Oramed Pharmaceuticals Inc (ORMP)

Price: $10.43 | BUY | Price Target: $23.00

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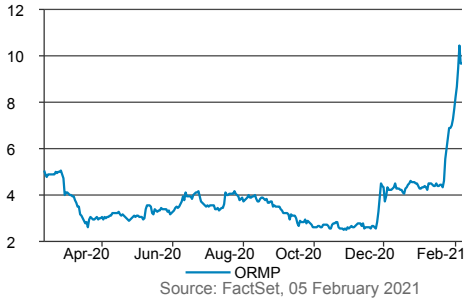
Market Data

Dividend Yield	0.00%
Average Daily Volume	716,290
Shares Out. (MM)	26.7
52 Week Range	$2.40 - $11.40
Market Cap ($M)	$278.1
Enterprise Value ($M)	$239.0

Estimates - Fiscal Year End: 12/31

	2020A		2021E		2022E	
	old	new	old	new	old	new
EBIT - --						
FY	-	(11.80)A	-	7.90E	-	(20.30)E
EPS - --						
FY	-	(0.56)A	-	0.29E	-	(0.76)E
P/E	NM		36.0x		NM	

Price Performance



Source: FactSet, 05 February 2021

A Pioneer in Oral Insulin for the Treatment of Diabetes

Oramed Pharmaceuticals is a platform technology pioneer in the field of oral delivery of protein-based medicines. Oramed is seeking to revolutionize the treatment of diabetes with ORMD-0801, the first oral insulin capsule potentially entering the diabetes market.

Initiating Coverage. We are initiating coverage of Oramed Pharmaceuticals with a BUY rating and a $23.00 target price. Our target implies a potential return of 121%. Our valuation model for Oramed is based on a risk-adjusted discounted cash flow model with a WACC of 13%.

Unique Platform Technology to Orally Deliver Protein-based Medicines. Oramed has developed a platform technology to deliver proteins through the gastrointestinal tract, preventing degradation in the stomach and stimulating absorption over the intestinal wall.

Large Commercial Opportunity. Oramed's products are targeting diseases such as diabetes, obesity and NASH, which represent large commercial opportunities. Lead drug ORMD-0801 targets a market worth an estimated $4.36 billion.

Oral Insulin for the Treatment of Diabetes. ORMD-0801, currently in Phase III trials, is designed to restore glycemic control and prevent disease progression, potentially reducing the need for insulin injections. Based on the analysis of existing data, we believe ORMD-0801 could become the first commercial oral insulin formulation for the treatment of diabetes.

Published: February 8, 2021 04:35PM EST Please see Important Disclosures in Appendix.

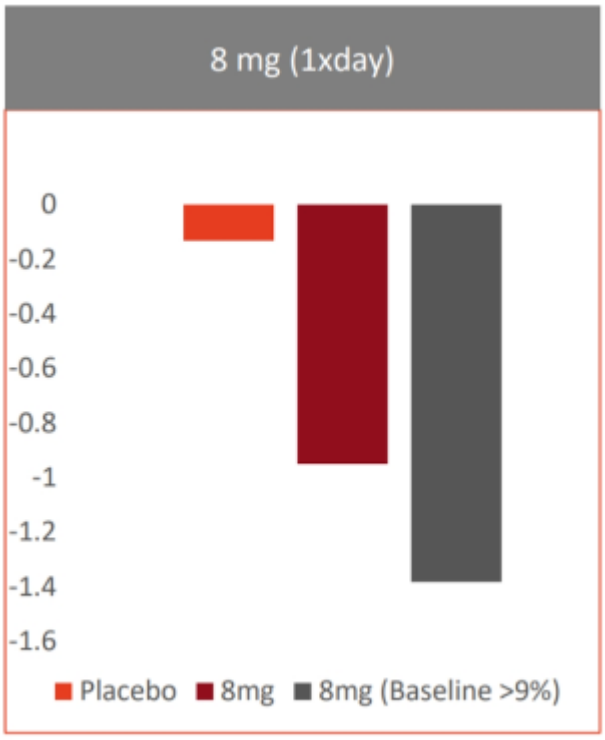
Executive Summary

We are initiating coverage of Oramed Pharmaceuticals Inc. with a BUY rating and $23.00 twelve-month target price. Using its proprietary platform technology, Oramed has developed a novel oral formulation of insulin, ORMD-0801, which is currently being evaluated in two Phase III clinical trials for the treatment of type 2 diabetes. Based on the analysis of existing clinical data, we believe ORMD-0801 will meet safety and efficacy end points in Phase III clinical trials, which will allow Oramed's management to file a BLA seeking approval of the drug for the treatment of type 2 diabetic patients. If ORMD-0801 is approved, Oramed will enjoy twelve years of market exclusivity.

Diabetes Mellitus is a chronic disease caused by deficiency in the production and/or metabolic effects of a hormone known as insulin. There are two types of diabetes mellitus, type 1 and type 2. Type 1 diabetes mellitus is caused by the lack of insulin production by beta-cells in the pancreas (often destroyed by autoimmunity), whereas type 2 is the result of deficiencies in insulin regulation of metabolism, primarily due to insulin-resistance by targeted tissues such as the liver, skeletal muscle and adipose tissue. Diabetes is clinically manifested by high levels of glucose in the blood (hyperglycemia). According to the International Diabetes Federation, there were an estimated 463 million people suffering from diabetes worldwide and an estimated 4.2 million patients died of the disease in 2019. Approximately 90% of all diabetic patients are diagnosed with type 2 diabetes. If left untreated, diabetic patients could suffer life-threatening complications. The risk of developing cardiovascular disease increases two to four fold with type 2 diabetes. The risk of developing type 2 diabetes increases seven fold for patients suffering from obesity. However, with proper treatment and chronic control of glycemia (blood glucose levels) in diabetic patients, the emergence of these complications could be delayed or prevented.

In Phase II clinical trials, Oramed demonstrated that the treatment of type 1 and type 2 diabetic patients with ORMD-0801 was safe and well tolerated, meeting primary efficacy endpoint of reducing HbA1c and preventing hyperglycemia (abnormally high blood glucose levels). Treatment of type 1 diabetic patients with ORMD-0801 (oral insulin) reduced the need for insulin injections. In February 2020, Oramed announced results from patients participating in Cohort B of the Phase IIb clinical trial. Patients receiving ORMD-0801 (8 mg) once-daily showed a 1.29% reduction in HbA1c since start of treatment (0.81% when adjusted for placebo effect). Patients with values of HbA1c higher than 9% at baseline, showed a 1.26% reduction (placebo-adjusted) in HbA1c after treatment with 8 mg of ORMD-0801 (once-daily) for 12 weeks. In our opinion, the results are clinically relevant and bode well for the potential of ORMD-0801, which we believe could meet primary safety and efficacy end points in Phase III clinical trials. In our view, Oramed Pharmaceuticals could become the first company in the industry's history to introduce an oral insulin treatment for diabetes mellitus.

Exhibit 1 – Results from the evaluation of 266-patients participating in a placebo-controlled, Phase IIb human clinical trial on the use of ORMD-0801 for the treatment of type 2 diabetes. The primary efficacy end point of the study was change in hemoglobin A1c (HbA1c) at week-12 post start of treatment. When adjusted for placebo effect, treatment with 8 mg dose of ORMD-0801 once-daily caused a 0.81 reduction in HbA1c. In patients with HbA1c levels higher than 9% at baseline, treatment with 8 mg of ORMD-0801 once-daily reduced HbA1c by 1.26% (placebo-adjusted). Results were statistically significant with a p value of 0.0276.



Source – Oramed Pharmaceuticals, Inc.

Oral insulin has significant advantages over commercially available formulations of injectable insulin. Treatment with oral insulin has an hepatocentric mechanism of action as the drug enters the liver first and the systemic circulation after. As a result, insulin levels are initially much higher in the liver than in peripheral tissues resembling normal physiological conditions. In contrast, injectable insulin gets to the systemic blood circulation and peripheral tissues first, reaching the liver later. As a result, insulin levels, after a diabetic patient received injectable insulin, are significantly lower in the liver relative to normal physiological conditions. In contrast, insulin levels in blood of diabetic patients receiving injectable insulin are relatively high (hyperinsulinemia), which could potentially cause significant side effect including severe hypoglycemia (a potentially life-threatening complication) and weight gain. We believe there is a need for oral insulin for the treatment of diabetic patients early in the disease, before progression to advance disease with microvascular and macrovascular complications, which represent the main cause of death in type 2 diabetes. In our view, Oramed's ORMD-0801 could improve the treatment algorithms for diabetes melliuts. ORMD-0801 could be used in combination with other anti-diabetes medicines including GLP-1 receptor agonists such as Novo Nordisk's Ozempic and Rybelsus, and Eli Lilly's Trulicity, as well as with drugs in the SGLT-2 class such as AstraZeneca's Farxiga and Lilly's Jardiance, for the treatment of type 2 diabetes.

In our opinion, Oramed has an experienced management team and a world-class scientific advisory board. In our view, Oramed has a robust intellectual property portfolio protecting inventions related to its oral protein delivery platform technologies, and its lead products for the treatment of diabetes, obesity and non-alcoholic

steatohepatitis (NASH), which combined represent a multibillion-dollar opportunity. Oramed's ORMD-0801 alone targets a commercial opportunity worth an estimated $4.36 billion. On January 21, 2021, Oramed announced that randomization of patients in its Phase III clinical trial on the use of ORMD-0801 for the treatment of type 2 diabetes had commenced. The news triggered a rally in the shares, which have climbed 130% since the announcement. As Oramed enters Phase III clinical trials, the last stage of clinical development before seeking drug approval, investors have started to recognize that Oramed could become the first company to introduce a commercially available oral insulin. Even after the recent rally, we believe that the current share price does not reflect the full value of Oramed's platform technologies and lead products. Assuming FDA approval of ORMD-0801 in 2024, we forecast revenue, net income and fully diluted EPS of $77.6 mm, $41.9 mm and $1.57 in F2025 (the first full year of ORMD-0801 commercialization). We value Oramed using a risk-adjusted discounted cash flow model based on a WACC of 13%. Based on our model, we calculate an implied risk-adjusted equity value of $492 mm. Based on the current share price of $10.43, our calculated 12-month target price of $23.00 corresponds to a potential implied return of 121%.

Investment Risks

• Oramed is a biotechnology company still developing its candidate medicines in human clinical trials. As such, the Company has incurred significant losses since inception. Oramed will face financial risks as it will have minimal recurring revenues until it commercializes its products, or executes a development and commercialization agreement with a potential partner, which could generate licensing fees, milestone payments, royalties and research funding.

• Oramed will be required to raise additional capital to fund its clinical programs. Management might fail to obtain the additional funding required to develop and commercialize their product candidates.

• Oramed and collaborators might fail to protect intellectual property rights.

• Oramed might not be able to retain key personnel to manage its business effectively.

• The Company will face clinical and regulatory risks as there is no guarantee that Oramed's candidate medicines will be safe and efficacious in human clinical trials, and that the Company might obtain clearance for commercialization by U.S. Food and Drug Administration (FDA). Third parties, CROs, involved in the execution of Oramed's clinical programs might not be able to enroll patients under desired timelines resulting on significant delays, and/or might fail to comply with rules and regulations.

• The FDA regulatory approval process is lengthy and complex. The FDA might disagree with the Company's clinical trial designs or interpretation of results. Thus Oramed might experience significant delays in clinical development and regulatory approval.

• The Company's management team might fail to enter into development and commercialization partnership agreements, or it might not be able to maintain its existing strategic collaborations.

• There are commercial risks as it is possible that Oramed's products might face competition in the market place. The competitive landscape in the biotechnology and pharmaceutical industries, in diabetes, endocrinology, obesity and hormone-related diseases, is dynamic, rapidly changing with the introduction of new technologies. It is possible that Oramed' competitors may develop superior therapies, which could negatively affect the Company's product sales.

• It is possible that Oramed's products might fail to obtain coverage and reimbursement in certain market segments, which could negatively affect sales of these products. There are no guarantees that the Company's products might be accepted by physicians, patients, insurance companies and other third party payors.

• Healthcare legislation reform measures in the United States and other jurisdictions may negatively impact the Company's business and results from operations. Changes to regulatory environment might affect suppliers and manufacturers of Oramed's products.

Company Description

Oramed Pharmaceuticals is a platform technology pioneer in the field of oral delivery solutions for drugs currently delivered via injection. Established in 2006, with offices in New York and Israel, Oramed has developed a novel Protein Oral Delivery (POD) technology. Oramed is seeking to revolutionize the treatment of diabetes through its proprietary lead candidate, ORMD-0801, which has the potential to be the first commercial oral insulin capsule for the treatment of diabetes. The Company is currently in Phase III clinical trials, under an Investigational New Drug application with the U.S. Food and Drug Administration, on the use of ORMD-0801 for the treatment of type 2 diabetes. In addition, Oramed is developing an oral GLP-1 (Glucagon-like peptide-1) analog capsule known as ORMD-0901.

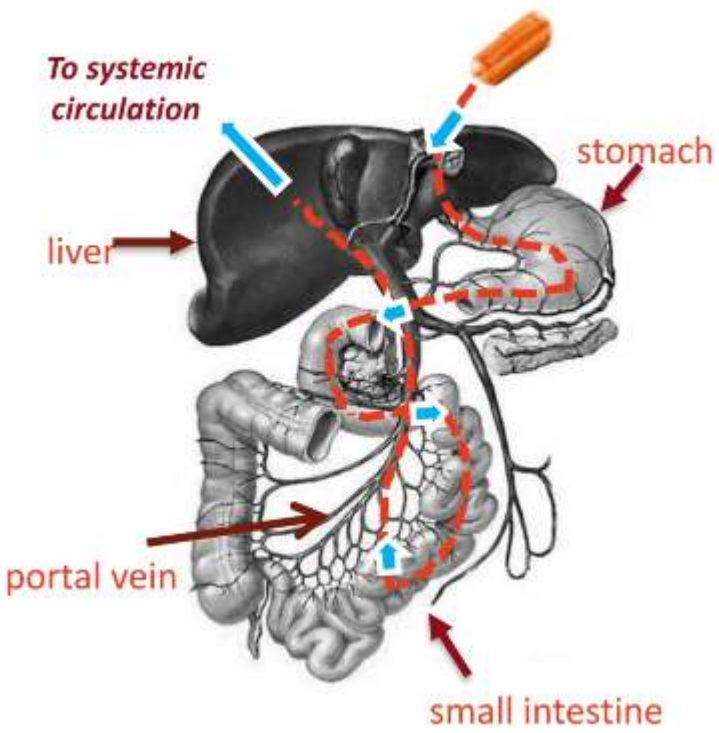
Technology – Preventing degradation of Protein-based drugs/Improving Absorption

Oramed's 'POD' (protein oral delivery) technology is designed to deliver protein-based therapeutics such as insulin via oral administration. The main goal of such a technology is the protection of candidate medicines (in the form of protein molecules) from proteases (proteolytic enzymes capable of breaking down proteins by hydrolysis). Using protease inhibitors, Oramed's technology is designed to prevent the degradation of orally delivered protein-based candidate medicines in the gastrointestinal track. Specialized protease inhibitors block the effects of proteases in the small intestine, sparing the drug protein molecule. The technology also includes an absorption enhancer supplement, which facilitates the protein-based drug passing across the intestinal barrier. To develop its lead product, oral insulin capsule known as ORMD-0801, Oramed's POD technology utilizes a three-pronged approach consisting of:

- Encapsulation of insulin;
- Protease inhibition;
- Use of a chelating agent to improve absorption through the intestinal wall.

Through encapsulation, insulin is protected from hydrolytic degradation in the stomach. The design allows for release of insulin in the small intestine. Protease inhibitors prevent degradation by enzymatic proteolysis in the brush border zone of the small intestine. The chelating agent sequesters calcium, which is required by many proteases, thus further protecting insulin from enzymatic degradation and facilitating small intestine's permeability to insulin. Oral administration of insulin permits the hormone to pass through the liver first, which is a more natural way of administering exogenous insulin. The direct placement of insulin into the systemic blood circulation after insulin injections, before reaching the liver, has been associated with multiple side effects, of which hipoglycemia (low sugar in the blood) is the most common. With oral insulin, the hormone will reach the liver through the portal vein, controlling the amount of insulin entering the systemic blood circulation thereafter, which resembles normal physiology.

Exhibit 2 – Oramed's oral insulin mimics the physiology of natural insulin. Unlike injectable insulin which enters systemic circulation (blood) and peripheral tissues first and liver second, Oramed's oral insulin enters the liver first and the systemic circulation and peripheral tissues after. This is important to maximize the effectiveness of insulin in regulating metabolism while reducing undesired side effects such as hypoglycemic episodes (abnormally and dangerous low levels of sugar in blood) and weight gain. The diagram shows how after oral administration, oral insulin (ORMD-0801) passes through the stomach into the small intestine, across the intestinal wall into the portal vein. Before entering the systemic circulation, oral insulin travels by the portal vein to the liver.



Source – Oramed Pharmaceuticals, Inc.

Product Pipeline

Oramed is currently in Phase III clinical trials on the use of its lead product ORMD-0801 for the treatment of diabetes (Exhibit 3). ORMD-0801 consists of an oral insulin capsule, which allows insulin to travel from the gastrointestinal tract via the portal vein to the liver and then to the bloodstream. This technology enables the passage of insulin to the liver first, resembling natural physiology, whereas insulin injections allows insulin to enter the blood circulation first (before reaching the liver), which magnifies the side effects of insulin treatment. Systemic insulin injections could cause hypoglycemic episodes, which could be dangerous and life-threatening in certain scenarios. This complication should not occur with ORMD-0801 treatment as it consists of oral administration of insulin ("liver first"). In 2017, the U.S. FDA communicated to Oramed that the regulatory pathway for the submission and potential approval of ORMD-0801 would be a biologics license application (BLA). As a result, the potential clearance by FDA could grant Oramed a period of twelve years of marketing exclusivity for ORMD-0801. Assuming that ORMD-0801 shows efficacy in pediatric populations, the FDA will grant Oramed an additional six months of market exclusivity.

Treatment of Type 2 Diabetic Patients with Oral GLP-1

Oramed is developing ORMD-0901, a novel oral treatment for type 2 diabetic patients. ORMD-0901 consists of an analog capsule of "glucagon-like peptide-1" (GLP-1), exenatide, to be administered orally. In 2005, injectable exenatide became the first GLP-1 receptor agonist approved by U.S. FDA. In a completed pharmacokinetic

(PK) study in healthy volunteers, treatment with ORMD-0901 showed positive results after a glucose challenge. ORMD-0901 is designed to lower blood glucose levels, reduce HbA1c, preserve beta cell function (insulin production), and promote weight loss.

Oral glucagon-like peptide-1 (GLP-1) is an incretin hormone known to stimulate the secretion of insulin from pancreatic beta cells. AstraZeneca's exenatide, an injectable GLP-1 analog, is currently marketed as two injectable formulations, Byetta (injectable exenatide, F2019 sales of $110 mm) and Bydureon (extended release ER exenatide, F2019 sales of $549 mm), for the treatment of type 2 diabetes. Oramed's ORMD-0901 consists of an orally ingestible GLP-1 capsule, developed using the Company's proprietary oral delivery technology (POD). Oramed believes an oral GLP-1 capsule will increase patient compliance, relative to injectables such as Byetta and Bydureon, resulting in a significant clinical benefit for type 2 diabetic patients. GLP-1 increases insulin production in the pancreas, reduces glucagon secretion in the liver, delays gastric emptying, induces a feeling or sensation of satiety in treated patients, which could reduce food intake resulting in weight loss. Oramed's management plans to start additional studies on the use of ORMD-0901 for the treatment of type 2 diabetes in 2021.

Exhibit 3 – Oramed's product pipeline

Source – Oramed Pharmaceuticals, Inc.

Oramed Pharmaceuticals is also developing its novel candidate medicines for the treatment of NASH and type 1 diabetes. Relative to the oral insulin type 2 diabetes programs, the NASH and type 1 diabetes clinical programs are still in early stages of clinical development.

Use of oral insulin capsule for the treatment of NASH

In June 2020, Oramed presented results from an open-label (no control patient group) clinical trial on the use of ORMD-0801 for the treatment of type 2 diabetic patients suffering from non-alcoholic steatohepatitis (NASH). A total of eight patients received 16 milligrams of ORMD-0801 (2 capsules of 8 mg each). After 12 weeks of treatment, ORMD-0801 was safe and well tolerated and reduced liver fat content (a statistically significant result with a p value of 0.035). Using "MRI-derived proton density fat fraction" (MRI-PDFF), Oramed demonstrated that treatment with ORMD-0801 resulted in a 30% reduction in liver fat content. In the trial, concentrations of gamma-glutamyltransferase (GGT), a biomarker of liver inflammation, were significantly lowered with ORMD-0801 12-week

treatment (p value of 0.008). To confirmed these results, Oramed is currently conducting Phase II clinical trials on the use of ORMD-0801 for the treatment of NASH.

Treatment of Type 1 Diabetes with Oral Leptin

In Q3/2020, Oramed conducted an exploratory study on the use of oral leptin for the treatment of type 1 diabetes. Leptin is a protein that reduces levels of the hormone known as glucagon. As a result, leptin reduces hunger causing weight loss, which makes this candidate medicine a potential treatment for metabolic distress associated with type 1 diabetes. The 10-patient proof of concept, exploratory study, measured pharmacokinetic and pharmacodynamics of Oramed's oral leptin in type 1 diabetic patients. Relative to placebo, treatment with leptin resulted in reduction of blood glucose levels during the first 30-180 minutes following the administration of leptin. In 2021, Oramed's management plans to commence a Phase II double-blind, placebo-controlled clinical trial on the use of oral leptin for the treatment of type 1 diabetes.

Other Potential Applications of POD Technology

Oramed's proprietary protein oral delivery (POD) technology could be utilized to orally deliver protein-based therapeutics (such as insulin and GLP-1 receptor agonist) and vaccines. The potential use of Oramed's POD technology to develop protein-based subunit vaccines is an important potential application, which could be implemented to develop oral vaccines for the prevention of respiratory diseases. In our opinion, Oramed's POD technology could be utilized to develop prophylactic vaccines for the prevention of influenza and SARS-CoV-2 infection (COVID-19).

Industry Overview

Treatment of Diabetes Mellitus to Prevent Disease-related Complications

If left untreated, diabetic patients could suffer life-threatening complications. The deficiency in production of insulin or resistance to metabolic effects of insulin can cause damage to various organs in the human body resulting in complications such as cardiovascular diseases, nerve damage (neuropathy), kidney damage (nephropathy) and eye diseases (retinopathy and blindness). However, with proper treatment and chronic control of diabetes, the emergence of these complications could be delayed or prevented.

In the early 1990's, the treatment of type 2 diabetes consisted primarily of insulin, sulfonylureas and metformin. Since then, significant progress has been made with several drug classes discovered and developed for the treatment of the disease. At present, there are twelve drug classes, with multiple drugs in each class, for the treatment of type 2 diabetes. Despite this progress, cardiovascular disease is still the main cause of death and disability for type 2 diabetic patients (Circulation 2016,133(24)2459-2502). However, the recent introduction of GLP-1 receptor agonists such as Novo Nordisk's Ozempic and Rybelsus, and Eli Lilly's Trulicity, have significantly reduced the risk of cardiovascular complications in type 2 diabetic patients. These novel GLP-1 receptor agonists represent a significant step forward in the management and treatment of the disease.

Improving long-term control of normal blood glucose levels (glycemic control) is critical to prevent diabetes' complications. The first robust evidence of this was provided by the landmark U.K. prospective diabetes study (UKPDS), which conclusively demonstrated how long-term glycemic control results in a reduction in the risk of developing microvascular complications and long-term macrovascular disease in type 2 diabetic patients (Lancet 1998, 352(9131)837–853; N Engl J Med 2008, 359(15)1577–1589).

The recent introduction of two novel drug classes for the treatment of type 2 diabetes, 1) "Sodium-glucose transport protein 2 inhibitors" (SGLT-2i) and 2) Glucagon-like-peptide-1 (GLP-1) receptor agonists, have significantly improved the long-term regulation of glucose metabolism, inducing weitht loss while minimizing the risk of hypoglycemia (Diabetes Metab Syndr Obes. 2019, 12, 2515-2529). In 2019, AstraZeneca's sales of Farxiga, a SGLT-2i drug, were $1.543 billion. Eli Lilly/Boeringher's Jardiance, another SGLT-2i drug, had annual sales of $944.2 mm in 2019. In the GLP-1 receptor agonist class, Eli Lilly's Trulicity 2019 sales were $4.13 billion. In the past, the need for subcutaneous

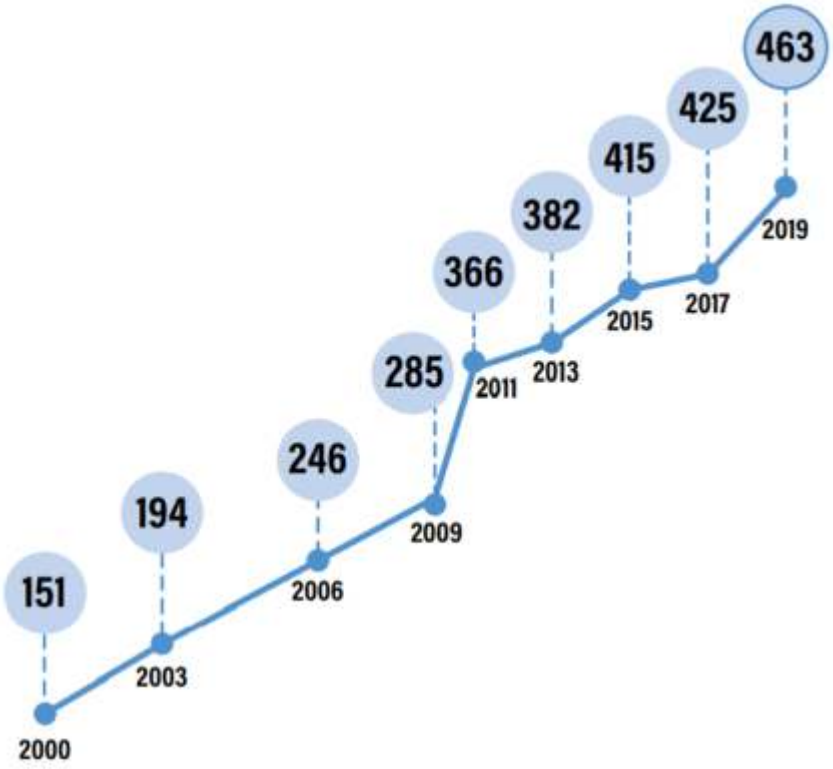
injections have been a hindrance for the GLP-1 receptor agonists class, but the recent introduction of Novo Nordisk's Rybelsus (an oral GLP-1 receptor agonist) in 2019 offers a significant improvement to the available drug portfolio for the treatment of type 2 diabetes.

GLP-1 is a 30 amino acid peptide hormone (GLP-1, 7-36) primarily secreted by specialized cells of the gastrointestinal tract known as "L" and "K" cells (Am J Physiol Endocrinol Metab 2006, 290(3)E550–559). Levels of GLP-1 significantly increase after a meal (consumption of glucose). Secreted GLP-1 binds to its receptor (GLPR) on pancreatic beta cells and other organs including the kidney and brain. The GLPR is a member of the G-protein-coupled receptor superfamily (Pharmacol Ther 2007, 113(3)546–593). The binding of GLP-1 to GLPR on pancreatic beta cells results in a significant increase in insulin production (incretin effect), which is regulated by elevated levels of cAMP in these cells.

GLP-1 delayes gastric emptying, increases feeling of satiety reducing caloric intake and causing weight loss. GLP-1 is also produced in the brain, in a discrete area at the lower brainstem (Prog Neurobiol 2010, 92(3)442–462). GLPR (the GLP-1 receptor) is present on the surface of many cells in the central nervous system (CNS) (J Comp Neurol 1999, 403(2)261–280). Treatment with GLP-1 suppresses appetite, causes taste aversion, and in experimental models, it changes behavior and memory. Recent data also demonstrates physiological effects of GLP-1 on the cardiovascular system, improving endothelial function and playing a role in VEGF-A signaling pathway (Cells 2019, 8(6); J Am Heart Assoc 2018, 7 (18):e009379).

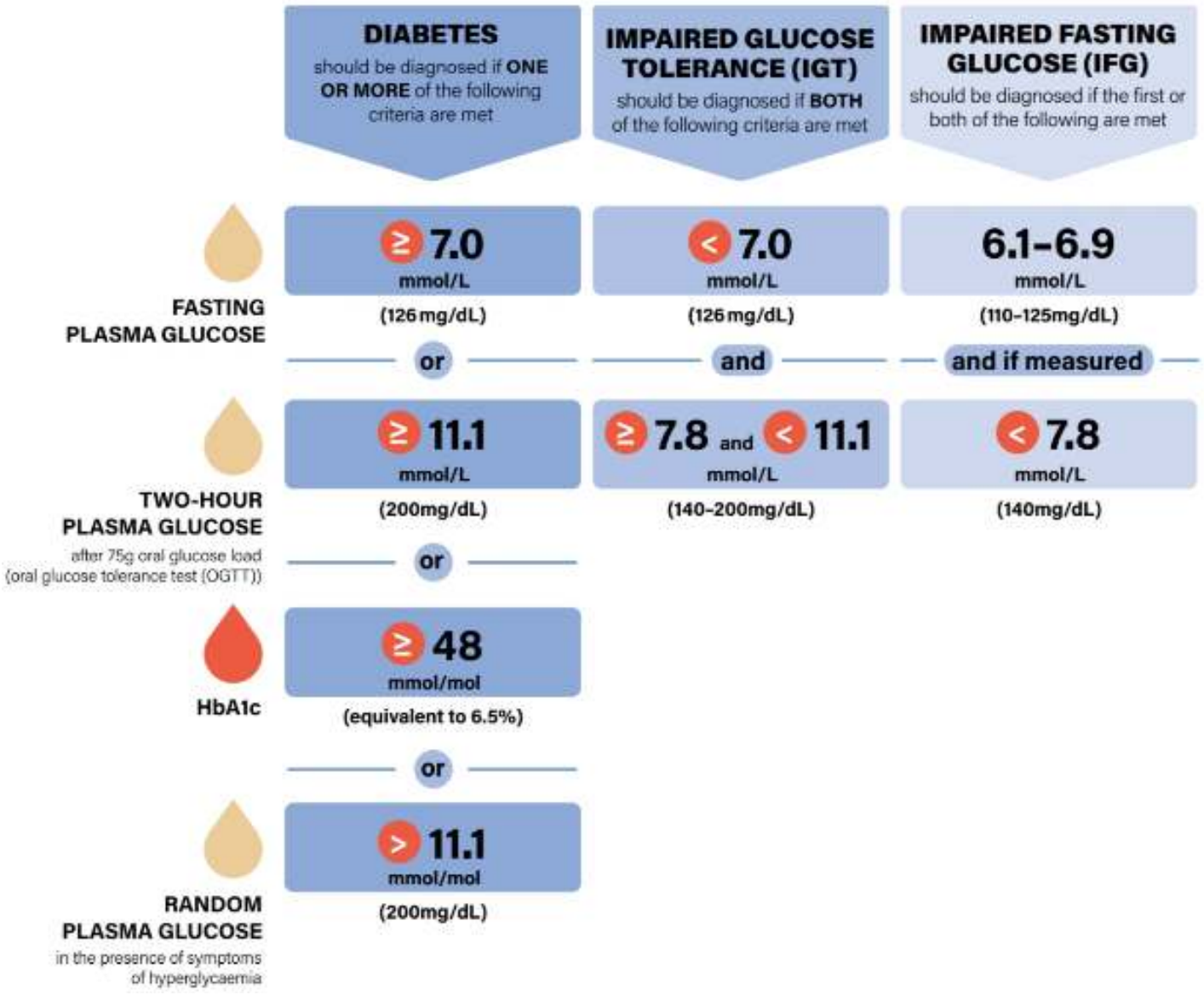
The complexity of treatment algorithms for type 2 diabetic patients has increased in recent years. Given that each drug class has advantages and disadvantages, the treatment of type 2 diabetes is currently tailored to each patient depending on drug's efficacy, durability of efficacy, cost, drug safety and related side effects, patient preference (compliance), and reduction of risk for cardiovascular and renal complications. Given oral insulin's good tolerability and safety profile, hepatocentric mechanism of action resembling normal physiology, and its role in glucose metabolism control early in the stage of disease, we believe that oral insulin, such as ORMD-0801, will be widely accepted by both physicians and patients. In our opinion, oral insulin could potentially be used in combination with GLP-1 receptor agonists.

Exhibit 4 – Prevalence of diabetes mellitus worldwide since the year 2000. In 2019, there was an estimated 463 million people suffering from diabetes worldwide, which represents a staggering increase relative to the estimated 151 million people suffering from the disease in 2000. The International Diabetes Federation predicts that 578 million people will suffer from diabetes in 2030.



Source – International Diabetes Federation (IDF)

Exhibit 5 – Diabetes Mellitus is diagnosed by the presence of high levels of glucose in the blood (hyperglycemia). The increase in levels of hemoglobin A1c (HbA1c) has become the preferred primary efficacy end point of most human clinical trials in diabetes. HbA1c measures long-term performance of a patient (average blood glucose levels for the past two to three months) when compared to other tests such as fasting blood glucose, which evaluates patient performance at the time of evaluation. A patient is diagnosed with diabetes when levels of fasting plasma glucose are equal or higher than 7 millimolar (mmol/L), or HbA1c is equal or higher than 48 mmol/mol (equivalent to 6.5%). The goal of diabetes therapy is to keep HbA1c below 7%. Fasting is defined as no caloric intake for at least 8 hours.



Source – International Diabetes Federation (IDF)

Oral Insulin for the treatment of Diabetes Mellitus

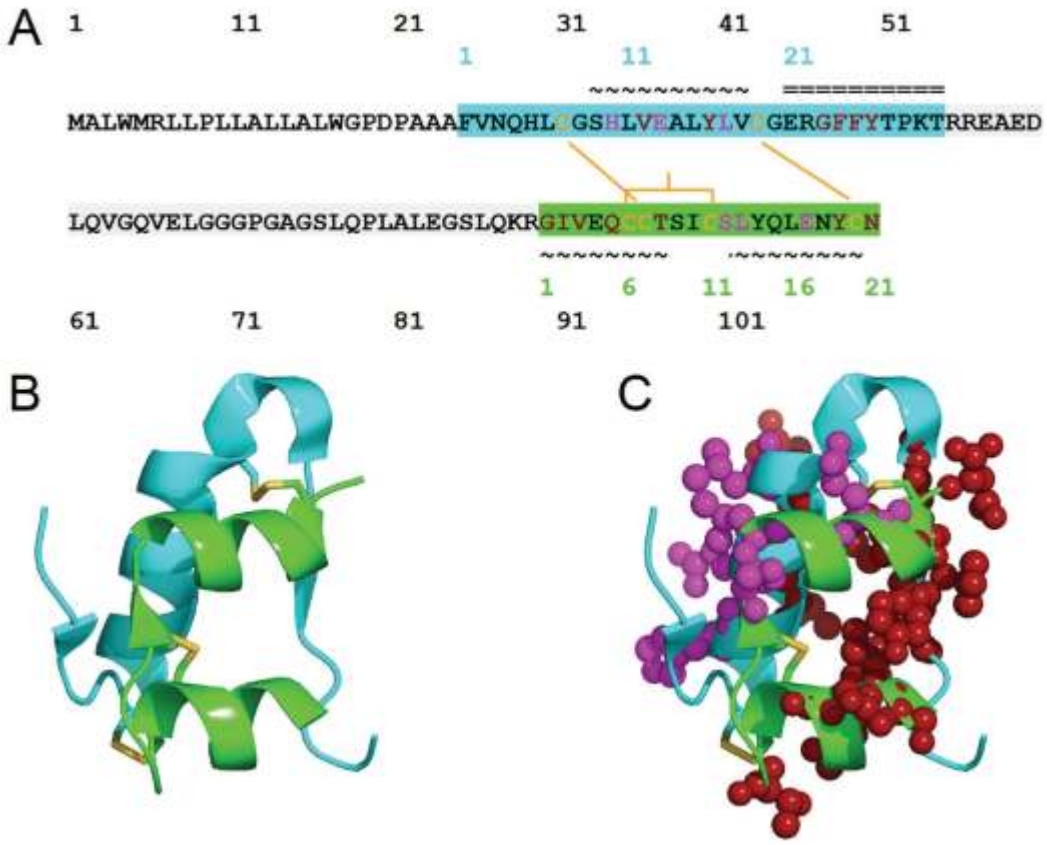
Diabetes Mellitus is a chronic disease caused by deficiency in a hormone known as insulin. This deficiency could be due to a lack of production of insulin by beta-cells in the pancreas, or deficiency in insulin-regulatory effects

on metabolic pathways, which could be due to insulin-resistance among other causes. Diabetes is manifested by high levels of glucose in the blood (hyperglycemia). Insulin is one of the main drug treatments for diabetes mellitus. Diabetes is a disease characterized by high levels of sugar in the blood (hyperglycemia). There are two types of diabetes:

Type 1 diabetes is primarily caused by lack of insulin production. The disease is caused by an autoimmune response attacking the beta islet cells in the pancreas, which are responsible for insulin secretion. Patients are treated with insulin injections. Eli Lilly conducted a 389-subject clinical trial on the use of its oral formulation of insulin to prevent type 1 diabetes. The subjects who enrolled in the trial were first/second-degree relatives of patients with type 1 diabetes. Relative to placebo, Lilly's oral insulin did not reduce the risk of developing diabetes in this high risk population (28.5% for insulin group compared to 33% for placebo control group). The data was not statistically significant (JAMA 2017, 318(19)1891–1902). Although oral insulin did not prevent the onset of diabetes in high risk subjects, insulin has been and still is the cornerstone treatment for type 1 diabetic patients. Type 1 diabetic patients require insulin injections daily. Without insulin treatment, these patients cannot survive.

Since its discovery in 1921, insulin has been the most important treatment for diabetes mellitus. Human insulin has a molecular weight of 5,808 dalton. Insulin is comprised of two polypeptidic chains. The A chain consists of 21 amino acid residues, whereas the B chain has 30 amino acid residues. Both chains are connected by disulfide bonds (Exhibit 6) (J Endocrinol Metab 2015, 5(5)273-283). In 1923, the Novel Prize Committe awarded the Nobel Prize in Physiology and Medicine to Dr. Frederick Banting and J.J.R. Macleod from the University of Toronto, Canada, for the discovery of insulin. In 1958, Frederick Sanger won the Nobel Prize for determining the primary structure (amino acid sequence) of insulin.

Exhibit 6 – The structure of human insulin. A) Amino acid residues sequence of human insulin (preproinsulin). Chain A (green) and Chain B (cyan). B) Secondary structure (tridimensional) of insulin. C) Spheres depict the insulin amino acid residues that bind to the insulin receptor.

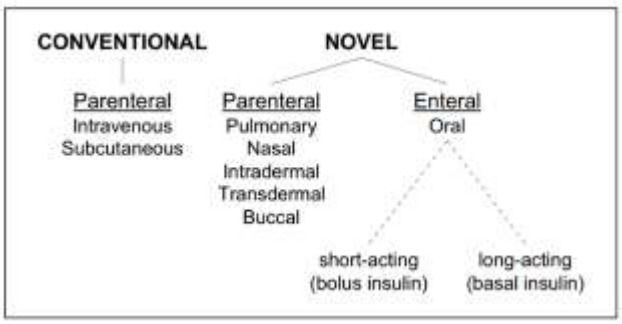


Source - J Endocrinol Metab 2015, 5(5)273-283

Approximately 90% of diabetic patients are diagnosed with type 2 diabetes, which increases the risk of developing cardiovascular disease by two to four fold. Obese patients have an estimated seven fold higher risk of developing type 2 diabetes. Type 2 diabetes is attributed to various pathological mechanisms, of which, insulin resistance plays a critical role. A type 2 diabetic patients produces insulin, but his tissues do not respond to the hormone. As a result, the body increases insulin production to compensate. As the disease progresses, beta-cells in the pancreas through attrition (overworking) claudicate in later stages of type 2 diabetes, given rise to a deficiency in insulin production. At diagnosis, most type 2 diabetic patients are treated with just diet and exercise, but if hyperglycemia persists, these patients are treated with one or a combination of glucose-lowering drugs including sulphonylureas, dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) analogues. When this combination treatment does not longer work, type 2 diabetic patients receive insulin therapy. As the disease progresses, type 2 patients will become insulin dependent just as type 1 diabetic patients.

There are different kinds of insulin formulations. The optimal insulin treatments are basal insulin and bolus insulin (Exhibit 7). Basal insulin treatment is designed to control glucose levels in fasting (before a meal) conditions, whereas bolus insulin is designed to lower glucose levels during and after a meal (prandial and post-prandial).

Exhibit 7 – Insulin could be administered via different routes. Novel insulin treatments, bolus and basal insulin, are designed, respectively, to control blood glucose levels during and after a meal (prandial, post-prandial), and during fasting (before a meal or pre-prandial) conditions and.



Source - Journal of Diabetes Science and Technology 2014, 8(3) 458–465

The use of insulin injections via subcutaneous administration in diabetes patients is often associated with cardiovascular complications and weight gain (J Environ Pathol Toxicol Oncol 2017, 36(4)283-291). Other complications of insulin injections include peripheral hyperinsulinemia, smooth muscle cell proliferation, diabetic macro and micro angiopathy, lipoatrophy (loss of subcutaneous fat) or lipohypertrophy (formation of fatty lumps on the skin).

To overcome the complications of insulin injections, one potential solution is the administration of insulin via the oral route (Nature Reviews Endocrinology 2019, 15, 191). The administration of inhaled insulin, intranasal, intrapulmonary routes, sublingual have been tried without success. Thus far oral insulin seems to be the best potential delivery method. However, the delivery of oral insulin has been challenging due to poor bioavailability, a low diffusion rate through the intestinal mucus layer and the effect of proteases (enzymes involved in breaking down proteins and peptides) capable of degrading insulin, which is a protein.

In type 2 diabetes, the convenience of oral insulin might allow for earlier commencement of insulin therapy in these patients, with improved compliance and long-term effects (Nature Commun 2020, 11, 3746, doi:10.1038/s41467-020-17487-9).

Among many challenges to overcome to develop a successful oral insulin regimen, there are two crucial pharmacological issues:

• Sufficient bioavailability;

• Clinical performance in terms of safety, efficacy and low pharmacodynamic variability.

Given the difficulty of overcoming these challenges, most efforts to develop an effective oral insulin treatment rarely pass the preclinical testing and do not reached human clinical trials.

The biotechnology industry has utilized different technologies to develop an effective oral insulin formulation, including the following (Ther Deliv 2015, 6, 973–987; J Diabetes Sci Technol 2014, 8, 458–465; Nat Rev Drug Discov 2016, 15, 425–439):

• Nanoparticles;

• Liposomes;

• Self-emulsifying systems;

• Hydrogels

The encapsulation of insulin into polymer-based nanoparticles could potentially improve insulin's oral bioavailability (Biotechnol Adv 2015, 33(6 Pt 3)1342-54). The industry has tried to develop an oral insulin formulation for the treatment of diabetes almost since insulin was discovered in 1921. The fact that there is no oral insulin in the market speaks volumes about the challenges of such endeavor. Different polymers have been used including chitosan, dextran, alginate, poly-gamma-glutamic acid, hyaluronic acid, poly-lactic acid, poly-lactide-co-glycolic acid, polycaprolactone, acrylic polymers and polyallylamine. There are no sufficient studies on the potential long-term safety of these polymers as insulin carriers. It is for this reason that natural polymers (chitosan, alginate, starch, pectin, casein, dextran, gelatin and cyclodextrin), which are potentially safer, are preferred as a method to encapsulate oral insulin (Int J Biol Macromol 2017, 103, 889-901). To overcome existing challenges, the industry has tried to optimize different nanocarriers including novel designs such as chitosan-based glucose-responsive nanoparticles, layer by layer technique-based nanoparticles and switterion (molecule with same number of positive and negative charges) nanoparticles (J Control Release 2017, 264, 247-275).

Given the importance of providing prandial (during intake of a meal) glycemic (blood glucose level) control, the effect of food on oral insulin absorption has to be investigated. The intake of oral insulin just prior to starting a meal seems to significantly hamper insulin absorption for most tested formulations. Given that fast-acting injectable insulin analogs are commercially available, we believe that an oral insulin formulation requiring administration of one hour or more before a meal will perform poorly in the market.

Advantages of Oral Insulin Treatment

Besides overcoming the challenges of needles and side-effects of parenteral insulin, medical scientists believe oral insulin has a more important clinical advantage. Oral insulin enters the portal vein and liver first, which has significant implications for the wellbeing of a diabetic patient. By going to the portal vein and liver before accessing peripheral tissues, oral insulin mimics the natural mechanism of insulin secretion and subsequent physiological effects (Diabetes Care 2002, 25(11)2074-2080; Diabetes Metab 2002, 28(2)133-137; Diabetes Technol Ther 2015, 17(6)379-384). In normal physiological conditions, the metabolism of glucose occurs primarily in the liver, where insulin exerts its effects after secretion by pancreatic cells. However, injectable insulin goes into the systemic circulation first, and then reaches the liver. The importance of insulin reaching the liver first, before reaching the systemic circulation, is paramount to avoid hyperinsulinemia (abnormally high levels of insulin in blood), hypoglycemia and other complications associated with insulin injections such as weight gain. Given that oral insulin resembles natural pancreatic insulin, scientists are hopeful that oral insulin will not be associated with hyperinsulinemia and hypoglycemic episodes seen with injectable insulin (Diabetes Care 2009, 32(8)1372-1377). Diabetic patients receiving insulin injections have a threefold increased risk of severe reactions including hypoglycemia (abnormally low levels of glucose in blood) relative to control patient groups (Endocrinol Metab Clin North Am 2012, 41(1)57–87). The main organs affected by hypoglycemia associated with insulin injections include the brain and heart. Potential cardiovascular complications resulting from severe hypoglycemia include cardiac ventricular repolarization and sudden death. Hypoglycemia associated with insulin injections occurs more often in type 1 diabetic patients than type 2, which is thought to be due to greater natural insulin production by pancreatic beta cells in type 2 diabetic patients as well as better preserved regulatory and protective responses in type 2 diabetes.

The advantages of delivering insulin directly into the portal vein have been demonstrated using intraperitoneal insulin infusions, direct intra-portal vein insulin administration and use of hepato-selective insulins. In addition, the use of long-acting parenteral insulin with a circulation depot (insulin detemir) has been shown to have higher liver selectivity.

In diabetic patients, there is often miss-regulation of growth hormone (GH) physiology. This phenomenon is thought to be caused by the lack of insulin or low levels of insulin (insulinopenia) in the portal vein. In contrast, when insulin levels in the portal vein are normal, there is an increase in the sensitivity of the liver to the presence of GH, which results in higher levels of insulin-like growth factor-1 (IGF-1) and better control of glucose and lipid metabolism. In clinical trials, the administration of insulin to type 1 diabetes patients by continuous intraperitoneal insulin infusion or

intraportally (into the portal vein), instead of subcutaneously, resulted in beneficial effects on the "growth hormone-insulin like growth factor1" axis (GH-IGF1-IGFBP axis).

Oral insulin treatment could potentially improve the insulin-to-glucagon ratio in the portal vein to favor hepatic glucose sequestration and restoration of glycogen storage in the liver. The replenishment of glycogen stores is important to combat episodes of hypoglycemia in diabetic patients as glycogenolysis (or degradation of glycogen) is an effective mechanism to normalize glucose levels in the blood.

Importance of variability associated with insulin treatment of diabetic patients

Given its known relatively narrow therapeutic window, the use of insulin doses needs tight monitoring, and requires a consistent and reproducible absorption index in diabetic patients. At present, the administration of insulin injections is still challenged by variability and inconsistencies of therapeutic effects among treated patients (Diabetes Obes Metab 2013,15(8)701-712). Most of the variability observed in diabetic patients treated with injectable insulin is attributed to variability in absorption, which varies from 20% to 55%. For oral insulin, given the intrinsic low bioavailability, this variability in absorption is probably amplified generating a significant challenge for the field. There is therapeutic variability among different treated patients, and also individual variability for a single treated patient over time. Oramed, which is emerging as a leader in oral insulin area, has achieved bioavailability of 5% to 8% with its candidate oral insulin compound ORMD-0801. After successfully completing Phase II clinical trials, Oramed will continue to monitor therapeutic variability in the Phase III clinical trials on the use of its oral insulin treatment for type 2 diabetes.

Importance of HbA1c in the monitoring and diagnosis of type 2 diabetes

Hemoglobin A1c (HbA1c) is currently the most useful biomarker for the diagnosis and monitoring of diabetes mellitus (Journal of Clinical Pathology 2019, 72, 12-19). HbA1c levels are directly correlated with the incidence of complications of diabetes mellitus. Diabetic patients suffering from complications such as diabetic nephropathy (kidney disease), diabetic neuropathy (neurological disease) and diabetic retinopathy (eye disease) have higher levels of HbA1c. Given that HbA1c accumulates inside the red blood cells, it becomes a long-term biomarker to monitor diabetic patients.

HbA1c, what is it?

By definition, HbA1c is a subfraction of glycated hemoglobin (hemoglobin protein with sugars attached to it). Glucose in the blood enters the erythrocyte (red blood cells) and is added to the N-terminal domain of hemoglobin beta chain. The higher the levels of blood glucose, the higher the levels of HbA1c inside red blood cells. Erythrocytes (red blood cells) contain hemoglobin, a protein responsible for oxygen transport to tissues. Red blood cells have a glucose receptor on the cell surface known as GLUT1 channel, which actively transports glucose from the extracellular millieu to the cell's interior through the cell membrane. As a result, levels of glucose in the extracellular and intracellular (inside red blood cell) environments are almost equivalent. HbA1c is a good biomarker for diabetes. The value of HbA1c reflects the average levels of glucose in blood, extracellular and intracellular millieu for the last 120 days. Thus HbA1c is a better estimate of chronic hyperglycemia (abnormally high sugar in blood) than acute changes in glucose metabolism. In clinical practice, a change in HbA1c of 5.5 millimolar or 0.5% is considered significant or clinically relevant for type 2 diabetic patients (Neth J Med 2014, 72, 462–6).

Correlation between high levels of HbA1c and Diabetes's complications

The GLUT1 channel responsible for transport of glucose through the cell membrane in red blood cells, which gives rise to HbA1c, is also present on the surface of cells in tissues involved in diabetes complications such as kidney, brain and nerves, and eye tissues. Chronic high levels of glucose in blood (hyperglycemia) in diabetic patients translate into high levels of glucose inside tissues, establishing a direct correlation between high levels of HbA1c and high levels of intracellular glucose in kidney, peripheral nervous system and eye tissues. There is a correlation between high levels of HbA1c in diabetic patients, and the incidence of diabetes complications in these patients.

Effect of oral glucose lowering agents in HbA1c levels

Although existing oral glucose lowering agents have limitations regarding safety and tolerability relative to Oramed's ORMD-0801, these compounds are effective in lowering mean HbA1c.

• In a reported study on the use of metformin in combination with sulfonylurea, pioglitazone or sitagliptin for the treatment of type 2 patients with baseline HbA1c higher than 11%, the treatment caused a reduction in HbA1c from 11.6% to 6.0% (Diabetes Metab J 2013, 37, 465-474). Notably, the patients enrolled in the study were "drug-naïve", meaning they have not taken oral glucose lowering agents before. This patient population is relatively easier to treat than patients with advanced disease, refractory to treatment.

• GlaxoSmithKline performed a study on the use of Avandamet (metformin in combination with rosiglitazone) for the treatment of type 2 patients with baseline HbA1c of 8.9%. This study showed a mean HbA1c reduction of 2.3%.

• In another trial, type 2 patients treated with metformin plus sitagliptin showed a 2.1% reduction in placebo-adjusted mean HbA1c from 8.8% at baseline (Diabetes Care 2007, 30, 1979-87). In this study, patients with baseline HbA1c of more than 9% showed a 2.6% reduction in HbA1c post-treatment.

• Type 2 diabetes patients with baseline mean HbA1c of 9.1% saw reductions of 2% when treated with metformin plus dapagliflozin (Int J Clin Pract 2012, 66, 446-456).

• The drug combination of exenatide and dapagliflozin lowered mean HbA1c by 2.2% in type 2 diabetic patients with baseline mean HbA1c of 10%. The same drugs, exenatide and dapagliflozin, when used as monotherapy resulted in reductions in mean HbA1c of 1.9% and 1.6%, respectively (Lancet Diabetes Endocrinol 2016, 4, 1004-1016).

• Studies comparing basal insulin to glucagon-like-peptide-1 (GLP-1) receptor agonists suggest superiority of GLP-1 receptor agonists with higher reductions in HbA1c (Lancet Diabetes Endocrinol 2014, 2, 464-473; Diabetes Obes Metab 2015, 17, 145-151).

Clinical Programs

Oramed will conduct two Phase III clinical trials on the use of oral insulin capsule, ORMD-0801, for the treatment of type 2 diabetes. Both trials are designed as placebo-controlled, double blind, multicenter Phase III clinical trials, which will enroll a total of 1,125 type 2 diabetic patients. Patients will receive treatment with ORMD-0801 for six months, and followed for another six months to monitor safety data. Final results from both clinical trials are expected in 2023. In our opinion, treatment with ORMD-0801 will show a clinical benefit in type 2 diabetic patients.

Phase III clinical trial ORA-013-1

The ORA-013-1 clinical trial is evaluating the safety and efficacy of ORMD-0801 in 675 patients suffering from type 2 diabetes, who have shown inadequate glycemic control despite of taking two or three oral glucose-lowering agents. This trial is being conducted in the United States.

On January 21, 2021, Oramed Pharmaceuticals announced that randomization of patients in ORA-013-1 Phase III clinical trial has commenced. The study is being conducted according to the U.S. FDA approved protocols. The randomized, double blind, ORA-D-013-1 Phase III clinical trial will enroll 675 type 2 diabetic patients (currently on two or three oral glucose-lowering medicines) across 75 clinical sites throughout the U.S. The primary efficacy endpoint of the trial is glycemic control (measuring reduction in HbA1c). Secondary endpoints include fasting plasma glucose at 26 weeks. Patients participating in the trial will be divided into three groups:

1. Patients will receive 8 mg ORMD-0801 twice-daily at night and 45 minutes before breakfast;

2. Patients will receive 8 mg ORMD-0801 once-daily at night, and will receive a placebo 45 minutes before breakfast;

3. Patients will receive placebo twice-daily at night and 45 minutes before breakfast.

All patients (three patient groups) will receive treatment for 6 months.

Phase III clinical trial ORA-013-2

The ORA-013-2 clinical trial will evaluate the safety and efficacy of ORMD-0801 in 450 type 2 diabetic patients showing inadequate glycemic control despite of treatment with metformin monotherapy or diet modification. This trial will be conducted in the U.S, Europe and Israel. The results from this study will complement results from ORA-013-1. Data from both clinical trials will become part of the BLA application seeking FDA approval to commercialize ORMD-0801 for the treatment of type 2 diabetic patients in United States.

Use of Oral Insulin for the Treatment of NASH

Oramed is currently conducting a Phase II clinical trial on the use of ORMD-0801 for the treatment of diabetic patients suffering from "non-alcoholic steatohepatitis" (NASH). The trial will be conducted in United States, Europe and Israel. The efficacy endpoints of the study are "MRI-derived proton density fat fraction" (MRI-PDFF) measured over 12 weeks, as well as change in liver fibrosis and liver steatosis. Oramed's management expects completion of this study in 2021. Prior results from studies on the use of ORMD-0801 for the treatment of NASH in diabetic patients were positive, showing a 30% relative reduction in fatty liver content (as measured by MRI-PDFF). Treatment with ORMD-0801 for 12 weeks also resulted in improvements in two critical endpoints: "gamma-glutamyltransferase" (GGT), which is a key biomarker for chronic hepatitis (liver inflammation), and "fasting insulin levels". In this study, treatment with ORMD-0801 was safe and well tolerated.

Treatment of Type 2 Diabetic Patients with Oral GLP-1

Oramed is developing ORMD-0901, a novel oral treatment for type 2 diabetic patients. ORMD-0901 consists of an analog capsule of "glucagon-like peptide-1" (GLP-1) to be administered orally. In a completed pharmacokinetic (PK) study in healthy volunteers, treatment with ORMD-0901 showed positive results after a glucose challenge. ORMD-0901 is designed to lower blood glucose levels, reduce HbA1c, preserve beta cell function (insulin production), and promote weight loss.

Oral glucagon-like peptide-1 (GLP-1) is an incretin hormone known to stimulate the secretion of insulin from pancreatic beta cells. Oramed's ORMD-0901 consists of an orally ingestible GLP-1 capsule, developed using the Company's proprietary oral delivery technology. In February 2019, Oramed completed a Phase I pharmacokinetic (PK) study to evaluate the safety and pharmacokinetic properties of ORMD-0901. Oramed's management plans to start additional studies on the use of ORMD-0901 for the treatment of type 2 diabetes in 2021. In terms of safety, monitoring patients for nausea, vomiting and diarrhea will be important as these side effects are common for the GLP-1 receptor agonist class of medicines. Thyroid cancer is common as well with the use of GLP-1 receptor agonists.

Treatment of Type 1 Diabetes with Oral Leptin

In Q3/2020, Oramed conducted an exploratory study on the use of oral leptin for the treatment of type 1 diabetes. Leptin is a protein that reduces levels of the hormone known as glucagon. As a result, leptin reduces hunger causing weight loss, which makes this candidate medicine a potential treatment for metabolic distress associated with type 1 diabetes. The 10-patient proof of concept, exploratory study, measured pharmacokinetic and pharmacodynamics of Oramed's oral leptin in type 1 diabetic patients. Relative to placebo, treatment with leptin resulted in a reduction of blood glucose levels during the first 30-180 minutes following the administration of leptin. In 2021, Oramed's management plans to commence a Phase II double-blind, placebo-controlled clinical trial on the use of oral leptin for the treatment of type 1 diabetes.

Prior Results from Oramed's Clinical Programs on the use of Oral Insulin for the Treatment of Diabetes

Oramed's oral insulin formulation, ORMD-0801, has been evaluated in several human clinical trials. More than 900 subjects have been treated with ORMD-0801. More than 10,000 doses of ORMD-0801 have been administered to

patients without any serious adverse events. In early clinical testing, five formulations of ORMD-0801 containing distinctive amounts of adjuvant were evaluated. In most studies, Oramed's formulations were effective lowering blood glucose in average between 11%-35% (Diabetes Obes Metab 2010, 12, 219-223). The most effective formulation significantly reduced blood glucose in 5 out of eight subjects, but three patients did not respond as well demonstrating the importance of therapeutic variability in this patient population.

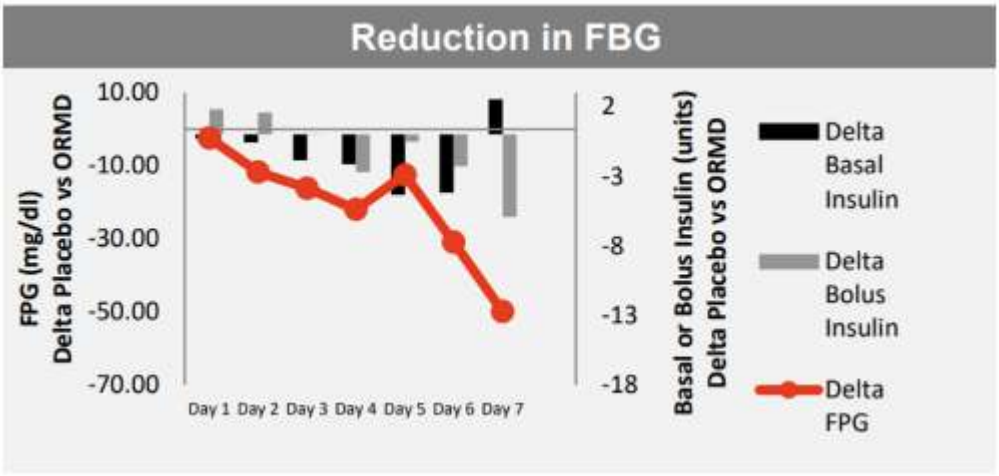
In another clinical trial, Oramed's oral insulin treatment increased levels of insulin in 61% of the treatment sessions, again demonstrating the importance of patient variability (Diabetes 2010, 59 (suppl 1)521). In these studies, oral insulin was administered between 10-90 minutes before a meal. In both type 1 and type 2 diabetic patients, the data showed that Oramed's oral insulin was safe and well tolerated over the six-week treatment period (once-daily dosing regimen). In type 1 diabetic patients with HbA1c higher than 7.5% (poorly controlled patients), Oramed's ORMD-0801 was efficacious in reducing blood glucose levels and HbA1c (PLOS ONE 2013, 8:e59524). During clinical development, Oramed has improved and optimized ORMD-0801 formulation and delivery technology, reducing interpatient and intra-patient variability.

In type 2 diabetes, insulin treatment is reserved for later stages of the disease. Oramed hopes to change this paradigm with its oral insulin by providing a safer version of insulin treatment with ORMD-0801. Oramed does not intend to replace parenteral insulin with its oral insulin capsule, but instead the Company plans to target early stages of type 2 diabetes mellitus to reduce excess hepatic glucose production, inhibit insulin resistance and restore hormonal balance between insulin and glucagon resulting in replenish glycogen storage in the liver. In addition, Oramed hopes to reduce the amount of injectable insulin needed by type 1 diabetic patients.

Results from Clinical Trial on the use of Oral Insulin for the Treatment of Type 1 Diabetes

In a clinical trial on the use of Oramed's oral insulin for the treatment of type 1 diabetic patients, the patients showed a significant reduction in postprandial (after meal was taken) glucose concentrations (PLOS ONE 2013, 8(4)e59524). When oral insulin was administered preprandially (before meal was taken), the treatment reduced both fasting blood glucose levels and reduced the requirement for fast-acting insulin doses (Diabetes Obes Metab 2010, 12(3)219-223).

Exhibit 8 – Results on the use of ORMD-0801 for the treatment of type 1 diabetes. This study included 25 patients suffering from type 1 diabetes. Participants received ORMD-0801 three times at mealtime for seven days. The primary efficacy end point of the trial was change in "exogenous insulin requirement". The graph shows "Fasting Plasma Glucose" (FPG) levels (FPG is the same as FBG or fasting blood glucose). Patients' fasting consists of eight hours without anything to eat or drink (except water) before testing. Levels of FPG above 126 mg/dl are a sign of diabetes mellitus. Treatment with ORMD-0801 resulted in lowering of FPG and a significant reduction in exogenous insulin requirement (both basal insulin and bolus insulin requirements were reduced).



Source – Oramed Pharmaceuticals, Inc.

Results from Clinical Trial on the use of Oral Insulin for the Treatment of Type 2 Diabetes

Oramed also conducted a clinical trial on the use of its proprietary oral insulin for the treatment of type 2 diabetes. In this study, patients received oral insulin for six weeks, once-daily at bedtime. The treatment lowered fasting blood glucose levels and reduced levels of CRP ("c-reactive protein"), a biomarker of inflammation. In a recently completed Phase IIb clinical trial, Oramed demonstrated that treatment with oral insulin lowers mean nighttime glucose levels and reduced the "mean 24-hour glucose", fasting glucose and daytime glucose.

Exhibit 9 – Results from a 180-patient, placebo-controlled, Phase II clinical trial on the use of ORMD-0801 for the treatment of type 2 diabetes. The clinical trial was conducted at 33 sites in the United States. Participating patients received one dose of ORMD-0801 every night for a period of 28 days. "Continuous Glucose Monitoring" (CGM) showed a reduction of glucose levels (nighttime CGM, mean % change, mean mg/dl change and median mg/dl change from run-in period) in treated patients (top three panels). Treatment with ORMD-0801 also met secondary endpoints including "24-hours glucose levels" in mg/dl, "fasting glucose" (5AM to 7AM), and "daytime glucose" (6AM to 10PM) measured from run-in period (bottom three panels). The results were statistically significant with p value of less than 0.05.

Source – Oramed Pharmaceuticals, Inc.

Oramed used a run-in period in the 180-patient Phase II clinical trial (Exhibit 9). A run-in period is a time period after patient inclusion, but before patient randomization, in a human clinical trial used to exclude certain patients from continuing their participation in the study. In general, patients are excluded from a clinical trial during a run-in period due to noncompliance to treatment or data collection or response to placebo. Approximately 5% of human clinical trials are designed with a run-in period.

Oramed's ORMD-0801 lowered HbA1c in type 2 diabetic patients in Phase IIb clinical trial

Oramed Pharmaceuticals conducted a 347-patient Phase IIb human clinical trial evaluating the use of oral insulin ORMD-0801 for the treatment of type 2 diabetes. The trial initially included 36 patient recruiting sites in the United States. Only 34 sites ended up participating in the trial as two sites were excluded due to "treatment by center interaction", which is caused by variability in several trial parameters across centers including differences in patient referral patterns, clinician skills, supportive care, implementation of the treatment arm design, clinical evaluation of patients. In the trial, 347 patients were enrolled (baseline HbA1c was measured) in the trial to receive ORMD-0801 treatment. The 347 patients represent the "intended to treat patient population" (ITT). As a result of the two recruiting sites excluded due to "treatment by center interaction", 49 patients were excluded from the trial. Only 298 patients were included in the primary analysis, and 266 patients were included in the final analysis of the data.

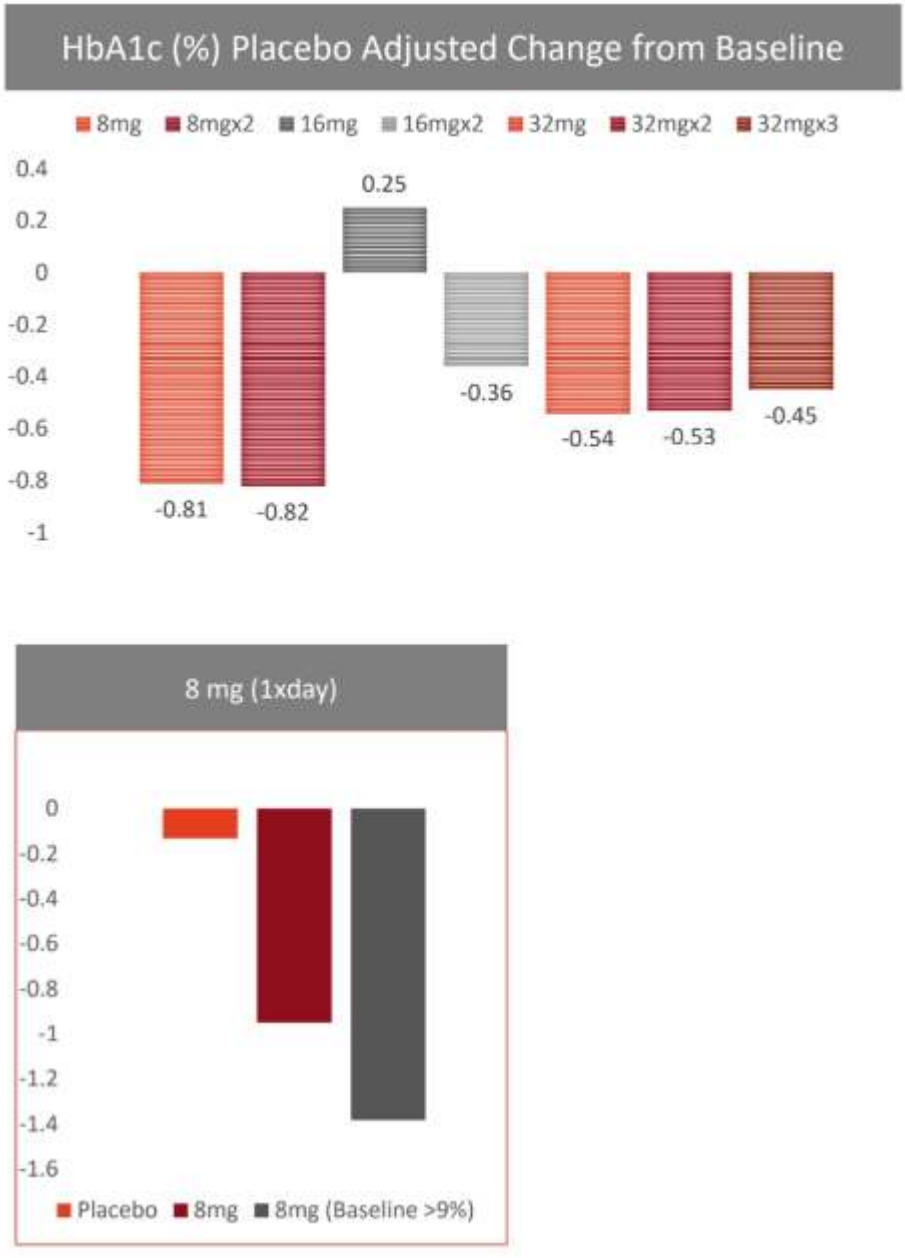
The trial was designed to treat all patients for a period of 90 days. At the time of enrollment, all patients were being treated with metformin, a glucose lowering drug. Besides metformin, approximately 60-70% of patients were receiving combinations of two or more other oral glucose lowering drugs including glibenclamide, glipizide, empagliflozin, pioglitazone, glimepiride, dapagliflozin, sitagliptin, glibomet, and ertugliflozin. Patients were split into seven cohorts to receive different doses of ORMD-0801 including total daily doses of 8 milligrams (mg), 16 mg, 32 mg, 64 mg and 96 mg per day (doses were administered once, twice or three times daily):

- 96 mg/day (32 mg X 3/day)
- 32 mg/day (32 mg X 1/day)
- 32 mg/day (16 mg X 2/day)
- 64 mg/day (32 mg X 2/day)
- 16 mg/day (8 mg x 2/day)
- 16 mg/day (16 mg X 1/day)
- 8 mg/day (8 mg X 1/day)

The primary efficacy end point of the study was mean change in hemoglobin A1c (HbA1) from baseline to week 12 post-initiation of treatment. Secondary end points included mean change in fasting blood glucose (FBG), continuous glucose monitoring (CGM) and changes in weight. The treatment of type 2 diabetes patients with ORMD-0801 was safe and well tolerated with no serious adverse events. In the trial, ORMD-0801 treatment met the primary and secondary end points in the study. The 8 mg once-daily dose of ORMD-0801 lowered HbA1c by 0.95% (0.81% when placebo-adjusted) (Exhibit 10). The data was statistically significant with a p value of 0.0276. In patients with HbA1c of more than 9% at baseline, treatment with ORMD-0801 lowered HbA1c by 1.26%. In our opinion, the results of the Phase IIb clinical trial demonstrate the potential of ORMD-0801 as a candidate oral insulin treatment for type 2 diabetes patients. The drug was safe and well tolerated in this patient population, and showed a clinically relevant reduction in HbA1c, which is an important predictor of long term therapeutic benefit.

Analysis by patient-cohorts - The Phase IIb clinical trial was divided into two patient cohorts: Cohort A and Cohort B. In an analysis of 209 patients who completed treatment with ORMD-0801 for 12 weeks in Cohort A, the patient group receiving ORMD-0801 twice daily showed a placebo adjusted 0.53% reduction in HbA1c (p value 0.042). Patients receiving ORMD-0801 three times daily did not show statistically significant reductions in HbA1c (p value of 0.093; a p value of more than 0.05 corresponds to a "not statistically significant result"). The scientific and medical rationale for the discrepancy between results from twice-daily and three times daily treatment regimens is not known. In February of 2020, Oramed announced results from patients participating in Cohort B of the Phase IIb clinical trial. Patients receiving ORMD-0801 (8 mg) once-daily showed a 1.29% reduction in HbA1c since start of treatment (0.81% when adjusted for placebo effect). Patients with values of HbA1c higher than 9% at baseline, showed a 1.26% reduction in HbA1c after treatment with 8 mg of ORMD-0801 (once-daily) for 12 weeks.

Exhibit 10 – Results from the evaluation of 266-patients participating in a placebo-controlled, Phase IIb human clinical trial on the use of ORMD-0801 for the treatment of type 2 diabetes. In total, 34 clinical trial sites in the United States participated in the study. Enrolled patients received 7 doses of ORMD-0801 for a period of 90 days. The primary efficacy end point of the study was change in hemoglobin A1c (HbA1c) at week-12 post start of treatment. Several doses of ORMD-0801 were tested in the trial (8 mg, 16 mg, 32 mg once, twice or three times daily). When adjusted for placebo effect, treatment with 8 mg dose of ORMD-0801 once-daily caused a 0.81 reduction in HbA1c. In patients with HbA1c levels higher than 9% at baseline, treatment with 8 mg of ORMD-0801 once-daily reduced HbA1c by 1.26% (placebo-adjusted). Results were statistically significant with a p value of 0.0276.



Source – Oramed Pharmaceuticals, Inc.

Based on the positive results from Phase II and Phase IIb clinical trials, Oramed Pharmaceuticals met with FDA regulators. As a result of this meeting, Oramed is conducting two Phase III clinical trials (ORA-D-013-1 and ORA-D-013-2) on the use of ORMD-0801 for the treatment of type 2 diabetes. Final results from these two studies are expected in 2023. Based on the data, Oramed plans to file a BLA seeking approval of the drug. Assuming the FDA grants approval in 2024, we expect Oramed to commercialize ORMD-0801 in the United States in 2025.

In our view, the reduction of HbA1c observed with ORMD-0801 treatment is of relatively less magnitude than what has been observed with injectable insulin and other oral glucose lowering agents in several studies. However, the excellent safety and tolerability of ORMD-0801 cannot be ignored. The hepato-centric mechanism of action of ORMD-0803, mimicking natural insulin by acting in the liver first, is also an attractive attribute of ORMD-0801 relative to other diabetic medications. Oramed might be able to demonstrate better preservation of insulin-producing, pancreatic beta-cells. Showing less variability in controlling blood glucose levels by CGM in Phase III clinical trials will be of paramount importance, and will allow Oramed to differentiate ORMD-0801 from other drug classes. Given ORMD-0801's attributes, we believe Oramed will target type 2 diabetic patients in early stages during initial commercialization of ORMD-0801. In our view, Oramed will likely target patients before disease progression with the aim to delay the need of insulin injections in this type 2 patient population.

Monitoring long-term safety of oral insulin

Experts believe that the chronic use of oral insulin will require surveillance to assess the long-term effects of large amounts of unabsorbed oral insulin lingering in the intestines. This will be important, especially given that insulin has shown mitogenic or growth factor potential, and modulatory effects on gastrointestinal physiology (Endocrinology 2011, 152(7)2546-2551; J Controlled Release 1997,46,89-98). Thus far, Oramed's oral insulin has been safe in human clinical trials, with no sign of potential toxicities from the effects of unabsorbed oral insulin.

Intellectual Property

Oramed has a robust intellectual property portfolio with patents protecting its proprietary technology and lead products in multiple jurisdictions across the world. Granted and pending patents protect inventions related to Oramed's technologies enabling the oral delivery of proteins (including oral insulin for the treatment of type 1 and type 2 diabetes, GLP-1 analog (exenatide) for the treatment of diabetes and oral insulin for the treatment of NASH). Oramed intellectual property portfolio includes patents issued by the United States, Swiss, German, French, U.K., Italian, Netherlands, Swedish, Spanish, Australian, Israeli, Japanese, New Zealand, South African, Russian, Canadian, Hong Kong, Chinese and Indian patent offices.

In total, Oramed's comprehensive intellectual property portfolio holds 79 patents, two of which were granted in 2020. Oramed has currently 26 patent applications pending, including compositions of matter and method of use patents. The Company has filed patents related to compositions, methods of production and oral administration of proteins. The expiration dates of many of these pending patents, if granted, will be between 2026 and 2039. Oramed has also certain trade secrets and unpatentable know-how, which the Company plans to protect by executing confidentiality agreements with their executives, directors, employees, scientific collaborators and business partners.

The main U.S. patents, patent number 10,058,593 (granted), 10,342,764 (granted), 10,398,762 (granted), US-2018-0369339-A1 (pending), 9,259,456 (issued) protect innovations related to composition of matter and method of use of technologies for oral administration of proteins. These patents will protect Oramed's candidate medicines ORMD-0801 and ORMD-0901, and technologies related to their oral administration for the treatment of type 1 and type 2 diabetes, as well as the use of protease inhibitors to prevent protein degradation and facilitate oral protein delivery. In addition, Oramed has filed some pending patents and PCT applications protecting inventions related to oil-based liquid oral formulations comprising insulin, GLP-1 analogue (exenatide), trypsin inhibitor (protease inhibitor), chelator of divalent cations (improve adsorption), surrounded by a coating to prevent degradation in the stomach.

In 2010, Oramed Ltd. and D.N.A. Biomedical Solutions Ltd. formed a joint venture for the establishment of Entera Bio Ltd. Under the terms of the agreement, Oramed out-licensed technology and related intellectual property to

Entera for the development of oral delivery drugs for certain indications. This intellectual property is unrelated to Oramed's patents protecting oral delivery technologies related to the use of oral insulin and GLP-1 analog. In 2015, Oramed Ltd. entered into a Technology License Agreement with HTIT (Hefei Tianhui Incubator of Technologies Co., Ltd., headquartered in Hefei, China). Under the terms of the agreement, Oramed granted HTIT an exclusive commercialization license in China, Macau and Hong Kong related to Oramed's oral insulin capsule, ORMD-0801. Oramed is entitled to receive milestone payments and royalties from product sales, which will be reduced upon the final expiration of Oramed's patents covering the technology in these jurisdictions.

Competitive Landscape

Since the discovery of insulin in 1921, there have been attempts to develop an oral version of insulin. However, the fact that not a single oral formulation of insulin is currently commercially available demonstrates the tremendous challenge this project represents. Given the relatively large commercial opportunity for an effective oral insulin formulation, we believe multiple competitors will continue innovating, using different technological approaches, to bring an oral insulin to market. At present, the only biotechnology company in pivotal Phase III clinical trials (seeking FDA approval) with an oral insulin capsule for the treatment of type II diabetes is Oramed.

Scientists at the Massachusetts Institute of Technology, Brigham and Women's Hospital in Boston, in collaboration with Novo Nordisk are working on the development of an oral insulin pill, which contains a micro-needle with a tip made of freeze-dried insulin. The pill is self-oriented, which has the advantage to inject insulin on the stomach wall in a controlled fashion, without misfiring. This program is still in preclinical development.

Novo Nordisk (NYSE: NVO) is a glocal leader in the diabetes area. Novo is developing various novel long-acting insulin analogs for the treatment of type 1 and type 2 diabetes, and has a strong presence in the GLP-1 receptor agonists segment of the diabetes market. Novo Nordisk did develop its own formulation of oral insulin, which was evaluated in Phase II clinical trials. Novo's oral insulin, OI388GT, had shown comparable results to Sanofi's Lantus (a type of injectable insulin, now a generic drug as patent has expired). Novo Nordisk, utilizing its former partner Emisphere's technology, was successful developing an oral tablet of GLP-1 analog. In 2010, Novo Nordisk entered into an exclusive development and license agreement with Emisphere to develop and commercialize oral formulations of Novo Nordisk's insulins using Emisphere's Eligen Technology. The Eligen Technology utilizes synthetic carriers to facilitate passive transport of a protein such as insulin through the intestinal wall.

Novo Nordisk completed six (five Phase I and one Phase II) clinical trials on the use of oral insulin for the treatment of type 1 and type 2 diabetes (Adv Drug Deliv Rev 2016, 106(Pt B)223-241). The drug delivery technology used by Novo Nordisk was originally developed by Merrion Pharmaceuticals. Merrion's technology, known as "gastrointestinal permeation enhancement technology" (GIPET), is based on micro-emulsions of oil and surfactant (mixture of fatty-acid derivatives) included in an enteric-coated gel capsule. The system was utilized by Novo Nordisk to improve the oral bioavailability of insulin. In 2015, Merrion sold the assets to Novo Nordisk. In 2016, Merriot winded up operations.

Using Merrion's GIPET technology, Novo Nordisk developed a novel oral insulin analogue with the potential to reduce glucose levels when administered 30 minutes before a meal. The GIPET technology utilizes sodium caprate as absorption enhancer. This candidate oral insulin has shown enhanced stability due to resistance to proteolytic degradation, ultra-low receptor affinity and strong albumin binding leading to improved bioavailability, longer plasma half-life in dog experimental models. All of these mentioned properties, combined with maintained potency, led Novo Nordisk to believe that oral insulin could be a superior treatment to parenteral subcutaneous insulin (Lancet Diabetes Endocrinol 2019, 7, 179–188; Clin Pharmacokinet 2019, 58, 1497–1504; Nature Commun 2020, 11, 3746, doi:10.1038/s41467-020-17487-9).

In March 2019, Novo Nordisk published on The Lancet Diabetes & Endocrinology results from a 50-patient Phase II randomized, double-blind, comparator clinical trial on the use of this Novo's oral insulin, I338, compared to insulin glargine (IGlar) for the treatment of type 2 diabetes. Oral insulin 338 (I338) is a long-acting, basal insulin analogue formulated in a tablet with the absorption-enhancer sodium caprate. IGlar (Lantus) is a long-acting, injectable basal insulin analogue (recombinant insulin). The trial was conducted at two research institutes in Germany. A total of 50

type 2 diabetic patients, naive to insulin (never received insulin treatment before the trial) were split into two groups: one group received treatment with I338 (N=25 patients) and the second group received IGlar (N=25 patients). The primary end point of the trial was treatment difference in FPG (fasting plasma glucose) concentration at 8 weeks. In the trial, mean FPG concentration for I338 patient group was reduced to from 9.7 (baseline) to 7.1 millimolar (mmol/L) after 8 weeks of treatment. The mean FPG concentration for the IGlar patient group was reduced from 9.1 millimolar to 6.8 millimolar after 8 weeks of treatment. The trial demonstrated that oral insulin was equivalent in efficacy to injectable insulin (The Lancet, Diabetes and Endocrinology 2019, 7(3)179-188). Despite the positive results of this study, Novo Nordisk decided to discontinue the clinical program as I338 was deemed not commercially viable as doses required were relatively high and too costly for large scale manufacturing. Regardless, the demonstration that I338 was effective for the treatment of type 2 diabetes is encouraging for other competitors in the field developing oral formulations of insulin (Nature Reviews Endocrinology 2019, 15, 191).

Novo Nordisk's oral insulin analogues do not have the same amino acid sequence as natural insulin (wild-type) as they contain mutations in the form of specific amino acid substitutions to render a molecule with higher half-life, approximately 70 hours, due to stronger binding to albumin, low affinity for its receptor (binding to insulin receptor results in insulin clearance). The binding to albumin also delays distribution to peripheral tissues, improving hepato-centric insulin action. It is difficult to explain why Novo Nordisk has discontinued the oral insulin program to focus on developing novel injectable insulin analogs. In our opinion, inter and intra patient variability of the response to oral insulin, combined with oral bioavailability challenges (requirement for relatively high doses to achieve desired efficacy), led to Novo Nordisk's management decision.

Unlike Oramed's oral insulin which has the intact amino acid sequence of natural insulin, Novo Nordisk's oral insulin formulations carry specific genetic substitutions. Novo Nordisk's team made two amino acid substitutions to stabilize the oral insulin molecule making resistant to proteolytic degradation. The engineered mutations included two substitutions in two positions of the insulin molecule (on position A14, replacing tyrosine for glutamic acid and on position B25, replacing phenylalanine for histidine). Further stability was achieved by incorporating a third mutation on position B27 (deletion of threonine). These mutations reduced insulin receptor affinity by threefold, increased solubility in acidic pH (5.5-6.5) found in small intestine (Nature Commun 2020, 11, 3746, doi:10.1038/s41467-020-17487-9). To improve absorption of oral insulin, the team engineered the modified insulin to have strong but reversible binding to albumin and reducing affinity for its receptor as insulin is normally cleared by internalization through its receptor.

Scientists at Novo Nordisk believe that ultra-long acting basal insulin analogues could potentially overcome the variability issue, which has been a significant challenge for the field (Nature Commun 2020, 11, 3746, doi:10.1038/s41467-020-17487-9). However, Novo Nordisk is not pressing forward to develop its novel engineered formulations of oral insulin. In contrast, Oramed is advancing its oral insulin candidate medicine into Phase III clinical trials for the treatment of type 2 diabetes.

Exhibit 11 – List of companies which entered human clinical trials to evaluate an oral insulin formulation in 2014. Novo Nordisk has discontinued development of oral insulin to focus on long-acting injectable insulin analogs. In contrast, Oramed has completed Phase II clinical trials and is currently conducting two Phase III clinical trials for the treatment of type 2 diabetes.

Company	Name	Product	Action	Development phase	Clinical trials	References[#]
Access Pharmaceuticals, Inc	CobOral™ Insulin	Coated insulin-loaded nanoparticles	Short	Preclinical		accesspharma.com
Aphios Corporation	APH-0907	Nanoencapsulated insulin/biodegradable polymer nanospheres	Short	Preclinical		aphios.com
Biocon/Bristol-Myers Squibb	IN-105	Conjugated insulin	Short	II	NCT01035801 CTRI/2008/091/000276 CTRI/2009/091/000479 CTRI/2009/091/001008	biocon.com, clinicaltrials.gov, ctri.nic.in, Khedkar et al[7]
Diabetology Ltd	Capsulin™ OAD	Insulin with delivery system Axcess™	Short	II		diabetology.co.uk, Luzio et al[11]
Diasome Pharmaceuticals, Inc	HDV-Insulin	Hepatic-directed vesicle-insulin (nanocarrier)	Short	III	NCT00521378 NCT00814294	diasome.com, clinicaltrials.gov
Emisphere Technologies, Inc	Eligen® Insulin	Insulin with chemical delivery agents (Eligen®)	Short	I	NCT00982254	emisphere.com, clinicaltrials.gov, Kapitza et al[13]
Jordanian Pharmaceutical Manufacturing Co PLC	JPM Oral Insulin	Liquid delivery system with insulin chitosan nanoparticles		I		jpm.com.jo, Badwan et al[16]
Novo Nordisk A/S	NN1952	Insulin analog with oral delivery system GIPET®	Short		NCT01028404	novonordisk.com, novonordisk-trials.com, clinicaltrials.gov
	OI338GT (NN1953)	Insulin analog with oral delivery system GIPET®	Long	I	NCT01334034 NCT01931137 NCT01796366	
	OI362GT (NN1954)	Insulin analog with oral delivery system GIPET®	Long	I	NCT01597713	
	OI287GT (NN1956)	Insulin analog with oral delivery system GIPET®	Long	I	NCT01809184	
Oramed, Inc	ORMD-0801	Insulin with protein oral delivery system POD™	Short	II	CTRI/2009/091/000371 NCT00867594 NCT01889667	oramed.com, clinicaltrials.gov, ctri.nic.in, Eldor et al,[17] Eldor et al[19]
Oshadi Drug Administration Ltd	Oshadi Icp	Insulin, proinsulin, and C-peptide in Oshadi carrier	Short	II	NCT01120912 NCT01973920 NCT01772251	clinicaltrials.gov
NOD Pharmaceuticals, Inc/ Shanghai Biolaxy, Inc	Nodlin	Insulin with bioadhesive nanoencapsulation (NOD Tech)	Intermediate	II	ChiCTR-TRC-12001872	chictr.org, Li et al[20]

Source - Journal of Diabetes Science and Technology 2014, 8(3) 458–465

In 2017, Sanofi entered into a collaboration agreement with Enteris Biopharma, a wholly-owned subsidiary of SWK Holdings Corporation (Nasdaq:SWKH), to develop an oral insulin formulation. Thus far, we have not seen any human clinical trials on this indication, but Enteris is developing a GLP-1 analog using its proprietary drug delivery technology.

Inhaled insulin has been commercially available since 2014. Inhaled insulin formulations have not performed well with lackluster sales. MannKind Corporation (MNKD) commercializes Afrezza, an inhaled formulation of insulin. In 2019, MannKind reported net Afrezza revenue of only $25.3 mm. Sales of inhaled insulin have been affected by poor reimbursement, concerns related to drug safety (higher incidence of respiratory symptoms, cough, slightly higher incidence of lung cancer in treated patients) and success of competing technologies. With the advent of superior injectable delivery technologies, superior parenteral insulin analogs, the industry continues to prefer parenteral over inhale insulin. In our opinion, this is also explained because inhaled insulin is equivalent to systemic insulin, which does not provide the advantages of oral insulin, which not only offer better patient compliance, but superior efficacy by acting through hepato-centric mechanisms mimicking the natural insulin. Inhaled insulin and parenteral insulin acts systemically, increasing levels of insulin in peripheral tissues relatively to the liver leading to higher incidence of side effects including hypoglycemia. In contrast, oral insulin administration results in higher levels of insulin in the liver, the natural physiological mechanism of this hormone.

Oramed is emerging as the global leader in oral insulin. Oramed has the most advanced clinical program in the space. Oramed announced results from its Phase IIb clinical trial on the use of oral insulin, ORMD-0801, for the treatment of type 2 diabetes in February 2020. In the study, once-daily and twice-daily 8 mg doses of ORMD-0801 significantly reduced hemoglobin A1c (HbA1c), a clinically relevant 0.6% reduction relative to placebo. The data was statistically significant. In the trial, ORMD-0801 was safe and well tolerated with no serious side effects. Oramed is planning two Phase III human clinical trials. The Company has the opportunity to be first to market with an oral insulin.

Betting on injectable insulin

Novo Nordisk's management team believes that developing an innovative insulin treatment is the most promising asset in its pipeline. Despite the pricing pressure in insulin markets, which started in the United States in the 2015/2016 time frame, Novo still believes its novel insulin, "icodec", which is injected only once a week (instead of daily as bestseller insulin Lantus, formerly from Sanofi, now a generic drug) will be embraced by the diabetes market. Novo Nordisk is in Phase I and Phase II clinical trials on the use of FSI965 and "Insulin icodec", new generation long-acting basal insulin analogues intended for once weekly dosing for the treatment of type 1 and type 2 diabetic patients. Novo is also conducting a Phase II clinical trial on the use of NNC0114-0006 (a monoclonal antibody targeting interleukin 21 (IL-21)) in combination with Victoza (GLP-1 receptor agonist) for the preservation of beta cell functions in recently diagnosed type 1 diabetic patients. Novo is also in Phase I clinical trials on the use of icosema (consisting of Ozempic in combination with novel insulin analog LAI287 (icodec)) for the treatment of type 2 diabetes. Novo is also in Phase I clinical trials on the use of "Insulin 147 & PCSK9i" for the treatment of diabetic patients with high LDL cholesterol ("bad cholesterol"). "Insulin 147 & PCSK9i" consists of a long-acting insulin analogue coupled via a linker to a proprietary PCSK9 inhibitory peptide. Diabetes patients with hypercholesterolemia (high levels of blood cholesterol) will benefit from "Insulin 147 & PCSK9i" (inhibitor of proprotein convertase subtilisin/kexin type 9) treatment.

Eli Lilly is a key competitor of Novo Nordisk. Lilly is in Phase II clinical trials with LY3209590 (basal insulin-Fc) for the treatment of diabetes. Lilly's "basal insulin Fc" is a large molecule comprised of an engineered insulin fused to an Fc domain to prolong insulin's half-life. Basal insulin Fc is designed to provide long-acting effects.

Competition in GLP-1 receptor agonist area

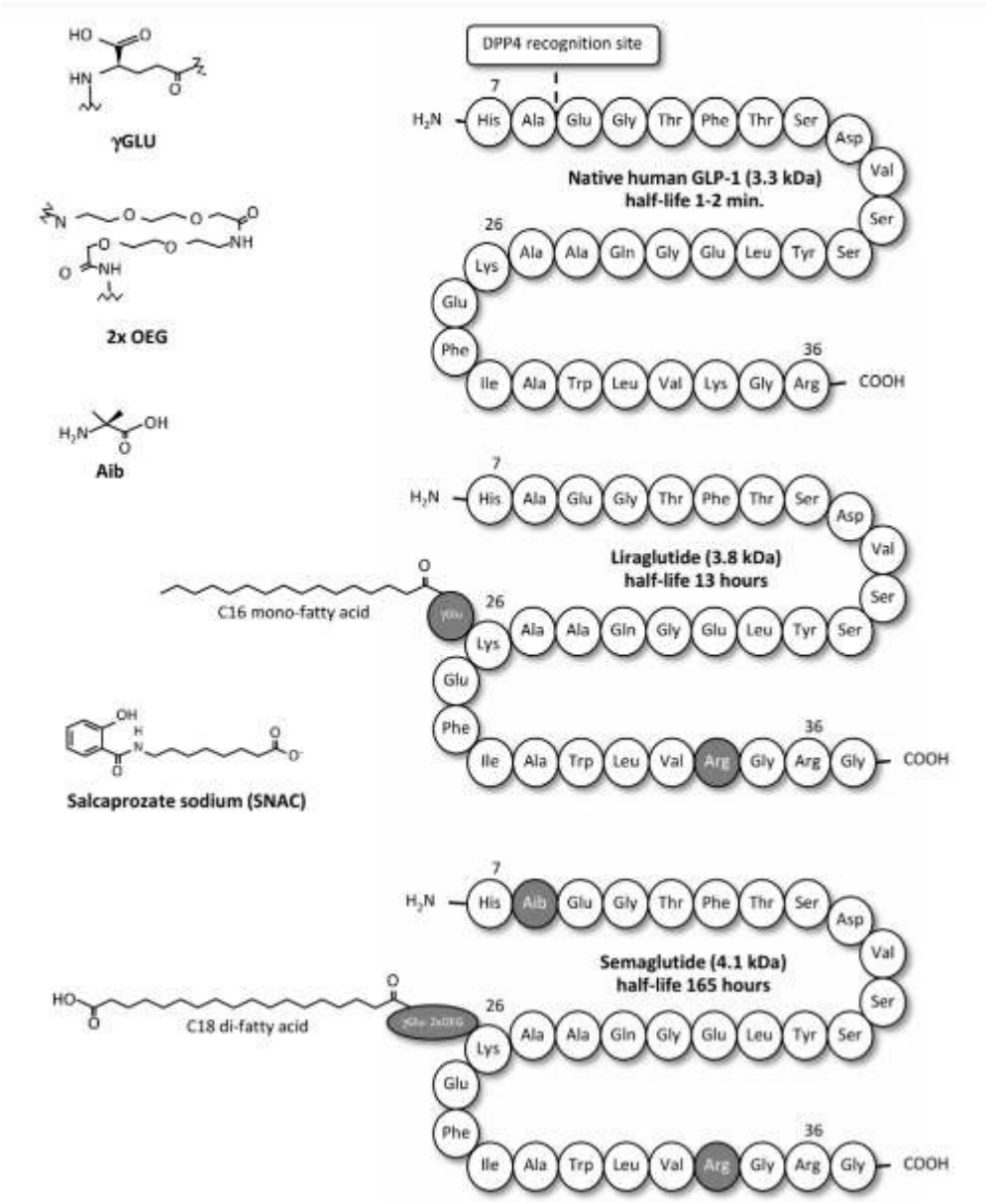
Novo Nordisk has developed a novel oral glucagon-like peptide 1 (GLP-1) receptor agonist known as Rybelsus (oral semaglutide) for the treatment of type 2 diabetes. Novo's Rybelsus is an oral formulation of injectable semaglutide. Novo Nordisk received the U.S. FDA approval for Rybelsus in 2019. Oramed will compete in this area as the Company is developing its own oral version of GLP-1 receptor agonist known as ORMD-0901 (oral exenatide).

Novo Nordisk continues to be the global market leader in the GLP-1 receptor agonist segment of the diabetes market with a 50.4% value market share. According to Novo, the market for GLP-1 receptor agonists has grown from 18% of the total diabetes market in 2019 to 22% in 2020. Novo Nordisk is commercializing three GLP-1 receptor agonist drugs: Ozempic, Victoza and Rybelsus (first FDA approved oral GLP-1 receptor agonist drug). On September 20, 2019, Novo Nordisk received FDA approval for its new oral GLP-1 receptor agonist drug Rybelsus (oral semaglutide) for the treatment of type 2 diabetes. For 2020, Novo reported annual sales of Rybelsus of $304 mm (first year of commercialization). Novo Nordisk's Ozempic (injectable semaglutide), a once-weekly injectable GLP-1 receptor agonist, had 2020 sales of $3.44 billion (a significant increase over the $1.65 billion and $264 mm reported, respectively, in 2019 and 2018). Treatment with Ozempic has shown weight-lowering benefits and reduction in risk for cardiovascular disease in type 2 diabetic patients (In January 2020, FDA approved Ozempic for cardiovascular risk reduction in type 2 diabetes).

Ozempic was discovered in 2012, internally, by a team of scientists at Novo Nordisk who were searching for a long-acting alternative version of Victoza (liraglutide). Ozempic's amino acid residues sequence shows 94% similarity to human GLP-1. Ozempic contains two amino acid substitutions at positions 8 (alanine for 2-aminoisobutyric acid) and 34 (lysine for arginine). The substitution at position 8 prevents the breakdown of Ozempic by DPP-4 (dipeptidyl peptidase-4) enzyme. Ozempic has relatively higher binding capacity to albumin in blood, which prolongs the drug's half life. In pharmacokinetic studies, Ozempic has a half life of 165 to 184 hours, which is sufficient for once-weekly dosing. After a 16-0 in favor vote by an agency panel, the U.S. FDA approved Ozempic for the treatment of type 2 diabetes in 2017.

Annual sales of Novo Nordisk's older GLP-1 receptor agonist, Victoza (liraglutide), were $3.04 billion in 2020 compared to $3.23 billion in 2019 (a 5.9% decline relative to prior year). Novo Nordisk's management believes that with Rybelsus and Ozempic, the Company will remain as a global leader on the use of GLP-1 receptor agonists for the treatment of type 2 diabetes. Novo Nordisk's management also indicated that Rybelsus is recommended for the treatment of earlier stages of disease, whereas Ozempic is more effective in type 2 diabetic patients with more advance disease. Management also mentioned that new data (LEADER trial) on the use of Victoza (liraglutide), showing that the drug reduces the risk of cardiovascular disease in treated diabetic patients, should revert a recent trend of declining sales.

Exhibit 12 – Structure of GLP-1 receptor agonists. Native human GLP-1 is a 30 amino acid peptide hormone (GLP 7-36) with a relatively short half-life of 1 to 2 minutes. Liraglutide (Novo Nordisk's Victoza) is a once-daily, subcutaneously injectable GLP-1 analogue with modifications at positions 26 (lysine plus fatty acid modification) and 34 (arginine replacing lysine). Liraglutide has plasma half life of 13 hours. Novo Nordisk's semaglutide (Ozempic) is a once-weekly, subcutaneous injectable GLP-1 analogue with modifications at positions 8 (alanine for Aib), 26 (fatty acid modification at lysine) and 34 (lysine for arginine). These modificantions enhance semaglutide's half life, which is approximately 165 hours. Salcaprozate sodium (SNAC) is an intestinal permeation enhancer.



Source - Diabetes Metab Syndr Obes. 2019, 12, 2515-2529

Eli Lilly (NYSE: LLY) is a global leader and key competitor in the diabetes area. In 1923, Lilly introduced the first commercial insulin for the treatment of diabetes. Annual sales of Eli Lilly's GLP-1 receptor agonist Trulicity (dulaglutide, LY2189265) were $4.13 billion in 2019 (the fifth year of commercialization for the treatmen of type 2 diabetes). In 2020, the FDA expanded the label of Trulicity to add cardiovascular disease risk reduction (reduction

in heart attacks, stroke and cardiovascular death) in type 2 diabetic patients. Eli Lilly's Trulicity consists of amino acid residues 7 to 37 of GLP-1 molecule linked to the Fc fragment of human IgG4 antibody (Curr Opin Mol Ther 2010, 12(6)790-797). The Fc fragment protects the GLP-1 molecule from inactivation by DPP-4 enzyme (dipeptidyl peptidase 4). In 2014, the U.S. FDA approved Trulicity for treatment of type 2 diabetic patients. Like other drugs in the GLP-1 receptor agonist class, Trulicity functions as an incretin stimulating the production of insulin by pancreatic beta cells. Pharmacokinetic studies demonstrated a 90 hours half life for Trulicity, which makes the medicine an ideal drug for once-weekly dosing.

Eli Lilly is in Phase III clinical trials with a novel drug known as tirzepatide. Eli Lilly's tirzepatide is a once-weekly injectable dual incretin treatment for type 2 diabetes, obesity and non-alcoholic steatohepatitis (NASH). Tirzepatide (LY3298176) is a large molecule with a dual mechanism of action acting as a coagonist for both the "gastric inhibitory polypeptide (GIP) receptor" and the GLP-1 receptor. Tirzepatide combines the incretin effects (increase in insulin production) of both GIP and GLP-1. In preclinical experimental models, GIP has been shown to reduce food intake and increase energy expenditure resulting in weight loss. The combination of GLP-1 receptor agonist effects with GIP receptor agonist amplifies the weight loss and glucose metabolic regulation. Lilly is in Phase III clinical trials with tirzepatide. In the SURPASS-1 Phase III clinical trial, treatment with tirzepatide significantly reduced HbA1c with almost 90% of type 2 diabetic patients reaching the standard of HbA1c of less than 7%, and more than half of the patients achieving HbA1c of less than 5.7%. At baseline, enrolled patients had a relatively short mean duration of diabetes of 4.7 years, with mean HbA1c of 7.9%. Approximately 54.2% of participating patients were treatment naive. Eli Lilly is also conducting a 12,500-patient Phase III clinical trial, SURPASS-CVOT, to evaluate a reduction in the risk for type 2 diabetic patients of developing cardiovascular disease. The study is being conducted head to head, non-inferiority/superiority trial, comparing tirzepatide with Trulicity (dulaglutide). The primary efficacy end point of the trial measures time to first ocurrence of MACE-3, a composite endpoint of CV (cardiovascular) death, myocardial infarction and stroke. Lilly expects it will take four years to complete the SURPASS-CVOT clinical trial.

Sanofi currently commercializes Soliqua, which consists of the combination of Lantus (basal insulin) plus lixisenatide (injectable GLP-1 receptor agonist). In 2019, sales of Soliqua were 122 million euros ($147 mm). Like AstraZeneca's exenatide, Sanofi's lixisenatide consists of a modified version of exendin-4, which was isolated from the Gila monster venom. In the 6,068-patient ELIXA clinical trial, treatment with lixisenatide was not better than placebo at reducing risk of cardiovascular disease, reducing HbA1c only by 0.27% (N Engl J Med 2015, 373(23)2247–2257). Both results are inferior to other GLP-1 receptor agonists in this drug class.

In coming years, we expect Novo Nordisk's Ozempic and Rybelsus to compete with Lilly's Trulicity for supremacy in the GLP-1 receptor agonist class. In clinical trials, Novo's Ozempic reduced cardiovascular risk in type 2 diabetes by 26% compared to Lilly's Trulicity 12%. In our opinion, it will be difficult for Oramed to compete in this class with ORMD-0901. The data from clinical trials will determine if Oramed's drug will be competitive. Thus far, Novo Nordisk is significantly ahead of Oramed as Rybelsus is already commercially available. Overall, data from trials with semaglutide (Ozempic) has been superior to exenatide (AstraZeneca's Byetta and Bydureon). Oramed will have to generate superior data to Novo's Rybelsus to become a key competitor in the GLP-1 receptor agonist drug class.

Treatment with AstraZeneca's exenatide did not reduce the risk of cardiovascular disease in a 14,752-patient, placebo-controlled, EXSCEL clinical trial (not superior to placebo, p value of 0.06, not statistically significant) (N Engl J Med 2017, 377(13)1228–1239). Exenatide is based on Exendin-4, a GLP-1 peptide found on the Gila monster's venom. Like AstraZeneca's exenatide, Sanofi's lixisenatide (another GLP-1 agonist based on Exendin-4) did not show superiority to placebo as demonstrated in ELIXA trial. In contrast, Novo Nordisk demonstrated that treatment with Ozempic (SUSTAIN-6 trial, 26% reduction), Victoza (LEADER trial, 13% reduction) and Rybelsus (PIONEER-6 trial, ongoing) reduced the risk of cardiovascular complications measured as MACE (major cardiovascular events such as heart attack, stroke or death) in patients with type 2 diabetes suffering from heart disease. Ozempic, Victoza and Rybelsus were clearly superior to placebo in reducing risk of cardiovascular complications in type 2 diabetic patients with known heart disease. In REWIND trial, treatment of type 2 diabetic patients with Eli Lilly's Trulicity (dulaglutide) reduced the risk of cardiovascular complications by 12% relative to placebo (hazard ration of 0.88, p

value of 0.026). Unlike exenatide and lixisenatide, Ozempic, Victoza, Rybelsus and Trulicity are based on modified human GLP-1 molecule.

In January 2020, the U.S. FDA approved a new indication for Ozempic to reduce the risk of MACE in type 2 diabetic patients with known heart disease. Cardiovascular disease is the main cause of death and disability for type 2 diabetic patients (Circulation 2016,133(24)2459-2502). In the 3,297-patient SUSTAIN-6 clinical trial, Ozempic reduced the estimated relative risk of MACE by 26% relative to placebo (hazard ratio of 0.74, 95% CI, p value of less than 0.001, a statistically significant result) (N Engl J Med 2016, 375, 1834-1844). In the SUSTAIN-6 trial, 58.8% of the participants had established cardiovascular disease (CVD) without chronic kidney disease (CKD), while 13.4% of the participants were suffering from both CVD and CKD. In PIONEER-6 clinical trial, treatment with Rybelsus reduced the risk of MACE (hazard ratio of 0.79, 95% CI). In June 2019, Novo Nordisk initiated a 9,642-patient SOUL CVOT Phase III clinical trial to further evaluate the effect of Rybelsus in reducing the risk of cardiovascular disease in type 2 diabetes. In our opinion, Oramed's ORMD-0901 has a relatively low probability to show superiority to Novo Nordisk's Rybelsus. ORMD-0901 consists of an oral formulation of exenatide, an inferior drug compared to semaglutide (Rybelsus, Ozempic).

Other competitors

Diabetology Ltd is a privately held British biotechnology company, located at the London Bioscience Innovation Centre, which is in Phase II clinical trials on the use of Capsulin OAD (oral insulin) for the treatment of type 1 diabetes and late stage type 2 diabetes. Capsulin OAD was developed using Diabetology's proprietary third-generation "Axcess delivery technology".

vTv Therapeutics (Nasdaq: VTVT), is developing TTP273, an oral GLP-1 receptor agonist, for the treatment of type 2 diabetes. The Company is currently in Phase II clinical trials and has signed a partnership with Huadong Medicine to develop and commercialize TTP273 in China.

Biocon, an Indian biotechnology company, is developing oral insulin Tregopil in Phase II clinical trials. Patients treated with Tregopil showed improved post-pandrial glucose excursion (change in glucose blood concentration after a meal). Biocon is developing Tregopil for the treatment of type 1 and type 2 diabetic patients.

Diasome Pharmaceuticals, a private company based in Cleveland, is developing an oral insulin formulation based on the Company's proprietary technology known as "hepatocyte directed vesicle" (HDV), which is designed to prevent hypoglycemia by restoring normal liver physiology in patients with diabetes. HDV consists of a nanoscale, frisbee-shaped carrier delivering approximately 100 insulin molecules per disc to the liver. Diasome is in Phase III clinical trials on the use of HDV-insulin for the treatment of type 1 diabetes.

Oshadi Drug Administration Ltd. is developing an oral insulin based on its oral carrier protein technology (J Endocr Soc 2019, 3 (Suppl 1), OR14-1). It is currently in Phase II clinical trials for the treatment of type 1 diabetes. The oral insulin formulation is designed to reduce the risk of hyperinsulinemia.

Exhibit 13 – Oral drugs for the treatment of diabetes mellitus. Novo Nordisk's NN9924 (oral semaglutide or Rybelsus) was approved by U.S. FDA in 2019. Oramed's ORMD-0801 is currently in Phase III clinical trials for the treatment of type 2 diabetes.

Table: Current candidates for oral delivery of biologics for diabetes

Name (company)	Delivery approach	Biologic application	Indication	Clinical trials
Capsulin OAD (Diabetology)	Capsule using the proprietary technology platform Axcess	Insulin	Type 2 diabetes mellitus (T2DM)	Phase II
NN9924 (Novo Nordisk)	Tablet with absorption-enhancing excipients	Semaglutide	T2DM	>25 trials, including phase III
ORMD-0801 (Oramed)	Oral insulin capsule that prevents enzyme degradation and enhances intestinal absorption	Insulin	Type 1 diabetes mellitus (T1DM) and T2DM	Multiple phase II
TTP273 (vTv Therapeutics)	Tablet	Glucagon-like peptide 1	T2DM	Phase II
Tregopil; formerly IN-105 (Biocon)	Tablet	Novel oral insulin molecule	T1DM	Phase I
Oral HDV Insulin (Diasome)	Capsule containing insulin targeted to the liver	Insulin	T2DM	Phase II/III
Oshadi Icp (Oshadi Drug Administration)	Oral formulation	Insulin	T1DM	Phase II

Source: *Nat Rev Drug Discov*[7]

Source – Nat Rev Drug Discov 2019,18(1)19–40

Review of Recent News

On January 21, 2021, Oramed Pharmaceuticals announced that randomization of patients in its first Phase III clinical trial on the use of oral insulin capsule ORMD-0801 for the treatment of type 2 diabetes (T2D) has commenced. The study is being conducted according to the U.S. FDA approved protocols. The randomized, double blind, Phase III clinical trial, known as "ORA-D-013-1", will enroll 675 type 2 diabetic patients (currently on two or three oral glucose-lowering medicines) across 75 clinical sites throughout the U.S. The primary efficacy endpoint of the trial is glycemic control (measured as HbA1c). Secondary endpoints include fasting plasma glucose at 26 weeks. Patients participating in the trial will be divided into three groups:

4. Patients will receive 8 mg ORMD-0801 twice-daily at night and 45 minutes before breakfast;

5. Patients will receive 8 mg ORMD-0801 once-daily at night, and will receive a placebo 45 minutes before breakfast;

6. Patients will receive placebo twice-daily at night and 45 minutes before breakfast.

All patients (three patient groups) will receive treatment for 6 months. The news of the commencement of ORA-D-013-1 clinical trial has triggered a rally in the shares, which have climbed 130% since the announcement. As Oramed enters Phase III clinical trials, the last stage of clinical development before seeking drug approval, investors have started recognizing that Oramed could potentially become the first biotechnology company to introduce a commercially available oral insulin. Even after the recent rally, we believe that the current share price does not fully reflect the value of Oramed's platform technologies and lead products.

On December 23, 2020, Oramed announced results from a proof-of-concept study on the use of the Company's oral leptin drug candidate. The study evaluated the safety and pharmacodynamics of oral leptin including effects on glucagon levels and glucose reduction and metabolism in type 1 diabetic patients. The study included ten patients, seven of which received one capsule of leptin and three received placebo. Following dosing (30-180 minutes), patients who received leptin showed a decrease in blood glucose levels relative to control group. Oramed's management plans to start a larger, placebo-controlled, double-blind clinical trial to further explore the effectiveness of the Company's oral leptin capsule for the treatment of diabetes. Oramed expects its oral leptin capsule to potentially compete in the obesity market, worth an estimated $15 billion.

On December 2, 2020, Oramed announced it has screened the first patients in a global Phase II clinical trial on the use of oral insulin capsule, ORMD-0801, for the treatment of non-alcoholic steatohepatitis (NASH). The trial will include a total of eight clinical sites. The study is being conducted in the United States (three clinical sites), European Union (three sites) and Israel (two sites). In a prior clinical trial, treatment with ORMD-0801, resulted in a 30% reduction in liver fat. In our view, confirmation of this result in ongoing study will allow Oramed to advance its program into Phase III clinical trials.

On November 24, 2020, Oramed announced it has screened the first patients in its global Phase III clinical trials on the use of ORMD-0801 for the treatment of type 2 diabetes. Both Phase III clinical trials, ORA-D-013-1 and ORA-D-013-2 are double-blind, randomized, placebo-controlled studies designed to enroll a total of 1,125 type 2 diabetic patients. Patients will be treated for six months but followed for twelve months (to collect additonal safety data), with first analysis of results to be performed after six months of treatment. In our opinion, treatment with ORMD-0801 will show a clinical benefit in type 2 diabetic patients.

On September 15, 2020, Oramed announced results from a diabetes market survey conducted by a third party research firm. The survey included interviews with healthcare providers (22 endocrinologists, 19 primary care physicians, nurse practitioners, physicians assistants and certified diabetes educators) as well as type 1 and type 2 diabetic patients. Participants were asked about ORMD-0801, an oral insulin capsule. Healthcare providers recommended the use ORMD-0801 (as it does not require needles, do not cause hypoglycemia or weight gain) for the treatment of:

- Type 2 diabetic patients currently taking oral medication;

- Type 2 diabetic patients eligible for treatment with insulin injections or basal insulin.

According to the survey, 91% of type 1 diabetic patients and 85% of type 2 diabetic patients were "extremely likely" or "very likely" to ask their doctors about ORMD-0801, and 80% of type 2 diabetic patients said that oral insulin is "extremely important" or "very important" to delay insulin injections.

On July 15, 2020, Oramed Pharmaceuticals announced that the FDA provided positive feedback during the company's End of Phase 2 (EOP2) meeting for Oramed's oral insulin (ORMD-0801). Based on the FDA's feedback, Oramed intends to initiate two Phase III clinical trials following FDA review of those trials protocols, and nonclinical documents. The FDA outlined its expectations for design of the ORMD-0801 Phase III trials as well as submission of the Biologics License Application (BLA) that would follow successful trials. Oramed plans to conduct the two Phase III clinical trials simulatenously.

Oramed's management plans to complete the two Phase III trials. Assuming the trials meet the end-points, management will submit the BLA, which when approved would grant a full 12 years of marketing exclusivity for ORMD-0801.

On June 15, 2020, Oramed Pharmaceuticals announced that its pilot study of its oral insulin candidate ORMD-0801 in type 2 diabetic patients with non-alcoholic steatohepatitis (NASH), has shown ORMD-0801 to be safe and well tolerated. The results show lowering of fatty liver content, as seen by "MRI-derived proton density fat fraction" (MRI-PDFF). The data was presented as a poster at the 80th American Diabetes Association (ADA) Scientific Sessions, held virtually on June 12-16, 2020.

The pilot, open-label study of the first 8 patients of a planned 40-patient multi-center study, aimed to assess the safety, tolerability, and early effects of 16 mg ORMD-0801 (2×8 mg capsules) on liver fat in type 2 diabetes patients with NASH. The 12-week, once-daily treatment had no serious adverse events, and induced an observed mean 6.9±6.8% reduction in liver fat content (p value of 0.035, a p value of less than 0.05 is considered statistically significant), relative reduction was 30% according to MRI-PDFF data. In parallel, concentrations of gamma-glutamyltransferase (GGT), a key marker of chronic hepatitis, were significantly lower after 12 weeks of treatment as compared to baseline (-14.6±13.1 U/L; p value of 0.008), as were fasting insulin levels (-96.5±206.0 pmol/L; p value of 0.035).

In addition to the NASH data, Oramed presented two posters illustrating ORMD-0801's impact on type-2 diabetes mellitus (T2DM). Oramed's poster presentations at ADA 2020 Conference included:

• "Oral Insulin (ORMD-0801) Effects on Glucose Parameters in Uncontrolled T2DM on Oral Antibiotic Drugs (OADs)", Presented by Dr. Julio Rosenstock, Director of the Dallas Diabetes Research Center and Scientific advisory board member at Oramed Pharmaceuticals

• "Oral Insulin–Induced Reduction in Liver Fat Content in T2DM Patients with Nonalcoholic Steatohepatitis (NASH)", presented by Dr. Miriam Kidron, Chief Scientific Officer at Oramed Pharmaceuticals

• "Evening Oral Insulin (ORMD-0801) Glycemic Effects in Uncontrolled T2DM Patients", presented by Dr. Julio Rosenstock.

On February 26, 2020, Oramed released top-line results from the second and final cohort of its Phase 2b trial evaluating the efficacy and safety of its lead oral insulin candidate, ORMD-0801, at lower dose regimens. ORMD-0801 has the potential to be the first commercially available oral insulin capsule for the treatment of diabetes. In the trial, the primary endpoints were successfully met as there was a 0.95% (0.81% placebo adjusted) Hb A1C reduction in diabetic patients treated once daily with 8 mg of ORMD-0801. The placebo-controlled, double-blinded, randomized, 90-day dose-ranging Phase 2b trial in type 2 diabetes patients with inadequate glycemic control on oral antihyperglycemic agents, assessed the change in A1C, the primary efficacy endpoint, from baseline to week 12, as well as safety endpoints, when ORMD-0801 was given in different regimens across three daily dose ranges (8 mg, 16 mg, 32 mg).

Patients randomized in the trial treated with 8 mg of ORMD-0801 once daily achieved an observed mean reduction of 1.29% from baseline and a least square mean reduction of 0.95% from baseline, or 0.81% adjusted for placebo (p value = 0.028). Patients who had A1C readings above 9% at baseline and received 8 mg of oral insulin once daily experienced a 1.26% reduction in A1C by week 12.

Treatment with ORMD-0801 at all doses demonstrated an excellent safety profile, with no serious drug-related adverse events and no increased frequency of hypoglycemic episodes or weight gain compared to placebo. The topline data from the second cohort represents the conclusion of the Phase 2b trial, and the company believes that the results now pave the way for FDA discussions regarding the initiation of a Phase 3 trial. Based on the results, Oramed's management plans to design Phase III clinical trials.

Review of Recent Financial Results

On January 14, 2021, Oramed released Q1/F2021 results for the three month period ended November 30, 2020. In both Q1/F2021 and Q1/F2020, revenues were $674,000. Revenues consist of proceeds related to license agreement with HTIT for the commercialization of ORMD-0801 in China, Macau and Hong Kong, recognized on a cumulative basis (using the input method). In the quarter, R&D expenses were $5.77 mm compared to $2.02 mm in Q1/F2020. The increase was primarily attributed to expenses related to the initiation of Phase III ORMD-0801 clinical trials. Stock-based compensation increased from $95,000 in Q1/F2020 to $137,000 in Q1/2020. As of November 30, 2020, Oramed incurred liabilities of $317,000 to pay royalties to the Israel Innovation Authority of the Israeli Ministry of Economy & Industry.

SG&A expenses were $727,000 in Q1/F2021 compared to $1.08 mm in Q1/F2020. The 33% decreased in G&A costs was primarily attributed to a reduction in legal expenses, partially offset by increased patent expenses and insurance policy. Stock-based compensation was $180,000 and $184,000, respectively, for Q1/2021 and Q1/2020. In the quarter, net financial income was $257,000 compared to net expense of $114,000 in Q1/F2020. The increase is primarily attributed to an increase in fair value of the ordinary shares of D.N.A Biomedical Solutions Ltd.

From inception until November 30, 2020, Oramed incurred losses in an aggregate amount of $98.18 mm. Oramed has financed its operations through several private placements of common stock, as well as public offerings of common stock. The Company has raised a total of $114.54 mm (net of transaction costs). Through the exercise of warrants and options, Oramed has received a cash consideration of $5.89 mm. As of November 30, 2020, Oramed had $14.93 mm in cash, $10.59 mm in short-term bank deposits and $12.70 mm in marketable securities. Management believes the current cash position will allow the Company to maintain current planned development activities and the corresponding level of expenditures for at least the next 12 months. In the quarter, operating activities used $6.15 mm in cash, compared to $3.0 mm in Q1/2020.

On February 27, 2020, Oramed entered into an underwriting agreement with National Securities Corporation in connection with a public offering of 5.25 mm shares of common stock, at an offering price of $4.00 per share. Oramed granted the underwriter a 45-day option to purchase an additional 787,500 shares of common stock at the public offering price (over-allotment option). Oramed also granted the underwriter, underwriter's warrants to purchase up to an aggregate of 7% of the shares of common stock sold in the offering at an exercise price of $4.80 per share. The net proceeds to Oramed from the offering were $19.894 mm. As of January 14, 2021, Oramed has sold 3,212,621 shares issued under a sales agreement for net proceeds of $14.397 mm. On December 1,2020, Oramed entered into a new equity distribution agreement pursuant to which the Company may, from time to time and at their option, issue and sell shares of common stock having an aggregate value of up to $40 mm. Oramed has filed Form S-3 and a prospectus with the U.S. Securities and Exchange Commission.

Financial Assumptions

• According to the American Diabetes Association (ADA) and CDC, there were an estimated 34.2 million people suffering from diabetes mellitus in the United States in 2020. According to the International Diabetes Federation (IDF), total expenditures related to diabetes mellitus were $294.6 billion in the United States in 2019, which makes the U.S. the country with higher diabetes-related expenditures worldwide (Exhibit 14).

• According to the CDC, there are an estimated 1.6 million people in United States suffering from type 1 diabetes, of whom 187,000 are pediatric patients.

• According to the International Diabetes Federation (IDF), there were an estimated 463 million people suffering from diabetes mellitus worldwide in 2019. The same year, the number of estimated global deaths due to diabetes mellitus was 4.2 million. IDF estimates total health expenditures related to diabetes of $760 billion worldwide, which will grow to $825 billion in 2030.

• Approximately 90% of all diabetic patients suffer from type 2 diabetes. The number of type 2 diabetic patients who will require insulin treatment as disease advances is estimated to be 7.4% to 15.5% of the total number of patients.

• We estimate a total market for type 1 diabetes of $25 billion. Type 1 diabetes mellitus has worse prognosis than type 2 diabetes.

• We estimate a total market for type 2 diabetes of $59 billion, and a total market for oral insulin of $4.36 billion.

• We assume an average wholesale annual end user price per patient for ORMD-0801 of $7,200 in the United States, which we believe is a conservative estimate given the current price of injectable insulins and other oral anti-hyperglycemic drugs (agents loweing blood glucose levels). The wholesale acquisition costs (WAC) for Novo Nordisk's Rybelsus (oral GLP-1 receptor agonist), Novo Nordisk's Ozempic (injectable GLP-1 receptor agonist) and Lilly/Boehringer Ingelheim's Jardiance (empagliflozin) are, respectively, $9,269, $9,615 and $5,915 per patient per annum.

• The annual cost per patient for various formulations of injectable insulin varies from $3,600 to $10,800. Lantus (insulin glargine, a generic drug, formerly from Sanofi) and Johnson & Johnson's Invokana (canagliflozin) have annual costs per patient between $3,157 to $3,600.

• Our ORMD-0801 price assumption is based on ORMD-0801 therapy meeting primary efficacy endpoints in ongoing Phase III clinical trials. We believe our price assumption for ORMD-0801 is conservative, especially given the drug's safety profile, superior patient compliance and potential clinical benefits of treating type 2 diabetic patients with oral insulin.

• For sales of ORMD-0801 in Europe, we assume an average wholesale annual price per patient of $1,250. In Europe, the wholesale acquisition cost (WAC) for Novo Nordisk's Rybelsus is $1,313 (Adv Ther 2020, 37, 1248-1259).

• Given the relatively early stage of development of ORMD-0901 clinical program and fierce competition in this area including global leaders such as Novo Nordisk and Eli Lilly, we do not forecast any revenue from ORMD-0901 at this time. To be conservative, we do not forecast any revenue from ORMD-0801's NASH indication and leptin program. However, we will reassess our opinion once additional clinical results become available.

• At present, we do not assume any revenue from sales of ORMD-0801 in China, related to Oramed's Technology License Agreement with HTIT (Hefei Tianhui Incubator of Technologies (HTIT) Co., Ltd., headquartered in Hefei, China) or from activities related to the joint venture agreement with D.N.A. Biomedical Solutions/Entera Bio. In 2015, Oramed and HTIT signed an agreement granting HTIT an exclusive commercialization license in the territory of China, Macau and Hong Kong related to Oramed's oral insulin capsule. Under the terms of the agreement, Oramed is entitled to certain royalties from product net sales and milestone payments up to a total of $37.5 mm. Through November 30, 2020, Oramed has received aggregate milestone payments of $20.5 mm out of the aggregate amount of $37.5 mm. On August 21, 2020, Oramed received a letter from HTIT disputing certain pending payment obligations estimated between $2 mm to $6 mm. Oramed and HTIT are trying to reach a mutually agreeable solution.

• We assume Oramed will sign a high value partnership with a global leader in the industry to complete development and commercialize ORMD-0801, which will include payments based on achieving certain regulatory and commercial milestones, plus a royalty from end-user sales.

• Assuming FDA approval of ORMD-0801 in 2024, we forecast total revenue, net income and fully diluted EPS of $77.6 mm/$41.9 mm/$1.57, $95.7 mm/$29.1 /$1.09 and $262.4 mm/$121.9 mm/$4.57, respectively, for F2025, F2026 and F2027 (Exhibit 15).

• Given that ORMD-0801 is a biologic, we expect Oramed to receive 12-years of market exclusivity upon FDA approval.

Exhibit 14 – List of top ten countries in the world with highest estimated health expenditures related to diabetes mellitus in 2019. With $294.6 billion, the U.S. is the country with the highest health expenditures worldwide.

Rank	Country or territory	Total diabetes-related health expenditure in 2019 (USD billion) (20-79 years)
1	United States of America	294.6
2	China	109.0
3	Brazil	52.3
4	Germany	43.8
5	Japan	23.5
6	Mexico	17.0
7	France	16.9
8	United Kingdom	14.1
9	Canada	12.3
10	Russian Federation	10.6

Source – International Diabetes Federation (IDF)

Valuation

We value Oramed using a risk-adjusted discounted cash flow model based on a WACC of 13%. The DCF model is risk-adjusted for probability of success in clinical development. We used a probability estimate to account for financial, clinical and regulatory risks, and based on data compiled by previous industry studies (Clinical Development Success Rates 2006-2015 by Bio (Biotechnology Innovation Organization), BioMedTracker and Amplion). Using the Gordon Growth Method, we calculate a terminal value of $2.15 billion (implied EV/EBITDA multiple of 6.3), and an implied risk-adjusted equity value of $492 mm. Based on current share price of $10.43, our calculated 12-month target price $23.00 corresponds to a potential implied return of 121%.

Exhibit 15 – Oramed Income Statement

INCOME STATEMENT	*Units*	FY 20	FY 21	FY 22	FY 23	FY 24	FY 25	FY 26	FY 27	FY 28	FY 29	FY 30
Revenue from Sales (U.S.)	*$ Millions*	$ -	$ -	$ -	$ -	$ -	$ 17.6	$ 90.3	$ 185.2	$ 284.7	$ 350.2	$ 398.9
Revenue from Sales (Rest of the World)	*$ Millions*	-	-	-	-	-	-	5.3	27.2	55.8	71.5	88.0
Revenue from Pharma Milestones	*$ Millions*	2.7	25.0	-	30.0	55.0	60.0	-	50.0	55.0	60.0	65.0
Revenue	*$ Millions*	2.7	25.0	-	30.0	55.0	77.6	95.7	262.4	395.6	481.8	551.9
Cost of Goods Sold	*$ Millions*	-	-	-	-	-	1.8	9.6	21.2	34.1	42.2	48.7
Gross Profit	*$ Millions*	2.7	25.0	-	30.0	55.0	75.9	86.1	241.2	361.5	439.6	503.2
Gross Margin							1.0	0.9	0.9	0.9	0.9	0.9
Research and Development	*$ Millions*	10.2	12.3	14.7	17.7	21.2	25.5	18.1	37.0	56.9	70.0	79.8
Selling General and Administrative	*$ Millions*	4.2	4.9	5.6	6.4	7.4	8.5	28.7	39.4	59.3	72.3	82.8
Depreciation and Amortization	*$ Millions*	-	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1
Total Operating Expenses		14.5	17.1	20.3	24.1	28.6	34.0	46.8	76.5	116.4	142.4	162.7
Operating Income	*$ Millions*	(11.8)	7.9	(20.3)	5.9	26.4	41.9	39.3	164.7	245.1	297.2	340.5
Interest Income (net)	*$ Millions*	0.2	-	-	-	-	-	-	-	-	-	-
Tax	*$ Millions*	-	-	-	-	-	10.9	10.2	42.8	63.7	77.3	88.5
Net Income	*$ Millions*	(11.5)	7.9	(20.3)	5.9	26.4	41.9	29.1	121.9	181.4	219.9	252.0
Earnings Per Share	*$ As Stated*	(0.56)	0.29	(0.76)	0.22	0.99	1.57	1.09	4.57	6.80	8.25	9.45
Fully Diluted Earnings Per Share	*$ As Stated*	(0.56)	0.29	(0.76)	0.22	0.99	1.57	1.09	4.57	6.80	8.25	9.45

Source – National Securities Corp.

Exhibit 16 – Oramed Balance Sheet

BALANCE SHEET	Units	FY 20	FY 21	FY 22	FY 23	FY 24	FY 25	FY 26	FY 27	FY 28	FY 29	FY 30
ASSETS:												
Current Assets:												
Cash and Equivalents, ST deposits & MS	$ Millions	$ 39.9	$ 38.2	$ 17.1	$ 23.8	$ 48.3	$ 86.7	$ 109.7	$ 220.9	$ 384.1	$ 581.0	$ 806.4
Accounts Receivable	$ Millions	-	2.5	-	3.0	5.5	7.8	9.6	26.2	39.6	48.2	55.2
Inventories	$ Millions	-	-	-	-	-	0.5	2.9	6.4	10.2	12.7	14.6
Supplies	$ Millions	-	-	-	-	-	-	-	-	-	-	-
Prepaid Expenses & Other Current Assets	$ Millions	0.6	1.7	2.0	2.4	2.9	3.4	4.7	7.6	11.6	14.2	16.3
Total Current Assets	$ Millions	40.5	42.4	19.2	29.2	56.7	98.3	126.8	261.1	445.5	656.1	892.4
Non-Current Assets:												
PPE & other	$ Millions	0.1	0.3	0.5	0.7	3.4	7.3	12.1	25.1	44.8	68.8	96.2
Long-term deposits & investment	$ Millions	0.0										
Long-term marketable securities	$ Millions	3.9	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
Intangibles, Intellectual Property	$ Millions	-	-	-	-	-	-	-	-	-	-	-
Employee rights & other	$ Millions	0.1										
Total Long Term Assets	$ Millions	4.1	3.9	4.1	4.3	7.1	10.9	15.7	28.7	48.4	72.4	99.8
Total Assets	$ Millions	44.6	46.3	23.3	33.5	63.7	109.3	142.4	289.9	493.9	728.5	992.3
Current Liabilities:												
Accounts Payable	$ Millions	0.6	1.2	1.4	1.7	2.0	2.4	3.3	5.4	8.1	10.0	11.4
Accrued Liabilities	$ Millions	1.1	1.2	1.4	1.7	2.0	2.4	3.3	5.4	8.1	10.0	11.4
Operating Lease Liabilities & other	$ Millions	0.1										
ST Deferred Revenue	$ Millions	2.7	0.1	-	0.1	0.2	0.2	0.3	0.8	1.2	1.4	1.7
Total Current Liabilities	$ Millions	4.5	2.5	2.8	3.5	4.2	5.0	6.8	11.5	17.5	21.4	24.4
Non-Current Liabilities:												
LT Deferred Revenue % Revenue	$ Millions	6.9	3.1	-	3.8	6.9	9.7	12.0	32.8	49.4	60.2	69.0
Employee rights upon retirement	$ Millions	0.0										
Provision for uncertain tax	$ Millions	0.0										
Operating lease liabilities	$ Millions	0.0										
Other liabilities	$ Millions	0.2										
Total Non-Current Liabilities	$ Millions	7.2	3.1	-	3.8	6.9	9.7	12.0	32.8	49.4	60.2	69.0
Total Liabilities	$ Millions	11.8	5.6	2.8	7.2	11.0	14.7	18.8	44.3	66.9	81.6	93.4
Equity:												
Common Stock and APIC	$ Millions	125.5	125.5	125.5	125.5	125.5	125.6	125.6	125.6	125.6	125.6	125.6
Retained Earnings	$ Millions	(92.6)	(84.8)	(105.1)	(99.2)	(72.9)	(31.0)	(1.9)	120.0	301.4	521.3	773.2
Total Equity:	$ Millions	32.9	40.7	20.4	26.3	52.7	94.6	123.7	245.6	427.0	646.9	898.9
Total Liabilities and Equity:	$ Millions	44.6	46.3	23.3	33.5	63.7	109.3	142.4	289.9	493.9	728.5	992.3

Source – National Securities Corp.

Exhibit 17 – Oramed Cash Flow Statement

STATEMENT OF CASHFLOWS	Units	FY 20	FY 21	FY 22	FY 23	FY 24	FY 25	FY 26	FY 27	FY 28	FY 29	FY 30
Net Income	$ Millions	$ (11.5)	$ 7.9	$ (20.3)	$ 5.9	$ 26.4	$ 41.9	$ 29.1	$ 121.9	$ 181.4	$ 219.9	$ 252.0
Non-Cash Charges												
Amortization of Intellectual Property	$ Millions	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Depreciation & Other	$ Millions	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1
Exchange differences & Other	$ Millions	0.5										
Change at fair value of investments	$ Millions	0.5										
Shares issued for services	$ Millions	0.0										
Stock-based compensation	$ Millions	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Cash Operating Charges												
Change in Accounts Receivable	$ Millions	0.0	-2.5	2.5	-3.0	-2.5	-2.3	-1.8	-16.7	-13.3	-8.6	-7.0
Inventories	$ Millions	0.0	0.0	0.0	0.0	0.0	-0.5	-2.3	-3.5	-3.8	-2.4	-2.0
Prepaid Expenses & Other Current Assets	$ Millions	0.4	-1.1	-0.3	-0.4	-0.5	-0.5	-1.3	-3.0	-4.0	-2.6	-2.0
Other	$ Millions	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Change in Accounts Payable	$ Millions	-0.8	0.6	0.2	0.3	0.3	0.4	0.9	2.1	2.8	1.8	1.4
Accrued Liabilities	$ Millions	-0.1	0.1	0.2	0.3	0.3	0.4	0.9	2.1	2.8	1.8	1.4
Change in deferred revenue	$ Millions	-2.7	-6.5	-3.2	3.8	3.2	2.9	2.3	21.3	17.0	11.0	9.0
Other Liabilities	$ Millions	-0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Liability for employee rights & other	$ Millions	0.0										
Deposits	$ Millions	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total Cash from Operating	$ Millions	-12.4	-1.5	-20.9	6.9	27.3	42.2	27.8	124.3	183.0	221.0	252.9
Cash Flow from Investing												
PP&E	$ Millions	-0.1	-0.2	-0.2	-0.2	-2.8	-3.9	-4.8	-13.1	-19.8	-24.1	-27.6
Short-term deposits	$ Millions	-27.2										
Mutual funds	$ Millions	-3.8										
Long-term deposits	$ Millions	0.0										
Held to maturity securities	$ Millions	-8.4										
Sale of short-term deposits	$ Millions	40.9										
Sale from held to maturity sec.	$ Millions	3.2										
Funds employee rights	$ Millions	0.0										
Total Cash from Investing	$ Millions	4.6	-0.2	-0.2	-0.2	-2.8	-3.9	-4.8	-13.1	-19.8	-24.1	-27.6
Cash Flow from Financing												
Equity Issuance	$ Millions	23.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Warrant Conversion & Other	$ Millions	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total Cash from Financing	$ Millions	23.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Effect of exchange rate	$ Millions	0.0										
Total Cash Flow	$ Millions	16.0	-1.7	-21.1	6.7	24.5	38.3	23.0	111.2	163.2	197.0	225.3
Last Period Cash Balance	$ Millions	3.3	39.9	38.2	17.1	23.8	48.3	86.7	109.7	220.9	384.1	581.0
New Cash Balance	$ Millions	39.9	38.2	17.1	23.8	48.3	86.7	109.7	220.9	384.1	581.0	806.4

Source – National Securities Corp.

Investment Thesis and Recommendation

In our view, the value of Oramed's oral protein delivery platform technologies, and the large commercial potential of its lead products for the treatment of diabetes, obesity and non-alcoholic steatohepatitis (NASH) is not fully reflected in the Company's current share price. Oramed's ORMD-0801 alone targets a commercial opportunity worth an estimated $4.36 billion. Based on the analysis of results from Phase II clinical trials, we believe that ORMD-0801 will meet primary efficacy endpoints in Phase III clinical trials, which could act as a positive catalyst for the stock. Assuming FDA approval of ORMD-0801 in 2024, we forecast revenue, net income and fully diluted EPS of $77.6 mm, $41.9 mm and $1.57 in F2025 (the first full year of ORMD-0801 commercialization). We value Oramed using a

risk-adjusted discounted cash flow model based on a WACC of 13%. Based on our model, we calculate an implied risk-adjusted equity value of $492 mm. Based on the current share price of $10.43, our calculated 12-month target price $23.00 corresponds to a potential implied return of 121%.

Management Team

Nadav Kidron

Chief Executive Officer, President & Director

Mr. Kidron serves as Chief Executive Officer & Director of Oramed Pharmaceuticals, which he co-founded in 2006. Mr. Kidron is an entrepreneur whose experience includes senior executive roles in a wide range of industries. He co-founded Entera Bio as a joint venture formed by Oramed and DNA Biomedical Solutions. He is a member of the IATI Board, and an international lecturer on Israel's entrepreneurial culture and the country's roots as an oasis of innovative ideas. He holds a bachelor's degree in law and an international master's in business administration, both from Bar-Ilan University in Israel. Mr. Kidron 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

Dr. Kidron serves as Chief Scientific Officer and Director of Oramed Pharmaceuticals, which she co-founded in 2006. Dr. Kidron is a pharmacologist and biochemist, who 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.

Josh Hexter

Chief Operating and Business Officer

Mr. Hexter serves as Chief Operating and Business Officer of Oramed Pharmaceuticals. Mr. Hexter has nearly two decades of prominent leadership, business development and operations know-how, entrepreneurialism and management experience in the life science sector. Prior to his current position, Mr. Hexter was Chief Business Officer of BrainsWay Ltd. (NASDAQ/TASE: BWAY). Previously, he served as the Chief Operating Officer of Oramed. Mr. Hexter has also served as Executive Director of Corporate In-Licensing at BioLineRx (NASDAQ/TASE: BLRX) and in the private equity and venture capital sector where he served as CEO of a VC-backed start-up. As founder and CEO of Biosensor Systems Design, Mr. Hexter was instrumental in shaping the company's strategic focus and in forging strategic 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.

Avi Gabay, CFO

Chief Financial Officer

Mr. Gabay serves as Chief Financial Officer of Oramed Pharmaceuticals. He joined Oramed in 2019. Prior to his appointment, from 2015 until 2019, Mr. Gabay served as a corporate controller at Orcam Technologies Ltd. Previously, he provided economic services in the advisory department of KPMG Israel, a certified public accounting firm and worked in the tax department of the law firm, Gornitzky & Co.

Mr. Gabay holds a bachelor's degree in law and accounting from Tel-Aviv University and is a certified public accountant in Israel and a member of the Israeli Bar Association.

Table of Risks

• Oramed is a biotechnology company still developing its candidate medicines in human clinical trials. As such, the Company has incurred significant losses since inception. Oramed will face financial risks as it will have minimal recurring revenues until it commercializes its products, or executes a development and commercialization agreement with a potential partner, which could generate licensing fees, milestone payments, royalties and research funding.

• Oramed will require to raise additional capital to fund its clinical programs. Management might fail to obtain the additional funding required to develop and commercialize their product candidates.

• Oramed and collaborators might fail to protect intellectual property rights.

• Oramed might not be able to retain key personnel to manage its business effectively.

IMPORTANT DISCLOSURES:

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200 Vesey Street, 25th Floor, New York, NY 10281

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				Investment Banking*
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NEUTRAL	5	18.52%	1	20.00%
SELL	0	0.00%	0	0.00%

**Investment banking services provided in the previous 12 months*

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NEUTRAL: the stock is likely to perform in-line with the industry over the next 12 months.

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