FROST & SULLIVAN

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Initiation of Coverage December 23, 2017

Oramed Pharmaceuticals Inc.: An emerging player in the huge orally delivered therapeutics segment of the global diabetes care market; we initiate our coverage with a price target of NIS 53.2

Stock Exchange: TASE, NASDAQ

Symbol: ORMP

Sector: Healthcare

Sub-sector: Pharmaceuticals

Stock price target: NIS 53.2

As of 20 December 2017 (source: TASE website):

Closing Price: NIS 30.8

Market Cap: NIS **409.9M**

# of Shares: 13.3M

Stock Performance (since TASE IPO): 4%

Average Daily Trading Volume (since TASE IPO): NIS 260K

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Company Overview

Oramed Pharmaceuticals Inc. (NASDAQ/TASE: ORMP) (hereinafter 'Oramed') is a biomedical company engaged in pharmaceutical research and development of protein and peptide molecules, 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: ORMD-0801-an oral insulin product, which aims to disrupt the treatmentparadigm for type 2 diabetes, and decrease the number of insulin injections needed for type 1 diabetes; and ORMD-0901-an oral GLP-1 receptor agonist, which increases physiological insulin secretion.

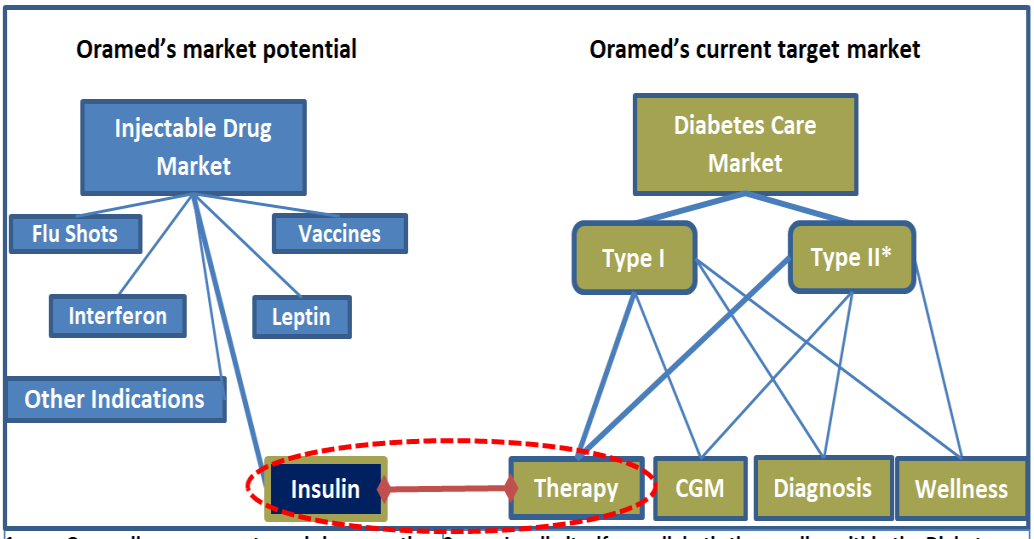
- Oramed's comfortable cash position is partly due to a $50 million licensing deal and a stock purchase agreement with Hefei Tianhui Incubator of Technologies Co. Ltd., which additionally includes up to 10% royalties on the net sales of the related commercialized products in China, Macau and Hong Kong. **The Chinese market is forecasted to yield the most lucrative growth in coming years, with the United States retaining the highest marginal revenue per patient.**
- Oramed's persistent and relatively successful focus on the oral delivery for the diabetes drug market is a commercially promising strategy with the potential for clinical expansion into other segments in the future. **By 2025, the projected diabetes market size will be about $170 billion, with oral delivery comprising about onethird.**
- **Oramed is advancing in its Phase 2b studies for ORMD-0801**, Oral insulin for T2DM. Phase 2b has been successfully completed, and a 90 days Hb1Ac (glycated haemoglobin) trial initiation is projected in the coming months.
- **ORMD-0801 (Oral Insulin for T1DM) and ORMD-0901 (Oral GLP-1 for T2DM) have respectively completed phase 2a and phase 1 FDA trials.**
- Should Oramed receive go-to-market approval from the FDA, the company will have to educate its market if they are to extract market share from other segments.
- In August 2017, the FDA advised that the regulatory pathway for the submission of ORMD-0801, would be a Biologics License Application (BLA). This grants **12 years marketing exclusivity for ORMD-0801**, if and when approved.
- It is assumed that the company will continue licensing its platform to other companies looking to convert injectable drugs into orally ingestible alternatives, as with Entera Bio Ltd. since 2010.
- **Thus, we evaluate Oramed equity value at $200.7M / NIS708.3M; price target to range between NIS 49.8 and NIS 56.6, a mean of NIS 53.2.**

Stock overview since TASE IPO July 12 2017 (Source: TASE website)

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, by 2022 this segment is estimated to reach a value of $42.3 billion, a CAGR of 8.8% since 2016. Insulin, and thereafter GLP-1, account for the overwhelming majority of the diabetes drug market. Additionally, Oramed's core business is its oral platform which enables the promotion of numerous domains as we present below.



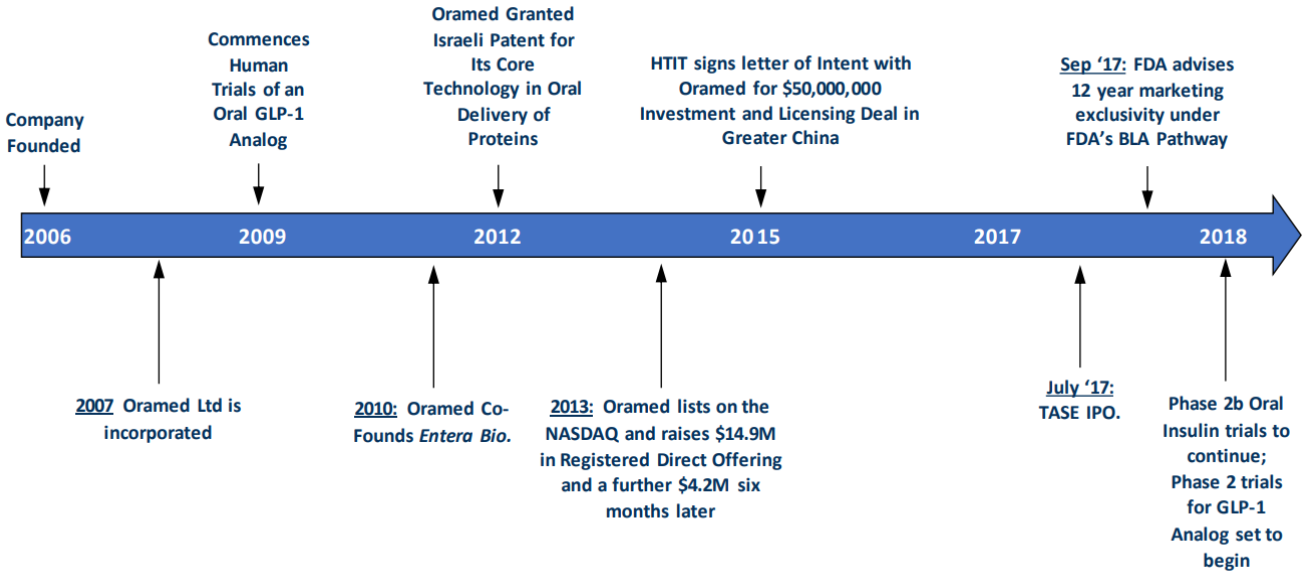
Source: Frost & Sullivan

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. Albeit, in December 2015, Oramed signed a $50M investment and licensing deal with HTIT granting the latter an exclusive commercialization license for ORMD-0801 in China, Macau and Hong Kong. Thus, the company has proven out licensing feasibility.

Oramed faces no current direct competitors in the Oral Insulin market; however should the big pharmaceutical players continue succeeding in developing injections which are efficiently administered at increasingly less frequent intervals, the added-value of Oral Insulin will decrease. Additionally, Oramed will be required to conduct an extensive "market education campaign", targeting both patients and physicians when and if its products are approved for market. The prospect 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.

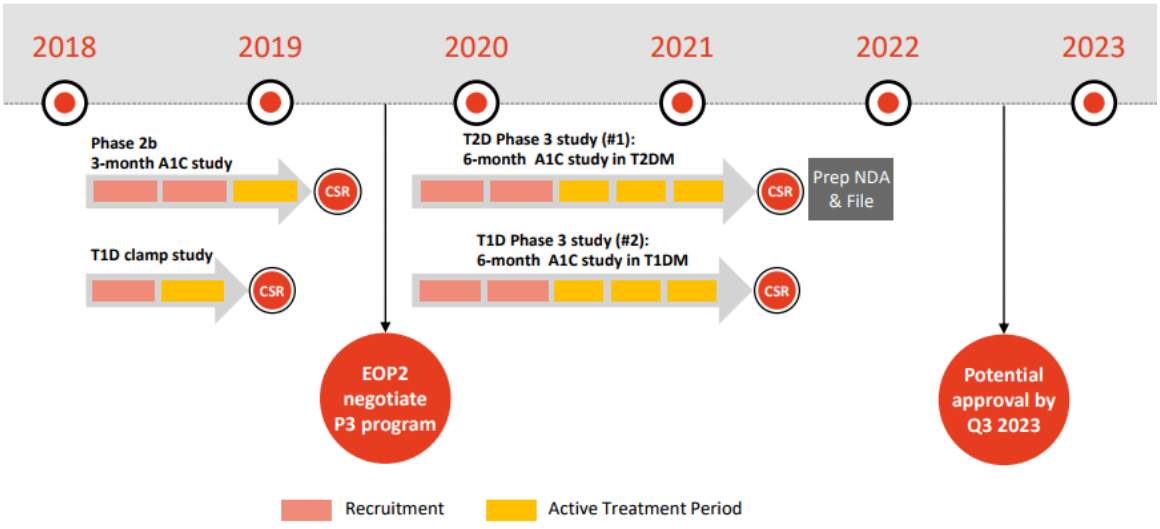
Thus, we view the investment in Oramed as a great opportunity for investors to participate in the quest for a game changing delivery method, not only in the diabetes domain, but also in a number of other indications that lack easily administered orally delivered solutions. Pending successful completion of the company's pivotal clinical trial with ORMD0801, we believe that the stock's potential will significantly increase.

Timeline of Significant Milestones



Sources: Oramed Ltd, Press Releases 2009-2017 – URL: http://www.oramed.com/category/press-releases/; Oramed Ltd. *Corporate Presentation*. November, 2017 – URL: http://www.oramed.com/investors/corporate-presentation/.

Anticipated Clinical Development Timeline of ORMD-0801



Source: Oramed's presentation September 2017

Upcoming Potential Catalysts

The company anticipates initiating two-three-month dosing Phase II clinical trials on type 2 diabetic patients in calendar year 2018, to be followed by two six-month Phase III clinical trials on both type 1 and type 2 diabetic patients, following which Oramed expects to file a Biologics License Application with a potential approval by the third quarter of calendar year 2023.

Program	Indication	Event	Significance	Timeline
ORMD0801	T_2 Diabetes	Initiation of 90 days Hb1Ac dose-ranging clinical trial	Medium	**Q1 2018**
		Initiation of Phase 3 multi center clinical trial	High	**Q4 2019**
ORMD0801	T_1 Diabetes	Initiation of Clamp study for quantifying insulin absorption	Medium	**Q1 2018**
		Initiation of Phase 3 multi center clinical trial	High	**Q4 2019**
ORMD0901	T_2 Diabetes	Final toxicology stydy results	Medium	**Q4 2017**
		IND (Investigational New Drug) application filing	Low	**Q1 2018**
		Pharmacokinetics clinical study	Medium	**Q1 2018**
		Initiation of Phase 2 trial under FDA IND	High	**H2 2018**
ORMD0801	Nonalcoholic steatohepatitis (NASH)	Expolaratory study	Medium	**Q4 2017**
Oral leptin	T_1 Diabetes	Proof-of-concept study	Low	**2018**

Upside scenarios	Downside scenarios
Oral administration of insulin aims to disrupt the treatment paradigm for type 2 diabetes	This paradigm shift will require conducting market education
Phase 3 clinical trials will start in 2019 – results are crucial for the company's future – upon success there is great economic potential in the company's platform	If Oramed does not meet its primary endpoints it will be a major setback for the company
The company has proven out-licensing experience. This can lead to new deals in different geographies.	If the deal with HTIT does not eventuate due to a lack of regulatory approval, it will setback further deals

Valuation Methodology

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 development 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 field of Life Sciences, rather than using the conventional terminal value, normally used by non- Life-Science companies.

Valuation Summary

We begin our pipeline valuation with ORMD-0801, and examine the 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 T2DM in 2016, and faces a 90-day HbA1c (glycated haemoglobin) study. We adopt the company's clinical and regulatory forecast. For T1DM, it completed phase 2a in 2014 and intend to initiate phase 3 clinical trials in 2019; for type 2, phase 3 clinical trials will initiate in Q4-2019. Another product is a combination of the oral insulin capsule ORMD-801 delivered with the oral GLP-1 ORMD-0901. We assume phase 2 will start in 2018.

- R&D costs: We extrapolate phase 3 R&D costs based on phase 2 costs. We assume $14M in R&D costs for trials of ORMD0801.

- Market size: Oramed is targeting ORMD-0801 as an early treatment for type 2 diabetes patients that are not taking insulin injections. We estimate that the potential market for this treatment is comprised of newly diagnosed T2DMD 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 with no additional extension. We assume 12 years of market exclusivity.

- Out-licensing agreement: We take Oramed's recent deal with HTIT in China. Oramed out licensed HTIT exclusive rights to ORMD-0801 in greater China based on $50M payments ($38M in milestone payments of which Oramed received $18M) and royalties (10%). We can extrapolate these numbers into few future deals to form in coming years.

- Success rates – the company engages in a high-risk therapeutic area in promoting its indications. Success rate data indicates higher success rates for the metabolic specialty (45%) 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%). 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 (see Appendix B).

Main valuation parameters

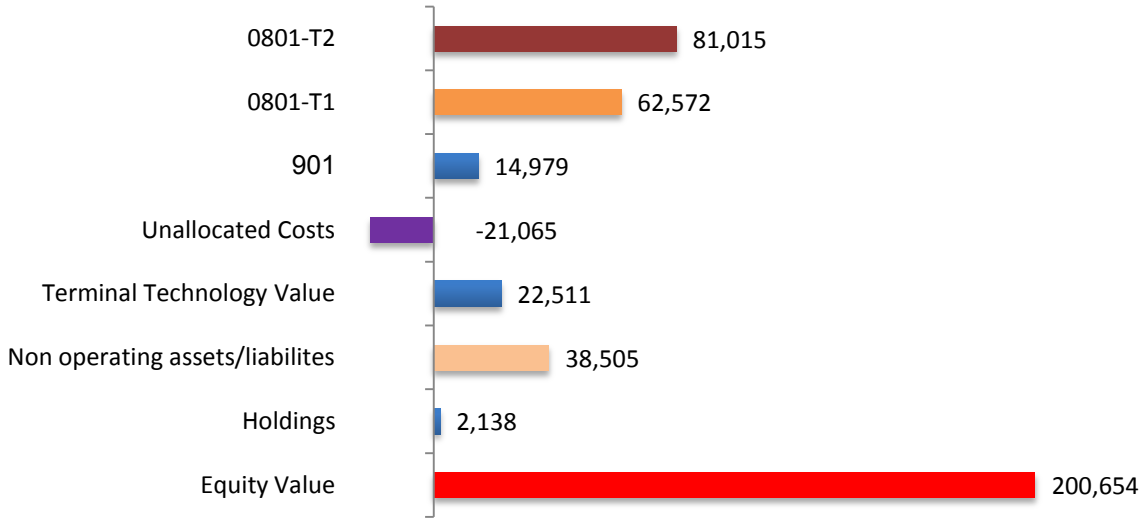
Indications	Current Development stage	Success Rate Phase II	Success Rate Phase III	Regulatory approval success rate	Launch	Patent period
ORMD-0801 T2DM	2b	100%	71%	86%	2024	2035
ORMD-0801 T1DM	2a	100%	71%	86%	2024	2035
ORMD-0901	2	45%	71%	86%	2024	2035

Equity Value

Non-operational assets/liabilities and unallocated costs

As of August 31, 2017, Oramed had $4.0M of available cash, $29.5M of short term and long term deposits and investment and $5.0M of marketable securities, i.e. a total of $38.5M in non-operating assets. The company has no loans. Oramed also has 6.92% holdings in DNA Biomedical Solutions Ltd (TASE: DNA). Frost and Sullivan's initiation analysis report on the company be found here. We evaluate the fair value of DNA Biomedical at $30.9M as of December 2017. Thus, Oramed holdings value amounted to $2.1M.

The equity valuation elements are presented in the table below:



Based on the aforementioned parameters, we evaluate Oramed equity value at $200.7M / NIS708.3M.[1]

Sensitivity Analysis

The table below presents Oramed's price target in relation to the capitalization rate and the market share ORMD0801 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 (see Appendix B) and 0.5% change in our estimation on Oramed's market share between 2% to 3.5% market share. Oramed has 13.3M 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 estimate the target price to range between NIS 49.8 and NIS 56.6; a mean of NIS 53.2.

[1] Exchange rates, here and throughout this report are taken at Israeli market close on 6 December 2017.

Contents

Company Structure

Oramed stock is traded both on the NASDAQ and on the Tel Aviv Stock Exchange (TASE), 67.6% of Oramed Inc. public are public holdings. Oramed has a <2% holding in Entera Bio Ltd, which continues to use their oral drug delivery platform. Entera is a subsidiary of DNA Biomedical Solutions (TASE: DNA), which co-founded the company along with Oramed. Oramed has a ~ 7% holding in DNA Biomed. In July 2015, Oramed signed a $50,000,000 deal with Hefei Tianhui Incubation 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 Incubation 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 available by injection. 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.

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'), type 2 diabetics (hereinafter 'T2DM'), and pre diabetics alike. The standard of care for T2DM includes oral and 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, but eventually, all patients' disease will progress, leading to daily insulin injections. 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; **ORMD-0801** - an oral insulin product for T2DM (completed Phase 2b), which aims to disrupt the early treatment pradigm for type 2 diabetes, and be given at prior to initiation of insulin injections. Additionally, this product is intened 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; and **ORMD-0901** - an oral GLP-1 receptor agonist product for T2DM (Phase 1 completed), which is intented to increase the physiological insulin secretion.

[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

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.[5]

The company's most advanced product (ORMD-0801 for T2DM) completed a Phase 2b clinical trial in 2016, and it is expected to initiate a 90 day treatment HbA1c study in Q1-2018, followed by a Phase 3 clinical trial. 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. 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 any case, Oramed will be challenged by in-direct and possibly future direct competitors. However, Oramed's comfortable cash position will make these arduous tasks less overwhelming.

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

[5] 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 (pre-diabetic, T1DM and T2DM) 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 drugs, 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.[6] Oral administration has many inherent advantages over injections including a better safety profile, ease of administration, consequent improved compliance, and suitability 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. A few examples are detailed below.[7]

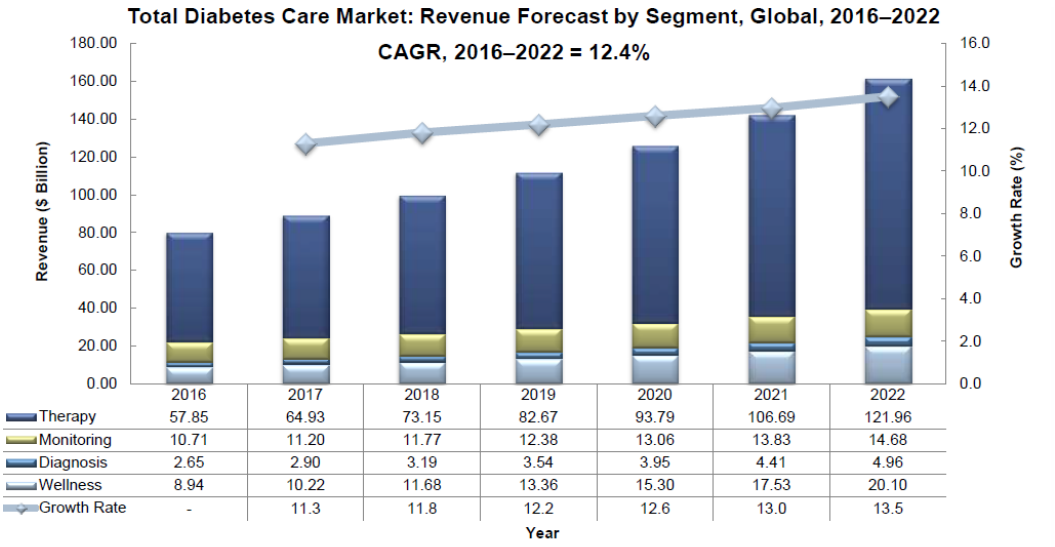
Investor (Country)	*Investee (Country)*	*Amount*	*Product*	*Date*
Johnson & Johnson (US)	Protagonist Therapeutics (US)	$50M	Inflammatory Bowel Disease injectables in pill form.	June 2017[8]
Hefei (Sinopharm) (PRC)	Oramed (IL)	$50M	Orally ingestible Insulin	Nov 2015[9]
Google Ventures, Novartis, AstraZeneca and many others (US)	Rani Therapeutics (US)	$70M	General platform, including; TNF-alpha inhibitors, interleukin antibodies, insulin and GLP-1.	Feb 2016[10]
25 major financial institutions (US)	Chiasma (US)	$26.4M (at 30.8.17)	Oral therapies for acromegaly (Phase III).	Via Nasdaq in 2017[11]

Source: Frost & Sullivan[12]

Diabetes encompasses hundreds of millions of patients worldwide, and this number is experiencing alarming growth, primarily due to increased public awareness, deterministic lifestyle factors, and improved access to care. According to Frost & Sullivan, by 2022 the Diabetes Care market will be valued at $161.69 billion with a CAGR of 12.4% since 2016.[13] Aside from medical segmentation into T1DM, T2DM and pre-diabetic patients, the market can be further segmented by the sequential stages of treatment; wellness (including interventions for pre-diabetics), diagnosis (Point-of-care testing and the like), continuous glucose monitoring (CGM), and therapies (such as insulin be it; injectable, oral, transdermal or inhalable). Oramed competes in the Therapy segment, which accounts for 72.2% of

[6] Brown T: *100 Most Prescribed, Best-Selling Branded Drugs through September*. Medscape. 3 November, 2014. URL: https://www.medscape.com/viewarticle/834273.
[7] Frost & Sullivan Research and Consulting Ltd: *Initiation of Coverage – DNA Biomedical Solutions*.
[8] https://www.businessinsider.com.au/protagonists-oral-peptides-pill-versions-of-blockbuster-drugs-2017-6?r=US&IR=T.
[9] http://www.reuters.com/article/oramed-china-idUSL8N13O0AO20151130.
[10] http://www.biospace.com/News/bay-area-startup-rani-therapeutics-tops-70-million/409783.
[11] Frost & Sullivan: *Initiation of Coverage* – DNA *Biomedical Solutions* (2017).
[12] http://mayafiles.tase.co.il/rpdf/1125001-1126000/P1125869-00.pdf
[13] 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. p.14.

the entire care market as of 2016.[14] By 2022, Frost & Sullivan estimates this figure to increase to 75.4%, corresponding to a therapy segment value of $121.96 billion, a CAGR of 13.2% since 2016.[15]

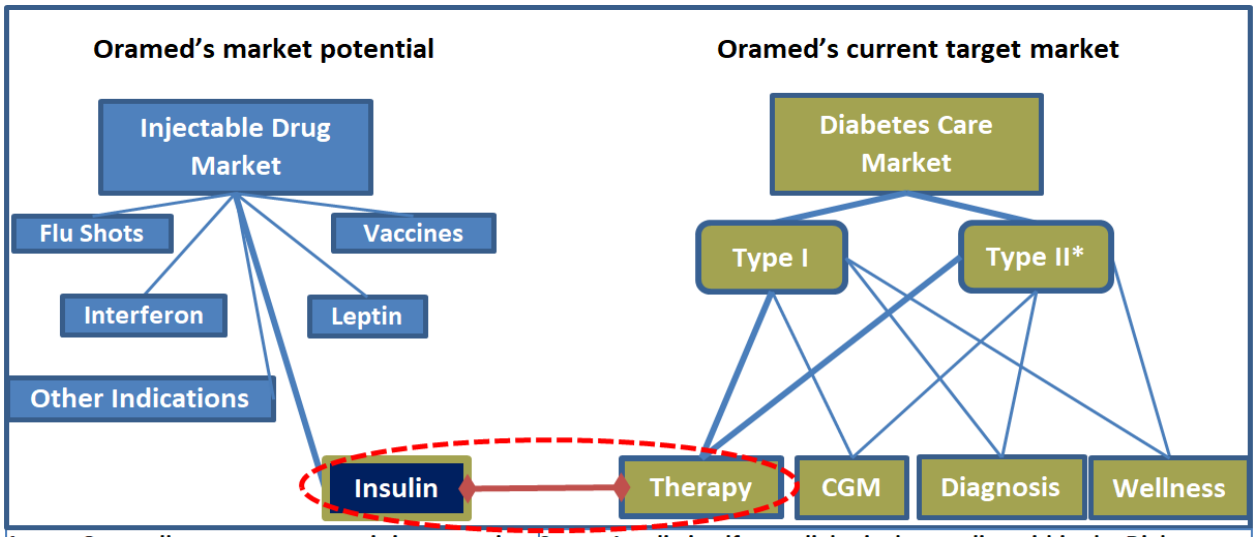


	2016	2017	2018	2019	2020	2021	2022
Therapy	57.85	64.93	73.15	82.67	93.79	106.69	121.96
Monitoring	10.71	11.20	11.77	12.38	13.06	13.83	14.68
Diagnosis	2.65	2.90	3.19	3.54	3.95	4.41	4.96
Wellness	8.94	10.22	11.68	13.36	15.30	17.53	20.10
Growth Rate	-	11.3	11.8	12.2	12.6	13.0	13.5

Year

Note: All figures are rounded. The base year is 2016. Source: Frost & Sullivan

Market Structure



1. **Oramed's core competency is in converting injectable solutions into orally ingestible ones. They are initially focusing on doing so for Insulin.**

2. **Insulin itself, as a diabetic therapy lies within the Diabetes Care Market as treatment for both Type I and Type II patients.**

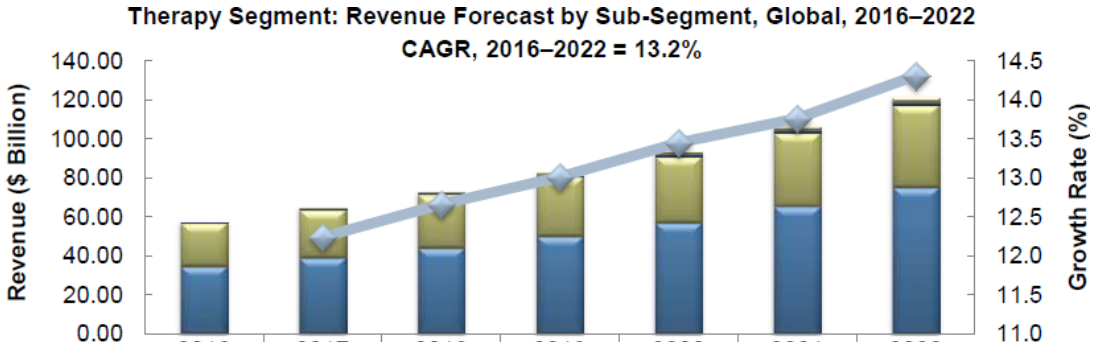
* *Within Type II, the pre-diabetic sub-segment feeds into the diagnosis/wellness markets.*

Market Size

Oramed's competency, 'Oral Drug Delivery', is the fastest growing and second most valuable therapy sub-segment behind injectable delivery, as demonstrated in the diagram below. Pending clinical and market success, oral solutions will acquire a greater share of the market in the long-term at the expense of the injections segment, given the aforementioned preference of patients, and physicians for orally ingestible therapies. In the short-medium term both methods of delivery will be used synchronously. **According to Frost & Sullivan, by 2022 the Oral drug delivery**

[14] Ibid. p.37
[15] Ibid. p.42

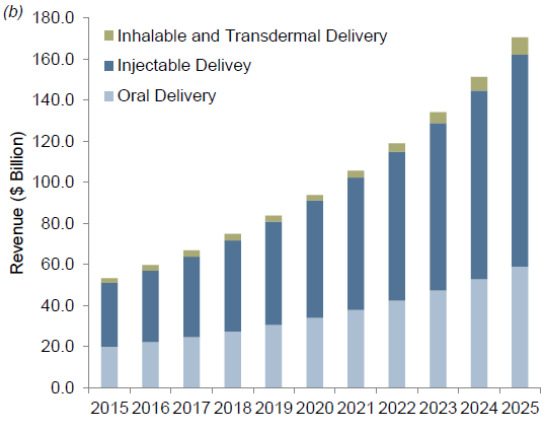
segment is estimated to reach a value of $42.3 billion, a CAGR of 8.8% since 2016. Insulin, and thereafter GLP-1, account for the overwhelming majority of the diabetes drug market.[16]



	2016	2017	2018	2019	2020	2021	2022
Inhalable Drug Delivery	0.28	0.48	0.77	1.10	1.60	2.19	2.99
Transdermal Patch Drug Delivery	0.49	0.59	0.69	0.80	0.97	1.13	1.34
Oral Drug Delivery	22.29	24.72	27.46	30.57	33.99	37.84	42.26
Injectable Drug Delivery	34.79	39.14	44.23	50.20	57.23	65.53	75.36
Growth Rate	-	12.2	12.7	13.0	13.5	13.8	14.3

Source: Frost & Sullivan

Another perspective from which Oramed's market can be analyzed is bottom-up from that of the drug, as a product, rather than the therapeutic deployment of these solutions at the point-of-care, as above. I.e. we can analyze market size based on Diabetes market and the way of drugs delivery in this domain (injections or oral delivery) or analyze the market based delivery methods in general as we forecast Oramed's potential will is high.



Source: Frost & Sullivan

From such a perspective, the broadest market is the Global Drugs Market, which can first be segmented by mode of delivery, and thereafter by target indication. The Global Injectable Drug Delivery Market was estimated at $404 billion in 2017, 10.4% of which comprised diabetes drugs, a 2017 segment value of $42 billion. **Diabetes drugs account for about 26% of the oral drug delivery market.**[17] Between 2015 and 2019, the total Diabetes Drug Delivery Market is set to grow from $53.4 billion to $83.8 billion, a CAGR of 11.9%. Between 2020 and 2025 the market is set to grow from $93.8 billion to $170.5 billion, a CAGR of 12.7%. The chart on the right details Frost & Sullivan's forecasted growth for the Diabetes Drug Market segmented by mode of delivery.[18]

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.[19] Accordingly, **pending Oramed's success in bringing orally deliverable insulin to market, insulin's share of the total diabetes drug market is, ceteris paribus, expected to grow substantially.**

[16] Frost & Sullivan: *Analysis of the Global Diabetes Drug Delivery Market* (2015).
[17] Frost & Sullivan: *Analysis of the Global Diabetes Drug Delivery Market*. 2015.
[18] 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.
[19] Frost & Sullivan: *Analysis of the Global Diabetes Drug Delivery Market* (2015).

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 markets. Solutions for T2DM diabetics may have the potential to treat the pre-diabetic sub-segment, if proven efficient. The convergence between Oramed's short-term and long-term pipelines demonstrates the great potential in the company's current R&D.[20] Oramed recently announced a drug candidate for weight management, an oral leptin capsule.[21] The alarming increase in obesity rates is a key market driver for 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.[22]

Pipeline	Market	Value (base year)	FV (year)	CAGR
Current	Insulin	$24 billion (2014)	$49 billion (2020)	8.5%
	GLP-1 Analog	$3 billion (2014)	$6.6 billion (2020)	9.1%
Future	Vaccines	$33 billion (2014)	$58 billion (2019)	8.6%
	Flu vaccines	$2.9 billion (2011)	$3.8 billion (2018)	3.4%
	Cancer Immunotherapy (Interferon)	$45.5 billion (2015)[12]	$117.1 billion (2022)[23]	8.7%
	Anti-obesity drugs (Leptin)	$1.1 billion (2016)[13]	$24.1 billion (2027)[24]	8.7%

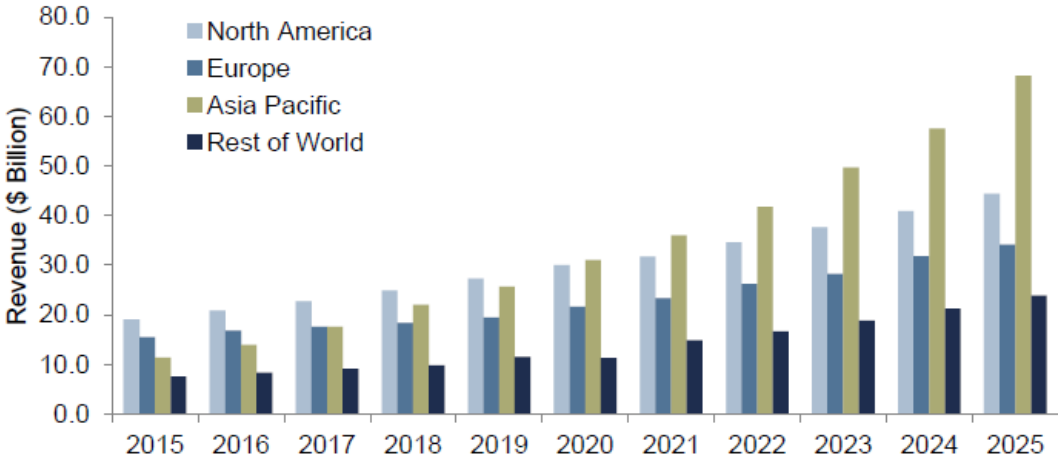
Market Profile

Demographic: The International Diabetes Federation estimates that the number of diabetics globally will rise to 642 million people by 2040, from 415 million in 2015. About 1 in 11 adults were diabetic as of 2015; this ratio is expected to increase to 1 in 10 by 2040. In 2015, the adult mortality for diabetics totaled 5 million, far greater than that for other deadly conditions; HIV/AIDS (1.5 million in 2013), tuberculosis (1.5 million in 2013), and malaria (600,000 in 2013). These figures are even more alarming considering that 47% of diabetics are undiagnosed. The long-term growth of patient numbers is largely the result of the number of children currently affected by the condition; 86,000 children develop T1DM diabetes annually, and 542,000 suffer from T1DM at present.[25]

[20] 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.
[21] **Leptin** is a naturally produced protein in fat cells, which inhibits hunger and regulates energy expenditure.
[22] Oramed Pharmaceuticals. *Corporate Presentation to Investors* (2017) – Figures are from this source unless indicated otherwise.
[23] Allied Market Research. LI 172244. May 2017. Available at URL: https://www.alliedmarketresearch.com/cancer-immunotherapy-market.
[24] 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.
[25] Frost & Sullivan: *Future of Diabetes Care Paradigms, Forecast to 2022* (2017).

Total Diabetes Care Market: Estimated Diabetic Population (Age 20-79 years)						
Region	**Diabetic Population 2015**	**Thereof undiagnosed 2015**	**Diabetic Population 2040**	**CAGR 2015-2040**	**Share of Global 2015**	**Share of Global 2040**
North America[26]	44.3M	13.5M (30%)	60.5M	1.25%	10.7%	9.4%
South /Central America	29.6M	11.5M (39%)	48.8M	2.02%	7.1%	7.6%
Africa	14.2M	9.5M (67%)	34.2M	**3.58%**	3.4%	5.3%
MENA	35.4M	14.5M (41%)	72.1M	2.89%	8.5%	11.2%
Europe	59.8M	23.3M (39%)	71.1M	0.69%	14.4%	11.1%
India[27]	78.3M	40.7M **(52%)**	140.2M	2.36%	18.9%	21.8%
Asia Pacific	**153.2M**	**79.6M (52%)**	**214.8M**	1.36%	**36.9%**	**33.5%**
World	415M	189M (47%)	642M	2.59%	100%	100%
Sources: Diabetes Atlas 2015; International Diabetes Federation; Frost & Sullivan						

Economic analysis: The economic burden of the disease is extremely disproportionate. In 2015, 11.6% of global healthcare expenditure was on diabetes, in dollar terms $643 billion. By 2040, global healthcare expenditure on diabetes will rise 19.2% from 2015 to total $802 billion.[28] Industry-wide revenue in the diabetes drug market is fast approaching $100 billion per annum. Between 2020 and 2021 the Asia Pacific will overtake North America as the diabetes industry with the highest output, as depicted in Frost & Sullivan's regionally segmented forecast below.[29] Consequently, Oramed's deal with Hefei Tianhui Incubation of Technologies Co. Ltd. is strategically sensible in this context. In addition, 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.[30]



Source: Frost & Sullivan

Geographic Analysis : The fastest growing diabetic population in the world is in Africa, which along with the Middle East and North Africa (MENA) and India, constitutes the world's most rapidly expanding markets. The number of diabetics in the region is unrivalled at 153.2 million, and similar to India, more than half are undiagnosed. By 2040

[26] Including the Caribbean
[27] Includes; Bangladesh, Bhutan, Myanmar, Nepal, and Pakistan.
[28] Ibid.
[29] Frost & Sullivan: *Analysis of the Global Diabetes Drug Delivery Market* (2015).
[30] http://www.jpost.com/HEALTH-SCIENCE/Study-huge-economic-cost-of-diabetes-NIS-85-billion-a-year-513564

the Asia Pacific market will reach 214.8M, at a healthy CAGR of 1.36% since 2015. Despite a detracting relative share of the global diabetic population, the sheer volume of patients and unparalleled expanding middle class means that the Asia Pacific will be the most populous market. **Nevertheless, in terms revenue it fails to compare to regions such as North America and therefore it will not be the key focus for industry players in the foreseeable future.**

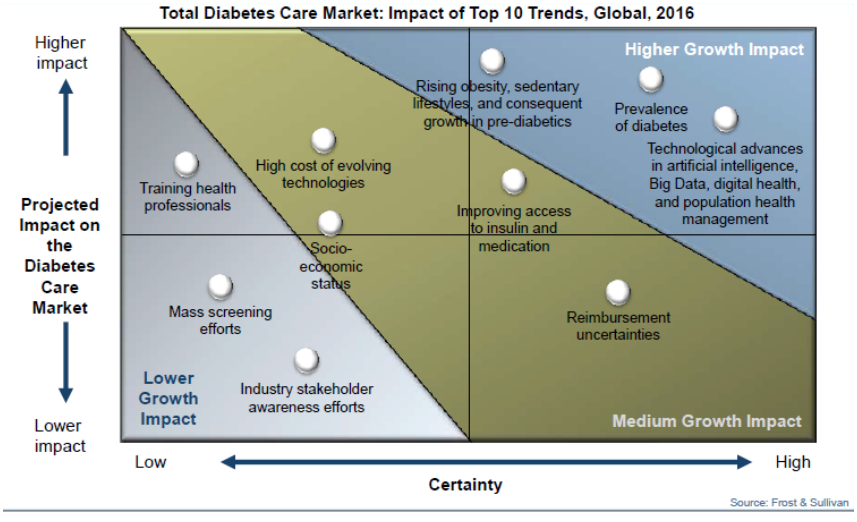
The Chinese Market

Oramed's focus on China is evident in its 2015 investment and licensing deal with HTIT, which included $50M in payments plus up to 10% royalty 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. Thirty years ago, less than 1% of the population was diabetic, and today that figure sits at about 12%. The global cost burden of diabetes is approximately $825 billion per annum, with the largest bills in China ($170 billion), the US ($105 billion), and India ($73 billion). These figures exclude work days lost due to diabetes, which would greatly increase the numbers if incorporated.[31] On a per patient basis, the average annual expenditure on a Chinese diabetic was $820.10 (USD-PPP).[32] The Chinese diabetes epidemic is largely result of the country's explosive economic growth.

The Chinese Diabetic Population sat at approximately 110M adults (aged between 20-79 years), in 2015. This is based upon a low estimate of 99.6M, and a high estimate of 133.4M translating to a national prevalence of 10.6% (9.6% low; 12.9% high), or an age-adjusted comparative prevalence of 9.8% (8.9% low; 12.1% high). The relatively high variance is indicative of China's well known lack of statistical transparency, especially when it comes to issues of human conscience. By 2040, China's diabetic population is expected to exceed 150M. An additional 26.7M Chinese suffered from impaired glucose intolerance in 2015, with that number set to rise to 34.6M by 2040. Incidence among children is also high with about 30,500 Chinese children suffering from T1DM Diabetes. China alone had 1.3 million deaths due to diabetes in 2015, with 40.8% of those deaths occurring in people aged below 60 years.[33]

Market Trends, Drivers and Consolidators

Trends: Frost & Sullivan predicts the following trends will disrupt the diabetes care market in the foreseeable future. The graph below 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); Lower, Medium and High Growth Impacts.[34]



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.

[31] Harvard T.H. Chan School of Public Health – News: Cost of diabetes hits 825 billion dollars a year. April 6, 2016. URL: https://www.hsph.harvard.edu/news/press-releases/diabetes-cost-825-billion-a-year/.
[32] International Diabetes Federation: *IDF Diabetes Atlas, 7th eds*. Brussels, Belgium: International Diabetes Federation, 2015. URL: http://www.diabetesatlas.org
[33] Ibid.
[34] 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

  - 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.
  - New products with gradually improving adoption include; drug combinations and better delivery mechanisms, insulin pumps, and advancements such as the artificial pancreas.
    - The latter of these are 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.

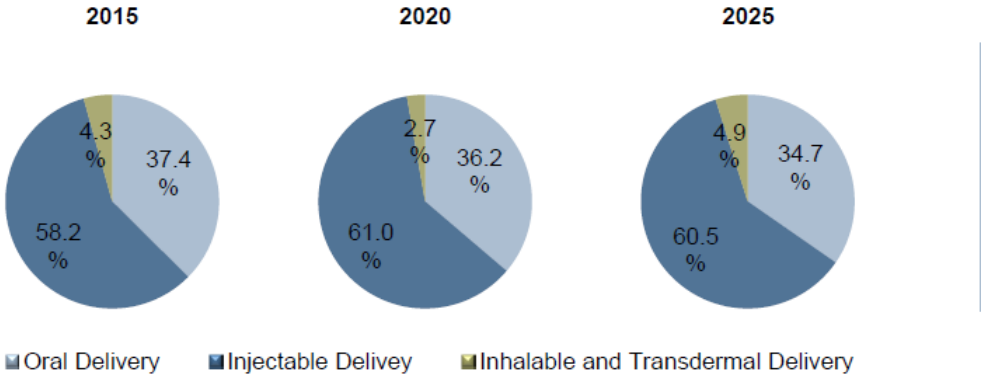
GLP-1 Prices as at November, 2017 (USD)		Insulin Prices as at November, 2017 (USD)	
		Novolin R/N/70-30	$24
		Humulin R	$100
		Basaglar	$227
Tanzeum	$492	Lantus	$274
Adlyxin	$577	Humulin N/70-30	$288
Trulicity	$641	Humalog 50-50/75-25	$322
Bydureon	$647	Toujeo	$347
Byetta	$684	Afrezza	$352
Victoza	$761	Apidra	$400
Saxenda	$1,186	Levemir	$409
		Tresiba	$452
		Humalog	$529
		Novolog/70-30	$538
		Soliqua 100/33	$656

The above prices are the maximum that an uninsured consumer should pay for said drug at a local pharmacy. Price based upon 5 solostar pens of 3ml, and if available, a generic.

Sources: Evaluate Pharma; GoodP$_x$

- **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 "one solution for all**".
- **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 cede market share in eight years.[35]

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



  - 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 adverse 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.

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.

In October 2016, Novo Nordisk announced that it was putting its clinical development of oral insulin on hold. This was despite early-stage data exhibiting **similar efficacy to the market gold-standard *Lantus* injection, developed by Sanofi**.[36] The development was halted for both economic and scientific reasons. Scientifically, the tablet's low insulin bioavailability meant that patients would have to take several of them, at regular intervals, to sufficiently replace a single injection. The low bio-availability diminishes patient demand, as the higher dosages and frequencies imply higher costs. On the supply side, the level of investment required for an oral solution to compete with increasingly less invasive injections would necessitate a price point that is simply too high to achieve that precise objective. Already, in 2016, Pharmacy Benefit Managers (PBMs) forced pharma companies to lower diabetes drug prices. The price of injectable diabetes drugs had increased up to 1000% in 20 years,[37] and given that the nature of the disease

[35] Frost & Sullivan: *Next Generation Diabetes Therapy and Drug Delivery Technologies*. March 2016.
[36] McConaghie A: *Oral insulin could still be a reality says Novo Nordisk*. Pharmasource. June 14, 2017. URL: https://pharmaphorum.com/news/oral-insulin-still-reality-says-novo-nordisk/
[37] Fernandez C.R: *Novo Nordisk pressured into Dropping Needle-Free Oral Insulin*. LabBioTech. November 1, 2016. URL: https://labiotech.eu/novo-nordisk-drops-oral-insulin/.

usually requires at least once-daily injections, the burden on patients was simply intolerable. As an example, **Eli Lilly's *Humalog* increased from $21 in 1996 to $255 in 2016**.[38]

Alongside announcing the suspension of oral insulin development, the Danish pharmaceutical giant revealed plans to heavily invest in development of an oral formulation for GLP-1 analogue semaglutide, which is also being developed by Oramed. Novo Nordisk invested some $2 billion to upgrade manufacturing facilities for the project. The high initial investment is again a blend between the science and economics. As a progressive disease, the longer one has diabetes, the more treatments he or she requires. Early administration of insulin has been shown to reduce long term dependency on higher dosages of medications, meaning less revenue for companies such as Novo Nordisk. On the contrary, early administration of GLP-1 activates pancreatic beta cells that are still functional. These eventually die off, and insulin becomes necessary, leading consumers to purchase an additional drug from the big pharmaceutical companies.[39]

Interestingly, several other market players have had similar experiences. Bristol Myers Squibb Co. dropped its development program with India's Biocon.[40] Pfizer lost $2.8 million from Exubera, an inhalable form of insulin, which also struggled to compete with injectable drugs, particularly in its market education campaign.[41] This is not to say that a similar fate necessarily awaits Oramed; its Phase II trials showed an extremely clean side effect profile, and its approach is markedly different as a small biomedical company rather than as a multinational pharmaceutical giant.[42] However, Oramed will need educate the market, and meanwhile these giants may speed up development of competing oral drugs. The existing infrastructure and R&D at these large companies would allow such drugs to quickly reach the market. However, the 12 years of FDA marketing exclusivity (part of Oramed's BLA) will prevent marketing of a similar compound based on the same mechanism of action, at least in the short term. In the long-term Oramed will look to partner with such pharma companies.

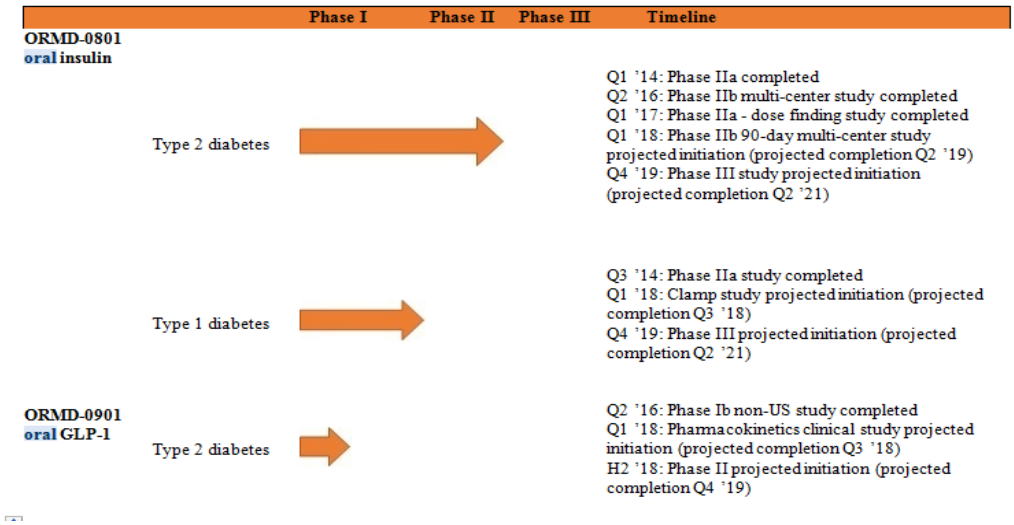
[38] Ibid.
[39] Winkler, M: *Something Strange is going on with Oral insulin*. Yahoo Finance. December 23, 2016. https://finance.yahoo.com/news/something-strange-going-oral-insulin-174117941.html.
[40] Ibid.
[41] Fernandez: *Novo Nordisk pressured into Dropping Needle-Free Oral Insulin*. 2016.
[42] Grinned, A: *Novo Nordisk vs. Oramed - A Second Look At The Battle For Oral Insulin*. Seeking Alpha. August 22, 2016. URL: https://seekingalpha.com/article/4001341-novo-nordisk-vs-oramed-second-look-battle-oral-insulin.

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 is for an oral formulation of Diabetes treatment, 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 facilitates large molecular transfers through intestinal barriers.

The first two products in the company's pipeline, human insulin hormone and 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. In 2017 Oramed completed a comprehensive 6-month toxicology study under conditions prescribed by the FDA Good Laboratory Practices regulations, in preparation for future Phase 3 clinical trial for T2DM and T1DM diabetes. The final report of this study is anticipated by the end of 2017.[43]

The company completed a Phase 2b clinical trial for oral insulin (ORMD-0801 for T2DM) in 2016, and it is expected to initiate a 90 day dose-ranging HbA1c clinical study in Q1-2018, followed by a Phase 3 clinical trial. Oral insulin is also indicated for T1DM; it completed a Phase 2a study in 2014, and is expected to commence a Phase 3 clinical trial in Q4 2019. A Phase 3 clinical trial for T1DM will be initiated in parallel to the Phase 3 for T2DM. The company's oral GLP-1 program, ORMD-0901, is moving forward as well, and there are plans to initiate a large multi-centre Phase 2 clinical study, in the US in H2-2018. Trials will be conducted in the US to support a future regulatory filing with the FDA for both diabetes indications.



Source: Oramed's annual report 2017

Other products in the pipeline include a combination therapy of the oral insulin capsule ORMD-801 with oral GLP-1 ORMD-0901. This combination drug was already tested on animals, showing a synergistic effect of the two active agents. At present, Oramed focuses its efforts on developing its flagship products oral insulin and oral GLP-1. Once further progress is made, the company intends to conduct additional studies with the oral combination therapy.[44]

Additionally, the company began developing during 2017 a new drug candidate, 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

[43] Oramed's annual report 2017
[44] Oramed's annual report 2017

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. According to Grand View Research, the overall obesity market is expected to reach $15.6 billion in 2024. Based on positive preclinical data, Oramed received in May 2017 from the Israeli Ministry of Health a regulatory approval to conduct a human proof-of-concept clinical study for a new oral leptin capsule.[45] The single dose study, planned to commence during 2018, is intended to evaluate its pharmacokinetic and pharmacodynamics (glucagon reduction) in 10 type 1 adult diabetic patients.

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).[46] This study is about to be intiated 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 of the liver. An exploratory study is planned to commence in Q4 2017.[47]

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.[48]

From a regulatory point of view, in September 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 12 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.[49]

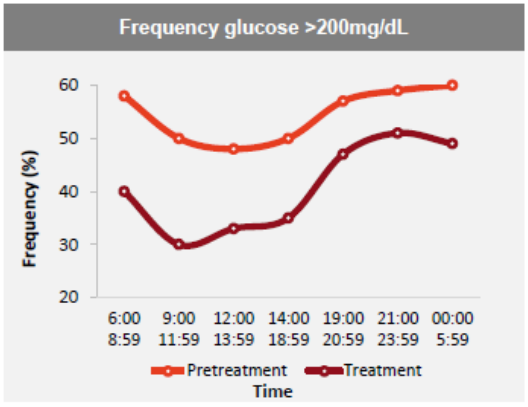
Regarding ORMD-0901, filing an IND is expected during Q1 2018, followed by a large Phase 2 clinical trial in the United States under an FDA IND.[50]

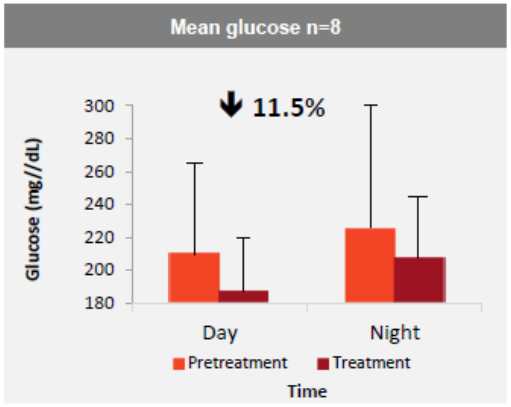
ORMD-0801 Oral insulin capsule for Type 1 Diabetes (T1DM)

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.

[45] JERUSALEM, May 2, 2017. PRNewswire
[46] JERUSALEM, Nov. 14, 2017. PRNewswire
[47] Oramed's annual report 2017
[48] Oramed's annual report 2016
[49] http://www.oramed.com/oramed-announces-successful-meeting-with-fda-for-oral-insulin/
[50] Oramed's annual report 2017

The company completed in 2013 a Phase 2a trial of ORMD-0801 in volunteers with brittle/uncontrolled T1DM, outside the US. The trial was an open-label study that enrolled 8 patients with uncontrolled T1DM. The trial was designed to monitor the glycemic stability following 1 capsule of 8 mg insulin administered, three times daily at meal time. The results showed that ORMD-0801 (a) appeared to be safe and well-tolerated for the dosing regimen, (b) reduced the high frequency spikes (above 200 mg/dl) and (c) reduced the daytime mean glucose by 11.5%.[51]



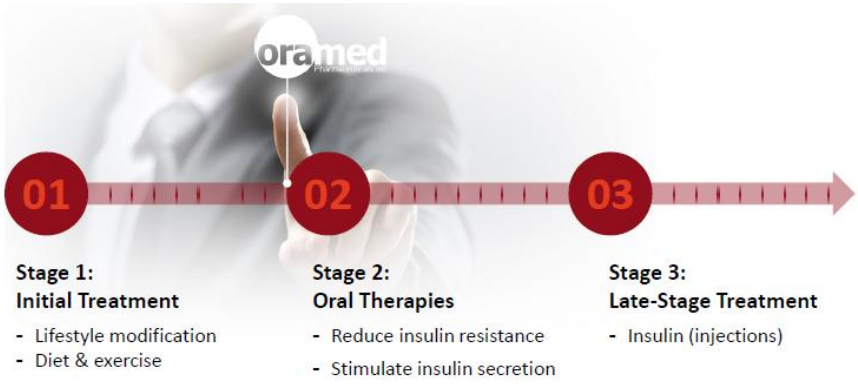


Source: [52] Consistent with the timing of administration, data shows a decrease in rapid acting insulin, a decrease in post-prandial glucose, a decrease in daytime glucose by continual glucose monitoring and an increase in post-prandial hypoglycemia in the active group

In 2014, the company conducted a Phase 2a US FDA study under an IND of ORMD-0801 in 25 volunteers with T1DM. The double blind fully randomized study had 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.

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 preserving their function, and may delay the requirement for injected insulin.



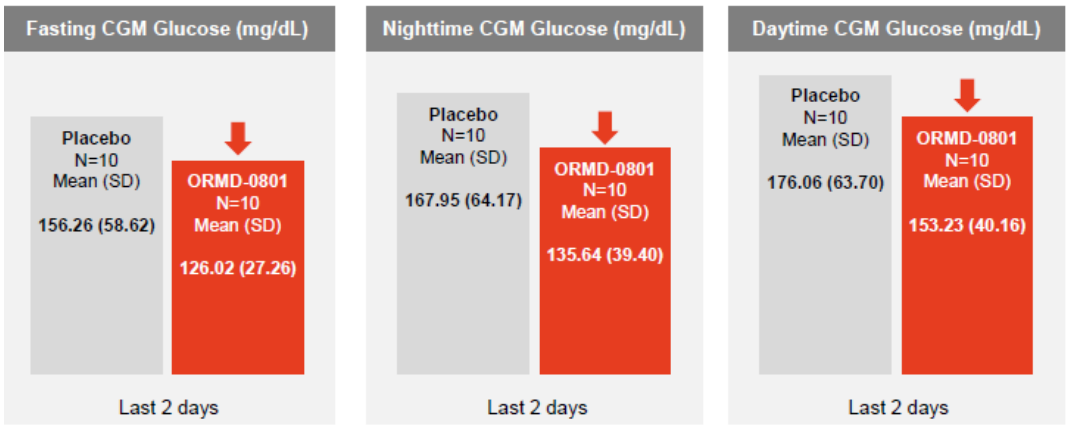
Source: Oramed's presentation September 2017

[51] Roy Eldor et al., PLOS ONE, Volume 8, Issue 4, e59524. 2013
[52] Oramed presentation Sep 2017

CLINICAL DATA

Oramed completed a series of Phase 1 and 2 clinical studies performed in Israel and South Africa. 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 diabetes 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 a reduced mean day-time and night-time glucose readings, and lowered fasting blood glucose concentrations when compared to placebo.



Source: Oramed's presentation Sep 2017

The company's latest clinical trial was a double-blind, randomized Phase 2b clinical trial performed in the US under a FDA IND. The trial included 180 T2DM diabetic patients for 28-day treatment, 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 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 l (glycated haemoglobin) levels, the most commonly used biomarker of glycaemic 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 intended. The benchmark for FDA approval stands at 0.5% HbA1c lowering.

Source: Oramed presentation Sep 2017

ORMD-0801 appears so far 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 with its oral insulin capsule Phase 2a results.

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

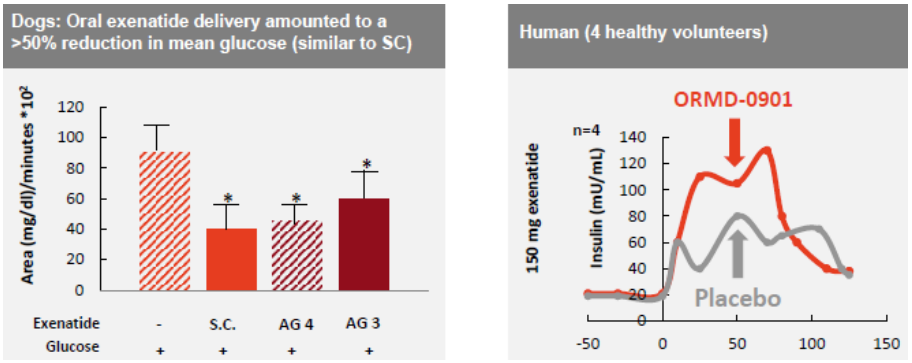
Oramed's oral GLP-1 capsule is based on Exenatide, a GLP-1 receptor analog which mimics the natural hormone in the body, with longer-lived residence in the circulation versus the native GLP-1 which is metabolized in less than 2 minutes. Exenatide induces insulin release at increased glucose levels and 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 orally delivered exenatide.

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.

A toxicology study was completed in 2017 with up coming final results by the end of the year, and the company is expected to file an IND[53] and move into a pharmacokinetics study followed by a Phase 2 trial in the United States that will be initiated by H2-2018.



Source: Oramed presentation September 2017

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.

1. ORMD-0801 for T2DM

ORMD-0801 for T2DM is an oral 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. **Lantus** (Glargine) of Sanofi is the most commonly prescribed long acting insulin

[53] **Investigational New Drug application** – A process by which a drug developer receives authorization from the US FDA to perform clinical trials in the US.

based on its well established safety profile and extensive clinical experience. In 2016, its sales reached almost $5 billion. The other biosimlar 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 competition landscape includes direct and indirect competition as follows:

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

- **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 an 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 those mentioned,[54] companies that develop oral insulin are at an early preclinical stage or discontinued their oral drug development such as in the case of Novo Nordisk. In 2016, **Novo Nordisk** discontinued its development of LAI-338, a new long-acting oral basal insulin analogue for daily administration for the treatment of type 1 and type 2 diabetes. Despite its promising results in Phase 2a, a much higher dose of insulin was required to achieve the desired glucose lowering effect. The low bioavailability made the drug non-commerciable, and therefore not worthy of investment.

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 (see Apendix C, T2DM management for more details), as detailed in the table below. 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.

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 the 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 be justifiable as a substitute for other classes of drugs currently given at earlier treatment stages. **We believe that the clinical profile of ORMD-0801 in its upcoming 90-day HbA1c trial will determine its position in the treatment profile for type 2 diabetes.**

[54] Data source: Pharmaprojects

In terms of cost, the existence of multiple classes of diabetes drugs and a wide competition landscape, allows payers to force discounts and rebates from manufactures in turn for favorable positioning. Accordingly, the net price paid for diabetes drugs is frequently much less than the Wholesale Acquisition Cost (WAC) primarily due to rebates negotiated with Pharmacy Benefit Management (PBM) organizations. 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 more it will correspond to a price increase. We assume that oral insulin will be priced with 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. In this context, the DPP4 inhibitor Januvia (Sitagliptin) of Merck has a premium price of $420 per 30 tablets/pack, but still it is the second best seller after the Glargine insulin injection. 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.

2. ORMD-0901 oral GLP-1

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

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. AstraZeneca's Byetta (exenatide) and Bydureon (exenatide extended release) are two GLP-1 class drugs that drive strong sales; combined full-year US sales for Bydureon/Byetta were $627m. Around 75% of their sales came from the new dual-chamber pen.[55]

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 are expected to further increase.

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

- **Novo Nordisk** is developing NN-9924, an oral GLP-1 drug for once-daily long acting treatment of T2DM based on its Semaglutide formulation. Semaglutide is a GLP-1 agonist injection (Ozempic), launched in December 5th, 2017,[56] with expected sales of $2.4b by 2022.[55] The oral GLP-1 couples Semaglutide with Emiphere's propietary oral delivery platform by using SNAC (Sodium N-[8-(2-hydroxybenzoyl) Amino] Caprylate) carrier technology. Currently the product is undergoing phase 3 clinical trials with results espected by 2018. So far, phase 2 trial results show significant, dose dependent reduction in HbA1c levels , as well as weight loss.[57]
- Another advanced product under clinical development is TTP273 developed by **TransTech Pharma** (now **vTv Therapeutics**), currently in phase 2 clinical trials for T2DM.[57]
- 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.[58]

The GLP-1R agonists market is expected to grow in coming years, but this growth will be accompanied by increased competition, as additional products are expected to reach the market, including products that combine insulin with GLP-1 agonist. Nevertheless, the benefit of an orally available GLP-1R agonist compared to the currently marketed

[55] Source: Evaluate Pharma
[56] http://www.pharmacytimes.com/print.php?url=/product-news/fda-approves-onceweekly-semaglutide-for-type-2-diabetes
[57] Source: Pharmaprojects
[58] Ma et al. Can J Biotech 1(1): 1-10. 2017

injected products is clear. We assume that ORMD-0901 oral GLP-1 will be priced at a premium over injected GLP-1, and that NN-9924 of Novo Nordisk, will be used as a comparable by its cost and efficiency, if approved for market.

The following table includes a partial list of all available drugs for T2DM, ranked by sales:

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	4,990	1,882	-15%
Januvia	Merck & Co	sitagliptin phosphate	Oral	Dipeptidyl peptidase (DPP) IV inhibitor	8/31/2006	7/26/2022	3,908	2,672	-6%
Victoza	Novo Nordisk	liraglutide [rDNA origin]	Injection	Glucagon-like peptide (GLP) 1 agonist	7/9/2009	8/22/2022	2,979	3,295	+2%
NovoRapid	Novo Nordisk	insulin aspart	Injection	Insulin analogue	9/30/1999	12/7/2014	2,339	1,981	-3%
Janumet	Merck & Co	metformin hydrochloride; sitagliptin phosphate	Oral	Dipeptidyl peptidase (DPP) IV inhibitor & biguanide	4/30/2007	7/26/2022	2,201	1,777	-4%
Humalog	Eli Lilly	insulin lispro	Injection	Insulin analogue	6/14/1996	5/7/2013	2,185	1,595	-5%
Levemir	Novo Nordisk	insulin detemir	Injection	Insulin analogue	6/30/2004	6/16/2019	2,004	996	-11%
Invokana	Johnson & Johnson	canagliflozin	Oral	Sodium glucose co-transporter (SGLT) 2 inhibitor	4/1/2013	2/26/2029	1,407	1,561	+2%
Human insulin & devices	Novo Nordisk	insulin (human)	Injection	Insulin	12/31/1984	-	1,301	1,007	-4%
Tradjenta	Boehringer Ingelheim	linagliptin	Oral	Dipeptidyl peptidase (DPP) IV inhibitor	6/15/2011	5/2/2025	1,248	1,338	+1%
NovoMix 30	Novo Nordisk	insulin aspart; insulin aspart protamine	Injection	Insulin analogue	6/30/2000	12/7/2014	1,229	1,045	-3%
Galvus	Novartis	vildagliptin	Oral	Dipeptidyl peptidase (DPP) IV inhibitor	6/30/2007	12/31/2022	1,193	1,038	-2%
Humulin R	Eli Lilly	insulin (human)	Injection	Insulin	1/1/1983	4/29/2000	1,078	1,022	-1%
Trulicity	Eli Lilly	dulaglutide	Injection	Glucagon-like peptide (GLP) 1 agonist	11/10/2014	12/31/2024	926	3,872	+27%
Farxiga	AstraZeneca	dapagliflozin propanediol	Oral	Sodium glucose co-transporter (SGLT) 2 inhibitor	11/30/2012	10/4/2025	835	1,686	+12%
Onglyza	AstraZeneca	saxagliptin hydrochloride	Oral	Dipeptidyl peptidase (DPP) IV inhibitor	8/1/2009	7/31/2023	720	473	-7%
Bydureon	AstraZeneca	exenatide synthetic	Injection	Glucagon-like peptide (GLP) 1 agonist	7/26/2011	6/30/2025	578	711	+4%
Toujeo	Sanofi	insulin glargine	Injection	Insulin analogue	3/30/2015	3/23/2028	567	1,438	+17%
Glucobay	Bayer	acarbose	Oral	Alpha glucosidase inhibitor	12/13/1993	2/27/2007	566	625	+2%
Diamicron	Les Laboratoires Servier	gliclazide	Oral	Sulphonylurea	1/15/1972	-	511	493	-1%

Tresiba	Novo Nordisk	insulin degludec	Injection	Insulin analogue	2/4/2013	9/25/2029	476	2,137	+28%
Nesina	Takeda	alogliptin benzoate	Oral	Dipeptidyl peptidase (DPP) IV inhibitor	6/15/2010	6/27/2028	454	530	+3%
Glucophage	Merck KGaA	metformin hydrochloride	Oral	Biguanide	12/31/1993	1/31/2002	429	666	+8%
Amaryl	Sanofi	glimepiride	Oral	Sulphonylurea	3/31/1996	10/6/2005	400	358	-2%
Insulin Analogues	Novo Nordisk	insulin	Injection	Insulin	9/30/1999	10/8/2014	322	282	-2%
Apidra	Sanofi	insulin glulisine	Injection	Insulin analogue	12/31/2004	1/25/2023	320	298	-1%
Glactiv	Ono Pharmaceutical	sitagliptin phosphate	Oral	Dipeptidyl peptidase (DPP) IV inhibitor	12/11/2009	-	272	231	-3%
Jardiance	Boehringer Ingelheim	empagliflozin	Oral	Sodium glucose co-transporter (SGLT) 2 inhibitor	8/1/2014	4/15/2027	256	1,752	+38%
Byetta	AstraZeneca	exenatide synthetic	Injection	Glucagon-like peptide (GLP) 1 agonist	6/9/2005	10/15/2017	254	69	-19%
Prandin	Novo Nordisk	repaglinide	Oral	Meglitinide	12/22/1997	7/11/2013	237	126	-10%
Tanzeum	GlaxoSmithKline	albiglutide	Injection	Glucagon-like peptide (GLP) 1 agonist	7/29/2014	12/31/2022	164	92	-9%
Seibule	Suzuken Group	miglitol	Oral	Alpha glucosidase inhibitor	1/11/2006	10/10/2015	161	59	-15%
Tenelia	Mitsubishi Tanabe Pharma	teneligliptin hydrobromide	Oral	Dipeptidyl peptidase (DPP) IV inhibitor	9/10/2012	-	153	245	+8%
Glyxambi	Boehringer Ingelheim	empagliflozin; linagliptin	Oral	Dipeptidyl peptidase (DPP) IV & sodium-glucose co-transporter (SGLT) 2 inhibitor	3/23/2015	4/15/2027	139	1,762	+53%
Insuman	Sanofi	insulin (human)	Injection	Insulin	4/30/1999	-	113	95	-3%
Actos	Takeda	pioglitazone hydrochloride	Oral	Peroxisome proliferator activated receptor (PPAR) gamma agonist	8/1/1999	8/17/2012	109	44	-14%
Metgluco	Sumitomo Dainippon Pharma	metformin hydrochloride	Oral	Biguanide	5/31/2010	-	104	48	-12%
Forxiga	Ono Pharmaceutical	dapagliflozin propanediol	Oral	Sodium glucose co-transporter (SGLT) 2 inhibitor	5/23/2014	-	72	146	+12%
Semaglutide	Novo Nordisk	semaglutide	Injection	Glucagon-like peptide (GLP) 1 agonist	12/31/2017	12/31/2031	-	2,422	n/a
Soliqua 100/33	Sanofi	insulin glargine; lixisenatide	Injection	Glucagon-like peptide (GLP) 1 agonist & insulin analogue	1/4/2017	7/1/2023	-	709	n/a
Semaglutide Oral	Novo Nordisk	semaglutide	Oral	Glucagon-like peptide (GLP) 1 agonist	12/31/2020	-	-	707	n/a
Ertugliflozin & Sitagliptin	Merck & Co	ertugliflozin; sitagliptin phosphate	Oral	Sodium-glucose co-transporter (SGLT) 2 & dipeptidyl peptidase (DPP) IV inhibitor	12/31/2017	12/31/2030	-	655	n/a

Source: Evaluate Pharma.

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 a 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) immunotherapy 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.[59]

Direct competitors for ORMD-0801 under development are those oral insulin projects previously mentioned as competitors for type 2 diabetes as well, 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, with its first pass of the liver, is projected to improve and restore the 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 insulin injections, which bypasses 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).

The following table shows the 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%

[59] Oramed's website

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

Financial Valuation and Projections

Financial Analysis

Revenue for 2017 annual report increased by 283% to $2.5M from $640K for 2016. The increase is attributed to additional milestone payments received in connection with the License Agreement. No revenue was recorded for 2015. Cost of revenues consists of royalties related to the License Agreement with HTIT that will be paid over the term of the License Agreement.

Research and development expenses were $10.3M in 2017 compared to $7.7M in 2016. These include costs are directly attributable to the conduct of research and development programs, including the cost of salaries, employee benefits, cost of materials, supplies, the cost of services provided by outside contractors, including services and expenses related to clinical trials, the full cost of manufacturing drugs for use in research and preclinical development.

General and administrative expenses increased by 12.5% from $2.5M in 2016 to $2.8M in 2017. The increase in costs incurred related to general and administrative activities during the 2017 fiscal year, reflects an increase in stock-based compensation costs, salaries and consulting expenses.

The net loss was $10.5M in 2017 similar to $11.0M in 2016.

Since the company's inception through August 31, 2017, aggregate losses amounted to $56.5M. As of August 31, 2017, Oramed had $4.0M in available cash, $29.5M of short term and long term deposits and investment and $5.0M of marketable securities, that is $38.5M in non-operating assets.

Operating activities burned cash of $5.8M in 2017 compared to $4.7M in 2016. Cash used in operating activities in 2017 primarily consisted of net losses resulting from research and development and general and administrative expenses, partially offset by changes in stock-based compensation expenses and deferred revenues, while cash provided by operating activities in 2016 primarily consisted of changes in deferred revenues due to the License Agreement partially offset by net losses resulting from research and development and general and administrative expenses.

To summarize, the company has financial stability. We assume no additional funds will be needed during 2018 to support further clinical and regulatory development.

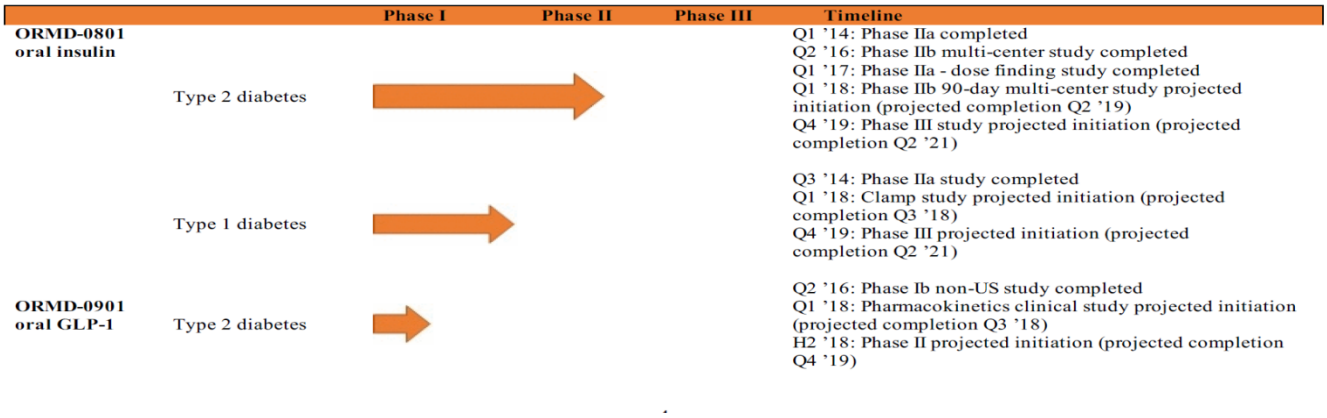
Valuation

Clinical development: Oramed's oral insulin capsule (ORMD-0801) is anticipated for use as a complementary agent to insulin injections in the treatment of T1DM and also has the potential to create a new paradigm in the treatment of Type 2 diabetes by oral delivery of insulin at an earlier stage of treatment.

We begin our pipeline valuation with ORMD-0801, and examine the program's scientific, regulatory and financial aspects:

Clinical/regulatory progress: The first two products in the company's pipeline are targeted towards T2DM, whereas the first product targets T1DM as well. Both products are based on the formulation of the carrier capsule, whereas the first pharmaceutical ingredient product is human insulin hormone, the second is GLP-1 analog. The company has completed phase 2b clinical trials of ORMD-0801 for T2DM, its oral insulin product, and ORMD-0801 for T2DM in 2016, and faces a 90 days dose-ranging HbA1c study..

We adopt the company's clinical and regulatory forecast. For T1DM, it completed phase 2a in 2014 and intends to initiate phase 3 clinical trial in 2019; for type 2 phase 3 clinical trials will begin in Q4 2019. Another product is a combination of the oral insulin capsule ORMD-801 delivered with the oral GLP-1 ORMD-0901.



Source: Company data, Annual report 2017

- R&D costs: We extrapolate phase 3 R&D costs based on phase 2 costs. We assume $14M R&D costs for ORMD0801.

- Market size: Oramed is targeting ORMD-0801 as an early treatment for 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) the equivalent number is 27 million people. We based our assumption on our market analysis presented above.

- Patent period: based on the company's data it has marketing exclusivity period of 12 years (BLA path) in the US.

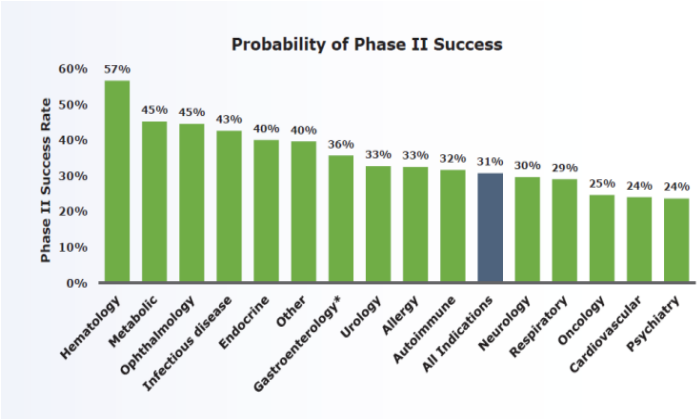
- Out-licensing agreement: reviewing recent out-licensing deals may shed light on the eagerness of pharmaceutical companies to license technologies in a specific field, the sums they are willing to pay for such technologies, and the structures of such deals. The table below summarizes deals in the insulin delivery field.

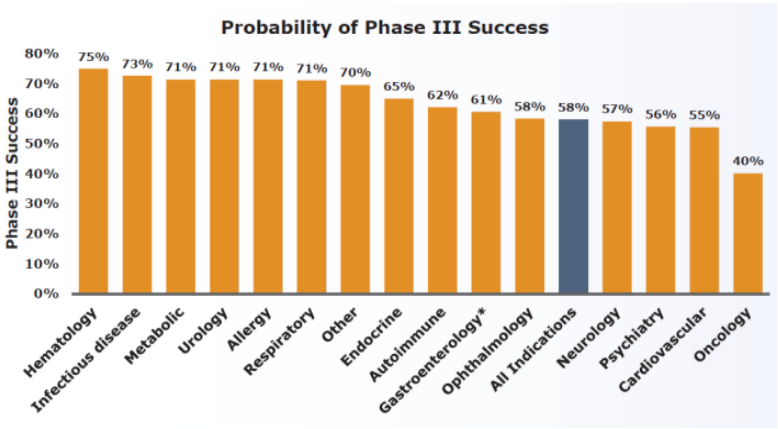
Oral insulin delivery licensing deals

Licensor	Licensee	Product	Deal terms	Development stage
Caisson Biotech	Novo Nordisk (2012)	Drug delivery technology	Total deal value: $100m. Upfront and milestone payments were not disclosed.	Discontinued
Emisphere	Novo Nordisk (2010)	Oral insulin	- $5m upfront payment. - $57.5 million in potential product development and sales milestone payments. - Unspecified royalties from sales.	Discontinued
Merrion	Novo Nordisk (2008)	Oral insulin	- Research collaboration fee - $3.5m/year. - $58m in potential product development and sales milestone payments. - Estimated 5% royalties from sales.	Discontinued
Nobex	GlaxoSmithKline (2002)	Oral insulin	- Total deal value: $283m. - Upfront and milestone payments were not disclosed.	Discontinued

We also take Oramed's recent deal with HTIT in China. Oramed out licensed HTIT exclusive rights to ORMD-0801 in greater China based on $50M payments ($38M in milestone payments, of which Oramed received $18M) and royalties (10%). We can extrapolate these numbers into few future deals to form in coming years.

Success rates – the company engages in a high-risk therapeutic area in promoting its indications. Success rate data indicates higher success rates for the metabolic specialty (45%) in comparison with the total average of all indications (31%) from phase II to phase III. Also, phase III success rates are higher (71%) than the success rate for all indications (58%). We address these clinical risks in our rNPV valuation for each indication.





Source: Clinical Development Success Rates, 2006-2015. Biomedtracker 2016.

Capitalization rate: We calculate our discount rate at 19.64% based on our CAPM model (see Appendix B).

Main valuation parameters

Indications	Current Development stage	Success Rate Phase II	Success Rate Phase III	Regulatory approval success rate	Launch	Exclusivity 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

Based on the aforementioned parameters, we evaluate Oramed's pipeline in $158.6M.

Technological Platform Valuation

Oramed's product pipeline is supported by the company's broad business and technological base. 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 field of life sciences, rather than using the conventional terminal value, normally used by non-life science companies, for the following reasons:

- The terminal value reflects a type of steady state in company sales with a certain fixed growth rate (g) based upon past data. This is not the case for life science companies, where the terminal value is derived from projects in development.

- The terminal value for a given company usually constitutes between 70-80% of its worth. In contrast, the main share of the value of a life science company is attributed to income generated during several years following product launch (for the most part, approximately 6-10 years), after which a certain decline occurs (for example, expiration of a patent, and the emergence of competing products).

The technological platform valuation is based on the average number of new projects that a company can yield annually. Estimating the capitalization value of future projects is based on pre-clinical and clinical development aspects, assessment of unallocated costs, and a higher capitalization rate than the one used during the forecast years, due to the uncertainty of the company's future projects.[60]

Main technology platform valuation points:

- We assume one new project every three years with an average value of $52.6M (equal to the average value of the current pipeline programs)
- Unallocated costs are mainly G&A and sales costs, with a similar share from the project's value as in the current pipeline programs
- We estimate unexpected costs to be 10% of the average value
- Statutory tax rate of 15% as Oramed is a US company
- The capitalization rate is higher than the one used in the pipeline valuation, reflecting the increased uncertainty
- It is assumed that the "platform" generates projects for n years: in our valuation, and based on the average patent period, n=19 years. We therefore subtract from the technological platform value all projects generated after n years (the exceeding projects).

The following formula reflects the value of the technology:

$$\mathrm{V(tech)} = \frac{(fVproject - (1+r)costs)}{r} * 1 - \frac{1}{(1+r)\text{^n}}$$

Main valuation parameters of the technological platform:

Average New Projects per Year	**0.25**
Project Value ($'000)	**52,855**
Unallocated Costs ($'000)	**-21,065**
Unexpected Costs ($'000)	**-5,286**
Tax	**15.0%**
Capitalization	**24.6%**
Terminal Technology Value ($'000)	**22,859**
Technology Value - 2017-2035 ($'000)	**348**
Technology Value ($'000)	**22,511**

[60] Bogdan & Villiger, "Valuation in Life Science - Practical Guide", 2008, Second Edition.

Equity Value

Non-operational assets/liabilities and unallocated costs

As of August 31, 2017, Oramed had $4.0M of available cash, $29.5M of short term and long term deposits and investment and $5.0M of marketable securities, i.e. $38.5M non operating assets. The company has no loans.

Oramed also has 6.92% holdings in DNA Biomedical Solutions Ltd (TASE: DNA). Frost and Sullivan's initiation analysis report on the company be found here. We evaluate the fair value of DNA Biomed at $30.9M as at December 2017. Thus, Oramed's holdings value amounts to $2.1M. **The equity valuation elements are presented in the below table:**

Equity value:

Pipeline Analysis		rNPV ($000s)
ORMD 0801	Type 2	81,015
ORMD 0801	Type 1	62,572
ORMD 0901	GLP-1	14,979
Total rNPV Pipeline		**158,566**
Unallocated Costs		-21,065
Terminal Technology Value		**22,511**
Enterprise Value		**160,011**
Non-operational assets/liabilities		**38,505**
D.N.A. Biomedical Solutions Ltd. (TASE: DNA)	6.92%	**2,138**
Equity Value		**200,655**

Based on the aforementioned parameters, we evaluate Oramed's equity value at $200.7M / NIS 708.3M.

Sensitivity Analysis

The table below presents Oramed's price target in relation to the capitalization rate and the market share ORMD 0801 will held. 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 (see Appendix B) and 0.5% change in our estimation on Oramed's market share between 2% to 3% market share. Oramed has 13.3M 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 estimate the price target to range between NIS 49.8 and NIS 56.6; a mean of NIS 53.2.

Price Forecast Risks

Biotech companies, particularly those in research and development stages, are relatively high-risk companies. Key risks that may affect Oramed include:

Delay/postponement of marketing regulatory approval decisions

In order for Oramed to market or out-license its products, it is necessary for them to receive marketing approval from regulatory agencies, such as the FDA (US) and EMA (EU). Our estimates regarding time to market are based on the assumption that these products will successfully complete Phase II and III clinical trials without significant delays. Failure to fulfill the clinical endpoints of these experiments will force the company to conduct additional clinical trials or abandon the development of certain projects. We consider this to be the main risk factor for the company's activity at this stage.

Risks involved in obtaining sources of financing, and stock trading

As a biotech holding company in the research and development stage, with minimal revenue from sales, Oramed will be required to conduct fundraising prior to becoming profitable, unless early licensing deals are made. Failure to raise funds, or fundraising under conditions that are not beneficial to the company, may affect its worth. In addition, the low level of tradability may deter some investors from buying Oramed stock.

General risks related to similar companies

The value of small companies in the biotech field could, to a relatively high degree, be affected by publications not related directly to their activities. Such publications may refer, for example, to competitors, macro trends in the healthcare sector, and political events.

Contact Details & Management

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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.

Josh Hexter, Chief Operating Officer, VP Business Development

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

Dr. Ronald Law, Chief Strategy Officer

Dr. Law serves as Chief Strategy Officer for Oramed Pharmaceuticals. He brings over 25 years academic and pharmaceutical industry experience in diabetes, cardiovascular disease, and obesity. During his industry career at Takeda Pharmaceuticals, Dr. Law served in a variety of roles spanning US Medical Affairs, Global Medical Affairs, Corporate Strategic Planning, Global Scientific Affairs and Intelligence, and R&D External Innovation. Prior to joining Takeda, Dr. Law was an Associate Professor of Medicine in the Endocrinology Division, UCLA School of Medicine. Dr.

Law received a PhD in Molecular Biology from UCLA and a JD from the Whittier College School of Law. He is a member of the American Diabetes Association and the American Heart Association.

Dr. Simon Bruce, VP Medical Affairs

Dr. Bruce serves as Vice President of Medical Affairs for Oramed Pharmaceuticals. Dr Bruce has made important contributions to new product development and clinical therapeutics in diabetes and metabolism over the past 20 years. He has broad experience across all phases of clinical development and has been responsible for clinical development strategy and execution from pre-IND to first-in-human through Phase 3 planning, execution and filing. He has led clinical development of multiple compounds in the metabolic and diabetes therapeutic areas including DPP4 and SGL T2DM inhibitors, GLP-1 agonists, leptin and prandial insulins among others. He has trained in Internal Medicine with sub-specialization in Endocrinology at the NIH. He has held positions of increasing responsibility in both large pharmaceutical and small to medium sized biotech companies. Most recently he served as Chief Medical Officer with Adocia Inc., working on ultra-rapid insulin in collaboration with Eli Lilly.

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

Appendicies

Appendix A - Financial Reports

	For the year ending	
Balance Sheet ($000s)	31.8.2016	31.8.2017
Current assets		
Cash	3,907	3,969
Short term deposits	24,254	13,293
Marketable securities	2,855	2,860
Restricted cash	16	16
Other assets	198	159
Total current assets	**31,230**	**20,297**
Long-term assets		
Long-term assets	11,043	16,232
Marketable securities	530	2,151
Employee rights	11	14
PPE	16	18
Total assets	**42,830**	**38,712**
Current liabilities		
A/P	1,411	2,716
Deferred revenues	2,162	2,449
Related parties	48	-
Total current liabilities	**3,621**	**5,165**
Long-term liabilities		
Deferred revenues	12,604	13,837
Employee rights	14	18
Others	401	454
Total Liabilities	**16,640**	**19,474**
Equity	**26,190**	**19,238**

	For the year ending			
Profit and Loss ($000s)	31.12.2014	31.12.2015	31.12.2016	31.12.2017
Revenues	-	-	641	2,456
Cost of revenues	-	-	490	187
Research and development, net	3,277	4,781	7,709	10,281
General and administrative	2,629	2,602	2,452	2,759
Financial income, net	214	150	381	691
Loss before taxes on income	- 5,692	- 7,233	- 9,629	- 10,080
Taxes (tax benefit)	4	- 1	1,335	400
Net loss	**- 5,696**	**- 7,232**	**- 10,964**	**- 10,480**

Appendix B - Capitalization Rate

Cost of equity capital (ke) represents the return required by investors. The capitalization rate is calculated using the CAPM (Capital Asset Pricing Model). It is based on a long-term 20-year T-bond with a market risk premium, and based on Professor Aswath Damodaran's (NYU) commonly used sample (www.damodaran.com). As of December 31, 2016, the US market risk is estimated at 5.69%. A three-year market regression Beta is 1.25, according to a sample of 426 companies representing the US biotechnology sector. We used an unleveraged beta of this sample, which is higher than a leveraged beta, due to high rate of cash versus debt. The implied CAPM is 7.8%.

CAPM model (ke) is estimated as follows:

$$ke = rf + \beta(rm-rf) + P$$

Oramed is a small cap company, in which marketability and size premiums need to be considered. Duff and Phelps data from 1963-2016 indicates that an 11.79% premium needs to be added to the CAPM for small cap companies. We therefore estimate the company's CAPM to be 19.64%.

CAPM Model		Value	Source
Long-term (20 years) T-bond	R(f)	0.76%	US Department of the Treasury (20Y)
Market risk premium	R(m)- R(f)	5.69%	based on Professor Damodaran's sample (1/17)
Beta unleveraged	β	1.25	Beta sample of 426 Drugs (Biotechnology) firms (1/17)
Cost of Capital	ke	7.8%	
Size Premium		11.79%	Duff and Phelps data, 10dz.
CAPM	CAPM	**19.64%**	

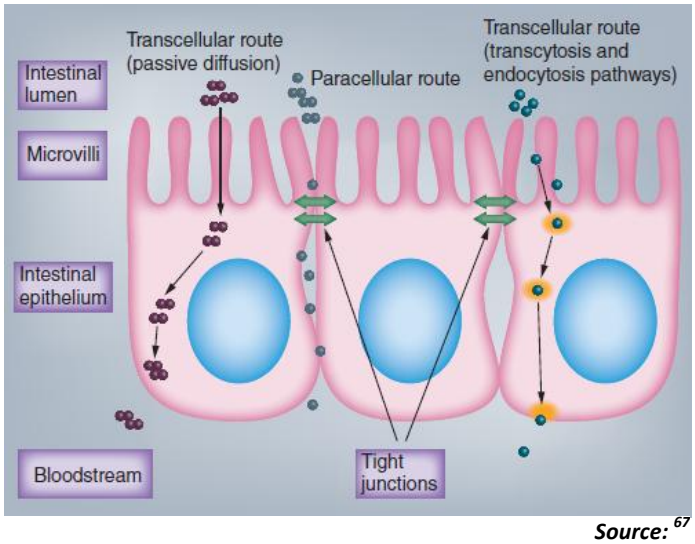
Appendix C - Technology and Clinical background

Technology background

Oramed's capsule development platform for oral delivery of peptides and proteins, 'Protein Oral Delivery Technology' (POD™), is based on over 30 years of research. This unique asset may be applied to an array of therapeutic substances such as peptides and proteins that are currently given as injectable alternatives, including, for example, vaccines and interferon signalling proteins.

Given their high selectivity, peptides and proteins have immense potential as therapeutics, compared with the typical small-molecule drugs that currently make up the majority of the pharmaceutical market.[61] Peptides can be designed to target a broad range of molecules, offering multiple advantages in fields such as oncology, immunology, infectious disease and endocrinology. The improved patient compliance with orally delivered therapies has seen a lot of interest in the development of systems allowing for the oral delivery of peptide and protein therapeutics.[62]

On the other hand, the gastrointestinal (GI) environment presents several obstacles for the delivery of therapeutic proteins that must remain intact and enter the bloodstream. Oral bioavailability of peptides is limited by degradation in the gastrointestinal (GI) tract due to harsh pH conditions and protease cleavage, as well as their inability to cross the epithelial barrier. These therapeutics tend to have a high molecular weight, low lipophilicity and charged functional groups that hamper their absorption.[63] Moreover, the food effect might change the rate and extent of absorption if the drug is administered before or after a meal or under fasting conditions.[64]



Source: [67]

Consequently, these characteristics lead to the low bioavailability of most orally administered peptides (<2%).[65] On top of that, even after the drug is absorbed, first-pass metabolism, known as the first-pass effect, can greatly reduce the fraction of a drug that reaches the systemic circulation through the liver. The liver metabolizes the drug, reducing the amount of the active, parent compound that enters systemic circulation.[66]

Methods to improve the bioavailability of protein therapeutics through oral administration can be broadly classified into categories of structural modifications, enzyme inhibitors, absorption enhancers and carrier systems. Despite these advancements, and promising results in clinical trials for some of these approaches,[67] realization of orally administered biologicals with its accompanying advantages remains an elusive goal.

Oramed's oral delivery platform

Oramed's technology for oral delivery of biological macromolecules addresses these challenges by co-administration of therapeutic proteins within a capsule carrier, including; **enteric coating** – to protect from degradation in the

[61] Craik, D. J. et al., Chem. Biol. Drug. Des. (2013) 136–147
[62] Maher S, et al., Drug Discovery. Today. Technol. (2012) 9(2), 113-119
[63] Aungst B, et al. . J. Control. Release. (1996) 41(1), 19–31
[64] Kidron, M., et al., J Diabetes Sci Technology (2009) 3(3), 562-567
[65] Bruno, B.et al., Therapy Delivery. (2013) 4(11), 1443–1467
[66] Pond SM, et al.,. Clin. Pharmacokinetic (1984) 9(1), 1–25
[67] Joël Richard , Ther. Deliv. (2017) 8(8), 663–684)

stomach**, protease inhibitors** – to slow the rate of protein degradation in the intestine**, absorption enhancer** – to promote absorption through the intestinal epithelium to the bloodstream by increasing membrane permeation, and an **emulsifier** – to enhance the drug solubility and bioavailability.

The platform carrier protease inhibitor cocktail, together with the absorption enhancer, are optimized for scale up manufacturing. Several peptides have been tested so far with Oramed's platform and have shown feasibility including GLP-1 analogue, glucagon, and leptin, to name a few. To date, the largest protein delivered by Oramed's capsule is human insulin consisting of 51 amino acids with a molecular weight of 5.8 kDa.[68] Oramed's mission is fully focused on using its platform technology for the delivery of human insulin for patients with diabetes, a disease of epidemic global proportions.

Clinical background

Oramed's primary mission is to provide an oral solution for diabetes

Diabetes is a metabolic disorder characterized by excess glucose in the blood (hyperglycemia) and disturbances in carbohydrate, fat and protein metabolism, resulting from defective insulin secretion or insulin action. The actual metabolic abnormalities encountered vary depending on the underlying cause of the disease.

Type 1 diabetes (T1DM) is an autoimmune disease with a strong genetic component that results from cell-mediated destruction of pancreatic β-cells, which are the primary source of insulin in the body. T1DM accounts for roughly 5% of the diabetes population, typically strikes during childhood (1-15 years of age), and is treated predominately by insulin injections and pumps.

Type 2 diabetes (T2DM) is the most prevalent form of diabetes, accounting for about 90% of the diabetic population. The pathophysiology of T2DM is distinct from that of T1DM in that the patient's pancreas may still produce insulin. Rather, onset of T2DM is characterized by insulin resistance, whereby the body's tissues fail to respond normally to insulin either by the under-production of insulin or inadequate use of insulin. In either case, the result is high, unregulated blood sugar levels, with increased production of glucose in the liver. Over time, blood glucose levels rise, a condition known as hyperglycaemia. Hyperglycaemic episodes, which are toxic to the insulin-producing β-cells of the pancreas, reduce the number of β-cells and impair the performance of those that remain, resulting in pathology similar to that seen in T1DM diabetic patients. Initially, T2DM diabetics produce excessive insulin, which results in hyperinsulinemia, a condition that is an early indicator for the disease and is associated with hypertension, obesity, and dyslipidaemia. Eventually, pancreatic insulin production decreases below normal, leaving the patient with hyperglycaemia and the need for exogenous insulin.

Hyperglycaemia can lead to serious complications including heart disease, eye complications, kidney disease, neuropathy, ulceration, gum disease, and infection of the feet, skin, and teeth. Hypoglycaemia (low blood glucose) occurs when blood glucose drops below normal levels. In diabetes patients treated with insulin, hypoglycaemia may be caused by excessive insulin administration (hyperinsulinemia). While hypoglycaemia is usually mild and can be treated quickly and easily, if left untreated, hypoglycaemia worsens and may cause confusion, clumsiness, or fainting. Severe hypoglycaemia can lead to seizures, coma, and even death.

T2DM diabetes is most prevalent in overweight adults with a genetic predisposition to the disease, and is treated initially with balanced diet and exercise. As the disease progresses, patients are treated with metformin and other classes of oral drugs, and eventually with insulin injections and other pharmacological interventions, should those earlier interventions have proved insufficient.

[68] Zhou Fu et l., Curr Diabetes Rev. (2013) Jan 1; 9(1): 25–53

Diabetes is typically diagnosed by fasting blood glucose levels (done after 8 hours fast) and/or after a glucose challenge. Excessive production of glucose at night by the liver is a significant challenge in diabetes management. Along with fasting blood glucose levels, the most commonly used biomarker of glycaemic control is glycated haemoglobin (HbA1c), which is also regularly used for monitoring the effectiveness of diabetes therapies, since it is a measure of glycaemic control over the previous three months. Ranges for fasting blood glucose and HbA1c used for diagnosis of diabetes and diabetes care are presented in the table below.

Summary of Fasting Glucose and HbA1c Levels in Diabetes

Indication	Fasting Glucose Level	HbA1c
Normal glucose metabolism	70 to 99 mg/dL	Up to 5.7%
Pre-diabetes (impaired fasting glucose)	100 to 125 mg/dL	5.7% to 6.4%
Diabetes	126 mg/dL and above (on more than one testing)	>6.5%
Hypoglycemia	<70 mg/dL	Not monitored
Hyperglycemia	>250mg/dL	>7.5%

All patients with T1DM diabetes, as well as around 40% of T2DM diabetics (after it has been determined that their blood glucose levels cannot be controlled by diet, weight loss, exercise, and oral medications), must monitor their blood sugar levels through frequent measures of blood glucose. Eventually, almost all patients with T2DM will administer doses of insulin via injections or an insulin pump, multiple times every day. The goal of T2DM treatment is to control blood sugar early, in order to prevent or delay the development of complications and, in those who already have them, to slow or halt their progression, if possible.

There is no "standard dose" for insulin. Insulin types differ in how fast they start to work and how long they last in the blood. Diabetes patients usually require 1-4 insulin shots a day. The best type(s) of insulin for each patient are those fit to achieve the best blood glucose control based on many factors, including the patient's individualized response to insulin, lifestyle choices (diet, alcohol consumption and exercise), willingness to go through multiple daily injections, and more.

Insulin treatment consists of fast-acting insulin taken prior to meals to stabilize blood sugar, and slow acting (basal) insulin, which helps to maintain stable insulin levels during fasting periods. The pharmacological treatment by the American Diabetes Association (ADA) guidelines recommends multiple daily insulin injections of basal and prandial insulin, or continuous subcutaneous insulin infusion (CSII) therapy, and the use of insulin analogs, especially if hypoglycaemia is a problem. Different types of injected insulin are currently available on the market, including rapid-acting, short-acting, intermediate-acting, long-acting and pre-mixed. For this reason, among others, the development of an altered insulin administration method (like oral insulin) has so far encountered many difficulties with regard to the precise control of glucose levels required and the high variability between different diabetes patients. Should oral insulin be developed and approved for market, it is not neccesarily poised to completely replace injected insulin, but to either postpone the initiation of insulin injections or to reduce the number of daily injections required.

Among the T2DM population, patients as well as physicians, struggle with the complexity of insulin regimes and the chances of weight gain, as well as the invasiveness of a needle prick. In addition, since the injected route of insulin administration is non-physiological, targeting mainly muscle and fat tissues and bypassing first pass of the liver, it may lead to hyperinsulinemia and consequent hypoglycaemic events.

T2DM treatment management

Treatment for type 2 diabetes is becoming complicated. There are multiple therapeutic classes, and multiple drugs available in each class. In addition, there are multiple types of insulin (both slow and fast acting), and different modes of delivery for each of them (e.g. pens, needle free injectors, pumps and inhalation products such as MannKind's Afrezza). Management of T2DM begins with Metformin as the standard first line therapy. However, eventually the disease will progress, requiring therapy in a combination of 3-4 theraputic classes, leading to daily insulin. Once on insulin therapy, patients begin with a basal insulin and add a prandial insulin when needed.
The following table details the different pharmacological classes for T2DM management from first line Metformin to insulin injections.[69] [70] [71]

Pharmacologic Class	Trading Name/Generic	Hypoglycemia	Weight Change	HbA1c	CVD Risk	Contraindications / Side Effects
Metaformin	Generic	No	Neutral	1.5	Minimal	Kidney, liver; GI side effects
SGLT-2 Inhibitors	Invokana, Farxiga, Jardiance	No	Loss	0.5-0.9	Protective	Genitourinary infections
GLP-1 Agonists	Victoza, Bydyreon, Byetta, Trulicity, Tanzeum	No	Loss	1.0-2.0	Protective	GI side effects, MTC
DPP4 Inhibitors	Januvia, Onglyza, Tradjenta	No	Neutral	0.6-0.8	None	None
Sulfonylureas	Generic	Yes	Gain	1.5	None	Minimal
Thiazolidinediones	Generic	No	Gain	0.5-1.4	Variable	CHF, liver
Long-acting Insulins	Tresiba, Lantus, Toujeo	Yes	Gain	1.5-2.5	TG, HDL improve	Hypoglycemia
Short-acting Insulins	Novolog, Humalog	Yes	Gain	1.5-2.5	TG, HDL improve	Hypoglycemia

Metformin (Glucophage) is the first line therapy, characterized by a robust HbA1c reduction without worsening other metabolic risk factors. Its price is affordable, and it can be, and commonly is, used in combination with other drugs.

Typically, **GLP-1** (Glucagon-like peptide) **agonists**, **SGLT2** (Sodium glucose co-transporter 2) **inhibitors,** or **DPP4** (Dipeptidyl Peptidase (DPP) IV) **inhibitors** constitute second and third treatment steps, and may be prescribed in either order. They are considered safe and contribute to weight loss. **SGLT2** drugs work by enhancing the excretion of glucose in urine, leading to reduction of blood glucose. AstraZeneca and Bristol-Myers Squibb were the first to receive regulatory approval (from the European Commission) for an SGLT2 inhibitor – Forxiga (dapagliflozin).
As for **GLP-1**, Amylin's twice-daily Exenatide (Byetta) was the first GLP-1 mimetic, first approved in 2005 for treatment of type 2 diabetes (later on acquired by AstraZeneca). The choice between the two favors GLP-1 with respect to its side effect profile and SGLT2 with respect to its cost.

[69] Diabetes Care. (2008) 31(1): 173-175
[70] Expert Opin Drug Saf. (2017) 16(3):351-363
[71] Diabetes Care. (2016) 39(5):717-25

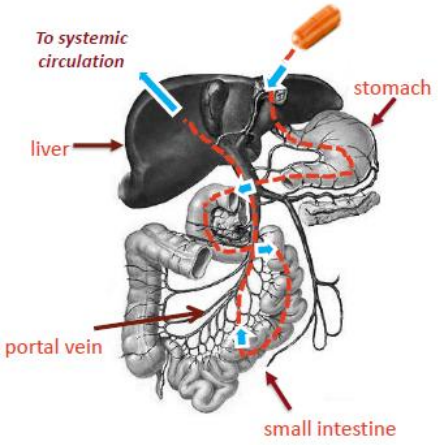
DPP4 inhibitors are also attractive despite their high cost, however, after these patents expire, it is expected that these drugs will increase in use, and also be deployed earlier on in the treatment timeline, given the lowered cost. DPP4 drugs block DPP4 enzyme, consequently increasing the GLP-1 and GIP incretin levels. The oral DPP4 blockbuster Januvia (of Merck), launched in 2006, is the second best seller in the type 2 diabetes drug market, turning over almost $4 billion in 2016 sales.[72]

Sulfonylures and **Thiazolidinedione** are drug classes which are used less these days due to the SGL2 and DPP4 alternative drug classes. Due to the risk of hypoglycemia, Sulfonylures are used less frequently, despite their low price. Thiazolidinedione class of drugs decreases the amount of fatty acids present in circulation, consequently increasing oxidation of glucose from the blood. However, they pose an increased risk of heart failure.

Oral delivery of insulin

Delivering insulin via an oral capsule is a worthy goal with two major potential benefits; increased compliance, and delivery of insulin via the portal vein to the liver.[73] The first pass of the liver mimics the physiologically endogenous insulin route, in which insulin is secreted from the pancreas and travels through the portal vein into the liver. In this way, the liver's management as the gate keeper of the body's glucose is achieved, with better blood glucose control. The externally-administered oral insulin is integrated into the physiological glucose-insulin cycle and compensates for the lack of naturally occurring insulin on demand. Potentially, this may improve the body's response to the treatment when compared to subcutaneously delivered insulin, which bypasses the liver. For this same reason, it is projected to have a more favourable impact on hypoglycaemia (low blood sugar), better safety profile, less hyperglycaemia (delivered insulin inhibits glucose overproduction).

Intravenous (IV), subcutaneous (SC), intrarectal, pulmonary and other delivery routes of insulin minimize the issue of absorption through the GI, and avoid or minimize the first-pass effect.[74] However, only a fraction of it reaches the liver. Additionally, since the injected route of insulin administration is non-physiological, targeting mainly muscle and fat tissues and bypassing the liver, it may lead to hyperinsulinemia and consequent hypoglycaemic events. Another issue is that it selectively promotes glucose uptake in fat and muscle cells and can lead to weight gain in patients.



Source: Oramed, Company Presentation. September 2017

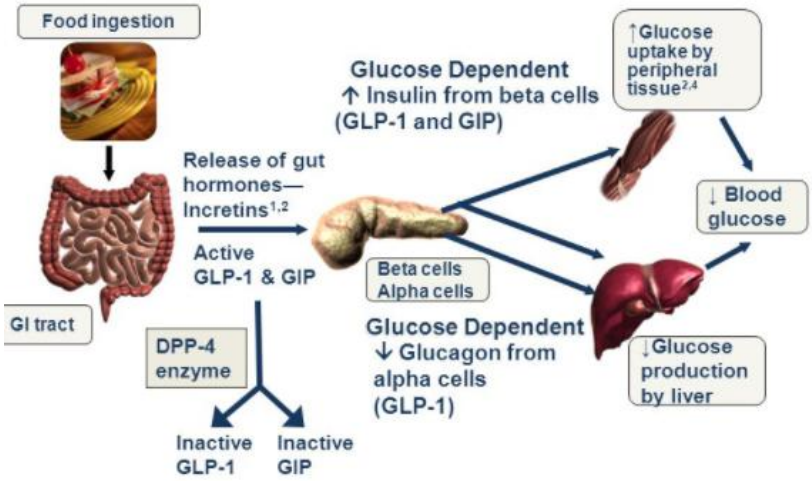
Oral delivery of GLP-1

Focusing on diabetes, Oramed also uses its platform technology to deliver Glucagon-like peptide 1 (GLP-1) analog for Type 2 diabetes patients.

GLP-1 is an incretin hormone –one of two incretins, which are intestinal-derived factors that facilitate insulin secretion following meals. The total insulin secreted after oral glucose accounts for at least 50% in response to incretins (the incretin effect).[75] GLP-1 is a 30-amino acid peptide released in significant quantities into the circulation within minutes of a meal and has multiple physiologic effects, including regulating gut motility, increasing the secretion of gastric acid and enzymes, and stimulating insulin secretion by pancreatic β-cells. Through activation of the GLP-1 receptor (GLP-1R), GLP-1 stimulates insulin secretion and suppresses glucagon secretion thereby lowering blood glucose. GLP-1 receptors are found in high concentrations on pancreatic β-cells and in multiple other tissues

[72] Evaluate Pharma
[73] Joël Richard , Ther. Deliv. (2017) 8(8), 663–684
[74] Brunton L. Book titled The Pharmacological Basis of Therapeutics, by McGraw-Hill Medical Publications
[75] Wook Kim et al., Pharmacol Rev. (2008) 60(4): 470–512

involving activation of several signalling pathways. GLP-1 improves β-cell sensitivity to glucose and may also enhance β-cell survival by increasing their neogenesis and proliferation, and decreasing apoptosis. GLP-1 is short-lived in the circulation because it is rapidly metabolized by the enzyme Dipeptidyl peptidase-4 (DPP-4), such that the half-life of native GLP-1 is less than two minutes.



Source: The role of incretins in glucose homeostasis. [76]

Due to the reduced incretin effect in patients with T2DM diabetes, increasing the levels of incretin hormones, especially GLP-1, is a natural approach to therapy. Exogenous administration of GLP-1 receptor (GLP-1R) agonists was shown to decrease fasting blood glucose and postprandial glucose concentrations, preserve β-cell function, restore insulin secretion and sensitivity, improve weight loss and does not cause hypoglycaemia.

Metformin, is the first line of pharmacologic treatment for T2DM diabetics. Oral medications, such as thiazolidinediones and sulfonylureas are considered second and/or third line therapies, which offer solid efficacy benefits, but are also associated with safety concerns and side effects. Other classes include SGLT2 (Sodium glucose co-transporter 2) inhibitors and DPP4 (Dipeptidyl Peptidase 4) inhibitors, which are more commonly used nowadays. When oral medication is not enough to control blood glucose levels, patients with T2DM diabetes are usually given a GLP-1R agonist treatment and/or insulin injections to regulate their blood sugar levels. Guidelines for the management of hyperglycaemia in T2DM diabetics acknowledge the benefit shown by GLP-1R agonists over traditional oral anti-diabetics in reducing blood glucose. As such, they are included in the guidelines published by the American Diabetes Association (ADA), the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinologists (ACE), and the National Institute for Health and Clinical Excellence (NICE) in the UK. Current delivery of GLP-1 agonist is only via injection.

[76] Dr. M Mukhyaprana Prabhu, India 2nd International Endocrine Conference, Current Status of Incretin Based Therapies in T2DM Diabetes, (2014) Chicago 20th Oct. URL:http://slideplayer.com/slide/5835316/.

Appendix D – Bios of Key Analysts

Kobi Hazan is the Lead Analyst at Frost & Sullivan Research & Consulting Ltd., a subsidiary of Frost & Sullivan in Israel. He has over 14 years of experience in capital markets, including; research, analysis, investment advisory, and management. Mr. Hazan served as a Fund Manager for provident and mutual funds at Analyst Ltd. and, since 2012, he owns and manages the Amida Israel Fund, a hedge fund specializing in Israeli equities. Kobi holds an Economics and Management degree from The College of Management Academic Studies. He is licensed as an Investment Advisor in Israel.

Saravanan Thangaraj is a Senior Research Analyst in the Transformational Health group at Frost & Sullivan. He has over four years of experience in management consulting and has advised clients on strategy and business. He has also authored many off the shelf industry insight reports during his time at Frost & Sullivan. Before Frost & Sullivan, he has worked as a Business Analyst for projects under the Life Sciences and Financial Services domains at a top multinational IT firm. He has also conducted research at top medical institutions in India, like The National Institute of Mental Health and Neuroscience (NIMHANS) in the Department of Psychopharmacology. His industry experience includes Biotechnology, Biopharmaceuticals, IVD, and Health Systems. Saravanan holds a Bachelor of Technology in Biotechnology and a Master of Business Administration from PSG College of Technology, India.

Dr. Tiran Rothman is an Analyst and Consultant at Frost & Sullivan Research & Consulting Ltd., a subsidiary of Frost & Sullivan in Israel. He has over 10 years of experience in research and economic analysis of capital and private markets, obtained through positions at a boutique office for economic valuations, as chief economist at the AMPAL group, and as co-founder and analyst at Bioassociate Biotech Consulting. Dr. Rothman also serves as the Economics & Management School Head at Wizo Academic College (Haifa). Tiran holds a PhD (Economics), MBA (Finance), and was a visiting scholar at Stern Business School, NYU.

Dr. Moria Kwiat is a specialist in the field of biotechnology. Moria holds a Ph.D. in Chemistry and nanotechnology, M. Sc. and B. Sc. in Biotechnology from Tel Aviv University. Moria has a broad scientific background in interdisciplinary fields and over 12 years of conducting original research, with expertise at the interface between biology and materials worlds. She has a strong track record of developing biosensors for diagnostics utilizing electrical devices. Moria is the co-author of multiple scientific papers with vast experience in scientific writing.

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