Oramed Pharmaceuticals

Initiation of Coverage

LifeSci Investment Abstract

Oramed Pharmaceuticals (NASDAQ: ORMP) is a clinical-stage pharmaceutical company specializing in the oral delivery of proteins for large disease indications. Lead candidate ORMD-0801 is an oral insulin candidate in Phase II development to control fasting blood glucose levels in diabetes. Oramed is also developing an oral glucagon-like peptide 1 (GLP-1) receptor agonist and an insulin/GLP-1 combination product.

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Key Points of Discussion

ORMD-0801 has the Potential to be the First Oral Insulin. Oramed is developing drug candidates based on a platform technology that enables the oral delivery of drugs that are currently only available by injection. This Protein Oral Delivery (POD™) platform has the potential to improve the therapeutic profile of the treatment. The Company's lead product candidate is ORDM-0801, designed for the oral delivery of insulin and is being tested as a treatment for diabetes mellitus. The pipeline also includes ORMD-0901, an oral formulation of the GLP-1 analog exenatide, and a product that combines the two therapies. ORMD-0801 has been tested in a Phase IIa trial in type 2 diabetes patients and Oramed is planning to follow up with a Phase IIb trial. A Phase IIa trial in type 1 diabetes will be enrolling patients in March 2014.

ORMD-0801 is an Oral Insulin Candidate for Early-Stage Diabetics. Oramed's lead product candidate is ORMD-0801, a potential first-in-class oral insulin product in Phase II development. The Company is using their proprietary POD™ technology to chaperone insulin through the digestive tract and facilitate absorption in the small intestine. Insulin absorbed via the small intestine passes through the portal vein and is delivered directly to

Ticker	ORMP
Price	$10.99
Market Cap (M)	$107
EV (M)	$83
Shares Outstanding (M)	9.7
Fully Diluted Shares (M)	11.9
Avg. Daily Vol.	887,168
52-week Range:	$5.00-$31.73
Cash (M)	$23.8
Net Cash/Share	$2.45
Debt (M)	$0.0
Annualized Cash Burn (M)	$3.5
Years of Cash Left	>5
Short Interest (M)	0.86
Short Interest (% of Float)	8.9%

FY Aug		2012A	2013A	2014A
EPS:	Q1	($0.08)A	($0.14)A	($0.14)A
	Q2	($0.17)A	($0.17)A	NA
	Q3	($0.09)A	($0.19)A	NA
	Q4	($0.22)A	($0.10)A	NA
	FY	($0.57)A	($0.59)A	NA

the liver, mimicking the physiological release of insulin from the pancreas. This method of delivery offers several potential advantages beyond the peripheral control of glucose:

- Inhibition of glucose secretion from the liver.
- Less glucose uptake in fat and muscle cells.
- Systemic exposure to insulin is minimized.

Oramed is developing ORMD-0801 to play a unique role in the treatment of diabetes. For type 1 diabetics, this treatment could lead to tighter glucose control with fewer injections, which would contribute to quality of life. The initial focus for the candidate is the reduction of fasting blood glucose (FBG) levels in type 2 diabetes (T2D) patients. In type 2 diabetes, ORMD-0801 has the potential to be used early in the disease course, which has the potential to delay the progression of symptoms. Early insulin therapy can preserve beta cell function in the pancreas. As the disease progresses, ORMD-0810 could be used in combination with anti-diabetics such as metformin.

Oramed has completed Phase II trials with ORMD-0801 in healthy subjects and patients with diabetes. To date, Oramed has administered over 1,600 doses of ORMD-0801 to over 150 study subjects. The data has allowed improvements to the formulation and progressed the treatment on a path towards a regulatory filing with the FDA. Two Phase II trials are planned for 2014, including a Phase IIa trial in T1D patients that will begin enrollment in March, and a Phase IIb in T2D patients expected to begin by the end of the year.

Oramed is Developing a Platform for the Oral Delivery of Proteins. The Protein Oral Delivery (POD) technology incorporates three key features to protect proteins during GI transport and enhance absorption into the bloodstream. First, an enteric (pH sensitive) coating protects proteins as they travel through the denaturing environment of the stomach, only degrading and releasing the contents of the pill in the small intestine. Second, protease inhibitors are packed alongside the proteins to locally inhibit protein-degrading proteases once the cargo is released. Finally, absorption enhancers facilitate the movement of proteins across the intestinal membrane and into the bloodstream. They are absorbed in a way that is more similar to natural physiological processes when compared to injections of therapeutic proteins. This feature has the potential to improve the body's response to the treatment. Oramed is applying the POD platform to deliver therapeutic proteins to patients with diabetes, a multi-billion dollar market with strong growth.

Phase IIa Data Expected at an Upcoming Scientific Conference. In January 2014, Oramed announced positive topline results from their most recent Phase IIa trial, reporting that ORMD-0801 was safe and well tolerated with no serious adverse events (AEs) in the study. The trial was a randomized, double-blind, placebo-controlled study that enrolled 30 patients with T2D that is inadequately controlled with diet and exercise or diet, exercise, and metformin. Patients were randomized to receive one of two doses of ORMD-0801 (460 or 690 IU) or placebo for 7 days following a 5-day, single-blind, outpatient, run-in period with placebo. The primary endpoint was

safety and tolerability as determined by the number of AEs. Secondary endpoints included pharmacokinetics, pharmacodynamics, change in FBG, change in fasting c-peptide, and change in fasting insulin compared to placebo. Oramed plans to report trial results at the 2014 GTC Diabetes Summit on April 24th, including data from the secondary endpoints.

Clinical Plans Underway for Oral GLP-1 Receptor Agonist. Oramed is expanding the application of their POD technology for oral delivery of the GLP-1 receptor agonist exenatide. GLP-1 is a peptide secreted by intestinal cells in the gut in response to nutrient ingestion that reduces blood glucose by stimulating insulin secretion and suppressing glucagon secretion. An oral version of exenatide would significantly increase patient convenience and has the potential to deliver the GLP-1 agonist in a more physiologically appropriate way. Preclinical studies have suggested that ORMD-0901 can stabilize blood glucose levels, and a clinical trial in healthy subjects suggests that ORMD-0901 can stimulate insulin secretion. Oramed is planning to launch an ex-US Phase Ib trial in the second quarter of 2014, while concurrently completing 90 day preclinical toxicology studies intended to pave the way to commencement of a US-based Phase IIb trial that is expected to start in the first half 2015.

Financial Discussion

Quarterly Financials. Oramed released financial results for the first quarter of their fiscal year 2014 on January 14th, 2014, reporting operating expenses of $1.2 million. Of the $1.2 million, $0.8 million was attributed to research and development and $0.4 million to general and administrative costs. The net loss for the first quarter was $1.1 million or $0.14/share, compared to $0.7 million or $0.14/share for the same period in 2013.

Recent Financing and Cash Position. Oramed completed a registered direct offering of shares in December 2013 to support ongoing development programs. The Company sold 1.58 million shares at an offering price of $10.00/share to yield gross proceeds of $15.8 million. With the resulting proceeds, Oramed finished the first fiscal quarter with an estimated $23.8 million in cash on hand.

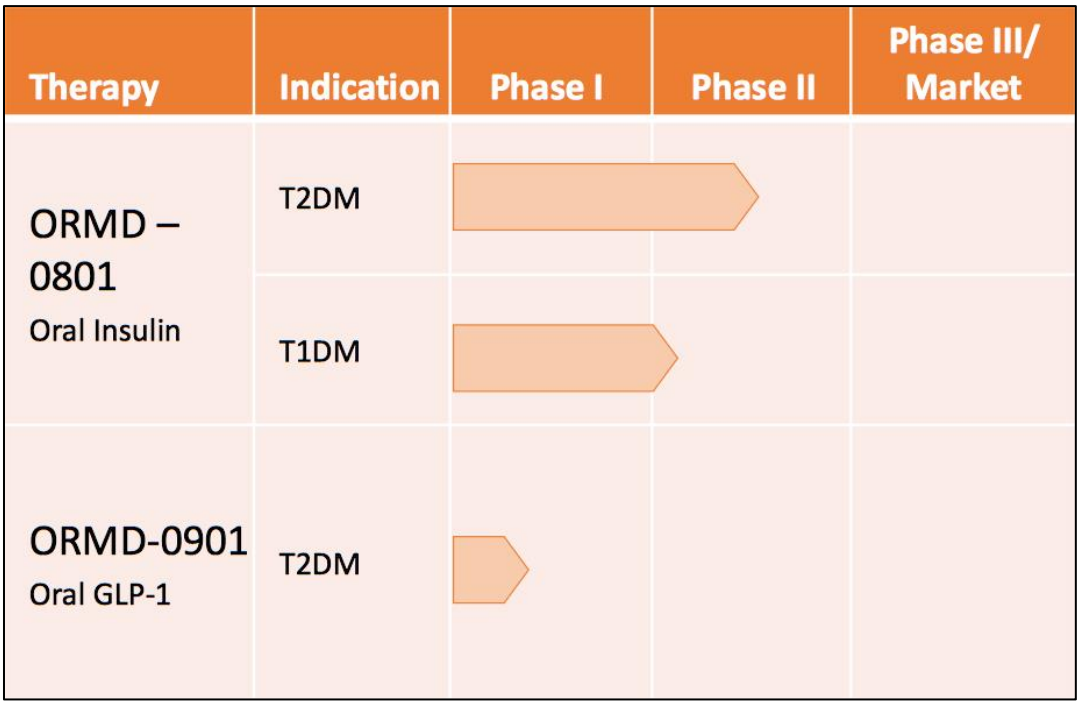
Expected Upcoming Milestones

- Q1 2014 – Launch Phase IIa trial with ORMD-0801 in type 1 diabetes patients.
- Q2 2014 – Initiate an ex-US Phase Ib trial with ORMD-0901.
- H2 2014 – Launch Phase IIb study with ORMD-0801 in type 2 diabetes patients.
- Q2 2014 – IND-enabling toxicology studies for ORMD-0901.
- H1 2015 – Initiate Phase IIb trial with ORMD-0901.

Company Description

Oramed is a clinical-stage pharmaceutical company specializing in the oral delivery of proteins for large disease indications. The Company is currently developing two products for the management of diabetes. ORMD-0801 is an oral insulin product candidate in Phase II development for patients with type 1 and type 2 diabetes. Oramed plans to initially focus on the reduction of fasting blood glucose levels, and ORMD-0801 is expected to be used in combination with anti-diabetics such as metformin, or after failure with metformin but prior to insulin replacement. Oramed recently announced positive topline results from a Phase IIa study, and the Company plans to launch two additional Phase II trials in 2014. ORMD-0901 is an oral version of the GLP-1 receptor agonist exenatide. Oramed plans to initiate IND-enabling studies and a Phase Ib trial in the second quarter of 2014. An overview of the Company's pipeline is illustrated in **Figure 1**.

Figure 1. Oramed Development Pipeline



Source: Oramed Corporate Presentation

ORMD-0801: Oral Insulin

Oramed is developing ORMD-0801 as a potential oral insulin product to offer a more convenient delivery of insulin in a way that more closely mimics the natural release of insulin from the pancreas than injectable products. The Company is using their proprietary protein oral delivery (POD) technology to chaperone insulin through the digestive tract and facilitate absorption in the small

intestine. Oral insulin is absorbed from the small intestine and flows into the portal vein and delivered directly to the liver, which acts to inhibit glucose secretion and to facilitate glucose uptake in peripheral cells. Oral insulin may offer advantages over currently available insulin replacement therapies, such as a potential reduction in the weight gain commonly associated with treatment. Oramed is developing ORMD-0801 to play a unique role in the treatment of diabetes, and the candidate is expected to be used both in type 1 diabetes patients and in type 2 patients in combination with anti-diabetics such as metformin, or after failure with metformin but prior to insulin replacement.

Oramed is expected to launch two Phase II trials in 2014 to further examine ORMD-0801 in patients with diabetes. The Company is launching a Phase IIa trial with ORMD-0801 in patients with T1D. Oramed's second upcoming trial is a multi-center Phase IIb study that will be conducted in the US. The trial is expected to begin in 2014.

Safety Profile. Oramed has conducted numerous safety studies in healthy volunteers and diabetes patients, including two recent Phase II trials. Both studies found ORMD-0801 to be safe and well-tolerated. Only mild cases of hypoglycemia were reported in one of the Phase II trials, and all cases resolved with no change to the dose of ORMD-0801. Other adverse events (AEs) were constipation, diarrhea, and increased bowel movement, which were also mild. No serious AEs were reported in either trial.

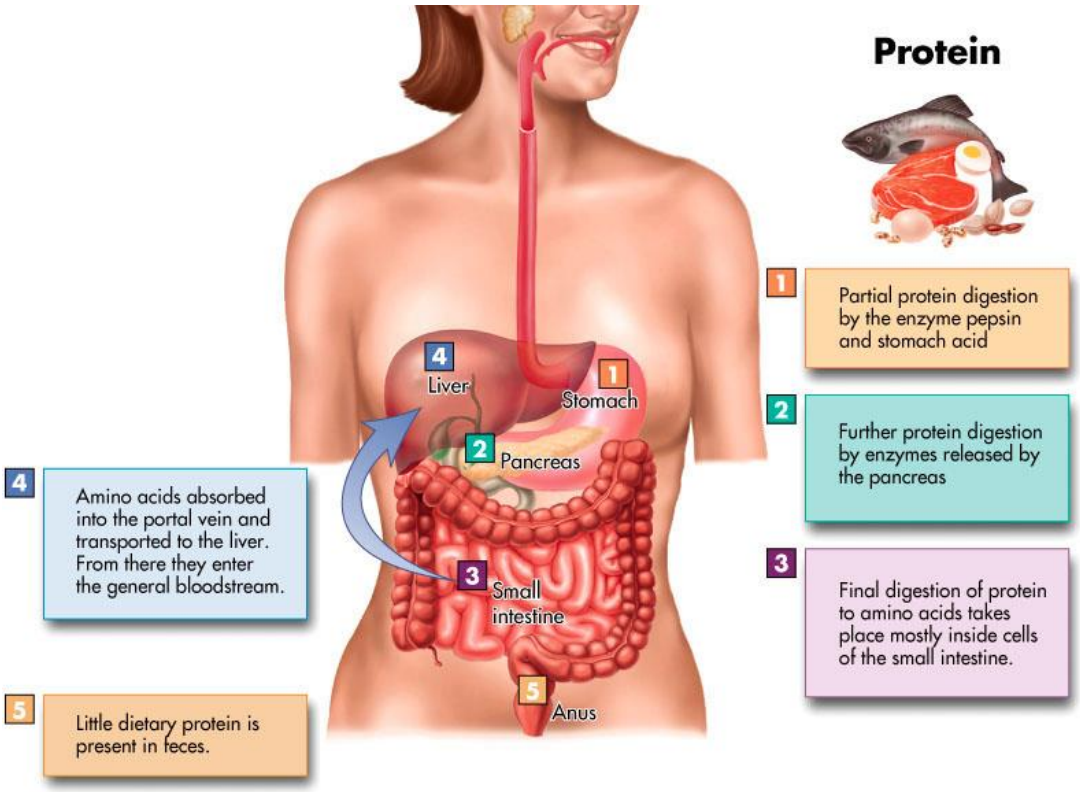
Oral Insulin Delivery

Delivering insulin via an oral pill is a goal that has existed since the discovery of the therapeutic value of insulin. An oral solution to insulin delivery has two major potential benefits that have not been realized due to the complexity of transporting an intact protein through the digestive system and achieving sufficient absorption. Oral insulin should help minimize the required supplies that patients must carry and has the future potential to eliminate the use of needles. The unappreciated potential benefit of oral insulin is the delivery of insulin via the portal vein to the liver, instead of the systemic exposure achieved by subcutaneous injections and oral inhalation. Pancreatic insulin travels the same route through the portal vein into the liver, and can influence the amount of glucose metabolism within the liver. Oramed's lead candidate ORMD-0801 is an oral insulin product that has been designed to mitigate the challenges of oral protein delivery.

Gastrointestinal Tract Challenges. The gastrointestinal (GI) tract is designed to breakdown and absorb food products, including proteins. The environment poses several challenges for the delivery of therapeutic proteins that must remain intact and enter the bloodstream. **Figure 2** shows the main digestive obstacles for proteins as they travel from the mouth towards the intestines. The harsh pH of gastric acids in the stomach helps to denature proteins and facilitate their cleavage by proteases. The stomach also mechanically churns food to increase the surface area and improve the efficiency of digestive reactions. Proteases are found throughout the digestive tract and some are secreted

directly by the pancreas. Cleavage of therapeutic proteins can completely eliminate any remaining structure and functionality. Finally, the intestines are designed to absorb small peptides, sugars, and fats, but not intact proteins so therapeutic proteins need assistance with absorption.

Figure 2. Challenges of Protein Delivery Via the Gastrointestinal Tract



Source: fgamedia.org[1]

Proprietary Protein Oral Delivery (POD™). Oramed has developed a platform technology to facilitate the oral delivery of drugs that are currently available only by injection. ORMD-0801 has been engineered with this technology to address the GI challenges faced by proteins. Oramed incorporates three components into its oral insulin product to protect the protein during GI transport and enhance absorption into the bloodstream. They components are:

- **Enteric Coating.** First, a pH sensitive coating protects the protein as it travels through the low pH environment of the stomach, only degrading and releasing the contents of the pill in the small intestine.
- **Protease Inhibitors.** Second, protease inhibitors are packed alongside insulin to locally inhibit proteases once the insulin is released.

[1] fgamedia.org/faculty/cholcroft/Bio45/miscellaneous_web_pages/Lectures/Proteins/ProteinRecommendations.html

- **Absorption Enhancers.** Finally, absorption enhancers facilitate the movement of insulin across the intestinal membrane and into the bloodstream.

Oramed has used the POD technology to deliver oral insulin to subjects in multiple clinical trials. Increases in blood insulin levels and corresponding decreases in glucose and c-peptide levels have been observed in patients treated with oral insulin. The POD technology therefore appears to facilitate the movement and absorption of intact insulin from the small intestine into the bloodstream.

Benefits of Insulin Delivery via the Portal Vein. The liver plays a key role in the regulation of blood glucose levels, and receives insulin directly from the pancreas via the portal vein. The portal vein is not a true vein, and is a vessel that carries most of the blood exiting the small intestine. After a meal, blood glucose levels rise and insulin is secreted into the liver, stimulating the conversion of glucose into glycogen via a process called glycogenesis in order to store glucose. After blood glucose levels begin to drop, insulin secretion is reduced and glycogenesis is halted. If additional glucose is necessary before the next meal, the liver metabolizes the glycogen back into glucose and releases the sugar into the bloodstream. Full depletion of glycogen from the liver stimulates gluconeogenesis, or the generation of glucose from other molecules such as fatty acids.

There are two problems associated with the non-physiologic, or systemic delivery of insulin. The first is that systemic insulin does not produce an adequate signal in the liver to inhibit glucose secretion. Instead, the liver may continue to release glucose despite ample blood glucose and insulin levels. In fact, studies in dogs have found that decreasing the amount of insulin flowing into the portal vein leads to an increase in net hepatic glucose output.[2,3] A study in mice also found that eliminating insulin signaling pathways in hepatocytes abolished the suppression of glucose output, further linking insulin signaling with glucose production.[4] The second issue with systemic insulin is that it selectively promotes glucose uptake in fat and muscle cells and can lead to weight gain in patients.

ORMD-0801 has the potential to offer delivery of insulin to patients that more closely mimics the natural physiological process. **Figure 3** shows a depiction of the organs of the digestive system including the stomach, liver, pancreas, intestines, and portal vein. Similar to natural delivery of insulin from the pancreas, absorption via the small intestine into the portal vein allows insulin to go directly into the liver. Once inside the liver, ORMD-0801 may suppress glucose secretion and gluconeogenesis and then continue to circulate and facilitate glucose transport into cells throughout the body.

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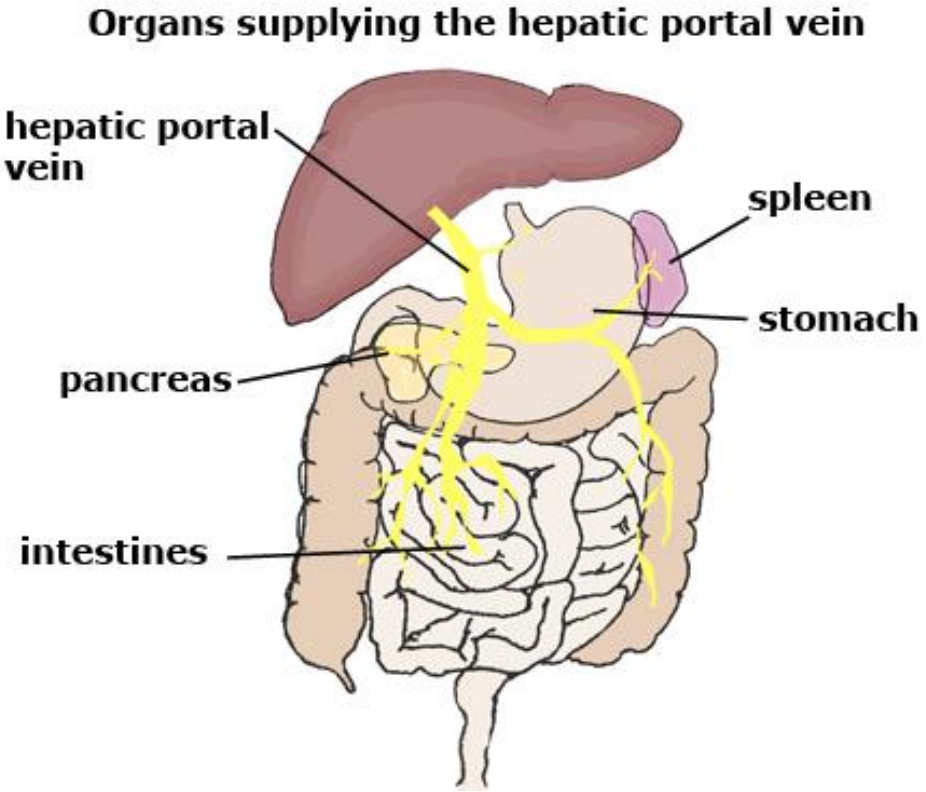
[2] Edgerton, D.S. et al., 2006. Insulin's direct effects on the liver dominate the control of hepatic glucose control. *Journal of Clinical Investigation*, 116(2), pp521-527.

[3] Sindelar, D.K. et al., 1998. Basal hepatic glucose production is regulated by the portal vein insulin concentration. *Diabetes*, 47(4), pp523-529.

[4] Michael, M.D. et al., 2000. Loss of insulin signaling in hepatocytes leads to severe insulin resistance and progressive hepatic dysfunction. *Molecular Cell*, 6, pp87-97.

Figure 3. The Portal Vein and Upper Digestive Organs



Source: University of the Cumberlands[5]

Preclinical Data and Early Human Studies

Work with ORMD-0801 in animals and healthy subjects provided the first clues that oral insulin can impact blood glucose levels. Oramed has expanded on these initial findings and is now conducting a clinical program to establish the safety and efficacy of ORMD-0801 in patients with diabetes.

Glucose Reduction in Pigs. Oramed has tested the impact of ORMD-0801 on blood glucose levels in pigs.[6] Oramed's other diabetes candidate ORMD-0901 and a combination of both candidates was also tested, although here we only highlight the data from ORMD-0801 treatment. Fasting animals were anesthetized with isoflurane and oral capsules of ORMD-0801 were delivered directly to the duodenum via an endoscope. Some animals received denkavit powdered milk (10 g/kg body weight) 30 minutes after delivery of the drug, while others remained in a fasting state.

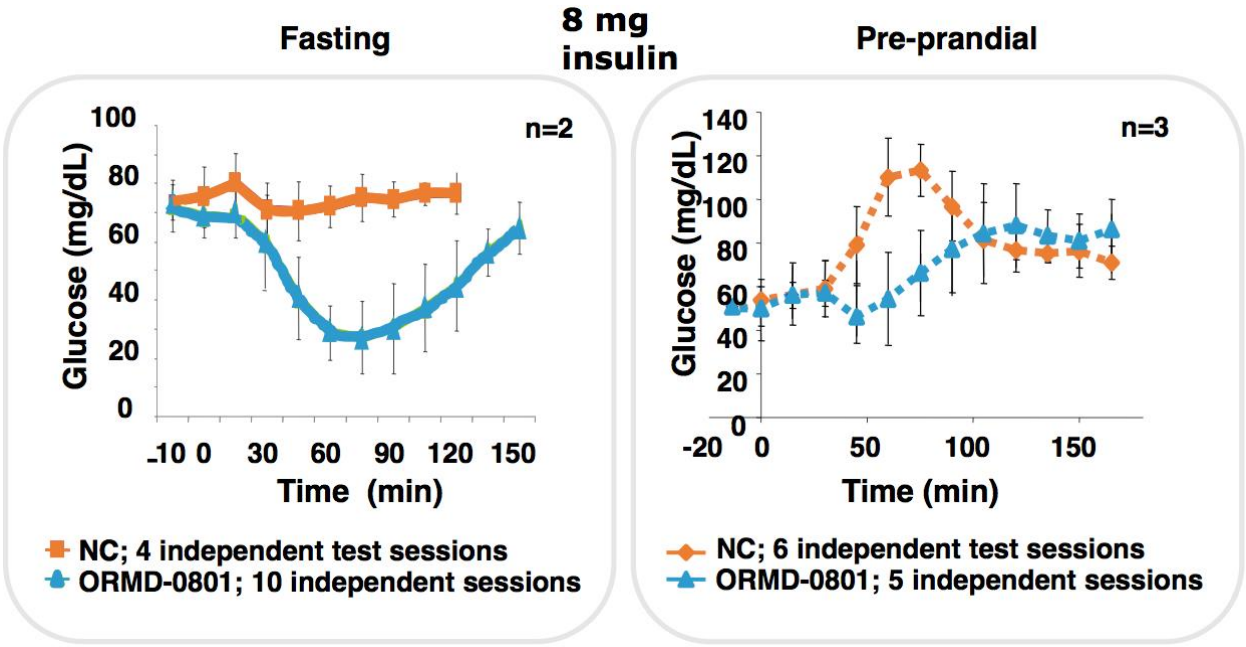
[5] www.ucumberlands.edu/academics/biology/faculty/kuss/courses/CirculatorySystem/IntroductionToCirculatorySystem.htm

[6] Eldor, R. et al., 2012. Concomitant oral insulin and exenatide therapies significantly curb postprandial glucose excursions in pigs. *American Diabetes Association 72nd Annual Scientific Sessions.*

Blood samples were collected from a central line catheter over a 240-minute monitoring period to assess blood glucose levels.

The left pane of **Figure 4** shows the blood glucose response for animals that continued fasting after administration of oral insulin. As shown in the graph, control animals (NC) experienced roughly stead blood glucose, while administration of ORMD-0801 caused a reduction in blood glucose levels with a trough around 75 minutes post-treatment. The right panel shows animals who received milk powder after treatment with oral insulin. For control animals (NC) that received ORMD-0801 before a meal (pre-prandial), there was a spike of blood glucose as expected, which is shown in the right panel of the figure. Administration of ORMD-0801 suppressed the spike in blood glucose. No animals experienced hypoglycemia or adverse events (AEs) from the treatment. These data provide pre-clinical proof of concept that ORMD-0801 impacts blood glucose levels.

Figure 4. ORMD-0801 Affects Blood Glucose Levels in Pigs



Source: Eldor, R. et al., 2012 & Oramed Presentation

Glucose Reduction in Healthy Subjects. Oramed enrolled 10 healthy, fasting, male subjects in a study designed to analyze safety and the impact of ORMD-0801 treatment on blood glucose levels.[7] Subjects received each of the following doses of oral insulin on four separate visits:

[7] Kidron, M. et al., 2013. A dose-response of blood glucose concentrations to orally delivered insulin in healthy subjects. *Diabetes Technology Society Meeting*.

- Single capsule with 8 mg of insulin (8 mg).
- Single capsule with 16 mg of insulin (16 mg).
- Two capsules with 8 mg of insulin each (8 + 8 mg).
- Two capsules, one with 8 mg of insulin and another with 16 mg of insulin (8 + 16 mg).

Blood glucose and c-peptide levels were monitored over a 300-minute period to establish the pharmacodynamic profile. C-peptide is a part of proinsulin and is a surrogate measure of pancreatic insulin secretion. The mean C-peptide and glucose area under the curve (AUC) was calculated for all subjects. AUC is a measure of the total levels of C-peptide or glucose. The baseline AUC was measured 0-40 minutes post-dose and was compared to the AUC of the best response period, defined as the 2-5 point range with each subject's best response.

No AEs were reported during the study, consistent with the preclinical animal data. **Figure 5** displays the AUC data for glucose and c-peptide. All four doses of ORMD-0801 led to a significant reduction in mean glucose AUC compared to baseline AUC of the same dose ($p<0.01$). Subjects experienced a greater response to the largest dose of insulin compared to the lowest dose ($p=0.012$). Overall, 7 of the 10 subjects achieved a greater than 10% decrease in glucose levels from baseline and were therefore considered responders. The mean C-peptide AUC was also significantly lower when compared to baseline for all tested doses ($p<0.003$).

Figure 5. Glucose and c-peptide Levels with Different Doses of Oral Insulin

	Glucose			C-peptide		
Dose of insulin	Baseline AUC (mg/dL)	Best period AUC (mg/dL)	Relative change in AUC (%)	Baseline AUC (mg/dL)	Best period AUC (mg/dL)	Relative change in AUC (%)
8 mg	84.4	76.6	-9.6	84.8	2.1	-18.1
16 mg	80.6	67.8	-15.7	76.6	1.8	-18.2
8 + 8 mg	81.2	69.7	-13.9	81.2	1.9	-18.3
8 + 16 mg	79.6	65.3	-17.6	78.4	1.8	-18.0

Source: Kidron, M. et al., 2013

The reduction in mean glucose levels in this study is evidence supporting the idea that oral insulin is being absorbed by the small intestine and impacting circulating glucose levels. The drop in C-peptide levels suggests that less pancreatic secretion of insulin is necessary due to the delivery of insulin via ORMD-0801. This human study and the animal data support Oramed's ongoing clinical trial program.

Diabetes

Diabetes is a chronic metabolic disease resulting in unregulated and persistently high blood sugar. Under normal physiological conditions, beta cells in the pancreas produce insulin to regulate blood sugar levels, keeping the levels from becoming toxic to the body. In the presence of elevated blood sugar levels insulin is released, causing the sugar to be taken up and stored by the liver, fat tissue, and muscles in the form of glycogen and triglycerides. This activity restores blood sugar to normal levels. When blood sugar levels are too low, glucagon is released by the alpha cells of the pancreas causing the breakdown of glycogen in the liver and muscles through glycogenolysis, releasing glucose into the blood and restoring blood sugar to normal levels. High blood sugar can lead to serious complications including heart disease, eye complications, kidney disease, neuropathy, ulceration, gum disease, and infection of the feet, skin, and teeth.

Diabetes is separated into two major types. Type 1 diabetes (T1D) results from the body making little to no insulin to properly regulate high blood sugar levels. This type makes up approximately 10% of diabetes, is most prevalent in children and young adults, and is treated predominately by insulin injections and pumps. Type 2 diabetes (T2D) results from improper response of the body to insulin, either by the under-production of insulin or inadequate use of insulin, both of which result in unregulated, high blood sugar levels. T2D is most prevalent in overweight adults with a genetic predisposition to the disease, and is treated initially by healthy eating and exercise. As patients progress they are treated with metformin and related drugs, and eventually with insulin injections and further pharmacological interventions when early interventions are not sufficient.

Type 1 Pathophysiology. T1D is caused by an autoimmune reaction that leads to destruction of pancreatic beta cells. Destruction of beta cells causes an absolute insulin deficiency and may be triggered by an environmental event such as a viral infection. Genetically determined susceptibility factors also increase the risk of this autoimmune phenomenon.

While T1D can be diagnosed at any age, patients often begin experiencing symptoms in childhood. The disease was historically called juvenile diabetes due to the earlier onset versus type 2, but the increasing prevalence of T2D in younger patients has led to a change in nomenclature. T1D patients are highly susceptible to diabetic ketoacidosis, which causes symptoms ranging from dehydration, nausea, and vomiting due to rapid weight loss and sometimes altered states of consciousness. Ketoacidosis is the result of the body trying to find alternative sources of sugar since it is not properly stored in the muscles and liver as in health people. Fat is broken down through lipolysis, which releases free fatty acids and glycerol, which is in turn converted to glucose for cellular use. The fatty acids are enzymatically reduced to ketones, resulting in increased ketone levels in bodily fluids and a decrease in pH. These combined effects lead to electrolyte loss and dehydration from excessive urination. Left untreated, diabetic ketoacidosis can be fatal.

Type 2 Pathophysiology. The pathophysiology of T2D is distinct from that of type 1 in that the patient's pancreas still produces insulin. Rather, T2D is characterized by insulin resistance, high blood glucose resulting from increased production of glucose in the liver, and deficient insulin secretion. As tissues become resistant to insulin, blood glucose levels rise, a condition known as hyperglycemia. This, in turn, stimulates an increase in insulin production by the pancreas. Initially type 2 diabetics produce excessive insulin, which results in hyperinsulinemia, a condition that is an early indicator for the disease and is associated with hypertension, obesity, and dyslipidemia. Eventually, pancreatic insulin production usually decreases below normal, leaving the patient with hyperglycemia and the need for exogenous insulin.

Diagnostic Guidelines for Diabetes

Type 1 Diagnosis. Popular tests involved in diagnosing T1D can be seen in **Figure 6**. A positive diagnosis requires abnormal test results on two separate days, although the second abnormal result can be from a different test. Other tests for T1D include glutamic acid decarboxylase antibody (GADA) and islet cell antibody (ICA) for younger patients and older adults who are not overweight and are not responding to hypoglycemic and lifestyle modification. Over 90% of patients who have T1D will be positive for at least one of these antibodies.

Figure 6. Recommendations for Diagnosing Type 1 Diabetes

Test	Results	Interpretation
HbA1c	≥6.5% or higher on 2 separate days	Diabetes
	<5.7%	Normal
Random plasma glucose	≥200 mg/dL on 2 separate days	Diabetes
	<140 mg/dL	Normal
Fasting plasma glucose	≥126 mg/dL on 2 separate days	Diabetes
	<100 mg/dL	Normal

Source: LifeSci Advisors

Type 2 Diagnosis. Popular tests involved in diagnosing T2D are outlined in **Figure 7**. As with T1D, a positive diagnosis requires abnormal test results on 2 separate days and can be from different tests. Impaired glucose tolerance (IGT) is similar to impaired fasting glucose (IFG) but is diagnosed with a confirmed oral glucose tolerance test (OGTT). Both IGT and IFG are risk factors for future diabetes and for cardiovascular disease.

Figure 7. Recommendations for Diagnosing Type 2 Diabetes

Test	Results	Interpretation
HbA1c	≥6.5% on 2 separate days 5.7–6.4% <5.7%	Diabetes IGT Normal
Random plasma glucose	≥200 mg/dL on 2 separate days 140–199 mg/dL <140 mg/dL	Diabetes IGT Normal
Fasting plasma glucose	≥126 mg/dL on 2 separate days 100–125 mg/dL on 2 separate days <100 mg/dL	Diabetes IGT Normal

Source: LifeSci Advisors

Therapeutic Intervention for Diabetes

Diabetes care is a complex disease to treat and requires multiple risk reduction strategies. A large body of evidence exists that supports a range of therapeutic and lifestyle interventions to improve diabetes outcomes based on the patients' diabetes type and personal circumstances.

Pharmacological Treatment Recommendations. According to the 2013 guidelines published by the American Diabetes Association (ADA), recommended therapy for T1D consists of the following:

- Multiple daily insulin injections – 3 to 4 injections per day of basal and prandial insulin – or continuous subcutaneous insulin infusion (CSII) therapy.
- Matching of prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity.
- Use of insulin analogs, especially if hypoglycemia is a problem.

Recommendations from the ADA for therapeutic treatment of T2D include the following:

- Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for T2D.
- If non-insulin monotherapy at maximal tolerated dose fails to achieve or maintain the A1C target over 3–6 months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin therapy.

- As the disease progresses, insulin therapy is eventually indicated for many patients with T2D.

In addition, the ADA recommends that newly diagnosed T2D patients who experience severe symptoms or highly elevated blood glucose levels or A1C should consider initial insulin therapy in addition to any other agents. Diabetes is a very individualized disease, so an individualized approach is necessary to make the best choice of therapeutic interventions.[8]

Metformin. Metformin is used as an adjunct to diet and exercise to improve glycemic control in adults and children with T2D. The drug decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity. There is generally little risk of developing hypoglycemia with the drug, and insulin secretion remains unchanged with therapy. Metformin is associated with extremely rare cases of lactic acidosis, prompting a boxed warning on the label, although the drug is generally safe and well tolerated. Sales of GlaxoSmithKline's *Glucophage* (metformin) have fallen from their peak of $2.1 billion in 2001 due to a patent expiration in the following year. However, the drug is still a mainstay of treatment for early-stage diabetics, and is commonly used in combination with other drugs. In fact, there are several approved drugs that incorporate metformin directly into their formulation to reduce pill burden. Oramed has examined ORMD-0801 in conjunction with metformin in a Phase II trial, and the combination of the two therapies may offer patients more stable control of FBG levels.

Glucophage is available in a standard formulation and as an extended release called *Glucagon XR*. Both versions have been shown to improve FBG levels, glycated hemoglobin (HbA_{1c}) levels, and insulin use. In a double blind, placebo-controlled study, *Glucophage* was compared to placebo in patients with T2D whose hyperglycemia was not adequately controlled with diet alone. After 29 weeks of treatment with up to 2,550 mg of *Glucophage* per day, FBG levels decreased significantly, which is shown in **Figure 8** ($p=0.001$). Baseline FBG decreased by 53 mg/dL with *Glucophage* treatment compared to baseline, whereas patients receiving placebo experienced an increase of 6.3 mg/dL. Similarly, HbA_{1c} also decreased in the *Glucophage* arm compared to baseline, and levels remained largely unchanged in the placebo arm ($p=0.001$).

[8] American Diabetes Association, 2013. Standards of Medical Care in Diabetes – 2013. Diabetes Care, 36(S1), ppS11-S66.

Figure 8. Change in Fasting Blood Glucose and Glycated Hemoglobin with *Glucophage* Treatment

	Glucophage (N=141)	Placebo (N=145)
Baseline fasting blood glucose (mg/dL)	241.5	237.7
change at final visit (29 weeks)	-53.0	6.3
Baseline glycated hemoglobin (%)	8.4	8.2
change at final visit (29 weeks)	-1.4	0.4

Source: Glucophage Prescribing Information

Through its impact on key pathologies of early-stage diabetes, metformin can actually delay progression to a clinical diagnosis of diabetes that requires insulin replacement. One randomized study of 3,234 individuals with elevated fasting and post-meal glucose levels examined the incidence of diabetes following treatment with placebo, 850 mg of twice daily metformin, or lifestyle modification.[9] After an average of 2.8 years, the incidence of diabetes in patients receiving metformin was 31% lower than for those treated with placebo.

Currently Available Insulin Delivery Methods

Effective insulin delivery for diabetic patients is a critical component of therapy, and there have been decades of research and numerous technological advances dedicated to novel insulin delivery products.[10,11] Although insulin delivery has become more convenient and less painful, the current paradigm of subcutaneous administration still dominates. Oramed is attempting to revolutionize the delivery of insulin by developing an oral product that may eventually eliminate the use of needles and deliver insulin more naturally via the portal vein of the liver. These features may positively impact glucose metabolism and enhance the benefits of insulin delivery.

Syringes. In 1922, insulin was administered to the first ever patient as an injection into the muscle tissue of the buttocks. Intramuscular delivery was short-lived, mostly due the considerable pain and discomfort of twice daily injections of 5 to 18 milliliters of liquid. Subcutaneous injections were found to equally stabilize blood glucose levels, and this is the primary route of delivery today. Syringes are the main tool for subcutaneous administration due to their low cost and the flexibility to mix different types of insulin, such as slow acting and fast acting versions for use while fasting and around meal times, respectively. The major drawbacks of syringes are pain and the

[9] Knowler, W.C. et al., 2002. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*, 346(6), pp393-403.

[10] Fry, A. et al., 2012. Insulin delivery device technology 2012: Where are we after 90 years? *Journal of Diabetes Science and Technology*, 6(4), pp947-953.

[11] Nitesh, S.C. et al., 2010. Recent advances in insulin delivery systems: An update. *World Applied Sciences Journal*, 11(22), pp1552-1556.

inconvenience of carrying, handling, and disposing of hazardous materials. The use of thinner needles has helped with the pain issue, and smaller prefilled syringes can make the process more convenient for patients.

Insulin Pens. Insulin pens constituted a major advance for patient convenience. Novo Nordisk A/S (NVO) introduced the first insulin pen in 1985 and, along with Eli Lilly (LLY), is still a leader in insulin delivery. Insulin pens allow users to deliver varying amounts of insulin via a dial function, and patients can track their daily use. The devices are designed to improve patient convenience and many new pens are fully disposable with automated needle replacement. The majority of diabetes patients in developed countries, except the US, have switched to insulin pens for obvious reasons. Patients find the pens easy to use and they are less likely to miss injections than with syringes.[12] Insulin pens also increase overall positive attitudes towards insulin therapy. However, traction in the US has been slow due to the higher costs of pens and lack of coverage by insurance companies.

Needle Free Injectors. Needle free (NF) injectors have been around since the 1950s for patients that are averse to needles. The loading of the devices is somewhat complex and requires additional equipment, keeping NF injectors from becoming as compact as insulin pens. Also, while NF injectors eliminate needle pain and any phobia associated with needles, they introduce a different type of pain and sometimes bruising, which can be offset the benefits. Cost is also a problem and reimbursement is sparse. These issues have limited NF injectors to a minority of diabetes patients.

Insulin Pumps. For patients that need insulin on a more frequent schedule, especially T1D patients, insulin pumps are a useful option. The pumps deliver insulin at low doses throughout the day with the option for larger boluses on-demand. Similar to insulin pens and NF injectors, the cost is sometimes prohibitive. These devices must also be worn continuously, which is burdensome for some patients.

Inhalation. A great deal of attention has recently been focused on developing a viable inhaled insulin product, especially on MannKind's (MNKD) development program. Pfizer (PFE) was the first successful company to receive FDA approval for inhaled insulin in 2006, and for one year unsuccessfully marketed *Exubera*. The device was bulky and inconvenient, and could not compete in the face of smaller insulin pens, despite their lingering needle pain issues. The inhalation route also limited patients to fast-acting insulin, and injections were necessary for longer-lasting versions. The withdrawal of *Exubera* led other companies to abandon their own inhaled insulin programs.

The most prominent ongoing inhalable insulin program is MannKind's *Afrezza*, which delivers a dry powder form of insulin directly to the lungs. In January 2011 MannKind received its second complete response letter (CRL) from the FDA delaying an approval decision for *Afrezza*. In their response, the FDA called for two additional Phase III trials, one each in T1D and T2D. The primary

[12] Graff, M.R. and McClanahan, M.A., 1998. Assessment by patients with diabetes mellitus of two insulin pen delivery systems versus a vial and syringe. *Clinical Therapeutics*, 20(3), pp486-496.

reason for the CRL and request for new trials was to further test and validate the safety and usability of the inhalation device itself, which had undergone a series of revisions. The company completed the required trials and in August 2013 reported favorable results, indicating that the treatment led to reduction in A1c levels, improvement of blood sugar management, and helped patients lose weight. The FDA has scheduled an advisory panel meeting for April 1, 2014, to discuss MannKind's current marketing application. An approval decision is expected to be made on or before April 15, 2014.

Need for Additional Therapies for Glycemic Control

Despite the positive features of metformin and other diabetes therapies, the majority of patients are unable to achieve glycemic control after many years on treatment. A large randomized study examined the ability of 4 different interventions to maintain glycemic control in patients with T2D.[13] A total of 4,075 patients were enrolled from 1977 to 1991 in 15 UK hospitals and randomized to diet alone, insulin, sulfonylurea, or metformin. FBG and HbA_{1c} levels were measured every 3 months for 3, 6, or 9 years. The dose of each medication was adjusted for each patient based on FBG values. **Figure 9** shows the percentage of patients who achieved FBG below 7.8 mmol/L or HbA_{1c} below 7%. The percentage of patients achieving each glycemic goal decreased over the 9-year follow up period. Only 13% and 18% of patients receiving metformin maintained HbA_{1c} and FBG, respectively. Insulin was the most effective intervention for both normal weight and overweight patients.

[13] Turner, R.C. et al., 1999. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with Type 2 diabetes mellitus. *The Journal of the American Medical Association*, 281(21), pp2005-2012.

Figure 9. Percentage of Subjects Achieving Glycemic Control Goals

Therapy	Hemoglobin A_{1c} <7.0%			Fasting Plasma Glucose <7.8 mmol/L		
	3 Years	6 Years	9 Years	3 Years	6 Years	9 Years
Normal weight and overweight patients						
Diet	25 (24-27)	12 (11-13)	9 (8-10)	19 (18-20)	11 (10-12)	8 (7-9)
Insulin	47 (46-49)	37 (35-38)	28 (26-29)	52 (50-54)	48 (46-50)	42 (40-44)
Chlorpropamide	53 (52-55)	39 (37-41)	28 (27-30)	51 (49-52)	39 (37-40)	28 (26-29)
Glyburide	47 (45-48)	29 (28-31)	20 (18-21)	41 (39-42)	27 (25-28)	20 (19-22)
Sulfonylurea	50 (48-52)	34 (33-36)	24 (22-26)	46 (44-47)	33 (31-34)	24 (23-26)
Overweight patients						
Diet	23 (21-25)	12 (10-13)	11 (10-13)	18 (16-20)	9 (8-11)	10 (9-12)
Insulin	34 (32-36)	37 (34-39)	24 (22-27)	44 (41-46)	41 (39-43)	38 (34-39)
Chlorpropamide	51 (49-53)	33 (31-35)	20 (18-22)	47 (45-50)	33 (31-36)	19 (17-21)
Glyburide	40 (38-42)	23 (21-25)	22 (20-25)	34 (32-37)	18 (17-20)	23 (21-26)
Sulfonylurea	45 (43-48)	28 (26-30)	21 (19-23)	41 (38-43)	26 (24-28)	21 (19-23)
Metformin	44 (42-46)	34 (32-37)	13 (11-15)	39 (36-41)	31 (29-33)	18 (16-20)

*Values are proportions (95% confidence intervals) expressed as percentages. To convert fasting plasma glucose to milligrams per deciliter, multiply by 18.

Source: Turner, R.C. et al., 1999.

This study suggests that many patients need additional therapies to help manage FBG levels over the long-term. ORMD-0801 is being developed specifically for this purpose, and could be indicated for patients prior to the full development of diabetes.

Disease Market Information

Diabetes affects approximately 347 million people worldwide,[14] including 19 million in the US who are diagnosed, and another 7 million undiagnosed.[15] The prevalence of diabetes is projected to increase at a rapid pace in the coming decades, reaching 366 million by 2030.[16] In 2010 it was estimated that 1.9 million new cases of diabetes were diagnosed in people aged 20 years and older in the US. Emerging markets represent a large share of the global diabetes population with India and China having the largest diabetic populations globally.

[14] Danaei, G. et al., 2011. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet*, 378(9785), pp31-40.

[15] American Diabetes Association. *2011 National Diabetes Fact Sheet*, Released January 26, 2011.

[16] Wild, S. et al., 2004. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care, 27(5), pp1047-1053.

According to a 2007 report issues by the American Diabetes Association, diabetes caused 71,382 deaths and was as a contributing factor to an additional 160,022 deaths that year. The total cost of diagnosed diabetes was $174 billion, which includes $116 billion for direct medical costs and $58 billion for indirect costs. Factoring in the additional costs of undiagnosed diabetes, pre-diabetes, and gestational diabetes brings the total cost of diabetes in the US in 2007 to a staggering $218 billion.

The global diabetes therapeutics market in 2010 was worth $32.7 billion and was led by insulin analogs, which captured 53% of the market. Thiazolidinediones are the next largest group of diabetes medications, making up approximately 17% of the market. The global diabetes market is expected to grow to approximately $39 billion by 2019, led by insulin products.

Non-Insulin Market. It is important to note that Oramed intends to develop ORMD-0801 to regulate fasting blood glucose (FBG) levels, not necessarily as a substitute for insulin replacement therapies. For example, ORMD-0801 would fill a role for type 2 diabetes patients after or in conjunction with anti-diabetic therapies such as metformin or thiazolidinediones, and before insulin replacement therapy. The market for treatments used alongside diet and exercise, such as metformin, has decreased due to several key patent expirations. However, some of these drugs achieved blockbuster status at the peak of their use.

The peak sales for three important diabetes products are shown in **Figure 10**, illustrating how large the market can be for treatments that target patients before insulin replacement. Metformin was sold as *Glucophage* by Bristol-Myers Squibb (BMY) and achieved peak sales of $2.1 billion in 2001 before its patents expired. The two thiazolidinediones *Actos* (pioglitazone) and *Avandia* (rosiglitazone) had peak sales of $3.8 and $2.3 billion, respectively. These sales numbers are driven by the large and growing incidence of diabetes, and a desire by patients to slow the progression of their disease. ORMD-0801 could provide a new way to control fasting blood glucose in these early stage diabetic patients.

Figure 10. Peak Sales of Select Non-Insulin Diabetes Treatments

Treatment Class	Brand Name	Peak Sales	Year of Peak Sales
Metformin	*Glucophage*	$2.1B	2001
Thiazolidinediones	*Actos*	$3.8B	2010
	Avandia	$2.3B	2006

Source: Company Reports

Insulin Market. The global insulin market is valued at approximately $19 billion based on the 2013 sales of top insulin products, and had a compound annual growth rate of 14.3% from 2006 to 2011. This includes fast acting, ultra-fast acting, and combination products. Examples of leading products currently on the market, with their respective insulin type and annual revenues, are shown in **Figure 11**. Sales of *Lantus* are expected to exceed $7 billion in 2013, and 5 other insulin products have achieved blockbuster status. The market will experience some interesting dynamics in the near future since *Humalog* is already off patent and *Lantus* will lose patent protection in 2015.

Figure 11. Worldwide Sales of Insulin Products (millions)

Product Name	Company	Insulin Type	2011	2012	2013
Lantus	Sanofi	Long-Lasting Analog	$5,387	$6,823	$3,780*
NovoRapid/NovoLog	Novo Nordisk	Fast-Acting Analog	$2,360	$2,893	$3,106
Humalog	Eli Lilly	Fast-Acting Analog	$2,368	$2,396	$2,611
Levemir	Novo Nordisk	Long-Lasting Analog	$1,416	$1,804	$2,129
NovoMix/NovoLog Mix	Novo Nordisk	Premix	$1,526	$1,722	$1,799
Humulin	Eli Lilly	Human	$1,249	$1,239	$1,316
Apidra	Sanofi	Fast-Acting Analog	$260	$316	$182*
Insuman	Sanofi	Human	$182	$186	$89*

*sales for first half of 2013

Source: LifeSci Advisors, Company Reports

With the growth of obesity in the Western and Eastern worlds, the market for diabetes care is expected to continue growing. Oramed is well positioned to deliver a more convenient product for these patients to manage the early symptoms of diabetes.

Clinical Data Discussion

Oramed has completed several clinical trials with ORMD-0801 in healthy subjects and patients with diabetes. To date, Oramed has administered 1,632 doses of ORMD-0801 to 153 study subjects. The

data gathered from these subjects has allowed the Company to make improvements to ORMD-0801 and start the path towards a regulatory filing with the FDA. A US Phase IIa trial was recently completed that demonstrated a positive safety profile, and Oramed is planning to announce the trial results at the upcoming GTC Diabetes Summit on April 23-25th. Two key Phase II trials are planned for 2014, including a Phase IIa trial in T1D that began enrolling patients in March 2014, and a Phase IIb in T2D patients is expected to begin by the end of the year.

Phase IIa Trial with 8 Patients with Type 1 Diabetes

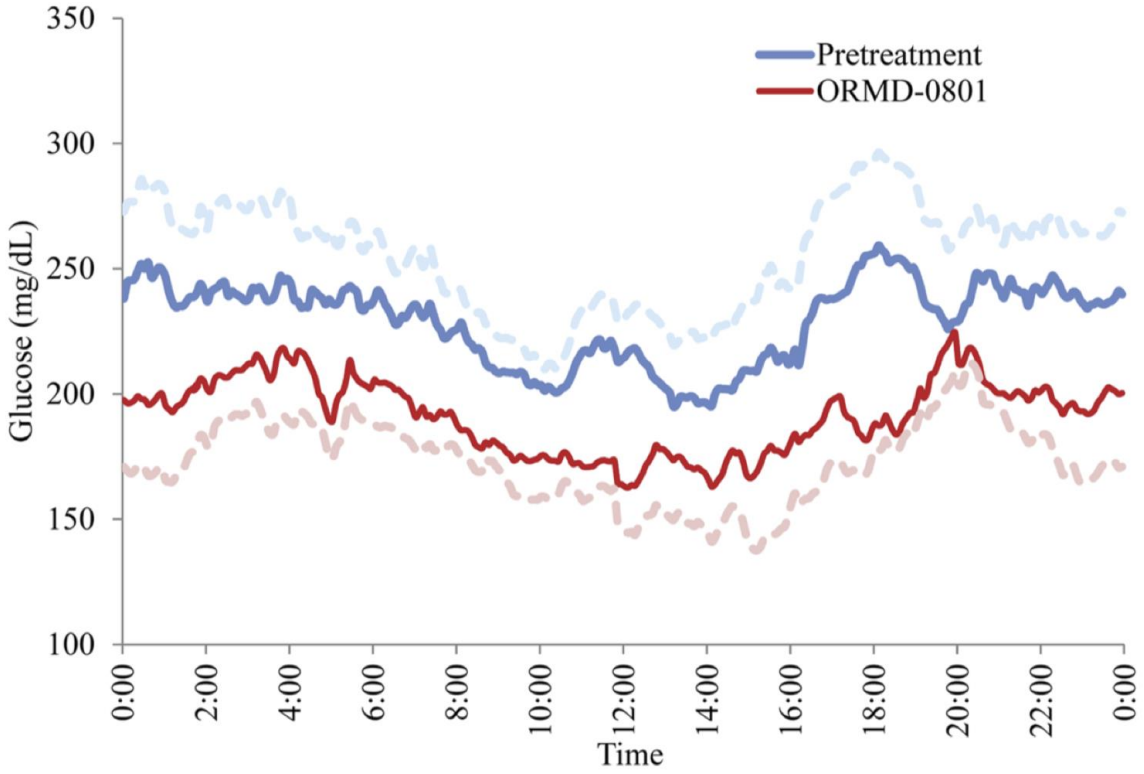
Oramed conducted a Phase IIa study with ORMD-0801 in patients with uncontrolled T1D alongside their daily insulin regime.[17] The trial was an open-label study that enrolled 8 patients with T1D. A continuous glucose monitoring device was used during the 15-day study period and patients were blinded to the readings. Baseline glucose behavior was assessed over 5 days followed by a 10 day treatment phase, where patients were asked to proceed with their normal food consumption and daily diabetes routine. ORMD-0801 was self-administered three times daily, 45 minutes prior to meals.

Results. Overall the treatment was found to be safe and well tolerated. No adverse events (AEs) or hypoglycemic attacks were reported during the study, and all liver function tests were positive. There was a slight increase in the number of glucose readings below 70 mg/dL in the treatment phase versus pretreatment.

Treatment with ORMD-0801 resulted in a significant decrease in mean glucose area under the curve (AUC), a measure of the total glucose levels over the treatment period (p=0.023). The greatest reduction in AUC occurred between 5-7pm as displayed in **Figure 12**. The blue lines are the mean glucose levels in six patients during the pretreatment phase, while the red lines are mean glucose readings in the same six patients treated with ORMD-0801. The dotted lines represent the corresponding standard errors.

[17] Eldor, R. et al., 2013. Glucose-reducing effect of the ORMD-0801 oral insulin preparation in patients with uncontrolled Type 1 diabetes: A pilot study. *PLOS One*, 8(4), e59524.

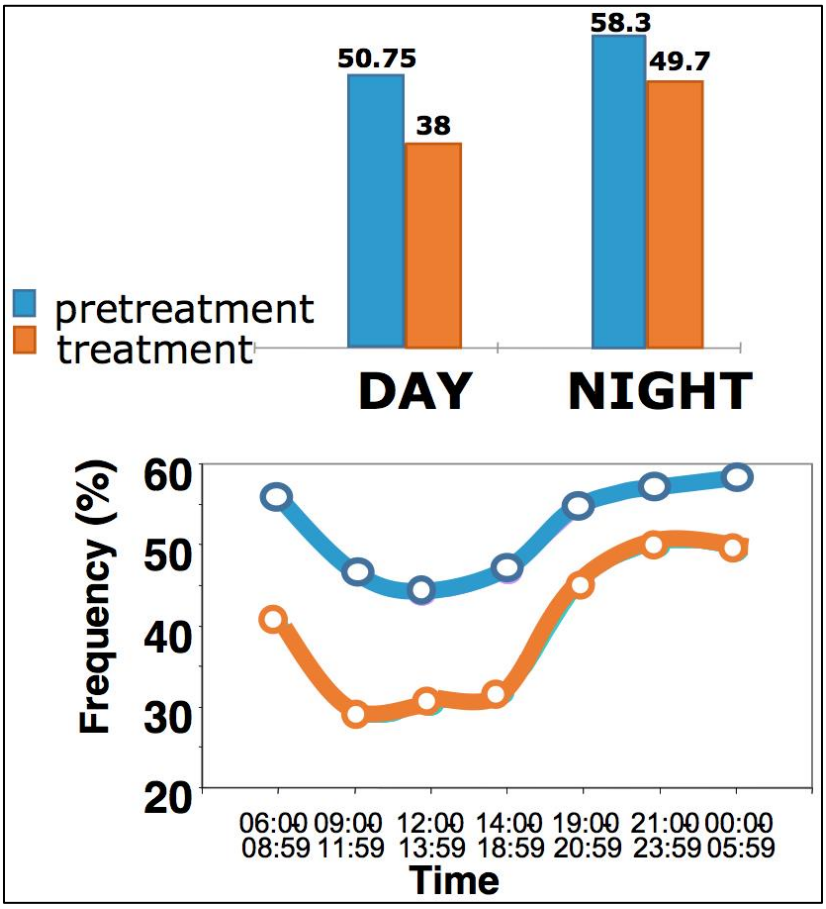
Figure 12. Glucose Levels Pretreatment and with ORMD-0801



Source: Eldor, R. et al., 2013

A diagnosis of type 1 diabetes can be made if blood glucose exceeds 200 mg/dL on two separate occasions at any time of the day. Treatment with ORMD-0801 resulted in a significant reduction in the number of patients with blood glucose levels greater than 200 mg/dL. The top panel of **Figure 13** shows the frequency of blood glucose readings above 200 mg/dL either pretreatment or with ORMD-0801. There were fewer readings that exceeded the threshold during the day than at night. The bottom panel of the figure displays similar information but at more intervals, and highlights the clear separation between pretreatment and ORMD-0801.

Figure 13. Frequency of Glucose Readings Above 200 mg/dL



Source: Oramed Presentation and Eldor, et al., 2012[18]

Overall this trial indicates that a combination of subcutaneous and oral insulin is safe and well tolerated in patients with uncontrolled T1D. The glucose profiles suggest that ORMD-0801 can stabilize blood glucose, and support further development of ORMD-0801 in the T1D population.

Phase IIb Trial with 29 Type 2 Diabetes Patients

Oramed conducted a Phase IIb trial in South Africa to evaluate the safety, tolerability, and efficacy of ORMD-0801 in patients with T2D. The trial was a multi-center, randomized, double-blind, placebo-controlled study that enrolled 29 subjects with T2D. Twenty-one subjects received 16 mg of oral ORMD-0801 each night at bedtime for a total of 6 weeks, and the remaining 8 subjects received placebo on the same schedule. Three subjects were on dietary management programs and the remaining 26 subjects were on dietary management programs and metformin (2.5 grams/day) prior

[18] Eldor, R. et al., 2012. Concomitant oral and subcutaneous insulin therapy toward stabilization of uncontrolled Type 1 Diabetes Mellitus (T1DM). *Diabetes Technology Meeting.*

to joining the study. Blood samples were collected in fasting subjects at the start and end of the study to monitor several diabetes-related metrics. The study objectives were safety, tolerability, and efficacy of ORMD-0801 compared to placebo at the end of the 6-week treatment period.

Results – Safety and Tolerability. ORMD0801 was found to be safe and tolerable, as no serious adverse events were reported during the 6-week treatment period. This was the first trial to test ORMD-0801 over an extended period of time, and no cumulative AEs were noted. **Figure 14** shows the AEs reported in patient diaries. Only two reports of hypoglycemia surfaced, and each case was mild. Other AEs were such as diarrhea resolved without an adjustment to the dose. No AEs were reported in the placebo group.[19]

Figure 14. Adverse Events Reported by Patients

AE	Severity	Action	Outcome	Notes
Hypoglycemia	Mild	Dose not changed	Recovered	Blood sugar – 12.0 mmol/L
Hypoglycemia	Unknown	Unknown	Unknown	Hypoglycemic on clinical symptoms
Constipation	Mild	Dose not changed	Not recovered	-
Diarrhea and skin rash	Mild	Dose not changed	Recovered	-
Diarrhea	Mild	Dose not changed	Recovered	-
Increased bowel movement	Mild	Not applicable	Recovered	-

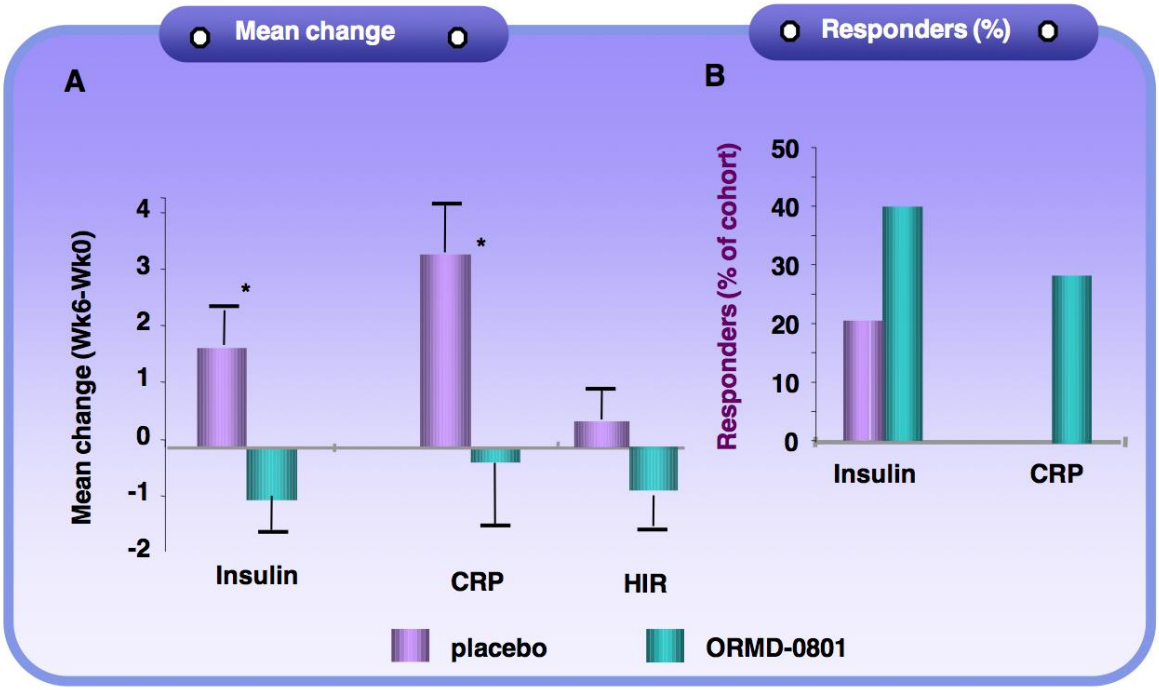
Source: Kidron, M. et al., 2010

Results – Insulin and CRP Levels. Several blood biomarkers were measured in patients at the beginning of the study and after 6 weeks of treatment. Blood samples were collected in the morning prior to a meal to assess fasting levels. The levels of insulin, C-reactive protein (CRP) were especially important to determine how well ORMD-0801 could attenuate insulin over-secretion and inflammation associated with diabetes. CRP is a marker of inflammation that is typically elevated in patients with diabetes. As shown in **Figure 15**, treatment with ORMD-0801 led to significantly lower levels of insulin and CRP versus placebo. ORMD-0801 treated patients experienced a decrease in mean insulin of -0.82 mU/L at the end of the 6-week study period compared to an increase of 1.58 mU/L for the placebo group (p=0.031). Furthermore, 40% of patients receiving ORMD-0801 were considered responders compared to only 20% for placebo patients. Responders were defined

[19] Kidron, M. et al., 2010. Extended exposure to an oral insulin formulation yields decreased insulin secretion in Type II diabetes subjects. *Annual Diabetes Technology Meeting.*

as patients with a 10% or more decrease in the level of the particular marker. Regarding CRP, the mean level of CRP decreased by -0.22 mg/L in patients receiving ORMD-0801 compared to a mean rise of 3.05 mg/L in the placebo-treated group (p=0.042). No patients in the placebo group were considered responders versus 25% of patients receiving ORMD-0801.[20]

Figure 15. Impact of ORMD-0801 on Insulin, CRP, and Insulin Resistance



Source: Eldor, R. et al., 2013

Patients in this trial were also analyzed using the homeostatic model assessment (HOMA) index, a measure of insulin resistance calculated using fasting glucose and insulin levels, which is shown as HIR on **Figure 15**. The data show a trend towards less insulin resistance in the ORMD-0801 arm versus placebo (p=0.07).

This Phase IIb trial demonstrated that ORMD-0801 appears safe and well tolerated in T2D patients, with little risk of hypoglycemia after administration just before sleep. The data also suggest that ORMD-0801 may impact disease in patients by reducing insulin over-secretion and CRP levels. An additional Phase IIb trial is expected to launch in 2014 and will support Oramed's efforts in the US to develop ORMD-0801 for T2D patients.

[20] Eldor, R. et al., 2013. Decreased CRP levels in response to a six-week, once-daily oral insulin regimen. *81st European Atherosclerosis Society Congress*.

Phase IIa Trial with 30 Patients with Type 2 Diabetes

Oramed conducted a Phase IIa trial in the US that was recommended by the FDA prior to a planned Phase IIb study. The trial was a randomized, double-blind, placebo-controlled study that enrolled 30 patients with T2D that is inadequately controlled with diet and exercise or diet, exercise, and metformin. Patients were randomized to receive one of two doses of ORMD-0801 (460 or 690 IU) or placebo for 7 days following a 5-day, single-blind, outpatient, run-in period with placebo. The primary endpoint was safety and tolerability as determined by the number of AEs. Secondary endpoints included pharmacokinetics, pharmacodynamics, change in FBG, change in fasting c-peptide, and change in fasting insulin compared to placebo.

Results – Safety. In January 2014, Oramed announced positive topline results from the Phase IIa trial, reporting that all primary and secondary endpoints were met. No serious AEs were reported, suggesting that ORMD-0801 is a safe and tolerable candidate for diabetes treatment. **Figure 16** shows the AE profile for all three study arms, which shows a balanced number of AEs across all arms.

Figure 16. Adverse Event Profile

	Placebo N=10	ORMD-0801 460 IU N=10	ORMD-0801 690 IU N=10
Subjects with at least 1 AE	5 (50%)	3 (30%)	4 (40%)
Vertigo	1 (10%)	0	0
Constipation	0	0	2 (20%)
Nausea	1 (10%)	1 (10%)	0
Urinary tract infection	1 (10%)	0	0
Headache	2 (20%)	3 (30%)	2 (20%)
Pruritus	1 (10%)	0	0

Source: Company

Oramed will report the results of this trial at the 2014 GTC Diabetes Summit scheduled for April 23-25. The Company announced previously that the trial met all secondary endpoints, a positive result for the upcoming Phase IIa and Phase IIb trial expected to launch in 2014.

Future Trials

Oramed is expected to launch two Phase II trials in 2014 to further examine ORMD-0801 in patients with diabetes. Both trials will be conducted in the US to support a future regulatory filing with the FDA both diabetes indications. The first is a randomized, double-blind, placebo-controlled

study enrolling 24 patients with T1D who will be treated for 7 days. The trial will begin enrolling patients in March.

Oramed's second upcoming trial is a multi-center Phase IIb study that will be conducted in the US. The required Phase IIa trial is now complete and Oramed can move forward with Phase IIb. The full trial details are not yet available, although we expect Oramed to enroll approximately 150 patients. We also expect the primary objective of the trial will be to establish a clear signal of efficacy with ORMD-0801 in terms of blood glucose response in order to move into registration trials. The trial is expected to begin by the end of 2014.

Other Drugs in Development

The development of oral insulin continues to attract serious attention as subcutaneous insulin products continue to reach blockbuster status. Novo Nordisk, a leader in diabetes management, recently announced plans to invest up to $3.7 billion to develop an oral insulin product. Smaller companies also have entered the race for the first oral insulin, although no company has a clinical program more advanced than Oramed.

IN-105 – Biocon. India's Biocon is developing IN-105 as an oral, prandial insulin product. IN-105 has been tested in several Phase I and Phase II trials and has demonstrated the potential to decrease blood glucose levels. However, Biocon announced in 2011 that a Phase III trial with IN-105 did not meet the primary endpoint, stalling further development. The trial was a double-blind, multi-center, placebo-controlled trial enrolling 264 patients with T2D. Background use of metformin was allowed. The primary endpoint was a 0.7% decrease in glycated hemoglobin (HbA1c) levels for patients receiving IN-105 versus placebo. HbA1c is a surrogate measure of blood glucose. There was no significant difference in HbA1c between the IN-105 and placebo. The trial did meet several secondary endpoints that found IN-105 to be safe and able to reduce post-prandial glucose levels compared to placebo.

The IN-105 program was revived at the end of 2012 when Biocon announced that Bristol-Myers Squibb (BMY) signed an option agreement for the right to obtain an exclusive worldwide license to the program. Biocon will conduct additional clinical trials up to the completion of Phase II studies. BMY will assume full development responsibilities beyond Phase II if the company exercises its option. Biocon would then receive a license fee, potential regulatory and commercial milestones, and potential royalties on sales outside of India. Biocon would retain all rights to IN-105 in India. This program is being developed to replace injectable insulin, and would not necessarily compete directly with ORMD-0801. The progress has also been stalled and we believe that Oramed's ORMD-0801 is at a more advanced level of development.

Capsulin – Diabetology. Diabetology is developing an oral version of the fast-acting insulin, insulin aspart. The insulin is mixed with a stabilizer and absorption enhancer in an enteric coated capsule to protect it from the digestive system. Diabetology has completed several early clinical trials in healthy subjects and patients with T1D. The most recent trial was a Phase IIa randomized, open-label, crossover study in 16 patients with T2D.[21] Two 6-hour isoglycemic clamp studies were conducted 11 days apart. Glucose clamps are performed to maintain a glucose infusion rate that equals the glucose uptake rate, which is a common technique for analyzing PK or PD. Patients received in random order 12 U of subcutaneous *Actrapid* on one study day and either 150 U or 300 U of capsulin on the other day. During the time between isoglycemic clamp studies, patients received 150 U of capsulin twice daily.

The amount of glucose required to keep blood glucose levels constant with both doses of capsulin was approximately 50% of the necessary amount with 12 U of *Actrapid*. This suggests that capsulin was less effective at stimulating glucose uptake in the cells compared to normal insulin. It also demonstrated a lack of dose response, since both doses has a similar result from the isoglycemic clamp studies. There were no adverse events reported, suggesting that capsulin is safe, or that the dose was suboptimal. This program may not be fully active, and no trials have been announced since the completion of the Phase IIa study.

Oral-lyn – Generex. Generex is not developing an insulin pill like Oramed, but is still focused on the alternative delivery of the hormone. Generex has a technology platform to facilitate the movement of large molecules across the inner lining of the mouth. The technology includes a surfactant, a solubilizer, a micelle-creating agent, and emulsifiers to help with penetration. Generex using the technology to create a buccal insulin product called Oral-lyn to manage glucose spikes in patients at mealtime. Oral-lyn is a tasteless, odorless liquid formulation of regular human insulin that is delivered into the mouth via an aerosol spray applicator. The candidate has been tested in approximately 40 clinical trials, including a Phase III study in the US. Generex was unable to secure FDA approval of Oral-lyn and currently has no plans to continue development of the candidate in the US. The company subsequently partnered with Shreya Life Sciences to target the Indian market. Shreya completed a successful Phase III trial in 2013 with Oral-lyn and has submitted a package to the Indian government for marketing approval. Oral-lyn is currently available in other select countries, including Ecuador, Lebanon, and Algeria.

Competitive Landscape

The global diabetes market is currently led by Novo Nordisk, Eli Lilly, and Sanofi. These major players hold dominant positions, potentially hindering market access for new entrants, but they also have a track record of acquiring promising new therapies. The continuous development of novel

[21] Luzio, S.D. et al., 2010. The glucose lowering effect of an oral insulin (Capsulin) during an isoglycaemic clamp study in person with type 2 diabetes. *Diabetes, Obesity and Metabolism*, 12(1), pp82-87.

molecules is being driven by a high and increasing prevalence of diabetes, large unmet needs, and a strong demand for safer and more efficacious insulin therapies. There is also a need for treatment options that help control the early indicators of diabetes, such as elevated fasting blood glucose (FBG), which is strongly predictive of diabetes development.[22] The existing anti-diabetes therapies that are used in conjunction with diet and exercise were developed decades ago, and the thiazolidinedione class of drugs contain boxed warnings regarding an increased risk of heart failure. Furthermore, an estimated 70-80% of patients are unable to achieve glycemic control after 9 years of treatment with anti-diabetes therapies,[23] suggesting that additional, safer options are needed that can effectively manage FBG and other indicators of diabetes. ORMD-0801 could fill a role alongside metformin and thiazolidinediones, or just after these treatments, and carve out a key position in the diabetes treatment paradigm that is relatively free of competition.

ORMD-0901: Oral GLP-1 Analog (Exenatide)

Oramed is developing an oral formulation of the glucagon-like peptide 1 (GLP-1) receptor agonist exenatide for the treatment of type 2 diabetes (T2D). As a formulation of an already approved drug, ORMD-0901 may qualify for a 505(b)(2) regulatory pathway, which could significantly reduce the time to approval. GLP-1 is a small peptide secreted by intestinal cells in the gut in response to nutrient ingestion that reduces blood glucose by stimulating insulin secretion and suppressing glucagon secretion. Three GLP-1 receptor agonists are FDA approved and on the market: Novo Nordisk's *Victoza* (liraglutide), and AstraZeneca's *Byetta* (exenatide) and *Bydureon* (exenatide extended release). These drugs are relatively new and are already driving strong sales due to their ability to improve glycemic control with a low risk of hypoglycemia.

Oramed is using its protein oral delivery (POD) technology to develop an oral version of exenatide, which would significantly increase patient convenience and preserve the peripheral/portal ratio of GLP-1, creating a more physiologically friendly delivery situation. Preclinical studies have demonstrated the ability of ORMD-0901 to stabilize blood glucose levels, and a clinical trial in healthy subjects suggests that ORMD-0901 can stimulate insulin secretion. Oramed is planning to launch a Phase Ib trial outside the US in the second quarter of 2014, while concurrently completing 90 day preclinical toxicology studies intended to pave the way to commencement of a US-based Phase IIb trial that is expected to start in the first half 2015.

[22] Unwin, N. et al., 2002. Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabetes Medicine*, 19(9), pp708-723.

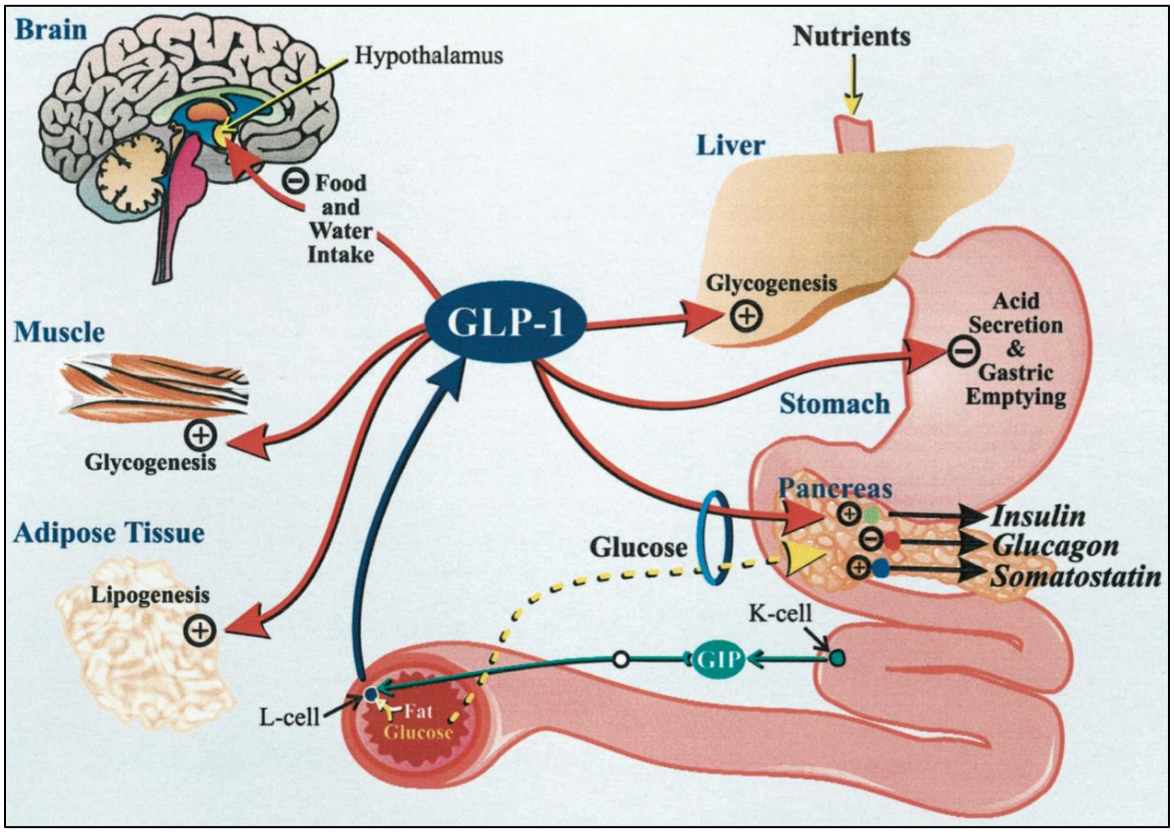
[23] Turner, R.C. et al., 1999. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with Type 2 diabetes mellitus. *The Journal of the American Medical Association*, 281(21), pp2005-2012.

Glucagon-Like Peptide 1

Glucagon like peptide 1 (GLP-1) is one of two incretins, which are intestinal-derived factors that facilitate insulin secretion following meals. An estimated 50-60% of total insulin secreted after oral glucose administration is due to incretins.[24] GLP-1 is a 30-amino acid peptide secreted by intestinal L-cells that promotes nutrient absorption via regulation of islet hormone secretion. Through activation of the GLP-1 receptor (GLP-1R), a G-protein-coupled receptor (GPCR), GLP-1 stimulates insulin secretion and suppresses glucagon secretion thereby lowering blood glucose.

GLP-1 has numerous activities in target organs, as indicated by **Figure 17**.[25] GLP-1 acts in the pancreas to stimulate insulin secretion and block glucagon secretion. In the liver, glycogenesis is blocked, reducing the overall glucose secretion from the organ. Furthermore, GLP-1 also slows the rate of absorption of nutrients into the blood stream by inhibiting acid secretion, delaying gastric emptying, and acting on the brain to increase satiety.

Figure 17. GLP-1 Mechanism of Action



Source: Kieffer, T.J. and Habener, J.F., 1999

[24] Baggio, L.L. and Drucker, D.J., 2007. Biology of incretins: GLP-1 and GIP. *Gastroenterology*, 132, pp2131-2157.
[25] Kieffer, T.J. and Habener, J.F., 1999. The glucagon-like peptides. *Endocrine Reviews*, 20(6) pp876-913.

Low Risk of Hypoglycemia. The effects of GLP-1 on the pancreas and liver facilitate the control of blood glucose levels in a natural, physiologic manner. The mechanism is dependent on the presence of elevated glucose, which reduces the risk of hypoglycemia, a common problem associated with insulin replacement therapy. This benefit has been demonstrated in human studies. One study examined 10 fasting T2D patients who were infused with GLP-1 or placebo.[26] Treatment with GLP-1 normalized fasting blood glucose levels that remained stable despite ongoing glucose infusion. The effect has also been demonstrated in the registration trials for approved GLP-1 agonists, and is a major advantage of this class of drugs.

Weight Loss Benefit of GLP-1. GLP-1's ability to delay gastric emptying and increase satiety can promote weight loss. Obesity has been increasing in prevalence worldwide and the majority of patients with type 2 diabetes (T2D) are either overweight or obese. Between 2009 and 2010 it was estimated that 35.7% of US adults were obese.[27] Americans have access to a stable food supply that often includes products with poor nutritional quality. The use of cars and jobs that require little physical activity has contributed to an increasingly sedentary lifestyle, and the corresponding rise in obesity. Unfortunately, obesity is a major risk factor for the development of many diseases including diabetes. In a large study that followed nearly 85,000 female nurses, being overweight or obese was the single greatest predictor of diabetes.[28]

Diabetes management has added to the obesity problem through the tendency of anti-diabetes drugs and insulin therapy to cause weight gain.[29] Sulfonylureas, thiazolidinediones, and insulin are associated with weight gain, whereas metformin and amylin analogs are weight neutral or associated with modest weight loss. GLP-1 agonists lead to weight loss. A meta-analysis of 21 randomized clinical trials where patients were treated for at least 20 weeks found that *Victoza* led to an average weight loss of approximately 5% of body weight. Weight loss in people with elevated blood glucose can reduce risk of developing diabetes. A randomized study of 3,234 non-diabetic individuals found that lifestyle modification reduced the incidence of diabetes by 58%.[30] Lifestyle modification included at least 150 minutes of physical activity per week and at least a 7% weight loss.

Preclinical Data

ORMD-0901 has been tested as a number of formulations in porcine and canine models.[31] Each formulation employed a different amount of exenatide or adjuvant such as a protectant or

[26] Nauck, M.A. et al., 1993. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in Type 2 (non-insulin-dependent) diabetic patients. *Diabetologia*, 36, pp741-744.
[27] Orgden, C.L. et al., 2012. Prevalence of obesity in the United States, 2009-2010. *NCHS Data Brief*, 82, pp1-7.
[28] Hu, F.B. et al., 2001. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *New England Journal of Medicine*, 345(11), pp790-797.
[29] Mitri, J. and Hamdy, O., 2009. Diabetes medications and body weight. *Expert Opinion on Drug Safety*, 8(5), pp573-584.
[30] Knowler, W.C. et al., 2002. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*, 346(6), pp393-403.
[31] Eldor, R. et al., 2010. Novel glucagon-like peptide-1 analog delivered orally reduces postprandial glucose excursions in porcine and canine models. *Journal of Diabetes Science and Technology*, 4(6), pp1516-1523.

absorption enhancer. **Figure 18** shows the 6 different formulations, the amount of exenatide, the amount of adjuvant, and the animal model in which they were tested. All formulations were administered as a 0.8 ml dose, ruling out any pharmacokinetic or pharmacodynamics issues related to the total dosing volume.

Figure 18. Formulation Tested in Preclinical Animal Models

Formulation	Adjuvant (mg)	Exenatide (µg)	Animal model
AG2	125	50	porcine
pAG3	125	75	canine
AG4	125	100	canine and porcine
AG6	125	150	porcine
EG3	75	75	porcine
RG3	75	75	porcine

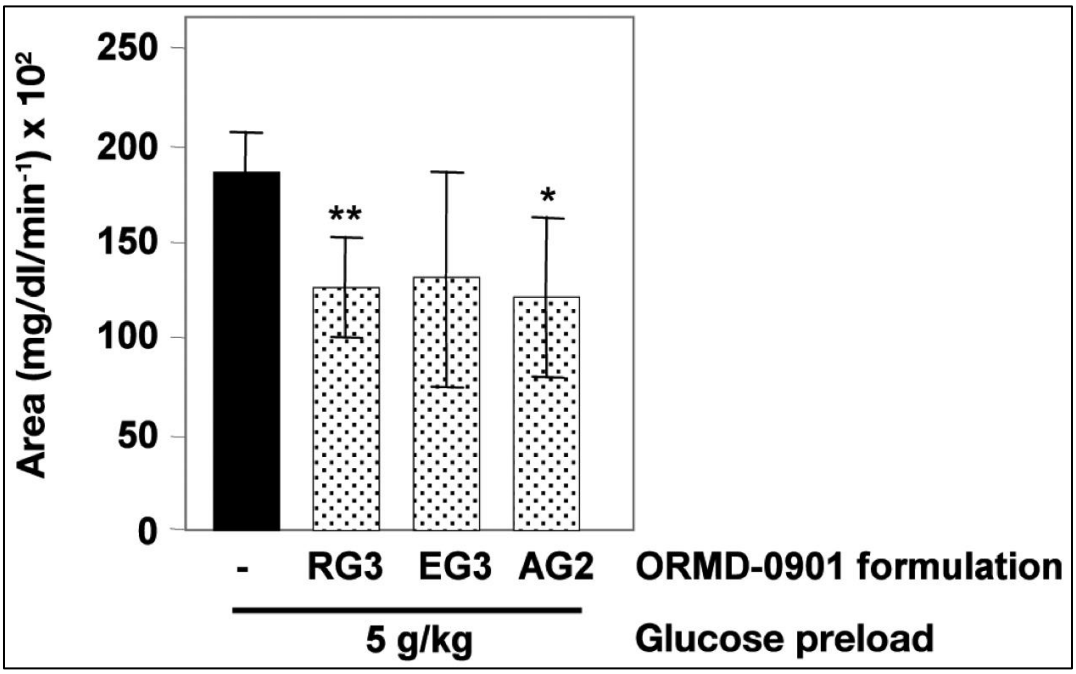
Source: Eldor, R. et al., 2010

The data suggest that ORMD-0901 can reduce glucose levels in both models, and prevent a glucose surge following glucose administration. ORMD-0901 was also well tolerated, supporting the upcoming launch of a Phase Ib trial in humans expected in the second quarter of 2014.

Porcine Model. In a study designed to examine the effects of portal vein absorption of exenatide, healthy, fasting, female pigs were administered a single dose of 50-150 µg exenatide directly into the intestine. Thirty minutes later, animals were challenged with 3 g/kg (n=6) or 5 g/kg (n=3) of oral glucose. The same animals were also challenged with oral glucose but did not receive ORMD-0901. Blood samples were collected every 15 minutes for up to 2.5 hours after dosing for pharmacodynamic analysis.

Blood glucose levels were measured using a glucometer and the area under the curve (AUC) between 1-120 minutes was calculated for all animals. The AUC was up to 43% lower in animals treated with ORMD-0901 compared to control. **Figure 19** shows the AUC for animals receiving no treatment and animals receiving three of the ORMD-0901 formulations after a 5 g/kg glucose load. The decrease in AUC was significant for RG3 and AG2 ($p=0.004$ and $p=0.041$, respectively).

Figure 19. Pharmacodynamics in Pigs Treated with ORMD-0901 Formulations

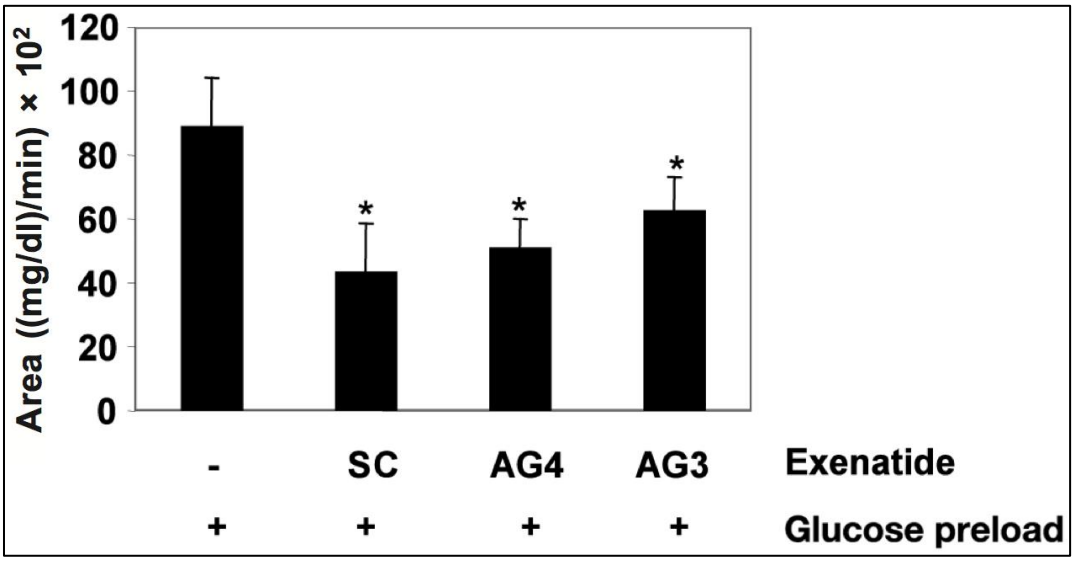


Source: Eldor, R. et al., 2010

Canine Model. Healthy, fasting beagles were administered a single dose of 75-100 μg exenatide directly into the intestine. Thirty minutes later, animals were challenged with oral glucose via 80 ml of a 50% dextrose solution plus 100 grams of food. The same animals were also challenged with oral glucose but did not receive ORMD-0901 or received a subcutaneous injection of 2.5 μg exenatide. Blood samples were collected for pharmacodynamic analysis every 15 minutes for up to 2.5 hours after dosing.

Blood glucose levels were measured using a glucometer and the area under the curve (AUC) between 1-150 minutes was calculated for all animals. There were 20 treatment sessions in dogs using ORMD-0901 formulations, and 18 out of the 20 times there was a decrease in the maximum level of glucose detected (C_{max}). Furthermore, the AUC was significantly lower in dogs that received formulations AG4 and AG3 compared to control animals, which is displayed in **Figure 20** ($p=0.068$). AG4 led to a 43% reduction in AUC and AG3 led to a 29% reduction. Treatment with subcutaneous (SC) exenatide attenuated the AUC by 51%.

Figure 20. Pharmacodynamics in Dogs Treated with ORMD-0901 Formulations



Source: Eldor, R. et al., 2010

These data indicate that ORMD-0801 can deliver exenatide and limit glucose spikes when animals are challenged with glucose. The impact on glucose spikes is comparable to subcutaneous exenatide in dogs, an important initial finding to suggest that ORMD-0901 could provide a similar benefit to patients as the reference GLP-1 receptor agonist but with enhanced convenience.

GLP-1 Market Estimates

The first GLP-1 receptor agonist was approved by the FDA in 2005, making this class of treatments new relative other diabetes therapies. *Byetta* (exenatide) was the first GLP-1 receptor agonist approved and was followed by an extended release formulation, *Bydureon* (exenatide extended release). *Byetta* achieved peak sales of $796.5 million in 2009 and has steadily lost market share for a variety of reasons including the launches of *Bydureon* and *Victoza* (liraglutide). The advantage with *Victoza* is that patients only need a single daily injection any time of the day, whereas *Byetta* must be self-administered twice a day, 60 minutes prior to a meal. *Bydureon* is taken weekly. Sales of *Victoza* were $2.18 billion in 2013, a 23% increase from 2012. GLP-1 receptor agonists are expected to continue gaining market share in the diabetes treatment space, due to the need for effective therapies to maintain glycemic control.

Clinical Data Discussion

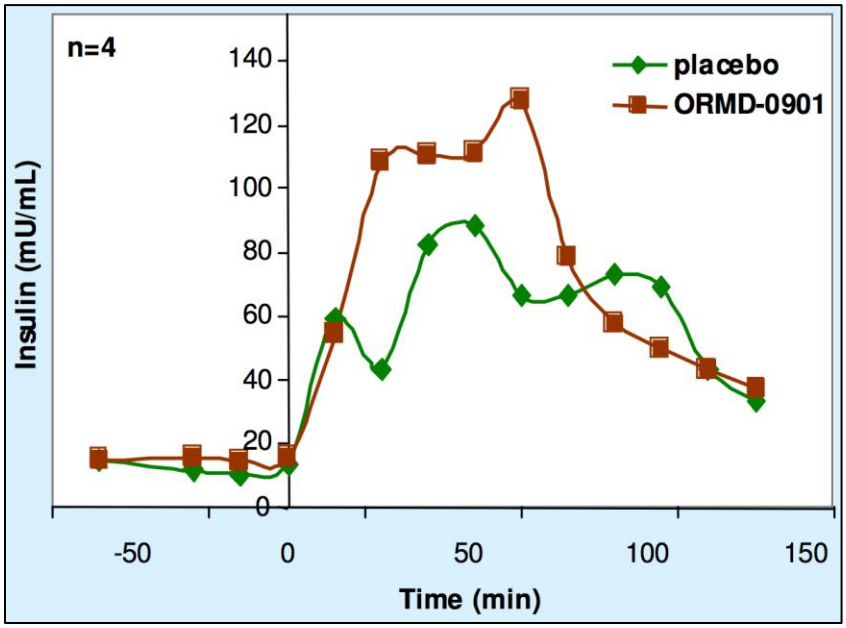
Oramed has completed a Phase I study in healthy volunteers to assess the safety of ORMD-0901 and the potential to stimulate insulin production.[32] The trial was a first-in-human, single-blind, two period study that enrolled 6 healthy, fasting, male volunteers. Study subjects were administered ORMD-0901 (150 μg exenatide) or placebo on separate visits and were challenged with 75 grams of oral glucose 60 minutes after treatment. Blood samples were collected at treatment, 30 minutes post-treatment, and 15 minutes thereafter up to 150 minutes post-treatment.

Study Results. Two subjects receiving placebo were not evaluated in a second visit due to adverse events (AEs), which excluded them from the efficacy analysis. However, ORMD-0901 was well tolerated in all 6 subjects on the second visit and no serious AEs were reported. ORMD-0901 was not associated with the common side effects typically reported with exenatide use, such as nausea, vomiting, diarrhea, and dyspepsia. This suggests that the oral delivery of exenatide may have the potential to reduce the incidence of common side effects.

While this analysis includes a very small number of patients, treatment with ORMD-0901 appears to have stimulated the release of insulin as indicated by an overall increase in the insulin area under the curve (AUC) for subjects receiving ORMD-0901 compared to placebo. AUC is a measure of the total insulin level across the study. Mean insulin AUC was 17.6% higher when subjects received ORMD-0901 versus placebo. **Figure 21** shows the mean insulin levels of subjects receiving ORMD-0901 or placebo across the entire study. The level of insulin peaked approximately 60-75 minutes after subjects received glucose.

[32] Eldor, R. et al., 2010. A single-blind, two-period study to assess the safety and pharmacodynamics of an orally delivered GLP-1 analog (exenatide) in healthy subjects. *American Diabetes Association Annual Meeting.*

Figure 21. Insulin Response Following ORMD-0901 or Placebo



Source: Eldor, R. et al., 2010.

These data are encouraging and suggest that ORMD-0901 may impact insulin secretion. Oramed is planning to launch a Phase Ib study outside of the US in the second quarter of 2014. IND enabling toxicology studies will also begin in the second quarter of 2014, and a Phase II trial could launch in the second quarter of 2015.

Intellectual Property

ORMD-0801. Oramed has issued and pending patents in several jurisdictions for methods and compositions for the oral administration of proteins. Patents have been approved or granted in Israel, Japan, the EU, Russia, China, Australia, New Zealand, and South Africa, and are expected to expire between 2026 and 2028. Patents are pending in several jurisdictions including the US, which if granted would expire between 2026 and 2032.

ORMD-0901. Oramed has patents issued and pending in several jurisdictions for methods and compositions for the oral administration of exenatide. Patents have been approved or granted in Australia, New Zealand, and Israel, and are expected to expire in 2028. Others are pending in several jurisdictions including the US. Additional protection for methods and compositions is being sought for the use oral of insulin and exenatide. Oramed has patents pending in several jurisdictions including the US that would expire in 2032 if granted.

Management Team

Nadav Kidron, Esq
Chief Executive Officer, President & Director

Nadav is an entrepreneur whose experience includes senior executive roles in a wide range of industries. Nadav currently serves as CEO & Director of Oramed Pharmaceuticals, which he founded in 2006. He is an Advisory Board Member for The Trendlines Group, a group that invests in and develops innovation-based businesses; a member on the Board of Directors of Entera Bio, a joint venture formed by Oramed and DNA Biomedical Solutions; and an international lecturer on Israel's entrepreneurial culture and the country's roots as an oasis of innovative ideas. He holds a Bachelor of Law Degree and an International Masters in Business Administration, both from Bar-Ilan University in Israel. Nadav is a fellow of the Merage Business Executive Leadership Program and a member of the Israeli Bar Association.

Miriam Kidron, Ph.D
Chief Scientific Officer & Director

Since founding Oramed Pharmaceuticals in 2006, Dr. Miriam Kidron has served as the company's chief scientist. A pharmacologist and biochemist, Kidron earned her PhD in biochemistry from the Hebrew University of Jerusalem. For close to 20 years, Dr. Kidron has been a senior researcher in the Diabetes Unit at Hadassah-Hebrew University Medical Center in Jerusalem, Israel, earning the Bern Schlanger Award for her work on diabetes research. She was formerly a visiting professor at the Medical School at the University of Toronto and is a member of the American, European and Israeli Diabetes Associations.

Yifat Zommer, CPA
Chief Financial Officer

Ms. Zommer joined Oramed in 2009, bringing with her financial management experience with publicly traded and private companies in the high-tech field of business. She previously served as CFO for Witech Communications Ltd and CTWARE Ltd. Prior to that she was an audit manager in PriceWaterhouseCoopers Israel, where she served for five years. Ms. Zommer holds a Bachelor of Accounting and Economics degree from the Hebrew University, a Business Administration (MBA) from Tel-Aviv University and a Master's degree in Law (LL.M.) from Bar-Ilan University, Israel. She is a certified public accountant (CPA) in Israel.

Ehud Arbit, M.D.
Director of Research and Development

Dr. Arbit joined Oramed in mid-2008, having previously served as the vice president of Medical Research at Emisphere Technologies, where he was a co-inventor of six patents related to drug delivery technology. Previously, Dr. Arbit has held distinguished academic positions as Professor at Cornell University Medical College, Member of the Sloan Kettering Cancer Center (MSKCC) and as Division director at Memorial Sloan Kettering Cancer Institute in New York. Dr. Arbit has numerous publications in peer reviewed journals and had served on the editorial boards of several medical journals.

Josh Hexter
Chief Operating Officer, VP Business Development

Josh Hexter joined Oramed as Chief Operating Officer and Vice President of Business Development in the spring of 2013. He brings to Oramed more than 15 years of prominent leadership, business development, operations know-how and management in biotechnology. Mr. Hexter was most recently Executive Director of Corporate In-Licensing at BioLineRx (NASDAQ: BLRX). Prior to joining BioLineRx, he worked in private equity and venture capital where he served as CEO of a VC-backed startup. As CEO of Biosensor Systems Design, Mr. Hexter was instrumental in shaping the company's strategic focus and in forging business development agreements with Fortune 100 companies in the areas of food safety, medical diagnostics and homeland security. Mr. Hexter earned a bachelor's degree from the University of Wisconsin and a master's degree in management from Boston University.

Risk to an Investment

We consider an investment in Oramed Pharmaceuticals to be a high-risk investment. Oramed is a development-stage company with no history of bringing a treatment to market, and currently has no FDA approved products in its portfolio. For any product candidate, early indications of efficacy do not necessarily translate into positive late-stage results. Oramed may be unable to obtain sufficient capital to fund planned development programs. There are regulatory risks associated with the development of any treatment and Oramed may not receive FDA approval for its candidates despite significant time and financial investments. Regulatory approval does not guarantee that the treatment will penetrate the market, and sales may not meet the expectations of investors.

DISCLOSURES

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Oramed Pharmaceuticals

3/18/2014

All values in Thousands except shares

	FY10A	FY11A	FY12A	FY13A	1Q14A
REVENUES	-	-	-	-	-
Research and development	1,464	1,159	1,681	2,272	751
Impairment of investment	-	-	-	-	-
General and administrative	1,509	1,276	1,203	2,032	418
Total Operating Expense	**2,973**	**2,435**	**2,884**	**4,304**	**1,168**
Operating Income (Loss)	**(2,973)**	**(2,435)**	**(2,884)**	**(4,304)**	**(1,168)**
Financial income	(25)	(33)	(13)	(180)	(46)
Gain on sale of investment	-	(1,033)	-	-	-
Impairment of securities	-	197	184	-	-
Financial expense	15	19	199	313	2
Net Income (Loss) Before Taxes	**(2,962)**	**(1,585)**	**(3,254)**	**(4,437)**	**(1,124)**
Income Tax	15	(24)	90	(205)	-
Net Income (Loss)	**$ (2,977)**	**$ (1,561)**	**$ (3,344)**	**$ (4,232)**	**$ (1,124)**
EPS - Basic and Diluted	**$ (0.62)**	**$ (0.29)**	**$ (0.57)**	**$ (0.59)**	**$ (0.14)**
Shares Out - Basic and Diluted	4,783,399	5,417,485	5,884,595	7,209,283	7,941,059

*fiscal year ends August 31