Efficacy and safety of ORMD-0801(Insulin Capsules) in patients with type 2 diabetes mellitus inadequately controlled with metformin over 28 days: a randomized, double-blind, placebo-controlled study. (ORA-D-007)

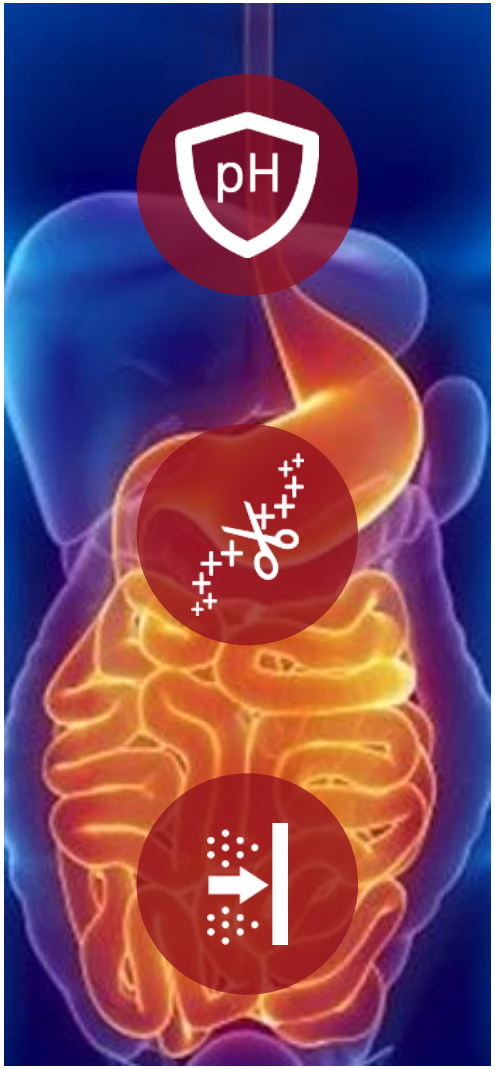
Roy Eldor [1], Joel Neutel [2], Ken Homer[3], Miriam Kidron [4]

1 Diabetes Unit, Institute for Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center , Tel Aviv, Israel.
2 OCRC, Tustin, California, USA
3 Integrium, LLC, Tustin, California, USA
4 Oramed Pharmaceuticals, Jerusalem, Israel.

Disclosures

- The study was conducted by ORAMED Inc., Jerusalem, Israel.
- Financial support was provided by ORAMED Inc., Jerusalem, Israel.
- R. Eldor is a member of ORAMED's scientific advisory board.
- M. Kidron is an employee and shareholder of ORAMED Inc., Jerusalem, Israel.

An Unsolved Challenge:
Proteins and Peptides do Not Survive the Digestive System



Harsh pH
Stomach acidity cleaves and shreds protein

Protease attack
Proteases attack and break down proteins

Absorption barrier
Most therapeutic proteins fail to be absorbed via the intestinal wall (barrier)

Oramed Technology Protects Drug Integrity and Increases Absorption

pH shield for passage through stomach
pH sensitive enteric coating protects capsule contents.
Capsule dissolves only once in small intestine

Protease protection
Protease inhibitors stave off and protect the active agent from protease attack

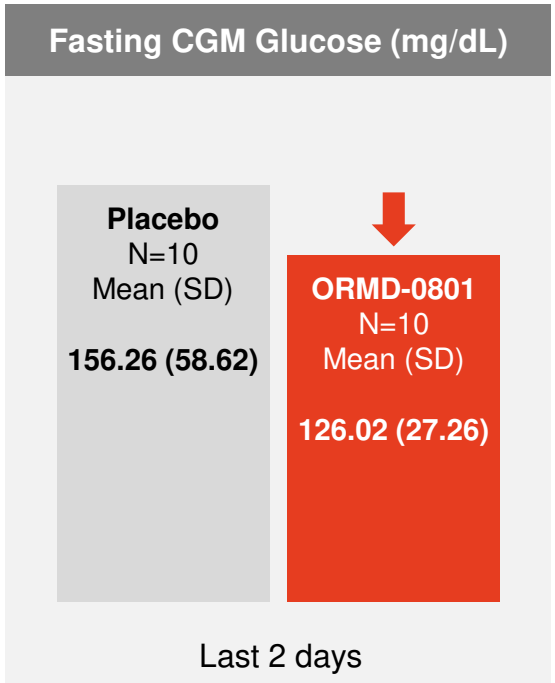
Absorption enhancement
Assists the permeation of proteins/peptides across intestinal membrane and into bloodstream

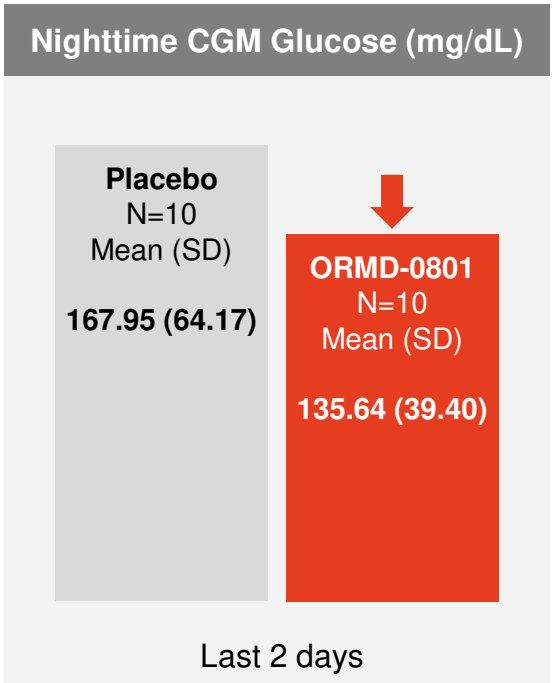
ORA-D-007 Study rationale

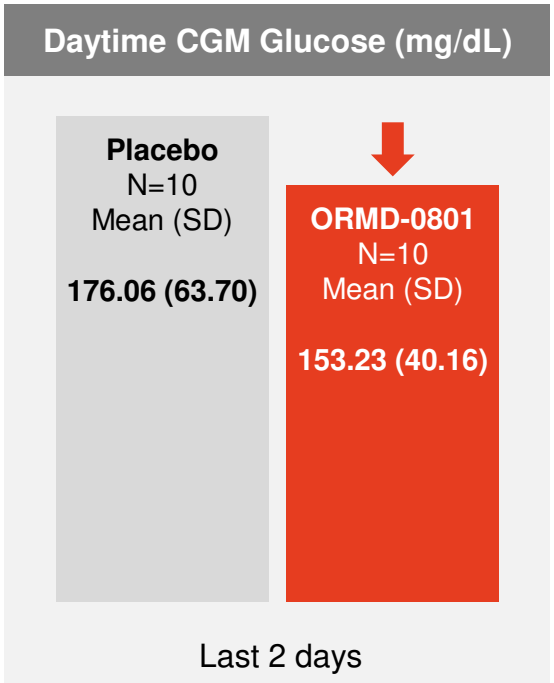
- ORMD-0801 is an oral formulation of recombinant human insulin based on ORAMED's Protein Oral Deliver Technology

In a previous Phase Iia study ORMD-0801 was Safe With no Serious Adverse Events

- 30 T2DM patients
- Primary objective: Safety and tolerability
- Secondary objective: Pharmacodynamic effects on mean nighttime glucose







ORA-D-007 Study rationale

- ORMD-0801 is an oral formulation of recombinant human insulin based on ORAMED's Protein Oral Deliver Technology
- Here we report the results from a Phase 2b placebo controlled study, aimed to assess the safety and efficacy of the addition of ORMD-0801 (16 mg insulin or 24 mg insulin) to metformin for 28 days in patients with T2DM.

Completed: 180 Patient FDA Phase IIb Study

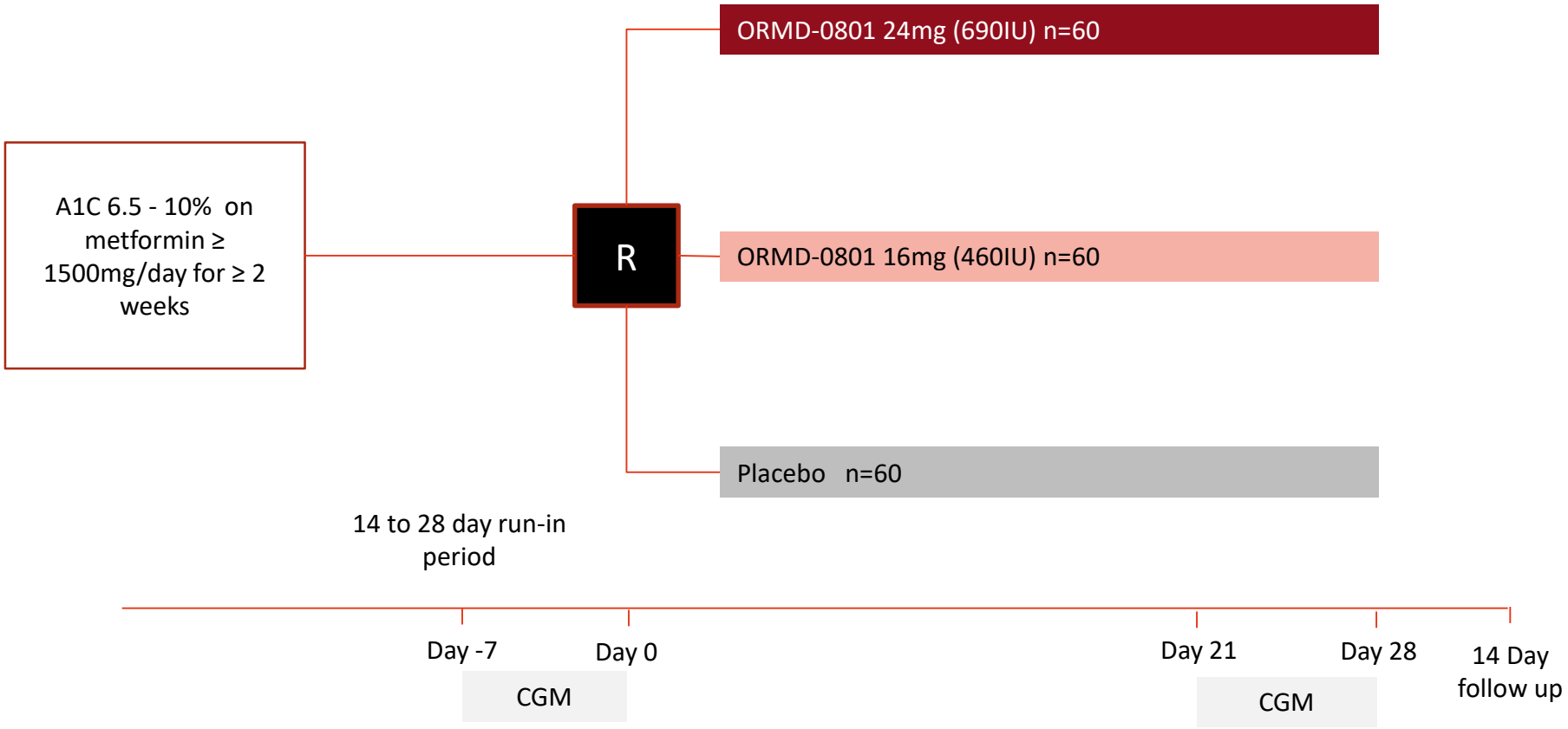
33 US sites

180 patients

28 day treatment

1 time a day at night

ORA-D-007 Study diagram



- CGM- continuous glucose monitoring

Inclusion/Exclusion criteria

- **Inclusion**
  - Adult patients with T2DM age 20-75 years, BMI 25-40kg/m2, who were on stable treatment with metformin (≥1500 mg/day) for at least 2 weeks and had HbA1c 6.5 - 10% at the screening visit
    - naïve with HbA1c ≥7.5were started on or titrated to ≥1,500 mg metformin daily for the two weeks
    - metformin monotherapy <1,500 mg daily and HbA1c ≥7.0% were titrated to ≥1,500 mg metformin daily for two weeks.
    - monotherapy other than metformin and HbA1c 6.5 - 9.5% had their current drug discontinued and were put on or ≥1,500 mg metformin daily for a two-week stabilization period.
    - Patients on metformin plus one additional drug (excluding insulin) with HbA1c 6 - 9.5% had the other drugs discontinued and only metformin ≥1,500 mg continued for the two weeks of stabilization.
- **Exclusion**
  - history of type 1 diabetes mellitus
  - fasting blood glucose >260 mg/dL at the end of Day -7/Visit 3
  - presence of any clinically significant endocrine disease
  - history of use of insulin for greater than one week in the last six months and any use of insulin in the last six weeks prior to randomization
  - history of gastrointestinal disorders with the potential to interfere with drug absorption

ORA-D-007 Study:
ORMD-0801 Endpoints and Objectives

01

Primary objectives

- Safety of ORMD-0801
- Evaluate PD effects of ORMD-0801 (pooled doses) on mean night glucose (6 hours after treatment)

02

Secondary objectives

- Evaluate PD effects of ORMD-0801 (pooled doses) on fasting blood glucose, morning blood insulin, c-peptide, triglycerides

03

Exploratory objectives

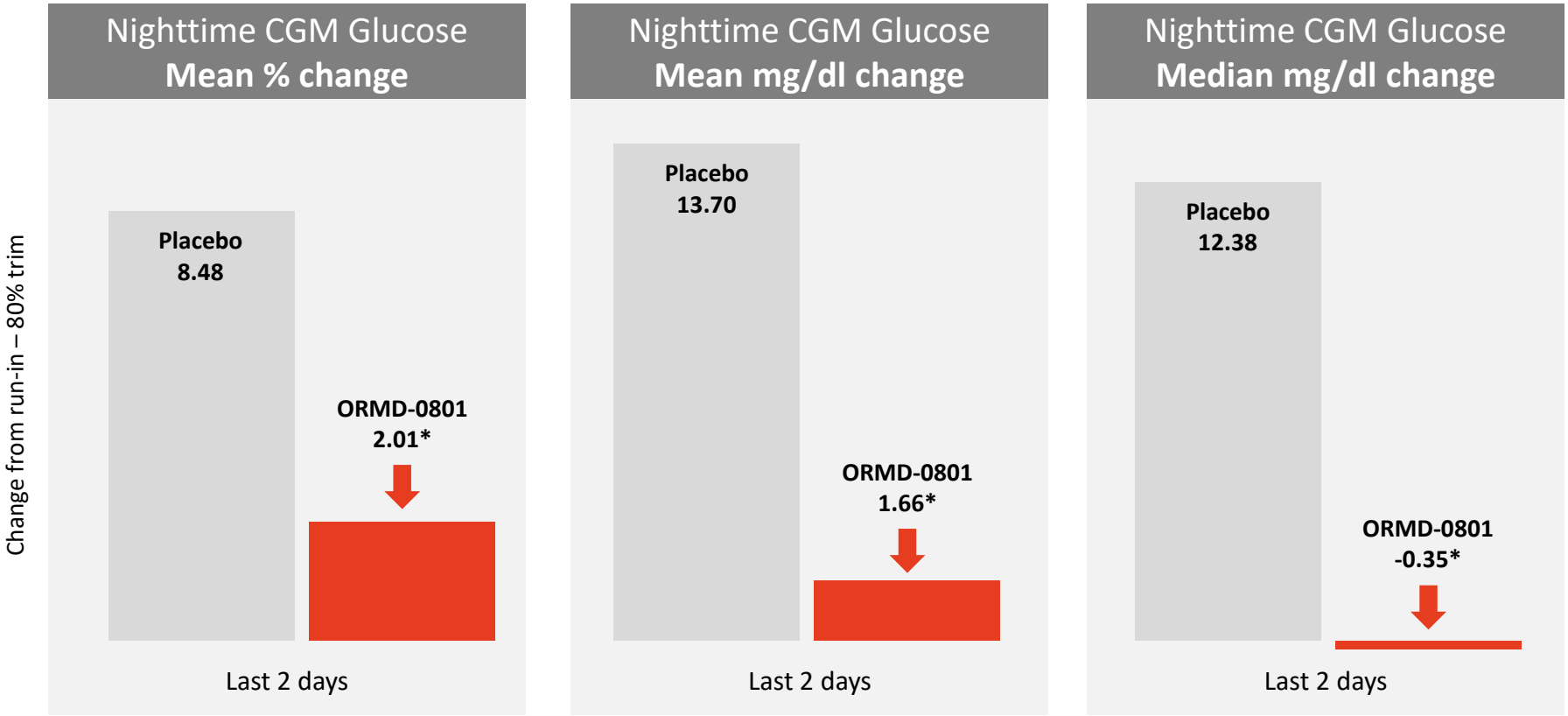
- Evaluate PD effects of ORMD-0801 (pooled doses) on HbA1c, CRP,24-hour fasting glucose, day CGM glucose levels, weight
- Evaluate immunogenicity of ORMD-0801 via anti-insulin antibody levels

Baseline characteristics

	Placebo (N=64)	ORMD-0801 16 mg (N=61)	ORMD-0801 24 mg (N=63)
Age (Mean ± SD)	58.6±9.2	57.9±8.0	57.3±8.8
Men, n (%)	29 (45.3)	39 (63.9)	34 (54.0)
Race, n (%)			
White	53 (82.8)	50 (82.0)	55 (87.3)
Black or African American	7 (10.9)	8 (13.1)	4 (6.3)
Asian	2 (3.1)	2 (3.3)	2 (3.2)
Native Hawaiian or Other Pacific Islander	2 (3.1)	1 (1.6)	0 (0)
Other	0(0)	0(0)	2 (3.2%)
Ethnicity N (%)			
Hispanic or Latino	31 (48.4)	32 (52.5)	36 (57.1)
Non-Hispanic or Latino	33 (51.6)	29 (47.5)	27 (42.9)

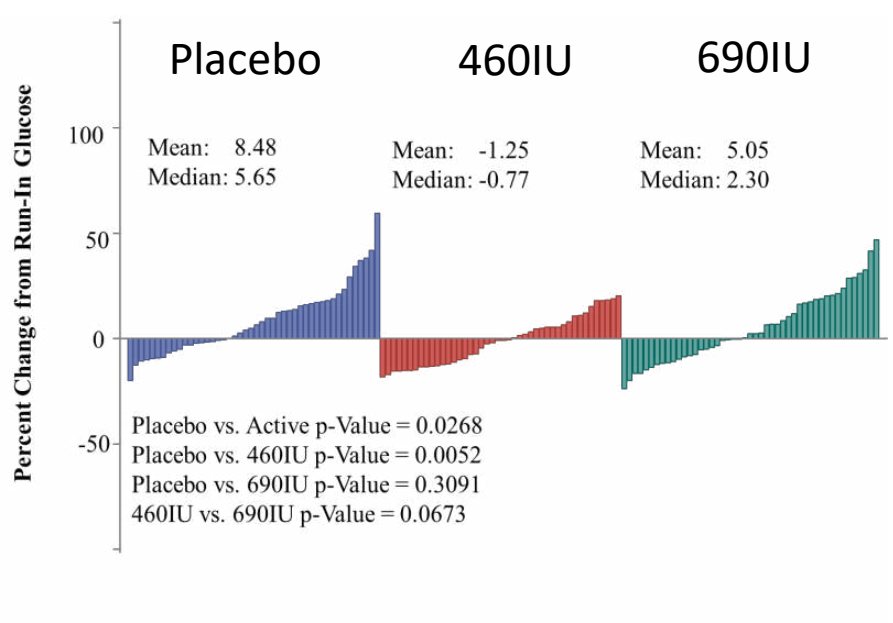
Primary Endpoint

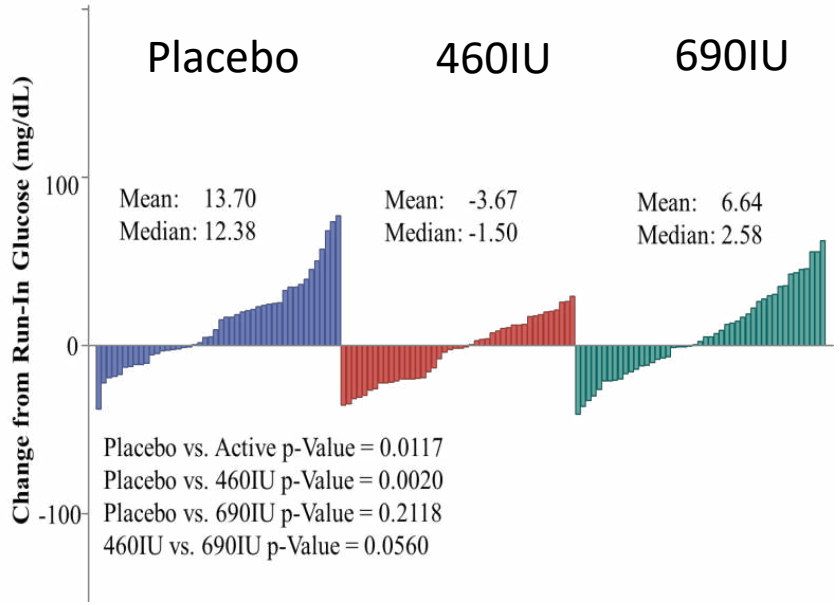
Safe and well tolerated oral delivery – No drug related serious adverse events



- Indicates Statistically Significant Difference from Placebo (p-Value<0.05)
- Data presented are analysis of 80% trimmed CGM data (data with 10% highest and lowest values for each treatment group removed

Primary objective - Waterfall plot



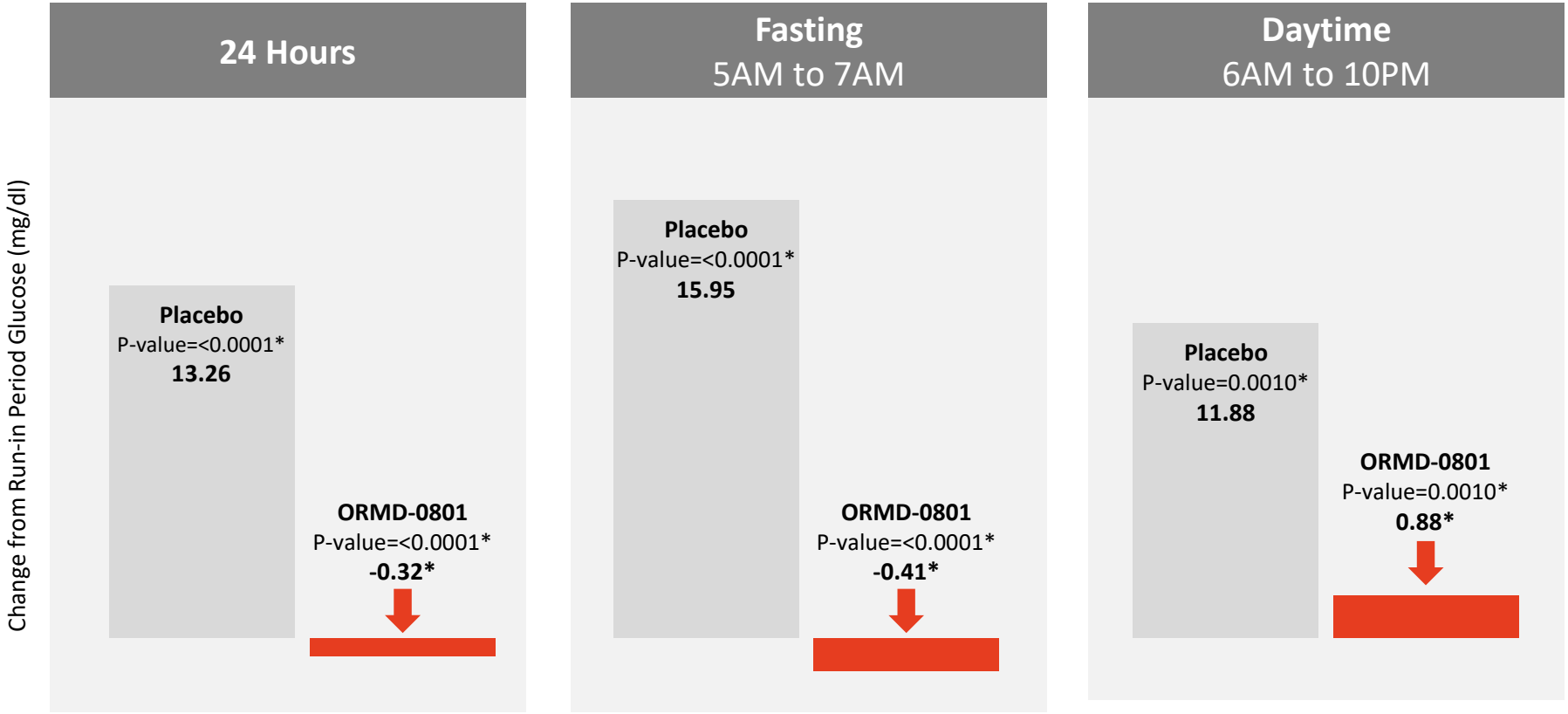


Change from baseline values as obtained from continuous glucose monitoring at 4 weeks - 80% trimmed data - ITT population.

Efficacy assessments using CGM data were based on the results from the two last days during the assessment period (run-in or active treatment

Other Continuous Glucose Monitoring Parameters

(Exploratory Objectives)



- Indicates p-Value<0.05
- Nighttime- 6 hours after dosing; 24-hour- 6am to 6am; fasting- 5am to 7 am; daytime 6am to 10pm.
- Change from baseline values as obtained from continuous glucose monitoring at 4 weeks - 80% trimmed data - ITT population.
- Efficacy assessments using CGM data were based on the results from the two last days during the assessment period (run-in or active treatment

HbA1c
(Exploratory Objective)

Day 29
Change from baseline

Placebo
0.20

ORMD-0801
-0.01*

* Indicates comparison to placebo p-Value<0.05

Baseline values and treatment outcomes at 4 weeks - ITT population

	Placebo (N=58)	ORMD-0801 16mg (N=54)	ORMD-0801 24 mg (N=60)	ORMD-0801 Combined (N=114)
Morning fasting serum insulin (pmol/L)				
N	58	52	60	112
Day 29- End of treatment mean ± SD	125.5 ± 82.3	114.4 ± 75.7	114.9 ± 72.9	114.7 ± 73.9
Change, mean ± SD	-4.82 ± 55.0	-5.32 ± 107.3	-3.65 ± 54.3	-4.4 ± 83.0
Morning fasting C-peptide (nmol/L)				
N	58	52	60	112
Day 29- End of treatment mean ± SD	0.9 ± 0.4	0.9 ± 0.4	0.8 ± 0.3	0.9 ±0.4
Change, mean ± SD	-0.0 ±0.3	0.0 ±0.4	-0.0 ± 0.3	-0.0 ± 0.3
Morning fasting triglycerides (mmol/L)				
N	58	53	60	113
Day 29- End of treatment mean ± SD	2.0 ± 1.1	1.9 ± 1.0	1.9 ± 0.9	1.9 ± 0.9
Change, mean ± SD	0.1 ± 0.7	0.1 ± 0.7	0.1 ± 0.7	0.1 ± 0.7
Weight (kg)				
N	58	54	60	114
Day 29- End of treatment mean ± SD	86.2 ± 16.5	90.5 ± 16.4	86.8 ± 19.7	88.5 ± 18.2
Change, mean ± SD	-0.5 ± 1.6	-0.29 ± 1.6	-0.0 ± 1.6	-0.2 ± 1.6

Analysis performed comparing to placebo using a one-way analysis of variance (ANOVA) model

Baseline values and treatment outcomes at 4 weeks - ITT population

	Placebo (N=58)	ORMD-0801 16mg (N=54)	ORMD-0801 24 mg (N=60)	ORMD-0801 Combined (N=114)
Alkaline Phosphatase (U/L), mean +SD				
N	62	59	63	
Day 29- End of treatment mean ± SD	83.5 ± 24.8	89.6 ± 26.7	82.7 ± 22.6	
Change, mean ± SD	-4.9 ± 13.6	-0.1 ± 15.2	-5.2 ± 12.4	
ALT (U/L)				
N	62	59	62	
Day 29- End of treatment mean ± SD	32.6 ± 19.1	32.0 ±14.7	30.7 ± 16.0	
Change, mean ± SD	3.6 ± 10.0	3.0 ± 10.7	0.7 ± 10.0	
AST (U/L)				
N	62	59	62	
Day 29- End of treatment mean ± SD	25.8 ± 11.1	26.4 ± 12.5	25.4 ± 11.4	
Change, mean ± SD	1.5 ± 6.8	1.9 ± 11.3	0.5 ± 7.8	
Bilirubin, total (mg/dL)				
N	62	59	63	
Day 29- End of treatment mean ± SD	0.5 ± 0.3	0.6 ± 0.4	0.5 ± 0.3	
Change, mean ± SD	0.0 ± 0.1	-0.0 ±0.2	-0.0 ± 0.2	

Analysis performed comparing to placebo using a one-way analysis of variance (ANOVA) model

Overview of Non-Hyperglycemic/Hypoglycemic Treatment-Emergent Adverse Events by Treatment Group- Safety Population

	Placebo	ORMD-0801	ORMD-0801
	N=64	460 IU	690 IU
	N (%)	N= 61	N= 63
		N (%)	N (%)
Total Adverse Events	34	34	42
TEAEs	19 (29.7)	19 (31.1)	19 (30.2)
Severe TEAE	0 (0)	1 (1.6)	0 (0)
Serious TEAE	0 (0)	1 (1.6)	0 (0)
Related TEAEs	2 (3.1)	0 (0)	0(0)
Related Severe TEAEs	0 (0)	0 (0)	0 (0)
Related Serious TEAEs	0 (0)	0 (0)	0 (0)
Withdrawal from treatment due to AE	0 (0)	1 (1.6)	0 (0)
Death due to AE	0 (0)	0 (0)	0 (0)

- 7 hyperglycemic events were reported across five patients evenly distributed among the treatment groups.
- One patient in each group experienced a hypoglycemic event.

Conclusions: ORA-D-007 Study Clearly Demonstrated the Safety and Blood Glucose Lowering Efficacy of ORMD-0801

Safe and well tolerated with no significant hyperglycemic event

Sustained and significant glucose reduction observed in every CGM parameter:

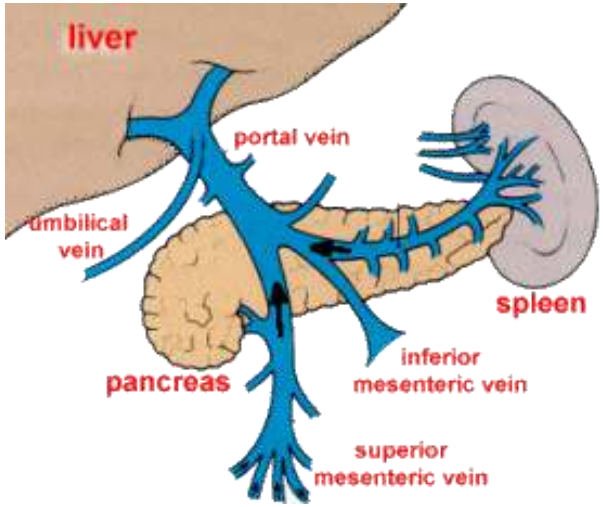
Fasting, Daytime, Nighttime, 24 hr

HbA1c showed a statistically significant difference in only 28 days of testing

No increase in peripheral insulin observed

ORMD-0801 – ORA-D-007 results support the potential MOA- Liver directed insulin

- Prolonged anti-hyperglycemic effect despite an expected short half life of regular insulin once absorbed into the blood stream.
- Lack of increase in hypoglycemia.
- Lack of increase in peripheral insulin.
- Lack of weight gain



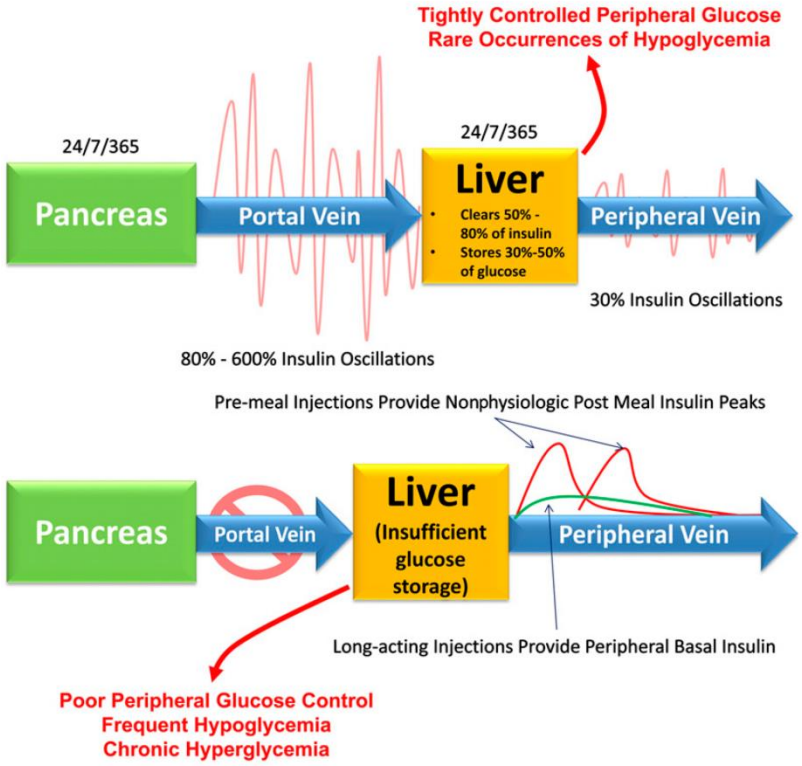


Figure on the right from Diabetes 2014;63:1445–1447

Acknowledgments

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