Horizon Scanning Structured Comment Form. HS795 - Drisapersen for treatment of Duchenne muscular dystrophy. 2015 Apr 13 [review date].

222. Expert Commenter 1488. (External, Clinical). Horizon Scanning Structured Comment Form. HS1020 - Eteplirsen for treatment of Duchenne muscular dystrophy. 2015 Apr 14 [review date].

223. Expert Commenter 1219. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1020 - Eteplirsen for treatment of Duchenne muscular dystrophy. 2015 Apr 14 [review date].

224. Expert Commenter 1546. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS1020 - Eteplirsen for treatment of Duchenne muscular dystrophy. 2015 Apr 21 [review date].

225. Expert Commenter 1170. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS1020 - Eteplirsen for treatment of Duchenne muscular dystrophy. 2015 Apr 20 [review date].

226. Expert Commenter 1473. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1020 - Eteplirsen for treatment of Duchenne muscular dystrophy. 2015 Apr 21 [review date].

227. Expert Commenter 1261. (External, Research/Scientific/Technical). Horizon Scanning Structured Comment Form. HS1020 - Eteplirsen for treatment of Duchenne muscular dystrophy. 2015 Apr 24 [review date].

228. Interian A, Lewis-Fernandez R, Dixon LB. Improving treatment engagement of underserved U.S. racial-ethnic groups: a review of recent interventions. Psychiatr Serv. 2013 Mar 1;64(3):212-22. Also available: http://dx.doi.org/10.1176/appi.ps.201100136. PMID: 23203442.

229. Erb M, Hoffmann-Enger B, Deppe H, et al. Features of idebenone and related short-chain quinones that rescue ATP levels under conditions of impaired mitochondrial complex I. PLoS ONE. 2012;7(4):e36153. Also available: http://dx.doi.org/10.1371/journal.pone.0036153. PMID: 22558363.

230. Haginoya K, Miyabayashi S, Kikuchi M, et al. Efficacy of idebenone for respiratory failure in a patient with Leigh syndrome: a long-term follow-up study. J Neurol Sci. 2009 Mar 15;278(1-2):112-4. Also available: http://dx.doi.org/10.1016/j.jns.2008.11.008. PMID: 19101701.

231. Haefeli RH, Erb M, Gemperli AC, et al. NQO1-dependent redox cycling of idebenone: effects on cellular redox potential and energy levels. PLoS ONE. 2011;6(3):e17963. Also available: http://dx.doi.org/10.1371/journal.pone.0017963. PMID: 21483849.

232. Raxone/Catena (idebenone). [internet]. Liestal (Switzerland): Santhera Pharmaceuticals Holding AG [accessed 2014 Oct 16]. [1 p]. Available: http://www.santhera.com/index.php?mid=53&vid=&lang=en.

233. Buyse GM, Goemans N, van den Hauwe M, et al. Idebenone as a novel, therapeutic approach for Duchenne muscular dystrophy: results from a 12 month, double-blind, randomized placebo-controlled trial. Neuromuscul Disord. 2011 Jun;21(6):396-405. Also available: http://dx.doi.org/10.1016/j.nmd.2011.02.016. PMID: 21435876.

234. Buyse GM, Voit T, Schara U, et al. Idebenone reduces loss of respiratory function in Duchenne muscular dystrophy - outcome of a phase III double blind, randomized, placebo-controlled trial (DELOS) [slide set]. Berlin (Germany): World Miracle Society (WMS); 2014 Oct 11. 29 p. Also available: http://www.santhera.com/downloads/Buyse_WMS_2014-DELOS.pdf.

235. Buyse GM, Voit T, Schara U, et al. Efficacy of idebenone on respiratory function in patients with Duchenne muscular dystrophy not using glucocorticoids (DELOS): a double-blind randomised placebo-controlled phase 3 trial. Lancet. 2015 May 2;385(9979):1748-57. Also available: http://dx.doi.org/10.1016/S0140-6736(15)60025-3. PMID: 25907158.

236. Santhera obtains US patent for use of Catena in the treatment of muscular dystrophies. [internet]. Liestal (Switzerland): Santhera Pharmaceuticals Holding AG; 2011 Aug 24 [accessed 2014 Oct 16]. [2 p]. Available: http://www.santhera.com/index.php?docid=212&vid=&lang=en&newsdate=201108&newsid=1540047&newslang=en.

237. Santhera receives FDA fast track designation for Raxone/Catena (idebenone) for the treatment of Duchenne muscular dystrophy. [internet]. Liestal (Switzerland): Santhera Pharmaceuticals Holding AG; 2015 Apr 9 [accessed 2015 Jun 11]. [2 p]. Available: http://www.santhera.com/index.php?docid=212&vid=&lang=en&newsdate=201504&newsid=1909640&newslang=en.

238. Santhera update on pre-NDA meeting with FDA on Raxone/Catena in Duchenne muscular dystrophy (DMD). [internet]. Liestal (Switzerland): Santhera Pharmaceuticals Holding AG; 2015 Jun 10 [accessed 2015 Jun 11]. [2 p]. Available: http://www.santhera.com/index.php?docid=212&vid=&lang=en&newsdate=201506&newsid=1927439&newslang=en.

239. Santhera reports new data and updates on regulatory filings for Raxone (idebenone) in Duchenne muscular dystrophy (DMD). [internet]. Liestal (Switzerland): Santhera Pharmaceuticals ; 2015 Nov 11 [accessed 2015 Dec 01]. [4 p]. Available: http://www.santhera.com/index.php?docid=212&vid=&lang=en&newsdate=201511&newsid=1966014&newslang=en.

240. Expert Commenter 1224. (External, Clinical). Horizon Scanning Structured Comment Form. HS1882 - Idebenone (Catena) for treatment of Duchenne muscular dystrophy. 2015 Oct 14 [review date].

241. Expert Commenter 1261. (External, Research/Scientific/Technical). Horizon Scanning Structured Comment Form. HS1882 - Idebenone (Catena) for treatment of Duchenne muscular dystrophy. 2015 Oct 15 [review date].

242. Expert Commenter 1192. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1882 - Idebenone (Catena) for treatment of Duchenne muscular dystrophy. 2015 Oct 20 [review date].

243. Expert Commenter 394. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS1882 - Idebenone (Catena) for treatment of Duchenne muscular dystrophy. 2015 Oct 14 [review date].

244. Expert Commenter 1219. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1882 - Idebenone (Catena) for treatment of Duchenne muscular dystrophy. 2015 Oct 21 [review date].

245. Expert Commenter 409. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS1882 - Idebenone (Catena) for treatment of Duchenne muscular dystrophy. 2015 Oct 15 [review date].

246. Haley S. Sickle cell disease orphan status lures pharma interest. New York (NY): Pink Sheet LLC; 2013 Sep 9. 6 p. Also available: http://www.pharmamedtechbi.com/publications/the-pink-sheet/75/36/sickle-cell-disease-orphan-status-lures-pharma-interest?p=1.

247. Manwani D, Frenette PS. Vaso-occlusion in sickle cell disease: pathophysiology and novel targeted therapies. Hematology Am Soc Hematol Educ Program. 2013;2013:362-9. Also available: http://dx.doi.org/10.1182/asheducation-2013.1.362. PMID: 24319205.

248. Niihara Y, Koh HA, Tran L, et al. A phase 3 study of L-glutamine therapy for sickle cell anemia and sickle B0-thalassemia. [internet]. Washington (DC): American Society of Hematology; 2014 Dec 7 [accessed 2014 Dec 18]. [2 p]. Available: https://ash.confex.com/ash/2014/webprogram/Paper70720.html.

249. NutreStore - frequently asked questions. [internet]. Torrance (CA): Emmaus Medical, Inc. [accessed 2014 Dec 22]. [3 p]. Available: http://nutrestore.com/faqs.

250. Emmaus Medical, Inc. A phase III safety and efficacy study of L-glutamine to treat sickle cell disease or sickle Bo-thalassemia. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2014 Dec 22]. [4 p]. Available: https://clinicaltrials.gov/ct2/show/NCT01179217 NLM Identifier: NCT01179217.

251. Emmaus Life Sciences, Inc. Form 10-Q: quarterly report pursuant to section 13 or 15(d) of the Securities Exchange Act of 1934 for the quarterly period ended September 30, 2014. Washington (DC): United States Securities and Exchange Commission; 2014 Sep 30. 34 p. Also available: http://www.sec.gov/Archives/edgar/data/1420031/000110465914080401/a14-19952_110q.htm.

252. Nutrestore. [internet]. Charlotte (NC): WeRX.com [accessed 2014 Dec 18]. [4 p]. Available: http://werx.org/price/NUTRESTORE/Philadelphia-PA.

253. Sickle cell disease (SCD): facts about sickle cell disease. [internet]. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2014 Jan 16 [accessed 2014 Oct 16]. [3 p]. Available: http://www.cdc.gov/ncbddd/sicklecell/facts.html .

254. Mayo clinic staff. Sickle cell anemia. [internet]. Rochester (MN): Mayo Foundation for Medical Education and Research (MFMER); 2014 Jun 11 [accessed 2014 Oct 16]. [9 p]. Available: http://www.mayoclinic.org/diseases-conditions/sickle-cell-anemia/basics/definition/con-20019348?p=1.

255. Sickle cell anemia: practice essentials. In: Medscape [internet]. New York (NY): WebMD LLC; 2014 Sep 15 [accessed 2014 Oct 16]. [16 p]. Available: http://emedicine.medscape.com/article/205926-overview#showall.

256. National Heart, Lung, and Blood Institute (NHLBI). Evidence-based management of sickle cell disease. Bethesda (MD): National Heart, Lung, and Blood Institute (NHLBI); 2014. 142 p. Also available: http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/sickle-cell-disease-report.pdf.

257. Expert Commenter 413. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS2091 - L-glutamine for prevention of vaso-occlusive crises in sickle cell disease. 2015 Feb 16 [review date].

258. Expert Commenter 395. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS2091 - L-glutamine for prevention of vaso-occlusive crises in sickle cell disease. 2015 Feb 11 [review date].

259. Expert Commenter 1192. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2091 - L-glutamine for prevention of vaso-occlusive crises in sickle cell disease. 2015 Feb 17 [review date].

260. Expert Commenter 1219. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2091 - L-glutamine for prevention of vaso-occlusive crises in sickle cell disease. 2015 Feb 18 [review date].

261. Expert Commenter 1441. (External, Clinical). Horizon Scanning Structured Comment Form. HS2091 - L-glutamine for prevention of vaso-occlusive crises in sickle cell disease. 2015 Mar 4 [review date].

262. Expert Commenter 663. (External, Clinical). Horizon Scanning Structured Comment Form. HS2091 - L-glutamine for prevention of vaso-occlusive crises in sickle cell disease. 2015 Feb 26 [review date].

263. Germain DP. Fabry disease. Orphanet J Rare Dis. 2010;5:30. Also available: http://dx.doi.org/10.1186/1750-1172-5-30. PMID: 21092187.

264. Amicus Therapeutics, Inc. form 10-K. Cranbury (NJ): Amicus Therapeutics, Inc; 2011 Mar 4. 332 p.

265. Pharmacological chaperones. Cranbury (NJ): Amicus Therapeutics; 2008. 11 p. Also available: http://www.amicustherapeutics.com/technology/pharmacologicalchaperones.asp.

266. Fabry disease. [internet]. Cranbury (NJ): Amicus Therapeutics, Inc. [accessed 2014 Nov 12]. [2 p]. Available: http://www.amicusrx.com/fabry.aspx.

267. Amicus Therapeutics announces additional positive phase 3 data from Fabry monotherapy study 011. [internet]. Cranbury (NJ): Amicus Therapeutics, Inc.; 2014 Oct 19 [accessed 2014 Nov 12]. [3 p]. Available: http://ir.amicustherapeutics.com/releasedetail.cfm?ReleaseID=876871.

268. Wu X, Katz E, Valle MCD, et al. A pharmacogenetic approach to identify mutant forms of (alpha)-galactosidase a that respond to a pharmacological chaperone for Fabry disease. Hum Mutat. 2011 Aug;32(8):965-77. Also available: http://dx.doi.org/10.1002/humu.21530. PMID: 21598360.

269. Germain DP, Giugliani R, Pastores GM, et al. Long-term safety of migalastat HCl in patients with Fabry disease. Cranbury (NJ): Amicus Therapeutics; 1 p.

270. Amicus Therapeutics announces positive results from phase 2 clinical trials of amigal for Fabry disease. [internet]. Cranbury (NJ): Amicus Therapeutics, Inc; 2007 Dec 19 [accessed 2011 Jul 13]. [2 p]. Available: http://ir.amicustherapeutics.com/releasedetail.cfm?ReleaseID=282662.

271. Bichet DG, Germain DP, Giugliani R, et al. Subjects with Fabry disease treated with migalast HCl continue to demonstrate stable renal function in phase 3 extension study. Cranbury (NJ): Amicus Therapeutics; 1 p.

272. Amicus Therapeutics. Physician initiated request for migalastat in individual patients with fabry disease. In: ClinicalTrials.gov [database online]. Bethesda (MD): U.S. National Library of Medicine (NLM); 2000- [accessed 2015 Jun 10]. [3 p]. Available: https://clinicaltrials.gov/ct2/show/NCT01476163 NLM Identifier: NCT01476163.

273. Amicus Therapeutics. Open-label phase 3 long-term safety study of migalastat (AT1001-041). In: ClinicalTrials.gov [database online]. Bethesda (MD): U.S. National Library of Medicine (NLM); 2000- [accessed 2015 Jun 10]. [4 p]. Available: https://clinicaltrials.gov/ct2/show/NCT01458119 NLM Identifier: NCT01458119.

274. Amicus Therapeutics. Open-label extension study of the long-term effects of migalastat HCL in patients with Fabry disease. In: ClinicalTrials.gov [database online]. Bethesda (MD): U.S. National Library of Medicine (NLM); 2000- [accessed 2015 Jun 10]. [4 p]. Available: https://clinicaltrials.gov/ct2/show/NCT02194985 NLM Identifier: NCT02194985.

275. Barlow C, Castelli J, Benjamin E, et al. Phase 3 (FACETS) of migalastat HCl for Fabry disease: post hoc GLA mutation-based identification of subjects likely to show a drug effect. Cranbury (NJ): Amicus Therapeutics; 2014. 1 p.

276. Giugliani R, Waldek S, Germain DP, et al. A Phase 2 study of migalastat hydrochloride in females with Fabry disease: Selection of population, safety and pharmacodynamic effects. Mol Genet Metab. 2013 May;109(1):86-92. Also available: http://dx.doi.org/10.1016/j.ymgme.2013.01.009. PMID: 23474038.

277. Germain DP, Giugliani R, Hughes DA, et al. Safety and pharmacodynamic effects of a pharmacological chaperone on alpha-galactosidase A activity and globotriaosylceramide clearance in Fabry disease: report from two phase 2 clinical studies. Orphanet J Rare Dis. 2012 Nov 24;7:91. Also available: http://dx.doi.org/10.1186/1750-1172-7-91. PMID: 23176611.

278. Amicus Therapeutics provides U.S. regulatory update for migalastat monotherapy. [internet]. Cranbury (NJ): Amicus Therapeutics; 2015 Oct 2 [accessed 2015 Nov 24]. [3 p]. Available: http://ir.amicustherapeutics.com/releasedetail.cfm?ReleaseID=934931.

279. Amicus has sights on Genzyme rare disease patients. [internet]. New York: Thomson Reuters [accessed 2011 Jul 13]. [2 p]. Available: http://uk.mobile.reuters.com/article/hotStocksNewsUS/idUKTRE71E7OF20110216.

280. Mandava P. Fabry disease overview of Fabry disease. In: Medscape [internet]. New York (NY): WebMD LLC; 2013 Jan 12 [accessed 2015 Jan 02]. [5 p]. Available: http://emedicine.medscape.com/article/1952086-overview.

281. Fabry disease. [internet]. New York (NY): National Kidney Foundation, Inc. [accessed 2015 Jan 02]. [3 p]. Available: https://www.kidney.org/atoz/content/fabry.

282. Expert Commenter 405. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS942 - Migalastat hydrochloride for treatment of Fabry disease. 2015 Mar 13 [review date].

283. Expert Commenter 1192. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS942 - Migalastat hydrochloride for treatment of Fabry disease. 2015 Mar 2 [review date].

284. Expert Commenter 420. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS942 - Migalastat hydrochloride for treatment of Fabry disease. 2015 Mar 3 [review date].

285. Expert Commenter 396. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS942 - Migalastat hydrochloride for treatment of Fabry disease. 2015 Mar 13 [review date].

286. Expert Commenter 1516. (External, Clinical). Horizon Scanning Structured Comment Form. HS942 - Migalastat hydrochloride for treatment of Fabry disease. 2015 Apr 13 [review date].

287. Expert Commenter 663. (External, Clinical). Horizon Scanning Structured Comment Form. HS942 - Migalastat hydrochloride for treatment of Fabry disease. 2015 Apr 20 [review date].

288. Reynolds T. Cholesteryl ester storage disease: A rare and possibly treatable cause of premature vascular disease and cirrhosis. J Clin Pathol. 2013 Nov;66(11):918-93. Also available: http://dx.doi.org/10.1136/jclinpath-2012-201302. PMID: 23999269.

289. Sebelipase alfa. [internet]. Lexington (MA): Synageva BioPharma Corp. [accessed 2015 Mar 31]. [3 p]. Available: http://www.synageva.com/research/sebelipase-alfa/.

290. Enzyme replacement cuts liver injury in LAL deficiency. In: Medscape Medical News [internet]. New York (NY): WebMD, LLC; 2015 Nov 18 [accessed 2015 Mar 31]. [2 p]. Available: http://www.medscape.com/viewarticle/835096_print.

291. FDA approves first drug to treat a rare enzyme disorder in pediatric and adult patients. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2015 Dec 8 [accessed 2015 Dec 08]. [5 p]. Available: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm476013.htm.

292. Jones SA, Plantaz D, Vara R, et al. Effect of sebelipase alfa on survival and liver function in infants with rapidly progressive lysosomal acid lipase deficiency. Mol Genet Metab. 2015;114(2):S59.

293. Valayannopoulos V, Malinova V, Honzak T, et al. Sebelipase alfa over 52 weeks reduces serum transaminases, liver volume and improves serum lipids in patients with lysosomal acid lipase deficiency. J Hepatol. 2014 Nov;61(5):1135-42. Also available: http://dx.doi.org/10.1016/j.jhep.2014.06.022. PMID: 24993530.

294. Balwani M, Burton B, Baric I, et al. Results of a global phase 3, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of sebelipase alfa as an enzyme replacement therapy in children and adults with lysosomal acid lipase deficiency. In: American Association for the Study of Liver Diseases (AASLD) Liver Meeting 2014; 2014 Nov 7-11; Boston (MA).

295. Burton BK, Balwani M, Feillet F, et al. A phase 3 trial of sebelipase alfa in lysosomal acid lipase deficiency. N Engl J Med. 2015 Sep 10;373(11):1010-20. Also available: http://dx.doi.org/10.1056/NEJMoa1501365. PMID: 26352813.

296. Synageva BioPharma Corp. Trial in children with growth failure due to early onset lysosomal acid lipase (LAL) deficiency/Wolman disease. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Dec 07]. [4 p]. Available: https://www.clinicaltrials.gov/ct2/show/NCT01371825 NLM Identifier: NCT01371825.

297. Synageva BioPharma Corp. A multicenter study of SBC-102 (sebelipase alfa) in patients with lysosomal acid lipase deficiency/ ARISE (acid lipase replacement investigating safety and efficacy). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Dec 07]. [4 p]. Available: https://www.clinicaltrials.gov/ct2/show/NCT01757184 NLM Identifier: NCT01757184.

298. Synageva BioPharma Corp. An expanded access protocol for sebelipase alfa for patients with lysosomal acid lipase deficiency. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Dec 07]. [3 p]. Available: https://www.clinicaltrials.gov/ct2/show/NCT02376751 NLM Identifier: NCT02376751.

299. Expert Commenter 1489. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS943 - Sebelipase alfa (Kanuma) for treatment of lysosomal acid lipase deficiency. 2015 Jul 16 [review date].

300. Expert Commenter 1547. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS943 - Sebelipase alfa (Kanuma) for treatment of lysosomal acid lipase deficiency. 2015 Jul 16 [review date].

301. Expert Commenter 1192. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS943 - Sebelipase alfa (Kanuma) for treatment of lysosomal acid lipase deficiency. 2015 Jul 29 [review date].

302. Expert Commenter 1576. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS943 - Sebelipase alfa (Kanuma) for treatment of lysosomal acid lipase deficiency. 2015 Jul 31 [review date].

303. Expert Commenter 1516. (External, Clinical). Horizon Scanning Structured Comment Form. HS943 - Sebelipase alfa (Kanuma) for treatment of lysosomal acid lipase deficiency. 2015 Aug 24 [review date].

304. Expert Commenter 1654. (External, Clinical). Horizon Scanning Structured Comment Form. HS943 - Sebelipase alfa (Kanuma) for treatment of lysosomal acid lipase deficiency. 2015 Oct 7 [review date].

305. Raczynska J, Habior A, Paczek L, et al. Primary biliary cirrhosis in the era of liver transplantation. Ann Transplant. 2014;19(1):488-93. Also available: http://dx.doi.org/10.12659/AOT.890753.

306. Floreani A, Franceschet I, Perini L, et al. New therapies for primary biliary cirrhosis. Clin Rev Allergy Immunol. 2015 Jun;48(2-3):263-72. Epub 2014 Oct 21. Also available: http://dx.doi.org/10.1007/s12016-014-8456-5. PMID: 25331740.

307. Farnesoid X receptor (FXR). [internet]. New York (NY): Intercept Pharmaceuticals, Inc. [accessed 2015 Feb 25]. [3 p]. Available: http://www.interceptpharma.com/research-development/fxr/.

308. Fang C, Filipp FV, Smith JW. Unusual binding of ursodeoxycholic acid to ileal bile acid binding protein: role in activation of FXRa. J Lipid Res. 2012 Apr;53(4):664-73. Also available: http://dx.doi.org/10.1194/jlr.M021733. PMID: 22223860.

309. Hofmann AF. Biliary secretion and excretion in health and disease: current concepts. Ann Hepatol. 2007 Jan-Mar;6(1):15-27. PMID: 17297425.

310. Pares A, Pencek R, Peters Y, et al. FXR agonism with obeticholic acid may attenuate bone mineral density decrease in subjects with primary biliary cirrhosis. J Hepatol. 2015;62:s786.

311. Lindor K, Hansen B, Pencek R, et al. A phase 3B, double blind, placebo controlled study evaluating the effect of obeticholic acid on clinical outcomes in subjects with primary biliary cirrhosis at elevated risk of progression to liver transplant or death. J Hepatol. 2015;62:s850-1.

312. Bowlus CL, Pockros PJ, Drenth J, et al. Obeticholic acid in PBC patients: The utility of titration based on therapeutic response and tolerability. Hepatology. 2014;60(Suppl. 1):353A.

313. Luketic VA, Invernizzi P, Trauner M, et al. Efficacy of obeticholic acid in primary biliary cirrhosis as assessed by response criteria associated with clinical outcome: A poise analysis. Hepatology. 2014;60(suppl 1):355A-6A.

314. Nevens F, Andreone P, Mazzella G, et al. An international phase 3 study of the FXR agonist obeticholic acid in PBC patients: Effects on markers of cholestasis associated with clinical outcomes and hepatocellular damage. Hepatology. 2014;60(suppl 1):347A-8A.

315. Hirschfield GM, Mason A, Luketic V, et al. Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid. Gastroenterology. 2015 Apr;148(4):751-61.e8. Epub 2014 Dec 11. Also available: http://dx.doi.org/10.1053/j.gastro.2014.12.005. PMID: 25500425.

316. Intercept Pharmaceuticals. Phase 3 study of obeticholic acid in patients with primary biliary cirrhosis (POISE). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Dec 07]. [5 p]. Available: https://clinicaltrials.gov/ct2/show/NCT01473524 NLM Identifier: NCT01473524.

317. Intercept Pharmaceuticals. Phase 3 study of obeticholic acid evaluating clinical outcomes in patients with primary biliary cirrhosis (COBALT). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Dec 07]. [6 p]. Available: https://clinicaltrials.gov/ct2/show/NCT02308111 NLM Identifier: NCT02308111.

318. Primary biliary cirrhosis. [internet]. New York (NY): Intercept Pharmaceuticals, Inc. [accessed 2015 Feb 25]. [5 p]. Available: http://www.interceptpharma.com/research-development/therapeutic-areas/primary-biliary-cirrhosis/.

319. Intercept Pharmaceuticals submits applications in the U.S. and Europe for marketing approval of obeticholic acid for the treatment of primary biliary cirrhosis. [internet]. New York (NY): Intercept Pharmaceuticals, Inc.; 2015 Jun 29 [accessed 2015 Jun 30]. [3 p]. Available: http://ir.interceptpharma.com/releasedetail.cfm?ReleaseID=919926.

320. Lammers WJ, van Buuren HR, Hirschfield GM, et al. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study. Gastroenterology. 2014 Dec;147(6):1338-49.e5; quiz e15. Also available: http://dx.doi.org/10.1053/j.gastro.2014.08.029. PMID: 25160979.

321. Actigall (ursodiol) [generic] pricing info. [internet]. Santa Monica (CA): GoodRx, Inc. [accessed 2015 Dec 04]. [10 p]. Available: http://www.goodrx.com/actigall.

322. Actigall [brand] pricing info. [internet]. Santa Monica (CA): GoodRx, Inc. [accessed 2015 Dec 04]. [10 p]. Available: http://www.goodrx.com/actigall?form=capsule&dosage=300mg&quantity=30&label_override=Actigall.

323. Mayo Clinic staff. Primary biliary cirrhosis. [internet]. Rochester (MN): Mayo Foundation for Medical Education and Research (MFMER); 2014 Nov 22 [accessed 2015 May 01]. [9 p]. Available: http://www.mayoclinic.org/diseases-conditions/primary-biliary-cirrhosis/basics/definition/con-20029377.

324. Primary biliary cirrhosis (PBC). [internet]. Philadelphia (PA): American Liver Foundation; 2015 Jan 14 [accessed 2015 May 01]. [2 p]. Available: http://www.liverfoundation.org/abouttheliver/info/pbc/.

325. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Primary biliary cirrhosis. Bethesda (MD): U.S. National Institutes of Health (NIH); 2014 Mar. 12 p. Also available: http://www.niddk.nih.gov/health-information/health-topics/liver-disease/primary-biliary-cirrhosis/Documents/PrimBiliaryCirrhosis_508.pdf.

326. Expert Commenter 25. (External, Clinical). Horizon Scanning Structured Comment Form. HS2090 - Obeticholic acid for treatment of primary biliary cirrhosis. 2015 Sep 28 [review date].

327. Expert Commenter 1546. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS2090 - Obeticholic acid for treatment of primary biliary cirrhosis. 2015 Sep 30 [review date].

328. Expert Commenter 394. (External, clinical). Horizon Scanning Structured Comment Form. HS2090 - Obeticholic acid for treatment of primary biliary cirrhosis. 2015 Sep 28 [review date].

329. Expert Commenter 1582. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS2090 - Obeticholic acid for treatment of primary biliary cirrhosis. 2015 Oct 2 [review date].

330. Expert Commenter 1192. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2090 - Obeticholic acid for treatment of primary biliary cirrhosis. 2015 Sep 30 [review date].

331. Expert Commenter 427. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2090 - Obeticholic acid for treatment of primary biliary cirrhosis. 2015 Oct 2 [review date].

332. Amblyopia. In: MedlinePlus [internet]. Bethesda (MD): National Library of Medicine (U.S.); 2012 Sep 18 [accessed 2013 May 06]. [2 p]. Available: http://www.nlm.nih.gov/medlineplus/ency/article/001014.htm.

333. Schwartz RH, Schuman AJ, Wei LL. Instrument-based vision screening: update and review. [internet]. Santa Monica (CA): Advanstar Communications, Inc.; 2014 Feb 01 [accessed 2014 Jun 17]. [8 p]. Available: http://contemporarypediatrics.modernmedicine.com/contemporary-pediatrics/news/instrument-based-vision-screening-update-and-review?page=full.

334. REBIScan. [internet]. Cambridge (MA): REBIScan, Inc. [accessed 2013 Jul 29]. [5 p]. Available: http://rebiscan.com/overview.

335. Nassif DS, Piskun NV, Hunter DG. The Pediatric Vision Screener III: detection of strabismus in children. Arch Ophthalmol. 2006 Apr;124(4):509-13. PMID: 16606876.

336. Beauchamp CL, Stager Sr DR, Stager Jr D, et al. High sensitivity and specificity of the pediatric vision scanner in detecting strabismus. J AAPOS. 2013 Feb;17(1):e18.

337. Yanni SE, Jost RM, Beauchamp CL, et al. Objective detection of amblyopia and strabismus... not just screening for risk. J AAPOS. 2012 Feb;16(1):e9.

338. Kane J, Omran SS, Donahue SP. Detecting amblyopia and strabismus in children with the pediatric vision scanner. J AAPOS. 2012 Feb;16(1):e20.

339. Jost RM, Yanni SE, Beauchamp CL, et al. Beyond screening for risk factors: objective detection of strabismus and amblyopia. JAMA Ophthalmol. 2014 Jul;132(7):814-20. Also available: http://dx.doi.org/10.1001/jamaophthalmol.2014.424. PMID: 24875453.

340. Jost RM, Felius J, Birch EE. High sensitivity of binocular retinal birefringence screening for anisometropic amblyopia without strabismus. J AAPOS. 2014 Aug;18(4):e5-e6. Also available: http://dx.doi.org/10.1016/j.jaapos.2014.07.017.

341. Center for Devices and Radiological Health (CDRH). Information sheet guidance for IRBs, clinical investigators, and sponsors: significant risk and nonsignificant risk medical device studies. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2006 Jan. 15 p. Also available: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf.

342. Vision Quest 20/20 and REBIScan announce collaboration. [internet]. Cambridge (MA): REBIScan [accessed 2014 Oct 01]. [3 p]. Available: http://rebiscan.com/news/.

343. REBIScan Quick pitch. [internet]. Powell (OH): Fundable.com [accessed 2014 Dec 11]. [6 p]. Available: https://www.fundable.com/rebiscan.

344. American Association for Pediatric Ophthalmology and Strabismus (AAPOS). Amblyopia. [internet]. San Francisco (CA): American Association for Pediatric Ophthalmology and Strabismus (AAPOS) [accessed 2013 May 06]. [4 p]. Available: http://www.aapos.org/terms/conditions/21.

345. Expert Commenter 1015. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS1866 - Pediatric Vision Scanner for strabismus and amblyopia screening. 2015 Sep 29 [review date].

346. Expert Commenter 1383. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS1866 - Pediatric Vision Scanner for strabismus and amblyopia screening. 2015 Oct 2 [review date].

347. Expert Commenter 428. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1866 - Pediatric Vision Scanner for strabismus and amblyopia screening. 2015 Oct 1 [review date].

348. Expert Commenter 1473. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1866 - Pediatric Vision Scanner for strabismus and amblyopia screening. 2015 Oct 20 [review date].

349. Expert Commenter 721. (External, Clinical). Horizon Scanning Structured Comment Form. HS1866 - Pediatric Vision Scanner for strabismus and amblyopia screening. 2015 Oct 5 [review date].

350. Expert Commenter 1654. (External, Clinical). Horizon Scanning Structured Comment Form. HS1866 - Pediatric Vision Scanner for strabismus and amblyopia screening. 2015 Oct 6 [review date].

351. Barion A, Zee PC. A clinical approach to circadian rhythm sleep disorders. Sleep Med. 2007 Sep;8(6):566-77. Also available: http://dx.doi.org/10.1016/j.sleep.2006.11.017. PMID: 17395535.

352. Unger EF. NDA approval for Hetlioz (tasimelteon) 20 mg oral capsules. NDA 205677. 2014 Jan 31.

353. FDA Advisory Committee recommends approval of Hetlioz for the treatment of non-24-hour-disorder (non-24) in the totally blind. [internet]. Washington (DC): Vanda Pharmaceuticals Inc.; 2013 Nov 14 [accessed 2014 Mar 31]. [2 p]. Available: http://phx.corporate-ir.net/phoenix.zhtml?c=196233&p=irol-newsArticle&ID=1877276&highlight=.

354. Hetlioz (tasimelteon) capsules, for oral use prescribing information. Washington (DC): Vanda Pharmaceuticals Inc.; 2014 Jan. 11 p.

355. Vanda Pharmaceuticals Inc. conference call to discuss FDA approval of Hetlioz (tasimelteon) for the treatment of non-24-hour sleep-wake disorder. FD (Fair Disclosure) Wire; 2014 Feb 3. 8 p.

356. Lockley SW, Dressman MA, Xiao C, et al. SUN-134 Tasimelteon treatment entrains the circadian clock and demonstrates a clinically meaningful benefit in totally blind individuals with non-24-hour circadian rhythms. In: ENDO 2013; June 15-18, 2013; San Francisco (CA). Endocrine Society; 2013 Jun 15. p. 1. Also available: https://endo.confex.com/endo/2013endo/webprogram/Paper7754.html.

357. Lockley SW, Dressman MA, Xiao C, et al. Reset study demonstrates that tasimelteon maintains entrainment of melatonin and cortisol in totally blind individuals with non-24-hour circadian rhythms. In: ENDO 2013; 2013 Jun 15-18; San Francisco (CA). Also available: http://phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9NTA5NjUzfENoaWxkSUQ9MTkwODg1fFR5cGU9MQ==&t=1.

358. Vanda Pharmaceuticals. Safety study of tasimelteon for treatment of non-24-hour-sleep-wake disorder in blind individuals with no light perception. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Jun 03]. [4 p]. Available: https://clinicaltrials.gov/ct2/show/NCT01218789 NLM Identifier: NCT01218789.

359. Hetlioz (tasimelteon) capsules. [internet]. Washington (DC): Vanda Pharmaceuticals Inc. [accessed 2014 Mar 31]. [2 p]. Available: https://www.hetlioz.com/.

360. Vanda Pharmaceuticals Inc, Vanda Pharmaceuticals Inc. Hetlioz (tasimelteon): medical review application number: 205677. Rockville (MD): U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research; 2013 May 31. 154 p.

361. Hetlioz pricing info. [internet]. Santa Monica (CA): GoodRx, Inc.; [accessed 2015 Nov 24]. [10 p]. Available: http://www.goodrx.com/hetlioz.

362. Hetlioz pricing information. [internet]. Santa Monica (CA): GoodRx, Inc. [accessed 2014 Apr 01]. [6 p]. Available: http://www.goodrx.com/hetlioz.

363. Vanda Pharmaceuticals reports first quarter 2015 financial results. [internet]. Washington (DC): Vanda Pharmaceuticals, Inc.; 2015 May 6 [accessed 2015 Jun 11]. [7 p]. Available: http://phx.corporate-ir.net/phoenix.zhtml?c=196233&p=irol-newsArticle&ID=2044890.

364. Regence Group. Medication policy manual: Hetlioz, tasimelteon. Policy no. dru349. Portland (OR): Regence Group; 2014 May 9. 6 p. Also available: http://blue.regence.com/trgmedpol/drugs/dru349.pdf.

365. Aetna, Inc. Pharmacy clinical policy bulletins: Aetna non-Medicare prescription drug plan: subject: sedative/hypnotics. [internet]. Hartford (CT): Aetna, Inc.; 2014 May 23 [accessed 2014 Dec 02]. [6 p]. Available: http://www.aetna.com/products/rxnonmedicare/data/2014/CNS/sedative-hypnotics.html.

366. Blue Cross and Blue Shield of Alabama. Hetlioz (tasimelteon) prior authorization (with quantity limit) program summary. East Birmingham (AL): Blue Cross and Blue Shield of Alabama; 1 p. Also available: http://www.bcbsal.com.

367. BlueCross BlueShield of Massachusetts. Pharmacy medical policy #697. Hetlioz (tasimelteon). [internet]. Boston (MA): BlueCross BlueShield of Massachusetts; 2014 Oct 01 [accessed 2014 Dec 02]. [4 p]. Available: http://www.bcbsma.com.

368. CIGNA Corporation. Drug list search results: Hetlioz. [internet]. Bloomfield (CT): CIGNA Corporation [accessed 2014 Dec 02]. [1 p]. Available: https://my.cigna.com/teamsite/cgi-bin/customer_care/member/drug_list/DrugList.cgi.

369. HealthPartners. Search the PreferredRx formulary - Hetlioz. [internet]. Minneapolis (MN): HealthPartners [accessed 2014 Dec 02]. [1 p]. Available: https://www.healthpartners.com/public/pharmacy/formularies/preferredrx/.

370. Humana, Inc. Hetlioz (tasimelteon) pharmacy coverage policy: prior authorization. Louisville (KY): Humana, Inc.; 2015 Mar 18. 4 p. Also available: http://www.humana.com.

371. Medica. Medica 2015 comprehensive preferred drug list (PDL). Minnetonka (MN): Medica; 2015 Nov 1. 171 p. Also available: https://www.medica.com/~/media/documents/pharmacy/non-hsa_preferred_drug_list_2015.pdf.

372. United HealthCare Services, Inc. Clinical pharmacy programs: prior authorization/medical necessity. Hetlioz (tasimelteon). Edina (MN): United HealthCare Services, Inc.; 2014 Dec 1. 3 p. Also available: http://www.unitedhealthcare.com.

373. Wellmark, Inc. Wellmark drug list: Hetlioz. [internet]. Des Moines (IA): Wellmark, Inc. [accessed 2014 Dec 02]. [2 p]. Available: http://pharmacy.wellmark.com/Controller?action=TierSearch2Select&rxid=15036.

374. Cataletto ME, Benbadis SR. Sleeplessness and circadian rhythm disorder. In: Medscape Reference [internet]. New York (NY): WebMD LLC; 2014 Feb 10 [accessed 2014 Apr 16]. [12 p]. Available: http://emedicine.medscape.com/article/1188944-overview.

375. Committee for Orphan Medicinal Products. Public summary of positive opinion for orphan designation of Tasimelteon for the treatment of non-24-hour sleep-wake disorder in blind people with no light perception. London (UK): European Medicines Agency (EMA); 2011 Mar 2. 5 p.

376. Expert Commenter 413. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS2049 - Tasimelteon (Hetlioz) for treatment of non-24-hour sleep-wake disorder. 2015 Mar 27 [review date].

377. Expert Commenter 82. (External, Clinical). Horizon Scanning Structured Comment Form. HS2049 - Tasimelteon (Hetlioz) for treatment of non-24-hour sleep-wake disorder. 2015 Apr 6 [review date].

378. Expert Commenter 1192. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2049 - Tasimelteon (Hetlioz) for treatment of non-24-hour sleep-wake disorder. 2015 Mar 23 [review date].

379. Expert Commenter 1321. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2049 - Tasimelteon (Hetlioz) for treatment of non-24-hour sleep-wake disorder. 2015 Mar 26 [review date].

380. Expert Commenter 1015. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS2049 - Tasimelteon (Hetlioz) for treatment of non-24-hour sleep-wake disorder. 2015 Mar 25 [review date].

381. Expert Commenter 1399. (External, Clinical). Horizon Scanning Structured Comment Form. HS2049 - Tasimelteon (Hetlioz) for treatment of non-24-hour sleep-wake disorder. 2015 Mar 25 [review date].

382. ReWalk personal exoskeleton system cleared by FDA for home use - revolutionary technology that allows individuals with spinal cord injury, such as paraplegia, to stand & walk receives clearance for personal use in the U.S. [internet]. Marlborough (MA): ReWalk Robotics, Inc.; 2014 Jun 26 [accessed 2014 Oct 07]. [3 p]. Available: http://rewalk.com/news/press-releases/rewalk-personal-exoskeleton-system-cleared-by-fda-for-home-use/.

383. ReWalk Robotics launches ReWalk 6.0: the company's sixth generation personal system for home & community use. [internet]. Marlborough (MA): ReWalk Robotics, Inc.; 2015 Jul 14 [accessed 2015 Nov 23]. [7 p]. Available: http://rewalk.com/rewalk-robotics-unveils-sixth-generation-personal-system-home-community-use-rewalk-6-0/.

384. Kronemyer B. Argo Medical and Ekso Bionics make strides with robotic walking devices. In: MedTech Insight [internet]. Bedminster (NJ): Elsevier Business Intelligence; 2013 Oct 28 [accessed 2013 Nov 14]. [3 p]. Available: http://www.elsevierbi.com/publications/medtech-insight/15/9/argo-medical-and-ekso-bionics-make-strides-with-robotic-walking-devices.

385. ReWalk: products, general description. [internet]. Yokneam Ilit (Israel): Argo Medical Technologies, Ltd. [accessed 2011 Jan 25]. [2 p]. Available: http://rewalk.com/products/.

386. ReWalk - personal. [internet]. Marlborough (MA): ReWalk Robotics, Inc. [accessed 2014 Oct 07]. [2 p]. Available: http://rewalk.com/products/rewalk-personal/.

387. FDA allows marketing of first wearable, motorized device that helps people with certain spinal cord injuries to walk. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2014 Jun 26 [accessed 2014 Oct 07]. [5 p]. Available: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm402970.htm.

388. James J Peters Veterans Affairs Medical Center. Home/work, community mobility skills in the ReWalk Exoskeleton in persons with SCI (VA_ReWalk2). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Jun 05]. [4 p]. Available: https://clinicaltrials.gov/show/NCT02118194 NLM Identifier: NCT02118194.

389. Rehabilitation Institute of Chicago. Identify training strategies for progressing exoskeleton users towards everyday functional ambulation. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Jun 05]. [4 p]. Available: https://www.clinicaltrials.gov/ct2/show/NCT02104622 NLM Identifier: NCT02104622.

390. Esquenazi A, Talaty M, Packel A, et al. The ReWalk powered exoskeleton to restore ambulatory function to individuals with thoracic-level motor-complete spinal cord injury. Am J Phys Med Rehabil. 2012 Nov;91(11):911-21. PMID: 23085703.

391. Zeilig G, Weingarden H, Zwecker M, et al. Safety and tolerance of the ReWalk exoskeleton suit for ambulation by people with complete spinal cord injury: a pilot study. J Spinal Cord Med. 2012 Mar;35(2):96-101. PMID: 22333043.

392. Benson I, Hart K, Tussler D, et al. Lower-limb exoskeletons for individuals with chronic spinal cord injury: Findings from a feasibility study. Clin Rehabil. 2015 Mar 11:Epub ahead of print. Also available: http://dx.doi.org/10.1177/0269215515575166. PMID: 25761635.

393. ReWalk Robotics reports first quarter 2015 financial results. [internet]. Marlborough (MA): ReWalk Robotics, Inc.; 2015 May 7 [accessed 2015 Jun 05]. [8 p]. Available: http://ir.rewalk.com/phoenix.zhtml?c=253715&p=irol-newsArticle&ID=2045194.

394. ReWalk Robotics reports second quarter 2015 financial results. [internet]. Marlborough (MA): ReWalk Robotics, Inc.; 2015 Aug 6 [accessed 2015 Nov 23]. [12 p]. Available: http://ir.rewalk.com/phoenix.zhtml?c=253715&p=irol-newsArticle&id=2076489.

395. Radick L. Argo preps 510(k) application for ReWalk exoskeleton for home use. Gray Sheet. 2012 Oct 29:4. Also available: https://www.pharmamedtechbi.com/publications/health-news-daily/2012/10/29/argo-preps-510k-application-for-emrewalkem-exoskeleton-for-home-use.

396. The durable medical equipment, prosthetics, orthotics, and supplies (DMEPOS) competitive bidding program. [internet]. Baltimore (MD): Centers for Medicare & Medacaid Services (CMS); 2013 Nov 01 [accessed 2014 Nov 03]. [8 p]. Available: http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/Downloads/DME_Ref_Agt_Factsheet_ICN900927.pdf.

397. Aetna, Inc. Clinical policy bulletin: lower limb prostheses. Number 0578. [internet]. Hartford (CT): Aetna, Inc.; 2015 Oct 23 [accessed 2015 Sep 24]. [39 p]. Available: http://www.aetna.com/cpb/medical/data/500_599/0578.html.

398. Anthem Insurance Companies. Powered robotic lower body exoskeleton devices. Policy #: OR-PR.00006. [internet]. North Haven (CT): Anthem Insurance Companies, Inc.; 2015 Jan 13 [accessed 2015 Jun 08]. [4 p]. Available: http://www.anthem.com/medicalpolicies/policies/mp_pw_c176719.htm.

399. Blue Cross and Blue Shield of Alabama. Powered exoskeleton for ambulation in patients with lower limb disabilities. Policy #: 575. East Birmingham (AL): Blue Cross and Blue Shield of Alabama; 2014 Dec. 6 p. Also available: http://www.bcbsal.com.

400. Blue Cross and Blue Shield of Massachusetts. Powered exoskeleton for ambulation in patients with lower limb disabilities. Policy number 718. Boston (MA): Blue Cross and Blue Shield of Massachusetts; 2015 May. 3 p. Also available: http://www.bcbsma.com.

401. Cigna Corporation. Lower limb orthoses and shoes. Coverage policy number 0150. Bloomfield (CT): Cigna Corporation; 2015 Aug 15. 34 p. Also available: https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies/medical/mm_0150_coveragepositioncriteria_foot_ankle_knee_orthotics.pdf.

402. HealthPartners. Investigational services - list of non-covered services. Policy #: I031-20. [internet]. Minneapolis (MN): HealthPartners; 2015 Nov 1 [accessed 2015 Nov 23]. [7 p]. Available: https://www.healthpartners.com/public/coverage-criteria/investigational-services-noncovered-services/.

403. Humana, Inc. Orthotics. Policy number: HGO-0330-024. Louisville (KY): Humana, Inc.; 2015 Oct 21. 55 p. Also available: http://apps.humana.com/tad/tad_new/Search.aspx?criteria=exoskeleton&searchtype=freetext&policyType=both.

404. Regence Group. Functional neuromuscular electrical stimulation. Medical policy #83.04. [internet]. Portland (OR): Regence Group; 2015 Feb 1 [accessed 2015 Jun 08]. [10 p]. Available: https://www.regence.com/.

405. Mayo Clinic staff. Spinal cord injury. [internet]. Rochester (MN): Mayo Foundation for Medical Education and Research (MFMER); 2011 Oct 22 [accessed 2012 Sep 20]. [12 p]. Available: http://www.mayoclinic.com/health/spinal-cord-injury/DS00460/.

406. Spinal cord trauma. In: PubMed Health [internet]. Bethesda (MD): National Library of Medicine (U.S.); 2011 May 14 [accessed 2012 Sep 20]. [6 p]. Available: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002061/.

407. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2039 - Wearable battery-powered exoskeleton (ReWalk Personal) to enable mobility in community or home setting for patients with paraplegia. 2015 Jan 9 [review date].

408. Expert Commenter 1383. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS2039 - Wearable battery-powered exoskeleton (ReWalk Personal) to enable mobility in community or home setting for patients with paraplegia. 2015 Jan 9 [review date].

409. Expert Commenter 399. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS2039 - Wearable battery-powered exoskeleton (ReWalk Personal) to enable mobility in community or home setting for patients with paraplegia. 2015 Jan 14 [review date].

410. Expert Commenter 1320. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2039 - Wearable battery-powered exoskeleton (ReWalk Personal) to enable mobility in community or home setting for patients with paraplegia. 2015 Jan 13 [review date].

411. Expert Commenter 1475. (External, Clinical). Horizon Scanning Structured Comment Form. HS2039 - Wearable battery-powered exoskeleton (ReWalk Personal) to enable mobility in community or home setting for patients with paraplegia. 2015 Jan 23 [review date].

412. Expert Commenter 1224. (External, Clinical). Horizon Scanning Structured Comment Form. HS2039 - Wearable battery-powered exoskeleton (ReWalk Personal) to enable mobility in community or home setting for patients with paraplegia. 2015 Feb 9 [review date].

413. Kung TA, Bueno RA, Alkhalefah GK, et al. Innovations in prosthetic interfaces for the upper extremity. Plast Reconstr Surg. 2013 Dec;132(6):1515-23. Also available: http://dx.doi.org/10.1097/PRS.0b013e3182a97e5f. PMID: 24281580.

414. Resnik L, Klinger SL, Etter K. User and clinician perspectives on DEKA arm: results of VA study to optimize DEKA arm. J Rehabil Res Dev. 2014;51(1):27-38. Also available: http://dx.doi.org/10.1682/JRRD.2013.03.0068. PMID: 24805891.

415. Resnik L, Klinger SL, Etter K. The DEKA Arm: its features, functionality, and evolution during the Veterans Affairs Study to optimize the DEKA Arm. Prosthet Orthot Int. 2014 Dec;38(6):492-504. Epub 2013 Oct 22. Also available: http://dx.doi.org/10.1177/0309364613506913. PMID: 24150930.

416. Tahir D. FDA approves advanced prosthetic arm. Gray Sheet. 2014 May 9:Article # 01140512017. Also available: http://www.pharmamedtechbi.com/.

417. Resnik L, Latlief G, Klinger SL, et al. Do users want to receive a DEKA Arm and why? Overall findings from the Veterans Affairs Study to optimize the DEKA Arm. Prosthet Orthot Int. 2014 Dec;38(6):456-66. Epub 2013 Nov 28. Also available: http://dx.doi.org/10.1177/0309364613506914. PMID: 24286806.

418. Resnik L, Borgia M. User ratings of prosthetic usability and satisfaction in VA study to optimize DEKA arm. J Rehabil Res Dev. 2014;51(1):15-26. Also available: http://dx.doi.org/10.1682/JRRD.2013.02.0056. PMID: 24805890.

419. VA Office of Research and Development. Home study of an advanced upper limb prosthesis. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Dec 02]. [5 p]. Available: https://clinicaltrials.gov/ct2/show/NCT01551420 NLM Identifier: NCT01551420.

420. DEKA prosthetic arm. [internet]. Manchester (NH): DEKA Research and Development Corporation [accessed 2014 Jun 20]. [2 p]. Available: http://www.dekaresearch.com/deka_arm.shtml.

421. United States: FDA approves marketing of DEKA ARM system. Thanke (India): TendersInfo; 2014 May 14. 1 p.

422. U.S. Food and Drug Administration (FDA). Product classification: upper extremity prosthesis with multiple simultaneous degrees of freedom and controlled via cutaneous electromyography. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA) [accessed 2014 Jun 19]. [2 p]. Available: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn_template.cfm?id=k121215.

423. Kirsner S. Getting advanced prosthetics to those who need them. [internet]. Boston (MA): Boston Globe Media Partners, LLC; 2014 Sep 14 [accessed 2015 Jul 27]. [5 p]. Available: https://www.bostonglobe.com/business/2014/09/13/the-biggest-challenge-for-advanced-prosthetics-may-getting-people-who-need-them/uRnjueXxHGX1c1kDOAxFUL/story.html .

424. Contract view release No: CR-125-15. [internet]. Washington (DC): U.S. Department of Defense (DOD); 2015 Jul 2 [accessed 2015 Dec 02]. [6 p]. Available: http://www.defense.gov/News/Contracts/Contract-View/Article/606883.

425. Castellanos S. Dean Kamen's 'Star Wars'-like robot arm wins FDA approval; still more work to be done. In: Techflash [internet]. Boston (MA): Boston Business Journal; 2014 Jun 02 [accessed 2014 Jul 25]. [5 p]. Available: http://www.bizjournals.com/boston/blog/techflash/2014/06/dean-kamens-star-wars-like-robot-arm-wins-fda.html?page=all.

426. Your Medicare coverage: orthotics and artificial limbs. [internet]. Baltimore (MD): Medicare.gov [accessed 2014 Jul 18]. [3 p]. Available: http://www.medicare.gov/coverage/orthotics-and-artificial-limbs.html.

427. Aetna, Inc. Clinical policy bulletin: myoelectric upper limb prostheses. Policy number: 0399. [internet]. Hartford (CT): Aetna, Inc.; 2015 Oct 23 [accessed 2015 Dec 02]. [14 p]. Available: http://www.aetna.com/cpb/medical/data/300_399/0399.html.

428. Anthem Insurance Companies, Inc.. Myoelectric upper extremity prosthetic devices. Guideline #: CG-OR-PR-05. [internet]. North Haven (CT): Anthem Insurance Companies, Inc.; 2015 Apr 7 [accessed 2015 Jul 22]. [4 p]. Available: https://www.anthem.com/medicalpolicies/guidelines/gl_pw_c169421.htm.

429. BlueCross BlueShield of Alabama. Myoelectric prosthetic and orthotic components for the upper limb. Policy #: 124. East Birmingham (AL): BlueCross BlueShield of Alabama; 2015 Aug. 13 p. Also available: https://m.bcbsal.org/providers/policies/final/124.pdf.

430. Blue Cross and Blue Shield of Massachusetts, Blue Cross and Blue Shield of Massachusetts. Myoelectric prosthetic components for the upper limb. Policy number 227. Boston (MA): Blue Cross and Blue Shield of Massachusetts; 2015 Jan. 5 p. Also available: http://www.bcbsma.com.

431. CIGNA Corporation. Prosthetic devices: upper limb myoelectric. Coverage policy number 0233. Bloomfield (CT): CIGNA Corporation; 2015 Nov 15. 7 p. Also available: https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies/medical/mm_0233_coveragepositioncriteria_myoelectric_prostheses.pdf.

432. HealthPartners. Upper limb prosthetics. Policy #: U008-01. [internet]. Minneapolis (MN): HealthPartners; 2015 Jan 10 [accessed 2015 Jul 22]. [3 p]. Available: https://www.healthpartners.com/public/coverage-criteria/upper-limb-prosthetics/.

433. Humana, Inc. Prosthetics. Policy number CPD-0331-016. Louisville (KY): Humana, Inc.; 2015 May 28. 35 p. Also available: http://www.humana.com.

434. Regence Group. Myoelectric prosthetic components for the upper limb. Policy no. 80. [internet]. Portland (OR): Regence Group; 2015 Dec 1 [accessed 2015 Dec 02]. [8 p]. Available: http://blue.regence.com/trgmedpol/dme/dme80.pdf.

435. UnitedHealthcare, Inc. Prosthetic devices, specialized, microprocessor or myoelectric limbs. Guideline number CS104.D. Atlanta (GA): UnitedHealthcare, Inc.; 2015 Apr 1. 20 p. Also available: http://www.unitedhealthcare.com.

436. Conyers D, Prigge P. The first 12 months after upper-limb amputation. inMotion; 2011 Jan/Feb. 2 p. Also available: http://www.amputee-coalition.org/inmotion/jan_feb_11/first_twelve_months_upper.pdf.

437. The occupational therapy role in rehabilitation for the person with an upper-limb amputation. Bethesda (MD): American Occupational Therapy Association, Inc.; 2011. 2 p. Also available: http://www.aota.org/-/media/Corporate/Files/AboutOT/Professionals/WhatIsOT/RDP/Facts/Upper%20Limb%20Amputee%20fact%20sheet.pdf.

438. Upper-limb prosthetics: part 2. Insights from those who have lost one arm. inMotion. 2007 Jul/Aug;17(4) Also available: http://www.amputee-coalition.org/inmotion/jul_aug_07/ue_prosthetic_pt2.html.

439. Hutchinson DT. The quest for the bionic arm. J Am Acad Orthop Surg. 2014 Jun;22(6):346-51. Also available: http://dx.doi.org/10.5435/JAAOS-22-06-346. PMID: 24860130.

440. Expert Commenter 1383. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS633 - Prosthetic arm with body-machine interface (DEKA Arm System) to restore natural arm functions after amputation. 2015 Sep 11 [review date].

441. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS633 - Prosthetic arm with body-machine interface (DEKA Arm System) to restore natural arm functions after amputation. 2015 Sep 4 [review date].

442. Expert Commenter 1320. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS633 - Prosthetic arm with body-machine interface (DEKA Arm System) to restore natural arm functions after amputation. 2015 Sep 4 [review date].

443. Expert Commenter 399. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS633 - Prosthetic arm with body-machine interface (DEKA Arm System) to restore natural arm functions after amputation. 2015 Sep 21 [review date].

444. Expert Commenter 1224. (External, Clinical). Horizon Scanning Structured Comment Form. HS633 - Prosthetic arm with body-machine interface (DEKA Arm System) to restore natural arm functions after amputation. 2015 Sep 25 [review date].

445. Expert Commenter 173. (External, Clinical). Horizon Scanning Structured Comment Form. HS633 - Prosthetic arm with body-machine interface (DEKA Arm System) to restore natural arm functions after amputation. 2015 Oct 7 [review date].