Rodman & Renshaw
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Oramed Pharmaceuticals, Inc. (ORMP)

Initiating Coverage

Healthcare

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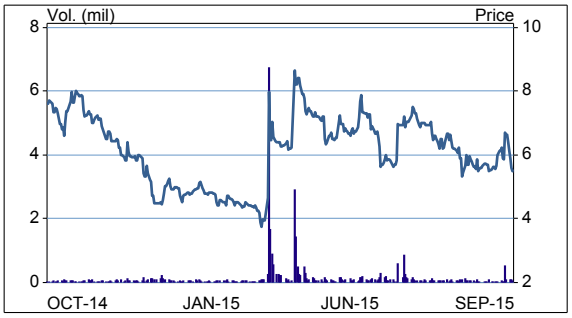
Optimizing Oral Insulin Delivery; Initiating Coverage with Buy and $24.00 Price Target

Stock Data	09/30/2015
Rating	Buy
Price	$5.47
Exchange	NASDAQ
Price Target	$24.00
52-Week High	$9.84
52-Week Low	$3.71
Enterprise Value (MM)	$55
Market Cap (MM)	$63
Public Market Float (MM)	9.4
Shares Outstanding (MM)	11.6
3 Month Avg Volume	87,108
Short Interest (MM)	0.72
Balance Sheet Metrics	
Cash (MM)	$17.20
Total Debt (MM)	$0.00
Total Cash/Share	$1.49
Book Value/Share	$1.97

EPS Diluted			
Full Year - Aug	2014A	2015E	2016E
1Q	(0.14)	(0.19)A	(0.19)
2Q	(0.12)	(0.16)A	(0.22)
3Q	(0.18)	(0.15)A	(0.23)
4Q	(0.16)	(0.18)	(0.23)
FY	(0.62)	(0.67)	(0.88)
FY P/E	NM	NM	NM



Risk-mitigated oral diabetes drug developer. We are initiating coverage of Oramed Pharmaceuticals, Inc., an emerging biotech firm developing novel formulations of well-known anti-diabetic drugs, with a Buy rating and a 12-month price target of $24.00 per share. In our view, Oramed constitutes a differentiated take on diabetes therapy, focusing on oral delivery of existing therapeutic agents like insulin and exenatide. We consider Oramed an attractive investment opportunity based on three attributes: (i) its focus on developing next-generation, orally-bioavailable formulations of drugs with known efficacy in diabetes (i.e., insulin and exenatide); (ii) potential for significant product sales generation and attractiveness to potential partners by targeting a substantial market of pandemic proportions in the form of diabetes; and (iii) the company's potential for applying its technology platform to the oral delivery of other peptide drugs. In our view, the positive pharmacokinetic data and favorable safety profile of Oramed's lead oral insulin drug candidate, ORMD-0801, lead us to believe that the currently-ongoing Phase 2b trial of this agent should yield positive data in the first half of next year.

Near-term Phase 2b data with elevated likelihood of success. In our view, Oramed's Phase 2b trial is well-positioned to validate the firm's lead drug candidate as a meaningful orally-bioavailable diabetes therapeutic. Firstly, insulin is a mainstay of diabetes therapy and remains the most validated means of glucose control today. Second, Oramed has already shown in Phase 2a development that fasting blood glucose (FBG) declined in patients given ORMD-0801. Finally, the design of the Phase 2b study is aimed at emphasizing night-time glucose control, which is the specific purpose for which Oramed's proprietary oral insulin capsule formulation was optimized. This 28-day study, which is designed to enroll up to 180 type 2 diabetic subjects, has already enrolled ~100 subjects and could complete enrollment before the end of this year.

Undervalued technology platform. Oramed currently trades at an enterprise value of <$50M, while the global diabetes market is estimated to be on track to exceed $40B by 2018. In our view, positive data from the firm's Phase 2b trial of ORMD-0801 could make ORMD-0801 the subject of a relatively near-term licensing transaction or might possibly serve as the catalyst for an acquisition of Oramed by an established participant in the diabetes market, potentially in 2016. Recent transactions in the diabetes space include the deal between MannKind Corp. and Sanofi S.A., in which Sanofi paid $150M upfront and promised a total of $775M in contingent milestones plus royalties on net sales of MannKind's inhaled insulin product, Afrezza®.

Valuation methodology. We have utilized a risk-adjusted net present value (rNPV) approach to assess Oramed's prospects. Factoring in a 12% discount rate, a 60% probability of success for ORMD-0801, and peak annual sales of $2.1B (on which Oramed would receive double-digit percentage royalties), we derive a total rNPV for ORMD-0801 of $130M. We add to this the additional value drivers of Oramed's pipeline, principally the firm's oral exenatide candidate ORMD-0901, to which we ascribe a collective valuation of $180M, to derive a total firm value of $357M. This translates into a price objective of $24.00 per share, assuming net cash of $47M and 15M shares outstanding as of the end of the fiscal third quarter of 2016.

Investment Thesis

Oramed Pharmaceuticals is an emerging biotechnology company developing novel therapeutic approaches for diabetes. The firm's lead candidate, ORMD-0801, is an orally-ingestible capsule-based formulation of insulin—a naturally-occurring hormone that lies at the root of the pathology in diabetes. A peptide hormone, insulin is produced primarily in the pancreas and plays a central role in the regulation of carbohydrate and lipid metabolism. There are two principal forms of diabetes mellitus: type 1 diabetes, which involves a failure by the body to produce insulin due principally to autoimmune destruction of the beta cells in the pancreas; and type 2 diabetes, which involves resistance to insulin by various cells in the body of the patient. The net result is effectively the same—inefficient glucose control and deficiencies in metabolic processes. Although insulin can be produced recombinantly and given via injection to insulin-deficient patients, the repeated injections are problematic and can cause issues with compliance. Accordingly, many firms have tried to develop orally-bioavailable forms of insulin. However, thus far none have been particularly successful. In our view, the Oramed solution could permit the introduction of the first truly effective orally-bioavailable insulin preparation. The approach is relatively low-risk from a clinical development perspective, in our view, because insulin's effectiveness and mechanism of action in diabetes patients is well-known and extensively characterized. Thus, the clinical program for ORMD-0801 should yield positive data, since Oramed's oral formulation has shown favorable pharmacokinetics. The firm is also developing an orally-bioavailable glucagon-like peptide 1 (GLP-1) receptor agonist, designated ORMD-0901. GLP-1 agonists are among the world's fastest-growing prescription diabetes drugs. Like insulin preparations, the GLP-1 agonist drugs currently on the market are principally administered via injection. Accordingly, we believe that Oramed could have a similar value proposition in this market. The firm's proprietary oral formulations are covered by U.S.-issued patents that we anticipate will initially expire in the 2026 to 2029 time frame without term extensions.

We are initiating coverage of ORMP with a Buy rating and a 12-month price target of $24.00 per share, based on a risk-adjusted net present value (rNPV) methodology. An investment in Oramed shares may entail significantly above-average risk and volatility. In our view, success in the ongoing Phase 2b trial should substantially increase Oramed's valuation and may position the firm as an acquisition target. We anticipate that positive data from this trial could, alternatively, enable Oramed to ink a licensing agreement for the U.S. rights to ORMD-0801, with a partner taking responsibility for Phase 3 development and commercialization of the product.

Table 1: Near-Term Catalysts and Upcoming Events

Event	Timing
Completed	
Initiation of enrollment in Phase 2b trial of ORMD-0801 oral insulin candidate in type 2 diabetes	**2Q15**
Non-binding term sheet received from Sinopharm Capital-Hefei to negotiate China rights to ORMD-0801	**3Q15**
Anticipated	
Consummation of licensing transaction on ORMD-0801 for China market	**3Q15**
Completion of enrollment in Phase 2b type 2 diabetes trial of ORMD-0801	Late 2015
Initiation of enrollment in Phase 2b trial of ORMD-0901 in type 2 diabetic patients	Late 2015 / Early 2016
Top-line data release from Phase 2b trial of ORMD-0801	**1H16**
Receipt of milestone payment from Chinese licensing partner on ORMD-0801	Mid-2016
Completion of enrollment in Phase 2b trial of ORMD-0901 in type 2 diabetics	2H16
Top-line data release from Phase 2b trial of ORMD-0901	**Late 2016**
Initiation of clinical development program on new peptide product candidate	Late 2016
Initiation of China development program for ORMD-0801	Late 2016
Consummation of U.S. licensing transaction on ORMD-0801	**Late 2016 / Early 2017**
Initiation of enrollment in Phase 3 development program for ORMD-0801 in type 2 diabetes	Mid-2017
Completion of enrollment in Phase 3 development program for ORMD-0801 in type 2 diabetes	Late 2018 / Early 2019
Top-line data from Phase 3 trial program in type 2 diabetes for ORMD-0801	**Early 2020**

Source: Company reports and Rodman & Renshaw estimates.

Valuation

The 12-month price target of $24.00 per share for ORMP is driven by a risk-adjusted net present value (rNPV)-based valuation approach. A discount rate of 12% was applied, based on the fact that the company's lead drug candidate ORMD-0801 has passed through early proof-of-concept testing and functions via a well-validated therapeutic mechanism of action, and given the fact that Oramed's second drug candidate, ORMP-0901, is a member of a well-known and substantially-validated drug class. Using this methodology, we generated a sum-of-the-parts valuation assessment, and derived a per share value of $24.00 (Exhibit 2, overleaf). In conducting our valuation analysis, the following assumptions were utilized:

- Near-term consummation of a licensing transaction on the China development rights for ORMD-0801, which would result in upfront payments to Oramed of $30 million in total.
- Completion of the ongoing Phase 2b trial of ORMD-0801 in late 2015 / early 2016.
- Positive data from this study, validating ORMD-0801 as a viable oral insulin candidate.
- Partnering of ORMD-0801 in late 2016 following successful completion of the Phase 2b trial.
- Initiation of pivotal development for ORMD-0801 in 2017, following completion of a U.S. partnership transaction on the product.
- Completion of U.S. clinical development by 2020, with regulatory filing shortly thereafter and potential market entry in late 2021.
- Future revenues are recorded by Oramed as royalties and milestone payments from a future putative U.S. or global (excluding China) commercialization partner, plus royalties from the China licensing partner as noted above.
- Application of a 12% discount rate to free cash flows, as we note that: (i) the diabetes sector currently involves a number of entrenched market participants with established product franchises; (ii) the firm's most advanced product candidates have all generated at least Phase 2 data, and carry below-average relative risk; and (iii) all of Oramed's programs involve candidates that work via established and well-validated mechanisms of action.

The above valuations and the projected cash position lead to the target price of $24.00 per share. We believe upside/downside to ORMP stock will be driven by several near-term catalysts:

1) Completion of the proposed China-specific licensing deal on ORMD-0801 this quarter;
2) Positive data from the currently-ongoing Phase 2b trial of ORMD-0801 in early 2016;
3) Consummation of a partnership transaction on the U.S. or global (ex-China) rights to ORMD-0801 in late 2016;
4) Initiation of pivotal development for ORMD-0801 in type 2 diabetes in late 2017.

Thus far, ORMD-0801 has shown an exemplary safety profile. This is to be expected, given the fact that it is derived from insulin, an endogenous human peptide with a specific and well-characterized mechanism of action involving the regulation of glucose metabolism. Unlike existing recombinant versions of insulin, which must be administered via injection, ORMD-0801 is formulated specifically to permit oral delivery. This confers a substantially more convenient dosing profile and enables Oramed to deploy the drug for a specific purpose—namely, night-time glucose control, which is known to be deficient in diabetics who take short-acting forms of injectable insulin. In our view, this constitutes a highly definable and differentiated market niche.

Thus, we consider Oramed an attractive investment from three perspectives—its risk-mitigated status as a biotech company developing a novel, orally-bioavailable formulation of a well-known molecule possessing a validated mechanism of action and a longstanding track record of therapeutic efficacy in the target indication of diabetes; its potential for significant revenue growth through the approval of a product aimed at an extremely large market of pandemic proportions; and the possibility for Oramed to develop additional drug candidates, such as ORMD-0901, by leveraging its patent-protected oral delivery technology platform that is optimized for peptides.

Table 2: Risk-Adjusted NPV-Based Valuation Methodology—ORMD-0801

ORMD-0801 - Global	
Total diabetes patients[1]	60MM
Patients seeking treatment[2]	12.5MM
Peak market share[3]	8%
Treatment revenue/prescription/course of therapy[4]	$1,500
Peak sales[5]	$2.1B
Peak royalty-based revenue to Oramed[6]	$260MM
Launch[7]	2021
Peak sales year	2026
Protection expires[8]	2030
Discount rate	12%
Probability of success[9]	60%
Risk-adjusted NPV[10]	$130MM
Technology platform NPV[11]	$50MM
NPV per share	$9.00
Estimated Net Cash Position ($MM; end-F3Q 2016)	$47MM
Additional Pipeline Value Drivers (ORMD-0901)	$130MM
Total firm value	$357MM
Shares Outstanding (MM; end-F3Q 2016)	15MM
Present value-derived price target	$24.00

Notes on assumptions:

[1] Type 2 diabetes mellitus patients - worldwide (only includes U.S. and European Union)
(Source: National Institute of Health, American Diabetes Association)

[2] Patients with type 2 diabetes seeking therapy
(Source: Rodman & Renshaw estimates)

[3] Peak market share - blended; factoring in competition from injected insulins, other oral insulins, incretin mimetics and other drugs

[4] Revenue/year/prescription - estimated to be higher than injected intermediate insulin (wholesale acquisition cost)

[5] Peak sales - treatment revenue/year x treated patients x peak market share

[6] Peak royalty-based revenue - applies estimated royalty rate (9 - 12.5%) on net sales of product by Oramed's partner

[7] Launch in 2021 (US) / 2022 (EU)

[8] Patent expiry starting in 2026 - 2030; Hatch-Waxman extensions may provide up to an additional five years of protection

[9] Probability of success - ORMD-0801 is in Phase 2 testing (oral insulin formulation, known to be an effective diabetes therapeutic)

[10] Cash flow fully taxed at 35% following launch; upfront payments and milestones cancel out operating loss carry-forwards

[11] Technology platform NPV contribution (application of oral delivery formulation to other peptides)

Source: Company reports and Rodman & Renshaw estimates.

We have utilized a 60% probability of success for ORMD-0801, based upon the fact that insulin represents a well-known therapeutic modality in diabetes and given the positive initial proof-of-concept results obtained from the early Phase 2 studies conducted with this candidate. While we acknowledge that these trials were relatively small (a total of 131 patients treated), over 1,400 doses of ORMD-0801 were administered and the safety profile of the drug was benign.

From our perspective, the likelihood of positive data being obtained from the Phase 2b trial in the U.S. is relatively high given the validated role of insulin in diabetes treatment. In addition, we note that successful extrapolation (i.e., prediction of success) from small proof-of-concept trials into larger, more robust studies—and indeed the pivotal setting—for drug candidates with validated mechanisms of action is relatively common. Recent examples include albiglutide, a long-acting glucagon-like peptide 1 (GLP-1) agonist now approved under the trade name Tanzeum®, which yielded positive data in a 40-patient study involving type 2 diabetics and subsequently generated positive data in a Phase 3 program that enrolled over 5,000 subjects; and remogliflozin etabonate, which yielded positive results from a 48-patient trial in type 2 diabetes and subsequently generated positive data from two Phase 2b trials that enrolled nearly 200 subjects.

Table 3: Risk-Adjusted NPV-Based Valuation Methodology—ORMD-0901

ORMD-0901 - Global	
Total diabetes patients[1]	60MM
Patients seeking treatment[2]	12.5MM
Peak market share[3]	2.6%
Treatment revenue/prescription/course of therapy[4]	$8,400
Peak sales[5]	$2.8B
Peak royalty-based revenue to Oramed[6]	$280MM
Launch[7]	2020
Peak sales year	2025
Protection expires[8]	2029
Discount rate	15%
Probability of success[9]	50%
Risk-adjusted NPV[10]	$130MM
Technology platform NPV[11]	$50MM
NPV per share	$9.00
Estimated Net Cash Position ($MM; end-F3Q 2016)	$47MM
Additional Pipeline Value Drivers (ORMD-0801)	$130MM
Total firm value	$357MM
Shares Outstanding (MM; end-F3Q 2016)	15MM
Present value-derived price target	$24.00

Notes on assumptions:

[1] Type 2 diabetes mellitus patients - worldwide (only includes U.S. and European Union)
(Source: National Institute of Health, American Diabetes Association)

[2] Patients with type 2 diabetes seeking therapy
(Source: Rodman & Renshaw estimates)

[3] Peak market share - blended; factoring in competition from injected insulins, other oral insulins, incretin mimetics and other drugs

[4] Revenue/year/prescription - estimated to be higher than injected intermediate insulin (wholesale acquisition cost)

[5] Peak sales - treatment revenue/year x treated patients x peak market share

[6] Peak royalty-based revenue - applies estimated royalty rate (7 - 10%) on net sales of product by Oramed's partner

[7] Launch in 2021 (US and EU)

[8] Patent expiry starting in 2029; Hatch-Waxman extensions may provide up to an additional five years of protection

[9] Probability of success - ORMD-0901 is entering Phase 2 (oral exenatide formulation, known to be effective diabetes treatment)

[10] Cash flow fully taxed at 35% following launch; upfront payments and milestones cancel out operating loss carry-forwards

[11] Technology platform NPV contribution (application of oral delivery formulation to other peptides)

Source: Company reports and Rodman & Renshaw estimates.

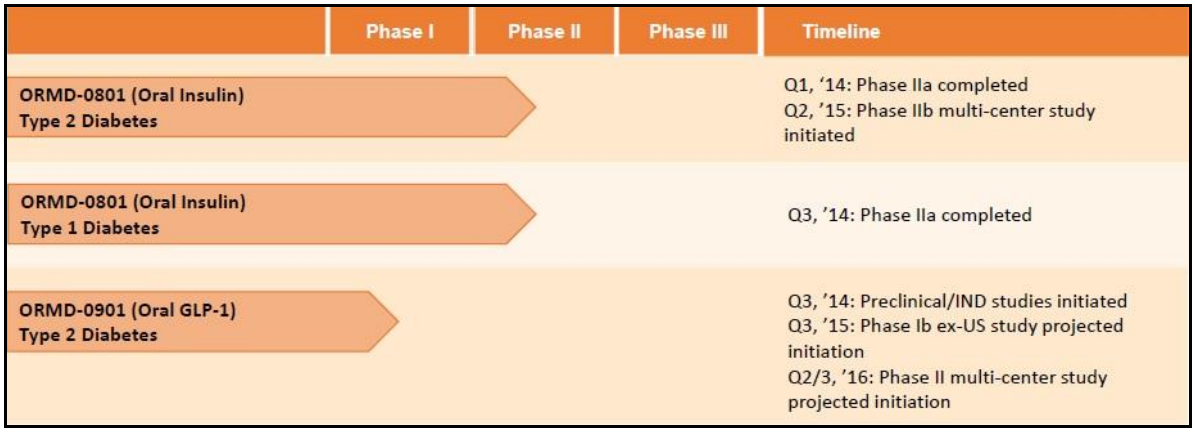
We have utilized a 50% probability of success for ORMD-0901, based upon the fact that glucagon-like peptide 1 (GLP-1) receptor agonism represents a well-known therapeutic modality in diabetes and given the positive initial proof-of-concept results obtained from the early Phase 2 studies conducted with this candidate. In our view, Oramed is likely to out-license this product candidate as well, given the substantial resources that would be required to adequately commercialize such a drug in the global diabetes market.

We expect the royalty rate for ORMD-0901 to be lower than that for ORMD-0801; namely, 7 – 10% for the oral exenatide product vs. 9 – 12.5% for the oral insulin candidate. This is based on our assumption that Oramed may not conduct Phase 2b testing of this agent prior to partnering the drug. We have utilized a higher discount rate applicable to future cash flows—namely, 15% for ORMD-0901 vs. 12% for ORMD-0801—to reflect the higher degree of competition posed by the longer-acting GLP-1 agonists to a putative orally-bioavailable exenatide product. As was the case in our assessment of ORMD-0801, we note that successful extrapolation (i.e., prediction of success) from small proof-of-concept trials into larger, more robust studies—and indeed the pivotal setting—for candidates with validated mechanisms of action is relatively common.

Company Overview

Oramed Pharmaceuticals was originally founded in 2006, based on a proprietary technology platform derived from the work of Dr. Miriam Kidron, the firm's chief scientist. In 2007, the company conducted several clinical studies of an orally-ingestible insulin capsule formulation, in order to assess both the safety/tolerability and absorption properties of what eventually became known as ORMD-0801, and elected to advance this candidate. Subsequently, Oramed also developed an orally-ingestible capsule formulation of exenatide, a well-characterized glucagon-like peptide 1 (GLP-1) receptor agonist, designated as ORMD-0901. This candidate has also been advanced into clinical testing and is being developed both as a single agent as well as in the form of a potential combination therapy with ORMD-0801. The pipeline is shown below.

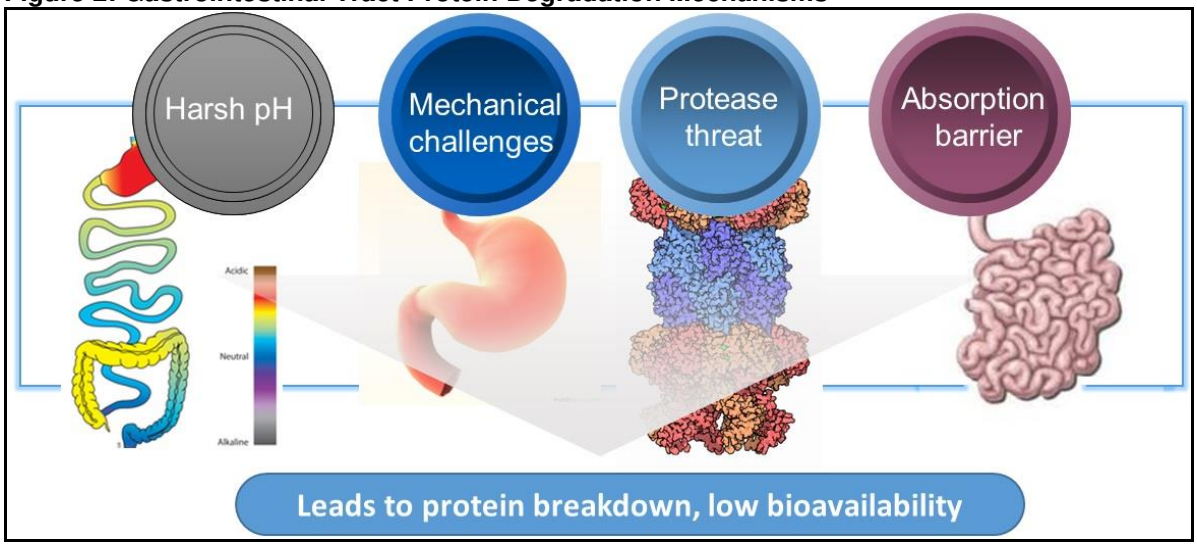
Figure 1: Oramed Pharmaceuticals Clinical-Stage Pipeline



Source: Company reports.

The firm has been working in parallel on both ORMD-0801 and ORMD-0901 for the past several years. The figure below shows how proteins are typically broken down in the gastrointestinal tract, preventing them from being efficiently delivered in oral form. The Oramed platform is designed to protect proteins from these degradation pathways. While oral delivery of biologics like insulin has long been attempted, prior results have been poor. In our view, Oramed could become a leader in the development and commercialization of an oral insulin product.

Figure 2: Gastrointestinal Tract Protein Degradation Mechanisms



Source: Oramed Pharmaceuticals, Inc.

ORMD-0801 (oral insulin capsules)—Development History

In November 2007, the company successfully completed animal studies in preparation for the Phase 1b clinical trial of ORMD-0801. In January 2008, Oramed commenced non-FDA-sanctioned Phase 1b clinical trials with its oral insulin capsule, in healthy human volunteers with the intent of dose optimization. In March 2008, the firm successfully completed these Phase 1b clinical trials. Subsequently, during the following month, Oramed commenced a non-FDA-sanctioned Phase 2a study to evaluate the safety and efficacy of its oral insulin capsule in Type 2 diabetic volunteers at Hadassah Medical Center in Jerusalem, Israel. In August 2008, the firm announced positive results from this trial. In July 2008, Oramed was given the green light by the Institutional Review Board Committee of Hadassah Medical Center to conduct a non-FDA-sanctioned Phase 2a study to evaluate the safety and efficacy of the oral insulin capsule on Type 1 diabetic volunteers. In September 2008, Oramed formally initiated this trial. In July 2009, the firm reported positive results from this study, indicating that ORMD-0801 could be deployed effectively as a therapy for both Type 1 as well as Type 2 forms of diabetes.

In April 2009, Oramed began a consulting service agreement with ADRES Advanced Regulatory Services Ltd. (ADRES), which was amended in February 2012, pursuant to which ADRES would provide services for the purpose of filing an Investigational New Drug (IND) application with the FDA to conduct a Phase 2 proof-of-concept study with ORMD-0801 according to agency requirements. The approval process and—if approved—registration for commercial use as an oral drug is expected to take several years. Oramed began a non-FDA-sanctioned Phase 2b study in South Africa in May 2009 to evaluate the safety, tolerability and efficacy of the oral insulin capsule on Type 2 diabetic volunteers. In May 2010, the firm reported that the capsule was found to be well-tolerated and exhibited a positive safety profile. No cumulative adverse effects were reported throughout this first study of extended exposure to the capsule.

In September 2010, the firm reported positive results from an exploratory clinical trial testing the effectiveness of its oral insulin capsule in type 1 diabetes patients suffering from uncontrolled diabetes. Unstable or labile diabetes is characterized by recurrent, unpredictable and dramatic blood glucose swings often linked with irregular hyperglycemia and sometimes serious hypoglycemia affecting type 1 diabetes patients. This completed exploratory study was a proof of concept study for defining a novel indication for ORMD-0801. We believe the encouraging results justify further development of the ORMD-0801 capsule in uncontrolled diabetes.

In February 2010, Oramed contracted with Vetgenerics Research G. Ziv Ltd., a clinical research organization, to conduct a toxicology trial on the firm's oral insulin capsules. In March 2011, the company reported the successful completion of the resulting comprehensive toxicity study for ORMD-0801. This study was completed under conditions prescribed by the FDA's Good Laboratory Practices (GLP) regulations.

Oramed inked a Master Services Agreement with Medpace, Inc. in September 2012 to retain Medpace as the contract research organization (CRO) for Oramed's upcoming Phase 2 clinical trial for ORMD-0801. This trial, the first proof-of-concept study to be conducted under FDA sanction for ORMD-0801, was originally expected to start in early 2013 in the U.S., and was expected to be completed in December 2013.

In March 2013, however, due to a request from the FDA, work on beginning this Phase 2 study was temporarily halted. Effectively, Oramed filed its Investigational New Drug (IND) application with the FDA on ORMD-0801 in December 2012, with the aim of securing permission to begin the Phase 2 clinical trial of ORMD-0801 in order to evaluate the safety, tolerability and efficacy of the candidate on patients with Type 2 diabetes. However, the FDA requested that a Phase 2a sub study be completed before Oramed could be allowed to proceed with the originally-envisaged Phase 2b trial. The Phase 2a sub study, which was an in-patient study with 30 individuals that began in July 2013, was completed in late 2014. In the wake of positive data, which reconfirmed the favorable safety profile of ORMD-0801, Oramed finalized plans to initiate a Phase 2b trial of ORMD-0801.

In May 2010, Oramed inked an agreement with SAFC Pharma (SAFC) in order to develop a process to produce one of Oramed's oral capsule ingredients and in June 2011, Oramed issued a purchase order to SAFC for producing the ingredient. In July 2010, Oramed established a Manufacturing and Supply Agreement (MSA) with Sanofi-Aventis Deutschland GmbH (Sanofi-Aventis, now known as Sanofi S.A.). According to the MSA, Sanofi is supplying Oramed with specified quantities of recombinant human insulin to be formulated with Oramed's proprietary encapsulation technology and used for clinical trials in the U.S.

On May 26, 2015, Oramed announced that it had submitted a study protocol for review to the FDA that described the plan for its proposed Phase 2b trial of ORMD-0801. This study, which is slated to enroll a total of 180 patients in a double-blinded, randomized, parallel-group design, has a 28-day treatment period and is aimed at validating the therapeutic profile of ORMD-0801 and further confirming the safety profile of the drug. The study protocol was filed under Oramed's existing open Investigational New Drug (IND) application. Subsequently, on June 30, 2015, Oramed announced the successful enrollment of the first patient into the Phase 2b trial. The firm has indicated that a total of 30 clinical sites in the U.S. are participating in this trial—the largest study that Oramed has ever conducted. We believe that, at this juncture, roughly 100 subjects have been randomized and that if enrollment continues according to the pace observed thus far, Oramed could announce completion of recruitment in this study by the end of 2015. If this turns out to be the timeline, Oramed could report top-line results from this study by the end of the first quarter of calendar 2016.

ORMD-0901 (oral exenatide capsules)—Development History

In September 2008, Oramed initiated the preclinical testing of ORMD-0901, an orally-bioavailable formulation of a known analog of GLP-1, a gastrointestinal hormone. The pre-clinical trials include animal studies which suggest that the GLP-1 analog (exenatide, derived from the exendin-4 molecule derived from the saliva of the Gila monster, *Heloderma suspectum*—a form of poisonous lizard), when combined with Oramed's absorption promoters, is absorbed through the gastrointestinal tract and retains its biological activity. Glucagon-like peptide-1 (GLP-1) is an incretin hormone - a type of gastrointestinal hormone that stimulates pancreatic insulin secretion. The incretin concept was hypothesized when it was noted that glucose ingested by mouth (oral) stimulated two to three times more insulin release than the same amount of glucose administered intravenously. In addition to stimulating insulin release, GLP-1 was found to suppress glucagon (a hormone involved in regulation of glucose) release from the pancreas, slow gastric emptying to reduce the rate of absorption of nutrients into the blood stream, and increase satiety. Other important beneficial attributes of GLP-1 are its effects of increasing the number of beta cells (cells that manufacture and release insulin) in the pancreas and, possibly, protection of the heart.

In September 2009, Oramed received approval from its Institutional Review Board to commence human clinical trials of ORMD-0901, its oral GLP-1 analog, after successful preclinical results were reported. The trials were conducted on healthy volunteers at Hadassah University Medical Center in Jerusalem. The first study monitored the responses of healthy males to a single dose delivered 60 minutes before a glucose load and was completed in December 2009. ORMD-0901 was well tolerated by all subjects and demonstrated physiological activity, as extrapolated from ensuing subject insulin levels when compared to those observed after treatment with placebo. In June 2012, Oramed presented an abstract that described the impact of the firm's oral insulin capsule formulation, ORMD-0801, when delivered in combination with its oral exenatide capsule formulation, ORMD-0901. The work that was presented assessed the safety and effectiveness of a combination of oral insulin and oral exenatide treatments delivered to pigs prior to food intake. The drug combination resulted in significantly improved blood glucose regulation vs. administration of each drug separately. In January 2013, Oramed began a clinical trial for its oral exenatide capsule on healthy volunteers and type 2 diabetic patients. In February 2013, the firm commenced an initial human clinical trial in type 2 diabetic patients with its oral insulin capsule delivered in combination with its oral exenatide capsule. This study yielded encouraging results that may provide indications of synergistic impact for both drugs when delivered simultaneously.

China Regional Licensing Transaction Overview—ORMD-0801

On July 7, 2015, Oramed announced that it had signed a non-binding Letter of Intent (LOI) for an investment and license agreement in China focused on Oramed's oral insulin candidate with Sinopharm Capital Management Co. Ltd. and Hefei Life Science & Technology Park Investments and Development Co., Ltd. (Sinopharm/Hefei) potentially valued at $50 million in upfront and near-term milestone payments, in addition to future royalties on net sales of the product in China. Oramed has received $500,000 in exchange for exclusively negotiating with Sinopharm/Hefei for 60 days, while the final terms of the agreement are being negotiated and finalized. On September 3, 2015, Sinopharm-Hefei and Oramed jointly agreed to extend the exclusivity period for negotiation of the licensing agreement by 45 days. Accordingly, we believe that the definitive licensing agreement could be finalized by late October 2015.

The transaction, which includes 10% royalties on sales of ORMD-0801, will allow Sinopharm/Hefei to purchase a roughly 10% stake in Oramed Pharmaceuticals and acquire rights for oral insulin in China. The terms are to be broken down as follows: Oramed is slated to sell Sinopharm/Hefei 1,155,367 shares of common stock for approximately $12 million. In addition, Oramed's wholly owned subsidiary, Oramed Ltd, is slated to license to Sinopharm/Hefei the exclusive rights to ORMD-0801 (oral insulin capsules) in China, for a total amount of $38 million, of which $18 million is slated to be paid upon the signing of the license agreement and the remaining $20 million is to be paid following the completion of Oramed's currently-ongoing Phase 2b trial in the U.S. and the release of data from this study.

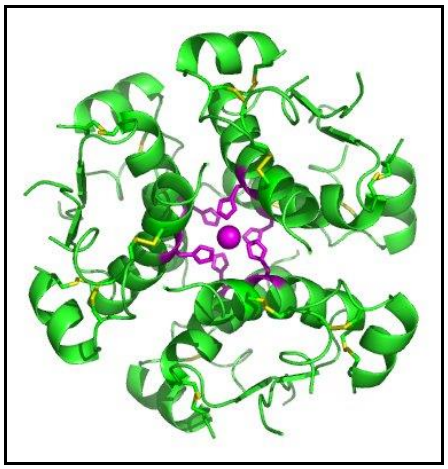
Sinopharm (China National Pharmaceutical Group Corporation) is the largest medical and healthcare group in China which is directly managed by the State-owned Assets Supervision and Administration Commission of the State Council (SASAC), with the core businesses of distribution, logistics, retail, scientific research and manufacture of healthcare related products. Sinopharm owns 11 wholly owned or holding subsidiaries, and six listed companies. The sales revenue of Sinopharm exceeded $39 billion in 2014. Sinopharm Capital Management Co. Ltd. is a professional asset management company within Sinopharm. Hefei Life Science & Technology Park Investments and Development Co., Ltd.'s (HLST) business focus includes industrial investment and incubation services; high-tech product R&D; technology transfer and related consulting services. HLST has state-of-the-art insulin production facilities located in Hefei, China.

From our perspective, this projected licensing deal could serve as an important benchmark underpinning the value of Oramed's oral insulin franchise. It could thus be utilized as a fulcrum in future partnering discussions that Oramed may hold with additional potential strategic collaborators in the wake of the completion of the ongoing Phase 2b trial. We note that: (i) Sinopharm-Hefei represents a highly credible commercialization partner for Oramed in China; (ii) the transaction is structured to include an equity investment at a price per share of approximately $10.39, a substantial premium to the current trading price of Oramed common stock; (iii) the transaction includes a total of $50 million in upfront and near-term milestones, indicating a front end-loaded structure that thus provides significant advantages to Oramed, including the ability to potentially offset the cash burn for a substantial period of time; (iv) Sinopharm-Hefei will provide Oramed with 10% royalties on net sales in China, which could represent a significant revenue stream for Oramed in future years.

Oramed Oral Formulation Platform Overview

Oramed's lead drug candidate is a proprietary, orally-ingestible capsule formulation of insulin. The structure of insulin (herein depicted as a hexamer, with the pink structures representing the histidine residues involved in binding zinc) is depicted below.

Figure 3: Insulin Structure

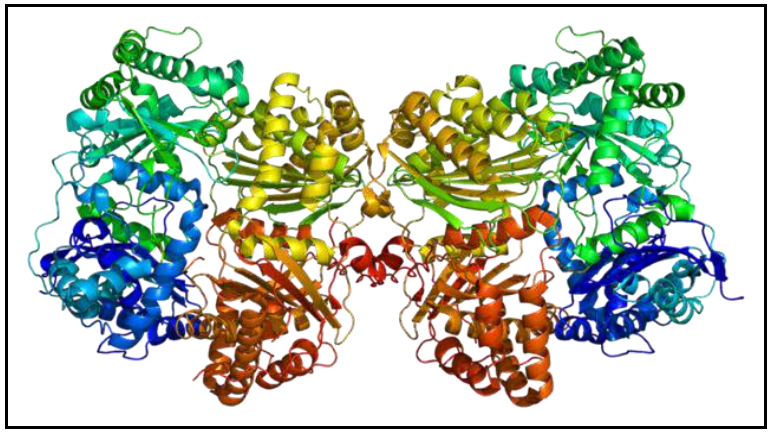


Source: Brookhaven Protein Data Bank.

Insulin is susceptible to protease degradation in the gastrointestinal tract, preventing its native form from being rendered orally-bioavailable for human therapeutic use. Several proteases attack insulin, but the most well-known insulin-specific protease is known alternatively as insulysin or insulinase, but chiefly as Insulin Degrading Enzyme (IDE), a large zinc-binding protease of the M16A metalloprotease sub-family known to cleave multiple short polypeptides of varying lengths.

IDE was first identified by its ability to degrade the B chain of the hormone insulin. This activity was observed over 50 years ago, though the enzyme specifically responsible for B chain cleavage was identified more recently. This discovery revealed considerable amino acid sequence similarity between IDE and the previously characterized bacterial protease pitrilysin, suggesting a common proteolytic mechanism. IDE knockout mice exhibit a diabetic phenotype, an emergent condition that arises as a response to hyperinsulinemia in the tissues. In addition, inhibitors of IDE administered in preclinical models have been shown to reduce the degradation of insulin that is given simultaneously via injection, demonstrating the central role that IDE plays in the catabolism of insulin.

Figure 4: IDE Molecular Structure

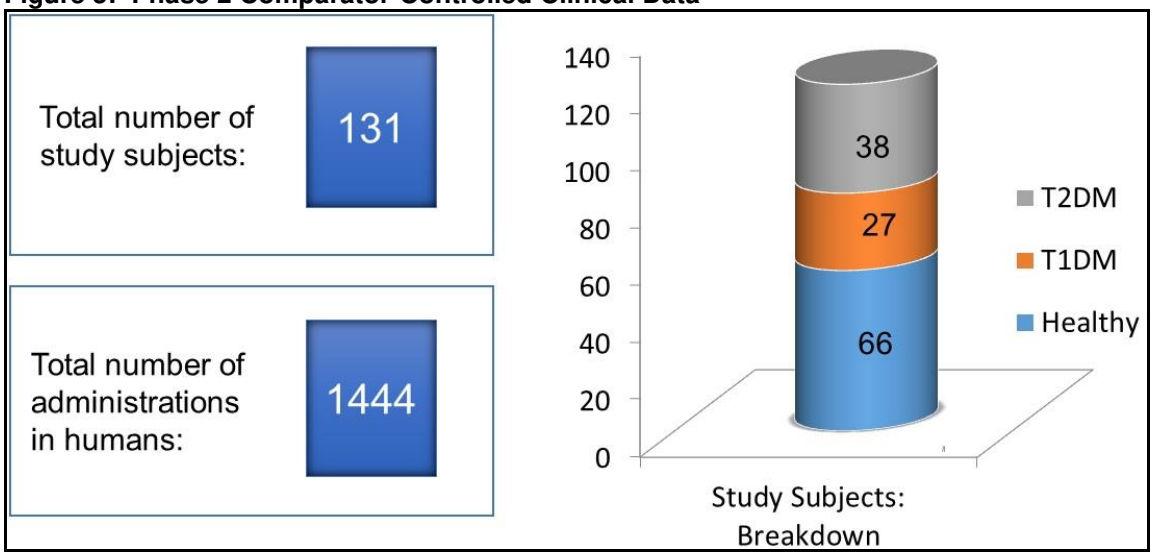


Source: Brookhaven Protein Data Bank.

ORMD-0801 Experimental Data

An overview of the proof-of-concept clinical data generated thus far with ORMD-0801 indicates, in our view, that the drug has encouraging activity in diabetic patients. We note that Oramed is developing this drug primarily to suppress elevated fasting blood glucose (FBG) levels, which are considered a significant issue in type 2 diabetics. The condition of elevated FBG levels typically arises as a result of excessive nocturnal glucose production from the liver. Roughly 70% of individuals with impaired FBG control develop type 2 diabetes. Approximately 80% of type 2 diabetics exhibit abnormal FBG levels and fail to achieve adequate glycemic control with older-generation anti-diabetic drugs such as metformin or TZDs. Even drugs currently used to control FBG levels have significant adverse events, leading to a substantial unmet need for drugs that control FBG levels in a more natural, physiologically-appropriate manner. The figure below depicts the number of patients who have been given ORMD-0801 in early proof-of-concept trials, and the total number of administrations of the drug that occurred in those studies.

Figure 5: Phase 2 Comparator-Controlled Clinical Data



Source: Oramed Pharmaceuticals, Inc.

The above figure demonstrates that a significant number of exposures to ORMD-0801 have already occurred, and that the drug has thus far exhibited a solid safety profile. We note that ORMD-0801 is eligible for submission via the 505(b)(2) pathway, which means that an abbreviated path to market can be envisaged that would allow Oramed and its potential collaborators to utilize existing safety and efficacy data generated with injectable insulin preparations in order to file an NDA in the U.S.

Oramed's methodology of dosing oral insulin has not only a dosing convenience rationale but also a physiological one. Since the blood glucose – insulin secretion system forms a closed loop in order to minimize systemic exposure to insulin above specific levels and maintain homeostasis – with peripheral insulin being responsible for glucose uptake in fat and muscle – it has been hypothesized that the most natural way to provide glucose control would be to optimize insulin delivery through the portal vein instead of attempting to deliver it systemically via intravenous or subcutaneous injection. First-pass hepatic metabolism extracts roughly 80% of secreted insulin.

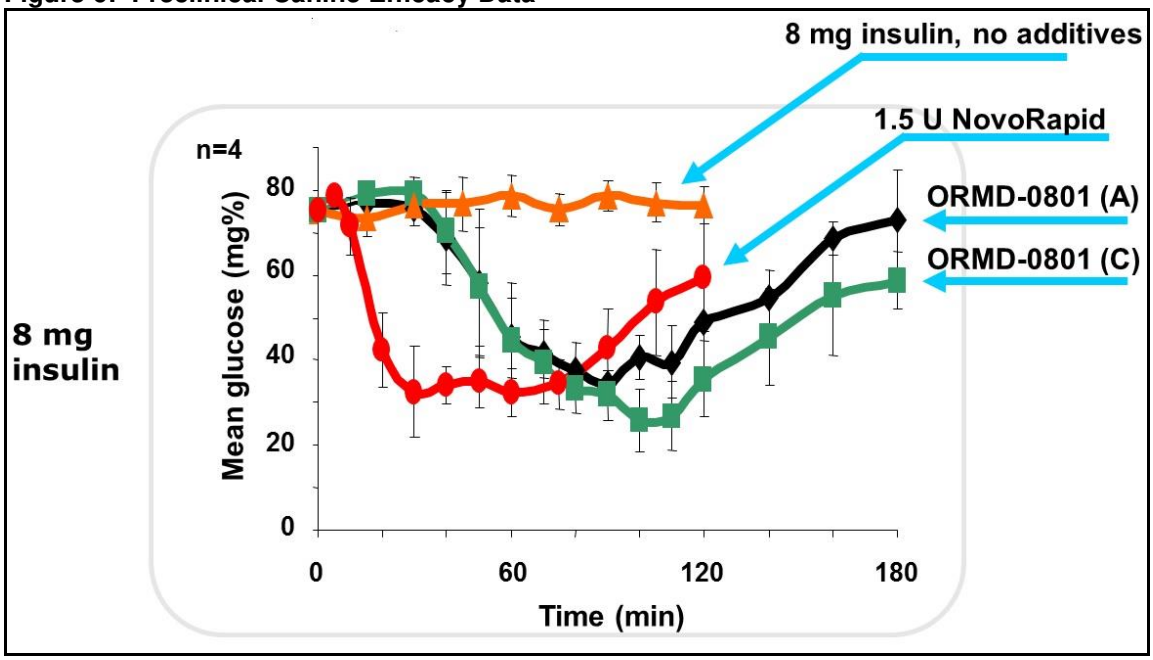
The system of dosing insulin orally in a protease-protected formulation is optimized to provide a more physiological presentation of insulin, thus enabling reduction of insulin resistance and stimulating endogenous insulin secretion. Oramed developed its capsule formulation specifically for this purpose. In our experience, this is one of the most rational approaches to diabetes therapy that we have come across.

Oramed's initial preclinical data with ORMD-0801 were promising. The drug was assessed in animal toxicology trials, with 28-day data showing no safety signals in Sprague-Dawley rats at doses three times above levels being deployed in human subjects.

Preclinical Efficacy Data

Proof-of-concept studies were done in beagle dogs as well as pigs. The figure below illustrates the data obtained with ORMD-0801 benchmarked vs. native insulin and NovoRapid™ in dogs.

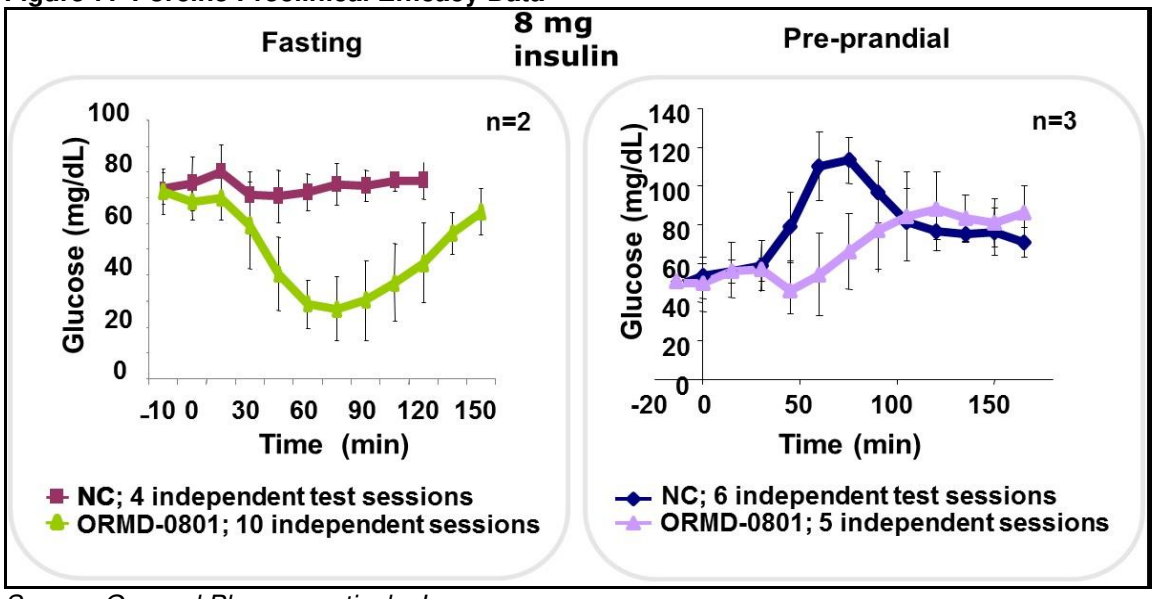
Figure 6: Preclinical Canine Efficacy Data



Source: Oramed Pharmaceuticals, Inc.

As seen above, a 60 – 75% drop in blood glucose levels was seen in in healthy, non-diabetic cannulated beagle dogs within 30 – 100 minutes of administration of therapy. The figure below shows similar data in pigs, in which similarly no hypoglycemia or adverse events were seen.

Figure 7: Porcine Preclinical Efficacy Data



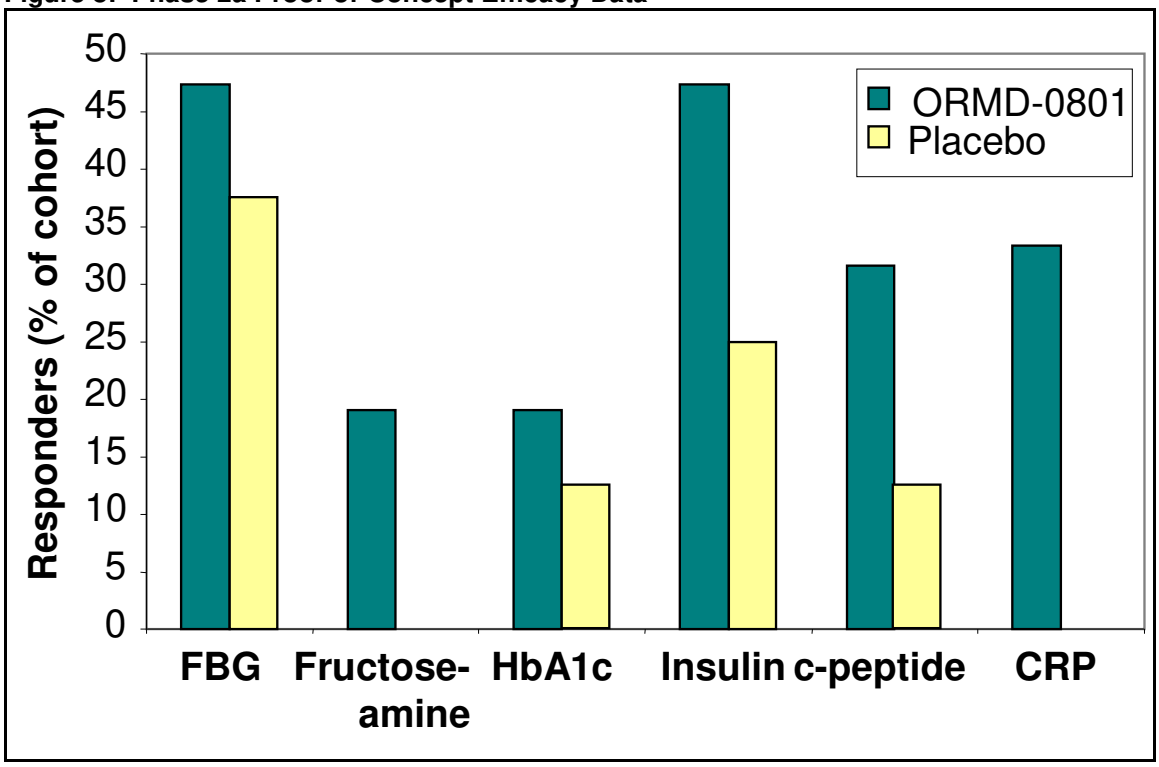
Source: Oramed Pharmaceuticals, Inc.

Type 2 Diabetes Phase 2 Proof-of-Concept Data

The firm's first proof-of-concept trial, conducted in Israel without FDA sanction, was a six-week study that enrolled 29 type 2 diabetics. Unusually for such a small study, it had a placebo-controlled, randomized, double-blinded design. In this trial, 21 patients received orally-ingestible insulin capsules at bedtime, while nine received placebo.

Safety data from this trial, which was concluded in August 2008, proved that the first extended exposure to ORMD-0801 was safe and well-tolerated. No serious adverse events were reported and no cumulative effects were observed. Although two hypoglycemic events were recorded, both were mild in severity. The efficacy results demonstrated that ORMD-0801 reduced markers of both hyperglycemia and inflammation. The percentages of patients showing clinically-relevant reductions n C-reactive peptide (CRP), fasting blood glucose, and HbA1c levels were all higher in the treatment cohort vs. placebo. We note that, as shown below, the difference in fasting blood glucose seen in this trial was not massive; however, the small size of the study and the limited duration made it unlikely that a significant difference would be seen.

Figure 8: Phase 2a Proof-of-Concept Efficacy Data



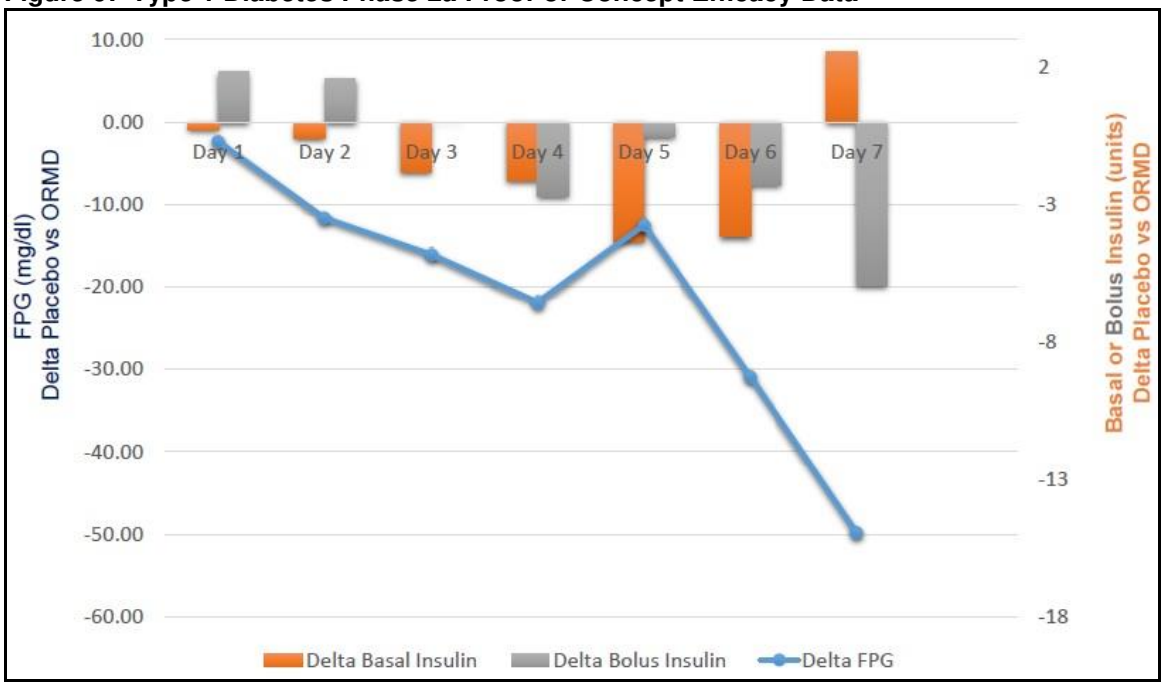
Source: Oramed Pharmaceuticals, Inc.

Oramed subsequently conducted a Phase 2a trial in the U.S. under an FDA-sanctioned IND. This study was stipulated to be necessary by the agency ahead of advancing ORMD-0801 into a formal Phase 2b trial. The Phase 2a trial was a 24-subject study being conducted on an in-patient basis. Although it was randomized and double-blinded, patients were only subjected to one week of treatment. The trial was, therefore, neither powered for efficacy signal detection nor designed with a sufficiently long treatment period to enable monitoring of treatment effect. The primary endpoint was safety and tolerability. Oramed reported data from this trial in 2014; as was originally anticipated, this data permitted the firm to move ORMD-0801 into a Phase 2b multi-site trial in the U.S., which is enrolling ~180 individuals and which is assessing the drug for a minimum of 24 weeks with the primary endpoint being reduction in FBG. Other endpoints include reductions in CRP, HbA1c and various other inflammatory and glycemic markers. We expect data from this trial to be available in early to mid-2016.

Type 2 Diabetes Phase 2a Proof-of-Concept Data

The data shown below were generated from the 24-patient U.S. Phase 2a trial. As shown below, a declining trend was observed over the course of the seven-day evaluation period in the study on fasting blood glucose. The company indicated that it believed the time course of FBG decline pointed to the possibility that even more FBG reduction could be achieved with prolonged dosing. The safety profile was also encouraging – at day 7, one patient (10%) in the placebo group had two hypoglycemic events and one (10%) had seven events; in the treatment arm, four patients (26.7%) had two hypoglycemic events, one (6.7%) had three events and two (13.3%) had four events. The fact that no drug-treated patients had more than four events indicated that the drug did not appear to dramatically increase the likelihood of hypoglycemia relative to placebo.

Figure 9: Type 1 Diabetes Phase 2a Proof-of-Concept Efficacy Data



Source: Oramed Pharmaceuticals, Inc.

Proof-of-Concept Activity in Type 1 Diabetes

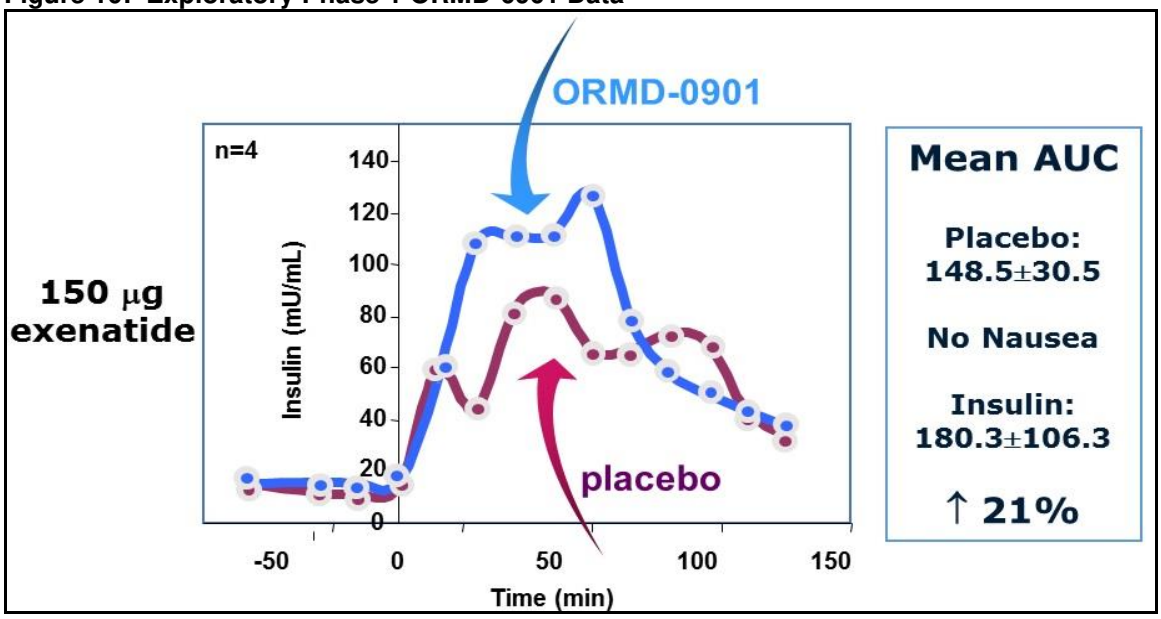
In addition to the Phase 2a trial in type 2 diabetics, Oramed also conducted an exploratory study in Israel evaluating ORMD-0801 in type 1 diabetes. ORMD-0801 effectively prevented the expected rise in fasting blood glucose (FBG) concentrations among type 1 diabetics, demonstrating its utility in both type 1 and type 2 diabetics.

Eight type 1 diabetics were treated in this study, with an 11.5% reduction in mean glucose levels recorded. The frequency with which glucose levels exceeded the 200mg/dL threshold was also reduced in the treatment arm, falling to 38% vs. 51% pre-treatment during the day and from 58% pre-treatment to 51% with treatment at night. The drug was also safe and well-tolerated. While Oramed does not currently plan to conduct any clinical trials in type 1 diabetics with ORMD-0801, we note that this market remains an untapped potential niche for the drug that the company could elect to assess further in future.

ORMD-0901 Experimental Data

In our view, Oramed's oral exenatide project, designated ORMD-0901, could potentially have the first mover advantage in the race to develop an orally-bioavailable GLP-1 agonist drug. ORMD-0901 is in Phase 2a development. We expect Oramed to begin clinical testing of ORMD-0901 in the U.S. in late 2015. The figure below depicts exploratory, placebo-controlled clinical data generated in four healthy volunteers with ORMD-0901 in a pre-prandial setting.

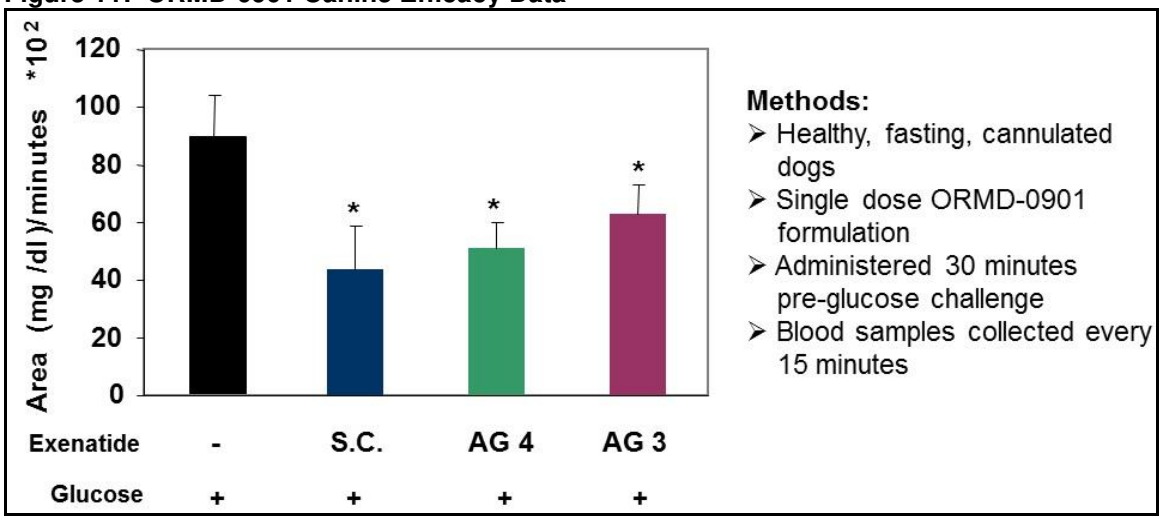
Figure 10: Exploratory Phase 1 ORMD-0901 Data



Source: Oramed Pharmaceuticals, Inc.

In healthy, fasting, cannulated beagle dogs, orally-ingestible formulations of exenatide using the Oramed proprietary platform demonstrated the ability to blunt so-called "glucose excursions" following glucose challenge. Subcutaneous exenatide delivery amounted to a 51% reduction in mean glucose $AUC_{0\text{-}150}$, while the oral formulations AG4 and AG3 prompted 43% and 29% reductions, respectively (p=0.068, demonstrating a treatment-related trend for the sample size).

Figure 11: ORMD-0901 Canine Efficacy Data

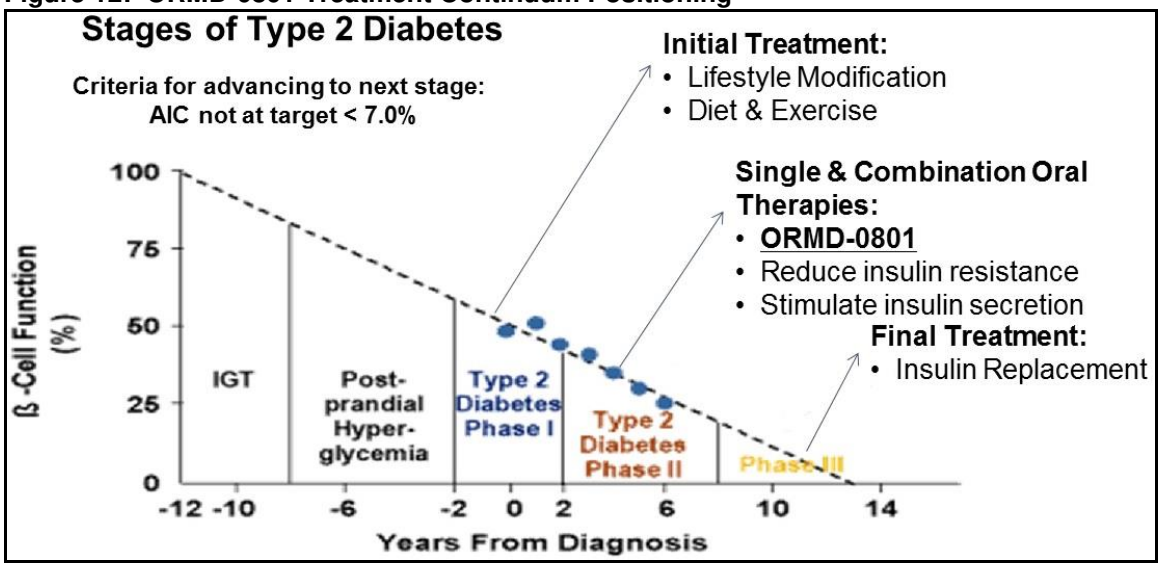


Source: Oramed Pharmaceuticals, Inc.

Diabetes Market Overview

We have assessed the opportunity for ORMD-0801 (an orally-ingestible capsule formulation of insulin) only in type 2 diabetes. It is important to note that Oramed is not attempting to replace injectable forms of insulin. Instead, the firm is trying to position ORMD-0801 as an earlier treatment option for patients with type 2 diabetes who have not yet had to resort to chronic insulin therapy. The goal would be to decrease insulin resistance as shown below, along with stimulating endogenous insulin secretion and attenuating some of the harm associated with hyperglycemic conditions that may build up overnight in type 2 diabetics. This is the rationale behind the evening administration time for ORMD-0801. The oral route of administration should be an important advantage for the drug in this market; our market assumptions do not factor in any usage in type 1 diabetes or as end-stage chronic insulin replacement.

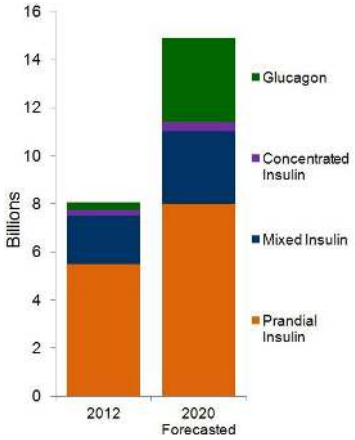
Figure 12: ORMD-0801 Treatment Continuum Positioning



Source: Oramed Pharmaceuticals, Inc.; Decision Resources.

The figure below shows the insulin drug market. As can be seen from the bar chart, this segment of the overall diabetes drug sector is expected to expand from roughly $8 billion in 2012 to over $15 billion in 2020 – a growth rate significantly in excess of the roughly 7% compound annual growth rate (CAGR) of the diabetes drug market overall.

Figure 13: Insulin Market Growth

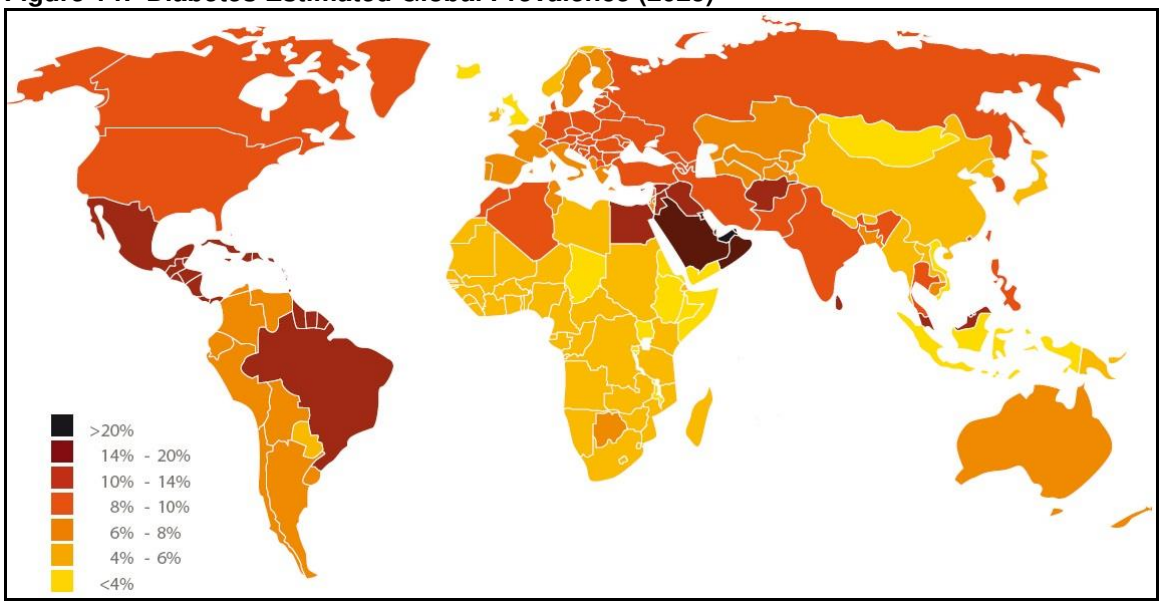


Source: Decision Resources.

ORMD-0801 Market Model—Type 2 Diabetes

We have modeled sales of ORMD-0801 in the target market, type 2 diabetes, within the contexts of the U.S. and the European Union only. In these territories, we have assumed roughly 8.5% prevalence of disease within the U.S. population and roughly 7% prevalence in Europe. This yields a patient population of approximately 12.5 million individuals, which is expected to rise to over 16 million people over the course of the next decade as the prevalence of type 2 diabetes continues to increase. The figure below shows that global prevalence of diabetes is likely to rise significantly over the next decade.

Figure 14: Diabetes Estimated Global Prevalence (2025)



Source: World Health Organization (WHO).

In our view, Oramed could price its therapy at a level significantly above that of currently-deployed injectable insulin formulations, primarily because of the convenience of administration associated with an orally-ingestible capsule. We expect that Oramed or its potential future commercialization partner could price ORMD-0801 at roughly $1,600 per patient annually in the U.S. and at $1,200 per patient annually in Europe.

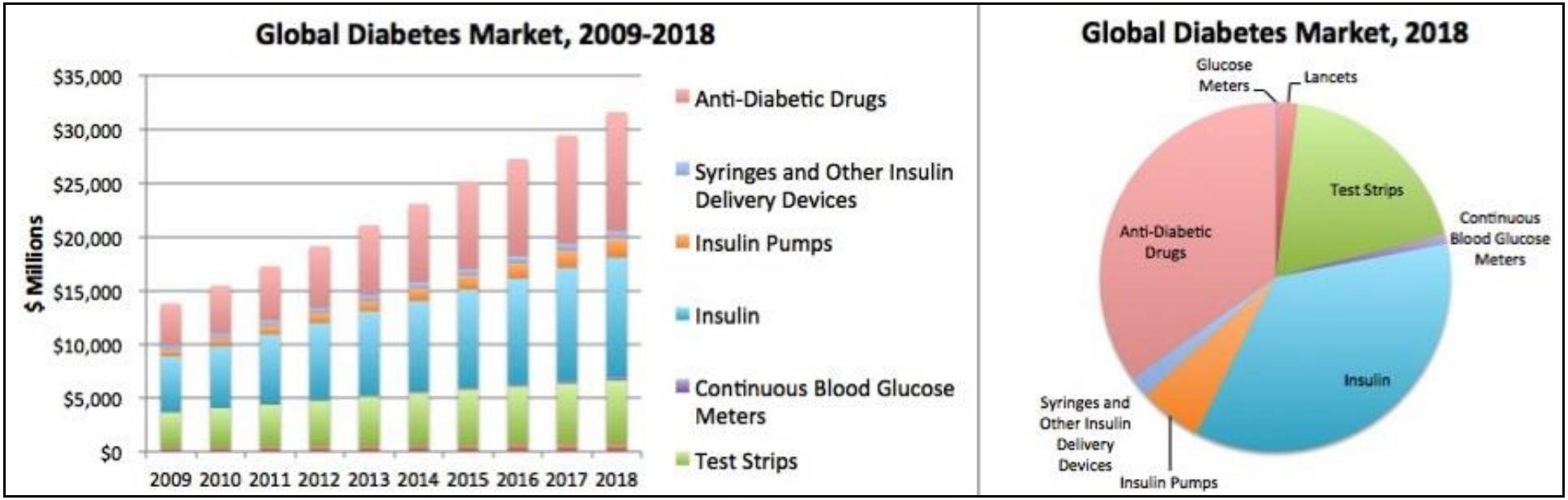
Since Oramed is a small, development-stage biotechnology company, we have assumed that ORMD-0801 would likely be out-licensed to a larger, more established firm – most likely a global participant in the diabetes market with an existing sales and marketing franchise in this domain. We believe that Oramed could elect to license out the global rights to ORMD-0801 following the completion of proof-of-concept Phase 2 development in the U.S. In our view, such a transaction would involve the payment of an upfront licensing fee, additional sums for attainment of development-stage as well as commercial milestones, and royalties on net sales of ORMD-0801. We have assumed that the net royalty rate to Oramed on sales of ORMD-0801 would be in the 9 – 12.5% range, factoring in Oramed's own obligations to its other licensing partners. Our valuation does not currently involve any accounting for upfront or milestone fees, which is likely to be conservative. We have utilized a 35% effective tax rate and a discount rate of 12%, and we assume that ORMD-0801 could be launched in the U.S. in 2021 and in Europe in 2022. While we have projected that Oramed's potential future partner is only likely to achieve approximately 10% market share at peak in the 2026 time frame and roughly 5.5% market share in Europe, these assumptions still yield a $2.1 billion peak sales number. In our view, considering the total net sales of insulin products currently at roughly $8 billion and given the projected growth in the overall diabetes market, these assumptions do not seem particularly aggressive.

Table 4: Oral Insulin (ORMD-0801) Estimated Sales—Type 2 Diabetes Market Size Model

	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
US Population	318,937,500	322,924,219	326,960,771	331,047,781	335,185,878	339,375,702	343,617,898	347,913,122	352,262,036	356,665,311	361,123,628	365,637,673	370,208,144	374,835,746	379,521,193	384,265,208	389,068,523
Patients with type 2 diabetes mellitus	27,109,688	28,094,407	28,772,548	29,132,205	29,496,357	30,204,437	30,925,611	31,312,181	31,703,583	32,456,543	32,862,250	33,638,666	34,059,149	34,859,724	35,674,992	36,505,195	36,961,510
Prevalence	*9%*	*9%*	*9%*	*9%*	*9%*	*9%*	*9%*	*9%*	*9%*	*9%*	*9%*	*9%*	*9%*	*9%*	*9%*	*10%*	*10%*
Patients seeking treatment	6,777,422	7,023,602	7,193,137	7,283,051	7,374,089	7,551,109	7,731,403	7,828,045	7,925,896	8,114,136	8,215,563	8,409,666	8,514,787	8,714,931	8,918,748	9,126,299	9,240,377
% seeking treatment	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%
ORMD-0801 Penetration Rate	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	2.1%	3.9%	5.7%	8.2%	9.5%	7.8%	5.6%	3.2%	1.9%
Patients on ORMD-0801								23,484	166,444	316,451	468,287	689,593	808,905	679,765	499,450	292,042	175,567
Average annual cost per patient ($)								1,600	1,648	1,697	1,748	1,801	1,855	1,910	1,968	2,027	2,088
U.S. ORMD-0801 sales ($ MM)								**38**	**274**	**537**	**819**	**1,242**	**1,500**	**1,299**	**983**	**592**	**367**
European Population	405,000,000	410,062,500	415,188,281	420,378,135	425,632,861	430,953,272	436,340,188	441,794,440	447,316,871	452,908,332	458,569,686	464,301,807	470,105,580	475,981,899	481,931,673	487,955,819	494,055,267
Patients with type 2 diabetes mellitus	29,160,000	30,344,625	31,139,121	31,528,360	31,922,465	32,321,495	33,598,194	34,018,172	34,890,716	36,232,667	37,144,145	37,608,446	38,548,658	40,458,461	41,446,124	42,452,156	43,476,863
Prevalence	*7%*	*7%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*9%*	*9%*	*9%*	*9%*
Patients seeking treatment	5,832,000	6,068,925	6,227,824	6,305,672	6,384,493	6,464,299	6,719,639	6,803,634	6,978,143	7,246,533	7,428,829	7,521,689	7,709,732	8,091,692	8,289,225	8,490,431	8,695,373
% seeking treatment	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%
ORMD-0801 Penetration Rate	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	1.8%	3.1%	4.5%	5.6%	5.2%	4.6%	2.5%	1.2%
Patients on ORMD-0801									34,891	130,438	230,294	338,476	431,745	420,768	381,304	212,261	104,344
Average annual cost per patient ($)									1,200	1,236	1,273	1,311	1,351	1,391	1,433	1,476	1,520
European ORMD-0801 sales ($ MM)									**42**	**161**	**293**	**444**	**583**	**585**	**546**	**313**	**159**
Total ORMD-0801 sales ($ MM)								**38**	**316**	**698**	**1,112**	**1,686**	**2,084**	**1,884**	**1,529**	**905**	**525**
Royalty rate to Oramed Pharmaceuticals								**9.0%**	**10.0%**	**11.0%**	**12.0%**	**12.0%**	**12.5%**	**12.5%**	**12.5%**	**12.5%**	**12.5%**
Total ORMD-0801 royalty revenue ($ MM)	0	0	0	0	0	0	0	**3**	**32**	**77**	**133**	**202**	**260**	**236**	**191**	**113**	**66**

Source: Rodman & Renshaw estimates.

Figure 15: Global Diabetes Market Evolution (2009 – 2018)

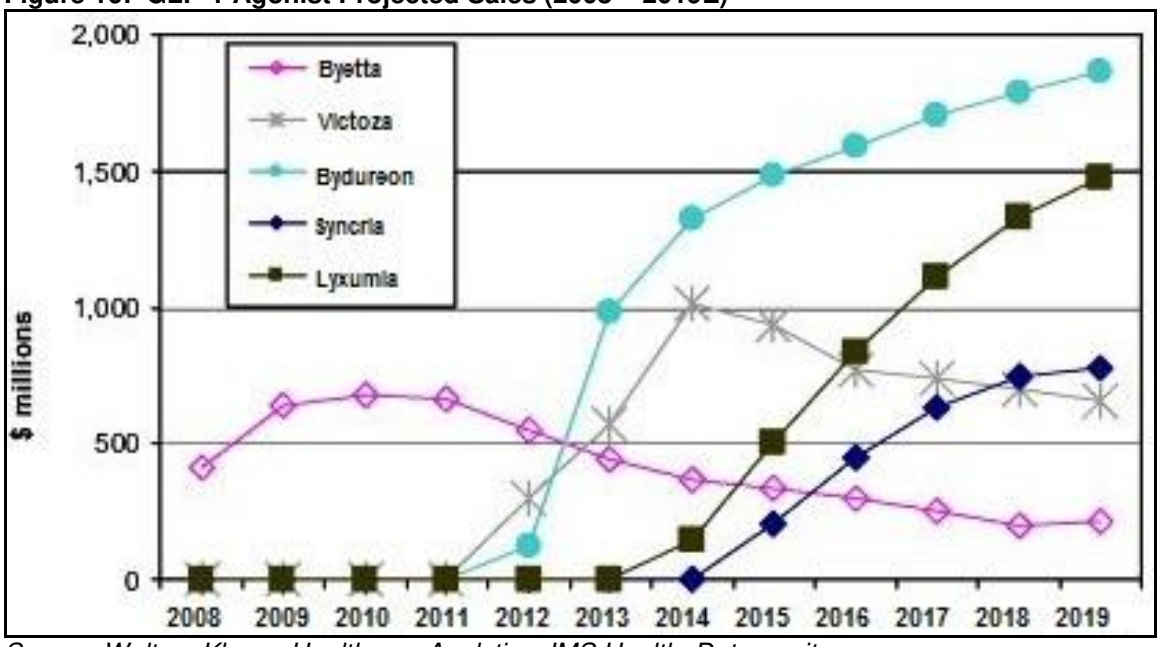


Source: Mediligence.

ORMD-0901 (Oral Exenatide) Market Model

We have modeled sales of ORMD-0901 in the target market – type 2 diabetes – within the context of the U.S. and Europe only. In our view, the oral exenatide product opportunity is potentially even more compelling than that of the oral insulin, since exenatide is still a highly-priced premium product and is also considered to have extremely high efficiency in achieving insulin sensitization among the currently-marketed anti-hyperglycemic drugs. The figure below shows how GLP-1 agonist product sales have evolved since these drugs were initially introduced.

Figure 16: GLP-1 Agonist Projected Sales (2008 – 2019E)



Source: Wolters Kluwer Healthcare Analytics; IMS Health; Datamonitor.

We expect that Oramed or its potential commercial partner could price ORMD-0901 at $8,000 per patient annually in the U.S. and at $6,000 per patient annually in Europe. This is comparable, in our view, to the pricing of other GLP-1 agonists. Similar to the case of ORMD-0801, we have assumed that ORMD-0901 would likely be out-licensed to a larger, more established firm – most likely a global participant in the diabetes market with an existing sales and marketing franchise in this domain. We believe that Oramed could elect to license out the global rights to ORMD-0901 following the completion of proof-of-concept Phase 2 development in the U.S. In our view, such a transaction would involve payment of an upfront licensing fee, other sums for attainment of development-stage as well as commercial milestones, and royalties on net sales of ORMD-0901.

In our model, the net royalty rate to Oramed on sales of ORMD-0901 is projected to be in the 7% – 10% range, factoring in obligations to other licensing partners. Our valuation does not account for any upfront or milestone fees. We utilize a 35% tax rate and 20% discount rate, aimed at factoring in the intense competition in the GLP-1 agonist space, and we assume that ORMD-0901 could be launched in the U.S. in 2019 and in Europe in 2020. While we have projected that Oramed's potential future partner is only likely to achieve 2.5% market share at peak in the 2026 time frame and roughly 2% market share in Europe, these assumptions still yield a $2.8 billion peak sales number. Victoza®, a once-daily injection, exceeded $1.7 billion in sales in 2013, less than four years post-approval. Eli Lilly's Trulicity® (dulaglutide), approved in September 2014, is also projected to exceed $1 billion in U.S. annual sales; it is an injectable as well (albeit once-weekly) and ready-to-use. Tanzeum® was approved in April 2014. Near-term competitive threats could emerge in the forms of Lyxumia®, ZP2929, MOD-6030 and other GLP-1 agonists that are not currently on the market.

Table 5: Oral Exenatide (ORMD-0901) Estimated Sales—Type 2 Diabetes Market Size Model

	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
US Population	318,937,500	322,924,219	326,960,771	331,047,781	335,185,878	339,375,702	343,617,898	347,913,122	352,262,036	356,665,311	361,123,628	365,637,673	370,208,144	374,835,746	379,521,193	384,265,208	389,068,523
Patients with type 2 diabetes mellitus	27,109,688	28,094,407	28,772,548	29,132,205	29,496,357	30,204,437	30,925,611	31,312,181	31,703,583	32,456,543	32,862,250	33,638,666	34,059,149	34,859,724	35,674,992	36,505,195	36,961,510
Prevalence	*9%*	*9%*	*9%*	*9%*	*9%*	*9%*	*9%*	*9%*	*9%*	*9%*	*9%*	*9%*	*9%*	*9%*	*9%*	*10%*	*10%*
Patients seeking treatment	6,777,422	7,023,602	7,193,137	7,283,051	7,374,089	7,551,109	7,731,403	7,828,045	7,925,896	8,114,136	8,215,563	8,409,666	8,514,787	8,714,931	8,918,748	9,126,299	9,240,377
% seeking treatment	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%
ORMD-0901 Penetration Rate	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.7%	1.1%	1.4%	1.7%	2.2%	2.5%	2.1%	1.7%	1.4%	1.1%	0.7%
Patients on ORMD-0901						0	54,120	86,108	110,963	137,940	180,742	210,242	178,811	148,154	124,862	100,389	64,683
Average annual cost per patient ($)						0	8,000	8,240	8,487	8,742	9,004	9,274	9,552	9,839	10,134	10,438	10,751
U.S. ORMD-0901 sales ($ MM)						**0**	**433**	**710**	**942**	**1,206**	**1,627**	**1,950**	**1,708**	**1,458**	**1,265**	**1,048**	**695**
European Population	405,000,000	410,062,500	415,188,281	420,378,135	425,632,861	430,953,272	436,340,188	441,794,440	447,316,871	452,908,332	458,569,686	464,301,807	470,105,580	475,981,899	481,931,673	487,955,819	494,055,267
Patients with type 2 diabetes mellitus	29,160,000	30,344,625	31,139,121	31,528,360	31,922,465	32,321,495	33,598,194	34,018,172	34,890,716	36,232,667	37,144,145	37,608,446	38,548,658	40,458,461	41,446,124	42,452,156	43,476,863
Prevalence	*7%*	*7%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*9%*	*9%*	*9%*	*9%*
Patients seeking treatment	5,832,000	6,068,925	6,227,824	6,305,672	6,384,493	6,464,299	6,719,639	6,803,634	6,978,143	7,246,533	7,428,829	7,521,689	7,709,732	8,091,692	8,289,225	8,490,431	8,695,373
% seeking treatment	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%
ORMD-0901 Penetration Rate	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.8%	1.1%	1.2%	1.4%	1.6%	1.8%	1.5%	1.3%	0.9%	0.5%
Patients on ORMD-0901							20,159	54,429	76,760	86,958	104,004	120,347	138,775	121,375	107,760	76,414	43,477
Average annual cost per patient ($)							6,000	6,180	6,365	6,556	6,753	6,956	7,164	7,379	7,601	7,829	8,063
European ORMD-0901 sales ($ MM)							**121**	**336**	**489**	**570**	**702**	**837**	**994**	**896**	**819**	**598**	**351**
Total ORMD-0901 sales ($ MM)							**554**	**1,046**	**1,430**	**1,776**	**2,330**	**2,787**	**2,702**	**2,353**	**2,084**	**1,646**	**1,046**
Royalty rate to Oramed Pharmaceuticals							**7.0%**	**8.0%**	**8.5%**	**9.0%**	**9.5%**	**10.0%**	**10.0%**	**10.0%**	**10.0%**	**10.0%**	**10.0%**
Total ORMD-0901 royalty revenue ($ MM)		0	0	0	0	**0**	**39**	**84**	**122**	**160**	**221**	**279**	**270**	**235**	**208**	**165**	**105**

Source: Rodman & Renshaw estimates.

Financial Review and Outlook

Revenue. As a development-stage firm, we expect Oramed to remain unprofitable for the next several years as ORMD-0801 and ORMD-0901 advance towards regulatory approval, a period that is likely to be characterized by gradually increasing R&D and G&A expenditures as the company conducts later-stage clinical trials. We anticipate that revenues will be realized primarily from milestone and royalty payments obtained through agreements inked with future licensing partners, with the most likely scenario involving a global (excluding China) transaction that could be inked in the wake of successful Phase 2b results, which are expected next year, along with a China-specific partnership that we anticipate to be consummated within the next few months. We project that overall royalty-based revenues will exceed $500 million in 2026, assuming launch of ORMD-0801 and ORMD-0901 in 2021 for type 2 diabetes in the U.S. and in 2022 for the same indication in Europe. In our view, global revenues from these two products alone could reach a peak of nearly $5 billion in aggregate annual sales by 2026.

Gross margins. As a development-stage company, there are historically no costs of goods sold. We project that the gross margins on both ORMD-0801 and ORMD-0901 are likely to exceed 90% upon launch, which should enable healthy cash flow generation.

Operating expenses. For fiscal 2015, we estimate roughly $7.3 million in operating expenses. We estimate R&D of only $4.6 million in fiscal 2015, as the company advances its lead drug candidates, ORMD-0801 and ORRMD-0901, through proof-of-concept development in the U.S. However, the R&D expense should rise in fiscal 2016 to $6.4 million, as larger trials for ORMD-0801 and ORMD-0901 begin enrollment.

Taxes. We assume a roughly 35% corporate tax rate after all net operating loss carry-forwards are exhausted. However, in our view the firm should not have significant tax liabilities prior to 2020. At the end of fiscal 2014, Oramed Pharmaceuticals had ~$6.6 million in U.S. federal net operating loss carry-forwards, expiring in the years 2025 through 2032.

Share count. The outstanding fully-diluted share count stands at roughly 13.5 million. The fully-diluted shares account for the conversion of 1.9 million shares in the form of options and warrants. Given the company's cash position, strategic goals, and capital structure, a share repurchase program is unlikely, in our view.

EPS. We forecast EPS of ($0.67) and ($0.88) for fiscal 2015 and 2016, respectively. Currently, we cannot estimate when the company is likely to achieve cash flow break-even or attain sustainable profitability. However, if ORMD-0801 demonstrates positive safety data and additional indications of efficacy in the ongoing Phase 2b trial, we anticipate that Oramed should be able to obtain a partnership or option-based licensing agreement on this compound. Upfront and other licensing fees could offset the firm's cash burn on a temporary basis.

Balance sheet. The firm held roughly $16.4 million in cash at the end of the fiscal third quarter of 2015, following the completion of a registered direct follow-on offering in June 2015, which raised gross proceeds of $5.36 million. We anticipate that the firm currently has sufficient resources to fund operations through the end of 2016. The potential near-term completion of a licensing transaction involving the China-specific commercial rights for ORMD-0801 could also provide Oramed with a significant influx of capital, which could substantially lengthen the firm's operational window.

Cash Flow. We estimate that the firm will consume a total of about $5.6 million in operating cash flows during fiscal 2015 and a further $8.9 million during fiscal 2016. We think additional funding may be required within the next 18 – 24 months to support envisaged operational activities, including the completion of additional clinical trials with both ORMD-0801 as well as ORMD-0901.

Intellectual Property Portfolio

Currently, Oramed is the holder of 24 patents, sixteen of which were issued in fiscal 2014, including patents issued by the Swiss, German, French, U.K., Italian, Netherland, Spanish, Australian, Israeli, Japanese, Russian, Canadian and Hong Kong Patent Offices that cover a part of the company's technology platform that allows for the oral delivery of proteins and patents issued by the Australian and Israeli Patent Offices that cover part of the technology for the oral delivery of exenatide.

In addition, Oramed currently holds 28 patent applications currently pending, with respect to various compositions, methods of production and oral administration of proteins and exenatide. Expiration dates for pending patents, if granted, will fall between 2026 and 2034. These do not take into account the potential impact of term extensions, for example those granted under Hatch-Waxman legislation provisions.

Table 6: Oramed Pharmaceuticals Patent Portfolio

Patent / Application Number	Title	Filing/Grant Date	Expiry Date*	Country	Description
PCT/IL2009/000223	Methods and compositions for oral administration of proteins	26/Feb/09		PCT	Directed to combination of 2 protease inhibitors
2009230718	Methods and compositions for oral administration of proteins	15/Oct/10	26-Feb-29	Australia	Notice of Allowance received
PI 0907077-0	Methods and compositions for oral administration of proteins	25/Sep/10	26-Mar-28	Brazil	Requested examination; Awaiting first office action.
2719272	Methods and compositions for oral administration of proteins	22/Sep/10	26-Feb-29	Canada	Request for examination due 26.2.14.
200980118673.4	Methods and compositions for oral administration of proteins	22/Nov/10	26-Feb-29	China	Awaiting Certificate of Patent.
9725603.6	Methods and compositions for oral administration of proteins	12/Oct/10	26-Feb-29	EU	Awaiting European Search Report/Examination Report
3996/KOLNP/2010	Methods and compositions for oral administration of proteins	25/Oct/10	26-Feb-29	India	Requested examination; Awaiting first office action
208165	Methods and compositions for oral administration of proteins	15/Sep/10	26-Feb-29	Israel	Responded to first Office Action; awaiting allowance
2011-501337	Methods and compositions for oral administration of proteins	24/Sep/10	26-Feb-29	Japan	Notice of Allowance received
588603	Methods and compositions for oral administration of proteins	9/Jul/12	26-Feb-29	New Zealand	Granted
2010/07522	Methods and compositions for oral administration of proteins	27/Dec/12	26-Feb-29	South Africa	Granted
2010141292	Methods and compositions for oral administration of proteins	26/Oct/10	26-Feb-29	Russia	Granted
12/934,754	Methods and compositions for oral administration of proteins	27/Sep/10	26-Feb-29	USA	Responded to first Office Action; awaiting allowance
PCT/IL2006/001019	Methods and compositions for oral administration of proteins	31/Aug/06		PCT	
2006288703	Methods and compositions for oral administration of proteins	5/Jan/12	8/31/2026	Australia	Granted
2,621,577	Methods and compositions for oral administration of proteins	31/Aug/06	8/31/2026	Canada	Pending
200680041231.0	Methods and compositions for oral administration of proteins	4/May/08	8/31/2026	China	Pending
6780455.9	Methods and compositions for oral administration of proteins	6/Mar/08	8/31/2026	EU	Pending
8113931.7	Methods and compositions for oral administration of proteins	24/Dec/08	8/31/2026	Hong Kong	Pending EP grant
1140/CHENP/2008	Methods and compositions for oral administration of proteins	6/Mar/08	8/31/2026	India	Pending
189956	Methods and compositions for oral administration of proteins	1/May/12	8/31/2026	Israel	Granted
5222727	Methods and compositions for oral administration of proteins	15/Mar/13	8/31/2026	Japan	Granted
PCT/IL2009/000461	Methods and compositions for oral administration of exenatide	3/May/09		PCT	
2009245294	Methods and compositions for oral administration of exenatide	19/Nov/10	5/3/2029	Australia	Pending
PI 0908292-1	Methods and compositions for oral administration of exenatide	5/Nov/10	5/5/2028	Brazil	Pending
2,723,434	Methods and compositions for oral administration of exenatide	3/Nov/10	5/3/2029	Canada	Pending
200980116254.7	Methods and compositions for oral administration of exenatide	5/Nov/10	5/3/2029	China	Pending; undergoing reexamination
9742563.1	Methods and compositions for oral administration of exenatide	2/Dec/10	5/3/2029	EU	Pending
11109635.9	Methods and compositions for oral administration of exenatide	12/Sep/11	5/3/2029	Hong Kong	Pending
4599/KOLNP/2010	Methods and compositions for oral administration of exenatide	2/Dec/10	5/3/2029	India	Pending
208967	Methods and compositions for oral administration of exenatide	27/Oct/10	5/3/2029	Israel	Pending
2011-508050	Methods and compositions for oral administration of exenatide	4/Nov/10	5/3/2029	Japan	Pending
589390	Methods and compositions for oral administration of exenatide	5/Mar/12	5/3/2029	New Zealand	Granted
2010/08090	Methods and compositions for oral administration of exenatide	29/Aug/12	5/3/2029	South Africa	Granted
2010146372	Methods and compositions for oral administration of exenatide	12/Nov/10	5/3/2029	Russia	Pending
13/855,346	Methods and compositions for oral administration of exenatide	2/Apr/13	5/3/2029	USA	Pending (Divisional)
PCT/IL2013/050091	Protease inhibitor-containing compositions and methods for producing and using them	31/Jan/13	31-Jan-33	PCT	Oramed-style compositions comprising improved SBTI
PCT/IL2013/050007	Methods and compositions for treating diabetes	3/Jan/13	3-Jan-33	PCT	Oramed-type combinations of insulin and exenatide
61/763,996	Methods and compositions for treating non-alcoholic fatty liver disease (NAFLD), hepatic steatosis, and sequellae thereof	13/Feb/13	to be determined	US provisional	Utility/PCT applications due 3-Jan-2014

Source: Company reports.

In mid-June 2015, Oramed reported that the Russian Federal Service for Intellectual Property had granted one of its patent applications, entitled "Methods and compositions for oral administrations of exenatide". We anticipate that further patent allowances and issuances should occur over the course of the coming months, as the company's intellectual property estate continues to mature.

Management Team

Nadav Kidron, Esq., M.B.A.
President, Co-Founder & Chief Executive Officer
The founder of Oramed, Nadav Kidron has served as CEO since the firm's inception in 2006. He is an Advisory Board Member for The Trendlines Group, a group that invests in and develops innovation-based businesses; a director of Entera Bio, a joint venture formed by Oramed and DNA Biomedical Solutions; and an international lecturer on Israel's entrepreneurial culture and its roots as a source of innovative ideas. He holds a Bachelor of Law Degree and an International Masters 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.
Co-Founder & Chief Scientific Officer
Since co-founding Oramed in 2006 with her son Nadav, Dr. Miriam Kidron has served as the firm's chief scientist. She originally earned her Ph.D. in biochemistry from the Hebrew University of Jerusalem. For nearly 20 years, Dr. Kidron has been a senior researcher in the Diabetes Unit at Hadassah-Hebrew University Medical Center in Jerusalem, Israel, earning the Bern Schlanger Award for her work on diabetes research. She was formerly a visiting professor at the Medical School at the University of Toronto and is a member of the American, European and Israeli Diabetes Associations.

Yifat Zommer, CPA, M.B.A.
Chief Financial Officer
Ms. Zommer joined Oramed in 2009. She previously served as CFO for Witech Communications Ltd and CTWARE Ltd. Prior to that she was an audit manager in PriceWaterhouseCoopers Israel, where she served for five years. Ms. Zommer holds a Bachelor of Accounting and Economics degree from the Hebrew University and a Master's degree in Business Administration (MBA) from Tel-Aviv University. She is a certified public accountant in Israel.

Josh Hexter
Chief Operating Officer / Vice-President, Business Development
Josh Hexter joined Oramed in the spring of 2013. He brings to Oramed more than 15 years of biotech industry experience in various operational and business development roles. He was most recently Executive Director of Corporate In-Licensing at BioLineRx Ltd. Previously, he worked in private equity and venture capital, where he served as CEO of a VC-backed startup, Biosensor Systems Design, where he was instrumental in shaping the company's strategic focus and in forging business development agreements with Fortune 100 companies. Mr. Hexter earned a bachelor's degree from the University of Wisconsin and a master's degree in management from Boston University.

Investment Risks

Financial outlook. Oramed Pharmaceuticals has incurred operating losses since its inception and, in our view, may not achieve sustainable profitability for several years. Although the firm has been able to obtain capital in order to fund its operations, it is not known whether the company will be able to continue this practice, or be able to obtain other types of financing to meet operating needs. While the company recently managed to successfully raise $5.36 million through a registered direct public offering to support the advancement of its lead pipeline drug candidate in the U.S., which in our view provides an operational window for at least the next 18 months, we believe that any additional broadening of the clinical-stage pipeline could require additional capital. Given these factors, shares of Oramed Pharmaceuticals may constitute above-average risk and volatility, in our opinion.

Regulatory risks. Drug development is a multi-year process that requires human clinical trials prior to market entry. Agencies responsible for the approval of drugs in various markets, including the U.S. Food and Drug Administration (FDA), may require more clinical data from Oramed Pharmaceuticals prior to granting approval for any of its regulatory applications, necessitating further trials. Review times at the FDA may prove longer than expected. Also, the agency could elect not to accept Oramed's – or its putative partner's – regulatory filings petitioning for approval of ORMD-0801 and ORMD-0901. If clinical data and/or other supporting evidence are not accepted or considered insufficient grounds for approval, marketing authorization for Oramed's lead products could be delayed or might not occur at all, preventing the firm from realizing the commercial potential of these agents.

Partnership risks. Oramed has embarked upon a development path that involves focusing on clinical advancement of its lead drug candidates in diabetes, while eschewing an emphasis on building commercial infrastructure and becoming a fully-integrated company. The firm aims to optimize the commercialization of its lead program by either partnering this agent with an established firm in the healthcare sector—preferably one with an established presence in diabetes—or by attracting acquisition interest from such a company. This introduces several elements of risk from a partnering / trade sale perspective – the possibility that the company's partnership deals may not involve terms that are lucrative enough to justify the investment that Oramed has made in the development of its lead drug candidates; the possibility that Oramed's partners do not invest sufficiently in the commercialization of Oramed's products; and the risk that the firm's partners may not be the best-positioned competitively to ensure maximal penetration of Oramed's drugs into their target markets. Further, should Oramed fail to attract a partner at all, the firm would have to raise substantial additional capital to fund establishment of a sales force. Such infrastructure may not be capable of supporting the launch of ORMD-0801 or ORMD-0901.

Over-specialization risk. While we view Oramed as a risk-mitigated investment opportunity because of the fact that both insulin and GLP-1 receptor agonists have been approved and prescribed for diabetes over many years, we note that the firm does not have a clinical pipeline beyond ORMD-0801 and ORMD-0901 and is heavily concentrated within the diabetes space, which is a highly competitive area replete with a large number of entrenched competitors. Accordingly, therefore, if the firm's lead drugs fail to show statistically significant efficacy and acceptable safety and tolerability in controlled trials, Oramed could lack strategic options.

Competitive landscape. Oramed is aiming to compete with other companies within the drug industry, many of which have more capital, more extensive research and development capabilities, and greater human resources. Some of these competitors include AstraZeneca, Bristol-Myers Squibb, Eli Lilly & Co., GlaxoSmithKline, Novo Nordisk and Sanofi S.A. These companies all have drugs already on the market for various forms of diabetes and many of their franchises are well-entrenched. In addition, these competitors may develop new or enhanced products or processes that may be more effective, less expensive, safer or more readily available than any products or processes that Oramed may be capable of developing. Finally, there are several generic versions

of injectable insulin already on the market, with more potentially being launched in the coming years, which may make it difficult for Oramed and / or its partners to establish a niche for ORMD-0801.

Geopolitical risks. Oramed's headquarters are presently located in the State of Israel, which has since its establishment in 1948 been subject to significant hostility from its predominantly Arab neighbors. Various geopolitical factors, including – but not limited to – civil unrest, terrorist actions, military aggression by the armed forces of Israel's neighbors, and / or the deployment of nuclear weapons by regimes hostile to the State of Israel could all have a material impact on Oramed's operational integrity and the firm's ability to execute on its strategic plan.

Intellectual property risks. The company relies on patents and trade secrets to protect its products from competition. A court might not uphold Oramed's intellectual property rights, or it could find that Oramed infringed upon another party's property rights. In addition, generics firms could potentially find loopholes in Oramed's intellectual property estate, which may enable them to launch generic versions of ORMD-0801 and/or ORMD-0901, in addition to other drugs that Oramed could develop in the future, prior to the expiration of patent protection.

Reimbursement outlook. Following the institution of broad-based healthcare reform policy, reimbursement agencies have grown more wary of systematically reimbursing for drugs that are either unnecessary or provide marginal benefit at excessive cost. If Medicare spending growth continues to outpace GDP growth, and the government's ability to fund healthcare becomes impaired, changes could be made to reimbursement policy that would negatively affect Oramed, despite what we believe to be the compelling value proposition inherent in both ORMD-0801 and ORMD-0901.

Additional risks. Oramed ended its most recently-reported quarter (3Q FY2015) with about $16.4 million in cash and equivalents. While the firm is not projected to burn a significant amount of cash near-term, the current cash balance is only likely to sustain operations through the next two or three quarters. Other sources of cash could include: licensing fees from partnerships, warrant and option exercises, or the issuance of more shares. If ORMD-0801 fails to demonstrate efficacy and safety in proof-of-concept development, Oramed may not be able to raise cash at all.

Industry risks. Emerging biotechnology and pharmaceuticals stocks are inherently volatile and increasingly subject to development and regulatory risk. Meeting or missing commercialization milestones may result in a significant change in the perception of the company and the stock price. We do not anticipate volatility subsiding in the near term.

For additional risk considerations, please refer to the company's SEC filings.

Appendix 1: Background on Diabetes

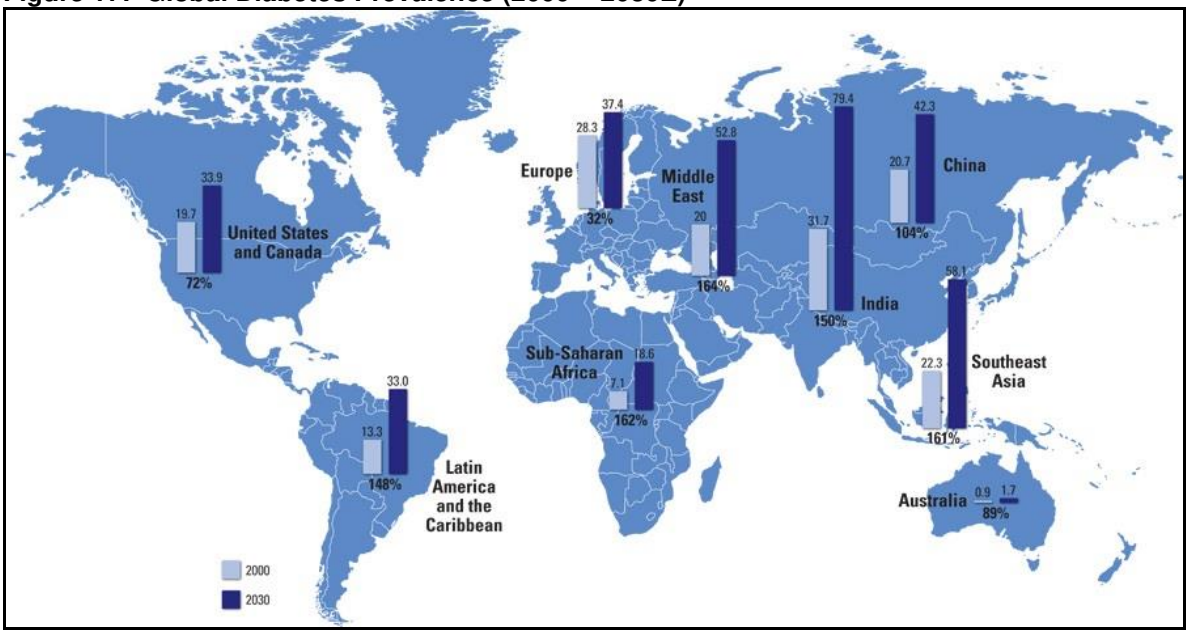
Diabetes Mellitus Overview
Metabolic diseases involving high blood sugar, either because the pancreas does not produce enough insulin, or because cells do not respond to endogenously-produced insulin (insulin resistance), are called diabetes mellitus (DM) and involve classical symptoms of polyuria (frequent urination), polydipsia (increased thirst), and polyphagia (increased hunger). There are three types:

- Type 1 DM (T1DM) results from failure to produce insulin, and currently requires the sufferer to inject insulin or wear an insulin pump. This form was previously known as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes".
- Type 2 DM (T2DM) involves insulin resistance, in which cells fail to use insulin properly, sometimes with absolute insulin deficiency. This was previously known as non-insulin-dependent diabetes mellitus (NIDDM) or "adult-onset diabetes".
- The third main form, gestational diabetes, occurs when pregnant women without prior diabetes history develop high blood glucose. It may precede T2DM.

Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes, which is induced by high doses of glucocorticoids, and several forms of monogenic diabetes.

Epidemiology
As shown below, the global incidence of diabetes is on the rise, particularly with respect to type 2 diabetes. Various lifestyle factors are typically considered to be the cause of this global "epidemic", with a reliance on a high-carbohydrate, high-fat diet the main culprit. As developing countries become more exposed to diets rich in refined foods – particularly refined sugar – the incidence of diabetes in those regions tends to rise.

Figure 17: Global Diabetes Prevalence (2000 – 2030E)



Source: New England Journal of Medicine.

While type 1 diabetes appears to require an environmental trigger and is known to have a genetic component, type 2 diabetes is due mainly to lifestyle factors and genetics. A number of factors are known to be crucial to development of type 2 diabetes, including obesity – defined by a body mass index (BMI) >30 – lack of physical activity, poor diet, stress, and urbanization.

The table below provides a summary of diabetes diagnostic criteria, which principally focus on levels of fasting blood glucose – the principal measure of glucose metabolism efficiency.

Table 7: Diabetes Diagnostic Criteria

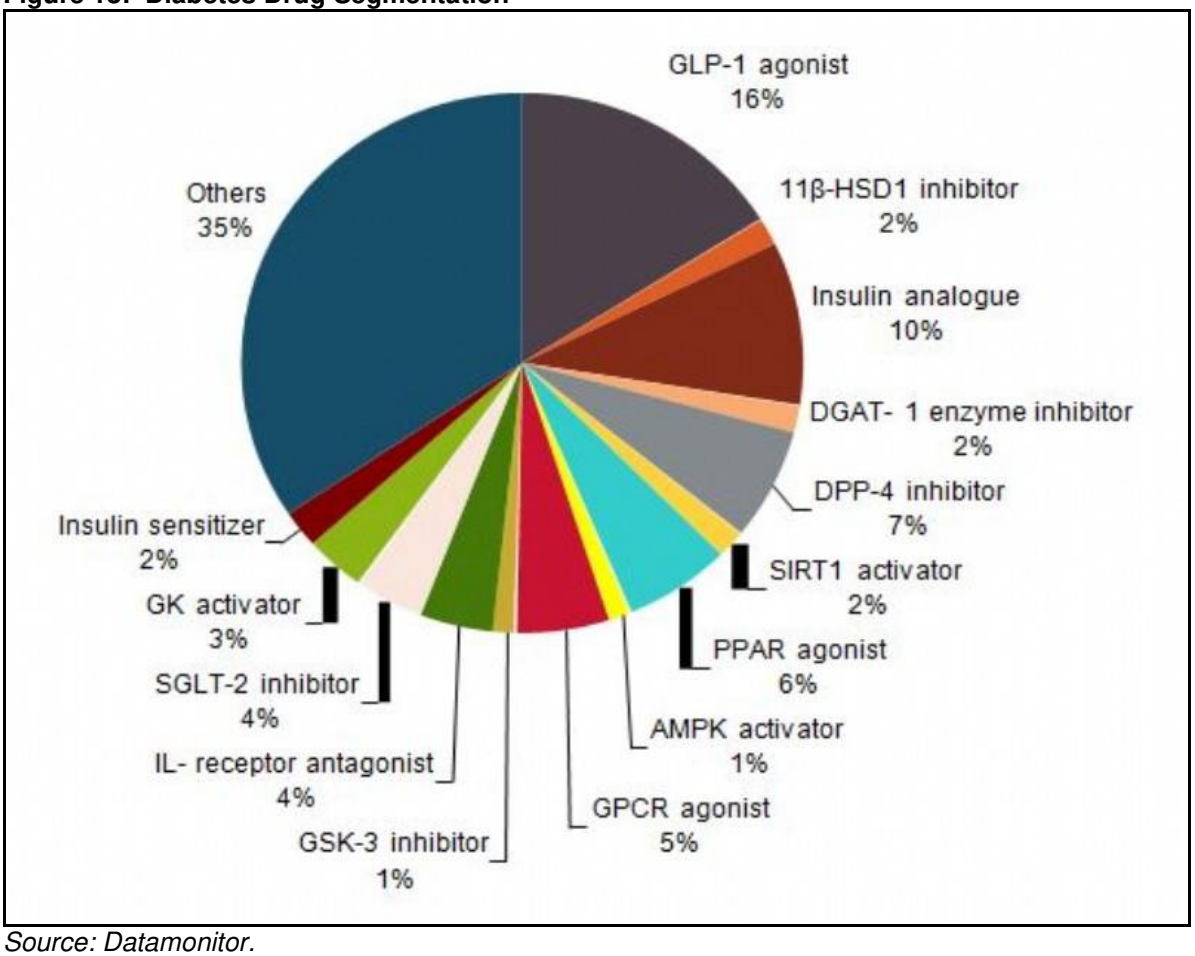
Condition	2 hour glucose	Fasting glucose	HbA_{1c}
	mmol/l(mg/dl)	mmol/l(mg/dl)	%
Normal	<7.8 (<140)	<6.1 (<110)	<6.0
Impaired fasting glycaemia	<7.8 (<140)	≥ 6.1(≥110) & <7.0(<126)	6.0–6.4
Impaired glucose tolerance	≥7.8 (≥140)	<7.0 (<126)	6.0–6.4
Diabetes mellitus	≥11.1 (≥200)	≥7.0 (≥126)	≥6.5

Source: American Diabetes Association (2010).

Therapy

Insulin remains a mainstay of therapy. Afrezza®, an inhalable formulation, was approved in the U.S. in mid-2014. Several firms, including Oramed, are developing oral formulations. Insulin sensitizers include biguanides (e.g. metformin) and thiazolidinediones (TZDs); incretin mimetics, such as GLP-1 agonists, DPP-IV inhibitors, and SGLT2 inhibitors, are also widely used.

Figure 18: Diabetes Drug Segmentation

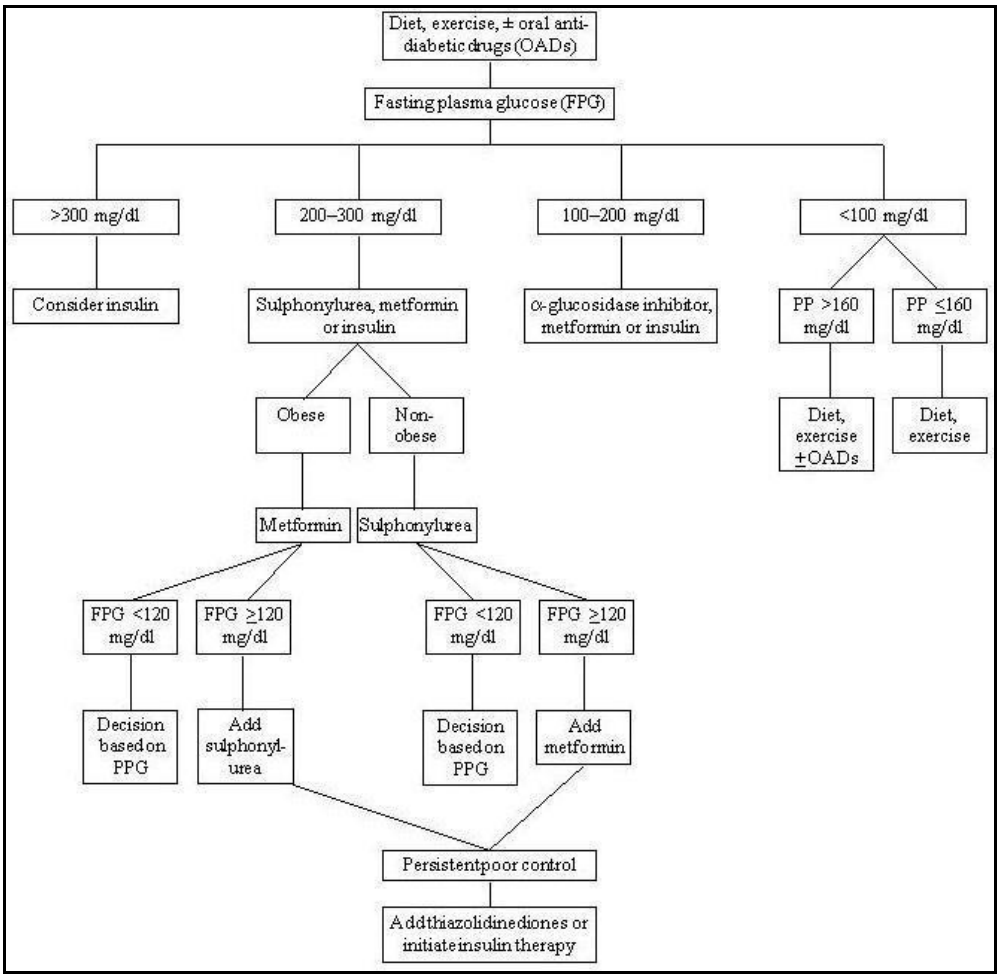


Source: Datamonitor.

Marketed Diabetes Drugs

The flow chart below shows the diabetes treatment continuum. Generally, early-stage diabetes is managed primarily using dietary management, insulin therapy, and supplementation with sulphonylurea, biguanides (e.g. metformin) and α-glucosidase inhibitors. If glucose control remains poor, other drugs may be added to the regimen.

Figure 19: Diabetes Treatment Decision Tree



Source: American Diabetes Association.

Recently, a range of other therapeutic drug classes have been developed in order to augment the armamentarium. These agents typically fall into two categories – incretin mimetics, aimed at mimicking the hormones that are typically produced naturally by the body to stimulate the release of insulin following a meal; and cardiovascular risk reduction agents – principally, peroxisome proliferator-activated receptor agonists such as the thiazolidinediones, which modulate PPARα and / or γ receptors.

Incretin Mimetics

This class of drugs represents the newest agents that have been developed primarily to address Type 2 diabetes. Incretin mimetics are designed to decrease the body's resistance to insulin and thereby permit a return to normalized glucose control. They fall into three principal categories – the glucagon-like peptide 1 (GLP-1) receptor agonists; the dipeptidyl peptidase IV (DPP IV) inhibitors, and the sodium-dependent glucose transporter 2 (SGLT2) inhibitors.

Glucagon-like peptide 1 (GLP-1) receptor agonists
The GLP-1 receptor agonists are peptidomimetic drugs that have been rationally designed to act as analogs of GLP-1 itself. They are aimed mainly at restoring insulin sensitivity.

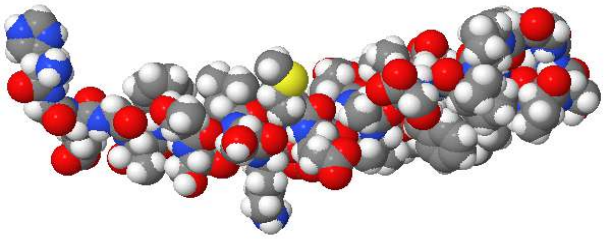
Byetta® / Bydureon® (exenatide)—AstraZeneca / Bristol-Myers Squibb
The first of the GLP-1 analogs to be approved to treat diabetes, Byetta® was developed by Amylin Pharmaceuticals following the 1992 work of Dr. John Eng at the VA Medical Center (Bronx, NY). Dr. Eng first isolated the hormone exendin-4 from the saliva of the Gila monster, a poisonous lizard found in desert locations across the southwestern U.S.

Figure 20: Gila Monster (*Heloderma suspectum*)

Source: Wikipedia.

It was observed that exendin-4 could mimic many of the actions of GLP-1 in humans. Amylin therefore elected to develop it as a drug.

Figure 21: Byetta (exenatide) Chemical Structure



Source: ADIS R&D Insight.

As depicted in the space-filling chemical structure above, exenatide is a 39-amino-acid peptide. The molecule functions as an insulin secretagogue, with gluco-regulatory effects. Exenatide was approved by the FDA on April 28, 2005 for patients whose diabetes was not well-controlled on other oral medication. The medication is injected subcutaneously twice-daily, typically abdominally, using a filled pen-like device.

The incretin hormones GLP-1 and glucose-dependent insulinotropic peptide (GIP) are produced by the L and K endocrine cells of the intestine following ingestion of food. GLP-1 and GIP stimulate insulin secretion from the beta cells of the islets of Langerhans in the pancreas. Only GLP-1 causes insulin secretion in the diabetic state; however, GLP-1 itself is ineffective as a clinical treatment for diabetes as it has a very short half-life *in vivo*. Exenatide bears 50% amino acid homology to GLP-1 and has a longer *in vivo* half-life. Commercially, the drug is produced by direct chemical synthesis. Historically, exendin-4 is naturally secreted in the saliva and concentrated in the tail of the Gila monster. Given this history, exenatide is sometimes referred to as “lizard spit”. Exendin-4 shares extensive homology and function with mammalian GLP-1, but is resistant to

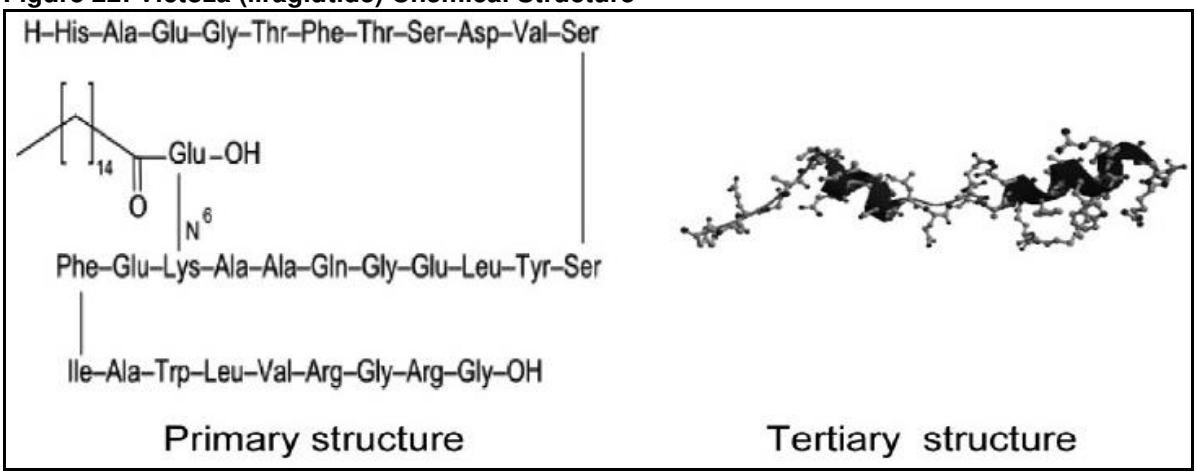
degradation by DPP-IV – which breaks down GLP-1 in mammals – allowing a longer pharmacological half-life. Subsequent clinical testing led to the discovery of the also-desirable glucagon and the appetite-suppressant (anorectic) effects of the drug.

Exenatide raises insulin levels quickly (within ten minutes of dosage), with insulin levels falling over the next couple of hours. A dose taken after meals has a much smaller effect on blood sugar than one taken beforehand. The effects on blood sugar diminish after six to eight hours. Byetta® is available at 5µg and 10µg dosage levels. Treatment begins with the 5µg dosage, which is increased in the absence of side effects. Amylin subsequently developed a longer-acting version of exenatide (Bydureon®), approved in January 2012 after lengthy delays. This product provides sustained delivery of exenatide, enabling once-weekly dosing – a significant advantage when the drug is administered via injection to patients who may already be required to take other injections. Bydureon® uses patented biodegradable microspheres – an Alkermes patented technology – to deliver exenatide in a sustained-release manner. The microspheres are composed of polylactide coglycolide acid polymer. Amylin was acquired by Bristol-Myers Squibb for $7 billion in June 2012, in a deal that also involved Bristol's expansion of an existing partnership with AstraZeneca, which paid Bristol $3.4 billion for access to the Amylin diabetes portfolio.

Victoza® (liraglutide)—Novo Nordisk

Liraglutide is a long-acting GLP-1 agonist developed by Novo Nordisk for the treatment of type 2 diabetes. The product was approved by the European Medicines Agency (EMA) on July 3, 2009, and by the FDA on January 25, 2010.

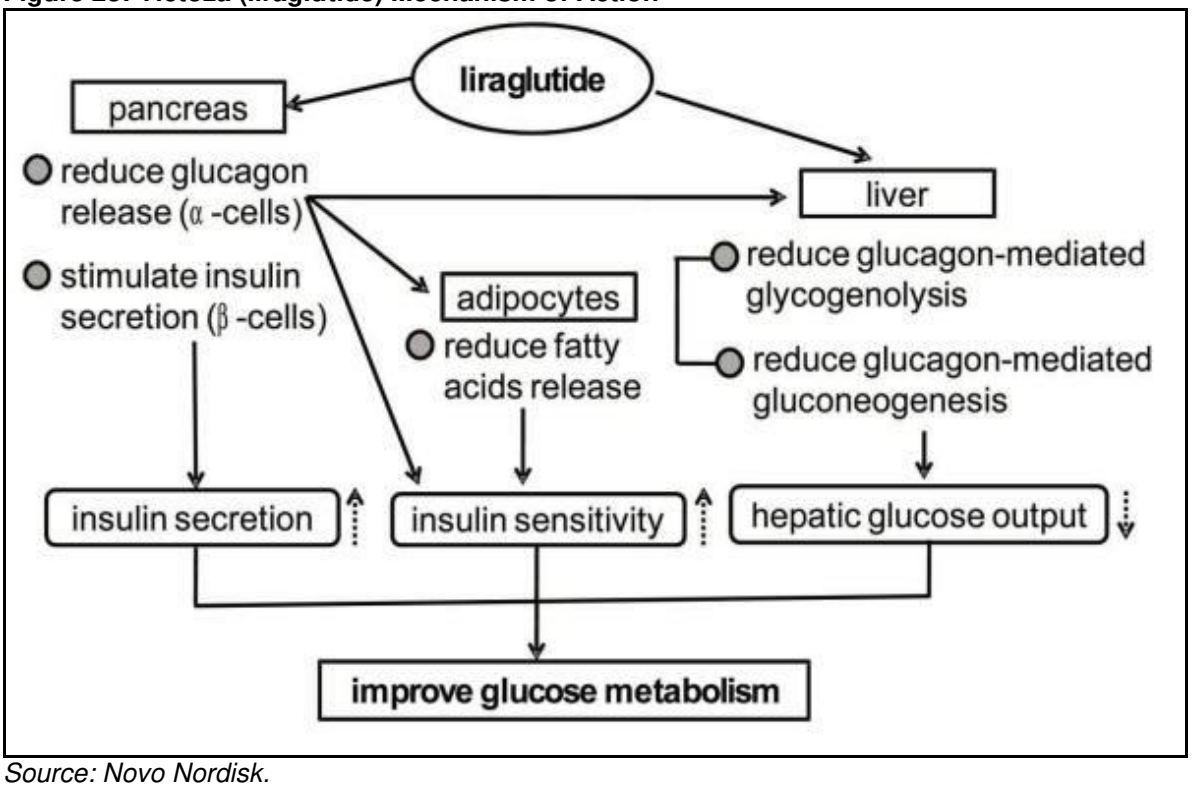
Figure 22: Victoza (liraglutide) Chemical Structure



Source: ADIS R&D Insight.

Liraglutide is an acylated human glucagon-like peptide-1 (GLP-1) agonist, with a 97% amino acid sequence identity to endogenous human GLP-1(7-37). GLP-1(7-37) represents less than 20% of total circulating endogenous GLP-1. Like GLP-1(7-37), liraglutide activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase by the stimulatory G-protein, G_s, in pancreatic beta cells. Liraglutide increases intracellular cyclic AMP (cAMP), leading to insulin release in the presence of elevated glucose concentrations. This insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia.

Figure 23: Victoza (liraglutide) Mechanism of Action



Source: Novo Nordisk.

In addition, liraglutide decreases glucagon secretion in a glucose-dependent manner. The mechanism of blood glucose lowering also involves a delay in gastric emptying. GLP-1(7-37) has a half-life of 1.5–2 minutes due to degradation by the ubiquitous endogenous enzymes, DPP-IV and neutral endopeptidases (NEP). Unlike native GLP-1, liraglutide is stable against metabolic degradation by both peptidases and has a plasma half-life of 13 hours after subcutaneous administration. The pharmacokinetic profile of liraglutide, which permits once-daily dosing, is a result of self-association that delays absorption, plasma protein binding and stability against metabolic degradation by DPP-IV and NEP.

Tanzeum® (albiglutide)

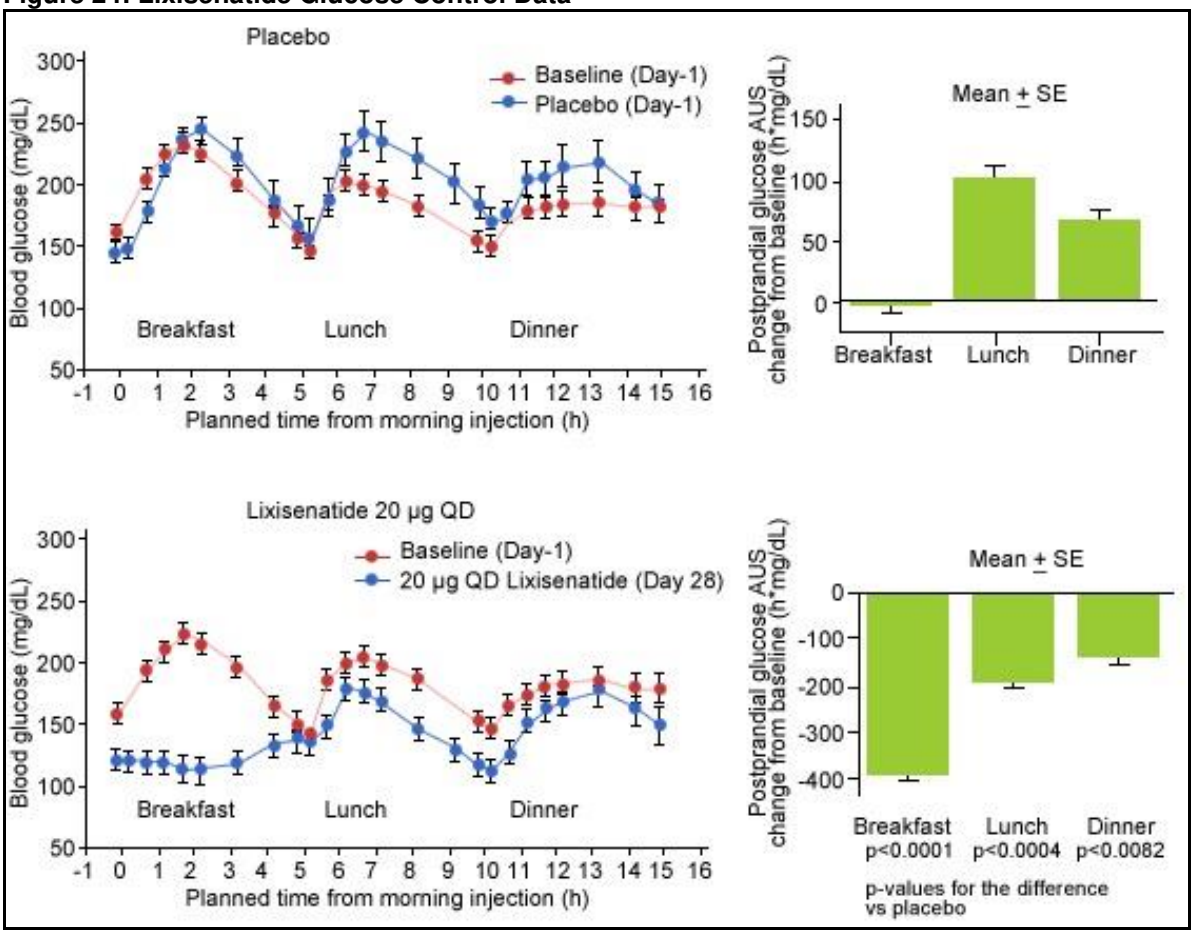
Tanzeum® (U.S.) / Eperzan® (Europe), which carries the generic name albiglutide, is a dipeptidyl peptidase-4-resistant glucagon-like peptide-1 (GLP-1) dimer fused to human albumin. Albiglutide has a half-life of four to seven days, which is considerably longer than the two most widely-used GLP-1 analogs currently on the market, exenatide (Byetta®) and liraglutide (Victoza®). However, it is likely to be viewed as slightly inferior to the pharmacokinetic profile of Bydureon®. GlaxoSmithKline, which obtained the rights to this drug through its relationship with and acquisition of Human Genome Sciences, filed for approval of albiglutide in the U.S. in January 2013 and in Europe in March 2013. The drug was subsequently approved on April 15, 2014.

GlaxoSmithKline presented data from five Phase 3 trials of albiglutide in June 2013. The primary efficacy endpoint for these studies was the change from baseline in HbA1c compared to placebo and/or active comparators assessed after one or two years of treatment. Secondary endpoints included fasting plasma glucose (FPG) and weight. These studies were specifically designed to assess durability of albiglutide effect on HbA1c and other continuous variables when used in various combination therapies, at different stages of the disease, and in various degrees of renal impairment. Albiglutide achieved the primary efficacy endpoint in these five studies, although a hierarchical analysis of non-inferiority to pioglitazone was not met in one of them.

Lyxumia™ (lixisenatide)—Sanofi S.A. / Zealand Pharma A/S

Another once-daily GLP-1 agonist, lixisenatide was developed by Zealand Pharma A/S and subsequently partnered with Sanofi S.A., which obtained approval for the drug in Europe in February 2013. It is marketed in various European countries under the trade name Lyxumia™.

Figure 24: Lixisenatide Glucose Control Data



Source: Zealand Pharma A/S.

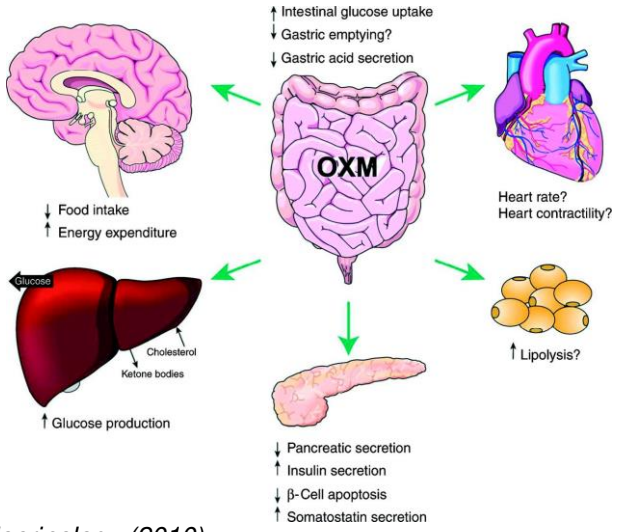
While lixisenatide was originally filed for approval in the U.S. and had been assigned a PDUFA date in December 2013, Sanofi elected to withdraw the regulatory submission in September 2013 after it became apparent that the FDA wanted to see long-term safety data from a large Phase 3 trial evaluating lixisenatide with respect to coronary event risk.

The Elixa trial is comparing lixisenatide against placebo in about 6,000 type 2 diabetics who had recently experienced an acute coronary event such as a heart attack. The goal is to see whether the drug affects cardiovascular outcomes for patients. Sanofi also began conducting a Phase 3 trial of lixisenatide in combination with Sanofi's long-acting insulin injection product, Lantus™, in 2014. Lantus™ loses patent protection in 2015 and the successful development of lixisenatide plus Lantus as a combination product could potentially enable Sanofi to extend the lifespan of its long-acting insulin franchise. We note that this strategy is very similar to the concept that Oramed is exploring with the combination of ORMD-0801 with ORMD-0901.

Oxyntomodulin Derivatives

Beyond the traditional GLP-1 receptor agonists, several newer agents in the incretin mimetic sub-class are currently being developed. Some of these agents are dual agonists of the GLP-1 and the glucagon receptor (e.g. oxyntomodulin and derivatives). The most well-known of these is ZP2929, which was also developed by Zealand Pharma and partnered with Boehringer Ingelheim.

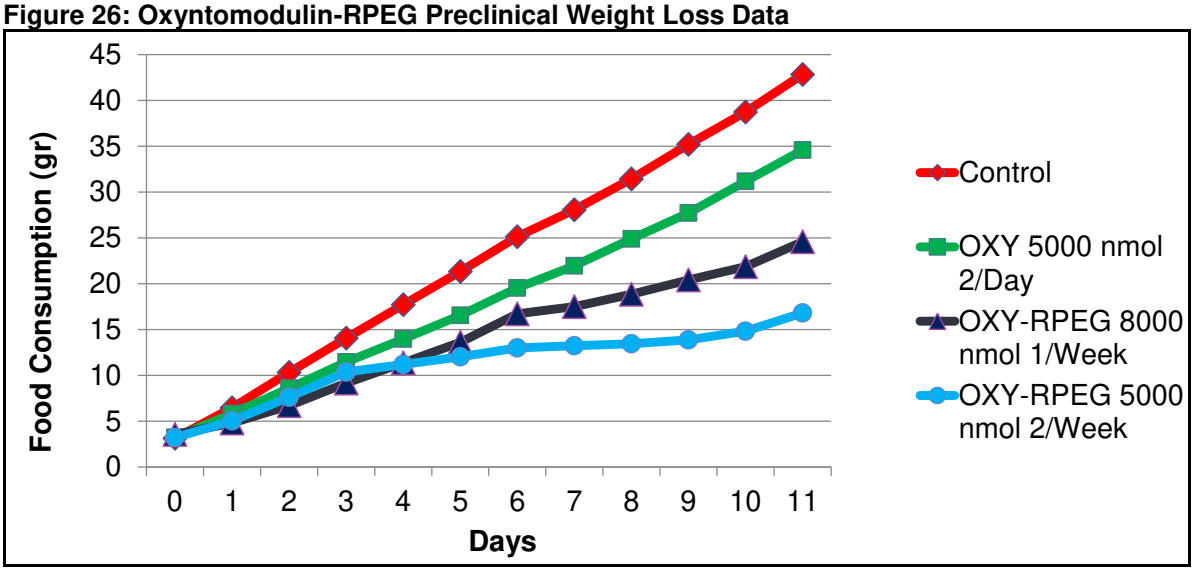
Figure 25: Oxyntomodulin Mechanism of Action



Source: Journal of Endocrinology (2010).

Another drug, MOD-6030, was developed using a proprietary technology platform for reversibly PEGylating centrally-acting peptides that was invented at the Weizmann Institute of Science in Israel. This drug, which is effectively a long-acting version of oxyntomodulin that preclinically demonstrated potential for semi-monthly dosing, was originally created by PROLOR Biotech, an emerging Israeli biotechnology firm that was acquired in an all-stock transaction by OPKO Health, a specialty pharmaceuticals and diagnostics firm founded by Dr. Phillip Frost. The data shown below that the drug functions as a potent anorectic with better efficacy than native oxyntomodulin.

Figure 26: Oxyntomodulin-RPEG Preclinical Weight Loss Data

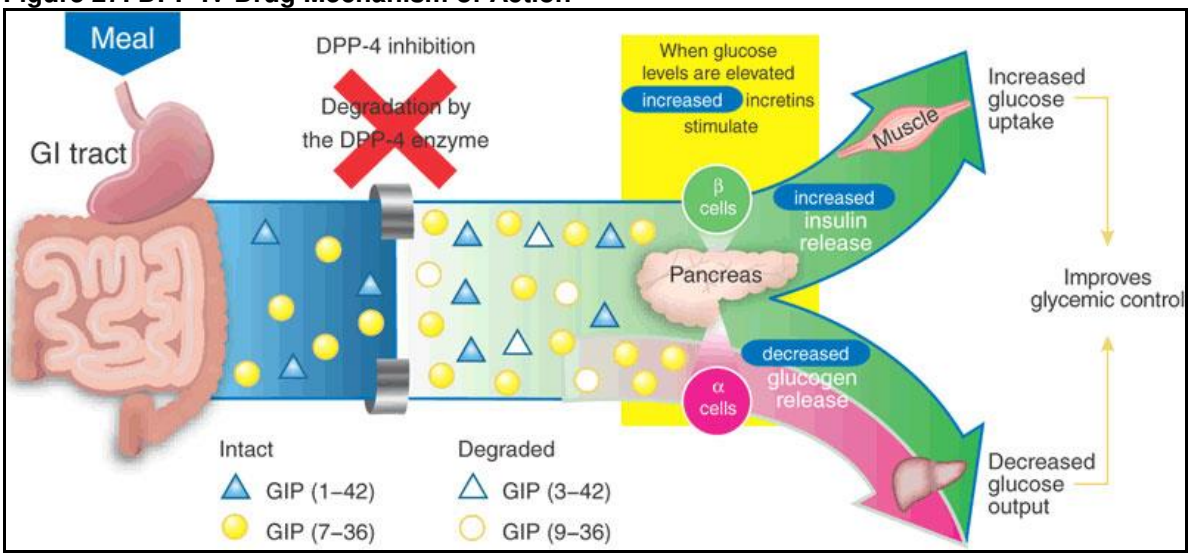


Source: PROLOR Biotech, Inc.

Dipeptidyl peptidase IV (DPP-IV) inhibitors

Also called gliptins, the DPP-IV) inhibitors were developed with the aim of providing diabetics with an orally-bioavailable way to achieve more reliable glucose control. These drugs are typically administered to type 2 diabetics already taking insulin. Glucagon increases blood glucose levels, and DPP-IV inhibitors reduce glucagon and blood glucose levels. DPP-IV inhibitors increase levels of the incretins – chiefly, glucagon-like peptide 1 (GLP-1) and gastric inhibitor polypeptide (GIP) – which inhibit glucagon release. This, in turn, increases insulin secretion, decreases gastric emptying, and decreases blood glucose levels. The figure below illustrates the mechanism of these drugs.

Figure 27: DPP-IV Drug Mechanism of Action



Source: Molecular Biology of the Cell (2005).

The DPP-IV inhibitors selectively block DPP-IV, which is an antigenic enzyme expressed on the surface of most cell types and is associated with immune regulation, signal transduction and apoptosis. It is an intrinsic membrane glycoprotein and a serine exopeptidase that cleaves X-proline dipeptides from the N-terminus of polypeptides. The first inhibitors were characterized in the late 1980s and 1990s. Each inhibitor was important to establish an early structure activity relationship (SAR) for subsequent investigation. The inhibitors are typically classified as either non-covalent or covalent binders. DPP-4 is a dipeptidase that selectively binds substrates that contain proline at the P1-position; thus, many DPP-4 inhibitors have five-membered heterocyclic rings that mimic proline, e.g. pyrrolidine, cyanopyrrolidine, thiazolidine and cyanothiazolidine. These compounds commonly form covalent bonds to the catalytic residue Ser630.

In 1994, researchers from Zeria Pharmaceuticals unveiled cyanopyrrolidines with a nitrile functional group, which was assumed to form an imidate with the catalytic serine. Concurrently other DPP-4 inhibitors without a nitrile group were characterized, but these contained other serine-interacting motifs, e.g. boronic acids, phosphonates or diacyl hydroxylamines. These compounds were not as potent because of the similarity of DPP-4 and prolyl oligopeptidase (PEP) and also suffered from chemical instability. In 1995, Ferring Pharmaceuticals published on two cyanopyrrolidine compounds, which had excellent potency and improved chemical stability.

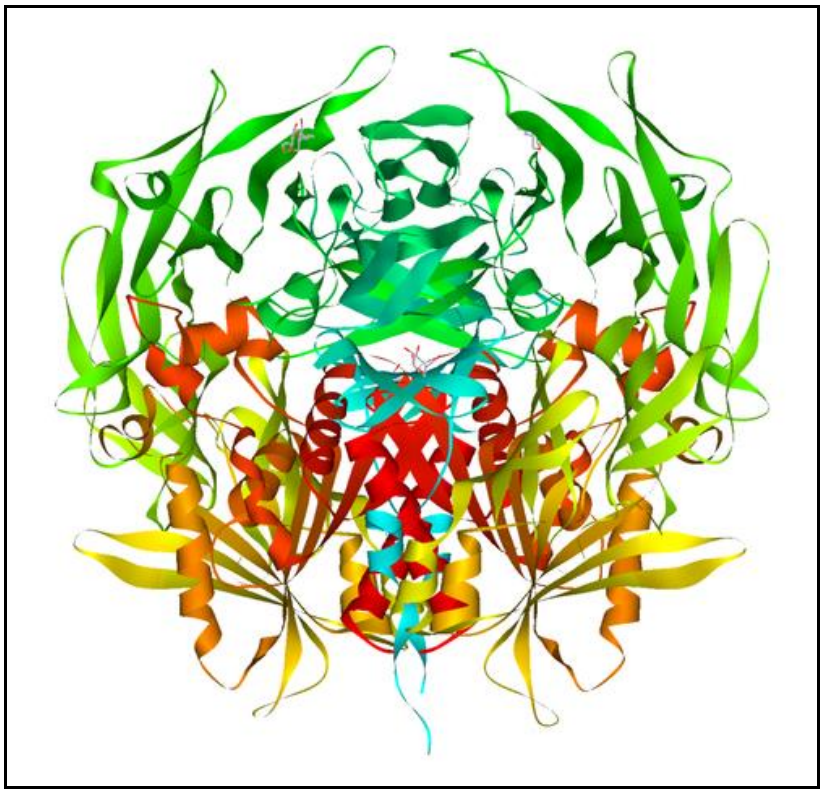
In 1995, Edwin Villhauer at Novartis started to explore N-substituted glycinyl-cyanopyrrolidines based on the fact that DPP-4 identifies N-methylglycine as a N-terminal amino acid. This group of new cyanopyrrolidines became the basis for a popular field of research in subsequent years. Some trials with dual inhibitors of DPP-4 and vasopeptidase were performed, since vasopeptidase inhibition is believed to enhance the anti-hyperglycemic effect of DPP-4 inhibition by stimulating insulin secretion.

Many structurally diverse DPP-4 inhibitors have been discovered. This is not surprising, considering the properties of the binding site:

1) A deep lipophilic pocket combined with several exposed aromatic side chains for achieving high affinity small molecule binding.
2) A significant solvent access that makes it possible to tune the physicochemical properties of the inhibitors that leads to better pharmacokinetic behavior.

The DPP-IV enzyme is a 766-amino acid transmembrane glycoprotein in the prolyloligopeptidase family with three components; a cytoplasmic tail, a transmembrane region and an extracellular head, which is divided into a catalytic domain and an eight-bladed β-propeller domain. The structure of the enzyme is depicted in the figure below.

Figure 28: DPP-IV Molecular Structure



Source: Brookhaven Protein Data Bank.

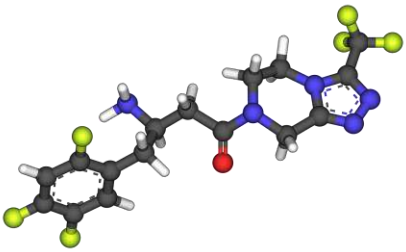
The first DPP-IV inhibitor drugs for type 2 diabetes were approved several years ago, with the initial product across the regulatory finish line being Merck & Co.'s sitagliptin. This agent was originally approved in October 2006. Merck and Novartis both had drug candidates under review at the FDA simultaneously, with the Novartis drug, vildagliptin, eventually being denied approval in the U.S. due to the fact that it was seen to cause skin rash in cynomolgus monkeys. Vildagliptin was eventually approved in various ex-U.S. markets, but has never been launched in the U.S. In our view, the FDA's decision was irrational and has remained controversial; it permitted Merck to enjoy a virtual monopoly of the DPP-IV inhibitor sector for several years, until AstraZeneca and Bristol-Myers Squibb finally obtained approval for Onglyza™ (saxagliptin) in July 2009.

Januvia™ (sitagliptin)—Merck & Co.

The DPP-IV inhibitors have proven to be extremely successful drugs from a commercial perspective, particularly the first of these agents to be launched, sitagliptin. Developed by Merck & Co., sitagliptin – originally identified as MK-0431 and currently known via its trade name Januvia™

– became the fastest-ramping launch in Merck's history. It has also been developed as an accompaniment to other oral anti-hyperglycemic agents, particularly thiazolidinediones (TZDs) and metformin – one of these combination products is called Janumet™. The sitagliptin structure is shown below.

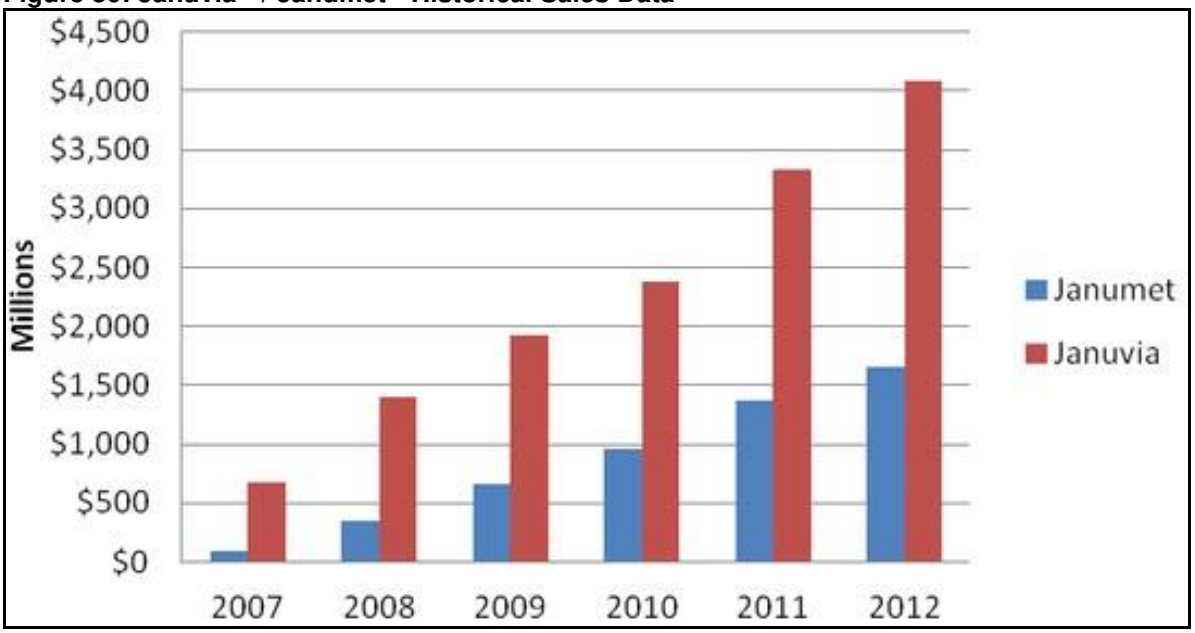
Figure 29: Januvia™ (sitagliptin) Chemical Structure



Source: ADIS R&D Insight.

The figure below shows the growth in the sales of both Januvia™ and Janumet™ – sometimes referred to as "Merck's dynamic diabetes duo." These are undoubtedly highly successful drugs – currently estimated to generate roughly $6 billion a year in sales for Merck – and have been heavily instrumental in changing the face of type 2 diabetes therapy. One of the main advantages for these drugs is the ability to achieve adequate glucose control in patients who are unresponsive or only partially responsive to biguanides and / or sulfonylureas, with the added benefit of lacking induction of hypoglycemia or weight gain, which is often an issue with sulfonylurea drug therapy.

Figure 30: Januvia™ / Janumet™ Historical Sales Data



Source: ADIS R&D Insight.

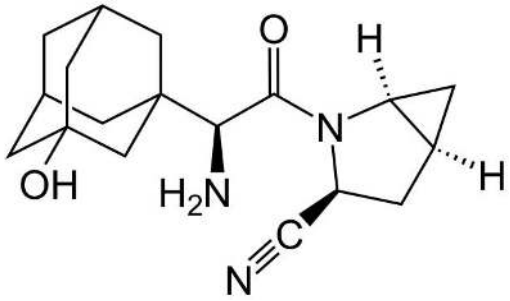
Januvia™ is comparatively less potent than the other gliptins, requiring dosing at 100mg/day. It must be dose-adjusted for those with impaired renal function to 25mg/day.

Onglyza™ (saxagliptin)—AstraZeneca / Bristol-Myers Squibb

Approved in July 2009, saxagliptin is currently deployed at a 5mg once-daily dosage. Its absorption is unaffected by food. Saxagliptin is metabolized mainly by cytochrome P450 (CYP) 3A4 to a major active monohydroxylated metabolite, 5-hydroxy saxagliptin, which is half as potent as saxagliptin. Approximately 75% of the total dose of saxagliptin is renally excreted (comprising

24% saxagliptin, 36% 5-hydroxy saxagliptin and minor metabolites of saxagliptin), while 22% of a saxagliptin dose was eliminated in the feces, mainly as metabolites. The drug is generally not dose-adjusted for patients with mild renal impairment, although it is usually given at half the normal dose to those with moderate-to-severe renal impairment or end-stage renal disease.

Figure 31: Onglyza™ (saxagliptin) Chemical Structure

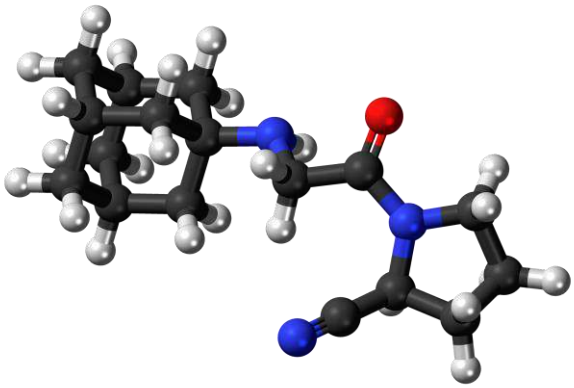


Source: ADIS R&D Insight.

Galvus® (vildagliptin)—Novartis AG

While it has never been approved in the U.S., Galvus® was initially approved in Europe in October 2007. Widely considered an under-appreciated drug, vildagliptin has achieved significant commercial success outside the U.S., with 2012 net sales of $910 million. Substantial traction has been achieved by Novartis with this agent in emerging markets. The typical dose is 50mg twice-daily. Its absorption is unaffected by food. Vildagliptin is extensively metabolized by the liver and has >90% bioavailability following a single oral dose. No dosage adjustment is required for liver disease although a 30% higher amount of inactive metabolites is retained in patients with severe liver disease. No dose adjustment is required for mild renal insufficiency; however, for patients with moderate-to-severe renal impairment, half the recommended dose is suggested.

Figure 32: Galvus® (vildagliptin) Chemical Structure

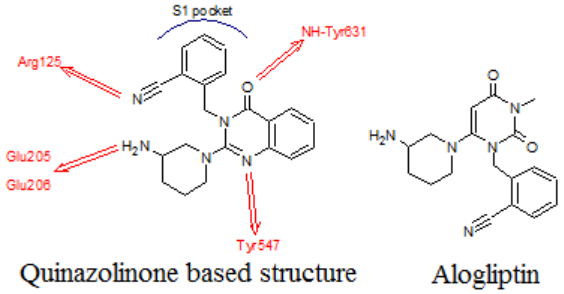


Source: ADIS R&D Insight.

Nesina (alogliptin)—Takeda Pharmaceutical Co. Ltd. / Furiex Pharmaceuticals

Originally developed by Syrrx, acquired by Takeda in 2005, alogliptin had a rough path to market in both the U.S. and Europe. The drug was filed with the FDA in December 2007 but failed to gain approval; subsequently, a pair of New Drug Applications (NDAs) were filed for both alogliptin as a single agent as well as in combination with pioglitazone. Both of these were rejected in 2012. Takeda, however, persisted and eventually obtained approval for alogliptin as a single agent (Nesina), in a combination formulation with metformin (Kazano), and in combination with pioglitazone as Oseni.

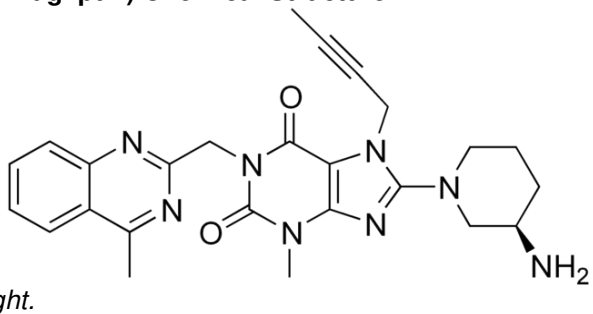
Figure 33: Nesina (alogliptin) Chemical Structure



Source: ADIS R&D Insight.

Tradjenta® (linagliptin)—Boehringer Ingelheim / Eli Lilly & Co.
Initially developed in Boehringer Ingelheim's labs as BI-1356, linagliptin was approved in the U.S. in May 2011. Dosed at 5mg once-daily, it is comparatively more potent than the earlier-generation agents, sitagliptin and vildagliptin. Only 5% is eliminated renally; thus, it appears safer than other gliptins in patients with kidney function impairment. Intriguingly, it has also shown preclinical activity in wound healing.

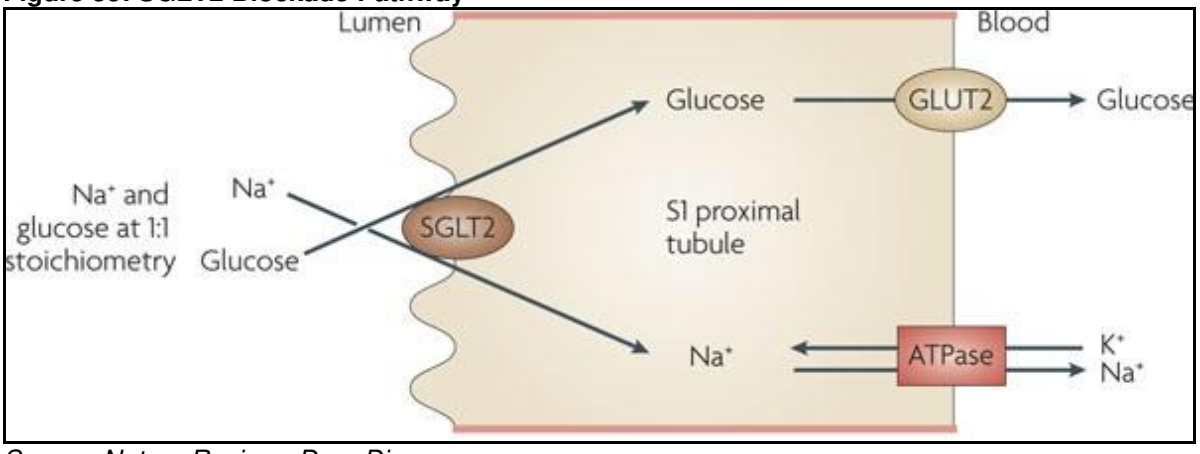
Figure 34: Tradjenta® (linagliptin) Chemical Structure



Source: ADIS R&D Insight.

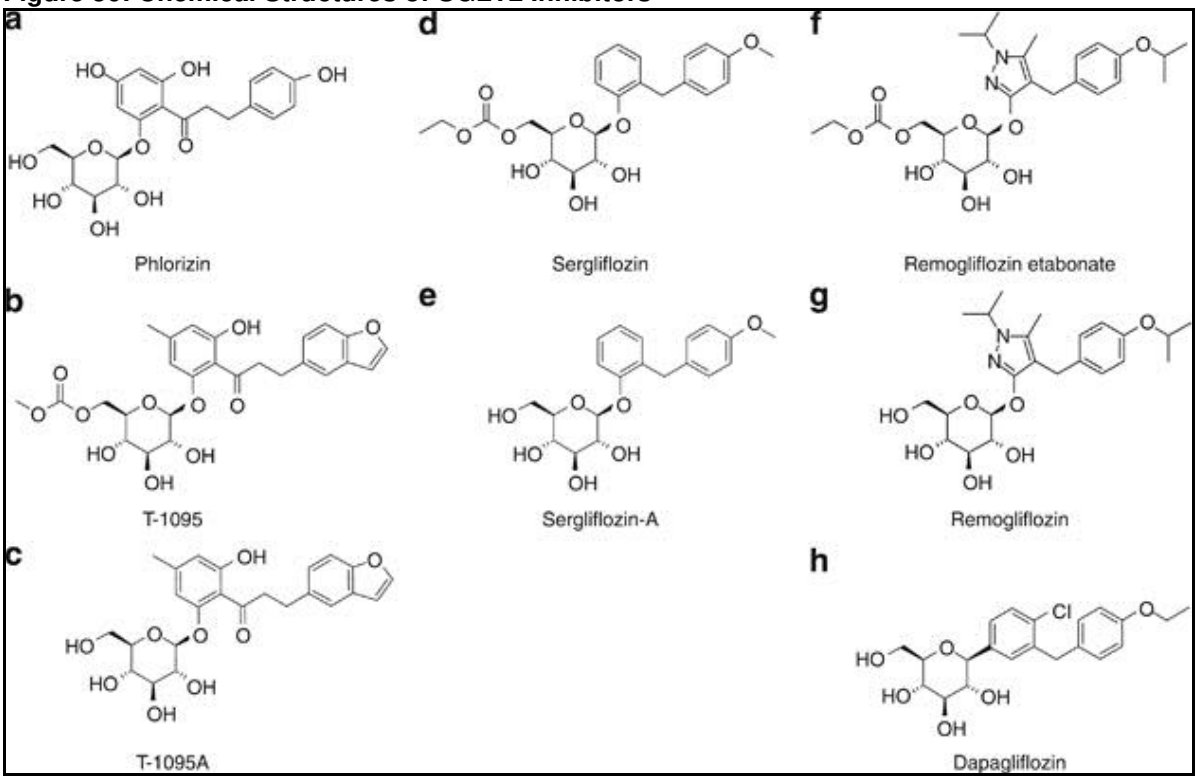
Sodium/glucose co-transporter 2 (SGLT2) inhibitors
The newest therapeutic sub-class of anti-diabetic drugs, the SGLT2 inhibitors interfere with the activity of SGLT2, a member of the glucose transport protein family that serves as the major co-transporter involved in glucose reabsorption in the kidney. The idea is that blockade of this protein would stimulate glucose excretion through the urine.

Figure 35: SGLT2 Blockade Pathway



Source: Nature Reviews Drug Discovery.

Figure 36: Chemical Structures of SGLT2 Inhibitors



Source: ADIS R&D Insight.

Forxiga™ (dapagliflozin) is approved in Europe and Australia but was rejected by the FDA due to safety concerns. Dapagliflozin was one of two drugs, along with saxagliptin, that were originally discovered in Bristol's laboratories to which AstraZeneca obtained partial rights. AstraZeneca and Bristol inked their global diabetes collaboration agreement in January 2007. This deal involved an upfront payment of $100 million by AstraZeneca to Bristol-Myers Squibb. From 2007 through 2009, the majority of development costs were to be funded by AstraZeneca. Any additional development costs will be shared equally. Bristol-Myers Squibb was also slated to receive additional payments of up to $650 million based on development and regulatory milestones. In addition, potential sales milestones of up to $300 million per product were also possible. The firms were to share profits and losses along with commercialization expenses equally on a global basis, excluding Japan. Bristol manufactures both products and books all sales.

In addition to Forxiga, Janssen Pharmaceuticals (a division of Johnson & Johnson) has an SGLT2 inhibitor called canagliflozin (trade name Invokana™), which won FDA approval in March 2013. This drug was originally developed by Mitsubishi Tanabe Pharma. However, an elevated risk of stroke has been observed in clinical trials.

Other agents in the SGLT2 inhibitor class include ipragliflozin (ASP1941), developed by the Japanese firm Astellas; empagliflozin (BI-10773), developed by Boehringer Ingelheim; tofogliflozin from Chugai Pharma, being developed in collaboration with Kowa and Sanofi S.A.; and remogliflozin etabonate, developed by GlaxoSmithKline. Ipragliflozin, empagliflozin and tofogliflozin have all recently received marketing approvals, with ipragliflozin and tofogliflozin currently available in Japan under the trade names Suglat® and Deberza®, respectively, and empagliflozin having recently been launched in the U.S. under the trade name Jardiance®. Remogliflozin is in Phase 2b testing currently and is being developed by Islet Sciences. We anticipate that, in the next 2 – 3 years, agents like ipragliflozin and tofogliflozin will probably be approved in the U.S.

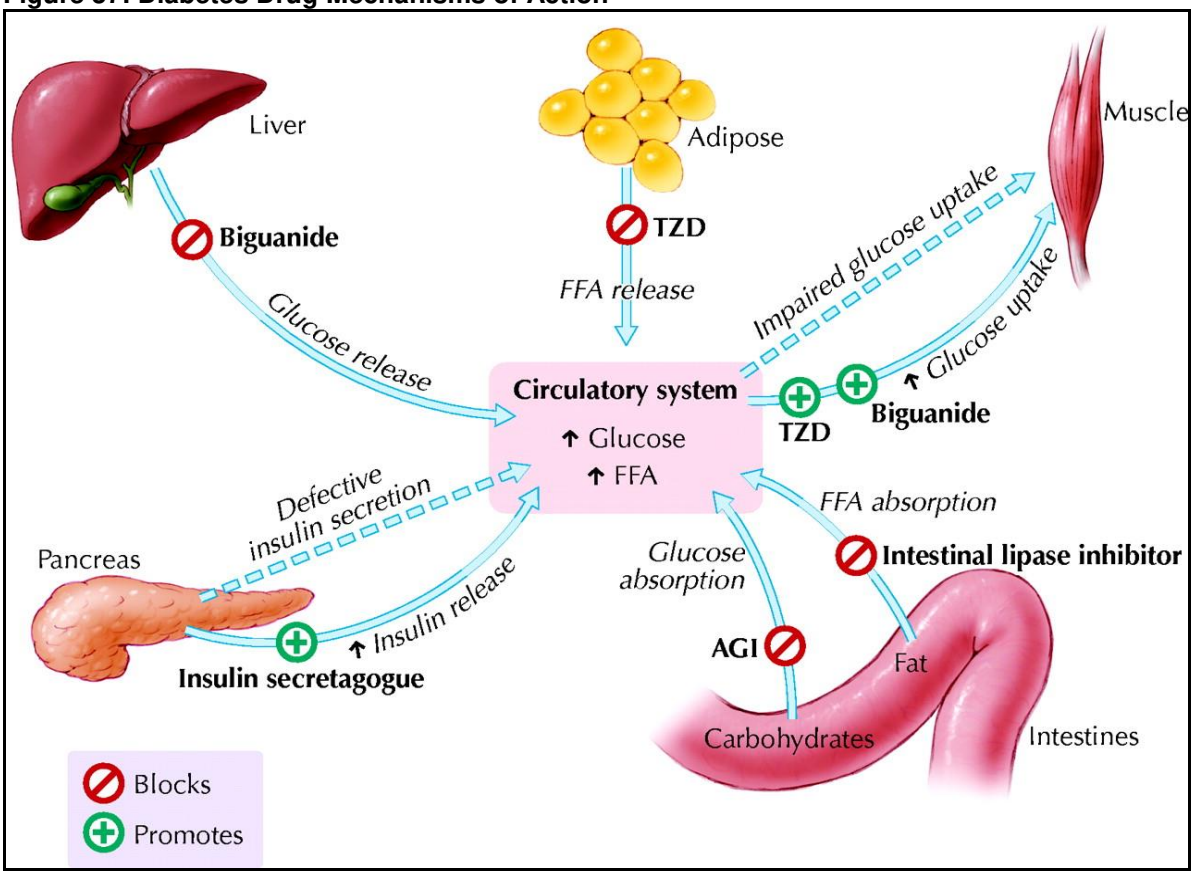
Older-Generation Agents
Other type 2 diabetes drugs include the biguanides (e.g., metformin), the sulfonylurea derivatives (e.g. chlorpropamide, glipizide, tolazamide) and the thiazolidinediones (TZDs, also known as glitazones, e.g. piloglitazone, rosiglitazone, and troglitazone).

Biguanides
These drugs were first characterized as components of *Galega officinalis* (French lilac) extracts, which were used in diabetes therapy for centuries. Introduced in the 1950s, the biguanide agent metformin is the only anti-diabetic drug that has been consistently shown to prevent the cardiovascular complications of diabetes. Metformin is still widely deployed, typically as the front-line therapy of choice for endocrinologists.

Sulfonylureas
These compounds bind to an ATP-dependent potassium ion (K^+) channel on the membranes of beta cells. This inhibits a tonic, hyperpolarizing efflux of potassium, thus causing the electric potential over the membrane to become more positive. The depolarization opens voltage-gated Ca^{2+} channels. The rise in intracellular calcium leads to increased fusion of insulin granulae with the cell membrane, and thus increased insulin secretion. There is also evidence that sulfonylureas sensitize β-cells to glucose, limit hepatic glucose production, and decrease lipolysis and hepatic insulin clearance.

Thiazolidinediones (TZDs)
These drugs act by activating peroxisome proliferator-activated receptors (PPARs). TZDs can reduce insulin resistance, modify adipocyte differentiation, inhibit angiogenesis, suppress leptin (stimulating appetite) and enhance adiponectin production.

Figure 37: Diabetes Drug Mechanisms of Action



Source: American Diabetes Association (ADA).

Anti-Diabetic Insulin Formulations

The table below summarizes the currently-marketed insulin formulations that have achieved regulatory approval. These are principally recombinantly produced.

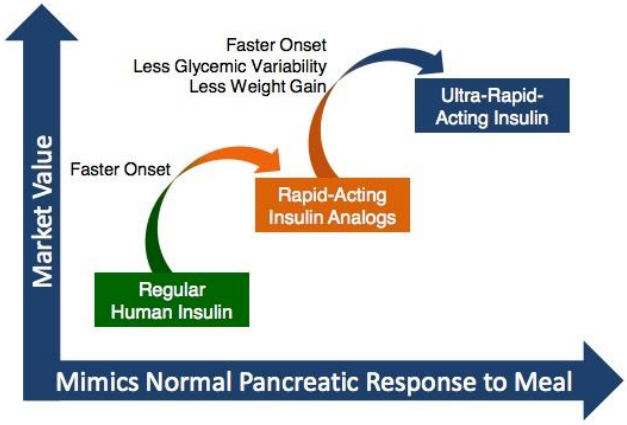
Table 8: Marketed Insulin Formulations

Brand Names	Onset	Peak	Duration	Role in Blood Sugar Management
Rapid-Acting				
Humalog	15-30 min.	30-90 min	3-5 hours	Covers insulin needs for meals eaten at the same time as the injection. This type of insulin is used with longer-acting insulin.
Novolog	10-20 min.	40-50 min.	3-5 hours	
Apidra	20-30 min.	30-90 min.	1-2.5 hours	
Short-Acting				
Regular (R) humulin	30 min-1 hour	2-5 hours	5-8 hours	Covers insulin needs for meals eaten within 30-60 minutes
Velosulin (for use in the insulin pump)	30 min-1 hour	2-3 hours	2-3 hours	
Intermediate-Acting				
NPH - Novolin (N)	1-2.5 hours	3-10 hours	18-24 hours	Covers insulin needs for about half the day or overnight. Often combined with rapid- or short-acting insulin.
Long-Acting				
Ultralente (U)	30 min-3 hours	10-20 hours	20-36 hours	Covers insulin needs for about one full day. This type of insulin is often combined with rapid- or short-acting insulin.
Lantus	1-1½ hour	No peak time	20-24 hours	
Levemir or detemir	1-2 hours	6-8 hours	Up to 24 hours	
Pre-Mixed				
Novolin 70/30	30 min.	2-12 hours	Up to 24 hours	These products are generally taken twice a day before mealtime.
Novolog 70/30	10-20 min.	1-4 hours	Up to 24 hours	
Humulin 50/50	30 min.	2-5 hours	18-24 hours	
Humalog mix 75/25	15 min.	0.5-2.5 hours	16-20 hours	

Source: Company reports; Wolters Kluwer competitive intelligence database.

The insulin market is becoming more segmented, with firms focused on developing either longer-acting insulin formulations that reduce injection frequency or faster-acting versions (see below).

Figure 38: Ultra-Rapid Insulin Advantages



Source: Biodel, Inc.

Table 9: Experimental Insulin Preparations—Competitive Landscape

Trade Name	Generic Name	Sponsor	Route of Administration	Mechanism of Action	Clinical Stage
NN1953	OI338GT	Novo Nordisk & Merrion Pharmaceuticals	oral	long-acting basal insulin analogue (includes adsorption enhacers)	Phase 1
NN1954	OI362GT	Novo Nordisk & Merrion Pharmaceuticals	oral	long-acting basal insulin analogue (includes adsorption enhacers)	Phase 1
NN1956	OI287GT	Novo Nordisk & Merrion Pharmaceuticals	oral	long-acting basal insulin analogue (includes adsorption enhacers)	Phase 1
BIOD-123	Oral Insulin	Biodel	oral	mimics first-phase insulin-release, reducing hepatic glucose production: maintains normal glucose levels	Phase 1
IN-105	Oral Insulin	Biocon & Bristol-Meyers Squibb	oral	orally delivered and targeted towards liver, absorbed in GI tract.	Phase 2
Capsulin	Capsulin	Diabetology	oral	protection of insulin from enzymatic digestion and facilitation of absorption across intestinal mucosa	Phase 2
Afrezza	Technospere Insulin	Mannkind Corporation	inhalation	ultra-rapid acting insulin powder	Phase 3
Oral-lyn	Oral Recosulin	Generex & Shreya Life Sciences	buccal spray	basal insulin spray that reduces hemoglobin A1c (HbA1c)	Phase 3

Source: Company Reports; EvaluatePharma; ADIS R&D Insight; ClinicalTrials.gov.

Appendix 2: Financial Statement Data

Table 10: Oramed Pharmaceuticals, Inc. (ORMP)—Historical Income Statements, Financial Projections

FY end August 31
$ in thousands, except per share data

	2014A					2015E							
	1QA	2QA	3QA	4QA	2014A	1QA	2QA	3QA	4QE	2015E	2016E	2017E	2018E
Revenue													
Product revenue	-	-	-	-	-	-	-	-	-	-	-	-	-
Research and other	-	-	-	-	-	-	-	-	-	-	-	-	-
Total revenue	-	-	-	-	-	-	-	-	-	-	-	-	-
Expenses													
Cost of product and service revenue	-	-	-	-	-	-	-	-	-	-	-	-	-
Research & development	751	673	1,089	764	3,277	1,302	1,136	915	1,200	4,553	6,400	9,100	12,200
Selling and marketing	-	-	-	-	-	-	-	-	-	-	-	-	-
General and administrative	418	512	814	885	2,629	600	538	719	900	2,757	5,000	7,600	10,400
Total expenses	1,168	1,186	1,903	1,649	5,906	1,902	1,674	1,634	2,100	7,310	11,400	16,700	22,600
Gain (loss) from operations	(1,168)	(1,186)	(1,903)	(1,649)	(5,906)	(1,902)	(1,674)	(1,634)	(2,100)	(7,310)	(11,400)	(16,700)	(22,600)
Other income/expense													
Financial income	46	74	79	25	225	27	38	51	60	176	265	246	318
Financial expense	(2)	(3)	(4)	(1)	(11)	(21)	(1)	-	-	(22)	-	(120)	(120)
Impairment of available-for-sale securities													
Total investment income and other	44	71	75	24	214	6	37	51	60	154	265	126	198
Loss before provision for income taxes	(1,124)	(1,115)	(1,828)	(1,625)	(5,692)	(1,896)	(1,637)	(1,583)	(2,040)	(7,156)	(11,135)	(16,574)	(22,402)
Deferred income tax benefit				(4)	(4)	-	-	-	-	-	-	-	-
Net loss/income	(1,124)	(1,115)	(1,828)	(1,629)	(5,696)	(1,896)	(1,637)	(1,583)	(2,040)	(7,156)	(11,135)	(16,574)	(22,402)
Net loss per share (basic)	(0.14)	(0.12)	(0.18)	(0.16)	(0.62)	(0.19)	(0.16)	(0.15)	(0.18)	(0.67)	(0.88)	(1.27)	(1.64)
Net loss per share (diluted)	(0.14)	(0.12)	(0.18)	(0.16)	(0.62)	(0.19)	(0.16)	(0.15)	(0.18)	(0.67)	(0.88)	(1.27)	(1.64)
Weighted average number of shares outstanding (basic)	7,941	9,128	9,888	10,029	9,244	10,142	10,482	10,828	11,439	10,723	12,586	13,052	13,627
Weighted average number of shares outstanding (diluted)	7,941	9,128	9,888	10,029	9,244	10,142	10,482	10,828	11,439	10,723	12,586	13,052	13,627

Source: Company Reports and Rodman & Renshaw estimates.

Table 11: Oramed Pharmaceuticals, Inc. (ORMP)—Historical Balance Sheets, Financial Projections

FY end August 31
$ in thousands, except per share data

	2014A					2015E							
	11/30	2/28	5/31	8/31	8/31/14A	11/30A	2/28A	5/31A	8/31	8/31/15E	8/31/16E	8/31/17E	8/31/18E
Assets													
Current assets:													
Cash and cash equivalents	1,371	3,253	2,475	1,762	1,762	6,656	1,102	3,847	2,307	2,307	(25)	(14,199)	(1,251)
Short-term deposits	5,459	18,634	12,005	18,481	18,481	17,026	16,351	12,549	12,549	12,549	12,549	12,549	12,549
Marketable securities	962	1,464	1,063	1,047	1,047	688	695	758	758	758	758	758	758
Restricted cash	16	16	61	16	16	16	16	16	16	16	16	16	16
Accounts receivable	-	-	-	-	-	-	-	-	-	-	-	-	-
Prepaid expenses	173	246	98	64	64	120	129	100	100	100	100	100	100
Related parties	5	2	1	330	330	-	-	-	-	-	-	-	-
Grants receivable	-	73	267	78	78	27	2	33	33	33	33	33	33
Total current assets	7,986	23,687	15,970	21,778	21,778	24,533	18,295	17,303	15,763	15,763	13,431	(743)	12,205
Property and equipment	9	12	14	14	14	15	13	8	8	8	8	8	8
Amounts funded in respect of employee retirement rights	6	6	7	7	7	7	7	12	12	12	12	12	12
Other assets	5	5	6,508	3	3	5	4,665	4,806	4,806	4,806	4,806	4,806	4,806
Total Assets	8,006	23,710	22,498	21,802	21,802	24,560	22,980	22,129	20,589	20,589	18,257	4,083	17,031
Liabilities and shareholder equity													
Current liabilities													
Accounts payable and accrued expenses	621	303	448	926	926	795	570	731	731	731	731	731	731
Related parties	-	-	-	-	-	32	35	34	34	34	34	34	34
Other current liabilities	47	47	47	47	47	-	-	-	-	-	-	-	-
Total current liabilities	669	350	495	973	973	827	605	765	765	765	765	765	765
Deferred revenue	-	-	-	-	-	-	-	-	-	-	-	-	-
Other long-term liabilities	-	-	-	-	-	-	-	-	-	-	-	-	-
Employee rights upon retirement	9	9	9	9	9	9	9	10	10	10	10	10	10
Long-term deferred tax liability	23	23	23	27	27	27	27	27	27	27	27	27	27
Total Liabilities	700	382	527	1,009	1,009	863	641	802	802	802	802	802	802
Shareholder's equity													
Common stock	95	117	119	121	121	129	129	129	130	130	131	131	133
Additional paid-in capital	30,124	46,726	47,574	48,040	48,040	53,191	53,463	53,971	53,970	53,970	60,572	60,572	93,120
Accumulated other comprehensive income	334	847	468	452	452	93	100	163	163	163	163	163	163
Deficit accumulated	(23,248)	(24,363)	(26,191)	(27,820)	(27,820)	(29,716)	(31,353)	(32,936)	(34,476)	(34,476)	(43,411)	(57,585)	(77,187)
Total shareholder's equity	7,305	23,328	21,971	20,793	20,793	23,697	22,339	21,327	19,787	19,787	17,455	3,281	16,229
Total liability and shareholder's equity	8,006	23,710	22,498	21,802	21,802	24,560	22,980	22,129	20,589	20,589	18,257	4,083	17,031

Source: Company Reports and Rodman & Renshaw estimates.

Table 12: Oramed Pharmaceuticals, Inc. (ORMP)—Historical Statements of Cash Flows, Financial Projections

FY end August 31
$ in thousands, except per share data

	2014A					2015E							
	1QA	2QA	3QA	4QA	2014A	1QA	2QA	3QA	4QE	2015E	2016E	2017E	2018E
Cash flows from operating activities													
Net loss	(1,124)	(1,115)	(1,828)	(1,629)	(5,696)	(1,896)	(1,637)	(1,583)	(2,040)	(7,156)	(11,135)	(16,574)	(22,402)
Adjustments for:													
Depreciation and amortization	2	1	1	2	6	1	2	1		4	-	-	-
Amortization of debt discount					-					-	-	-	-
Exchange differences	(22)	(11)	20	(16)	(29)	(9)	(27)	1		(35)	-	-	-
Stock based compensation	204	129	707	428	1,468	300	264	465	500	1,529	2,200	2,400	2,800
Common stock issued for services	64	-	-	38	102	26	-	43		69	-	-	-
Gain on sale of investment	(18)	(26)	(36)	4	(76)					-	-	-	-
Impairment of investments					-					-	-	-	-
Impairment of available for sale securities					-					-	-	-	-
Imputed interest					-					-	-	-	-
Exchange of warrants					-					-	-	-	-
Changes in fair value of warrant liabilities					-					-	-	-	-
Change in operating assets & liabilities										-	-	-	-
Prepaid expenses and other current assets	(25)	(142)	(45)	(107)	(319)	325	16	(2)		339	-	-	-
Restricted cash					-					-	-	-	-
Accounts payable and accrued expenses	170	(318)	145	478	475	(146)	(222)	160		(208)	-	-	-
Liability for employee rights upon retirement	1	-	-	-	1			1		1	-	-	-
Provision for uncertain tax position					-					-	-	-	-
Total change in operating assets & liabilities	146	(460)	100	371	157	179	(206)	159	-	132	-	-	-
Cash flows from operating activities	**(748)**	**(1,482)**	**(1,036)**	**(802)**	**(4,068)**	**(1,399)**	**(1,604)**	**(914)**	**(1,540)**	**(5,457)**	**(8,935)**	**(14,174)**	**(19,602)**
Cash flows from investing activities													
Purchase of property and equipment	(5)	(4)	(3)	(2)	(14)	(2)	-	-		(2)	-	-	-
Purchase of short term deposits	(4,300)	(14,300)	(29,645)	(7,505)	(55,750)	(820)	(5,405)	(5,300)		(11,525)	-	-	-
Proceeds from sale of short term deposits	4,100	1,136	29,705	7,598	42,539	2,300	1,450	8,951		12,701	-	-	-
Proceeds from sale of investment and marketable securities	43	37	58	(1)	137					-	-	-	-
Funds in respect of employee rights upon retirement		(1)	-	(1)	(2)			(1)		(1)	-	-	-
Other				2	2	(2)	2			-	-	-	-
Cash flows from investing activities	**(162)**	**(13,132)**	**115**	**91**	**(13,088)**	**1,476**	**(3,953)**	**3,650**	**-**	**1,173**	**-**	**-**	**-**
Cash flows from financing activities													
Proceeds from sales of common stocks and warrants - net of issuance expens		14,887	-	-	14,887	4,833	-	-	-	4,833	6,603	-	32,550
Proceeds from exercise of warrants and options		1,490	261	2	1,753	-	8	-		8	-	-	-
Receipts on account of shares issuances		118	(118)		-								
Proceeds from convertible notes			-		-					-	-	-	-
Proceeds from short term note payable			-		-					-	-	-	-
Cash flows from financing activities	**-**	**16,495**	**143**	**2**	**16,640**	**4,833**	**8**	**-**	**-**	**4,841**	**6,603**	**-**	**32,550**
Net increase/ decrease in cash and cash equivalents	**(910)**	**1,881**	**(778)**	**(709)**	**(516)**	**4,910**	**(5,549)**	**2,736**	**(1,540)**	**557**	**(2,332)**	**(14,174)**	**12,948**
Effect of exchange rate	9	1	-	(4)	6	(16)	(5)	9	-	(12)	-	-	-
Cash and cash equivalents, beginning of period	2,272	1,371	3,253	2,475	2,272	1,762	6,656	1,102	3,847	1,762	2,307	(25)	(14,199)
Cash and cash equivalents, end of period	1,371	3,253	2,475	1,762	1,762	6,656	1,102	3,847	2,307	2,307	(25)	(14,199)	(1,251)

Source: Company Reports and Rodman & Renshaw estimates.

.

Public companies mentioned in this report:

AstraZeneca PLC (AZN; not rated)
Bristol-Myers Squibb Company (BMY; not rated)
Eli Lilly and Company (LLY; not rated)
GlaxoSmithKline plc (GSK; not rated)
Johnson & Johnson (JNJ; not rated)
MannKind Corporation (MNKD; not rated)
Merck & Co. Inc. (MRK; not rated)
Novartis AG (NVS; not rated)
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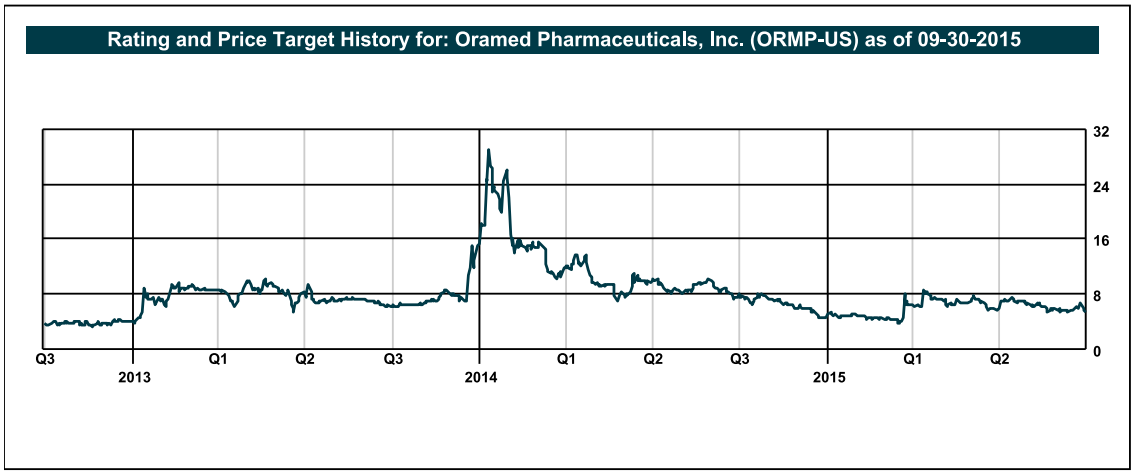

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