

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

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## **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](http://www.ahrq.gov)

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**Prepared by:**

ECRI Institute  
5200 Butler Pike  
Plymouth Meeting, PA 19462

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## **Statement of Funding and Purpose**

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

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

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

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## Preface

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

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

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

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

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

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# Executive Summary

## Background

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

## Methods

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

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

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest (COI). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs.

No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

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

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

## Results

The table below lists the 15 topics for which (1) preliminary phase III data for drugs or phase II or III data for devices or procedures were available; (2) information was compiled by April 26, 2012, in this priority area; *and* (3) we received six to eight sets of comments from experts between February 2011 and April 15, 2012. (Fifty-two topics in this priority area were being tracked in the system as of May 2012.) For purposes of this report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present four summaries on five topics (indicated below by an asterisk) that emerged as having potential high impact on the basis of experts’ comments and their assessment of potential impact.

### Priority Area 07: Diabetes

Topic	High Impact Potential
1. *Artificial pancreas for treatment of diabetes	High
2. *Bariatric surgery for resolution of type 2 diabetes mellitus (T2DM) in patients with body mass index <35 kg/m <sup>2</sup>	High
3. *Buccal insulin (Oral-lyn) therapy for type 1 diabetes mellitus (T1DM) and T2DM requiring insulin	Moderately high
4. D-tagatose for treatment of T2DM	No high-impact potential at this time
5. *Exenatide extended-release (Bydureon) for treatment of diabetes	Lower range of high impact
6. *Exenatide subcutaneous pump (Duros) for treatment of diabetes	Lower range of high impact
7. GFT 505 for treatment of T2DM and prediabetes	No high-impact potential at this time
8. Inhaled insulin (Technosphere) therapy for T1DM or insulin-dependent T2DM	No high-impact potential at this time
9. InsuPatch for improving pump-infused insulin absorption	No high-impact potential at this time
10. Off-label salsalate for treatment of T2DM	No high-impact potential at this time
11. SGLT2 inhibitor (ASP1941) for treatment of T2DM	No high-impact potential at this time
12. SGLT2 inhibitor (BI-10773) for treatment of T2DM	No high-impact potential at this time
13. SGLT2 inhibitor (dapagliflozin) for treatment of T2DM	No high-impact potential at this time
14. SGLT2 inhibitor (LX-4211) for treatment of T2DM	No high-impact potential at this time
15. Ultra-long-acting insulin (degludec) for treatment of T2DM	No high-impact potential at this time

## Discussion

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) estimated that in 2010, 18.8 million Americans had some form of diagnosed diabetes, and an estimated 7.0 million had undiagnosed diabetes. 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. In 2010, NIDDK incidence statistics indicated that about 1.9 million new cases of diabetes were diagnosed that year in adults 20 years of age or older. The American Diabetes Association Task Force recently 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 the disease is diagnosed, patients undergo a medical evaluation to classify the disease type, detect any complications, review glycemic control challenges, and establish a treatment plan, including establishing goals for blood glucose levels and glycated hemoglobin (HbA<sub>1C</sub>). The HbA<sub>1C</sub> test measures how much hemoglobin has bonded to blood cells over a 3- or 4-month period with a single blood draw and 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 generally encourage patients to achieve an HbA<sub>1C</sub> level of 7% because this value has been shown to reduce diabetes-associated complications. However, these targets are individualized according to clinician judgment about the optimal goal for a specific patient. For T2DM, a variety of self-administered oral antidiabetes agents, alone or in combination, are generally tried as first-line medical 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 onset of the disease in at-risk patients and improving diabetes management and adherence to treatment plans. 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 development of a system and systems are in pilot studies.

- **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 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 in the operation of a CLS.
- **Potential for High Impact:** High

## **Bariatric Surgery for Patients with Body Mass Index <35**

- **Key Facts:** Current guidelines specify that bariatric surgery is indicated for individuals who are morbidly obese (i.e., body mass index [BMI]  $>40 \text{ kg/m}^2$ ) or individuals with a BMI  $>35 \text{ kg/m}^2$  and an associated comorbidity. One such qualifying comorbidity is diabetes, which is highly correlated with obesity. However, outcomes showing resolution of T2DM in patients who have undergone bariatric surgery has generated interest in the potential of bariatric surgery to treat T2DM in less obese patients (i.e., BMI  $<35 \text{ kg/m}^2$ ). The cost of the surgery would vary depending on the choice of procedure (e.g., Roux en Y; lap banding; sleeve gastrectomy). Currently, insurers generally do not cover bariatric surgery in patients at these BMIs. Depending on the procedure chosen, the cost would range from about \$10,000 to \$40,000 per procedure.
- **Key Expert Comments:** Overall, experts commenting on this topic believe that bariatric surgery has significant potential to lead to remission or cure of T2DM in mildly to moderately obese individuals, and they believe that its use in this patient population would significantly shift the care model and care setting. However, given the high risks associated with some bariatric surgery procedures and the long-term lifestyle changes mandated by the treatment, experts believe its use in this population would be highly controversial and careful patient selection would be important. They questioned whether patients would opt for surgery and whether clinicians would want to advise the surgery in this patient population. Given the high number of people with T2DM whose BMI is in the 30-to-35  $\text{kg/m}^2$  range, adoption of the procedure as an option for those who do not achieve target blood glucose levels with less drastic methods could have a very large impact on the health care system in terms of infrastructure (bariatric surgery services) and shifts in processes of care (from lifestyle changes and medication for diabetes to surgery).
- **Potential for High Impact:** High



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

- **Key Facts:** Many patients who require exogenous insulin consider injections burdensome, yet 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 to injected human insulin was expected to be completed in September 2011, but appears to be ongoing. Oral-lyn is currently available under a U.S. Food and Drug Administration (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 needle-less 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 due in part to the fact that this product 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

## New Exenatide Formulations to Improve Diabetes Treatment Adherence

- **Key Facts:** Two therapies are in development for treating T2DM to improve efficacy, tolerability (reducing nausea), and patient adherence to treatment recommendations. They are extended-release exenatide for injection (Bydureon™, Amylin Pharmaceuticals, Inc., San Diego, CA) and implanted continuous subcutaneously delivered exenatide (ITCA 650, Intarcia Therapeutics, Inc., Hayward, CA, via the Duros® pump system).
  - 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. In August 2011, the manufacturers of Bydureon, which at that time included Eli Lilly and Co., announced that FDA had acknowledged resubmission of their new drug application (NDA). In November 2011, Amylin Pharmaceuticals and Eli Lilly announced the end of their partnership for developing exenatide, leaving sole development responsibility to Amylin Pharmaceuticals. An FDA action date was set for January 28, 2012.
  - ITCA 650 is a proprietary formulation of exenatide that remains stable at body temperature for extended periods of time and can be administered continuously using

the implantable Duros subcutaneous continuous delivery system. The Duros 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 after releasing final 48-week results from its phase II trial. The company reported that the drug resulted in improved glycemic control and was well tolerated at all doses, starting from 20 mcg/day and transitioning to 40, 60, or 80 mcg/day. The company also reported the drug led to reduced body weight after 24 and 48 weeks of treatment.

- **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 adherence to treatment recommendations. However, experts noted that the benefit might be incremental relative to existing forms of exenatide and other GLP-1 analogs.
- **Potential for High Impact:** Lower range of high impact

# **Diabetes Mellitus Interventions**

## Artificial Pancreas for Treatment of Diabetes

An artificial pancreas is a closed-loop system (CLS) composed of an external or implantable insulin pump, a real-time continuous glucose monitor, and a specialized glucose sensor that detects glucose levels and uses advanced computer algorithms to coordinate insulin delivery.<sup>1</sup> 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.<sup>1</sup>

First-generation artificial pancreas systems are known as low-glucose suspend (LGS) systems. In these systems, either insulin delivery automatically shuts off when blood glucose levels drop below a preset threshold, indicating hypoglycemia (reactive LGS), or the monitor can use control algorithms to predict and prevent potential hypoglycemic events (predictive LGS).<sup>2</sup>

Artificial pancreas technology aims to monitor patient blood glucose levels and automatically respond to these levels by pumping out appropriate doses of insulin based on a computer-driven algorithm.<sup>3</sup> Second-generation artificial pancreas systems are known as control-to-range (CTR) systems and control-to-target (CTT) systems. A CTR system functions similarly to an LGS, but aims to reduce hypoglycemic episodes by adjusting a patient's insulin dose once blood glucose levels drop below a preset threshold. A CTT system automatically sets a target glucose level to be consistently maintained, using an insulin-only system or a bi-hormonal system that mimics normal liver stimulation by the pancreas using two separate computer algorithms to deliver insulin and glucagon boluses.<sup>2</sup>

Zisser and colleagues (2011) released an evaluation of the CLS artificial pancreas 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.”<sup>4</sup> 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.”<sup>4</sup>

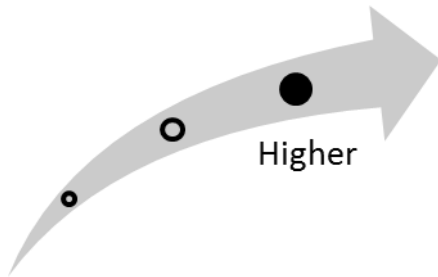
While many proof-of-concept studies of CLSs have been performed, and while all the necessary component parts of a CLS exist, a truly portable CLS for routine use is several years from realization because major advances in sensor technology and artificial pancreas software algorithms are needed, as is a developer that is able and willing to integrate the disparate components into a single CLS.<sup>5</sup> Another barrier to approval is the U.S. Food and Drug Administration (FDA) guideline for CLS studies. In June 2011, FDA stated that this intervention's sponsors would need to produce results showing use of these systems will “prevent or reduce the length and severity of hypoglycemia events better than conventional systems consisting of an infusion pump and continuous glucose monitoring system” to notify patients when blood glucose levels are not within normal range.<sup>6</sup> In December 2011, FDA issued a second guidance document for artificial pancreas systems to facilitate the clinical development of the fully closed loop system.<sup>3,7</sup>

## Clinical Pathway at Point of This Intervention

Patients receiving a diagnosis of type 1 diabetes (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.<sup>8</sup>

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<sub>1c</sub>) goals. The HbA<sub>1c</sub> 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<sub>1c</sub> level of 7% because this value has been shown to reduce the complications associated with T2DM.

**Figure 1. Overall High Impact Potential: Artificial pancreas for treatment of diabetes**



Overall, experts commented that 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 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 the operation of a CLS. Development of disparate parts of a CLS has been ongoing for years; however, no single entity has taken on development and integration of the hardware and software required for a CLS. 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.<sup>9-14</sup> Experts agreed that a CLS that could link continuous glucose monitors and insulin pumps with seamless feedback to appropriately control patients' blood glucose levels in an automated fashion is a long-standing, significant, unmet need. However, many experts noted that an off-the-shelf version of the artificial pancreas would most likely not be available for many years.

Experts observed that early versions of a CLS 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 a CLS. Additionally, experts indicated that these systems would likely need significant upkeep by users and physicians to ensure their proper function. While experts envisioned 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. If sufficient refinement of the systems should occur, experts believe, it could eventually simplify diabetes care for patients and physicians, because the CLS would automate a number of functions currently performed by the patient (e.g., blood glucose testing, insulin administration).

Relative to current treatments, experts envisioned small care-setting shifts, noting that patients would need to have the device implanted and, depending on the ultimate design of the system, might need to return to the physician's office to have the insulin pump reservoir filled.

Experts also suggested that use of the artificial pancreas could increase scientific understanding of diabetes, citing the significant amounts of data that such systems would generate.

Experts also envisioned 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.

## Bariatric Surgery for Resolution of T2DM in Patients With Body Mass Index <35 kg/m<sup>2</sup>

Current guidelines specify that bariatric surgery is indicated for individuals who are morbidly obese (i.e., body mass index [BMI] >40 kg/m<sup>2</sup>) or individuals who are obese with a BMI >35 kg/m<sup>2</sup> and an associated comorbidity that is expected to improve with weight loss. One such qualifying comorbidity is diabetes, which is highly correlated with obesity. Studies of outcomes of patients with T2DM who have undergone bariatric surgery have demonstrated that more than three-fourths of these patients are able to achieve glycemic control without the use of antidiabetes medications. Basing their opinions on this success, physicians have become interested in the potential of bariatric surgery to treat T2DM in obese patients with BMI <35 kg/m<sup>2</sup>. Currently, insurers generally do not cover bariatric surgery in patients at a lower BMIs, and patients would bear the cost, which would vary depending on the bariatric procedure selected.

Bariatric surgeries are classified as purely restrictive, mostly restrictive, or mostly malabsorptive.<sup>15</sup> Restrictive procedures cause weight loss by limiting the amount of food that can be eaten at a meal. Malabsorptive procedures reduce the body's absorption of food.<sup>16,17</sup> The most common form of bariatric surgery is Roux-en-Y gastric bypass (RYGB) surgery. RYGB has both restrictive and malabsorptive features. For restriction, the stomach is separated (using staples or another method) into a small upper portion and a large lower portion. Food enters only the upper portion (the gastric pouch). The small intestine is cut 15 to 50 cm distal to the ligament of Treitz. The distal small intestine is connected to the gastric pouch, permitting the emptying of food. This creates one limb (the "Roux," or alimentary limb) of a Y-shaped construction. Completion of the Y portion of the reconstruction involves performing an anastomosis (jejunojejunostomy) to connect the proximal end to the side of the Roux limb at least 45 cm downstream to prevent reflux of bile and pancreatic juices into the proximal gastric pouch. The two limbs meet and form a common limb at the most distal section of the small intestine, where food and digestive fluids mix.<sup>15</sup> The most common purely restrictive procedure is laparoscopic adjustable gastric banding (LAGB) in which a band is placed around the upper part of the stomach, which reduces the amount of food that can be ingested.<sup>15</sup> Other, less common procedures include the malabsorptive laparoscopic ileal interposition linked to a diverted sleeve gastrectomy, the malabsorptive biliopancreatic diversion, and the malabsorptive laparoscopic duodenojejunal bypass.<sup>15,17,18</sup>

While bariatric procedures have been shown to be effective in managing T2DM, the procedures are not without serious risks; 10% to 20% of patients undergoing RYGB surgery experience serious complications (e.g., surgical leaks, hernia, wound infection, bowel obstruction), and 1% of patients die of complications. Additionally, RYGB is irreversible and results in permanent anatomic alterations. After surgery, patients require continual dietary supplements to avoid vitamin deficiency and malnutrition.<sup>19</sup>

Schauer and colleagues (2012) presented data from a study assessing medical therapy plus RYGB or sleeve gastrectomy in 150 obese patients.<sup>20</sup> The authors reported, "The proportion of patients with the primary end point was 12% (5 of 41 patients) in the medical-therapy group versus 42% (21 of 50 patients) in the gastric-bypass group ( $p=0.002$ ) and 37% (18 of 49 patients) in the sleeve-gastrectomy group ( $p=0.008$ ). Glycemic control improved in all three groups, with a mean glycated hemoglobin level of  $7.5\pm1.8\%$  in the medical-therapy group,  $6.4\pm0.9\%$  in the gastric-bypass group ( $p<0.001$ ), and  $6.6\pm1.0\%$  in the sleeve-gastrectomy group ( $p=0.003$ ). Weight loss was greater in the gastric-bypass group and sleeve-gastrectomy group ( $-29.4\pm9.0$  kg and  $-25.1\pm8.5$  kg, respectively) than in the medical-therapy group ( $-5.4\pm8.0$  kg) ( $p<0.001$  for both comparisons)."<sup>20</sup> Patients in the RYGB group and sleeve-gastrectomy group reduced pharmacotherapy use.

Geloneze and colleagues (2010) presented data from a study in which 40 patients with T2DM and a BMI of 30–35 kg/m<sup>2</sup> were treated using RYGB. At 1 year postsurgery, patients exhibited improvement in multiple aspects of T2DM. Percent glycated hemoglobin (HbA<sub>1c</sub>) went from a mean of 9.08% to a mean of 6.04% (66% of patients with HbA<sub>1c</sub> less than 6%; 22% of patients with HbA<sub>1c</sub> from 6% to 7%). Additionally, 50% of patients were able to discontinue use of antidiabetes medications for glycemic control.<sup>21</sup>

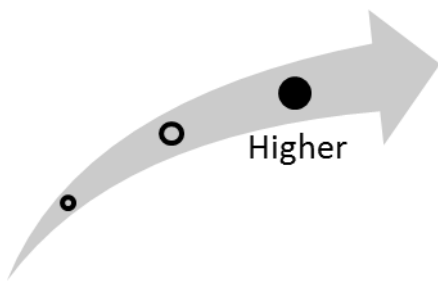
DeMaria and colleagues (2010) published a retrospective analysis of outcomes from patients with T2DM and a BMI of 30 to 35 kg/m<sup>2</sup> whose data were in the Bariatric Outcomes Longitudinal Database. The majority of these patients underwent RYGB (n=109) or LAGB (n=109), and data suggested early effectiveness of these surgical treatments for resolving T2DM.<sup>22</sup>

In February 2011, FDA approved the use of the LAP-BAND adjustable gastric banding system (Allergan, Inc., Irvine, CA) in patients with a BMI of 30–34 kg/m<sup>2</sup> and an associated comorbidity.<sup>23</sup> Surgical procedures such as RYGB are not subject to FDA marketing approval; they may also be performed on less-obese patients, although the procedure is not covered by Medicare or most private third-party payers for patients with BMI <35 kg/m<sup>2</sup>.

## Clinical Pathway at Point of This Intervention

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 hypoglycemic agent (e.g., metformin, sulfonylurea derivative, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 [GLP-1] analog) and combination therapy if monotherapy is not sufficiently effective. The disease's progressive nature typically results in the need for a proportion of affected people to take insulin for adequate blood glucose control. Basal insulin may be added to existing hypoglycemic agents to achieve glycemic control; however, many patients with T2DM will eventually employ more intensive insulin regimens, which typically include a long-acting insulin once or twice per day (basal insulin) plus a short-acting insulin with meals (prandial insulin) to cover increases in glucose levels after meals.<sup>24,25</sup> Bariatric surgery would provide another treatment option for T2DM in patients who are obese and not achieving adequate blood glucose control with medication or insulin.

**Figure 2. Overall High Impact Potential: Bariatric surgery for resolution of T2DM in patients with body mass index <35 kg/m<sup>2</sup>**



Overall, experts commenting on this topic believe that bariatric surgery has the potential to lead to remission or cure of T2DM in mildly to moderately obese individuals, and its use in this patient population would significantly shift the care model and care setting. However, given the high risks associated with some forms of bariatric surgery and the long-term lifestyle changes mandated by the treatment, experts believe its use in this population would be highly controversial. They questioned whether patients would opt for surgery and whether clinicians would want to advise the surgery in this patient population. Given the large number of people with T2DM whose BMI is in the 30-to-35 kg/m<sup>2</sup> range, adoption of the procedure as a treatment for those who do not achieve adequate control



of blood glucose with less drastic methods could have a very large impact on the health care system in terms of infrastructure (bariatric surgery services) and shifts in processes of care (from medication to surgery). 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, health systems, and health administration backgrounds, provided perspectives on this topic.<sup>26-31</sup> Experts believe that there is a significant unmet need for novel treatments for T2DM, especially potentially curative treatments such as bariatric surgery. One clinical expert stated, “Although any weight loss and, therefore, any bariatric procedure may improve insulin resistance, the RYGBP does appear to improve diabetes by both weight dependent and weight independent mechanisms.”<sup>31</sup> The majority of experts also thought that the theory of using bariatric surgery to treat obese patients with T2DM who do not meet the current BMI limits is sound, citing the effectiveness of bariatric surgery in resolving T2DM in morbidly obese patients. However, multiple experts noted the lack of studies of long-term outcomes for patients with BMI <35 kg/m<sup>2</sup>. Additionally, one expert with a research background noted that the mechanism of action by which bariatric surgery affects diabetes is unclear and, therefore, it might not be as efficacious in patients with lower BMIs as in those typically accepted for the surgery. In this vein, multiple experts observed that bariatric surgery in this patient population has significant potential to inform our scientific understanding of obesity, diabetes, and the metabolic syndrome.

Experts believe that use of bariatric surgery in this patient population would represent a significant shift in treatment models for this condition. Relative to current medical management of T2DM in the home setting, use of bariatric surgery would shift some of these patients to inpatient surgical procedures as well as increase the need for services involved in postsurgical management of bariatric surgery patients (e.g., dietary supplementation). One expert with a clinical perspective also noted that initiation of treatment with this therapy might be offered and commence sooner, ultimately reducing “the overall burden of disease on society.”<sup>31</sup> Given the large number of potentially eligible patients in the United States, widespread use of bariatric surgery to treat T2DM in mildly obese patients could necessitate increases in bariatric surgery infrastructure and staffing.

This shift in care model also has implications for the cost of T2DM treatment. Experts agreed that while use of bariatric surgery in this patient population would generate high upfront costs, it has the potential to reduce long-term costs through improved control of diabetes symptoms and/or reduced need for antidiabetes medications.

Experts suggested that patients might be very reluctant to opt for this treatment, given its invasiveness, high adverse event rate of some of the procedures, and the requirement for long-term changes in dietary intake. However, experts also cited the potential for bariatric surgery to resolve T2DM and prevent future secondary complications of diabetes as a reason why some patients might opt for the treatment. Experts believe that considerable controversy would surround the risk-benefit profile of the treatment and questioned whether physicians would be likely to recommend this option to patients.

## **Buccal Insulin (Oral-lyn) Therapy for Type 1 Diabetes or Type 2 Diabetes That Requires Insulin**

Diabetes is often treated by providing the patient with exogenous insulin, which is typically administered by injection or continuous infusion using an insulin pump.<sup>32</sup> 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 with diabetes who could benefit from it.<sup>32</sup> Therefore, novel insulin delivery methods that do not involve injection are being 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 way of Generex's proprietary inhaler known as the RapidMist™ Diabetes Management System, which stores the liquid insulin and delivers about 100 doses in mist form.<sup>33</sup> The patient puffs on the inhaler in a similar fashion 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.<sup>34</sup> 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 recent 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.<sup>35</sup> Additionally, administration of buccal insulin was generally reported as being well tolerated in the studies; however, some patients experienced mild transient dizziness during dosing.<sup>35</sup> A phase III trial comparing use of Oral-lyn as a prandial insulin to injected human insulin was initiated in April 2008.<sup>36</sup> The trial is tracking HbA<sub>1c</sub> 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.<sup>36</sup> Although the trial's estimated completion date was September 2011, it appears to be ongoing.<sup>36</sup>

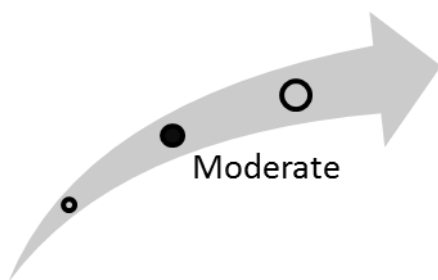
Oral-lyn is currently available in the United States to patients with life-threatening diabetes and no other treatment options, and it is approved under FDA's treatment investigational new drug program.<sup>37</sup>

## **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.<sup>25</sup> 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 once or twice per day (basal insulin) plus a short-acting insulin with meals (prandial insulin) to cover postmeal increases in glucose levels.<sup>25</sup>

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. The progressive nature of the disease typically results in the need for many people with T2DM to take insulin for adequate blood glucose control. Basal insulin may be added to existing hypoglycemic agents to achieve glycemic control; however, many patients with T2DM will eventually use insulin in the same manner as patients with T1DM.<sup>24,25</sup>

**Figure 3. Overall High Impact Potential: Buccal insulin (Oral-lyn) for treatment of diabetes**



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 due in part to the fact that 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.<sup>38-44</sup> 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®, Pfizer, Inc., New York, NY) that FDA approved but was subsequently withdrawn 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 inhaled insulin and device that comprised inhaled insulin, so these concerns are likely not very 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 those patients who are insulin dependent. Another research expert noted that another clinical trial compared this intervention to behavioral and dietary therapy, not other available treatment modalities for T1DM and T2DM treatment. While most

experts opined additional data is necessary to determine this intervention's effect on health outcomes, several experts agreed that an alternate route of administration could greatly benefit this patient population, with one health systems expert explaining "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..."<sup>44</sup> While several experts were convinced increased patient compliance 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 of the injected insulin treatment, one expert envisioned a significant impact 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)."<sup>44</sup>

Experts generally agreed that, provided this intervention was 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.

## New Exenatide Formulations to Improve Diabetes Treatment Adherence

Injectable glucagon-like peptide-1 (GLP-1) agonists available in the United States include Byetta®, a short-acting form of exenatide administered as a fixed-dose, subcutaneous injection administered twice daily and liraglutide (Victoza®), a longer-acting GLP-1 agonist developed by Novo Nordisk a/s (Bagsvaerd, Denmark) that is injected once per day. Two therapies are currently in development for treating T2DM to improve drug efficacy and tolerability as well as patient adherence. They are extended-release exenatide (exenatide once-weekly [EQW]; Bydureon™, Eli Lilly and Co., Indianapolis, IN, Amylin Pharmaceuticals, Inc., San Diego, CA, and Alkermes, Inc., Waltham, MA) and subcutaneously delivered exenatide (ITCA 650, Intarcia Therapeutics, Inc., Hayward, CA, via Duros® pump system)

EQW is an extended-release GLP-1 receptor agonist formulation that would allow 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]).<sup>45</sup> As the microsphere degrades in the bloodstream, exenatide is slowly released.<sup>45</sup> The microsphere technology used in EQW has also been used in other extended-release drugs such as extended-release naltrexone (Vivitrol®, Alkermes, Inc., Waltham, MA) and extended-release risperidone (Risperdal®, Consta®, Johnson & Johnson, New Brunswick, NJ).<sup>45</sup> In clinical trials, EQW was administered at a dose of 2 mg per week.<sup>45</sup>

Buse and colleagues (2011) reported results from a phase III trial comparing EQW efficacy versus liraglutide in 921 T2DM patients. The authors reported, “Change in HbA1c 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 HbA1c <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.”<sup>46</sup>

Blevins (2011) 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<sub>1c</sub> 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.<sup>47</sup>

In July 2011, Amylin Pharmaceuticals, Eli Lilly, and Alkermes announced the formal submission of a reply to the complete letter response issued by FDA over potential safety concerns.

Along with updates to safety information about ongoing or completed studies, included in the response were recent results showing that “exenatide, at and above therapeutic levels, did not prolong the corrected QT interval in healthy individuals as defined by the FDA’s published guidance.”<sup>48</sup> In August 2011, the companies announced that FDA had acknowledged resubmission of the application for extended-release exenatide. In November 2011, Amylin Pharmaceuticals and Eli Lilly announced the end of their partnership for development of exenatide, leaving sole development responsibility to Amylin Pharmaceuticals.<sup>49</sup> Amylin stated plans to continue its commercialization pathway in the United States. FDA approved EQW 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.”<sup>50,51</sup>

ITCA 650 is another proprietary formulation of exenatide that remains stable at body temperature for extended periods of time and can, therefore, be administered as a continuous subcutaneous infusion. 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. The intervention ITCA 650 is a novel use of this stable formulation of exenatide with Duros.<sup>52,53</sup>

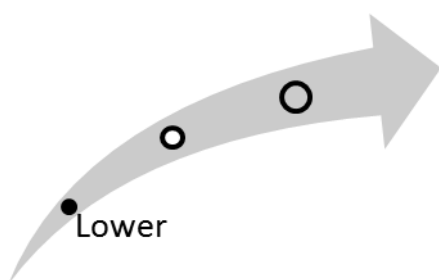
Intarcia reported final results from its phase II program on ITCA 650 in September 2011 and announced a collaboration with Quintiles (Durham, NC) to begin a phase III program of six trials by the end of 2011.<sup>54,55</sup> After an initial 12-week treatment period comparing the drug (20 or 40 mcg/day) with twice-daily exenatide injections, treatment continued at one of four dosing levels: 20, 40, 60 or 80 mcg/day through week 24, and patients could continue for an additional 24 weeks for a total of 48 weeks of treatment. Eighty-five percent of enrolled patients continued and the company reported in September 2011 that sustained reductions were observed in HbA<sub>1c</sub>, fasting plasma glucose, and weight across all treatment arms between 24 and 48 weeks. The greatest reductions were reported in the 60 and 80 mcg/day groups but were not statistically different between those two groups.<sup>56</sup>

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 marketing approval from FDA for the Duros technology.<sup>52,57,57,57-59</sup> Intarcia licensed exclusive rights for use of Duros from ALZA Corp.

## **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. The progressive nature of the disease typically results in the need for many people with T2DM to take insulin for adequate blood glucose control. Basal insulin may be added to existing hypoglycemic agents to achieve glycemic control; however, many patients with T2DM will eventually use insulin in the same manner as patients with T1DM.<sup>24,25</sup>

**Figure 4. Overall High Impact Potential: New exenatide formulations to improve diabetes medication adherence**



Overall, experts opined that subcutaneous exenatide and extended-release exenatide have potential to improve diabetes treatment by improving release mechanisms of exenatide while reducing frequency of injection and reducing nausea, thus potentially improving patient adherence to treatment recommendations. However, experts noted that this represents an incremental benefit to existing forms of exenatide and other GLP-1 analogs. Experts expressed a desire for further data evaluating safety and efficacy of these modifications to exenatide compared with existing forms. 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.<sup>60-65</sup> Perspectives on extended-release exenatide (Bydureon) were received from six experts.<sup>66-71</sup> Given that these two therapies are geared towards extending release and improving efficacy of exenatide, expert comments have been combined or synthesized to represent opinions on modifications to exenatide.

Experts agreed that while any new therapy for treating diabetes would be welcome, these new modifications to exenatide may be incremental and minimally address the unmet need. In the case of subcutaneous exenatide, most experts said that exenatide is already available in the twice-daily injectable form. One expert with a clinical perspective believes that while continuous release of exenatide without injection may improve patient adherence, “long term efficacy is uncertain because tachyphylaxis may develop in response to constant exposure to exenatide.”<sup>65</sup> In the case of once-weekly exenatide, most experts were optimistic about its potential to address the unmet need. While some experts referenced the existence of GLP-1 agonists on the market, one expert said that this therapy could reduce HbA<sub>1c</sub> 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 analogs already on the market. One expert with a clinical perspective believes that the mechanism of action for subcutaneous infusion of exenatide would “deliver a constant dose over long periods, in contrast to sharp peaks resulting from twice daily injections.”<sup>65</sup> The same expert noted that regardless of delivery system, subcutaneous exenatide would still induce nausea that is purportedly reduced, according to the manufacturer. Several experts noted that subcutaneous exenatide use would also result in effective weight loss. In regards to extended-release exenatide, one expert with a research perspective believes that while 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.”<sup>66</sup>

Collectively, 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 expert with a clinical perspective 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.

According to expert comments, extended-release exenatide and subcutaneous exenatide use would have minimal impact on clinical and patient learning curves. Experts believe that the previous existence of and exposure to injectable forms of exenatide and other GLP-1 analogs would minimize a patient’s learning curve with regards to extended-release exenatide. Most experts believe that in the case of subcutaneous exenatide, the learning curve for clinicians would be minimal based on the perceived simplicity of the procedure. One expert with a clinical perspective believes, “There would need to be some education on how to insert the device, but based on the information, it is not difficult.”<sup>64</sup> Another expert stated that it would only take a few minutes to implant the Duros osmotic pump subcutaneously, implying that the level of difficulty regarding the procedure is relatively low.

Experts were divided with regard to the potential impact of these modifications to exenatide on costs. While some experts believe that per-patient costs would increase with both forms of exenatide, some experts 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.”<sup>68</sup> 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 expert with a clinical perspective added, “Physicians may have to be reimbursed for the procedure. However, it is possible that the long-term cost of miniosmotic pump insertion and subcutaneous exenatide infusion will be similar or cheaper than twice daily exenatide injections.”<sup>65</sup>



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