Zacks Small-Cap Research

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Oramed Pharmaceuticals (ORMP-NASDAQ)

ORMP: Zacks Company Report

ORMP: Positive data from Phase IIb ORMD-0801 reported, a significant de-risk event for the company.

Current Price (08/10/16)	$7.97
Valuation	**$30.00**

OUTLOOK

Oramed has a unique, proprietary protein oral delivery (POD™) platform technology with a mid-stage pipeline. The company's lead candidate ORMD-0801 is an oral insulin targeting the huge insulin market. The company just reported positive data from the Phase IIb ORMD-0801 study for type 2 diabetes. The company's second lead candidate ORMD-0901 is an oral formulation of GLP-1 analog exenatide, which will enter into Phase IIb study in 4Q16. We estimate ORMD-0801/0901 to reach the market in 2018 and 2019 respectively.

We are optimistic about the prospect of the company and value its shares at $30 per share.

SUMMARY DATA

52-Week High	**$9.57**
52-Week Low	**$5.32**
One-Year Return (%)	**29.74**
Beta	**0.43**
Average Daily Volume (sh)	**173,930**
Shares Outstanding (mil)	**13**
Market Capitalization ($mil)	**$118**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**N/A**
Insider Ownership (%)	**N/A**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2016 Estimate	**N/A**
P/E using 2017 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Avg.,**
Type of Stock	**Small-Growth**
Industry	**Med Products**
Zacks Rank in Industry	**N/A**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Nov)	Q2 (Feb)	Q3 (May)	Q4 (Aug)	Year (Aug)
2015	0.00 A	0.00 A	0.00 A	0.00 A	0.00 A
2016	0.00 A	0.13 A	0.16 A	0.20 E	0.49 E
2017					1.50 E
2018					12.00 E

Earnings per Share
(EPS is operating earnings before non recurring items)

	Q1 (Nov)	Q2 (Feb)	Q3 (May)	Q4 (Aug)	Year (Aug)
2015	-$0.19 A	-$0.15 A	-$0.15 A	-$0.18 A	-$0.67 E
2016	-$0.21 A	-$0.14 A	-$0.15 A	-$0.19 E	-$0.69 E
2017					-$0.31 E
2018					-$0.34 E

Zacks Projected EPS Growth Rate - Next 5 Years % **N/A**

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WHAT'S NEW

Oramed Reports Additional Positive Data from Phase IIb ORMD-0801 Study

Background of the Phase IIb (ORA-D-007) Study

ORA-D-007 is a double-blind, randomized, 28-day **Phase IIb** clinical trial designed to assess the safety and efficacy of **ORMD-0801** in **type II** diabetics. The trial will evaluate ORMD-0801 over a longer treatment period (28-day vs 7-day in the Phase IIa study) and will have statistical power to give greater insight into the drug's efficacy.



The Phase IIb trial was initiated on June 30, 2015 and conducted at 33 clinical sites in the United States.

Primary Objectives:

- To evaluate the pharmacodynamics effects of ORMD-0801 on mean nighttime glucose (determined using continuous glucose monitoring (CGM)).
- To evaluate the safety of ORMD-0801, including incidence of hypoglycemia.

Secondary Objectives:

- To evaluate changes from baseline in fasting blood glucose (FBG), morning fasting serum insulin, c-peptide, and triglycerides.

Exploratory Objectives:

- To evaluate the immunogenicity of ORMD-0801 through quantitation of anti-insulin antibodies.
- To evaluate changes from baseline in HbA1c, 24-hour, fasting and daytime glucose levels on CGM, weight, and C-Reactive Protein (CRP).

Initial Top Line Data

On May 18, 2016, Oramed announced **positive top-line data** from the **Phase IIb** study. The study achieved its primary objective: a significant reduction of weighted mean night-time glucose in patients treated with oral insulin ORMD-0801.

This study showed a statistically significant decrease in the primary endpoint, pooled night-time glucose mean percentage change of 6.47% from run-in, between placebo and active cohorts (p=0.0268).

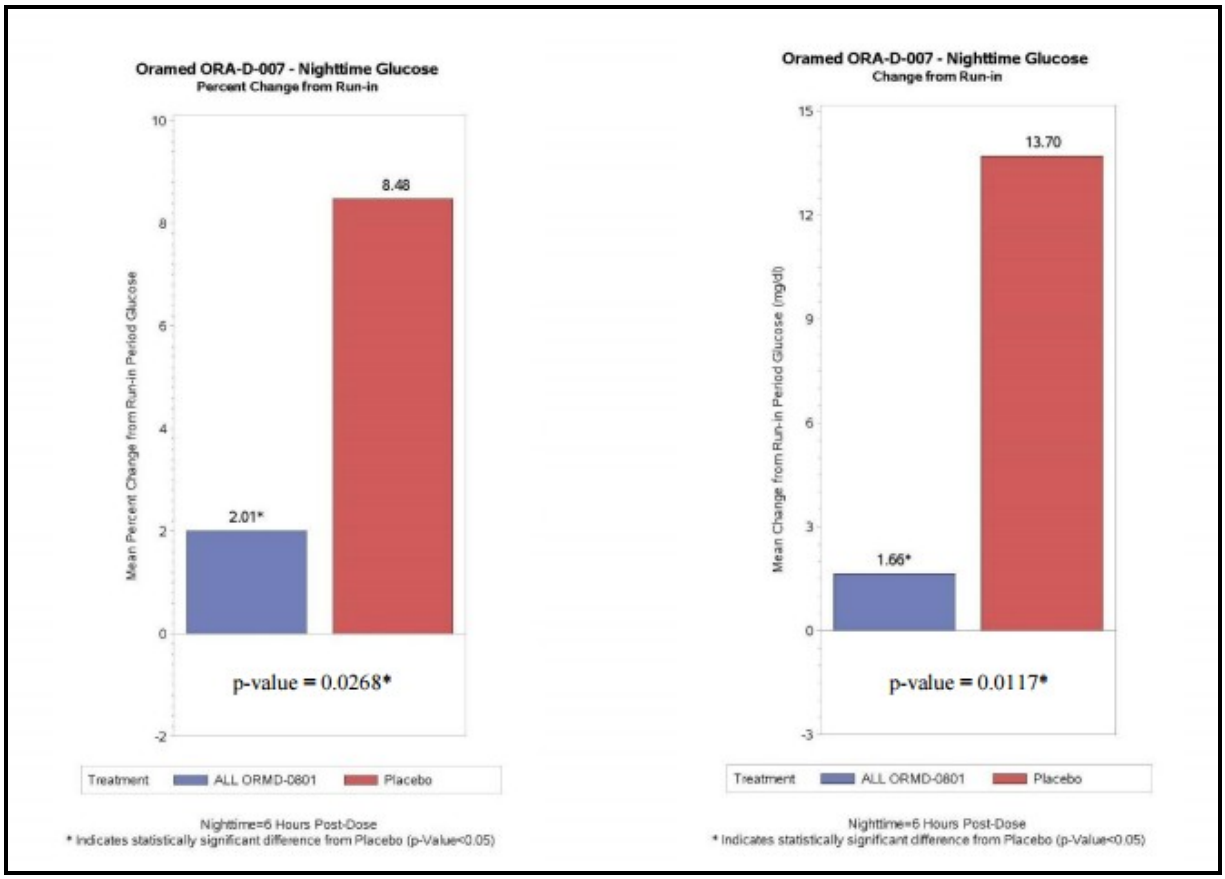
Further, the study demonstrated a good safety profile of ORMD-0801 with no drug related serious adverse events.

Additional Data

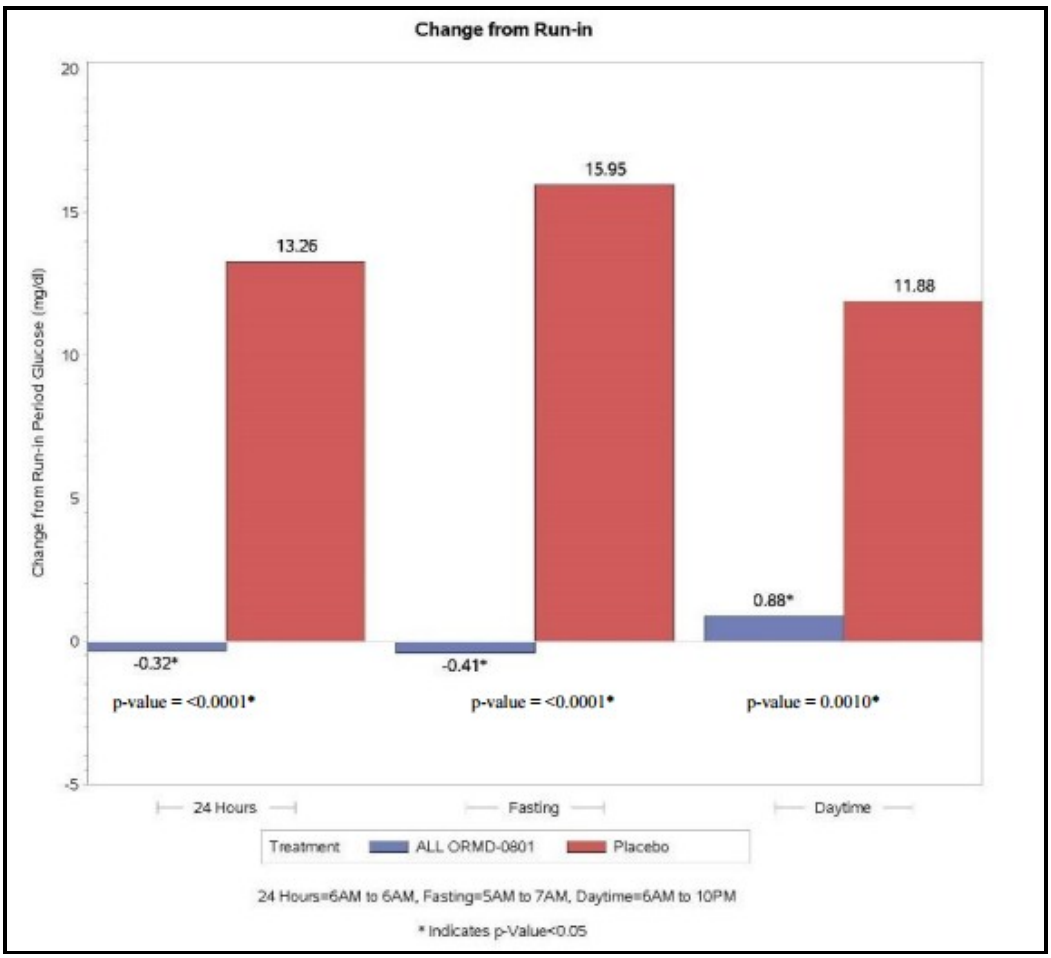
On July 28, Oramed reported **additional data** from the Phase IIb trial. In addition to positive topline data showing the study successfully met its primary efficacy and safety endpoints announced on May 18, the new data indicated a statistically significant lowering of glucose relative to placebo **across several endpoints.**

Due to technical inaccuracies that can occur in any diabetes study, measuring glucose changes with continuous glucose monitors (CGM), data can include extreme outliers. To reduce variability, trimming of unlocked, fully blinded information was conducted. In the current summary, the 80% trimmed data (data excluding the 10% highest and lowest values) is presented.

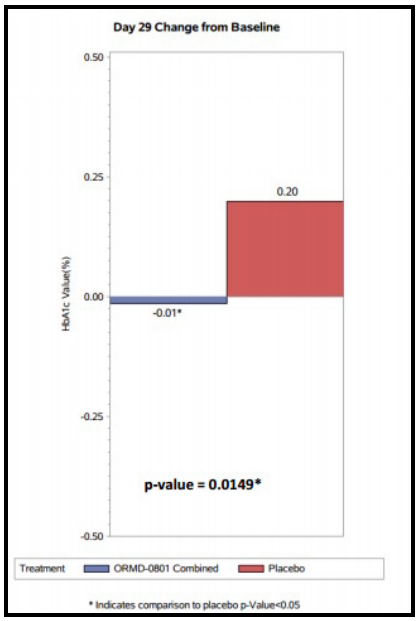
In the study, the mean nighttime glucose showed a significant difference in mean change from run-in (13.70 mg/dL for placebo vs. 1.66 mg/dL for the pooled ORMD-0801 arms with a p= 0.0117). ORMD-0801 was safe and well tolerated, with no drug related serious or severe adverse events and no statistically significant differences in laboratory values or vital signs.



Other secondary and exploratory objectives of the study included evaluating the effect of ORMD-0801 on mean 24-hour glucose, fasting glucose, and daytime glucose. The mean 24-hour glucose showed a highly significant difference in mean change from run-in (13.26 mg/dL for placebo vs. -0.32 mg/dL for ORMD-0801, p <0.0001). The mean fasting glucose showed a highly significant difference in mean change from run-in (15.95 mg/dL for placebo vs. -0.41 mg/dL for ORMD-0801, p <0.0001). The mean daytime CGM glucose showed a highly significant difference in mean change from run-in (11.88 for placebo vs. 0.88 for ORMD-0801, p= 0.0010).



There was a statistically significant difference in change in HbA1c at Day 29 (0.20% for placebo vs.-0.01% for ORMD-0801, p= 0.0149). It is important to note that due to the kinetics of change of HbA1c, a four week study is insufficient to fully appreciate the potential positive impact of ORMD-0801 on HbA1c.



ORMD-0801 did not show a significant difference in change in morning fasting serum insulin, C-Peptide, or triglycerides.

The study demonstrated a good safety profile of ORMD-0801 with no drug related serious adverse events.

Adverse Events

	Placebo (N=64)	ORMD-0801 460IU (N=61)	ORMD-0801 690IU (N=63)
Number of Reported Adverse Events:	34	34	42
Number (%) of Subjects With at Least One:			
Treatment Emergent Adverse Event (TEAE)	19 (29.7)	19 (31.1)	19 (30.2)
Severe TEAE	0 (0.0)	1 (1.6)	0 (0.0)
Serious TEAE	0 (0.0)	1 (1.6)	0 (0.0)
Drug-related TEAE	2 (3.1)	0 (0.0)	0 (0.0)
Drug-related severe TEAE	0 (0.0)	0 (0.0)	0 (0.0)
Drug-related serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to withdrawal of study drug	0 (0.0)	1 (1.6)	0 (0.0)
TEAE with outcome of death	0 (0.0)	0 (0.0)	0 (0.0)

Hypoglycemic Events

	Placebo (N=64)	ORMD-0801 460IU (N=61)	ORMD-0801 690IU (N=63)
Number (%) of Subjects with a Hypoglycemic Event:	1 (1.6)	1 (1.6)	1 (1.6)

Our Takeaways from the Phase IIb Study

The positive data from the Phase IIb trial is a significant **de-risk event** for Oramed in our opinion. The top line data further confirm the efficacy and safety of ORMD-0801, an orally delivered intestinally absorbed insulin, from previously reported results including the Phase IIa study.

With the positive top line data from the Phase IIb trial, we believe the company will move forward with a pivotal Phase III trial when they get some feedback from the FDA. We estimate a Phase III trial could start as early as in late 2016 or early 2017.

The positive top line results also triggered some milestone payments from HTIT.

On June 21, Oramed received $6.5 million milestone payment from Hefei Tianhui Incubator of Technologies Co. Ltd. (HTIT). The payment follows Oramed's positive top-line results from its Phase IIb trial.

On August 2, Oramed received another milestone payment of $4 million from HTIT, following Oramed's report of additional positive efficacy and safety data from the Phase IIb trial.

Per the terms of the agreement signed in December 2015, Oramed granted HTIT exclusive rights for commercialization of ORMD-0801 in Greater China. The up to $50 million license deal includes multiple milestone payments aggregating $38 million, with a $3 million upfront payment received by Oramed upon execution of the agreement, plus a $12 million investment made by HTIT in Oramed at $10.39 per share in December 2015. Oramed will receive a 10% royalty on net sales of ORMD-0801 and related commercialized products in Greater China.

We Continue to be Bullish on Oramed Shares

We continue to be bullish on the Oramed story and maintain our valuation at $30 per share based on the positive results from the Phase IIb study.

Oramed is a mid-stage development biotech company with a current focus on diabetes. Over the years, the company has developed a unique, proprietary protein oral delivery (POD) platform technology. This is the core value for the company and differentiates the company from other biotech companies in our view.

Base on its POD platform, Oramed has built a pipeline with focus on oral insulin **(ORMD-0801**) and oral GLP-1 analog (**ORMD-0901**).

Oral insulin mimics the role of natural insulin, therefore has many advantages over injectable insulins including better control of blood glucose and less side effects. The company has completed a **Phase IIa** study of ORMD-0801 for T2DM and reported positive data. The positive data from the **Phase IIb** study is a significant de-risk event for the company. We estimate a pivotal **Phase III** trial could start in late 2016 or early 2017.

Based on the company's current development plan, we estimate ORMD-0801 to be approved by the FDA in late calendar 2018 for both type 1 and type 2 diabetes. Peak sales could be over $1 billion in 5 years after approval.

The company's second candidate is ORMD-0901, an oral formulation of exenatide (Byetta) for T2DM. The company expects to initiate a **Phase IIb** study in 4Q16. Oramed plans to pursue the **505(b)(2) pathway for** ORMD-0901. If everything goes Oramed's way, ORMD-0901 could be approved in late 2019. Peak sales should be in the neighborhood of $500 million.

We are very pleased to see that the company has been pursuing collaboration opportunities for its clinical programs. The recent deal with China based Hefei Tianhui Incubator of Technologies Co.is especially encouraging. The deal not only boosts the company's balance sheet in a non-dilutive way, but further validates the company's POD technology and its clinical program ORMD-0801. We should be able to see more deals in the near future when data from the Phase IIb trial prove to be positive.

Furthermore, we see great potential of the company's POD platform for other indications. Oral delivery of protein is a breakthrough technology and has great potential for oral delivery of other biologics. Therefore, pipeline expansion should be easy once the work for oral insulin/GLP-1 has been validated in clinical studies. Actually, the company has a feasibility study currently running with a big pharma company using this pharma's proprietary peptide with Oramed POD delivery technology.

With respect to valuation, we think current share price does not reflect the intrinsic value of the company. Currently, Oramed shares are trading at about $8.00, which values the company at $105 million in market capitalization based on 13 million outstanding shares. This is a discount compared to its peers. Based on our above discussions, ORMD-0801 and ORMD-0901 will be approved by the FDA in 2018 and 2019 respectively. We assign a probability of 75% for ORMD-0801 and 30% for ORMD-0901 for approval at this time. Based on our financial model, Oramed will become cash flow positive in 2019 with an EPS of $0.15 based on revenue of $52.5 million. EPS will grow to $2.54 in fiscal 2012 based on total revenue of $255 million. A 35x P/E multiple and 25% discount rate are used to arrive at our fair value of $30.00 per share. Our price target values the company at $390 million in market cap, which is still conservative in our view.

But keep in mind **the risks**. As we discussed, Oramed is still a mid-stage development biotech company. Our valuation assumes the final approval of either ORMD-0801 or ORMD-0901 or both, which we only assign 75% and 30% probability at this time. In order for the two candidates to reach the market, the company still needs to overcome both clinical and regulatory hurdles which have proven to be high. But the reward is also apparent. Once the company moves further with the two candidates, value will be

created for shareholders with a higher probability of approval. Generally speaking, we think the stock has a typical high risk/high return profile, which could be appropriate for investors with a high risk tolerance and relatively long investment horizon.

Update on Fiscal Third Quarter Financials

Revenue for fiscal second quarter ended May 31, 2016 totaled $0.163 million.

Revenue consisted of proceeds related to the License Agreement with HTIT that are recognized over the term of the License Agreement through June 2023. The license agreement was closed in December 2015. No revenues were recorded in fiscal second quarter ended February 28, 2015.

R&D expenses for fiscal 3Q16 were $1.7 million, compared to $0.9 million for the same period of last year. The increase was mainly attributable to expenses related to clinical trials and mainly the Phase IIb clinical trial.

G&A expenses for fiscal 3Q16 were $0.56 million, from $0.72 million for the three months ended May 31, 2015.

Net loss for the fiscal 3Q16 was $1.9 million ($0.15 per share), as compared to a net loss of $1.6 million ($0.15 per share) for fiscal 3Q15.

As of May 31, 2016, Oramed held $24.7 million in cash, short term deposits and marketable securities with no debt.

In December 2015, the company completed deal valued at up to $50 million in investment and milestone payment with China based Hefei Tianhui Incubator of Technologies Co., Ltd. (HTIT) for exclusive rights to market ORMD-0801 in China, Hong Kong and Macau.

Pursuant to the agreements, Oramed sold HTIT 1,155,367 restricted shares of Common Stock at a price of $10.39 per Share, for an aggregate amount of **$12 million**. Under the terms of the agreement, Oramed has granted HTIT exclusive rights for commercialization of ORMD-0801 in Greater China. The license includes multiple milestone payments aggregating **$38 million** and up to a **10% royalty**, based on net sales of the product in China.

The positive data from the Phase IIb study triggered two milestone payments of total $10.5 million.

HTIT (partially owned by Sinopharm Group Company Limited) has state of the art insulin production facilities in Hefei, China. China has the largest number of diabetics in the world. If ORMD-0801 is finally approved in China, we believe the royalties from China sales will have a significant impact on Oramed's future revenues and earnings.

This deal not only boosted the company's balance sheet, but more importantly validates the company's POD technology and its clinical programs.

Oramed has a burn rate at about $10 million per year. Current cash plus the proceeds from this deal will be able to fund the company's operations well into calendar 2018 according to our financial model.

INVESTMENT THESES

The Unique Protein Oral Delivery (POD™) Technology

Over the years, Oramed has developed a unique proprietary platform technology: protein oral delivery **(POD™)** that allows for the oral delivery of protein drugs presently administrated only via injection.

There are many attractive advantages of oral drug delivery. These include increased patient comfort and compliance, reduced risk of infection, simpler application in pediatric medicine, first-pass metabolism preceding systemic exposure, and cost effectiveness. All these advantages have positioned oral delivery the most popular and preferred route of drug administration, especially for small molecules.

However, there are two major obstacles to the oral delivery of **protein-based medications**:

- Degradation by harsh acids and proteolytic enzymes within the gut;
- Absorption blocked by the physical barrier posed by the wall of the small intestine, which blunts translocation of large particles.

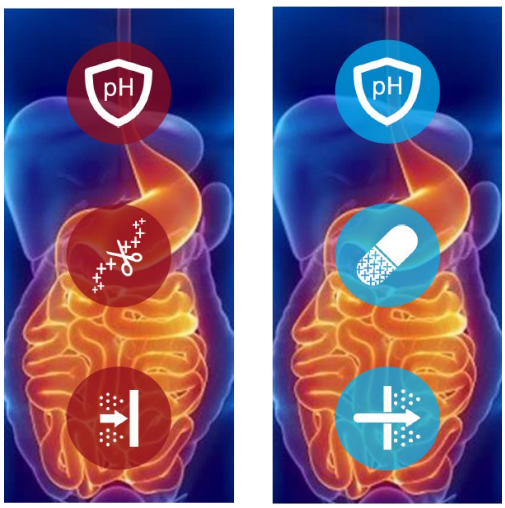
The end result is the jeopardization of the integrity and potency of orally ingested proteins. Thus, most protein-based pharmaceuticals cannot be taken in tablet form, and are typically provided in injectable forms, where they are delivered directly to the blood circulation.

Oramed POD™ (Protein Oral Delivery) technology has been uniquely designed to:

- protect orally delivered proteins from detrimental enzymatic activity within the gastrointestinal tract;
- and to enhance their absorption across the intestinal wall.

In order to prevent the degradation of proteins in the gastrointestinal tract, the active protein is encapsulated in a capsule that features a highly protective coating that remains intact in the most acidic segments of the gut, as well as enzymatic support provided by specialized **protease inhibitors**.

To promote the protein's absorption, an **absorption enhancer** supplement is used to facilitate protein passing across the intestinal barrier.



Regular Oral Delivery of Protein (left) vs POD Technology (right)

By preventing protein breakdown in the gastrointestinal tract and promoting its crossing the small intestine, this breakthrough solution brings oral protein drug delivery significantly closer to a reality.

Oramed POD™ technology allows insulin to travel from the gastrointestinal tract via the portal vein to the liver and then the bloodstream, revolutionizing the manner in which insulin is delivered. It enables its passage in a more physiological manner than current delivery methods of insulin. This technology is a

platform that has the potential to deliver medications and vaccines orally that today can only be delivered via injection.

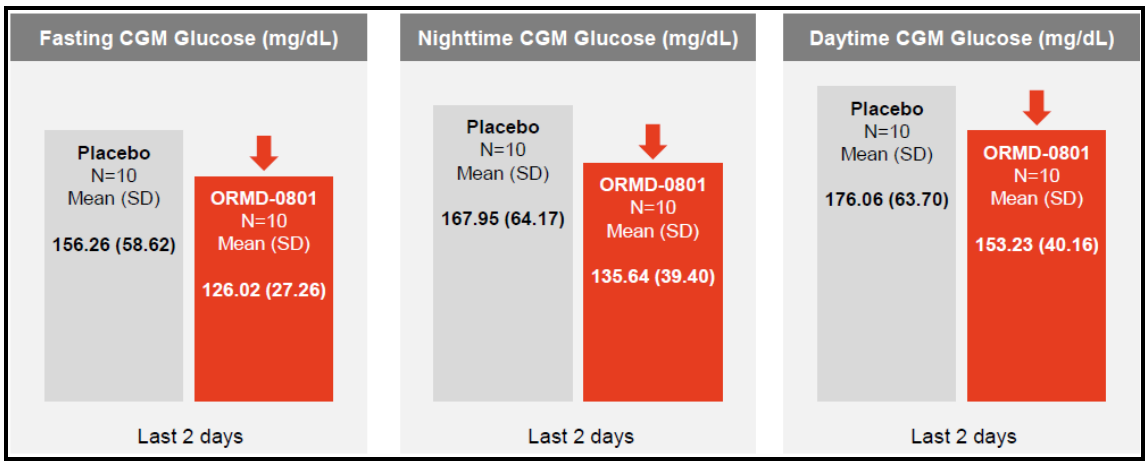
ORMD-0801 for Type 2 Diabetes (T2DM)

ORMD-0801 is an oral insulin capsule, the company's flagship candidate developed using the company's unique POD™ technology for the treatment of **type 2 diabetes (T2DM).**

Oramed completed a **Phase IIa** study of ORMD-0801 in **1Q14**. This is a randomized, double-blind, placebo-controlled 7-day study to assess the safety, PK and PD of multiple oral bedtime doses of ORMD-0801 in adult patients with T2DM. This study enrolled 30 T2DM patients. The primary objective of this Phase IIa study is to evaluate the safety and tolerability of ORMD-0801. Secondary objective is to evaluate the pharmacodynamic effects on mean nighttime glucose level.

ORMD-0801 was safe and well tolerated for dosing regimen. No hypoglycemic events were observed at any point during the study in any member of the treatment group. No related adverse events were observed.

In this trial, ORMD-0801 also demonstrated sustained glucose reduction at night, day and mean fasting glucose test compared to placebo as measured by continuous glucose monitoring (CGM).



Based on the encouraging Phase IIa data, Oramed initiated a **Phase IIb** trial of ORMD-0801 for the treatment of T2DM in **June 2015**.

The company has reported positive data from the completed Phase IIb trial in July 2016. We estimate a pivotal **Phase III** trial could start in late 2016 or early 2017.

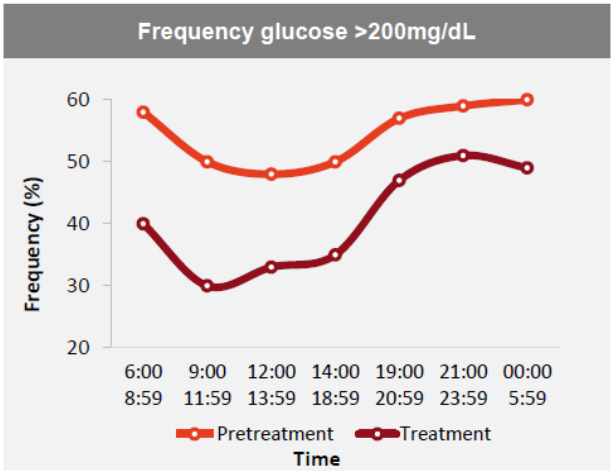
ORMD-0801 for Type 1 Diabetes (T1DM)

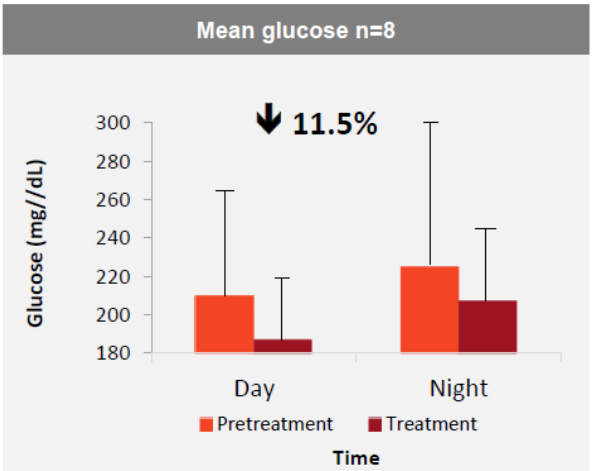
Oramed is also evaluating ORMD for the treatment of **type 1 diabetes (T1DM).**

T1DM patients are usually treated with 2 types of injectable insulin replacement therapy. Long-acting insulin (basal) helps maintain stable insulin levels during fasting periods and rapid-acting insulin (bolus) prior to each meal helps to stabilize blood sugar.

Oramed seeks to replace the mealtime (bolus) insulin doses with oral insulin ORMD-0801.

In a **preliminary clinical study**, ORMD-0801 demonstrated consistent lowering of glucose levels in uncontrolled/brittle type 1 diabetic patients both at day and night. The agent also reduced the frequency of glucose above the level of 200 mg/dL.



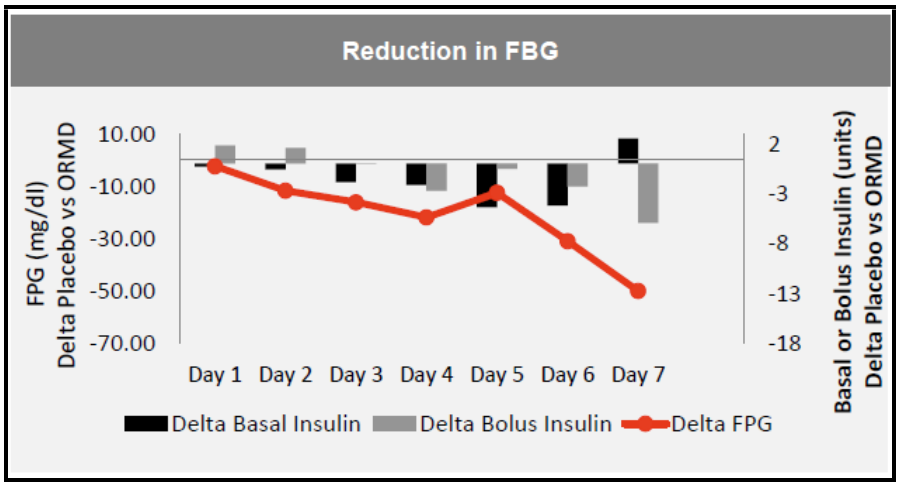


Oramed completed a FDA approved **Phase IIa** study of ORMD-0801 in **3Q14** for the treatment of T1DM. This was a prospective, randomized, double-blind, placebo controlled study. 25 patients with established Type 1 diabetes were enrolled into the study. Patient (15/25) took ORMD-0801 3 times a day at mealtime for 7days. Glucose level was measured using a continuous glucose monitoring (CGM) device.

The primary objective of this Phase IIa study is to evaluate the change in exogenous insulin requirements in T1DM patients.

ORMD-0801 showed consistent and accumulative effect of lowering blood glucose levels (fasting blood glucose/fasting plasma glucose, FBG/FPG, red line), day and night, compared to control group. ORMD-0801 also reduced the use of both basal insulin and bolus insulin.

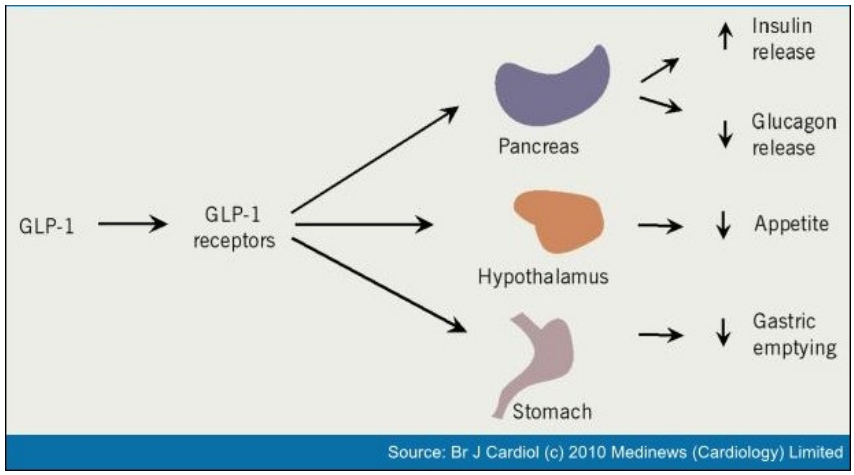
The oral insulin was safe and well tolerated for the pre-meal dosing regimen in this study.



The company has meetings planned in the next couple weeks with the JDRF to look at doing something together in pushing forward T1DM. In addition, the company is getting feedback from our KOLs on the best path forward for this indication. Some of the feedback to date has been to simply have a small T1DM population within the Phase III study (along with T2DM). This seems like the likely best path forward to inexpensively include T1DM on the FDA label.

ORMD-0901 for Type 2 Diabetes

Glucagon-like peptide 1 **(GLP-1)** belongs to the hormonal family of **incretins** that enhance the secretion of insulin. The major sources of GLP-1 are the L-cells in the lining of small intestine. The pancreas and the central nervous system (CNS) also secrete this hormone in smaller quantities. GLP-1 stimulates the release of insulin from the pancreas; it also increases the volume of cells in the pancreas which produces insulin (beta cells) and regulates and controls the release of glucagon. GLP-1 acts on appetite centers in brain, slowing the emptying process in stomach and increasing the feeling of fullness during and between the meals.

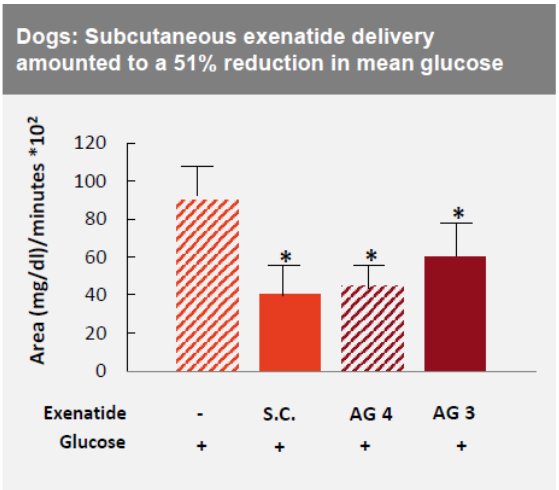


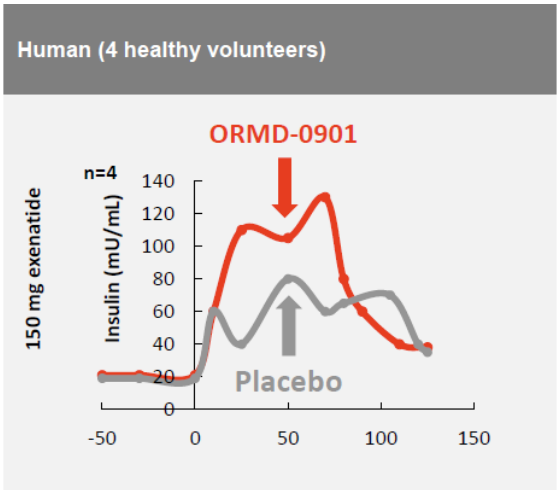
ORMD-0901 is oral GLP-1 analog (**oral exenatide**). Exenatide, a GLP-1 analog, is currently marketed in injectable form only, and is indicated for treatment of type 2 diabetes. Exenatide induces insulin release at increased glucose levels and causes a feeling of satiety, which results in reduced food intake and weight loss.

ORMD-0901, based on the company's POD™ technology, could significantly increase compliance and become a valuable tool in the treatment of diabetes.

In a **small scale preliminary proof of concept** study, ORMD-0901 demonstrated excellent glucose reduction efficacy in both animals (dogs) and human healthy volunteers.

In the following graph, the left showed a couple formulations of ORMD-0901 seemed to have similar efficacy to the injectable GLP-1 (lowering glucose). The right showed increase insulin in humans after taking ORMD-0901– as GLP-1 promotes insulin production/secretion.





Oramed submitted the pre-IND package to the FDA in 3Q13, and is currently conducting IND-enabling toxicity studies.

The company hopes to finish off the 90-day toxicity studies by 3Q16, and files an IND and start a **Phase II** study in 4Q16. The company may pursue the **505(b)(2) pathway**.

The 505(b)(2) regulatory pathway may reduce the drug development risks and costs by using prior findings of safety and/or efficacy for an approved product. In ORMD-0901 case, part of the safety and efficacy data from the injectable exenatide formulation may be used for the filing of a NDA for ORMD-0901.

An **ex-US Phase Ib** study of ORMD-0901 has been initiated in Israel. It's a small study to look at proof of concept (POC) and to glean some small dosing information. Data from this trial will be available by 1Q/2Q16. Data from this small study will help the company design the Phase II study.

ORMD-0801 Target the Huge Insulin Market

Oramed is developing ORMD-0801 for both T1DM and T2DM, a multibillion-dollar market.

T1DM is autoimmune disease. The body destroys its own insulin-producing (beta) cells, leaving patients completely dependent on external insulin sources. It's estimated that 5-10% of diabetics have T1DM and up to 37 million people worldwide have T1DM.

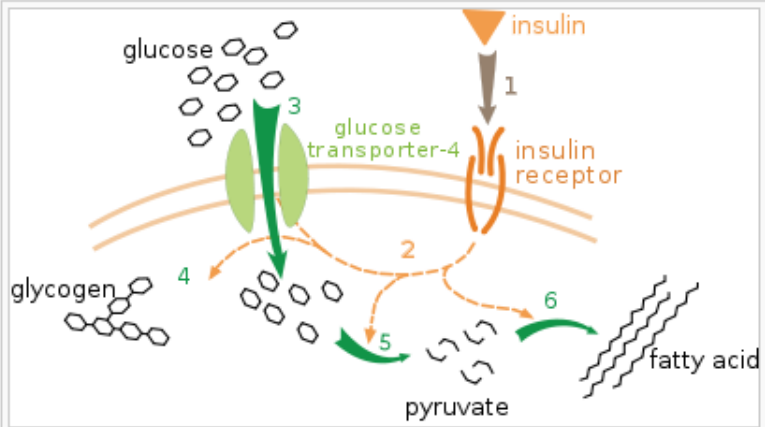
T2DM is metabolic. The body becomes insulin resistant. Injections may be used to make up for the pancreas's inability to create sufficient insulin to keep blood sugar at normal levels. About 371 million people worldwide suffer from T2DM.

Insulin and Diabetes

Before the discovery of insulin, diabetes was a feared disease that most certainly led to death. The discovery of insulin at the University of Toronto in 1921-22 was one of the most dramatic events in the history of the treatment of disease, which led to the **Nobel Prize** in Physiology or Medicine awarded to Dr. Banting and Dr. Macleod in 1923 for their discovery of insulin.

Insulin is a peptide hormone produced by beta cells in the pancreas. It regulates the metabolism of carbohydrates and fats by promoting the absorption of glucose from the blood to skeletal muscles and fat tissue and by causing fat to be stored rather than used for energy. Insulin also inhibits the production of glucose by the liver.

In healthy people, insulin is provided within the body in a constant proportion to remove excess glucose from the blood, which otherwise would be toxic. When blood glucose levels fall below a certain level, the body begins to use stored glucose as an energy source through glycogenolysis, which breaks down the glycogen stored in the liver and muscles into glucose, which can then be utilized as an energy source. As a central metabolic control mechanism, its status is also used as a control signal to other body systems (such as amino acid uptake by body cells). In addition, it has several other anabolic effects throughout the body.



Effect of insulin on glucose uptake and metabolism. Insulin binds to its receptor (1), which starts many protein activation cascades (2). These include translocation of Glut-4 transporter to the plasma membrane and influx of glucose (3), glycogen synthesis (4), glycolysis (5) and triglyceride (6).

Source: Wikipedia

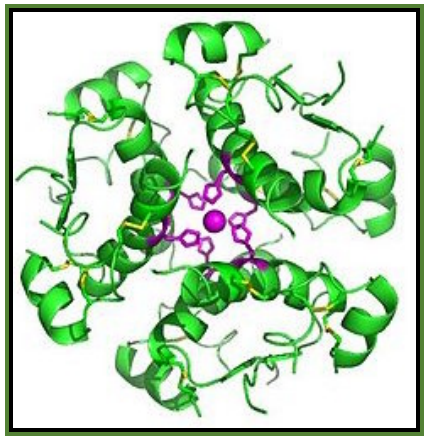
When control of insulin levels fails, **diabetes mellitus** (simply called diabetes) can result. As a consequence, insulin is used medically to treat some forms of diabetes mellitus.

In people with **type 1 diabetes (T1DM)**, The beta cells have been destroyed, and the pancreas no longer makes insulin. Therefore, patients with T1DM depend on external insulin for their survival because the hormone is no longer produced internally.

People with **type 2 diabetes (T2DM)** make insulin, but their bodies don't respond well to it. Therefore, patients with T2DM are often insulin resistant and, because of such resistance, may suffer from a "relative" insulin deficiency. Some patients with type 2 diabetes may eventually require insulin if dietary modifications or other medications fail to control blood glucose levels adequately. Over 40% of those with Type 2 diabetes require insulin as part of their diabetes management plan.

The human insulin protein is composed of 110 amino acids, and has a molecular mass of 5808 Da. It is a dimer of an A-chain and a B-chain, which are linked together by disulfide bonds. The crystal structure of insulin in the solid state was determined by Dorothy Hodgkin; she was awarded the **Nobel Prize** in Chemistry in 1964. Insulin is on the WHO Model List of Essential Medicines, the most important medications needed in a basic health system.

The following picture shows the high-resolution model of six insulin molecules assembled in a hexamer, highlighting the threefold symmetry, the zinc ion holding it together (pink sphere), and the histidine residues (pink sticks) involved in zinc binding. Inactive insulin is stored in the body as a hexamer, while the active form is the monomer.



Insulin Structure

Classification of Insulin

There are different types of modern human insulin (insulin analogs) depending on how quickly they work, when they peak, and how long they last. Following is a list and brief description of different types of insulin.

- Rapid-acting insulin, begins to work about 10-15 minutes after injection, peaks in about 1 hour, and continues to work for 2 to 4 hours. Types: Insulin glulisine (Apidra), insulin lispro (Humalog), and insulin aspart (NovoLog).

- Regular or Short-acting insulin usually reaches the bloodstream within 30 minutes after injection, peaks anywhere from 2 to 5 hours after injection, and is effective for approximately 3 to 6 hours. Types: Humulin R, Novolin R.

- Intermediate-acting insulin generally reaches the bloodstream about 2 hours after injection, peaks 4 to 12 hours later, and is effective for about 18 hours. Types: NPH (Humulin N, Novolin N).

- Long-acting insulin reaches the bloodstream several hours after injection and tends to lower glucose levels fairly evenly over a 24-hour period. Types: Insulin detemir (Levemir) and insulin glargine (Lantus).

- Premixed insulins combine specific amounts of intermediate-acting and short-acting insulin in one bottle or insulin pen. Premixed insulin can be helpful for people who have trouble drawing up insulin out of two bottles and reading the correct directions and dosages. It is also useful for those who have poor eyesight or dexterity and is convenient for people whose diabetes has been stabilized on this combination.

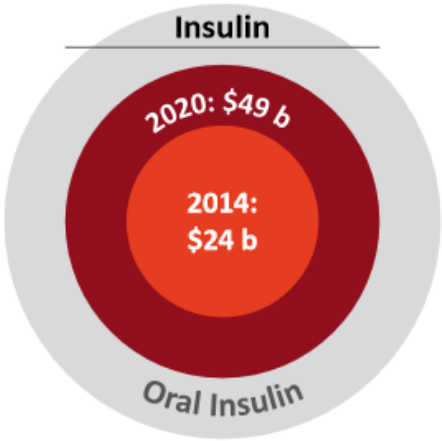
- In 2015 an inhaled insulin product, **Afrezza**, became available in the U.S. Afrezza is a rapid-acting inhaled insulin that is administered at the beginning of each meal and can be used by adults with type 1 or type 2 diabetes. Inhaled insulin begins working within 12 to 15 minutes, peaks by 30 minutes, and is out of the body in 180 minutes. Afrezza must be used in combination with injectable long-acting insulin in patients with type 1 diabetes and in type 2 patients who use long-acting insulin.

Type of Insulin/Brand Names	Onset	Peak	Duration	Role in Blood Sugar Management
Rapid-Acting				
Lispro (Humalog)	15-30 min.	30-90 min	3-5 hours	Rapid-acting insulin covers insulin needs for meals eaten at the same time as the injection. This type of insulin is often used with longer-acting insulin.
Aspart (Novolog)	10-20 min.	40-50 min.	3-5 hours	
Glulisine (Apidra)	20-30 min.	30-90 min.	1-2½ hours	
Regular/Short-Acting				
Regular humulin/novolin	30 min. -1 hour	2-5 hours	5-8 hours	Short-acting insulin covers insulin needs for meals eaten within 30-60 minutes.
Velosulin (insulin pump)	30 min. -1 hour	2-3 hours	2-3 hours	
Intermediate-Acting				
NPH (N)	1-2 hours	4-12 hours	18-24 hours	Intermediate-acting insulin covers insulin needs for about half the day or overnight. This type of insulin is often combined with a rapid- or short-acting type.
Long-Acting				
Insulin glargine (Lantus)	1-1½ hour	No peak time. Insulin is delivered at a steady level.	20-24 hours	Long-acting insulin covers insulin needs for about one full day. This type is often combined, when needed, with rapid- or short-acting insulin.
Insulin detemir (Levemir)	1-2 hours	6-8 hours	Up to 24 hours	
Pre-Mixed				
Humulin 70/30	30 min.	2-4 hours	14-24 hours	These products are generally taken two or three times a day before mealtime.
Novolin 70/30	30 min.	2-12 hours	Up to 24 hours	
Novolog 70/30	10-20 min.	1-4 hours	Up to 24 hours	
Humulin 50/50	30 min.	2-5 hours	18-24 hours	
Humalog mix 75/25	15 min.	30 min.-2½ hours	16-20 hour	

The Insulin Market

Insulin is one of the most important pharmaceuticals in the world and represents a multibillion dollar market. More than ninety years after the discovery of insulin, the therapy remains a staple of treatment for both type 1 and type 2 diabetes.

According to P&S Market Research, the global human insulin market was valued at $24 billion in 2014. The market is expected to grow at a compound average growth rate (CAGR) of 12.5% during the period 2015 to 2020, to reach $49 billion by 2020. This doesn't take into account oral insulin and the potential to really enlarge this market via giving insulin earlier in the therapeutic paradigm. The growth is fueled by the growing prevalence of diabetes and the progressive nature of the disease.



On the basis of insulin type, the **insulin analogs** (modern human insulin) commands the larger share in the global market. The modern human insulin is expected to grow at a CAGR of 13% during 2015 to 2020. The modern human insulin can be further categorized as long acting human insulin, rapid acting human insulin and premixed human insulin; wherein, the long acting human insulin commands the largest share in modern human insulin market but the premixed human insulin exhibited the highest growth rate.

In Asia-Pacific, the human insulin market is expected to witness a higher CAGR of 13.9% during the period 2015 to 2020, to achieve $12 billion value by 2020.

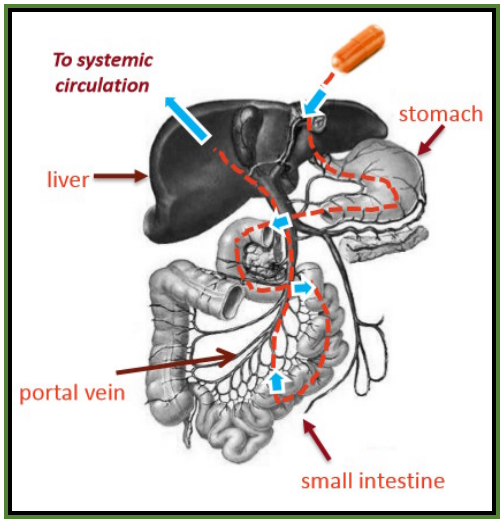
The global human insulin market has a fragmented structure with large number of companies operating in the market. The key players in the human insulin market include Sanofi, Novo Nordisk A/S, Eli Lilly and Company, GlaxoSmithKline Plc, Pfizer, Inc., Merck & Co., and Julphar.

Advantage and Opportunity for ORMD-0801

We believe **ORMD-0801** could command a nice market share in the global insulin market if approved. ORMD-0801 is an **oral formulation** of insulin and holds many advantages compared to injectable insulin including increased patient comfort and compliance, reduced risk of infection, simpler application in pediatric medicine, first-pass metabolism preceding systemic exposure, and cost effectiveness.

Specifically, endogenous insulin is produced by the pancreas and delivered to the body via the liver. Injected insulin is introduced directly to the bloodstream with only a fraction of it reaching the liver. This can cause excess sugar to be stored in fat and muscle which often results in weight gain. This may also cause hypoglycemia. While oral insulin (such as ORMD-0801) like natural insulin is delivered first to the liver. This should lead to:

- Better blood glucose control;
- Reduced hypoglycemia: liver metabolizes 80%;
- Reduced hyperglycemia: insulin closes down glucose overproduction/secretion;
- Reduced weight gain (neutral): vs. SC insulin focus on glucose disposal leads to substantial weight gain.



Oral insulin (ORMD-0801) is more like endogenous insulin for delivery

All these advantages position ORMD-0801 as a key player in the global inulin market.

Oramed is developing ORMD-0801 for both type 1 and type 2 diabetes, and targeting this new agent for the management of **excessive production of glucose at night**: a significant challenge in diabetes management.

Excessive nocturnal glucose production by the liver is frequently demonstrated in diabetes patients, which leads to a high fasting blood sugar (**FBG**), measured after an 8-hour fast. High FBG test results are a key concern in diabetes management. Current treatment is suboptimal. In only 20% of patients, blood sugar is regulated with medication and return FBG to normal levels.

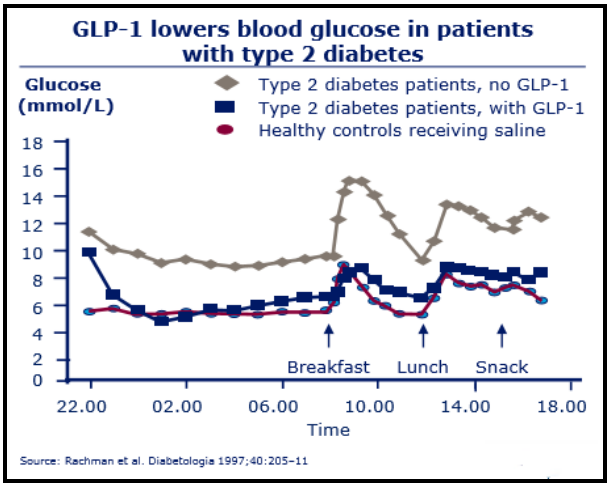
The **first indication** of ORMD-0801 reduces excessive nocturnal glucose production in the liver by acting the same way that natural insulin does.

Based on the company's current development plan, we estimate ORMD-0801 to be approved by the FDA in late calendar 2018 for both type 1 and type 2 diabetes. Peak sales could be well over $1 billion in 5 years after approval.

Another Big Market for Oramed ORMD-0901 (Oral GLP-1)

The glucagon-like peptide-1 **(GLP-1)** analogs mimic the action of GLP-1 and increase the incretin effect in patients with type 2 diabetes, stimulating the release of insulin. GLP-1 analogs have additional effects in reducing glucagon, slowing gastric emptying, and inducing satiety. In clinical practice they are associated with significant reductions in glycosylated haemoglobin (HbA_{1c}), weight loss and a low risk of hypoglycaemia. Beneficial effects have also been observed on blood pressure and lipids.

Endogenous GLP-1 is rapidly cleaved by dipeptidyl peptidase-4 (DPP-4). GLP-1 analogues mimic endogenous GLP-1 activity but are resistant to DPP-4 deactivation, resulting in prolonged activity. Therefore, both **GLP-1 analogs and DPP-4 inhibitors** are a new class of drugs for the treatment of type 2 diabetes.

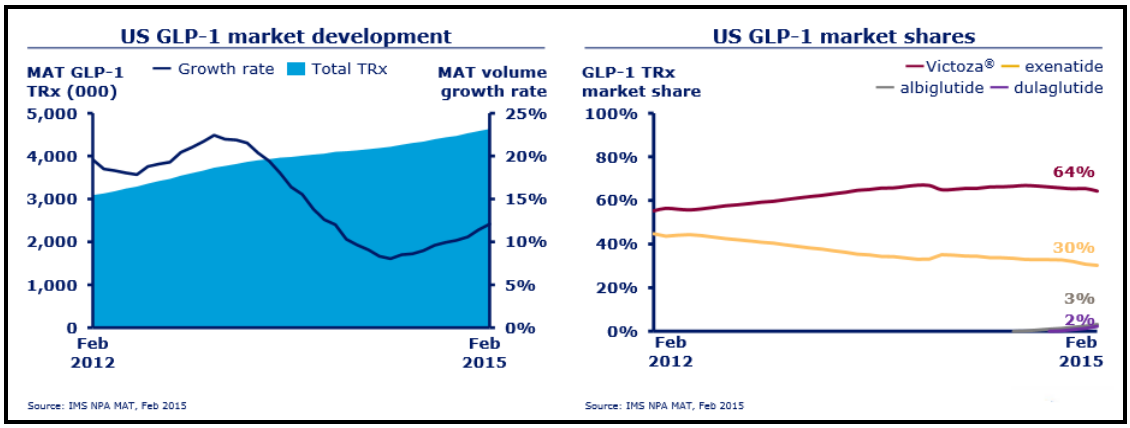


There are quite a few GLP-1 analogs currently available in the market. **Exenatide (Byetta)** was approved by the FDA in 2005. **Bydureon** (once-weekly formulation of exenatide) was approved by the FDA in 2012. Both Byetta and Bydureon were developed by Amylin Pharmaceuticals. Bristol-Myers Squibb acquired Amylin in 2012 and sold its global diabetes business to its collaboration partner AstraZeneca in 2013.

Liraglutide (Victoza, Saxenda) was approved in 2010 by the FDA and is marketed by Novo Nordisk. With 71% global market share, Victoza is currently the market leader in the GLP-1 segment.

Other big players in the GLP-1 market include Sanofi (**Lixisenatide**/Lyxumia, approved in 2013 in EU, under the FDA review), GSK (**Albiglutide**/Tanzeum, approved by the FDA in 2014) and Eli Lilly (**Dulaglutide**/Trulicity, approved by the FDA in 2014).

In the US, GLP-1 market continues to grow with Victoza and exenatide holding the majority of market share (over 94%). Victoza sales reached $2 billion while exenatide franchise sales reached $0.8 billion in 2014.



Like oral insulin, oral exenatide will have the same advantages as oral insulin.
When we discuss the market opportunity for ORMD-0901, we not only look at the current GLP-1 market, but also need to look at the **DPP-4 inhibitors** market since DPP-4 inhibitors are orally available. It is estimated that DDP-4s have a market of 3-5x the GLP-1 market due to its oral availability.

Merck's **Januvia** was the first DPP-4 inhibitor approved for type 2 diabetes. Newer drugs in this family include **Onglyza** (AstraZeneca), and **Trajenta** (**Eli Lilly)**, as well as combinations which mix the DPP-4 inhibitor with metformin. These drugs are Janumet (Merck), Kombiglyze (AstraZeneca), and Jentadueto

(Eli Lilly). Takeda is the new comer in this market with three DPP-4 inhibitor products approved: **Nesina** (alogliptin), Kazano (alogliptin and metformin HCl), and Oseni (alogliptin and pioglitazone).

Merck's Januvia/Janumet dominate the DPP-4 world with a total of $6 billion in 2014 sales followed by Onglyza/Kombiglyze franchise sales of $820 million in 2014. Trajenta/Jentadueto sales was $329 million and Nesina franchise sales was $369 million (¥44.3 billion) in 2014.

Oramed plans to start a **Phase II** study of ORMD-0901in 4Q16 pursuing the **505(b)(2) pathway**. We estimate ORMD-0901 to be approved in late 2019. Peak sales should also be over $1 billion.

INCOME STATEMENT

	2015 (Aug)					2016 (Aug)					2017 (Aug)	2018 (Aug)	2019 (Aug)	2020 (Aug)	2021 (Aug)
$ in million except per share data	Q1	Q2	Q3	Q4	FYE	Q1	Q2	Q3	Q4	FYE	FYE	FYE	FYE	FYE	FYE
Grant revenue	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
License/Royalties	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.13	$0.16	$0.20	$0.49	$1.50	$2.00	$2.50	$3.00	$5.00
Product revenue	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$10.00	$50.00	$100.00	$250.00
Total Revenues	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.13**	**$0.16**	**$0.20**	**$0.49**	**$1.50**	**$12.00**	**$52.50**	**$103.00**	**$255.00**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CoGS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	10.50	20.60	51.00
Gross Income	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.13**	**$0.16**	**$0.20**	**$0.49**	**$1.50**	**$12.00**	**$42.00**	**$82.40**	**$204.00**
Gross Margin	-	-	-	-	-	-	-	100.0%	100.0%	100.0%	100.0%	100.0%	80.0%	80.0%	80.0%
R&D	$1.30	$1.14	$0.92	$1.43	$4.78	$1.90	$1.31	$1.72	$2.00	$6.93	$10.00	$15.00	$20.00	$25.00	$35.00
% R&D	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SG&A	$0.60	$0.54	$0.72	$0.75	$2.60	$0.55	$0.73	$0.56	$0.85	$2.68	$5.50	$10.00	$15.00	$20.00	$35.00
%SG&A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other Expenses	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Operating Income	**($1.9)**	**($1.7)**	**($1.6)**	**($2.2)**	**($7.4)**	**($2.4)**	**($1.9)**	**($2.1)**	**($2.7)**	**($9.1)**	**($14.0)**	**($13.0)**	**$7.0**	**$37.4**	**$134.0**
Operating Margin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	52.55%
Other Net	$0.0	$0.0	$0.1	$0.1	$0.2	$0.1	$0.1	$0.2	$0.1	$0.4	$0.0	$0.0	($0.1)	($0.1)	($0.1)
Pre-Tax Income	**($1.9)**	**($1.6)**	**($1.6)**	**($2.1)**	**($7.2)**	**($2.4)**	**($1.8)**	**($1.9)**	**($2.6)**	**($8.7)**	**($14.0)**	**($13.0)**	**$6.9**	**$37.3**	**$133.9**
Income taxes(benefit)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$6.7
Tax Rate	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Reported Net Income	**($1.9)**	**($1.6)**	**($1.6)**	**($2.1)**	**($7.2)**	**($2.4)**	**($1.8)**	**($1.9)**	**($2.6)**	**($8.7)**	**($14.0)**	**($13.0)**	**$6.9**	**$37.3**	**$127.2**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Net Margin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Diluted Shares Out	10.1	10.8	10.8	11.5	10.8	11.6	12.7	13.1	13.5	12.7	45.0	38.0	45.0	48.0	50.0
Reported EPS	**($0.19)**	**($0.15)**	**($0.15)**	**($0.18)**	**($0.67)**	**($0.21)**	**($0.14)**	**($0.15)**	**($0.19)**	**($0.69)**	**($0.31)**	**($0.34)**	**$0.15**	**$0.78**	**$2.54**
One time charge	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*
Non GAAP Net Income	**($1.9)**	**($1.6)**	**($1.6)**	**($2.1)**	**($7.2)**	**($2.4)**	**($1.8)**	**($1.9)**	**($2.6)**	**($8.7)**	**($14.0)**	**($13.0)**	**$6.9**	**$37.3**	**$127.2**
Non GAAP EPS	**($0.19)**	**($0.15)**	**($0.15)**	**($0.18)**	**($0.67)**	**($0.21)**	**($0.14)**	**($0.15)**	**($0.19)**	**($0.69)**	**($0.31)**	**($0.34)**	**$0.15**	**$0.78**	**$2.54**

Source: company filings and Zacks estimates

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