

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

Priority Area 07: Diabetes Mellitus

Prepared for:

Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. HHSA290201000006C

Prepared by:

ECRI Institute
5200 Butler Pike
Plymouth Meeting, PA 19462

December 2012

Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). 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

This document is in the public domain and may be used and reprinted without special permission. Citation of the source is appreciated.

Suggested citation: ECRI Institute. AHRQ Healthcare Horizon Scanning System Potential High-Impact Interventions: Priority Area 07: Diabetes Mellitus). (Prepared by ECRI Institute under Contract No. HHSA290201000006C.) Rockville, MD: Agency for Healthcare Research and Quality. December 2012. <http://www.effectivehealthcare.ahrq.gov/reports/final.cfm>.

Preface

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

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

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

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

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

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

Contents

Executive Summary	ES-1
Background	ES-1
Methods	ES-1
Results	ES-2
Discussion	ES-3
Diabetes Mellitus Interventions	1
Artificial Pancreas for Treatment of Diabetes	2
Buccal Insulin (Oral-Lyn) Therapy for Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus Requiring Insulin	5
Fluocinolone Acetonide Implant (Iluvien) for Treatment of Diabetic Macular Edema	8
New Exenatide Formulations (Bydureon; ITCA 650 with Duros Pump) for Treatment of Type 2 Diabetes Mellitus	11
Ranibizumab (Lucentis) for Treatment of Diabetic Macular Edema	15
References	18
Figures	
Figure 1. Overall high-impact potential: artificial pancreas for treatment of diabetes	3
Figure 2. Overall high-impact potential: buccal insulin (Oral-lyn) therapy for type 1 diabetes mellitus and type 2 diabetes mellitus requiring insulin	6
Figure 3. Overall high-impact potential: fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema	9
Figure 4. Overall high-impact potential: new exenatide formulations (Bydureon; ITCA 650 with Duros pump) for treatment of type 2 diabetes mellitus	13
Figure 5. Overall high-impact potential: ranibizumab (Lucentis) for treatment of diabetic macular edema	16

Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identifying new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, review of more than 15,000 leads about potential topics has resulted in identification and tracking of about 1,600 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 950 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 annually. Topics eligible for inclusion are those interventions expected to be within 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

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

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

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

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the potential high-impact range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as 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 14 topics for which (1) preliminary phase III data for drugs, at least phase II data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled by September 21, 2012, in this priority area; *and* (3) we received six to nine sets of comments from experts between February 2011 and October 19, 2012. (Fifty-five topics in this priority area were being tracked in the system as of October 19, 2012.) For this report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present five summaries on six topics (indicated below by an asterisk) that emerged as having potential for high impact on the basis of experts’ comments.

Priority Area 07: Diabetes

Topic	High-Impact Potential
1. *Artificial pancreas for treatment of diabetes	High
2. *Buccal insulin (Oral-lyn) therapy for type 1 diabetes mellitus and type 2 diabetes mellitus requiring insulin	Moderately high
3. *Exenatide extended-release (Bydureon) for treatment of diabetes	Lower end of the potential high-impact range
4. *Exenatide subcutaneous pump (ITCA 650 with Duros pump) for treatment of type 2 diabetes mellitus	Lower end of the potential high-impact range
5. *Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema	Moderately high
6. GFT 505 for treatment of type 2 diabetes mellitus and prediabetes	No high-impact potential at this time
7. Inhaled insulin (Technosphere) therapy for type 1 diabetes mellitus or insulin-dependent type 2 diabetes mellitus	No high-impact potential at this time
8. InsuPatch for improving pump-infused insulin absorption	No high-impact potential at this time
9. Off-label salsalate for treatment of type 2 diabetes mellitus	No high-impact potential at this time
10. *Ranibizumab (Lucentis) for treatment of diabetic macular edema	Moderately high
11. SGLT2 inhibitor (ASP1941) for treatment of type 2 diabetes mellitus	No high-impact potential at this time
12. SGLT2 inhibitor (BI-10773) for treatment of type 2 diabetes mellitus	No high-impact potential at this time
13. SGLT2 inhibitor (dapagliflozin) for treatment of type 2 diabetes mellitus	No high-impact potential at this time
14. SGLT2 inhibitor (LX-4211) for treatment of type 2 diabetes mellitus	No high-impact potential at this time

Discussion

Diabetes is a significant and growing health problem. The National Institute of Diabetes and Digestive and Kidney Diseases has estimated that in 2010, 18.8 million Americans had some form of diagnosed diabetes and an estimated 7.0 million had undiagnosed diabetes; about 79 million Americans aged 20 years or older were deemed to have prediabetes. About 5% to 10% of cases are type 1 diabetes mellitus (T1DM), and most of the other cases are type 2 diabetes mellitus (T2DM). T2DM prevalence is about 25% in the population aged 65 years or older and nearly 40% of those 80 years of age or older, but age of onset is trending younger. The American Diabetes Association Task Force has developed a revised classification system based on etiology rather than treatment mode. T1DM results from a chronic autoimmune condition in which the immune system attacks and destroys insulin-producing pancreatic beta cells, leading to chronically elevated blood glucose levels. Without supplemental insulin intervention, the condition is fatal. Patients with T1DM take multiple daily insulin injections, or specially selected patients may use an external insulin pump for subcutaneous infusion.

After diagnosis and disease-type classification, patients undergo evaluation to detect complications, review glycemic control challenges, and establish treatment goals and plan, including target glycated hemoglobin (HbA_{1c}) levels. The HbA_{1c} test is a single blood draw conducted every 3–4 months that measures how much hemoglobin has bonded to blood cells over that period. It is the accepted standard for monitoring diabetes management goals. Ongoing, patients receive a treatment plan and are taught how to self-manage day-to-day care. Clinicians generally encourage patients to achieve an HbA_{1c} level of 7% because this value has been shown to reduce diabetes-associated complications. However, targets are individualized according to clinician judgment about the optimal goal for a specific patient, taking into account the patient's medical characteristics and age. For T2DM, several self-administered, oral antidiabetes agents, alone or in combination, are generally tried as first-line therapy. These include biguanides, sulfonylureas, alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, and dipeptidyl peptidase-4 inhibitors. Many patients with T2DM do not meet treatment goals and require additional therapy with one of two types of injected antidiabetes agents: subcutaneous insulin or a glucagon-like peptide-1 (GLP-1) agonist. Insulin supplementation has become increasingly common with T2DM.

New treatments in development for all types of diabetes focus on delaying disease onset in at-risk patients and improving diabetes management and treatment adherence. New drugs and drug-delivery modalities are intended to optimize efficacy to enable patients to meet and maintain near-normal glycemia without excursions high or low, to improve patient adherence to treatment regimens, and to reduce acute excursions (i.e., hyperglycemia, hypoglycemia), weight gain, and secondary complications (i.e., nephropathy, neuropathy, retinopathy).

Artificial Pancreas for Treatment of Diabetes

- **Key Facts:** An artificial pancreas or closed-loop system (CLS) (an external or implantable insulin pump, real-time continuous glucose monitor, and a small computing device with software and algorithms to detect glucose levels and coordinate with insulin delivery) is considered by many to be the ideal management strategy for patients on intensive insulin therapy. Researchers are developing two types of systems: reactive and predictive low-glucose suspend systems. In reactive systems, patients or clinicians preset a blood glucose threshold, and the pump automatically shuts off when that reading is reached. In predictive systems, the monitor uses control algorithms that predict when the patient's blood glucose is projected to decrease to a dangerously low level. Although many proof-of-concept studies of

CLSs have been performed and although all the necessary component parts of a CLS exist, a truly portable CLS for routine use is several years from realization because major advances in sensor technologies and artificial pancreas software algorithms are needed, as is a developer that is able and willing to integrate the disparate components into a single CLS. The Juvenile Diabetes Foundation has committed significant resources to developing a system, and systems are in pilot studies. On November 9, 2012, the U.S. Food and Drug Administration (FDA) issued guidance for developers titled, “The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Artificial Pancreas Device Systems” to guide trial conduct and regulatory submissions.

- **Key Expert Comments:** Overall, experts commented that a CLS has significant potential to simplify the way in which patients with T1DM manage the disease to achieve near-normal glycemia and avoid acute (i.e., hypoglycemia, hyperglycemia) and long-term complications (i.e., nephropathy, neuropathy, retinopathy). Such a system, they opined, would likely be indicated for only a subset of the T1DM population, and success of operating a CLS is largely dependent on a multidisciplinary care team and a highly motivated patient.
- **Potential for High Impact:** High

Buccal Insulin (Oral-Lyn) Therapy for Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus Requiring Insulin

- **Key Facts:** Many patients who require exogenous insulin consider injections burdensome, but continuous subcutaneous insulin pumps are appropriate for relatively few patients. Therefore, novel insulin delivery methods that do not involve injection are being sought. A noninjectable insulin in development, Oral-lyn™ (Generex Biotechnology Corp., Toronto, Ontario, Canada), is a liquid formulation of human insulin delivered as a buccal spray. It is administered by a proprietary inhaler similar to an asthma inhaler. Absorption is limited to the mouth with no entry into the lungs, and absorption is faster, with a shorter total duration of activity, because of the rich vascularity of the buccal mucosa, potentially making buccal insulin an ideal insulin to control glycemic excursions after meals. A phase III trial comparing use of Oral-lyn as a prandial insulin with injected human insulin was expected to be completed in September 2011, but the National Clinical Trials database listed the trial as ongoing, but not recruiting participants, at 74 sites, as of November 13, 2012. Oral-lyn is available under an FDA treatment investigational new drug program to patients in the United States with life-threatening diabetes and no other treatment options.
- **Key Expert Comments:** Overall, experts providing comments on this topic thought that buccal insulin has potential to improve diabetes treatment by providing a needleless alternative to injectable insulin, which could transition more patients to insulin therapy and potentially improve patient insulin-dosing treatment adherence. However, experts noted that buccal insulin’s efficacy has not yet been conclusively demonstrated and that trials of the drug were moving slowly. This may be, in part, because this is the only product of the company developing it, and funding to complete the required trials may be an issue.
- **Potential for High Impact:** Moderately high

Fluocinolone Acetonide Implant (Iluvien) for Treatment of Diabetic Macular Edema

- **Key Facts:** According to the World Health Organization, people with diabetes who do not receive appropriate eye care have a 25% to 30% chance of developing clinically significant

diabetic macular edema (DME) with moderate or greater vision loss. The main treatment for DME was macular focal/grid laser photocoagulation until August 2012, when FDA approved Lucentis[®] (ranibizumab injection), which is administered as a once-monthly injection into the eye. Iluvien (Alimera Sciences, Inc., Alpharetta, GA) is a tiny tube containing 190 mcg of fluocinolone acetonide that is injected into the back of the eye with a 25-gauge needle in a single, in-office procedure. Over 2–3 years, the tube releases a constant, low flow of medication; thus, patients need not return for monthly injections, as is required with Lucentis. The exact mechanism by which fluocinolone acetonide functions in DME treatment is unknown, but it is thought to work by the combined vasoconstrictive, anti-inflammatory, and antipruritic qualities inherent to corticosteroids such as fluocinolone. In November 2011, FDA issued a complete response letter requesting that the company provide two additional safety and efficacy studies before resubmitting a new drug application. The company met with FDA in June 2012, and based on the outcome of that meeting, declared intentions to resubmit data from two previously completed phase III trials (FAME[™] studies) to address FDA concerns. The company also intends to continue enrolling patients in its physician utilization study of the Iluvien inserter, which had been temporarily halted in November 2011. The drug/device has been approved in Europe. If approved in the United States, this drug would compete with the recently approved Lucentis and aflibercept (Eylea[®] injection); the latter is in phase III trials for treating DME.

- **Key Expert Comments:** Overall, experts thought this intervention could offer a long-lasting, single-injection pharmacotherapy alternative to laser photocoagulation for treating DME. While some experts believe the risk of adverse events could affect clinician adoption of this intravitreal implant, experts opined that patients would likely be willing to accept this intervention if restoring vision to any degree was the end result. Experts thought that the intervention would reduce per-patient treatment costs, compared with costs of laser photocoagulation. Experts expected costs to be significantly greater with this intervention than with off-label use of anti-VEGF (vascular endothelial growth factor) agents used for DME but lower than the cost of laser photocoagulation.
- **Potential for High Impact:** Moderately high

New Exenatide Formulations (Bydureon; ITCA 650 with Duros Pump) for Treatment of Type 2 Diabetes Mellitus

- **Key Facts:** Two therapies for treating T2DM, one in development and one recently FDA approved, are intended to improve efficacy, tolerability (reducing nausea), and patient treatment adherence. These therapies are extended-release exenatide for injection (Bydureon[™], Amylin Pharmaceuticals, Inc., San Diego, CA; in June 2012, Bristol-Myers Squibb, New York, NY, announced its intention to acquire Amylin) and ITCA 650 delivered subcutaneously using the Duros pump[®] (Intarcia Therapeutics, Inc., Hayward, CA).

Extended-release exenatide is a controlled-release, once-weekly formulation delivered by subcutaneous injection. It is intended to mimic the function of GLP-1, a naturally occurring hormone that stimulates release of native insulin and inhibits glucagon release, lowering blood glucose levels. GLP-1 also has been observed to promote a feeling of fullness and satiety, purportedly reducing intake of exogenous glucose. FDA approved once-weekly exenatide in January 2012 for treating T2DM. Reported costs of Bydureon from 11 U.S. pharmacies range from \$354 to \$469 per month or about \$4,250 per year; the lower rates take into account availability of a \$50 discount coupon. Many third-party payers provide coverage and require prior authorization and quantity limits.

ITCA 650 is a proprietary formulation of exenatide that has been reported to remain stable at body temperature for delivery up to 12 months, based on data presented thus far. It is administered continuously using the implantable Duros subcutaneous delivery system. The delivery system (which is also being evaluated for delivering drugs for hepatitis and weight loss) is a semipermeable, osmotic mini-pump that a physician or physician assistant inserts into the patient's arm or abdomen during an outpatient procedure that takes about 5 minutes. In September 2011, the company announced plans for its phase III trial and reported that the drug resulted in improved glycemic control and was well tolerated at doses starting from 20 mcg/day and transitioning to 40 and 60 mcg/day. The company also reported that the drug led to reduced body weight after 24 and 48 weeks of treatment. In November 2012, the company reported that the drug was successfully delivered continuously and with stability for as long as 12 months at doses of 10, 40, and 60 mcg; it also reported that the drug was stable when stored for up to 3 years at 40 °C.

- **Key Expert Comments:** Experts commenting on these topics believe that both formulations have potential to improve diabetes treatment by expanding access to exenatide while reducing frequency of injections and nausea, thereby potentially improving patient treatment adherence. However, some experts noted that the benefit would likely be incremental relative to existing forms of exenatide, other GLP-1 agonists, and other available adjunctive pharmacotherapies for T2DM treatment.
- **Potential for High Impact:** Lower end of the potential high-impact range

Ranibizumab (Lucentis) for Treatment of Diabetic Macular Edema

- **Key Facts:** According to the World Health Organization, people with diabetes who do not receive appropriate eye care have a 25% to 30% chance of developing clinically significant DME with moderate or greater vision loss. Until the approval of Lucentis in August 2012, the main treatment modality was macular focal/grid laser photocoagulation, because no other pharmacotherapies were approved by FDA for treating DME. Ranibizumab (Lucentis, Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland, and Novartis International AG, Basel, Switzerland) is a humanized, recombinant, immunoglobulin G1, kappa isotope, monoclonal antibody fragment targeted against human VEGF-A, FDA approved for treating wet age-related macular degeneration and macular edema with retinal vein occlusion. Ranibizumab's mechanism of action allows it to bind to multiple subtypes of VEGF-A. This binding action causes an inhibiting effect, which prevents the growth of new blood vessels under the macula. Because growth of new blood vessels is prevented, the likelihood of vascular leakage and neovascularization is reduced; thus, vision loss as a result of fluid and protein buildup under the macula may be slowed. Investigators in two phase III trials (RISE and RIDE trials) tested ranibizumab in patients with DME and reported positive results in June 2011. Since the FDA approval in August 2012 of ranibizumab injection for DME treatment, financial analysts indicate the initial uptake of Lucentis in 0.3- and 0.5-mg injections by retina specialists and general ophthalmologists, has been "robust," based on quantities being stocked by these clinicians. Reported cost of an injection is about \$1,170. Some third-party payers reimburse for the drug, and some of those require prior authorization. Genentech offers payment assistance to qualified patients. This drug will compete with other drugs in phase III trials, such as Iluvien and aflibercept (Eylea injection).
- **Key Expert Comments:** Some experts thought that the frequency of intravitreal ranibizumab administration might pose a barrier to patient treatment adherence, limiting its ability to significantly improve patient outcomes and potentially affecting patient

acceptance. Experts thought that the per-patient cost of approximately \$20,000 annually associated with ranibizumab use might pose a barrier to adoption by patients. However, experts thought this intervention could significantly halt disease progression and improve visual acuity as a stand-alone or adjunctive therapy with laser photocoagulation.

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

Diabetes Mellitus Interventions

Artificial Pancreas for Treatment of Diabetes

Artificial pancreas device system (APDS) technology aims at monitoring patient blood glucose levels and automatically responding to these levels by pumping out appropriate doses of insulin based on a computer-driven algorithm.¹ Many proof-of-concept trials are ongoing both in the United States and internationally, and much of the research is supported by the Juvenile Diabetes Research Foundation. Although all the necessary components of APDSs exist, continued advances in sensor technology and software algorithms are needed to enable companies to develop a single APDS that can successfully undergo FDA-approved investigational device exemption trials to support a premarket approval application. To that end, FDA's guidelines, "The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Artificial Pancreas Device Systems," published November 9, 2012, are intended for sponsors of APDS IDE studies that are intended to support a PMA for "single patient use in the home environment." FDA also states, "For the purposes of this document, the APDS refers to low glucose suspend systems, as well as closed loop control systems." FDA states that the guidelines are "nonbinding recommendations."

In the November 2012 guidance document, FDA defines the components of APDSs as follows, stating also that they are categorized as Class III devices:²

- Glucose monitoring devices—a continuous glucose monitor (CGM) and blood glucose device (BGD) used for calibrating the CGM (where applicable) and checking sensor performance as needed plus associated reagents/test strips
- APDS control algorithm
- Infusion pump—Fluid infusion set for the complete fluid pathway from, and including, the drug reservoir or fluid source container (e.g., bag, cassette, vial, syringe), infusion set, extension sets, filters and valves, clamps, up to and including the patient connection
- Components and accessories (e.g., power cord, wireless controller)

This definition includes what has been previously termed as a closed-loop system (CLS)³ as well as first-generation systems termed as low-glucose suspend (LGS) systems.

For an implantable CLS, an endocrinologist administers local anesthesia and surgically implants the insulin pump and glucose monitor subcutaneously on opposite sides of the abdomen. The insulin reservoir is placed beneath the skin and is refilled every 2–3 months via transcutaneous injection.³

In LGSs, insulin delivery automatically shuts off when blood glucose levels drop below a preset threshold indicating hypoglycemia (reactive LGS), or the monitor uses control algorithms to predict and prevent potential hypoglycemic events (predictive LGS).⁴

In 2012, Nimri and colleagues published results of a feasibility study to establish overnight closed-loop glucose control and reduce nocturnal hypoglycemia using an MD-Logic artificial pancreas algorithm in four adults and three adolescents (7 total patients) given a diagnosis of type 1 diabetes mellitus (T1DM). The authors concluded the following:⁵

The mean percentage of time spent in the near normal glucose range of 63–140mg/dL was 83±16%, and the median (interquartile range) was 85% (78–92%) for the overnight closed-loop sessions compared with 34±31% and 27% (6–57%) in the homecare open-loop setting, respectively. During the overnight closed-loop sessions at dinner alone 92±9% of the sensor values ranged within target range, compared with 73±19% for the sessions following exercise (P = 0.03). No hypoglycemic (< 63 mg/dL) events occurred during the closed-loop sessions.

In 2011, Zisser and colleagues released an evaluation of a CLS in 10 patients showing that this intervention can "safely regulate glycemia in patient with type 1 diabetes even following a meal

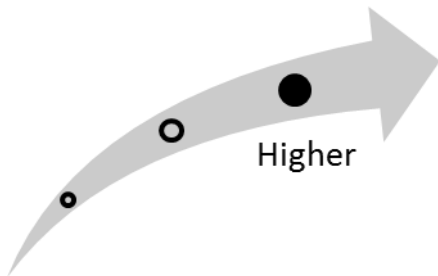
challenge, without prior meal information.”⁶ The controller successfully brought subjects back to the euglycemic range, and the CLS system “recognized all of the unannounced meals and gave appropriate meal boluses of insulin. The average percent time in the target glucose range (80 to 180 mg/dL) was 77% with one episode of mild hypoglycemia.”⁶

Clinical Pathway at Point of This Intervention

Patients with T1DM require insulin therapy. For type 2 diabetes mellitus (T2DM), a variety of self-administered, oral antidiabetes agents, alone or in combination, are generally tried as first-line medical therapy. The first-line drug therapies include biguanides, sulfonylureas, alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, and dipeptidyl peptidase-4 inhibitors. Despite the availability of oral antidiabetes drugs, many patients with T2DM do not achieve treatment goals and require additional therapy with one of two types of injected antidiabetes agents: subcutaneous insulin or a glucagon-like peptide 1 (GLP-1) agonist.⁷

Upon diagnosis, patients undergo medical evaluation to classify the disease type, detect any complications, review glycemic control challenges, and establish a treatment plan, including establishing target blood glucose levels and glycated hemoglobin (HbA_{1c}) goals. The HbA_{1c} test measures the average amount of glucose in a patient’s blood over a 3- or 4-month period with a single blood draw. It is the accepted standard for measuring successful diabetes management. Ongoing, patients are given a treatment plan and are taught how to self-manage their day-to-day care. Clinicians encourage patients to achieve an HbA_{1c} level of 7% because this value has been shown to reduce some of the complications associated with T2DM.

Figure 1. Overall high-impact potential: artificial pancreas for treatment of diabetes



Overall, experts commented that APDSs have significant potential to simplify the way patients with T1DM manage the disease to achieve near-normal glycemia and avoid acute (i.e., hypoglycemia, hyperglycemia) and long-term complications (i.e., nephropathy, neuropathy, retinopathy). Such a system, they opined, would likely be indicated for only a subset of the population with T1DM, and patients would need to be highly motivated and able to operate the system. Experts thought that patients would also need access to a highly trained, multidisciplinary care team 24 hours a day, 7 days a week, to address any issues that might arise with operating an APDS. Development of disparate parts of an APDS has been ongoing for years; however, no single entity has taken on development and integration of the hardware and software required for an APDS. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this topic.⁸⁻¹³ The experts agreed that an APDS that could link CGMs and insulin pumps with seamless feedback to appropriately control patients’ blood glucose levels in an automated fashion

would address a long-standing, significant, unmet need. One research expert stated, “A gap exists because we don’t have a method of convincing the pancreas to once again produce insulin (for example) and [an] insulin pump and glucose monitor are important pieces of the solution, but we do need a software component that bridges the gap between the two pieces.”⁹ A clinical expert opined that there is a significant need for a treatment method that provides enhanced glycemic control without requiring burdensome glucose monitoring by patients.¹²

Experts generally agreed that while preliminary data look promising regarding improved glucose control for patients with T1DM, longer safety and efficacy studies are needed before they can properly determine whether this system will significantly improve patient health outcomes. One clinical expert said that this device is still in its infancy and will require more refining before becoming appropriately available in the clinical setting. One research expert stated that this device has potential to limit variable swings in glucose levels, thus improving short- and long-term glucose control. In terms of health disparities, experts generally agreed that anticipated per-patient costs and access to the coordinated care needed to properly use and maintain this device will serve as barriers to reducing health disparities.

Experts observed that early versions of an APDS would likely be highly complicated to operate and would be indicated only for a subset of patients who are highly motivated to learn to use the technology and who have access to a multidisciplinary diabetes care team trained in use of an APDS. Additionally, experts indicated that these systems would likely need significant upkeep by users and physicians to ensure their proper function. While experts thought that the initial use of these systems would be limited, they saw significant potential for these systems to become widely used after a period of refinement. One clinical expert explained, “A large percentage of patients with type 1 diabetes would very likely elect for implantation of an artificial pancreas if given the option...will place high demand for and rapid adoption of this technology.”¹² If sufficient refinement of the systems should occur, most experts believe, it could eventually simplify diabetes care for patients and physicians by reducing the “need for intermittent self glucose monitoring and self administration of insulin...”¹² Relative to current treatments, experts envisioned small care-setting shifts, noting the potential reduction in hospitalizations related to adverse events.

Experts noted that both patients and physicians would widely accept and adopt this device for T1DM treatment. However, one health systems expert explained that early versions of the artificial pancreas could require more monitoring by clinicians, at which point “provisions would also need to be made to reimburse clinicians for the increased time required to oversee the patients.”¹³

Experts also thought that early versions of the artificial pancreas would be expensive and most likely lead to increased upfront costs for patients using the systems. However, experts believe that refinement of the systems and wider adoption would eventually reduce their upfront costs. Additionally, several experts noted that the high cost of the artificial pancreas system could be offset somewhat by improved glycemic control, which could result in fewer adverse health outcomes in these patients.

Buccal Insulin (Oral-Lyn) Therapy for Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus Requiring Insulin

Exogenous insulin is required by patients with T1DM and sometimes by patients with T2DM. Insulin is typically administered by injection or continuous infusion using an insulin pump.¹⁴ However, many patients consider insulin injections burdensome, and not all patients are candidates for insulin pump use, which can reduce adoption of or adherence to insulin treatment by patients who could benefit from it.¹⁴ Therefore, novel insulin delivery methods that do not involve injection are sought.

One such noninjectable insulin in development is a liquid formulation of human insulin delivered as a buccal spray, called Oral-lyn[™] (Generex Biotechnology Corp., Toronto, Ontario, Canada). Using a buccal spray formulation requires transforming liquid insulin into an aerosol in combination with a pharmaceutical-grade chemical propellant. This allows for delivery to the buccal mucosa by Generex's proprietary inhaler known as the RapidMist[™] Diabetes Management System, which stores the liquid insulin and delivers precisely metered doses in mist form.¹⁵ The patient puffs on the inhaler in a fashion similar to an asthma inhaler to administer the insulin. Absorption is limited to the membranes of the mouth and throat, with no pulmonary entry. This technology allows for much faster insulin absorption and a shorter total duration of activity because of the rich vascularity of the buccal mucosa, making buccal insulin an ideal prandial (mealtime) insulin.¹⁵ Based on results from clinical studies, the manufacturer purports buccal insulin is absorbed and eliminated faster than subcutaneously administered insulin and lowers blood glucose and C-peptide levels more effectively, without major hypoglycemic episodes.

Twenty-five trials of buccal insulin have been completed since 1999. A 2010 review summarized the preliminary data as demonstrating that the amount of insulin absorbed by patients was directly proportional to the amount of buccal spray administered and that buccal insulin had a faster onset and shorter duration of action than injected insulin.¹⁶ Additionally, administration of buccal insulin was generally reported as being well tolerated in the studies; however, some patients experienced mild, transient dizziness during dosing.¹⁶ A phase III trial comparing use of Oral-lyn as a prandial insulin with use of injected human insulin was initiated in April 2008.¹⁷ The trial is tracking HbA_{1c} levels and rate of hypoglycemic episodes in 500 patients with T1DM who were using an intermediate-acting basal insulin and were randomly assigned to receive either Oral-lyn or injectable insulin as prandial insulin.¹⁷ Although the trial's estimated completion date was September 2011, the National Clinical Trials database, as of November 13, 2012, indicated the trial was ongoing at 74 sites but no longer recruiting patients.¹⁷

Oral-lyn is currently available in the United States only to patients with life-threatening diabetes and no other treatment options under FDA's treatment investigational new drug program.¹⁸

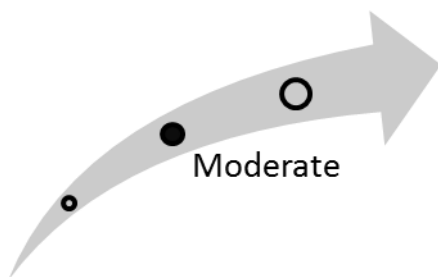
Clinical Pathway at Point of This Intervention

T1DM typically occurs early in life and results from a chronic autoimmune condition that leads to the destruction of pancreatic cells responsible for producing insulin.^{19,20} Treatment for T1DM includes self-injection or infusion of insulin to maintain blood glucose levels. Frequent daily blood glucose monitoring, using fingerstick blood tests or electronic continuous glucose monitors, helps the individual with diabetes to self-administer the proper amount of insulin. Also essential to successful blood glucose management are diet, exercise, and lifestyle changes. Patients using insulin therapy generally use a long-acting insulin typically once per day plus a short-acting insulin with meals (prandial insulin) to cover postmeal increases in glucose levels.²¹ Other forms of insulin

include rapid-acting (a prandial insulin), intermediate-acting (typically combined with a rapid-acting or short-acting insulin), and premixed insulin (a combination of intermediate-acting and short-acting insulin).²¹

T2DM typically occurs later in life (although incidence in a younger population has been growing as a result of obesity) and results from development of peripheral insulin resistance and an insulin-secretory defect. Initial treatment of T2DM includes diet control, exercise, and self-monitoring of blood glucose. If these measures are inadequate, physicians also prescribe medication to control blood sugar levels. First-line treatment typically involves a single oral hypoglycemic agent; however, if adequate glycemic control is not achieved, a combination of hypoglycemic agents with different mechanisms of action may have additive therapeutic effects and result in better glycemic control. Despite combined hypoglycemic therapy, many patients with T2DM can still fail to meet treatment goals and require additional therapy with one of two types of injected antidiabetic agents: subcutaneous insulin or a glucagon-like peptide 1 (GLP-1) agonist.⁷

Figure 2. Overall high-impact potential: buccal insulin (Oral-lyn) therapy for type 1 diabetes mellitus and type 2 diabetes mellitus requiring insulin



Overall, experts providing comments on this topic believe that buccal insulin has potential to improve diabetes treatment by providing a noninjectable alternative to injectable insulin, which could transition more patients to insulin therapy and potentially improve patient adherence to insulin dosing. However, experts noted that buccal insulin's efficacy has not yet been conclusively demonstrated and that trials of the drug were moving slowly. This may be because, in part, this product is the only product of the company developing it, and funding to complete the required trials may be an issue. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, provided perspectives on this topic.²²⁻²⁸ The experts agreed that the current lack of a noninjectable insulin represents a significant unmet need. Experts suggested that many patients delay adoption of insulin therapy or have poor adherence to recommended insulin dosing because of their dislike of injections and that buccal insulin could improve these aspects of insulin therapy. However, one expert noted potential limitations of buccal insulin in meeting this unmet need. One research expert noted the previous failure of an inhaled, noninjectable insulin product (Exubera[®]) that FDA approved but that the manufacturer (Pfizer, Inc., New York, NY) subsequently withdrew from the market. Poor adoption of this inhaled insulin product was part of the reason for its withdrawal. Buccal insulin and the device used to administer it are very different from the Exubera inhaled insulin, so these concerns are likely not relevant to this product.

Experts were divided on this intervention's potential to improve patient health outcomes. Most experts noted a lack of efficacy trials as a reason for skepticism over Oral-lyn's ability to improve

patient outcomes, with two research experts stating that preliminary trials assessed patients with impaired glucose intolerance as opposed to insulin-dependent patients. Another research expert noted that another clinical trial compared this intervention to behavior and dietary therapy, not other available treatment modalities for T1DM and T2DM treatment. While most experts opined that additional data are necessary to determine this intervention's effect on health outcomes, several experts agreed that an alternate administration route could greatly benefit this patient population, with one health systems expert explaining that "the recently completed trial suggests significant improvement in Hgb A1c levels with use of Oral-lyn and no report of hypoglycemia or other adverse effects in the 'several hundred' test subjects."²⁸ While several experts were convinced that increased patient adherence could reduce health disparities, other experts suggested the intervention's cost could ultimately increase disparities.

While most experts suggested that buccal insulin would have a small impact on diabetes treatment because it would replace only some injected-insulin treatments, one expert thought a significant impact would be seen in the way patients with T2DM who need insulin are treated. This expert cited the willingness of many patients to transition from injected insulin to an oral hypoglycemic medication and suggested that the availability of a noninjectable insulin could shift the point in disease progression at which many patients with T2DM adopt insulin use. This clinical expert noted, "the impact would be primarily on a reduction in care provided in the inpatient setting (both acute hospital and longterm care settings)."²⁸

Experts generally agreed that, provided this intervention is deemed safe and effective, clinician and patient adoption would be high, citing clinicians' willingness to prescribe a less invasive means than daily subcutaneous injections for insulin administration. However, one expert cautioned that this intervention could potentially be useful only to those individuals adamantly refusing insulin injection.

Experts generally agreed on Oral-lyn's potential impact on health care costs. One research expert suggested that buccal insulin would be only marginally more expensive than regular insulin, causing a minimal impact on health care costs. However, many experts opined that the increased cost of buccal insulin has the potential to be offset by improved treatment outcomes and less need to treat complications of poor glycemic control in patients with diabetes. Overall, experts opined that this technology has moderately high potential for impact on the health care system, provided additional efficacy and safety studies are favorable.

Fluocinolone Acetonide Implant (Iluvien) for Treatment of Diabetic Macular Edema

Diabetic macular edema (DME) is a thickening or swelling of the retina caused by fluid leaking from blood vessels within the macula in patients with diabetes mellitus.²⁹ The swelling that occurs as a result of fluid buildup distorts central vision, mainly affecting an individual's ability to see form, color, and detail. Patients gradually lose their ability to focus on objects in their central field of vision over a period of months or years as the disease progresses.²⁹ People with diabetes who go untreated for eye care have a 25% to 30% chance of developing moderate vision loss.³⁰ Until the August 2012 approval of Lucentis[®], no pharmacologic treatment was available for DME. Lucentis is given in ongoing monthly injections, and a pharmaceutical approach that does not require injections as often would address an unmet need and perhaps increase adherence to treatment.

Iluvien (Alimera Sciences, Inc., Alpharetta, GA) consists of a tiny tube containing 190 mcg of fluocinolone acetonide that is injected into the back of the eye with a 25-gauge needle in a single, in-office procedure.^{31,32} The injection is given once, and over a period of 2–3 years, the tube releases a constant, low flow of medication. The estimated daily dosage dispensed by the implant was 0.23 mcg.³² The exact mechanism by which fluocinolone acetonide functions in DME treatment is unknown, but it is thought to be due to the combined vasoconstrictive, anti-inflammatory, and antipruritic qualities inherent to corticosteroids such as fluocinolone.³³ Whereas current FDA-approved management and treatment options are designed to slow or halt damage, clinical trials with Iluvien have demonstrated that damage can be reversed, and in many cases patients can regain a portion of the vision lost due to DME.³²

In February 2011, Alimera Sciences reported results from a 2-year, phase III trial assessing the efficacy and safety of 0.23 and 0.45 mcg of fluocinolone in 956 patients with DME. Authors reported, “Trial A and B data combined demonstrated a statistically significant effect at week three. This effect was maintained throughout the 36 months, with 28.7% of Iluvien [low dose] patients and 16.2% of control patients ($p=0.002$) having an improvement in BCVA [best corrected visual acuity] of 15 letters or greater over baseline at month 24, 31.4% versus 15.1% at month 30 ($p<0.001$), 29% versus 17.3% at month 33 ($p=0.004$) and 28.7% versus 18.9% at month 36 ($p=0.018$).”³⁴

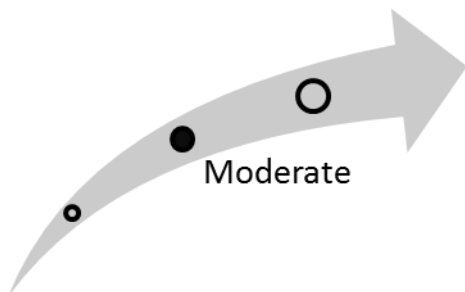
In June 2010, the company submitted a new drug application (NDA) for Iluvien and FDA granted Iluvien priority review by the end of summer 2010, but FDA issued a complete response letter in November 2011 requiring further trials before approval could be granted.^{35,36,37} The company met with FDA in June 2012, and based on the outcome of that meeting, declared intentions to resubmit data from two previously completed phase III trials (FAME[™] studies) to address FDA concerns.³⁸ The company also intends to continue enrolling patients in its physician utilization study of the Iluvien inserter, which had been temporarily halted in November 2011.³⁸ This drug/device has been approved in Europe.

Clinical Pathway at Point of This Intervention

A patient who presents with DME undergoes a history and physical examination, including an assessment of the individual's history of vision and eye disease and risk factors for DME, including diabetic history (T1DM at higher risk), older age, poor glucose control, pregnancy, hypertension, and increased lipid levels.³⁰ Using a high magnification ophthalmoscope, the ophthalmologist can identify the retinal thickening that indicates macular edema. Yellow exudates and poor visual acuity may also be detected. DME treatment focuses on glycemic control, optimal blood pressure control, and macular focal/grid laser photocoagulation. Laser photocoagulation reduces the risk of moderate

visual loss, but some patients experience permanent visual loss even after intensive treatment. New advances in devices, pharmacotherapies, and surgical techniques have shown promise in treating DME.³⁰

Figure 3. Overall high-impact potential: fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema



Overall, experts thought that this intervention could offer an alternative to laser photocoagulation for treating DME, for which no FDA-approved treatments exist to restore vision. While some experts believe risk of adverse events could minimize clinician adoption of this intravitreal implant, experts opined patients would be willing to accept this intervention if restoring vision to any degree was the end result. Experts thought reduced per-patient costs to be associated with this intervention, compared with laser photocoagulation but thought costs would be significantly greater with this intervention when compared with off-label use of other anti-VEGF (vascular endothelial growth factor) agents. However, its potential to significantly restore vision or slow progression of disease suggests that this intervention has moderate potential impact. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on the fluocinolone acetonide implant.³⁹⁻⁴⁴ Most experts agreed that treatment options for DME are limited, with laser photocoagulation being an invasive intervention that can only slow progression of disease. One expert stated that no FDA-approved treatments are available to improve vision in these patients. However, one clinical expert explained there are already available treatments that slow progression of DME and that there is relative uncertainty as to whether this intervention could improve visual acuity.

Most experts agreed the fluocinolone acetonide implant has potential to significantly improve patient health outcomes, with one health systems expert stating, “once vision has been lost, any treatment that can return some sight is important.”⁴¹ However, this same expert remained skeptical based on results of clinical trials, which the expert believes is a reason the FDA did not approve the NDA for this intervention. A clinical expert also remained skeptical of this intervention’s potential to improve health outcomes, mentioning that “in its present form, the small benefits provided by Iluvien in the reported clinical trials are superceded by the adverse effects in terms of a significantly increased risk of cataracts and increased intra-ocular pressures (glaucoma).”³⁹ Most experts suggested this intervention would not affect health disparities, particularly because of its costs and third-party payers’ unwillingness to cover the implant.

Experts generally agreed that this intervention’s potential to disrupt the current health care delivery infrastructure would be minimal, saying that intravitreal injections are becoming more commonplace in the physician’s office. One research expert noted this intervention could obviate

the need for more invasive surgical intervention, moving treatment setting from the operating room to the physician's office. Although some experts opined that this intervention would minimally disrupt current patient management, others believe this intervention could become the standard of care if proven effective and safe, thus increasing patient management in the retinal specialists' office. However, one clinical expert states, "...[G]iven the incidence of side-effects with this intervention the treatment of these symptoms would involve a moderate disruption of long-term treatment of these patients."³⁹

Expert opinions were mixed regarding clinician and patient acceptance. Several experts opined that provided the fluocinolone acetonide implant is deemed safe and effective, clinicians would willingly adopt this intervention and patients would eagerly accept an implant capable of restoring their vision. However, in terms of clinician acceptance, a health systems expert opined that adoption could be less, given the severity of adverse events associated with this intervention. In terms of patient acceptance, this same expert conceded patients could be willing to accept the risk of adverse events for the chance of restoring vision. Experts commenting on potential financial impacts of the intervention believe per-patient cost would be increased when compared with off-label use of drugs, including triamcinolone and bevacizumab, but thought costs could be reduced when compared with laser photocoagulation. Overall, experts believe that, given FDA-approved treatments aimed to improve vision in patients with progressive DME do not exist, the fluocinolone acetonide treatment has moderate potential for high impact in this patient population.

New Exenatide Formulations (Bydureon; ITCA 650 with Duros Pump) for Treatment of Type 2 Diabetes Mellitus

Two therapies for treating T2DM, one in development and one recently approved, are intended to improve drug efficacy and tolerability as well as patient adherence to treatment recommendations. They are as follows:

- Extended-release exenatide (exenatide once-weekly [EQW]; Bydureon[™], Eli Lilly and Co., Indianapolis, IN, Amylin Pharmaceuticals, Inc., San Diego, CA [in June 2012, Bristol-Myers Squibb, New York, NY, announced intention to acquire Amylin], and Alkermes, Inc., Waltham, MA)
- Subcutaneously delivered exenatide (ITCA 650, Intarcia Therapeutics, Inc., Hayward, CA, via Duros pump system)

EQW is a GLP-1 receptor agonist formulation that allows for once-weekly dosing compared with once- or twice-daily dosing with current GLP-1 receptor agonist formulations. This formulation consists of injectable exenatide encapsulated in microspheres consisting of a biodegradable polymer (poly [D,L lactic-co-glycolic acid]).⁴⁵ As the microsphere degrades in the bloodstream, exenatide is slowly released.⁴⁵ The microsphere technology used in EQW has also been used in other extended-release drugs such as extended-release naltrexone (Vivitrol[®]) and extended-release risperidone (Risperdal[®], Consta[®]).⁴⁵ In clinical trials, EQW was administered at a dose of 2 mg per week.⁴⁵ FDA approved once-weekly exenatide in January 2012 as “an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings.”^{46,47} Reported costs of Bydureon from 11 pharmacies in the United States range from \$354 to \$469 per month or about \$4,250 per year; the lower rates take into account availability of a \$50 discount coupon.⁴⁸ Many third-party payers provide coverage and require prior authorization and quantity limits.⁴⁹⁻⁵⁶

In 2011, Buse and colleagues reported results from a phase III trial comparing EQW efficacy with liraglutide in 921 patients with T2DM. The authors reported,

Change in HbA_{1c} at endpoint was greater in subjects taking Lira (-1.48%, SE [standard error] 0.05) than in those taking EQW (-1.28%, 0.05; treatment difference 0.21%, 95% CI [confidence interval] (0.08, 0.34) using mixed model repeated measures analysis and the difference did not meet the non-inferiority criteria. More subjects taking Lira achieved HbA_{1c} <7% (n=271, 60.2%) than those taking EQW (n=241, 52.3%) p=0.008. Subjects taking Lira lost more weight (-3.58 kg, SE 0.18) than those taking EQW (-2.68 kg, SE 0.18; treatment difference 0.90 kg, 95% CI [0.40, 1.41]). There was no major hypoglycemia during the study. Minor hypoglycemia was experienced by 50 (10.8%) EQW-treated subjects and 40 (8.9%) Lira-treated subjects (p=0.374 for treatment difference). Subjects taking Lira and EQW had similar decreases in systolic and diastolic blood pressure (SBP; -3.5 and -2.5; DBP; -0.5 and -0.5, respectively). Changes in other cardiovascular biomarkers (lipids, high sensitivity C-reactive protein, brain natriuretic peptide) were similar between groups at endpoint.⁵⁷

In 2011, Blevins and colleagues reported results from a phase III trial of extended-release exenatide. Patients received standard exenatide 5 mcg twice daily for 4 weeks followed by 10 mcg twice daily for 20 weeks or exenatide extended release 2 mg once weekly. At 24 weeks, the once-weekly group produced significantly greater changes from baseline (least squares mean ± se) in HbA_{1c} than twice daily (-1.6±0.1% vs. -0.9±0.1%; p<0.0001) and fasting plasma glucose (-35±5 mg/dL vs. -12±5 mg/dL; p=0.0008). Similar reductions in mean body weight from baseline to week

24 were observed in both groups (-2.3 ± 0.4 kg and -1.4 ± 0.4 kg). Both treatments were generally well tolerated. Transient and predominantly mild to moderate nausea, the most frequent adverse event, was less common with once-weekly administration (14%) than with twice daily (35%). Injection-site reactions were infrequent but more common with once-weekly dosing. No major hypoglycemia events occurred.⁵⁸

ITCA 650, a proprietary form of exenatide delivered subcutaneously and continuously through the Duros pump,^{59,60} is purported to remain stable at body temperature for as long as a year, according to the most recently presented data.⁶¹ The Duros delivery system is a semipermeable, osmotic mini-pump that a physician or physician assistant inserts into the patient's arm or abdomen during an outpatient procedure that takes about 5 minutes. The matchstick-sized device delivers a continuous dose of exenatide over an extended period of time, which is intended to minimize the nausea associated with twice-daily dosing. Duros technology has been available since 2000 and is being tested for delivery of other types of drugs as well.

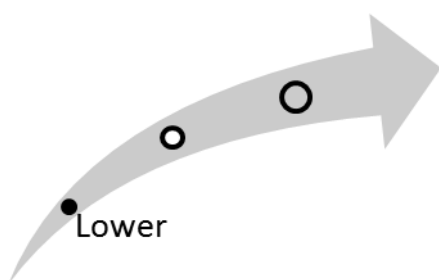
After successfully completing phase II trials, Intarcia announced a collaboration with Quintiles, Inc. (Durham, NC) in September 2011 to begin a phase III program of six trials.^{62,63} In the completed phase II trials, after an initial 12-week treatment period of 20 or 40 mcg/day compared with twice-daily exenatide injections, treatment continued at one of four dosing levels: 20, 40, 60 or 80 mcg/day through week 24. Patients could continue for an additional 24 weeks for a total of 48 weeks of treatment. Eighty-five percent of those enrolled continued, and the company reported that sustained reductions were observed in HbA_{1c} levels, fasting plasma glucose, and weight across all treatment arms between 24 and 48 weeks.⁶⁴ In November 2012 at the Diabetes Technology Meeting in Bethesda, MD, the company reported that the drug resulted in improved glycemic control and was well tolerated at doses starting from 20 mcg/day and transitioning to 40 and 60 mcg/day, delivered continuously and with stability for as long as 12 months; the drug was also reported to be stable when stored for up to 3 years at 40°C.⁶¹

ALZA Corp., a unit of Johnson & Johnson, Inc. (New Brunswick, NJ), manufactures the Duros drug delivery technology that can be used for a range of indications. In 2000, the company received FDA marketing approval for the Duros technology.^{59,65-67} Intarcia has licensed exclusive rights for use of Duros from ALZA. In October 2012, the manufacturer stated plans to commence a phase III trial in January 2013, having completed analysis of phase II trial results to determine an optimal dosing regimen for the planned trial.⁶⁸

Clinical Pathway at Point of This Intervention

T2DM is a chronic disease that typically occurs later in life (although incidence in a younger population has been growing as a result of obesity) and results from development of peripheral insulin resistance and an insulin-secretory defect. Initial treatment of T2DM includes diet control, exercise, and self-monitoring of blood glucose. If these measures are inadequate, physicians also prescribe medication to control blood sugar levels. First-line treatment typically involves a single oral hypoglycemic agent; however, if adequate glycemic control is not achieved, a combination of hypoglycemic agents with different mechanisms of action may have additive therapeutic effects and result in better glycemic control. Despite combined hypoglycemic therapy, many patients with T2DM can still fail to meet treatment goals and require additional therapy with one of two types of injected antidiabetic agents: subcutaneous insulin or a glucagon-like peptide 1 (GLP-1) agonist.⁷

Figure 4. Overall high-impact potential: new exenatide formulations (Bydureon; ITCA 650 with Duros pump) for treatment of type 2 diabetes mellitus



Overall, experts opined that these new formulations of exenatide have potential to improve diabetes treatment by improving exenatide release mechanisms while reducing injection frequency and nausea, potentially improving patient adherence to treatment recommendations. However, experts noted that these benefits are incremental relative to existing exenatide forms and other GLP-1 agonists. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on subcutaneous exenatide using Duros.⁶⁹⁻⁷⁴ Perspectives on extended-release exenatide (Bydureon) were received from seven experts, with clinical, research, and health systems backgrounds.⁷⁵⁻⁸¹ Given that these two therapies are geared toward extending release and improving efficacy of exenatide, expert comments have been combined or synthesized to represent opinions on modifications to exenatide.

Experts reviewing subcutaneous exenatide generally agreed that this mode of delivery could improve patient adherence and therefore significantly address an unmet need. One research expert opined, “Patients with T2D who are not well managed on metformin alone and who may benefit from GLP-1 [agonists] are often discouraged by the injection requirement-compliance can be low.”⁷⁰ Opinions were mixed regarding extended-release exenatide’s ability to address an unmet need. While some experts agreed that any new therapy for treating diabetes would be welcome, this form of exenatide may be incremental and minimally address the unmet need. Two research experts commented that this drug would simply add to the list of adjunctive drugs for T2DM treatment. Other experts believed once-weekly exenatide could significantly improve adherence. While some experts referenced the existence of GLP-1 agonists on the market, one expert said that this therapy could reduce HbA_{1c} levels and better reduce fasting glucose levels when compared with similar medications.

Experts generally believe that the underlying mechanisms for both modifications to exenatide appear sound, in large part because of the existence of currently approved forms of exenatide and other GLP-1 agonists already on the market. Several experts referred to early clinical studies as evidence this delivery mechanism controls glucose levels similarly to injectable GLP-1 agonists while potentially improving treatment adherence. Several experts noted that subcutaneous exenatide use would also result in effective weight loss. In regards to extended-release exenatide, one research expert believes that although clinical studies show that this therapy could be marginally effective, this intervention will not significantly improve patient health outcomes. However, one clinical expert noted, “In terms of improving glycemic control, extended-release exenatide is more effective than oral antidiabetic drugs, and twice daily exenatide injection, but slightly inferior to once daily liraglutide injection. Extended-release exenatide has an advantage of once weekly injection, which

could potentially improve compliance.”⁷⁵ A research expert agreed with this drug’s potential to improve adherence but cautioned that “the microsphere technology in the extended-release formulation requires patients to use a larger-bore needle and may cause more injection-site adverse events [than] conventional daily dosings.”⁸¹

Experts commenting on both modifications to exenatide believe that as long as these forms of exenatide therapy do not pose risk of serious adverse events (i.e., cardiac abnormalities, carcinomas), patient adherence to treatment recommendations and quality of life would improve with its use, thus improving patient health outcomes. Referring to subcutaneous exenatide, one clinical expert was uncertain whether subcutaneous infusion of exenatide via the Duros osmotic pump would improve patient health outcomes when compared with twice-daily exenatide and other comparators but agreed it could improve adherence to treatment.

Experts were divided with regard to the potential impact of these modifications to exenatide on costs. Some experts believe that per-patient costs would increase with both forms of exenatide, and others noted that an increase in patient adherence and subsequent decrease in disease complications would lower long-term, per-patient costs. Regarding extended-release exenatide, one expert stated, “Initially, the cost would be increased for the patient and the third party payers when compared to cheaper generic products. It is cheaper than once daily competing product (Victoza). But overall, it would be less expensive for patients, third party payers, and healthcare facilities if the patient would be able better manage their diabetes.”⁷⁷ Some experts were undecided on the potential impact on cost, making a case for an increase or decrease in per-patient cost. In regards to subcutaneous exenatide, one clinical expert added, “If this intervention provides significant long-term reduction in glycohemoglobin and prevents complications [of] diabetes, the cost of the device is likely to be minimal in comparison to the dollars saved from the complications of diabetes.”⁷⁴

Ranibizumab (Lucentis) for Treatment of Diabetic Macular Edema

DME is a thickening or swelling of the retina caused by fluid leaking from blood vessels within the macula in patients with diabetes mellitus.²⁹ The swelling that occurs as a result of fluid buildup distorts central vision, mainly affecting an individual's ability to see form, color, and detail. Patients gradually lose their ability to focus on objects in their central field of vision over a period of months or years as the disease progresses.²⁹ People with diabetes who go untreated for eye care have a 25% to 30% chance of developing moderate vision loss.³⁰ Until ranibizumab's approval, FDA had not approved any pharmacotherapies for treating DME. This drug is now set to compete with or complement macular focal/grid laser photocoagulation as the primary treatment modality for DME and will compete with other DME treatments in development (e.g., Iluvien, Eylea) should they reach market.

Ranibizumab (Lucentis, Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland, and Novartis International AG, Basel, Switzerland) is a humanized, recombinant, immunoglobulin G1, kappa isotope, monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A), originally FDA-approved for wet age-related macular degeneration and macular edema with retinal vein occlusion treatment.⁸² Ranibizumab's mechanism of action allows it to bind to multiple subtypes of VEGF-A, causing an inhibiting effect, which prevents the growth of new blood vessels under the macula. This prevention reduces the likelihood of vascular leakage and neovascularization; thus, vision loss as a result of fluid and protein buildup under the macula is also reduced. The recommended dose for ranibizumab is 0.3 mg (0.05 mL) once monthly (every 28 days) by intravitreal injection.⁸³ Treatment is often required indefinitely or until reversal of vision loss.⁸⁴

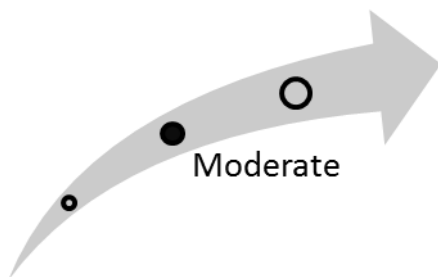
Boyer and colleagues (2011) presented results from the combined RIDE and RISE clinical trials evaluating ranibizumab in 759 patients receiving a diagnosis of DME with baseline visual acuity of 20/40 to 20/320. Authors reported 62.2% to 63.2% of patients receiving intravitreal ranibizumab improved visual acuity to the 20/40 baseline for driving in the RIDE and RISE trials, respectively. In terms of achieving the primary endpoint of a gain of at least 15 letters on the Early Treatment Diabetic Retinopathy Study scale over baseline, 33.6% and 44.8% of patients, respectively, receiving a 0.3 mg dose of ranibizumab and 45.7% and 39.2% of patients, respectively, receiving a 0.5 mg dose of ranibizumab achieved endpoints compared with 12.3% and 18.1% of patients, respectively, treated with sham.⁸⁵ The percentage of patients receiving a 0.5 mg dose of ranibizumab who gained at least 10 letters (2 lines on the eye chart) was 65.6%. In terms of eyesight deterioration (loss of 3 lines on the eye chart), fewer than 4% of patients treated with ranibizumab were reported compared with 8.5% to 10.2% of patients, respectively, treated with sham.⁸⁵

In August 2012, FDA approved ranibizumab injection for DME treatment based on the RISE and RIDE phase III trial results.⁸⁶ When approved, the reported estimated cost of an injection was about \$1,170.⁸⁷ Although the U.S. Centers for Medicare & Medicaid Services has no national coverage determination for ranibizumab for treating DME, at least one private, major, third-party payer that publishes its policies online has a policy that describes coverage for ranibizumab 0.3 mg intravitreal injection to treat DME.⁸⁸ Payers covering the drug may require prior authorization.⁸⁹ Genentech has a patient assistance program to help defray costs for qualified patients.⁸⁹

Clinical Pathway at Point of This Intervention

A patient who presents with DME receives a history and physical, including an assessment of the individual's history of vision and eye disease and risk factors for DME, including diabetic history (T1DM at higher risk), older age, poor glucose control, pregnancy, hypertension, and increased lipid levels.³⁰ Using a high-magnification ophthalmoscope, the ophthalmologist can identify the retinal thickening that indicates macular edema. Yellow exudates and poor visual acuity may also be detected. Treatment for DME is focused on glycemic control, optimal blood pressure control, and macular focal/grid laser photocoagulation. Laser photocoagulation reduces the risk of moderate visual loss, but some patients experience permanent visual loss even after intensive treatment. New advances in pharmacotherapy and surgical techniques have shown promise in treating DME.³⁰

Figure 5. Overall high-impact potential: ranibizumab (Lucentis) for treatment of diabetic macular edema



Experts thought ranibizumab could offer a desirable alternative to laser photocoagulation for treating DME, for which no FDA-approved pharmacotherapy existed before ranibizumab's approval for this indication. Some experts thought that the frequency of intravitreal administration of ranibizumab might pose a barrier to patient adherence to treatment recommendations, limiting its ability to significantly improve patient outcomes and potentially affecting patient acceptance. Experts thought significant costs would be associated with this intervention, particularly if it is used as an adjunctive therapy to laser photocoagulation. However, its potential to significantly restore vision or slow progression of disease suggests that this intervention has moderate potential impact. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered comments on this intervention.⁹⁰⁻⁹⁵ All experts agreed that treatment options for DME are limited, with laser photocoagulation being an invasive intervention with a variable degree of efficacy. One research expert stated that with regards to photocoagulation, "preliminary data suggests limited effectiveness of laser treatment at [1] year and an unknown risk of permanent visual loss."⁹⁰ Another research expert stated that the increasing number of people receiving a diagnosis of diabetes warrants more treatment options for managing DME. Experts also agreed that before Lucentis, no FDA-approved treatments were available to improve vision in these patients. One clinical expert opined, "at this time this [is] the only successful [treatment] available with high yield success."⁹⁵ Regarding ranibizumab's potential to improve patient health outcomes, one clinical expert expressed satisfaction with this drug's efficacy not only in research, but also in the clinical setting. Although another clinical expert mentioned this drug's potential efficacy based on two phase III trial results, this expert cautioned that only 30% to 40% responded to this therapy and

expressed concern over potential selection bias in trials because this drug was not directly compared with laser therapy.⁹⁴

Altogether, experts generally agreed that ranibizumab for treating DME has the potential to significantly improve patient health outcomes, believing this drug could be a more practical, less expensive option when compared with laser photocoagulation. In terms of this intervention's potential to affect health disparities, opinions were mixed among experts, with several experts arguing that the frequency of intravitreal injections would increase nonadherence among patients in rural and low socioeconomic areas, increasing disparities. Several experts thought the pricing of ranibizumab in terms of dollars per quality-adjusted life-years would be significantly more expensive than laser photocoagulation, therefore widening the barrier for the economically disadvantaged. However, one researcher stated that intravitreal injections would be more accessible for disadvantaged patient populations than surgical options, therefore reducing health disparities.

Experts were mixed on this intervention's potential to disrupt the current health care delivery infrastructure, with some suggesting that an effective intravitreal drug would not significantly affect current care settings and other experts arguing that the increase in physician visits to receive a monthly intravitreal injection and followup compared with a one-time outpatient laser photocoagulation procedure could significantly change the current infrastructure.

All experts agreed that this intervention's potential for clinician and patient acceptance is high because more effective therapy to treat DME is needed. Regarding clinician acceptance, one clinical expert said clinician adoption is likely given the "convenience and ease of delivery. Most ophthalmologists are probably using intra vitreal injections for [age-related macular degeneration] treatments with minimal side effects."⁹⁴ In terms of per-patient costs for ranibizumab, experts opined that costs are going to be significantly more than laser photocoagulation. One clinical expert stated that although costs are currently high, per-patient costs and costs to insurers will decrease over time. A health systems expert opined that despite its cost, this drug will "probably become a standard procedure either independently or (more likely) along with photocoagulation."⁹³

References

1. U.S. Food and Drug Administration (FDA). Artificial pancreas system: FDA's efforts to advance the artificial pancreas system and the challenges ahead. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2011 Dec 1 [accessed 2011 Dec 15]. [2 p]. Available: <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/ArtificialPancreas/default.htm>.
2. Guidance for industry and Food and Drug Administration staff: the content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) applications for artificial pancreas device systems. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2012 Nov 9. 63 p. Also available: <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM259305.pdf>.
3. Gebel E. The artificial pancreas. [internet]. Alexandria (VA): Diabetes Forecast; 2010 Sep [accessed 2011 Dec 16]. [7 p]. Available: <http://forecast.diabetes.org/print/2382>.
4. U.S. Food and Drug Administration (FDA). Types of artificial pancreas device systems. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2011 Dec 1 [accessed 2012 Apr 10]. [2 p]. Available: <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/ArtificialPancreas/ucm259555.htm>.
5. Nimri R, Atlas E, Ajzensztejn M, et al. Feasibility study of automated overnight closed-loop glucose control under MD-logic artificial pancreas in patients with type 1 diabetes: the DREAM Project. *Diabetes Technol Ther* 2012 Aug;14(8):728-35. PMID: 22853723
6. Artificial pancreas passes first test in patients with type 1 diabetes. In: *Medical Economics* [internet]. ModernMedicine; 2011 Jun 27 [accessed 2011 Aug 18]. [1 p]. Available: <http://license.icopyright.net/user/viewFreeUse.act?fluid=MTM1MDc4OTM%3D>.
7. Eckman AS. Type 2 diabetes. In: *MedlinePlus* [internet]. Bethesda (MD): National Library of Medicine (U.S.); 2010 May 10 [accessed 2011 Mar 17]. [7 p]. Available: <http://www.nlm.nih.gov/medlineplus/ency/article/000313.htm>.
8. Expert Commenter 161. (External, Clinical). Horizon Scanning Structured Comment Form. HS55 - Artificial pancreas for treatment of diabetes. 2012 Oct 10 [review date].
9. Expert Commenter 402. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS55 - Artificial pancreas for treatment of diabetes. 2012 Sep 21 [review date].
10. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS55 - Artificial pancreas for treatment of diabetes. 2012 Sep 13 [review date].
11. Expert Commenter 425. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS55 - Artificial pancreas for treatment of diabetes. 2012 Sep 17 [review date].
12. Expert Commenter 547. (External, Clinical). Horizon Scanning Structured Comment Form. HS55 - Artificial pancreas for treatment of diabetes. 2012 Sep 26 [review date].
13. Expert Commenter 651. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS55 - Artificial pancreas for treatment of diabetes. 2012 Oct 10 [review date].
14. Mastrandrea LD. Inhaled insulin: overview of a novel route of insulin administration. *Vasc Health Risk Manag* 2010;6:47-58. PMID: 20234779
15. Generex Biotechnology. Rapidmist. [internet]. Toronto (ON): Generex Biotechnology [accessed 2012 Nov 14]. [3 p]. Available: <http://www.generex.com/index.php/id/261>.
16. Pozzilli P, Raskin P, Parkin CG. Review of clinical trials: update on oral insulin spray formulation. *Diabetes Obes Metab* 2010 Feb;12(2):91-6. PMID: 19889002
17. Generex Biotechnology Corp. Active comparator study of Generex Oral-lyn spray and injected human insulin. In: *Clinicaltrials.gov* [internet]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2011 Feb 16]. [4 p]. Available: <http://clinicaltrials.gov/show/NCT00668850>
NLM Identifier: NCT00668850.

18. Generex announces USFDA approval of use of company's flagship buccal insulin product, Generex oral-lyn, under the USFDA'S treatment investigational new drug (IND) program. [internet]. Worcester (MA): Generex Biotechnology Corporation; 2009 Sep 10 [accessed 2011 May 20]. [2 p]. Available: <http://investor.generex.com/releasedetail.cfm?ReleaseID=408392>.
19. National diabetes statistics, 2011 [NIH Publication No. 11-3892]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH); 2011 Feb. 12 p. Also available: http://diabetes.niddk.nih.gov/dm/pubs/statistics/DM_Statistics.pdf.
20. Eckman AS. Type 1 diabetes. In: MedlinePlus [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2010 May 5 [accessed 2011 Mar 17]. [8 p]. Available: <http://www.nlm.nih.gov/medlineplus/ency/article/000305.htm>.
21. Types of insulin for diabetes treatment. [internet]. New York (NY): WebMD, LLC [accessed 2012 Nov 21]. [3 p]. Available: <http://diabetes.webmd.com/guide/diabetes-types-insulin>.
22. Expert Commenter 1170. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS405 - Buccal insulin (Oral-lyn) for treatment of diabetes. 2012 Apr 16 [review date].
23. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS405 - Buccal insulin (Oral-lyn) for treatment of diabetes. 2012 Apr 16 [review date].
24. Expert Commenter 409. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS405 - Buccal insulin (Oral-lyn) for treatment of diabetes. 2012 Apr 20 [review date].
25. Expert Commenter 547. (External, Clinical). Horizon Scanning Structured Comment Form. HS405 - Buccal insulin (Oral-lyn) for treatment of diabetes. 2012 Apr 18 [review date].
26. Expert Commenter 1169. (PRI, Clinical). Horizon Scanning Structured Comment Form. HS405 - Buccal insulin (Oral-lyn) for treatment of diabetes. 2012 Apr 18 [review date].
27. Expert Commenter 425. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS405 - Buccal insulin (Oral-lyn) for treatment of diabetes. 2012 Apr 19 [review date].
28. Expert Commenter 651. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS405 - Buccal insulin (Oral-lyn) for treatment of diabetes. 2012 Apr 23 [review date].
29. Callanan D, Elliott D, Ip M, et al. Diabetic macular edema: update and treatment options. In: Medscape Education [internet]. New York (NY): WebMD, LLC; 2007 Jun 18 [accessed 2011 Mar 29]. [7 p]. Available: <http://www.medscape.org/viewarticle/557986>.
30. Hampton R Sr, Mavrikakis E. Macular edema in diabetes: overview. In: Medscape Reference [internet]. New York (NY): WebMD, LLC; 2011 Mar 29 [updated 2011 Oct 10]. [accessed 2011 Mar 29]. [1 p]. Available: <http://emedicine.medscape.com/article/1224138-overview>.
31. ILUVIEN for diabetic macular edema (DME). [internet]. Alpharetta (GA): Alimera Sciences, Inc.; 2011 [accessed 2011 Apr 22]. [1 p]. Available: <http://www.alimerasciences.com/Products/iluvien.aspx>.
32. Alimera announces positive results from the two phase 3 FAME trials of Iluvien in patients with diabetic macular edema. [internet]. Alpharetta (GA): Alimera Sciences, Inc.; 2009 Dec 23 [accessed 2011 Apr 22]. [2 p]. Available: <http://investor.alimerasciences.com/releasedetail.cfm?ReleaseID=458284>.
33. Thomson Reuters Integrity [database online]. Barcelona: Thomson Reuters [accessed 2011 Apr 25]. Iluvien. [15 p]. Available: <https://integrity.prous.com>.
34. Alimera announces positive 36-month results from the completed phase 3 FAME study of ILUVIEN in patients with diabetic macular edema. [internet]. Alpharetta (GA): Alimera Sciences, Inc.; 2011 Feb 3 [accessed 2011 Apr 22]. [3 p]. Available: <http://investor.alimerasciences.com/releasedetail.cfm?ReleaseID=547652>.

35. Alimera Sciences submits Iluvien NDA to the FDA for the treatment of diabetic macular edema. [internet]. Alpharetta (GA): Alimera Sciences, Inc.; 2010 Jun 29 [accessed 2011 Apr 22]. [2 p]. Available: <http://investor.alimerasciences.com/releasedetail.cfm?ReleaseID=483444>.
36. Alimera Sciences' Iluvien receives FDA priority review for the treatment of diabetic macular edema. [internet]. Alpharetta (GA): Alimera Sciences, Inc.; 2010 Aug 30 [accessed 2011 Apr 22]. [2 p]. Available: <http://investor.alimerasciences.com/releasedetail.cfm?ReleaseID=503420>.
37. Alimera Sciences receives complete response letter from FDA for ILUVIEN. [internet]. Alpharetta (GA): Alimera Sciences, Inc.; 2011 Nov 11 [accessed 2011 Dec 6]. [3 p]. Available: <http://investor.alimerasciences.com/releasedetail.cfm?ReleaseID=623128>.
38. Alimera Sciences reports third quarter 2012 financial results. [internet]. Atlanta (GA): Alimera Sciences, Inc.; 2012 Nov 7 [accessed 2012 Nov 15]. [4 p]. Available: <http://investor.alimerasciences.com/releasedetail.cfm?ReleaseID=719464>.
39. Expert Commenter 935. (External, Clinical). Horizon Scanning Structured Comment Form. HS849 - Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema. 2012 Jan 5 [review date].
40. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS849 - Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema. 2012 Jan 10 [review date].
41. Expert Commenter 675. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS849 - Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema. 2011 Dec 21 [review date].
42. Expert Commenter 144. (External, Research/Scientific/Technical). Horizon Scanning Structured Comment Form. HS849 - Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema. 2012 Jan 4 [review date].
43. Expert Commenter 408. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS849 - Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema. 2012 Jan 24 [review date].
44. Expert Commenter 398. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS849 - Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema. 2012 Feb 3 [review date].
45. DeYoung MB, MacConell L, Sarin V, et al. Encapsulation of exenatide in poly-(D,L-lactide-co-glycolide) microspheres produced an investigational long-acting once-weekly formulation for type 2 diabetes. *Diabetes Technol Ther* 2011 Nov;13(11):1145-54. PMID: 21751887
46. FDA approves Bydureon -- the first and only once-weekly treatment for type 2 diabetes. [internet]. San Diego (CA): Amylin Pharmaceuticals, Inc.; 2012 Jan 27 [accessed 2012 Feb 20]. [4 p]. Available: <http://phx.corporate-ir.net/phoenix.zhtml?c=101911&p=irol-newsArticle&ID=1653756>.
47. Bydureon (exenatide extended-release for injectable suspension) risk evaluation and mitigation strategy (REMS). NDA 022-200. San Diego (CA): Amylin Pharmaceuticals, Inc.; 2012 Jan 27. 11 p. Also available: <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM289674.pdf>.
48. Bydureon. [internet]. Santa Monica (CA): GoodRx, Inc.; 2012 Nov [accessed 2012 Nov 15]. [4 p]. Available: <http://www.goodrx.com/bydureon>.
49. Pharmacy clinical policy bulletins. Aetna non-Medicare prescription drug plan. Subject: insulins. [internet]. Hartford (CT): Aetna, Inc.; 2012 Mar 9 [accessed 2012 Apr 4]. [6 p]. Available: http://www.aetna.com/products/rxnonmedicare/data/2012/ENDO2012/insulins_2012.html.
50. Anthem Insurance Companies, Inc. Bydureon (exenatide extended release) prior authorization. North Haven (CT): Anthem Insurance Companies, Inc.; 3 p. Also available: <http://www.anthem.com>.
51. Blue Cross and Blue Shield of Alabama. Clinical program updates. East Birmingham (AL): Blue Cross and Blue Shield of Alabama; 2012 Apr 1. 5 p. Also available: <http://www.bcbsal.com>.

52. CIGNA Corporation. Drug list search results: bydureon. [internet]. Bloomfield (CT): CIGNA Corporation [accessed 2012 Apr 4]. [1 p]. Available: [https://my.cigna.com/teamsite/cgi-bin/customer_care/member/drug_list/DrugList.cgi?class_name=Antihypergly-%20Incretin%20Minetuc%20\(GLP-1%20RECEP.%20AGONIST\)&Pid=&search_by=class&LeanIndicator=&referer=](https://my.cigna.com/teamsite/cgi-bin/customer_care/member/drug_list/DrugList.cgi?class_name=Antihypergly-%20Incretin%20Minetuc%20(GLP-1%20RECEP.%20AGONIST)&Pid=&search_by=class&LeanIndicator=&referer=).
53. Humana, Inc.. Medicare plans: provider drug search results for Bydureon. [3 p]. Louisville (KY): Humana, Inc.; Available: http://apps.humana.com/prescription_benefits_and_services/execreq.asp?processcode=3&srcsite=physician&productid=4&ndc=66780021904&view=m.
54. Regence Group. Regence BlueShield (Washington) retail medication quantity limits. [internet]. Portland (OR): Regence Group; 2012 Feb 2 [accessed 2012 Apr 4]. [3 p]. Available: <http://www.regencrx.com/learn/priorAuth/washingtonPriorAuth.html>.
55. Regence Group. Regence BlueCross BlueShield of Oregon retail medication quantity limits. [internet]. Portland (OR): Regence Group; 2012 Feb 13 [accessed 2012 Apr 4]. [3 p]. Available: <http://www.regencrx.com/learn/priorAuth/oregonPriorAuth.html>.
56. Wellmark, Inc.. Prior authorization request: GLP-1 agonists (Byetta/Victoza/Bydureon). Des Moines (IA): Wellmark, Inc.; 1 p. Also available: www.wellmark.com.
57. Buse JB, Nauck MA, Forst T, et al. Efficacy and safety of exenatide once weekly versus liraglutide in subjects with type 2 diabetes (DURATION-6): a randomised, open-label study. In: European Association for the Study of Diabetes (EASD) 47th Annual Meeting ; 2011 Sep 12-16; Lisbon (Portugal). Also available: <http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=30964a21-d6b2-45c5-a5ef-cfbb92828f1d&cKey=3f9e5651-7432-436e-be7c-908556d97b8d&mKey=%7bBAFB2746-B0DD-4110-8588-E385FAF957B7%7d>.
58. Blevins T, Pullman J, Malloy J, et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. J Clin Endocrinol Metab 2011 May;96(5):1301-10. Epub 2011 Feb 9. PMID: 21307137
59. Intarcia presents positive ITCA 650 phase 2 study results for type 2 diabetes at EASD. [internet]. Hayward (CA): Intarcia Therapeutics, Inc.; 2010 Sep 22 [accessed 2010 Dec 17]. [4 p]. Available: <http://www.intarcia.com/IntarciaPresentsPositiveITCA650Phase2StudyResultsforType2DiabetesatEASD.html>.
60. What is the DUROS technology? [internet]. Hayward (CA): Intarcia Therapeutics, Inc. [accessed 2010 Dec 17]. [1 p]. Available: <http://www.intarcia.com/technology.html>.
61. Yang B, D'Vaz R, Negulescu C, et al. ITCA 650 for zero-order continuous delivery of exenatide at therapeutic levels using 3-, 6-, and 12-month mini-pumps. In: Diabetes Technology Meeting; 2012 Nov 8-10; Bethesda (MD). Also available: <http://www.intarcia.com/documents/Intarcia%201252D%20poster.pdf>.
62. Intarcia and Quintiles sign letter of intent for innovative global collaboration to advance ITCA 650 in type 2 diabetes. [internet]. Hayward (CA): Intarcia Therapeutics, Inc.; 2011 Oct 21 [accessed 2011 Nov 14]. [3 p]. Available: <http://www.intarcia.com/media/press-releases/2011-oct-21-LOI-Quintiles.html>.
63. Intarcia presents positive phase 2 48-week results from ITCA 650 study at the American Diabetes Association 71st scientific sessions. [internet]. Hayward (CA): Intarcia Therapeutics, Inc.; 2011 Jun 28 [accessed 2011 Aug 18]. [4 p]. Available: <http://www.intarcia.com/media/press-releases/2011-jun-28-itca-650.html>.
64. Intarcia presents compelling 48-week results for ITCA 650 - data underlines the promise to become the first injection-free GLP-1 therapy at the 47th Annual EASD Meeting in Lisbon. [internet]. Hayward (CA): Intarcia Therapeutics, Inc.; 2011 Sep 14 [accessed 2011 Nov 14]. [5 p]. Available: <http://www.intarcia.com/media/press-releases/09%2014%2011%20ITCA%20650%20Phase%202%20Presentation%20EASD%202011.html>.
65. American Diabetes Association (ADA). Standards of medical care in diabetes. V. Diabetes care. Diabetes Care 2010 Jan;33 Suppl 1:S16-29.
66. Raine R, Cartwright M, Richens Y, et al. A qualitative study of women's experiences of communication in antenatal care: identifying areas for action. Matern Child Health J 2010 Jul;14(4):590-9. PMID: 19554436

67. ALZA Corporation. [internet]. FundingUniverse [accessed 2010 Dec 17]. [4 p]. Available: <http://www.fundinguniverse.com/company-histories/ALZA-Corporation-Company-History.html>.
68. Intarcia announces presentation of analysis used for dose selection for global ITCA 650 phase 3 program for type 2 diabetes at EASD. [internet]. Hayward (CA): Intarcia Therapeutics, Inc.; 2012 Oct 3 [accessed 2012 Nov 14]. Available: <http://www.intarcia.com/media/press-releases/10%2003%2012%20ITCA%20650%20EASD%20Ph3%20Dose%20Select%20FINAL.html>.
69. Expert Commenter 161. (PRI, Research/Scientific/Technical). Horizon Scanning Structured Comment Form. HS180 - Subcutaneous exenatide (DUROS) for treatment of type II diabetes. 2012 Aug 29 [review date].
70. Expert Commenter 404. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS180 - Subcutaneous exenatide (DUROS) for treatment of type II diabetes. 2012 Aug 6 [review date].
71. Expert Commenter 420. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS180 - Subcutaneous exenatide (DUROS) for treatment of type II diabetes. 2012 Jul 31 [review date].
72. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS180 - Subcutaneous exenatide (DUROS) for treatment of type II diabetes. 2012 Jul 31 [review date].
73. Expert Commenter 433. (External, Health Systems). Horizon Scanning Structured Comment Form. HS180 - Subcutaneous exenatide (DUROS) for treatment of type II diabetes. 2012 Aug 22 [review date].
74. Expert Commenter 547. (External, Clinical). Horizon Scanning Structured Comment Form. HS180 - Subcutaneous exenatide (DUROS) for treatment of type II diabetes. 2012 Aug 14 [review date].
75. Expert Commenter 809. (External, Clinical). Horizon Scanning Structured Comment Form. HS190 - Extended-release exenatide (Bydureon) for treatment of diabetes. 2012 Apr 24 [review date].
76. Expert Commenter 410. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS190 - Extended-release exenatide (Bydureon) for treatment of diabetes. 2012 Apr 26 [review date].
77. Expert Commenter 660. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS190 - Extended-release exenatide (Bydureon) for treatment of diabetes. 2012 Apr 26 [review date].
78. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS190 - Extended-release exenatide (Bydureon) for treatment of diabetes. 2012 Apr 26 [review date].
79. Expert Commenter 1169. (PRI, Clinical). Horizon Scanning Structured Comment Form. HS190 - Extended-release exenatide (Bydureon) for treatment of diabetes. 2012 Apr 25 [review date].
80. Expert Commenter 420. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS190 - Extended-release exenatide (Bydureon) for treatment of diabetes. 2012 Apr 24 [review date].
81. Expert Commenter 396. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS190 - Extended-release exenatide (Bydureon) for treatment of diabetes. 2012 Jul 31 [review date].
82. Lucentis (ranibizumab injection) labeling. [internet]. San Francisco (CA): Genentech USA, Inc.; 2006 June [accessed 2007 Aug 20]. [7 p]. Available: <http://www.fda.gov/cder/foi/label/2006/125156lbl.pdf>.
83. Lucentis (ranibizumab injection) highlights of prescribing information. [internet]. South San Francisco (CA): Genentech, Inc.; 2012 Aug [accessed 2012 Nov 14]. [8 p]. Available: <http://www.gene.com/gene/products/information/pdf/lucentis-prescribing.pdf>.
84. Ferrone PJ, Jonisch J. Ranibizumab dose comparison for the treatment of diabetic macular edema. In: Association for Research in Vision and Ophthalmology (ARVO) 2011 Annual Meeting; 2011 May 1-5; Fort Lauderdale (FL). Also available: <http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=58710de1-542c-41d9-9a9d-79a4eb8d99cf&cKey=97c2f412-90d0-4667-9b0d-708cb6bf2d6a&mKey=%7b6F224A2D-AF6A-4533-8BBB-6A8D7B26EDB3%7d>.

85. Phend C. ADA: anti-VEGF 'impressive' in sharpening vision. [internet]. Little Falls (NJ): Medpage Today, LLC; 2011 Jun 28 [accessed 2011 Jul 14]. [5 p]. Available: <http://www.medpagetoday.com/tbprint.cfm?tbid=27333>.
86. U.S. Food and Drug Administration (FDA). FDA approves Lucentis to treat diabetic macular edema. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2012 Aug 10 [accessed 2012 Aug 30]. [2 p]. Available: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm315130.htm>.
87. Moore A. FDA approves eye drug for diabetics. [internet]. New York (NY): Medical Daily; 2012 Aug 11 [accessed 2012 Nov 15]. [4 p]. Available: <http://www.medicaldaily.com/articles/11448/20120811/diabetes-eye-disease-fda-us-lucentis.htm>.
88. CIGNA Health Corporation. Cigna medical coverage policy: vascular endothelial growth factor (VEGF) inhibitors for ocular use. Policy number 1206. [internet]. Bloomfield (CT): CIGNA Health Corporation; 2012 Sep 15 [accessed 2012 Nov 14]. [7 p]. Available: http://www.cigna.com/assets/docs/health-care-professionals/coverage_positions/ph_1206_coveragepositioncriteria_VEGF.pdf.
89. Benefits investigation. [internet]. South San Francisco (CA): Genentech USA, Inc. [accessed 2012 Nov 15]. [2 p]. Available: <http://www.genentech-access.com/lucentis/hcp/see-how-we-can-help/our-services>.
90. Expert Commenter 405. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS737 - Ranibizumab (Lucentis) for treatment of diabetic macular edema. 2012 Oct 17 [review date].
91. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS737 - Ranibizumab (Lucentis) for treatment of diabetic macular edema. 2012 Oct 5 [review date].
92. Expert Commenter 428. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS737 - Ranibizumab (Lucentis) for treatment of diabetic macular edema. 2012 Sep 13 [review date].
93. Expert Commenter 433. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS737 - Ranibizumab (Lucentis) for treatment of diabetic macular edema. 2012 Oct 17 [review date].
94. Expert Commenter 935. (External, Research/Scientific/Technical). Horizon Scanning Structured Comment Form. HS737 - Ranibizumab (Lucentis) for treatment of diabetic macular edema. 2012 Sep 26 [review date].
95. Expert Commenter 1171. (External, Clinical). Horizon Scanning Structured Comment Form. HS737 - Ranibizumab (Lucentis) for treatment of diabetic macular edema. 2012 Oct 8 [review date].