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Initiation of Coverage 2 30 December 2018

Company Overview

Oramed Pharmaceuticals Inc. (NASDAQ/TASE: ORMP) (hereinafter 'Oramed') is a biomedical company engaged in pharmaceutical research and development of a technology platform that enables oral delivery of proteins, that are currently only available by injection. The company's initial pipeline targets the diabetes care market, and its long-term pipeline is strategically guided by this foundation. The company advances two independent clinical programs that target the diabetes market: 1) ORMD-0801, an oral insulin product, which aims to disrupt the treatment paradigm for type 2 diabetes and decrease the number of insulin injections needed for type 1 diabetes, and 2) ORMD-0901-an oral GLP-1 receptor agonist, which better balances blood sugar.

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Oramed Pharmaceuticals Inc. is engaged in transforming injectable drugs into oral ones; company is progressing multiple clinical trials targeting diabetes and diabetes related indications; catalyst rich 2019 ahead; We maintain our target price of NIS 53.2.

Stock Exchange: TASE, NASDAQ

Symbol: ORMP

Sector: Healthcare

Sub-sector: Pharmaceuticals

Stock price target: NIS 53.2

As of 30 December 2018 (source: TASE website):

Closing Price: NIS 11.4

Market Cap: NIS **197.4M**

# of Shares: 17.4M

Stock Performance (since TASE IPO): -63%

Average Daily Trading Volume (since TASE IPO): NIS 103K

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Highlights

As of August 31, 2018 the company has cash, cash equivalents, short-term and long-term deposits and marketable securities of $46.8M, enough to promote its strategic plan into 2019.

Oramed's persistent and relatively successful focus on oral delivery for the diabetes drug market is a commercially promising strategy with the potential of clinical expansion into other segments in the future. By 2025, the diabetes market size is projected to be about $170 billion with a CAGR of 12.7% (2020 to 2025). Oral delivery is projected to comprise about one third of the market.

It is assumed that the company will continue licensing its platform to other companies looking to convert injectable drugs into orally ingestible alternatives, as it has done with Entera Bio Ltd. since 2010 and Hefei Tianhui Incubator of Technologies Co. Ltd (HTIT) in 2015.

- In April 2018, the company initiated a phase 2b clinical trial of ORMD-0801. Once the three-month Phase IIb dose-ranging clinical trial successfully meets its primary endpoints, the company anticipates initiating two six-month Phase III clinical trials on both type 1 and type 2 diabetic patients.
- In June 2018, Oramed initiated a glucose clamp study which will quantify insulin absorption in type 1 diabetic patients treated with ORMD-0801.
- In August 2017, the FDA advised that the regulatory pathway for the submission of ORMD-0801 would be a Biologics License Application (BLA). This would grant **12 years marketing exclusivity for ORMD-0801**, if and when approved.
- On September 17th, Oramed announced that the FDA has cleared its Investigational New Drug ("IND") application for human trials of its oral GLP-1 analog capsule, ORMD-0901. The Company plans to initiate a Phase 1 pharmacokinetic (PK) trial for ORMD-0901 in Q1 2019.
- On October 4th, the company enrolled the first patient in an exploratory clinical study of its oral insulin capsule, ORMD-0801, in the treatment of nonalcoholic steatohepatitis (NASH).

Financially, we updated our economic model as company has advanced its clinical programs and raised capital as reported in our previous analysis report, published on 24th July, 2018:

We increase our valuation of Oramed's equity at $244.7M / NIS 920M; Our target price estimation remains in a range between NIS 49.8 and NIS 56.6, a mean of NIS 53.2.

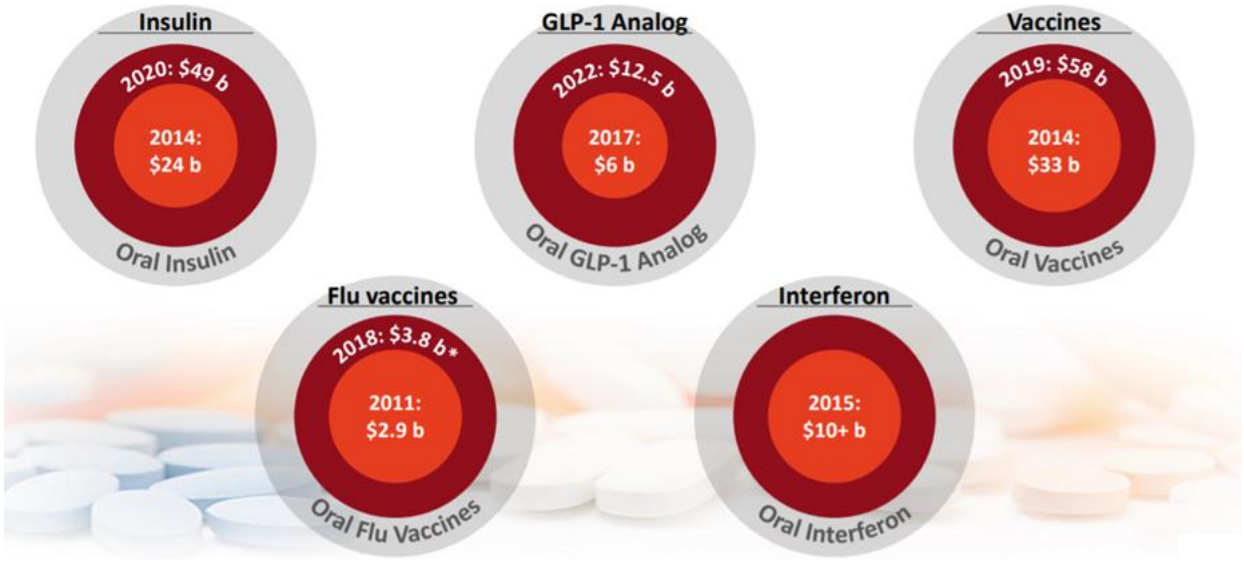
Upcoming Catalyst Roadmap

Drug Candidate	Indication	Catalyst	Timeline
ORMD-0801 (oral insulin)	Type 2 Diabetes	Completion of Phase IIb 90-day multi-center study	Q4 2019
	Type 1Diabetes	Completion of Clamp study	Q1 2019
		Food effect trial PK/PD completion	Q2 2019
	Nash	Completion of exploratory clinical study	Q1 2020
ORMD-0901 (oral GLP-1)	Type 2 Diabetes	Initiation of Pharmacokinetics clinical study	Q1 2019
		Completion of Pharmacokinetics clinical study	Q2 2019
		Phase II projected initiation	Q4 2019
Oral Leptin	Obesity	Initiation of P.O.C. study	2019
		Completion of P.O.C. study	Late 2019

Executive Summary

Investment Thesis

Oramed is an emerging player in the orally delivered therapeutics segment of the global diabetes care market. According to Frost & Sullivan, with a CAGR of 8.8% since 2016, this segment is estimated to reach a value of $42.3 billion by 2022. Insulin, and afterwards GLP-1, account for the overwhelming majority of the diabetes market. Oramed's core business is its oral platform which enables the promotion of numerous domains as we present below:



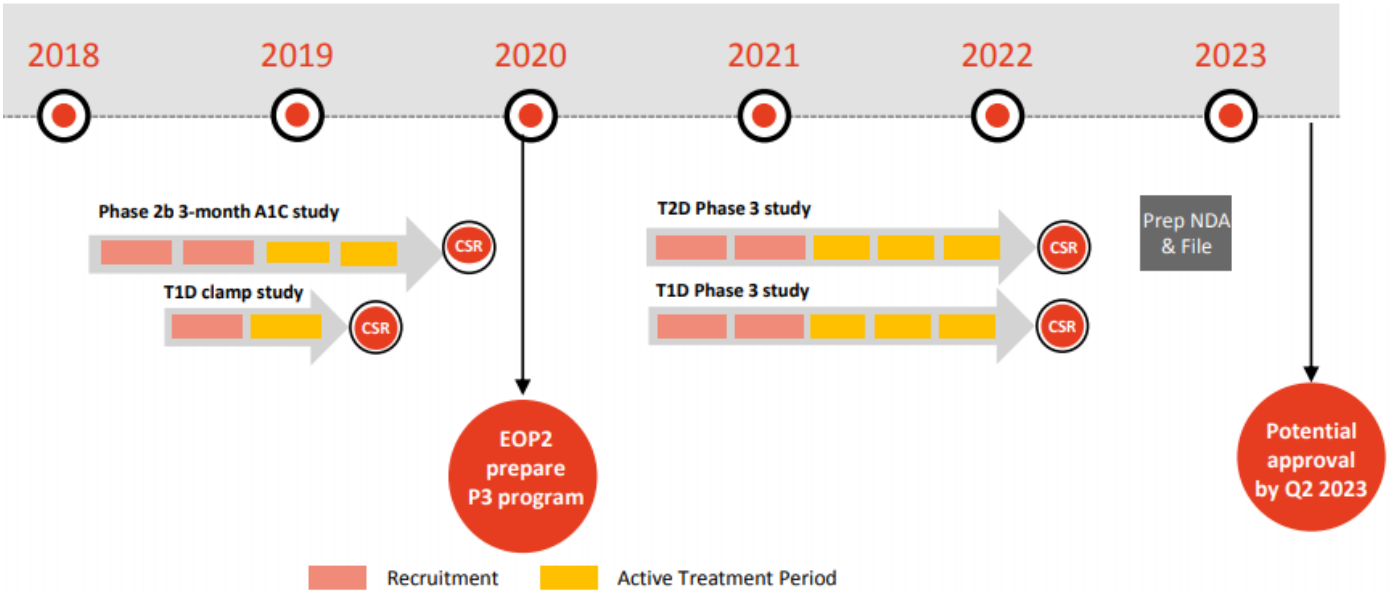
Source: Oramed investor presentation, November 2018

The current target market is very attractive financially, however, is rather competitive given the number of orally deliverable non-insulin solutions which are administered in conjunction with increasingly infrequent insulin injections. In July 2018, Oramed raised $18.1 and has as of August 31, 2018 cash, cash equivalents, deposits and investments totaling $46.8M that and can support the companies activities into 2019.

Oral insulin administration has an intrinsic physiological advantage in balancing blood sugar versus insulin given by injection. Oramed faces no current significant direct competitors in the oral Insulin market; nevertheless, should the big pharmaceutical players continue succeeding in developing injections which are efficiently administered at increasingly less frequent intervals, the added-value in terms of compliance to patients of oral insulin will decrease accordingly. Additionally, Oramed will be required to conduct a "market education campaign", targeting both patients and physicians when and if its products are approved for market. The probability of this campaign's success is undeterminable at this stage; however Oramed's comfortable cash position and 12-year market exclusivity will prove to be reliable assets in this pursuit.

Thus, we view the investment in Oramed as a great opportunity for investors to participate in the quest for a game changing delivery method, not only in the diabetes domain, but also in a number of other indications that lack easily administered orally delivered solutions. Pending successful completion of the company's clinical trial with ORMD-0801 (the company's oral insulin product), we believe that the stock's potential will significantly increase.

Anticipated Clinical Development Timeline of ORMD-0801



Source: Oramed Investors presentation, November 2018

Upcoming Potential Catalysts

Program	Indication	Event	Significance	Timeline	Status
ORMD-0801 (Oral Insulin)	Type 2 diabetes	Initiation of Phase IIb 90-day multi-center study	High	Q2 2018	Achieved
		Completion of Phase IIb 90-day multi-center study	High	Q4 2019	On track
		Initiation of Phase III trials	High	Q3 2020	On track
		Completion of Phase III trials	High	Q3 2022	On track
		FDA marketing approval	High	Late 2023	Expected
	Type 1 diabetes	Initiation of Clamp study	Low	Q2 2018	Achieved
		Completion of Clamp study	High	Q1 2019	On track
		Food effect trial PK/PD initiation	High	Q2 2018	Achieved
		Food effect trial PK/PD completion	High	Q2 2019	On Track
		Initiation of Phase III trials	High	Q3 2020	On track
		Completion of Phase III trials	High	Q3 2022	On track
		FDA marketing approval	High	Late 2023	Expected
	NASH	Initiation of exploratory clinical study	Low	Mid 2018	Achieved
		Completion of exploratory clinical study	Low	Q1 2020	On track
ORMD-0901 (Oral GLP-1)	Type 2 diabetes	Initiation of Pharmacokinetics clinical study	Low	Q1 2019	On track
		Completion of Pharmacokinetics clinical study	Low	Q2 2019	On track
		Phase II projected initiation	High	Q4 2019	On track
		Phase II projected completion	High	Q1 2020	On track
Oral Leptin	Obesity	Initiation of P.O.C. study	Low	2019	On track
		Completion of P.O.C. study	Low	Late 2019	On track

Financial Valuation and Projections

Annual financial analysis

Revenues are related to the license agreements that are recognized over the period from which the Company is entitled to the respective payments and through June 2023. Revenues for fiscal 2018 totaled $2,449,000, consistent with $2,456,000 for fiscal 2017.

Cost of revenues consists of royalties related to the license agreements that will be paid over the term of the agreements in accordance with revenue recognition accounting and the Law for the Encouragement of Industrial Research, Development and Technological Innovation, 1984, as amended, including any regulations or tracks promulgated thereunder, or the R&D Law. Cost of revenues for fiscal 2018 decreased to income of $86,000 compared to a cost of $187,000 in 2017. The decrease is attributed to a decrease from 3.5% to 3% in the royalties the company was obligated to pay the Israeli Innovation Authority (IIA) due to the amendment of the applicable regulations, and due to no additional milestone payments having been received during fiscal 2018, a percentage of which would have also gone to the IIA.

Research and development expenses for fiscal 2018 increased by 16.5% to $11,979,000 from $10,281,000 in fiscal 2017. The increase is mainly attributed to expenses related to the Phase IIb three-month dose-ranging clinical trial, the clamp study and the oral leptin development and is partially offset by a decrease in expenses related to toxicology studies and scaled-up process development and production of the Company's oral capsule ingredients. During fiscal 2018, stock-based compensation costs totaled $575,000, as compared to $1,134,000 during fiscal 2017. The decrease is mainly attributable to the progress in amortization of awards granted in prior periods and is partially offset by an increase due to awards granted to employees and a consultant during fiscal 2018 and 2017.

General and administrative expenses increased by 48% from $2,759,000 for fiscal 2017 to $4,083,000 for fiscal 2018. The increase is mainly attributable to an increase in stock-based compensation costs and expenses related to the relocation of the Chief Executive Officer to New York, where the Company leases an office and has its principal executive office. During fiscal 2018, as part of the general and administrative expenses, the Company incurred $972,000 related to stock-based compensation costs, as compared to $440,000 during fiscal 2017. The increase is mainly attributable to awards granted to employees and directors during fiscal 2018 and 2017.

Operating activities amounted to $14,657,000 in fiscal 2018 compared to $5,831,000 used in fiscal 2017. Cash used in operating activities in fiscal 2018 resulted in a net loss and consisted of research and development and general and administrative expenses and changes in deferred revenues, while cash used by operating activities in fiscal 2017 resulted in a net loss and primarily consisted of research and development and general and administrative expenses, partially offset by changes in stock-based compensation expenses and deferred revenues.

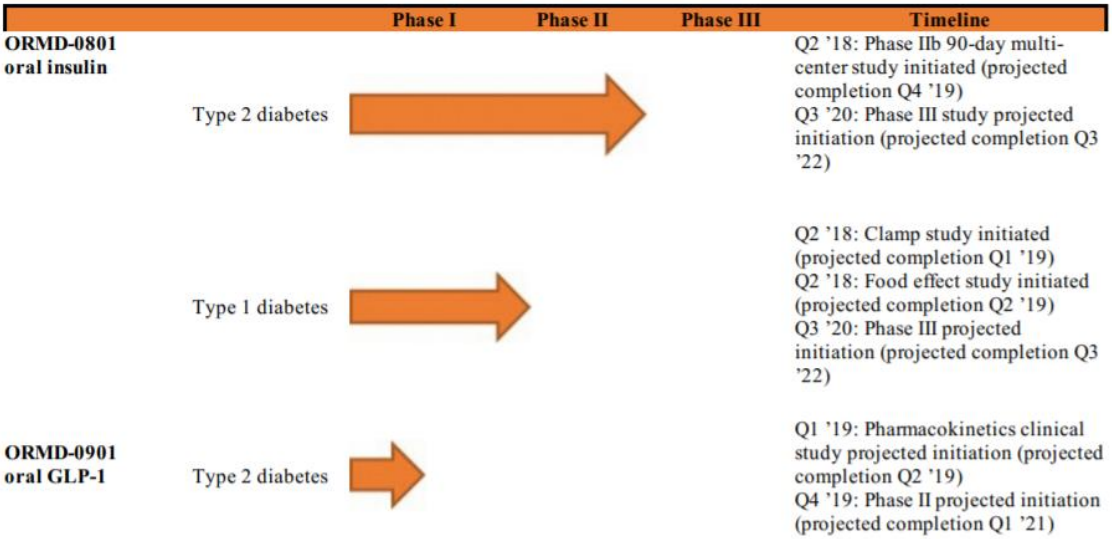
Cash, cash equivalents, short-term and long-term deposits and marketable securities as of August 31, 2018 total $46,790,000.

To summarize, the company has financial stability. We assume no additional funds will be needed into 2019 to further support clinical and regulatory development.

Valuation Summary

We published our full valuation 12 months ago on **December 23, 2017** (for more information refer to it). We examine each program's scientific, regulatory and financial aspects:

- Clinical/regulatory progress: The company completed phase 2b clinical trials for ORMD-0801, its oral insulin product for type 2 diabetes mellitus (T2DM), in 2016, and faces an additional 2b 90-day HbA1c (glycated hemoglobin) study. Phase 3 clinical trials are planned for Q3 of 2020. We adopt the company's clinical and regulatory forecast. For type 1 diabetes mellitus T1DM, it completed phase 2a in 2014 and intends to initiate phase 3 clinical trials in Q3 of 2020 as well. An additional product the company is looking to develop is a combination of both the oral insulin capsule ORMD-801 and the oral GLP-1 ORMD-0901.



Source: Company data, Annual report 2018

- R&D costs: We extrapolate phase 3 R&D costs based on phase 2 costs. We therefore assume $14 million in R&D costs for the phase 3 trials of ORMD-0801.

- Market size: Oramed is positioning ORMD-0801 to target early treatment of type 2 diabetes patients that are not taking insulin injections. We estimate that the potential market for this treatment is comprised of newly diagnosed T2DM patients (during the first 3 years from diagnosis), either already using nighttime insulin injections or taking oral medications. In the US, each year approximately 2 million people are diagnosed with T2DM, and in the rest of the world (ROW) that number is 27 million. We based our assumption on our market analysis presented below.

- Patent period: based on the company's data and with no additional extension, we assume the patent period to hold until 2035.

- Out-licensing agreements: We use Oramed's recent deal with HTIT in China. Oramed out licensed exclusive rights to ORMD-0801 in greater China in exchange for a $50 million payment ($38 out of the $50 million in milestone payments of which Oramed has so far received $18 million and the remaining $12 out of the $50 million as an investment in Oramed shares) as well as up to 10% royalties. We can extrapolate the value of future deals from these numbers.

- Success rates – the company engages in a high-risk therapeutic area. Success rate data indicates higher success rates for metabolic indications (45%), which Oramed's drug candidates target, in comparison with the total average of all indications (31%) from phase II to phase III. Also, the phase III success rate is higher (71%) than the success rate for all indications (58%) for this category. We address these clinical risks in our rNPV valuation for each indication.

- Capitalization rate: We calculate our discount rate at 19.64% based on our CAPM model.

Main valuation parameters

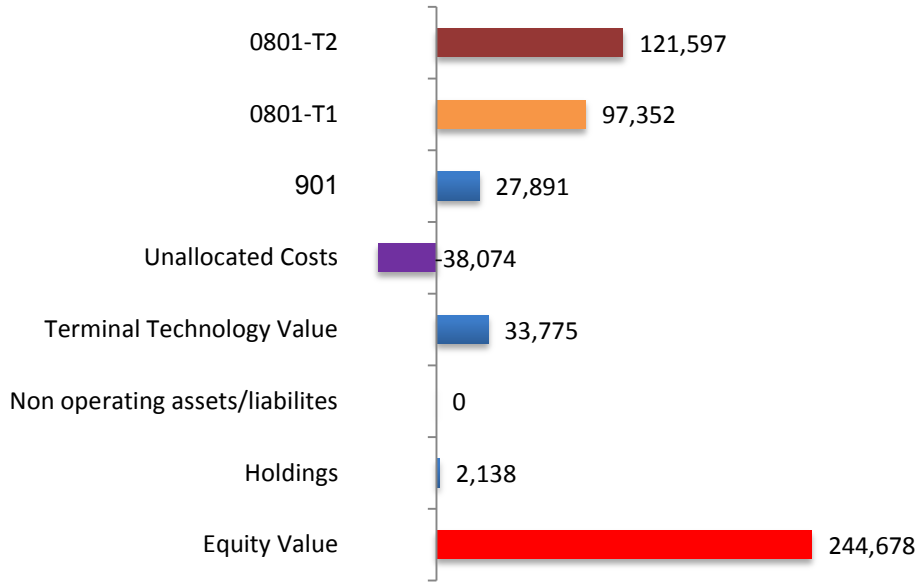
Indications	Current Development stage	Success Rate Phase II	Success Rate Phase III	Regulatory approval success rate	Launch	Patent period
ORMD-0801 T2DM	2b	100%	71%	86%	2024	2035
ORMD-0801 T1DM	2a	100%	71%	86%	2024	2035
ORMD-0901	2	45%	71%	86%	2024	2035

Equity Value

Non-operational assets/liabilities and unallocated costs

As of August 31, 2018 the company has cash, cash equivalents, short-term and long-term deposits and marketable securities of $46.8M. The company has no loans. Oramed has 6.92% holdings in DNA Biomedical Solutions Ltd (TASE: DNA). We evaluate the fair value of DNA Biomedical at $30.9M as of December 2017. Frost and Sullivan's initiation analysis report on DNA can be found here. Thus, Oramed's holdings are valued at $2.1M.

The equity valuation elements are presented in the table below:



Based on the aforementioned parameters, we value Oramed's equity at $244.7M / NIS920.0M.[1]

[1] Exchange rates, here and throughout this report are taken at Israeli market close on 23 December 2018.

Sensitivity Analysis

The table below presents Oramed's price target in relation to the capitalization rate and the market share ORMD-0801 will hold. This figure is based on our market research and specifically on our competitive analysis. We set a range of 0.5% change from our CAPM model and 0.5% change in our estimation of Oramed's market share estimated between 2% to 3.5%. Oramed has 17.4M shares.

Sensitivity Analysis - Capitalization Rate and market share of ORMD-0801 vs. Equity Value

Market share % Cap. Rate:	2%	2.5%	3.0%	3.5%
18.6%	52.6	56.3	60.1	63.8
19.1%	51.1	54.7	58.3	61.8
19.6%	**49.8**	**53.2**	**56.6**	60.0
20.1%	48.5	51.7	54.9	58.2
20.6%	47.3	50.3	53.4	56.5

We therefore estimate the target price to range between NIS 49.8 and NIS 56.6; a mean of NIS 53.2.

Valuation Methodology

The following is the methodology we used to arrive at the valuation above. R&D company valuations are challenging due to a non-cash valuation with a long time-to-market in most cases. Methods typically used for company valuations, such as asset valuation or multiplier methods, are incompatible with the valuation of R&D companies. In such companies, the current status of business cannot be analyzed by the capital in the balance sheet, and in most cases cannot be compared to similar companies due to their uniqueness, in both technological and financial aspects.

As part of a discounted cash flow (DCF), the accepted method used in financial valuations, there are several modifications to an R&D company's valuation. In general, there are three primary methods within the DCF method:

1. **Real Options** - valuation method designated for pre-clinical and early-stage clinical programs/companies where the assessment is binary during the initial phases, and based upon scientific-regulatory assessment only (binomial model with certain adjustments).
2. **Pipeline Assessment** - valuation method used for programs/companies prior to the market stage. The company's value is the total discounted cash flow plus unallocated costs and assessment of future technological basis. The assessment of the future technological basis is established based on the company's ability to "produce" new clinical and pre-clinical projects and their feed rate potential.
3. **DCF Valuation** - similar to companies not operating in the life sciences field, this method applies to companies with products that have a positive cash flow from operations.

Oramed's valuation was conducted under the "Pipeline Assessment" method, suitable for the developmental stages of the company's products. The company's valuation is calculated by examining the company as a holding company vis-à-vis existing projects, with risk-adjusted net present value (rNPV) capitalization to the net present value, including weighting of several scenarios. These primarily include analysis of the company's income, evaluated in accordance with scientific/technological assessment, based on various sources and estimates relating to the market scope, the degree of projected market success, and regulatory risk.

The weighted average of company revenue in the pharmaceutical and medical equipment market is based on the following data:

- Total Market - market potential for the product/product line

- Market Share – the company's ability to penetrate the market during the forecast period
- Peak Sales - peak sales of the company/product during the forecast period
- Annual Cost of Treatment – estimated annual cost per patient, based on updated market studies
- Success Rate - chances for success of clinical trials and transition to the next phase in the examined sub-field

Valuation of Oramed's "technological basis" is, in fact, a valuation of the company's "residual value". This valuation was conducted using the "Feed Rate" methodology that is common in the life sciences field, rather than using the conventional terminal value, normally used by non life science companies.

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Company Structure

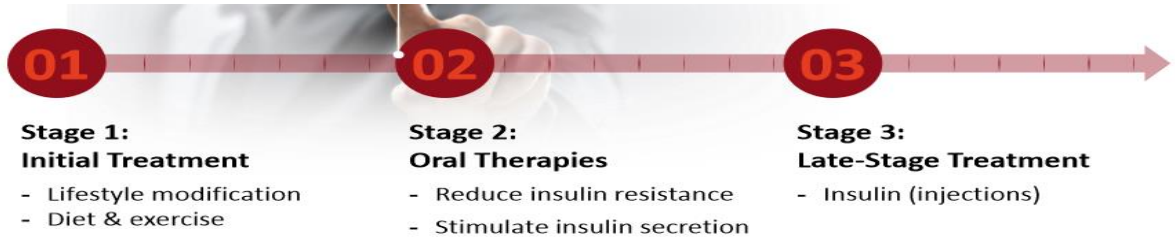
Oramed stock is traded both on the NASDAQ and on the Tel Aviv Stock Exchange (TASE). Oramed has a <2% holding in Entera Bio Ltd, which continues to use Oramed's oral drug delivery platform. Entera is a subsidiary of DNA Biomedical Solutions (TASE: DNA), which co-founded Entera along with Oramed. Oramed has a ~ 7% holding in DNA Biomedical Solutions. In July 2015, Oramed signed a $50,000,000 deal with Hefei Tianhui Incubator of Technologies Co. Ltd. granting the latter an exclusive commercialization license for ORMD-0801 in China, Macau and Hong Kong, conditional upon up to 10% royalties being paid to Oramed. Hefei Tianhui Incubator of Technologies Co. Ltd. acquired 1,155,367 shares in Oramed, translating, at the time, to a roughly 10% stake in the company.[2]

Holdings of Oramed	
Company	***Holding***
Oramed Ltd. (Israeli subsidiary)	100%[3]
D.N.A. Biomedical Solutions Ltd. (TASE: DNA) *	6.92%[4]

Company Overview

Oramed Pharmaceuticals Inc. (NASDAQ/TASE: ORMP) (hereinafter 'Oramed') is a US biomedical company engaged in pharmaceutical development of an oral capsule containing protein and peptide molecules, that are currently only delivered by injection. To do this Oramed uses a patented oral delivery system called POD™ (Protein Oral Delivery) in which an enteric-coated capsule protects the drug (protein or peptide) during transit through the stomach and releases the drug in the small intestine. Further adjuvants (registered pharmacopoeial or GRAS substances) protect the drug from degradation and also enhance its absorption across the intestinal wall[5]. The company's mission is to utilize their proprietary oral drug delivery technology, which is based on over 30 years of research, to address gaps in orally delivered therapeutics. Its initial pipeline targets the diabetes care market and their long-term pipeline is strategically guided by this foundation. Worth mentioning that Oramed has a strong, long term vision for transforming the way diabetes is managed by offering its products at a very early stage as a means for slowing down or even stopping the deterioration altogether.

Oramed's target in the broadest sense is the injectable drug market. However, its **underlying designation is to disrupt the therapy segment of the diabetes care paradigm** by offering oral-based drugs to type 1 diabetics (hereinafter 'T1DM') patients, type 2 diabetics (hereinafter 'T2DM') patients, and pre diabetics alike. The standard of care for T2DM includes injectable drug delivery systems for both non-insulin and insulin drug classes. Oral medications (non-insulin) are usually first-line therapies due to their ease of use and patient compliance (metformin is the first medication prescribed for type 2 diabetes), but eventually, the disease will progress in all patients, leading to daily insulin injections, as can be seen in the figure below.



[2] http://www.oramed.com/sinopharm-capital-hefei-signs-letter-of-intent-with-oramed-for-50000000-investment-and-licensing-deal-in-china-2/
[3] Oramed Inc. Consolidated Financial Statements for the year ending 31 August 2017.
[4] https://www.tase.co.il/Eng/General/Company/Pages/companyDetails.aspx?subDataType=0&companyID=001435&shareID=01103852
[5] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4455450/

Source: Oramed presentation, November 2018

Injections are notorious for poor patient compliance due to difficulty in patient self-administration, pain after administration and inconvenience. Injections are consequently also unpopular at the point-of-care, particularly so in the case of diabetes, which is a chronic (life-long) disease often requiring treatments to be administered a number of times per day. These conditions demonstrate the potential for Oramed's pipeline to reach exceptional turnover rates in the long-term.

Accordingly, the company's pipeline consists of the orally delivered drug candidates: 1) **ORMD-0801** - an oral insulin product for T2DM (Phase 2b), which aims to offer a new platform for management of diabetic treatment, and to be given prior to initiation of insulin injections. Additionally, this product is intended for the treatment of T1DM (Phase 2a completed), as a complementary agent to insulin injections, given before each meal (bolus insulin doses). This could potentially decrease the number of insulin injections for type 1 diabetes patients. 2) **ORMD-0901** - an oral GLP-1 receptor agonist product for T2DM (Phase 1 completed), which is intended to increase physiological insulin secretion.

The company's long-term pipeline includes plans to expand into oral replacements for other injectable treatments such as vaccines and flu shots and it is furthermore assumed that the company will continue licensing its platform to other companies looking to convert injectable drugs into orally ingestible alternatives.[6]

The company's most advanced product (ORMD-0801 for T2DM) completed a Phase 2b clinical trial in 2016. In September 2017, the FDA advised that the regulatory pathway for submission of ORMD-0801 would be a Biologics License Application (BLA) that will grant the company 12 years of marketing exclusivity for ORMD-0801, if approved, and an additional six months of exclusivity if the product also receives approval for use in pediatric patients. This will give the company a chance to educate physicians to prescribe an insulin drug at earlier stages of the condition, and ensure its reimbursement by insurers, thereby increasing the likelihood for Oramed to gain a significant share of the market.

In November 2018, the company announced that it achieved successful randomization of more than 50% of the expected 285 patients for its 90-day dose-ranging Pivotal Phase 2b clinical study testing ORMD-0801 that was initiated in April 2018 and is designed to generate meaningful data for both efficacy (HbA1c) and safety endpoints. Following, on September 17th, the FDA cleared its Investigational New Drug (IND) application for human trials of its oral GLP-1 analog capsule ORMD-0901.

Finally, Oramed's main market focus is in the US, which is likely to remain the market with the highest marginal revenue per patient due to its uniquely privatized healthcare system. Oramed's deal with Hefei Tianhui Incubator of Technologies Co. Ltd. has cemented its position in the Chinese market, widely considered the market with the most promising prospect of growth in diabetic care.

[6] Oramed Pharmaceuticals Inc. *Addressing the multi-billion dollar Injectable Drug Markets with Oral Formulations*. Corporate Presentation to Investors. June 2017. URL: http://www.oramed.com/investors/corporate-presentation/.

Market Overview

Oramed is developing treatments for diabetics (T1DM, T2DM, and pre-diabetic) and as such can be categorized as a competitor in the therapy segment of the diabetes care market. Therein, Oramed seeks to offer oral solutions for injectable insulin and GLP-1, with further products covering more indications in both its medium and long-term pipelines.

Oramed's platform for oral delivery of biological macromolecules consists of an oral capsule that facilitates effective oral administration and absorption of intact proteins through the gastrointestinal (GI) tract. The company's focus is on insulin, currently the best-selling injection on the market, and accordingly, that with the most lucrative potential in oral form.[7] Oral administration has many inherent advantages over injections, including a better safety profile, ease of administration, consequent improved compliance, slow release that may extend the duration of action, it is preferred by patients, and it is suitable for those sensitive to injections. Consequently, the treatment tends to be more receptive both among patients, and at the point-of-care. In general, the market potential for orally ingestible alternatives, for various indications, is lucrative.

Market Size

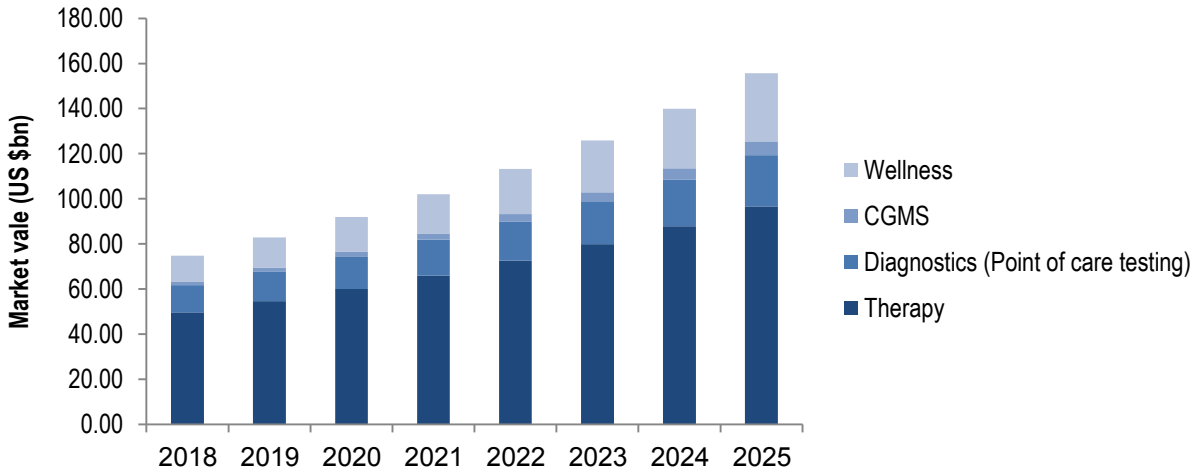
Diabetes affects hundreds of millions of patients worldwide, and this number is experiencing alarming growth, primarily due to increased public awareness and deterministic lifestyle factors. The diabetes care market will grow from $74.77 billion to $155.66 billion with a CAGR of 11.0% between the forecast period 2018-2025 (Frost and Sullivan analysis). Aside from medical segmentation into T1DM, T2DM, and pre-diabetic patients, the market can be further segmented by the sequential stages of treatment; therapies (such as insulin be it injectable, oral, transdermal or inhalable). Oramed competes in the therapy segment, which accounts for 66.34% of the entire diabetes care market in 2018. By 2025, Frost & Sullivan estimates this figure to contract to 62.10%, corresponding to a therapy segment value of $96.66 billion with a CAGR of 10% since 2018. The diagnosis (point-of-care testing such a glucose testing and Hb1Ac testing) segment value will increase from $12.10 billion in 2018 to $22.69 billion by 2025, with a CAGR of 9.4%. The Continuous Glucose Monitoring (CGM) segment value will increase from $1.37 billion to $6.12 billion between 2018-2025 with a CAGR of 23.9%, the segment market share will increase from 1.83% to 3.93% of the total diabetes care market during the same forecast period. The wellness (including interventions for pre-diabetics) segment value will increase from $11.7 billion to $30.19 billion between 2018-2025 with a CAGR of 14.5%. This segment's market share will increase from 15.65% to 19.39% during the same forecast period (Frost and Sullivan analysis).

Global Diabetes Mellitus Market Value by Segment (amounts in billions of dollars)									
Diabetes Mellitus Care market segments	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**CAGR**
Therapy	49.60	54.56	60.02	66.02	72.62	79.88	87.87	96.66	10.0%
Diagnostics (Point of care testing)	12.10	13.24	14.48	15.84	17.33	18.96	20.74	22.69	9.4%
CGMS	1.37	1.69	2.10	2.60	3.22	3.99	4.94	6.12	23.9%
Wellness	11.70	13.40	15.34	17.57	20.11	23.03	26.37	30.19	14.5%
Total	**74.77**	**82.89**	**91.94**	**102.03**	**113.28**	**125.86**	**139.92**	**155.66**	**11.0%**
Growth rate	-	10.86%	10.92%	10.97%	11.03%	11.11%	11.17%	11.25%	

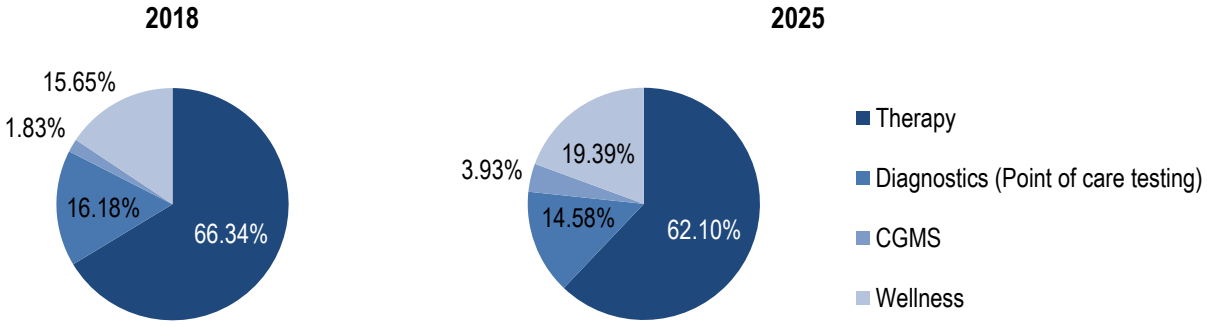
[7] Brown T: *100 Most Prescribed, Best-Selling Branded Drugs through September*. Medscape. 3 November, 2014. URL: https://www.medscape.com/viewarticle/834273.

Global Diabetes Mellitus market share by segment								
Diabetes Mellitus Care market segments	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**
Therapy	66.34%	65.82%	65.28%	64.71%	64.11%	63.47%	62.80%	62.10%
Diagnostics (Point of care testing)	16.18%	15.97%	15.75%	15.52%	15.30%	15.06%	14.82%	14.58%
CGMS	1.83%	2.04%	2.28%	2.55%	2.84%	3.17%	3.53%	3.93%
Wellness	15.65%	16.17%	16.68%	17.22%	17.75%	18.30%	18.85%	19.39%
Total	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**

Global Diabetes Mellitus care and Therapy, Diagnostics (point of care testing), Continuous Glucose Monitoring Testing (CGMS) and Wellness segment value (US $bn): Top panel; and market share (%): Bottom Panel: (Forecast period 2018-2025). Frost & Sullivan analysis



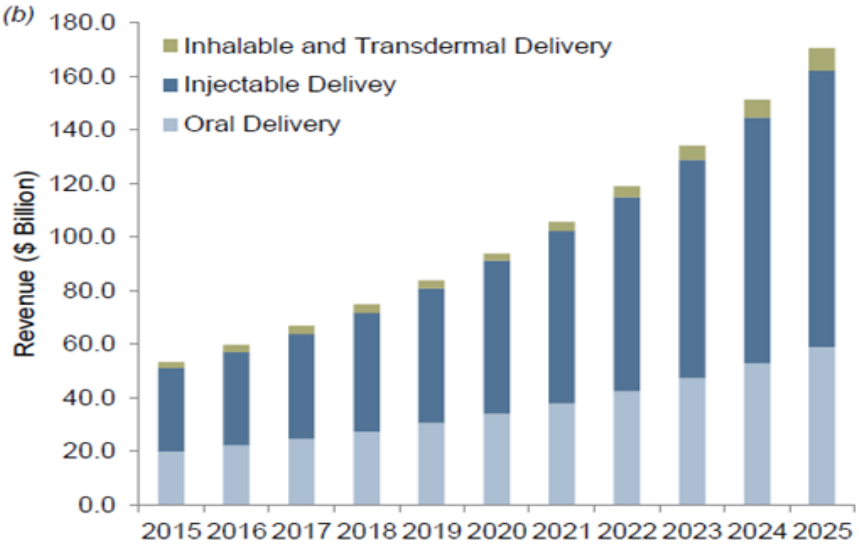
Global Diabetes Mellitus care revenue forecast by sub-segment (Therapy, Diagnostics (point of care testing), Continuous Glucose Monitoring Testing (CGMS) and Wellness, 2018-2025. CAGR 2018-2025, 11.0%. Frost & Sullivan analysis



Global Diabetes Mellitus care Market Share forecast by sub-segment (Therapy, Diagnostics (point of care testing), Continuous Glucose Monitoring Testing (CGMS) and Wellness, 2018-2025. CAGR 2018-2025, 11.0%. Frost & Sullivan analysis

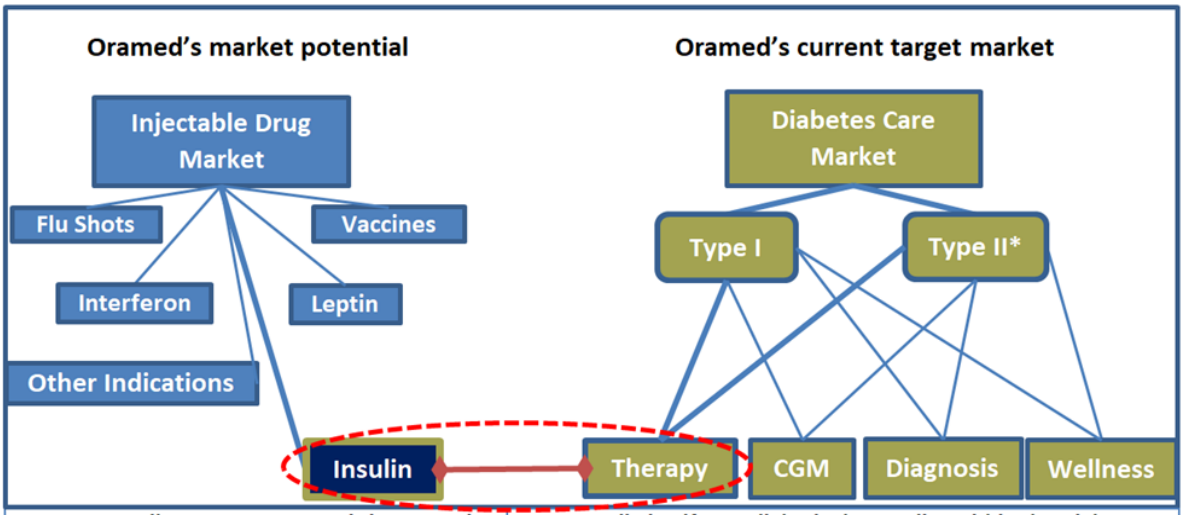
The chart below details Frost & Sullivan's forecasted growth for the Diabetes Drug Market segmented by mode of delivery.[8]

[8] Frost & Sullivan: *Next Generation Diabetes Therapy and Drug Delivery Technologies – Global Diabetes Epidemic Adds Urgency to R&D Initiatives, Inhalable and Transdermal Delivery on Upward Trajectory*. Global Transformational Health Research Team. March 2016.



The global insulin market comprises approximately 60% of the total diabetes drug delivery market. Insulin is currently available only in the form of injections (aside from a small inhalable segment), which are generally perceived as painful, causing patients with poor glycemic control to postpone taking insulin shots for up to seven years. It has been reported that 73% of T2DM diabetes patients delay insulin injection therapy, and of those, approximately 25% refuse insulin despite their physician's recommendation.[9] Accordingly, **pending Oramed's success in bringing orally deliverable insulin to market, insulin's share of the total diabetes drug market is, ceteris paribus, is expected to grow substantially.**

Market Structure



Market Strategy

As previously discussed, Oramed's insulin-focused strategy ideally positions the company to maximize its initial reach and revenues, and use these to expand into other endocrinological market segments, and then into other clinically associated market segments. This convergence between Oramed's short-term and long-term pipelines demonstrates

[9] Frost & Sullivan: *Analysis of the Global Diabetes Drug Delivery Market* (2015).

the great potential in the company's current R&D.[10] In addition, solutions for T2DM diabetics may have the potential to treat the pre-diabetic sub-segment, if proven efficient. Oramed also recently announced a drug candidate for weight management, an **oral leptin capsule**.[11] The alarming increase in obesity rates is a key driver of the increase in T2DM patients, who are far more numerous, and growing far more rapidly than those with T1DM diabetes. This drug candidate can be seen as a continuation of their diabetes R&D given the overlapping patient populations for obesity and diabetes. The table below detailing the potential revenues from Oramed's current and future pipelines asserts the strategic soundness of the company's approach.[12]

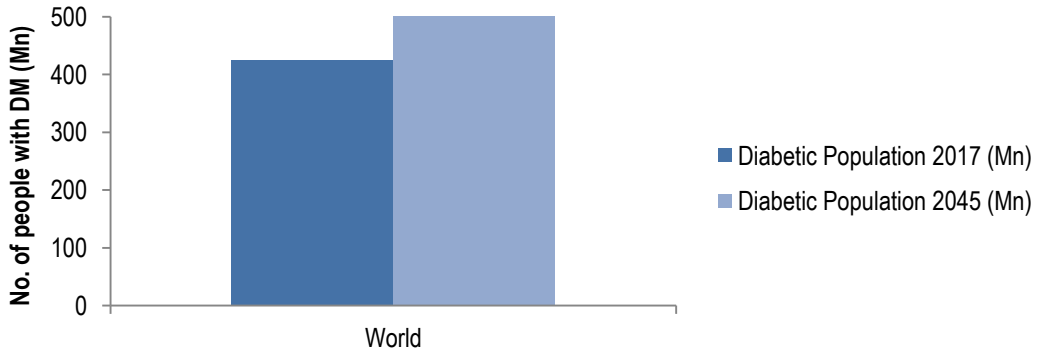
Market for current pipeline	Value (base year)	FV (year)	CAGR
Insulin	$35.1 billion (2017)	$68.92 billion (2025)	8.8%
GLP-1 Analog	$5.24 billion (2018)	$14.2 billion (2025)	13.3%[13]
Anti-obesity drugs (Leptin)	$1.1 billion (2016)[13]	$24.1 billion (2027)[14]	32.4%

Table: Value of drug market segments for Oramed expansion

Market Profile

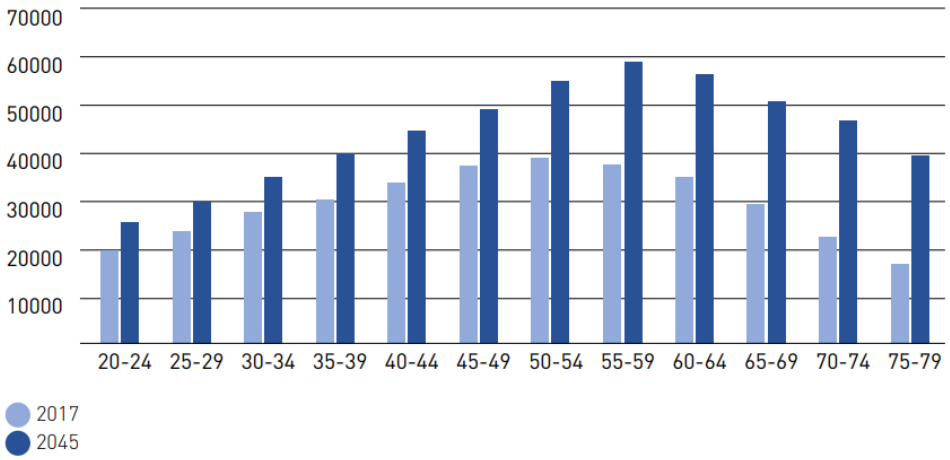
Demographic:

Diabetes in all forms is now affecting more than 425 million people in 2017 and is predicted to affect 629 million by 2045. Simultaneously, a further 352 million patients with impaired glucose tolerance are at high risk of developing diabetes mellitus. Approximately, 49% of potential diabetes mellitus cases are undiagnosed. By the end of 2017 the number of deaths associated with diabetes mellitus complications was predicted at 5 million. T2DM accounts for 90% of all diabetes mellitus cases, which equates to 382.5 million patients. It is estimated that the number of people with impaired glucose tolerance (IGT) or pre-diabetes was 352.1 million in 2017 and is expected to increase to 587 million by 2045. In 2017, the number of diabetes mellitus patients aged 65 years and over will increase from 98 million to 191 million (95% increase) by 2054. Moreover, the number of diabetes mellitus patients aged 65 years or under will increase from 327 million to 438 million (34% increase) during the same forecast period. The number of T1DM patients below the age of 20 has exceeded 1 million. It is predicted that by 2045 there will a 7% increase in the number of people with diabetes mellitus living in rural areas, and a 70% increase in people with diabetes mellitus living in urban areas. (Diabetes Atlas 2017; International Diabetes Federation)



Graph: Number of people with DM in 2017 and 2045 (Image acquired from: Diabetes Atlas 2017; International Diabetes Federation)

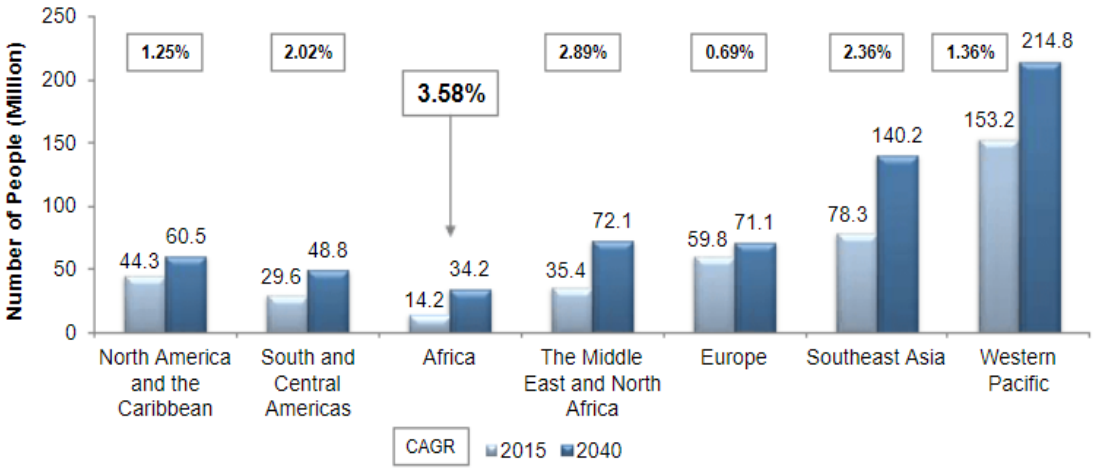
[10] Zeng, Grant: *Oramed Pharmaceuticals (NASDAQ: ORMP): Zacks Company Report*. Chicago, IL: Zacks Small-Cap Research. 10 July 2017. pp.2-3. URL: http://www.oramed.com/wp-content/uploads/2017/07/Zacks-update-July-2017.pdf.
[11] **Leptin** is a naturally produced protein in fat cells, which inhibits hunger and regulates energy expenditure.
[12] Oramed Pharmaceuticals. *Corporate Presentation to Investors* (2017) – Figures are from this source unless indicated otherwise.
[13] http://www.digitaljournal.com/pr/3968335
[14] Visiongain: *Global Anti-Obesity Drugs Market Forecast 2017-27*. PHA 0161. 12 January 2017. Available at URL: https://www.visiongain.com/Report/1772/Global-Anti-Obesity-Drugs-Market-Forecast-2017-2027.

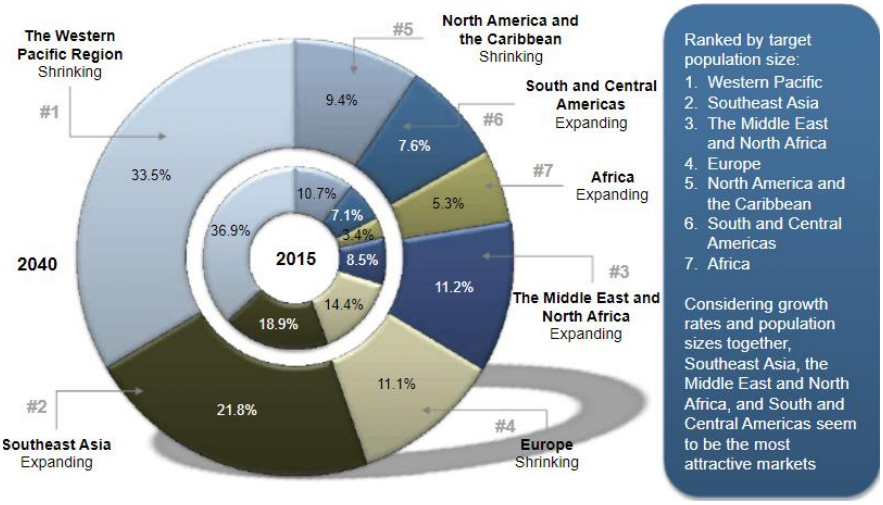


Graph: Number of people (in thousands) with impaired glucose tolerance (IGT), a pre-diabetic state, IGT by age group, 2017 and 2045 (Image acquired from: Diabetes Atlas 2017; International Diabetes Federation)

Economic analysis: The economic burden of the disease is extremely disproportionate (spending per capita). The increasing health burdens associated with diabetes mellitus such as premature mortality, disability due to complications, and lower quality of life, has impact on a socio economic scale. By the end of 2017, total diabetes mellitus global healthcare expenditure reached $727 billion for 20-79 year olds (an 8% growth from 2015) and represents 12% of all global spending on adults. This is projected to increase to $776 billion for 20-79 year olds and to almost $1 trillion, taking into consideration 18-99 year olds, by 2045. The two regions with the highest incidence of diabetes mellitus are the Western Pacific followed by Southeast Asia, but they are not the two regions with the highest diabetes mellitus healthcare expenditure. This title belongs to the U.S. and Europe.

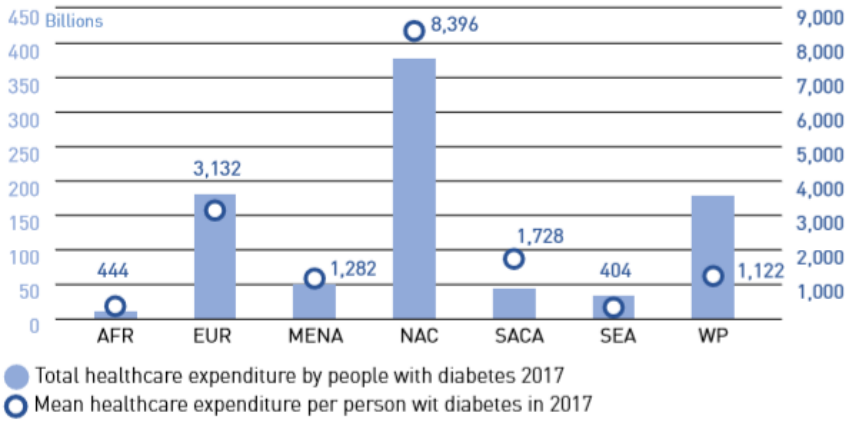
Ten countries account for 90% of total diabetes mellitus healthcare expenditure, with the US accounting for almost half this expenditure at a cost of $348 billion. The US is followed by China, Germany, and then India, which together only spend half of what the US does on diabetes mellitus. The countries with the highest yearly cost per person with diabetes are the US at $11,638, followed by Luxembourg and Monaco at $8,941, and $8,634, respectively. Eight of the top ten countries with the greatest diabetes expenditure per person are from Europe but these countries are not necessarily the ones with the greatest overall spending (IDF, annual report 2017, 8th edition). As can be seen in the figure below, the regions with the projected highest growth in diabetic population from 2015 to 2040 are primarily Africa and the Middle East and North Africa followed by Southeast Asia, South and Central Americas, Western Pacific, North America and the Caribbean, and Europe.





Total Diabetes Care Market: Estimated Diabetics (20–79 years) by Region, Global, 2015 and 2040 (Source: Frost and Sullivan 2017: Future of Diabetes Care Paradigms, Forecast to 2022)

The North American and Caribbean region has the highest diabetes expenditure of any region and accounted for about half of the total amount spent globally on diabetes in 2017. The region with the second highest diabetes expenditure is Europe with costs amounting to $181 billion, followed by the Western Pacific at 179 billion, which correspond to 23%, and 17%, respectively, of the total global spending. The other four regions spent significantly less on diabetes, despite being home to 27% of the cases, and were responsible for only 9% of the total spending.

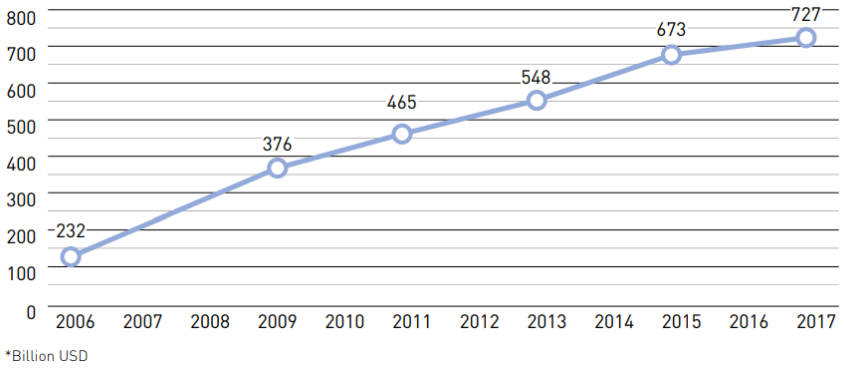


***Total healthcare expenditure on diabetes and mean expenditure per person with diabetes (ID) (20-79 years) in 2017 by IDF region (IDF, annual report 2017, 8th edition*)**

Diabetes imposes a large economic burden on the global health-care system and the wider global economy. This burden can be measured through direct medical costs, indirect costs associated with productivity loss, premature mortality, and the negative impact of diabetes on nations' gross domestic product. Direct medical costs associated with diabetes include expenditures for preventing and treating diabetes and its complications (emergency care, inpatient hospital care, medications and medical supplies etc.).

Oramed's parallel focus on the North American market is also a sound short-medium term strategy. In the long-term, **the US, Oramed's home market, is likely to remain that with the highest marginal revenue per patient due to its uniquely privatized healthcare system.** In November 2017, a joint study by *Clalit* Health Services and Israel's

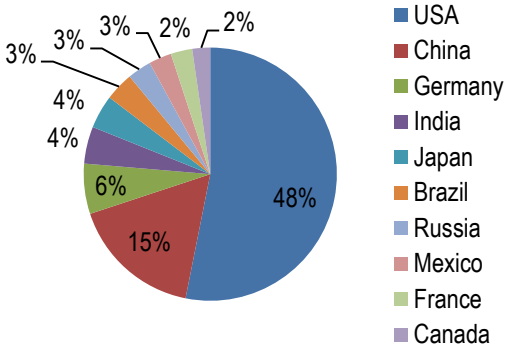
National Insurance Institute found the economic burden of Diabetes to total around NIS 8.5 billion ($2.45 billion) per annum. Considering Israel's relatively small population of 8.6 million, it can certainly be inferred that there is significant demand for innovative treatments in one of Oramed's target market.[15]



Graph: Total healthcare expenditure by people with diabetes (20-79 years). Image acquired from: Diabetes Atlas 2017; International Diabetes Federation

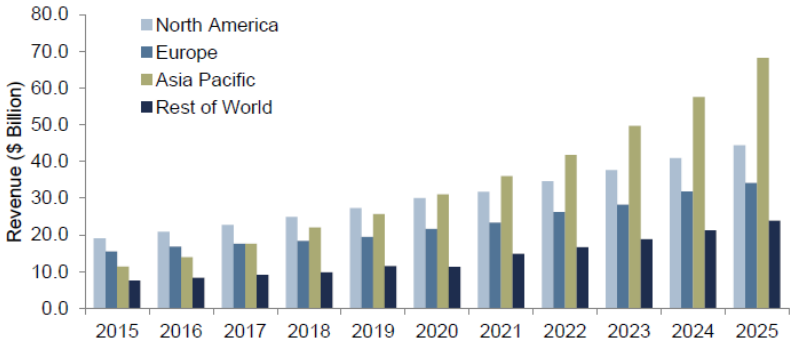
Country	diabetes mellitus expenditure ($bn)	% of total global diabetes mellitus expenditure
USA	348	48%
China	110	15%
Germany	42	6%
India	31	4%
Japan	28	4%
Brazil	24	3%
Russia	20	3%
Mexico	19	3%
France	18	2%
Canada	15	2%
Top 10	655	90%
Global	**727**	**100%**

Table: Top 10 countries for total healthcare expenditure in 2017 (20-79 years). Data acquired from Diabetes Atlas 2017; International Diabetes Federation)



Graph: Percentage Diabetes Mellitus expenditure per top 10 country of total diabetes mellitus expenditure ($bn) per top 10 countries. Data acquired from Diabetes Atlas 2017; International Diabetes Federation)

[15] http://www.jpost.com/HEALTH-SCIENCE/Study-huge-economic-cost-of-diabetes-NIS-85-billion-a-year-513564



Graph: Revenue in the diabetes drug market by region. Frost & Sullivan analysis

Every region of the globe is expected to see an increase in the number of people diagnosed with DM. The Western Pacific and South East Asia regions will continue to be diabetes mellitus hotspots up to 2045 reaching new heights of 183 million and 151 million patients, respectively. North Africa and the Middle East (MENA), Africa, and South East Asia will witness the highest increases in people diagnosed with Diabetes Mellitus between 20-79 years, with increases of 156%, 110% and 84%, respectively. However, in 2017 approximately 49% of the total diabetes population remains undiagnosed with Africa, South East Asia, and the Western Pacific showing the highest proportion of undiagnosed diabetes populations at 69%, 57% and 54%, respectively (IDF, annual report 2017, 8th edition).

Total Diabetes Care Market: Estimated Diabetic Population (Age 20-79 years)							
Region	Diabetic Population 2017 (Mn)	% undiagnosed 2017	Diabetic Population 2045 (Mn)	% increase 2017-2045	CAGR 2017-2045	Share of Global 2017	Share of Global 2045
North America & Caribbean	46	38%	62	35%	1.07%	11%	10%
South /Central America	26	40%	42	62%	1.73%	6%	7%
Africa	16	69%	41	156%	3.42%	4%	7%
MENA	39	49%	82	110%	2.69%	9%	13%
Europe	58	38%	67	16%	0.52%	14%	11%
South East Asia	82	57%	151	84%	2.20%	19%	24%
Western Pacific	159	54%	183	15%	0.50%	37%	29%
World	425	49%	629	48%	1.41%	100%	100%
Sources: Diabetes Atlas 2017; International Diabetes Federation; Frost & Sullivan							

Table*: *Number of people diagnosed and undiagnosed with DIABETES by region in 2017 and 2045 (Data acquired from: Diabetes Atlas 2017; International Diabetes Federation)

The Chinese Market

Oramed's focus on China is evident by its 2015 licensing deal with HTIT, which included $50M in payments ($38 out of the $50 million are milestone payments of which Oramed has so far received $18 million, and the remaining $12 out of the $50 million were an investment in Oramed shares) as well as up to 10% royalties on net sales. **The Chinese Oral Diabetic Drugs Market** constitutes a disproportionate share of the Asian Pacific segment. China has the largest number of diabetics in the world, and the condition has become a national epidemic. The country's diabetes market size is increasing rapidly year by year. It is predicted that the total market size will be close to $6.67 billion in 2022. As such, China will become a major battleground for any pharma company attempting to maintain a position in this space[16].

[16] *http://www.pharmexec.com/diabetes-market-china*

The Chinese Diabetic Population:

As of 2017, 114.4 million Chinese (8.2% of the country's population) have diabetes mellitus. Furthermore, there are an additional 48.6 million adults 20-79 years of age with impaired glucose tolerance who are at future risk of developing diabetes. It had a healthcare expenditure of $109.8 billion for diabetes (15% of global diabetes expenditure) in 2017 (IDF, annual report 2017, 8th edition). By 2040, China's diabetic population is expected to exceed 150 million. The incidence of the disease among children is also high, with about 30,500 Chinese children suffering from T1DM. China alone had 1.3 million deaths due to diabetes in 2015, with 40.8% of those deaths occurred in people under 60 years of age.

2017 and 2045 (projected)

2017			2045		
Rank	Country/territory	Number of people with diabetes	Rank	Country/ territory	Number of people with diabetes
1	China	114.4 million (104.1-146.3)	1	India	134.3 million (103.4-165.2)
2	India	72.9 million (55.5-90.2)	2	China	119.8 million (86.3-149.7)
3	United States	30.2 million (28.8-31.8)	3	United States	35.6million (33.9-37.9)
4	Brazil	12.5 million (11.4-13.5)	4	Mexico	21.8 million (11.0-26.2)
5	Mexico	12.0 million (6.0-14.3)	5	Brazil	20.3 million (18.6-22.1)
6	Indonesia	10.3 million (8.9-11.1)	6	Egypt	16.7million (9.0-19.1)
7	Russian Federation	8.5 million (6.7-11.0)	7	Indonesia	16.7million (14.6-18.2)
8	Egypt	8.2million (4.4-9.4)	8	Pakistan	16.1 million (11.5-23.2)
9	Germany	7.5 million (6.1-8.3)	9	Bangladesh	13.7 million (11.3-18.6)
10	Pakistan	7.5 million (5.3-10.9)	10	Turkey	11.2 million (10.1-13.3)

Table: Top ten countries/territories for number of people with diabetes (20-79 years), 2017 and 2045

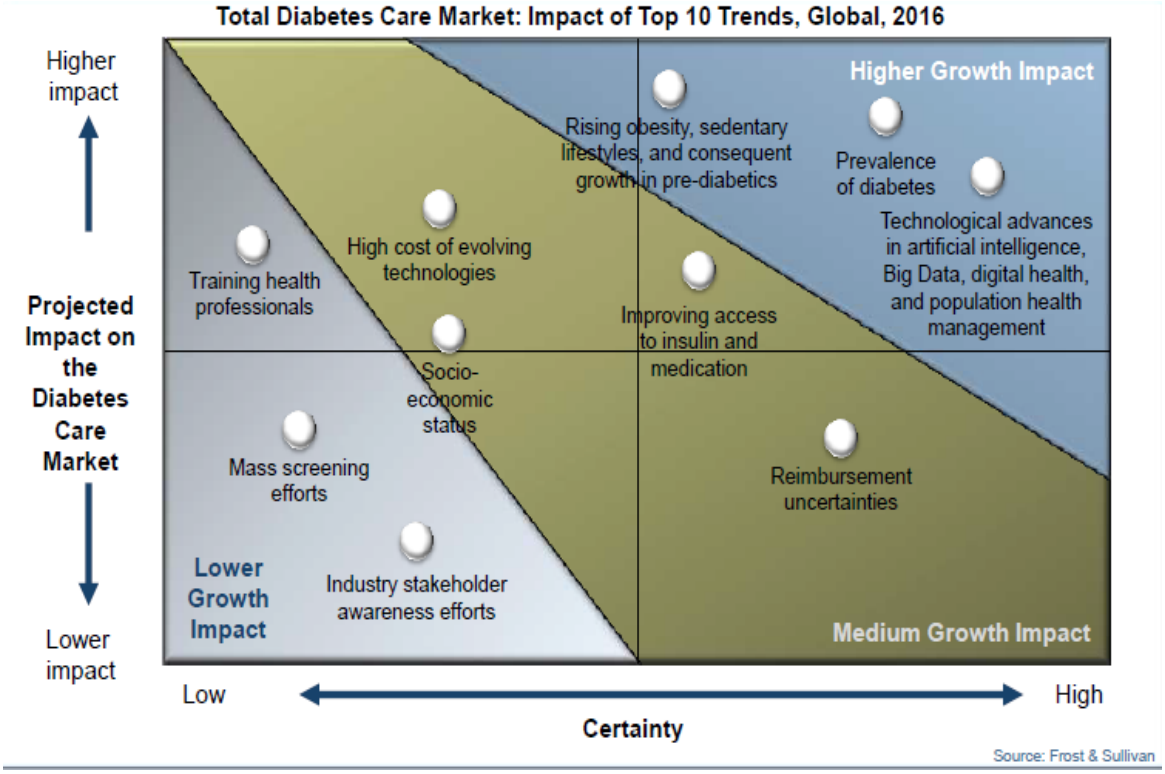
Contrary to the global market, insulin and oral hypoglycemic agents make up the majority of the Chinese diabetes market. So far, new drugs and local drugs have not gained much favor, however, the situation is changing. Patent expirations, the accelerated approval process for imported drugs, the entry of generic providers, and the medical insurance reform, are all leading to a new wave of diabetes medications that will change the market structure in China.

In 2017, the Chinese Ministry of Human Resources and Social Security published its newest version of the "National Basic Medical Insurance, Industrial Injury Insurance, and Maternity Insurance Drug List". Following the list, they released a notice to include an additional 36 kinds of medicines into the drug list. This will greatly impact the structure of the diabetes market in China, as the 36 new agents will now be covered by insurance companies.

Global Market Trends, Drivers, and Constraints

Trends:

Frost & Sullivan predicts the following trends will disrupt the diabetes care market in the foreseeable future. The graph places these trends on two axes. The horizontal parameter is likelihood, and the vertical parameter is the projected impact on the market. Accordingly, there are three areas of growth impact for the following top 10 trends (from left to right): low, medium, and high impact on growth.[17]



Market Drivers:

- **Rising prevalence of diabetes globally**
  - Rising awareness of the disease and the importance of treatment.
  - The diabetic population is growing fastest in APAC, Latin America and Africa.
  - Rising rates of causative factors such as; a sedentary lifestyle, sugar intake and obesity.
- **Both T1DM and T2DM diabetes are chronic illnesses, with no cure available.**
  - As such, both require lifelong monitoring and management, from the point of diagnosis until death, resulting in serious financial burden to patients.
- **If a diabetic therapeutic can prove itself effective in the long-term the reimbursement coverage is invariably generous.**
- Needle/prick phobia and religious reasons (against blood draws) are responsible for lack of adherence or even discontinuation of therapy, affecting long-term patient care and market growth.
  - Oramed and other companies in the oral diabetic drug delivery market can capture these patients should they succeed in bringing an oral solution to market.
- **Gaps in available treatments drive market demand for innovation**
  - Innovations in the diagnosis and monitoring segments of the diabetes care market will drive the therapy segment. More diagnoses mean more patients seeking treatment, and better glucose monitoring means fewer patients skipping dosages.

[17] Frost & Sullivan: *Future of Diabetes Care Paradigms, Forecast to 2022 – Innovations to Disrupt Diabetes Wellness, Diagnosis, Monitoring, and Therapy*. Global Transformational Health Research Team. March 2017

- New products with gradually improving adoption include: drug combinations, better delivery mechanisms, insulin pumps, and advancements such as the artificial pancreas.
    - The latter of these is only feasible in the long-term, thus opening a window of opportunity for the oral treatments sector in the short-medium term.

Constraints

- **The increase in the cost burden for consumers of drugs and insulin**
    - **The evolving reimbursement** landscape has resulted in higher deductibles, co-pays, premiums, and other out-of-pocket costs, which are likely to further increase costs for diabetics.
- **Competitive Pricing -** The presence of several participants in the market has resulted in competitive pricing.

DM Drug class	Name	2017, (USD)	2018, (USD)	% change
GLP-1	Tanzeum	$492.00	$553.48	12%
GLP-1	Adlyxin	$577.00	$623.96	8%
GLP-1	Trulicity	$641.00	$770.83	20%
GLP-1	Bydureon	$647.00	$697.71	8%
GLP-1	Byetta	$684.00	$748.05	9%
GLP-1	Victoza	$761.00	$917.19	21%
GLP-1	Saxenda	$1,186.00	$1,261.74	6%
Insulin	Novolin R/N/70-30 *	$24.00	$152.26	534%
Insulin	Humulin R	$100.00	$163.74	64%
Insulin	Basaglar	$227.00	$349.22	54%
Insulin	Lantus	$274.00	$289.90	6%
Insulin	Humulin N/70-30	$288.00	$163.74	-43%
Insulin	Humalog 50-50/75-25	$322.00	$305.73	-5%
Insulin	Toujeo	$347.00	$397.27	14%
Insulin	Afrezza	$352.00	$319.49	-9%
Insulin	Apidra	$400.00	$290.28	-27%
Insulin	Levemir	$409.00	$315.18	-23%
Insulin	Tresiba	$452.00	$514.51	14%
Insulin	Humalog	$529.00	$295.29	-44%
Insulin	Novolog/70-30	$538.00	$591.92	10%
Insulin	Soliqua 100/33	$656.00	$709.89	8%
**Price reduction due to pharma initiatives to subsidize cost of treatment*				

Table: % change in GLP-1 and Insulin drug prices (2017 to 2018). Source Evaluate pharma, Drugs.com.

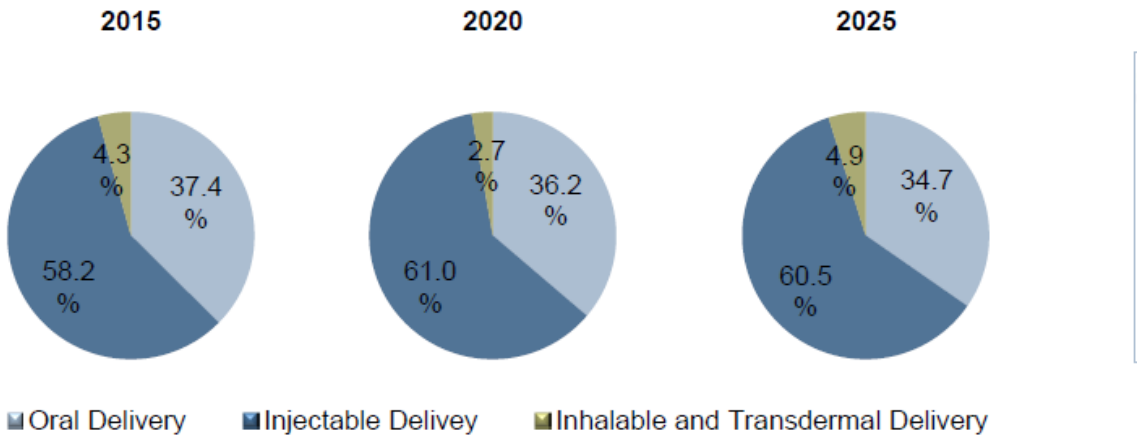
The entrance of companies such as Walmart and Amazon into the generics sector may prove a long term consolidator.

- **Diabetes is a condition which exhibits symptoms of differing extents in each patient; therefore no drug will be a "cookie cutter" solution.**
- **Rigid regulatory requirements**, given the chronic nature of the disease and the large number of patients → **delays time to market.**
- Despite the preference for oral medications over injections, **Frost & Sullivan and other leading firms forecast that injections will remain competitive**, and that the injectable segment will only begin to give up market share in eight years.[18]

[18] Frost & Sullivan: *Next Generation Diabetes Therapy and Drug Delivery Technologies.* March 2016.

- Oral delivery will thereafter compete with a declining injectable segment; however this will require an **extensive market education campaign** beforehand**.**
- **Injections are becoming far LESS invasive** and needles have been shortened in the latest injection pens. Furthermore, there are several needle free devices and more advanced insulin pumps that have recently gone to market.
- Consumers, already being averse to the currently inconclusive efficacy of oral solutions, may be immune to market education campaigns, and prefer trusted injectable solutions as the gold standard for treatment, especially given their decreasing invasiveness.

Diabetes Therapy and Drug Delivery, Market Forecast, Global, 2015–2025. Source: Frost & Sullivan



Graph: Drug delivery market forecast, Global, 2018-2025. Frost & Sullivan Analysis

Market Players

Oral insulin has been a dream of pharmaceutical companies for over a decade. **Large pharma multinationals such as Novo Nordisk and Merck** have been down this drug development path before, and their experience reveals a great deal about the market's conditions for current drug candidates such as those in Oramed's pipeline. At present, the competition in the diabetes market is fierce. Traditional insulin is still the most popular drug category and accounts for about half of the market. The rest is shared among GLP-1 receptor agonists (17%), DPP-4 inhibitors (21%), and SGLT2 inhibitors (6%), which are regarded as the rising stars. The current global diabetes market is mainly divided by four giant players, Novo Nordisk, Sanofi, Eli Lilly, and Merck. Combined, they account for about 72% of the market[19].

For decades, researchers have been trying to develop insulin and GLP-1 that can be taken orally, rather than by injection. However, insulin is a very large protein and because of its size the digestive system treats it like other proteins, attempting to degrade it into smaller components (amino acids) before being absorbed into the bloodstream.

There is a trend in the market to shift away from the highly competitive and increasingly smaller insulin business to less mature and growing segments of the diabetes market such as oral therapeutics[20]. In February 2018, Novo Nordisk announced positive Phase III trial results for its oral version of semaglutide, a GLP-1 based treatment for type 2 diabetes. This could potentially be the first oral GLP-1 treatment on the market. The oral version of semaglutide could make the treatment even more accessible to patients. The Phase III results show that 80% of

[19] http://www.pharmexec.com/diabetes-market-china
[20] https://www.thepharmaletter.com/article/8-10-years-ahead-of-field-in-oral-delivery-senior-execs-say-novo-nordisk-is-becoming-a-glp-1-company

patients receiving the highest dose had low long-term blood sugar levels, compared to only 34% of patients treated with a placebo. Semaglutide's GLP-1 mechanism of action may be more effective, since its double action of increasing insulin and decreasing glucagon could result in a more widespread lowering of blood sugar levels[21]. Furthermore, Novo Nordisk hopes to leverage promising weight loss data in order to also market the drug as an obesity therapy, which could be a game changer for diabetic patients.[38]

In September 2018, Chugai Pharmaceutical Co. Ltd. and Eli Lilly and Company announced a license agreement for OWL833, Chugai's oral non-peptide GLP-1 receptor agonist. OWL833 is a Phase 1-ready asset that is being studied for the treatment of type 2 diabetes. Under the terms of the agreement, Lilly will receive worldwide development and commercialization rights to OWL833. Chugai will receive an upfront payment of $50 million and is eligible for milestone payments based on achievement of certain predetermined milestones. If the molecule is successfully commercialized, Chugai will also be eligible for royalty payments. [22]

Despite Novo Nordisk terminating its program to bring the first oral insulin to market in October 2016, the company presented preliminary data in June 2017, which showed the formulation, O1338GT, to be as effective as Sanofi's insulin injectable Lantus in controlling blood glucose levels. However, there are still reservations from big pharma to advance the drug further mainly due to unfavorable economics and feasibility of investment required to make an oral version an alternative to the cheaper injectable form, coupled with a negative climate around highly priced insulin, and federal pressure to curb high drug prices.[23]

Emerging R&D studies are demonstrating novel ways in which oral insulin can reduce blood glucose levels by overcoming the natural barrier to entry of the gastro intestinal tract. Chlorine and geranate (CAGE) ionic liquid has been shown to be effective in reducing blood glucose levels in vivo by protecting insulin from enzymatic degradation in rats and demonstrates exceptional pharmacokinetic and pharmacodynamic outcomes.[24] CAGE has already proven itself to be efficient for delivering antibiotics and insulin through skin. It is considered ideal for oral insulin delivery because it can protect insulin from enzyme degradation, reduce the viscosity of the mucus layer on the intestine thereby improving how insulin permeates across it, and it can pass through the tight junctions of the intestinal wall.[25]

[21] https://labiotech.eu/medical/oral-glp-1-diabetes-treatment

[22] https://www.businesswire.com/news/home/20180926005486/en/Chugai-Lilly-Enter-License-Agreement-Oral-GLP-1.

[23] https://pharmaphorum.com/news/oral-insulin-still-reality-says-novo-nordisk/.

[24] https://www.empr.com/news/oral-insulin-choline-geranate-cage-ionic-liquid-reduced-blood-glucose-levels/article/778429/.

[25] https://physicsworld.com/a/ionic-liquid-formulation-makes-oral-insulin-pill/.

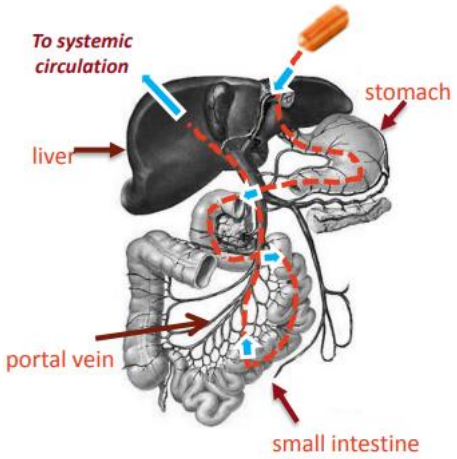
The top ten pharmaceutical companies in diabetic treatment and revenues[26].

Product

Oramed's unique proprietary platform technology is a drug carrier capsule that can be applied to an array of proteins and peptides. The company addresses macromolecule drugs presently administered only via injection. It has shown feasibility for several proteins. Oramed's initial development effort aims to create an oral formulation to treat diabetes, not only as a first indication, but also as a foundational basis from which the platform can be fully leveraged in the field. Its carrier platform consists of two key product features, the first being a molecular protection system preventing drug breakdown of the therapeutic drug delivered into the gut, and the second component facilitating large molecular transfers through intestinal barriers.

The first two products in the company's pipeline, human insulin hormone and a GLP-1 analog, both target T2DM. Additionally, the first of these also targets T1DM. Both products are based on the formulation of the carrier capsule.

Diabetes is a metabolic disease in which the body's inability to produce enough insulin causes elevated levels of glucose in the blood. In Type 1 diabetes, the body destroys its own beta cells which results in a complete dependence on external sources of insulin. In type 2 diabetes, the body becomes insulin resistant; in most cases insulin injections are the answer. Only a fraction of injected insulin, which is introduced directly to the bloodstream, reaches the liver. This can cause excess sugar to be stored in fat and muscle, which often results in weight gain, and may also cause hypoglycemia. On the contrary, oral insulin, like natural insulin, is delivered first to the liver, resulting in better blood glucose control, reduced hypoglycemia, reduced hyperglycemia, and reduced weight gain.



Other products in the pipeline include a combination therapy of the oral insulin capsule ORMD-0801 with ORMD 0901, oral GLP-1. This combination drug was already tested on animals, showing a synergistic effect of the two active agents. At present, Oramed is focusing its efforts on developing its flagship products oral insulin and oral GLP-1 separately. Once further progress is made, the company intends to conduct additional studies with the oral combination therapy.[27]

Additionally, the company began developing a new drug candidate during 2017, a weight loss treatment in the form of an oral leptin capsule. Leptin, also known as the "obesity hormone" is a naturally produced protein in fat cells, which inhibits hunger and regulates energy expenditure. Obesity patients are resistant to leptin because their bloodstreams usually exhibit higher levels of the protein. This mirrors the resistance of T2DM diabetics to insulin; indeed correlation has been found between the two. Furthermore, leptin has been shown to improve glucose levels in T1DM. Based on positive preclinical data, in May 2017 Oramed received regulatory approval to conduct a human proof-of-concept clinical study for a new oral leptin capsule from the Israeli Ministry of Health.[28] The single dose study, planned to commence during 2019, is intended to evaluate the capsule's pharmacokinetics and pharmacodynamics (glucagon reduction) in ten type 1 adult diabetic patients.

[26] https://www.igeahub.com/2018/05/19/top-10-pharmaceutical-companies-2018-diabetes/
[27] Oramed's annual report 2017
[28] JERUSALEM, May 2, 2017. PRNewswire

In November 2017, Oramed received approval from the Israeli ministry of health to initiate an exploratory clinical study of its oral insulin capsule ORMD-0801 in patients with nonalcoholic steatohepatitis (NASH).[29] This study is about to be initiated for a period of 3 months to assess the effectiveness of ORMD-0801 in reducing liver fat content, inflammation and fibrosis in patients with NASH. The approval is based on preclinical and clinical studies of ORMD-0801 in diabetics, which have revealed that the oral insulin capsule has the ability to reduce inflammation in the liver. Results from the study are expected in Q1 2019.

Regulation & Intellectual Property

Oramed has issued and pending patents in relevant jurisdictions with respect to various compositions, methods of production and oral administration of proteins and exenatide (GLP-1 agonist), including in the; American, Swiss, German, French, British, Italian, Dutch, Spanish, Australian, Israeli, Japanese, Russian, Canadian, Hong Kong, Chinese, European and Indian patent offices. Expiration dates for pending patents, if granted, will fall between 2026 and 2034.[30]

- On May 9th 2018, the Canadian Intellectual Property Office granted Oramed a patent titled, "Methods and Compositions for Oral Administration of Exenatide". The patent covers Oramed's invention of an oral glucagon-like peptide-1 (GLP-1) analog[31].
- On July 24th 2018, the Japanese Intellectual Property Office granted Oramed the same patent, also titled, “Methods and Compositions for Oral Administration of Exenatide.” The patent covers Oramed’s invention of an oral glucagon-like peptide-1 (GLP-1) analog[32].

From a regulatory point of view, in August 2017, the FDA advised that the regulatory pathway for submission of ORMD-0801 would be a Biologics License Application (BLA). Such a pathway would grant a full twelve years of marketing exclusivity for ORMD-0801 if approved. On top of this, an additional six months of exclusivity can be granted if the product also receives approval for use in pediatric patients.[33]

Regarding ORMD-0901, on September 17th 2018, Oramed announced that the U.S. Food and Drug Administration (FDA) has cleared its investigational New Drug (IND) application for human trials of its oral GLP-1 analog capsule[34]. The company’s planned phase 1 pharmacokinetic (PK) study is a fully-randomized, single-blind, placebo-controlled 4-way crossover study, which will evaluate safety in addition to the pharmacokinetics of ORMD-0901 compared to a placebo and to open label Byetta®, a GLP-1 analog currently on the market, in up to 15 healthy subjects. Upon its completion, they anticipate initiating a broader phase 2 study of ORMD-0901 in the U.S. in 2019.

ORMD-0801 Oral insulin capsule for Type 1 Diabetes (T1DM)

Oramed's approach to oral insulin delivery is via a carrier capsule that is digested. The integration of externally-administered insulin into the physiological glucose-insulin cycle better compensates for the lack of naturally occurring insulin on demand. Current methods of insulin administration for diabetes patients involve injections and/or continuous subcutaneous insulin infusion with an external pump. Insulin treatment of T1DM consists of fast-acting (bolus) insulin prior to each meal to stabilize blood sugar, and slow acting (basal) insulin, which helps to maintain stable insulin levels during fasting periods. Oramed’s oral insulin capsule is anticipated for use as a complementary agent to insulin injections in the treatment of T1DM, potentially eliminating the need for insulin before each meal (bolus insulin doses). This treatment regimen should allow for fewer daily injections and a lower frequency of blood glucose fluctuations.

[29] JERUSALEM, Nov. 14, 2017. PRNewswire
[30] Oramed’s annual report 2016
[31] https://www.prnewswire.com/news-releases/oramed-granted-canadian-patent-for-glp-1-analog-capsule-300454015.html
[32] https://www.oramed.com/oramed-granted-japanese-patent-for-glp-1-analog-capsule/
[33] http://www.oramed.com/oramed-announces-successful-meeting-with-fda-for-oral-insulin/
[34] https://www.oramed.com/oramed-receives-fda-clearance-for-ind-application-for-its-oral-glp-1-analog-capsule/

In 2014, the company conducted a phase 2a US FDA study under an IND for ORMD-0801 in 25 volunteers with T1DM. The double blind fully randomized study consisted of seven days of treatment with oral insulin given three times a day at mealtime. The results showed that ORMD-0801 appeared to be safe and well-tolerated for the dosing regimen in this study and that patients on ORMD-0801 successfully decreased their external (injected) insulin while simultaneously decreasing their blood glucose.

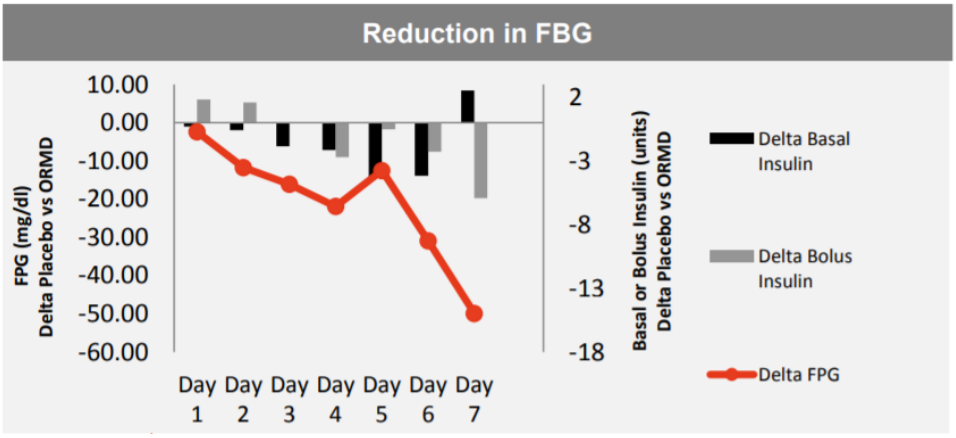


Figure: Phase IIa study, Reduction in FBG (fasting blood glucose) results in T1DM patients. Source: Oramed's corporate presentation.

ORMD-0801 Oral insulin capsule for Type 2 Diabetes (T2DM)

Oramed's approach to oral insulin treatment in T2DM patients with elevated fasting plasma glucose (FPG) levels focuses on night time dosing, prior to initiation of insulin injections. According to the company, the pharmacokinetic profile of its oral insulin capsule can optimally influence the excessive night time glucose production from the liver, which causes FPG elevation. If started early enough in the course of the disease (when patients have better pancreatic β-cell reserve), this approach may assist in controlling daytime glucose levels, reduce the strain on β-cells and potentially preserve their function, and may delay the requirement for injected insulin.

Clinical Data

Oramed completed a series of phase 1 and 2 clinical studies performed in Israel and the US. These studies evaluated the safety and efficacy of the company's oral insulin capsule, ORMD-0801, in healthy volunteers, as well as T1DM and T2DM diabetic patients.

In 2014 the company completed a double-blind, randomized phase 2a clinical trial in the US under an FDA IND, which evaluated the pharmacodynamic effects of ORMD-0801 on mean night time glucose in 30 volunteers with T2DM on diet alone, or diet and monotherapy with Metformin. The oral insulin capsule was administered at bed-time over a treatment period of 7 days. The results were determined using a Continuous Glucose Monitor (CGM), an FDA-approved device that provides continuous insight into glucose levels throughout the day and night. According to the company, the results exhibit a sound safety profile, as well as reduced mean day-time and night-time glucose readings, and lowered fasting blood glucose concentrations when compared to a placebo.

The company performed a double-blind, randomized phase 2b clinical trial in the US under an FDA IND. The trial included 180 T2DM patients treated over 28 days, and was completed in 2016. The trial was designed to assess the safety and efficacy of ORMD-0801. No serious drug related adverse events were observed. Its primary objective was to evaluate the effect of ORMD-0801 on mean night time glucose. The results indicate a statistically significant lowering of glucose relative to a placebo across several endpoints, including mean 24-hour glucose, fasting blood glucose, and day time glucose. In addition, a statistically significant change from baseline was observed in HbA1c

(glycated hemoglobin) levels, the most commonly used biomarker of glycemic control, which is also regularly used for monitoring the effectiveness of diabetes therapies. Nevertheless, the four week study is insufficient to fully appreciate the potential positive impact of ORMD-0801 on HbA1c. Therefore, a 90 day dose-ranging HbA1c clinical study is being performed. The benchmark for FDA approval stands at 0.5% HbA1c lowering.

The study consists of 285 subjects, among them approximately 265 with T2DM, and is performed over a 2-week, single-blind placebo run-in period followed by a 12-week treatment period. The total 12-week treatment period included a part 1 "dose escalation" interval and a part 2 stable dose "maintenance" interval. The stable dose interval is sufficient to allow for a robust assessment of treatment effect based on the mean change from baseline in HbA1C (A1C). The trial's primary endpoints are safety profile and HB1Ac over 90 days and its length is 18-24 months.

So far, ORMD-0801 appears to have a sound safety profile, which is expected given the use of human insulin as the active ingredient, a product already commonly used via injections. Pharmacokinetic and pharmacodynamic profiles have indicated bioavailability (absorption into the blood) of 5%, which is higher in comparison to the bioavailability shown by Novo Nordisk in its oral insulin capsule phase 2a results.

ORMD-0901 Oral GLP-1 analog capsule for Type 2 Diabetes (T2DM)

Oramed's oral GLP-1 capsule is based on exenatide, a GLP-1 receptor analog which mimics the natural hormone in the body, with longer-lived residence in the circulation versus native GLP-1, which is metabolized in less than 2 minutes. Exenatide induces insulin release at increased glucose levels and causes a feeling of satiety, which results in reduced food intake and weight loss. Exenatide does not cause hypoglycaemia and has a good safety profile, although it can cause minor side effects such as vomiting. Exenatide is currently marketed only in injectable form for the treatment of type 2 diabetes.

Clinical Data

Preclinical studies have suggested that ORMD-0901 can stabilize blood glucose levels, as it preserves the biological activity of exenatide via oral delivery.

Oramed's initial clinical trial in healthy volunteers and T2DM patients was conducted outside the US in 2016. In this study, subjects were separately administered either ORMD-0901 (150 µg exenatide) or a placebo. Findings suggested that ORMD-0901 is safe and well tolerated, and can stimulate insulin secretion.

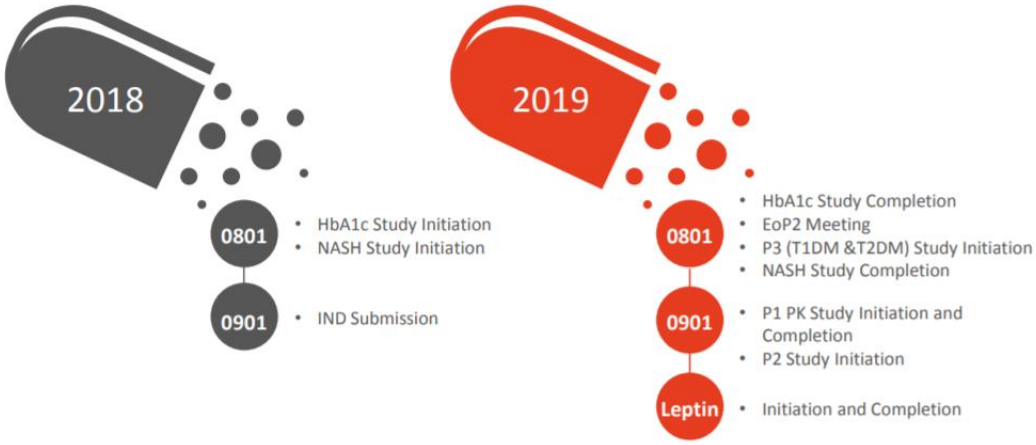
The company received clearance for its Investigational New Drug (IND) application for human trials of the oral GLP-1 analog capsule ORMD-0901[35]. The company is planning a phase 1 pharmacokinetic (PK) study that will evaluate safety in addition to the pharmacokinetics of ORMD-0901 compared to a placebo and to open label Byetta® in up to 15 healthy subjects. Upon its completion, a broader phase 2 study of ORMD-0901 will be performed in the US in 2019.

Non-Alcoholic Steatohepatitis (NASH)

Nonalcoholic steatohepatitis (NASH)[36] is the most severe form of non-alcoholic fatty liver disease (NAFLD), which is characterized by the presence of an abnormal accumulation of fat in the liver that can progress to liver cell injury and inflammation. Hepatocellular injury and inflammation – sometimes called necroinflammation – are commonly considered as the drivers of disease progression, or as the underlying causes of the disease. As NASH evolves, over time it can result in excessive scarring in the liver (fibrosis), a natural response to injury which can lead to liver cirrhosis or liver cancer.

[35] https://www.oramed.com/oramed-receives-fda-clearance-for-ind-application-for-its-oral-glp-1-analog-capsule/
[36] https://www.the-nash-education-program.com/what-is-nash/

Israel's Ministry of Health has granted the Company approval to initiate an exploratory clinical study of its oral insulin capsule ORMD-0801 in patients with nonalcoholic steatohepatitis (NASH). The proposed three-month treatment study will assess the effectiveness of ORMD-0801 in reducing liver fat content, inflammation and fibrosis in patients with NASH.



Anticipated development milestones; Oramed investor presentation, November 2018.

Competitive Analysis

T2DM

Both **ORMD-0801** oral insulin **and ORMD-0901** oral GLP-1 products are intended to be used for treatment after Metformin, as second and third line therapies. Both products target a disease stage prior to initiation of insulin injections, which involves mostly oral drugs**.** In type 2 diabetes patients, ORMD-0801 is not currently positioned to replace injected insulin, but to either postpone the initiation of insulin injections or to reduce the number of daily insulin injections required.

There are multiple therapeutic classes for this stage of the disease, and different classes can treat the same segment of patients according to their responsiveness. As such, most of the top ten diabetes players have portfolios of products consisting of several different therapeutic classes intended for the same stage of the disease, including; Novo Nordisk, Sanofi, Merck, Elli Lilly, Johnson & Johnson, Takeda, Bayer and others.

ORMD-0801 for T2DM

ORMD-0801 for T2DM is orally delivered insulin, given at bedtime to reduce the fasting blood glucose (FBG) levels, prior to initiation of insulin injections. Numerous branded and biosimilar **long acting insulin injection** products are available, differing in their duration of action. Sanofi's **Lantus** (glargine) is the most commonly prescribed long acting insulin based on its well established safety profile and extensive clinical experience. In 2016, its sales reached around $5 billion. The other biosimilar insulin injections such as **Tresiba** are perceived to be a better insulin with longer duration of action, less variability and lower risk of hypoglycemia, but are limited due to payer's pushback. ORMD-0801 is not anticipated to be comparable in potency to these drugs, but rather delay the use of insulin injections, or act as an add-on for insulin products of longer duration. Its competitive landscape includes direct and indirect competition as follows:

Direct competition to Oramed's ORMD-0801 includes oral insulin delivery technologies, most of which share the advantages of insulin absorption via the gastrointestinal tract.

- **Generex's Oral-lyn** was launched as a short-acting buccal insulin for the treatment of T1DM and T2DM. Oral-lyn is a liquid insulin formulation that is delivered using Generex's RapidMist oral drug delivery technology that facilitates the movement of large molecules across the inner lining of the mouth. Generex was unable to secure FDA approval of Oral-lyn or to market the product in the US. Oral-lyn is currently available in selected countries, including India, Ecuador, Lebanon, and Algeria.
- **Biocon's IN-105** (tregopil) is an oral tablet formulation of ultra rapid-acting insulin for the treatment of T2DM and T1DM, currently on a pivotal phase 3 trial under an IND in India for T2DM, and phase 2 for type one diabetes.
- **Diasome's oral insulin HDV** is a Hepatocyte-Directed Vesicle (HDV) insulin capsule for oral delivery, for the treatment of type 1 and type 2 diabetes, currently in Phase 2.
- **Diabetology's Capsulin IR** is an oral insulin delivered to those with T1DM and late-stage T2DM; currently in Phase 2.

Other than mentioned, Novo Nordisk is developing two additional tablets of long acting insulin analogues (NN1953 and NN1954), currently on phase I for T1DM and T2DM[37] [38].

On the 26th of April this year, Emisphere announced that it has amended its existing 2015 Development and License Agreement with Novo Nordisk for the development and commercialization of oral formulations of four classes of Novo Nordisk's investigational molecules targeting major metabolic disorders, including diabetes and obesity, using Emisphere's oral Eligen® Technology[39].

Indirect competition includes all approved second and third line pharmacological classes for T2DM patients that are given prior to insulin injections, including SGLT2, GLP-1 analogs, DPP4 inhibitors, Sulfonylures and Thiazolidinedione drug classes. Additionally, oral insulin may be used as an add-on for T2DM patients whose insulin injection treatment regimens entail a longer duration of action, such as once-weekly or once-monthly injections.

In the table below are the top 20 drugs for diabetes treatments including their patent expiry dates, sales and compound annual growth rate (CAGR). Sanofi's **Lantus** is the major insulin drug in the market. Due to the loss of patents, the drug has competition in the form of a biosimilar by the name of **Basaglar**, produced by **Eli Lilly**. After the loss of market share due to Basaglar, Sanofi has been switching over as many patients as possible to their newer drug, Toujeo, to fill the sales gap. Toujeo is a long-acting human insulin analogue with duration of action up to 36 hours that is used to lower blood glucose.

The top 10 global companies manufacturing diabetes drugs collectively hold a market share of 93.2%. They are Novo Nordisk (29.7%), Sanofi (18.4%), Merck & Co. (14.1%), Eli Lilly (11.8%), AstraZeneca (5.7%), Boehringer Ingelheim (3.9%), Johnson & Johnson (3.2%), Novartis (2.9%), Takeda (2.2%) and Bayer (1.3%)[40]. Sanofi's Lantus tops the top 10 list with sales of around $5 billion in 2016, accounting for approximately 22.29% of the total sales of top 10 brands. Revenue for the top ten diabetes drugs in 2016 is lower than revenue for 2015's top ten diabetes drugs by 2.256%.

[37] https://www.researchgate.net/figure/Oral-insulin-delivery-technologies-undergoing-clinical-trials_tbl1_281056677
[38] https://www.researchgate.net/figure/Oral-Insulin-Delivery-Systems-Undergoing-Clinical-Trials_tbl1_236138553
[39] http://ir.emisphere.com/news-releases/news-release-details/emisphere-amends-license-agreement-novo-nordisk
[40] https://www.igeahub.com/2017/11/09/top-20-diabetes-drugs-2017/

TOP 20 Diabetes Drug Treatments (revenues in millions)

Rank	Product	Generic Name	Pharmacological Class	Company	Patent Expiry	2017	2018	2024	CAGR
1	Tresiba	insulin degludec	Insulin analogue	Novo Nordisk	**Jun 2029**	1,113	1,325	2,657	**+13%**
2	NovoRapid	insulin aspart	Insulin analogue	Novo Nordisk	Dec 2014	3,043	2,985	2,368	-4%
3	Lantus	insulin glargine	Insulin analogue	Sanofi	Feb 2015	**5,223**	4,263	2,162	-12%
4	Humalog	insulin lispro	Insulin analogue	Eli Lilly	May 2013	2,865	3,063	1,835	-6%
5	Basaglar	insulin glargine	Insulin analogue	Eli Lilly	-	432	830	1,475	**+19%**
6	Toujeo	insulin glargine	Insulin analogue	Sanofi	**Mar 2028**	922	1,037	1,446	+7%
7	NovoMix 30	insulin aspart; insulin aspart protamine	Insulin analogue	Novo Nordisk	Dec 2014	1,558	1,564	1,394	-2%
8	Humulin R	insulin (human)	Insulin	Eli Lilly	Apr 2000	1,335	1,334	1,190	-2%
9	Human insulin & devices	insulin (human)	Insulin	Novo Nordisk	-	1,530	1,476	1,072	-5%
10	Levemir	insulin detemir	Insulin analogue	Novo Nordisk	**Jun 2019**	2,145	1,792	1,025	-10%
11	Fiasp	insulin aspart	Insulin analogue	Novo Nordisk	**Jun 2030**	13	89	772	**+80%**
12	Insulin Analogues	insulin	Insulin	Novo Nordisk	Oct 2014	491	597	517	+1%
13	Humulin R	insulin (human)	Insulin	3SBio	-	29	108	504	**+50%**
14	Ryzodeg	insulin aspart; insulin degludec	Insulin analogue	Novo Nordisk	**Sep 2029**	75	122	440	**+29%**
15	Basalog	insulin glargine	Insulin analogue	Mylan	-	-	5	433	n/a
16	Afrezza	insulin (human)	Insulin	MannKind	**Jun 2030**	9	20	382	**+70%**
17	Apidra	insulin glulisine	Insulin analogue	Sanofi	**Jan 2023**	426	432	374	-2%
18	Admelog	insulin lispro	Insulin analogue	Sanofi	-	-	50	313	n/a
19	Lusduna	insulin glargine	Insulin analogue	Merck & Co	-	-	13	172	n/a
20	Insuman	insulin (human)	Insulin	Sanofi	-	121	115	91	-4%

Source: Evaluate Pharma

Currently, **Oramed has the most advanced product in pipeline**. It is anticipated that oral administration of insulin, involving its passage through the liver, will lead to improvement and renewal of insulin's physiological gradient. Should it prove clinical efficiency, physicians will likely prescribe insulin earlier, in line with the common treatment paradigm and American Diabetic Association (ADA) healthcare guidance, which support earlier administration of insulin in T2DM patients. Moreover, it may delay the requirement of insulin injections, or else be given as an add-on drug to a weekly long acting injection. Nevertheless, patients will need to overcome psychological barriers related to their stage of the disease and the use of insulin as a last resort, in order for the use of oral insulin to be justifiable as a substitute for other classes of drugs currently given at earlier treatment stages.

In terms of cost, the existence of multiple classes of diabetes drugs and a wide competitive landscape, allows payers to force discounts and rebates from manufactures in turn for favorable positioning. We believe that the price comparator for ORMD-0801 will be to 'add-on' oral drugs that are given at an earlier stage of the disease. The higher the insulin dosage required to achieve the therapeutic effect, the higher the cost will be. We assume that oral insulin will be priced at a premium compared with injected insulin, and that 2nd and 3rd tiered therapies, such as DPP4s inhibitors will be used as target price benchmarks. According to Oramed, the price of its oral insulin will be in line with other second and third line therapies (DPP4, SGLT-2, GLP-1 and insulin), ranging between $5 and $13.

ORMD-0901 (oral GLP-1) for T2DM

ORMD-0901 is an oral formulation of the glucagon-like peptide 1 (GLP-1) receptor agonist exenatide for the treatment of T2DM.

Direct competition to Oramed's ORMD-0901 includes oral GLP-1 inhibitor drugs, which all share the advantages of GLP-1 absorption via the gastrointestinal tract.

- **Novo Nordisk's** oral semaglutide is a GLP-1 analogue taken once daily as a tablet, which would be more convenient for patients than treatments administered by injections. The Phase III results show that 80% of patients receiving the highest dose had low long-term blood sugar levels, compared to 34% of patients treated with a placebo[41]. If launched, it may be the first oral GLP-1 treatment for T2DM to enter the market. Semaglutide's GLP-1 mechanism of action may be more effective, since its double action of increasing insulin and decreasing glucagon could result in a more widespread lowering of blood sugar levels. The oral GLP-1 couples Semaglutide with Emiphere's proprietary oral delivery platform by using SNAC (Sodium N-[8-(2-hydroxybenzoyl Amino Caprylate) carrier technology.
- Tokyo-based Chugai Pharmaceutical is handing over global rights to **OWL833**, an oral, non-peptide GLP-1 receptor agonist that has been put through a preclinical program and is aimed straight for a phase I study[42]. Eli Lilly payed $50 million upfront and signed off on a set of milestones that were not disclosed but likely add up to a significant amount — if they go the distance.
- Another advanced product under clinical development is TTP273 developed by **TransTech Pharma** (now **vTv Therapeutics**), currently in phase 2 clinical trials for T2DM.[43] TTP273 has been identified using TTP Translational Technology®, as an orally bioavailable, potent, non-peptide agonist of GLP-1 for the treatment of type 2 diabetes. TTP273 has completed a 3 month phase 2 study in patients with T2DM where it demonstrated a statistically significant reduction in HbA1c[44].
- Other companies that are actively involved in developing oral formulations of GLP-1 in earlier preclinical stages include **Diabetology Ltd**, which uses its Axcess® oral drug delivery system, and **Biolaxy** which is developing an oral exenatide, Nodexen, using the nanoparticle oral delivery (NOD) technology platform.[45]

The GLP-1R agonists market is expected to grow in the coming years, but this growth will be accompanied by increased competition, as additional products are expected to reach the market, including products that are a combination of insulin and a GLP-1 agonist. Nevertheless, the benefit of an orally available GLP-1R agonist compared to the currently marketed injected products is clear. We assume that ORMD-0901 oral GLP-1 will be priced at a premium over injected GLP-1, and that Novo Nordisk's semaglutide, will be used as a comparable by its cost and efficiency, if approved for market.

Indirect competition to ORMD-0901, as part of the GLP-1R agonist class, includes other drug classes such as SGLT-2 and DPP4 inhibitors, which are all available by oral delivery.

Exenatide is currently marketed only in injectable form. The launch of Victoza (liraglutide), a GLP-1 analog, by Novo Nordisk in 2010 boosted the GLP-1R agonist market size to $1.7b in 2011, as Victoza became a blockbuster in its second year on the market. In 2016, Victoza's sales reached $3b and in 2017 it holds a 55 percent share in the GLP-1 agonist market, but it is expected that Eli Lilly's Trulicity will be stealing market share from Victoza.

North America is estimated to hold the largest market share in the GLP- 1 market because of reimbursement for GLP-1 drugs. Japan holds the highest share in the Asia Pacific region. According to the International Diabetes

[41] https://labiotech.eu/medical/oral-glp-1-diabetes-treatment/
[42] https://endpts.com/eli-lilly-picks-up-an-oral-glp-1-from-a-big-roche-sub-for-50m-in-cash-plus-deal-and-its-not-a-peptide/
[43] Source: Pharmaprojects
[44] http://www.vtvtherapeutics.com/pipeline/ttp273
[45] Ma et al. Can J Biotech 1(1): 1-10. 2017

Federation, Japan and Australia have the highest per capita expenditure of more than $3 Billion in the Asia Pacific region. The Middle East and Africa markets are expected to grow with the highest CAGR, at 19 percent[46].

In December 2017 the FDA approved Novo Nordisk's Ozempic (Semaglutide), a once weekly GLP-1 which is expected to give tough competition to Trulicty and hold Novo Nordisk's market share. Semaglutide is the fourth once weekly injectable after Asterazenca's Bydureon, Trulicity and Tanzeum (soon to be discontinued). Sanofi has launched Soliqua a combination of insulin and GLP-1 which is also expected to witness robust growth in the forecast period.

Top GLP-1 Antagonists (revenues in millions)

Product	Generic Name	Company	Patent Expiry	2017	2018	2024	CAGR	WW Phase (Current)
Trulicity	dulaglutide	Eli Lilly	Dec 2024	2,030	3,081	5,087	+14%	Marketed
Ozempic	semaglutide	Novo Nordisk	Jan 2029	-	229	4,307	n/a	Marketed
Semaglutide Oral	semaglutide	Novo Nordisk	Dec 2031	-	-	2,305	n/a	Phase III
Xultophy	insulin degludec; liraglutide	Novo Nordisk	Dec 2029	111	254	1,027	+37%	Marketed
Victoza	liraglutide [rDNA origin]	Novo Nordisk	Aug 2022	3,521	3,855	894	-18%	Marketed
Bydureon	exenatide synthetic	AstraZeneca	Oct 2025	574	600	702	+3%	Marketed
Soliqua 100/33	insulin glargine; lixisenatide	Sanofi	Jul 2025	29	93	345	+42%	Marketed
Bydureon	exenatide synthetic	3SBio	Dec 2028	-	4	116	n/a	Marketed
Adlyxin	lixisenatide	Sanofi	Jul 2020	29	41	67	+13%	Marketed
Byetta	exenatide synthetic	AstraZeneca	Oct 2017	176	128	66	-13%	Marketed
Efpeglenatide	efpeglenatide	Sanofi	Apr 2030	-	-	44	n/a	Phase III
Exenatide Synthetic	exenatide synthetic	Amneal Pharmaceuticals	-	-	11	39	n/a	Filed
ORMD-0901	exenatide	Oramed Pharmaceuticals	-	-	-	21	n/a	Phase I
Byetta	exenatide synthetic	3SBio	Dec 2020	19	23	11	-8%	Marketed
Exenatide Synthetic	exenatide synthetic	Teva Pharmaceutical Industries	-	-	5	4	n/a	Marketed
Tanzeum	albiglutide	GlaxoSmithKline	Dec 2022	112	36	-	n/a	Marketed

Source: Evaluate Pharma

[46] https://www.mordorintelligence.com/industry-reports/glucagon-like-peptide-1-agonists-market

T1DM

T1DM is treated predominately by insulin injections and pumps. An increased number of T1DM patients use an insulin pump with continuous glucose monitoring, however a considerable percentage of the patients do not reach balanced glycemic control with injections. Insulin is the most common class of drug for T1DM. Nevertheless, there are various SGLT2 inhibitor products, sublingual, and oral drugs under development, as well as early stage (animal models) immunotherapies for prevention of auto-immune destruction of pancreatic beta cells.

Oramed's **ORMD-0801** oral insulin capsule is anticipated for use **as a complementary agent to insulin injections in the treatment of T1DM**, potentially eliminating the need for insulin before each meal (bolus insulin doses). This treatment regimen should allow for fewer daily injections and a lower frequency of blood glucose fluctuations in cases of unstable and brittle T1DM.[47]

Direct competitors for ORMD-0801 under development are those oral insulin projects previously mentioned as competitors for type 2 diabetes, such as Biocon's IN-105, Diasome's HDV and Diabetology's Capsulin IR.

Indirect competitors for ORMD-0801 include all available insulin products (as listed in the table below) in which ORMD-0801 will take a share from if approved.

In T1DM, the liver is often insulin-deprived. Orally administered, intestinally absorbed insulin, in its first pass through the liver, is projected to improve and restore insulin's physiological gradient. The externally-administered insulin is integrated into the physiological glucose-insulin cycle and compensates for the lack of naturally occurring insulin on demand. In addition, an oral replacement for prandial insulin injections is attractive and may improve compliance, as these injections are given three times/day. However with a fixed prandial insulin capsule, it might be challenging to titrate a variable dose depending on the size of a meal.
ORMD-0801, oral insulin for T1DM, may potentially improve the body's response to the treatment when compared to subcutaneously delivered insulin injections, which bypass the liver. For this reason, ORMD-0801 should be less susceptible to causing hypoglycemia (low blood sugar), while still having an impactful effect on hyperglycemia (delivered insulin closes down glucose overproduction).

[47] Oramed's website

Worldwide Sales of T1DM Insulin Products (in millions)

Product	Company	Generic Name	Routes of Admin.	Pharmacological Class	First Launch (WW)	Patent Expiry	2016	2022	CAGR
Lantus	Sanofi	insulin glargine	Injection	Insulin analogue	6/30/2000	2/12/2015	1,332	502	-15%
NovoRapid	Novo Nordisk	insulin aspart	Injection	Insulin analogue	9/30/1999	12/7/2014	624	529	-3%
Humalog	Eli Lilly	insulin lispro	Injection	Insulin analogue	6/14/1996	5/7/2013	583	426	-5%
Levemir	Novo Nordisk	insulin detemir	Injection	Insulin analogue	6/30/2004	6/16/2019	535	266	-11%
Human insulin & devices	Novo Nordisk	insulin (human)	Injection	Insulin	12/31/1984	-	347	269	-4%
NovoMix 30	Novo Nordisk	insulin aspart; insulin aspart protamine	Injection	Insulin analogue	6/30/2000	12/7/2014	328	279	-3%
Humulin R	Eli Lilly	insulin (human)	Injection	Insulin	1/1/1983	4/29/2000	288	273	-1%
Toujeo	Sanofi	insulin glargine	Injection	Insulin analogue	3/30/2015	3/23/2028	151	384	+17%
Tresiba	Novo Nordisk	insulin degludec	Injection	Insulin analogue	2/4/2013	9/25/2029	127	571	+28%
Insulin Analogues	Novo Nordisk	insulin	Injection	Insulin	9/30/1999	10/8/2014	86	75	-2%
Apidra	Sanofi	insulin glulisine	Injection	Insulin analogue	12/31/2004	1/25/2023	86	79	-1%
Insuman	Sanofi	insulin (human)	Injection	Insulin	4/30/1999	-	30	25	-3%
Basen	Takeda	voglibose	Oral	Alpha glucosidase inhibitor	9/6/1994	-	22	15	-6%
SciLin	Bayer	insulin (human)	Injection	Insulin	6/30/2010	-	19	19	-1%
Basaglar	Eli Lilly	insulin glargine	Injection	Insulin analogue	8/3/2015	-	18	196	+49%
Ryzodeg	Novo Nordisk	insulin aspart; insulin degludec	Injection	Insulin analogue	12/31/2014	9/25/2029	9	60	+36%
Symlin	AstraZeneca	pramlintide acetate	Injection	Amylin receptor agonist	4/30/2005	3/16/2019	3	12	+25%
Sotagliflozin	Lexicon Pharmaceuticals	sotagliflozin	Oral	Sodium glucose co-transporter (SGLT) 1/2 inhibitor	12/31/2018	12/31/2028	-	280	n/a
Fiasp	Novo Nordisk	insulin aspart	Injection	Insulin analogue	1/31/2017	12/31/2030	-	106	n/a
Sotagliflozin	Sanofi	sotagliflozin	Oral	Sodium glucose co-transporter (SGLT) 1/2 inhibitor	12/31/2018	12/31/2028	-	42	n/a
Suglat	Astellas Pharma	ipragliflozin L-proline	Oral	Sodium glucose co-transporter (SGLT) 2 inhibitor	4/17/2014	-	-	40	n/a
Total							**4,589**	**4,447**	**-1%**

Source: Evaluate Pharma

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Nadav Kidron, CEO/Director

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

Miriam Kidron Ph.D, Chief Scientific Officer/Director

Dr. Kidron serves as Chief Scientific Officer and Director of Oramed Pharmaceuticals, which she co-founded in 2006. Dr. Kidron is a pharmacologist and biochemist, who earned her PhD in biochemistry from the Hebrew University of Jerusalem. For close to 20 years, Dr. Kidron has been a senior researcher in the Diabetes Unit at Hadassah-Hebrew University Medical Center in Jerusalem, Israel, earning the Bern Schlanger Award for her work on diabetes research. She was formerly a visiting professor at the Medical School at the University of Toronto and is a member of the American, European and Israeli Diabetes Associations.

Hilla Eisenberg CPA, Chief Financial Officer

Ms. Eisenberg serves as Chief Financial Officer of Oramed Pharmaceuticals. She joined Oramed in 2016 and prior to her appointment as CFO served as the Company's Finance Manager. Prior to joining Oramed, she provided audit and accounting services at a certified public accounting firm in Israel and served as an auditor at PwC Israel (Kesselman & Kesselman) including a short relocation to PwC New York. Ms. Eisenberg brings to Oramed very strong financial experience with an assortment of publicly traded and private companies. Ms. Eisenberg holds a bachelor's degree in accounting and economics from Tel-Aviv University and is a certified public accountant (CPA) in Israel.

Mark Haselton Ph.D, MBA, VP Business Development

Dr. Hasleton serves as Oramed's Vice President of Business Development. Mark has over 15 years Pharma / Biotech experience including Medical, Marketing, R&D and Business Development. Prior to joining the Oramed, Mark served in several leadership and pharmaceutical development roles. From 2010 to 2018, he served in Business Development and later as Senior Director of Portfolio – Global New Therapeutic Entities at Teva Pharmaceutical Industries Ltd. Prior to joining Teva, from 2007 to 2010, Mark was at Bristol Myers Squibb Co, in the UK and then in the European business as EMEA Business Operations Manager for MSLs in the region. Mark has a PhD in molecular biology and cancer research from the Imperial College London, UK, a MRes in molecular biology from the University of Manchester, UK and an MBA from Tanaka Business School, Imperial College London, UK.

Source: http://www.oramed.com/about-us/management/

Appendices

Appendix A - Financial Reports

	For the year ending	
Balance Sheet ($000s)	31.8.2018	31.8.2017
Current assets		
Cash	4,996	3,969
Short term deposits	20,875	13,293
Marketable securities	4,592	2,860
Restricted cash	-	16
Other assets	574	159
Total current assets	**31,037**	**20,297**
Long-term assets		
Long-term assets	13,542	16,232
Marketable securities	2,785	2,151
Employee rights	16	14
PPE	17	18
Total assets	**47,397**	**38,712**
Current liabilities		
Accounts payable	2,058	2,716
Deferred revenues	2,449	2,449
Payable to related parties	46	-
Total current liabilities	**4,553**	**5,165**
Long-term liabilities		
Deferred revenues	11,388	13,837
Employee rights	20	18
Others	324	454
Total Liabilities	**16,285**	**19,474**
Equity	**31,112**	**19,238**

	For the year ended August 31st	
Profit and Loss ($000s)	31.08.2018	31.08.2017
Revenues	2,449	2,456
Cost of revenues	(86)	187
Research and development, net	11,979	10,281
General and administrative	4083	2,759
Financial income, net	800	691
Loss before taxes on income	12,727	10,080
Taxes (tax benefit)	-	400
Net loss	**12,727**	**10,480**

Credit to Experts: Dr. Tiran Rothman, Dr. Hadar Cohen-HaLevy

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