Evening Oral Insulin (ORMD-0801) Glycemic Effects in Uncontrolled T2DM Patients

Roy Eldor[1], Alexander Fleming[2], Joel Neutel[3], Kenneth Homer[4], Miriam Kidron[5], Julio Rosenstock[6]

[1]Institute of Endocrinology, Metabolism & Hypertension, Tel-Aviv Sourasky Medical Center; [2]Kinexum LLC, Harpers Ferry, WV, USA; [3]Orange County Research Center, Tustin, CA, USA; [4]Integrium LLC, Tustin, CA, USA; [5]Oramed Pharmaceuticals, Jerusalem, Israel; [6]Dallas Diabetes Research Center, Dallas, TX, USA

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Presenter: Julio Rosenstock
Oramed Pharmaceuticals: Scientific advisory board member

Co-author: Roy Eldor
Oramed Pharmaceuticals: Medical consultant

Co-author: Alexander Fleming
Oramed Pharmaceuticals: Scientific advisory board member

Co-author: Joel Neutel
Integrium: Clinical Research Organization for this study

Co-author: Kenneth Homer
Integrium: Clinical Research Organization for this study

Co-author: Miriam Kidron
Oramed Pharmaceuticals: Chief Scientific Officer

BACKGROUND/OBJECTIVE

ORAL INSULIN

Systemically administered insulin is associated with risk of hypoglycemia and weight gain. Portally infused insulin brings to a more rapid and pronounced suppression of hepatic glucose production, reduced fasting blood glucose concentrations and to reduced circulating peripheral insulin levels. Orally delivered insulin is expected to similarly mimic physiological gradients and natural sites of action.

BARRIERS

Protein-based drugs are poorly absorbable owing to their high molecular weight and hydrophilicity. Furthermore, they are susceptible to mechanical and enzymatic degradation along the gastrointestinal tract (GIT). Numerous works have demonstrated the protective role of protease inhibitors (PIs) against degradative threats along the GIT, when incorporated in drug formulations.

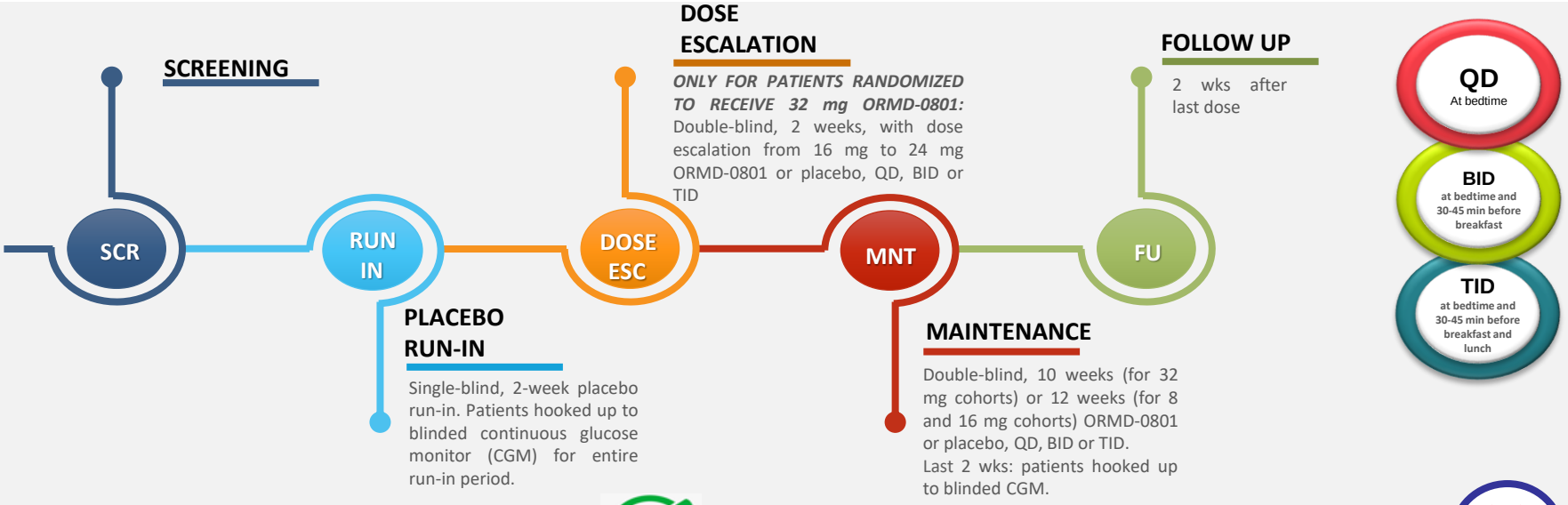
ORMD-0801

ORMD-0801 is a novel oral human insulin formulation, which integrates both a species-specific protease inhibitor that provides a protective environ for active ingredients, and a potent absorption enhancer that promotes absorption of the active ingredient across the intestinal epithelium.

OBJECTIVE

This randomized, placebo-controlled, multi-center, phase 2b, dose-finding study aimed to assess the efficacy of 12 weeks of 8, 16 and 32 mg ORMD-0801, administered once, twice or three times daily in 419 T2DM subjects.

STUDY DESIGN



INCLUSION CRITERIA

- Adult patients, with T2DM diagnosis at least 6 months prior to study
- HbA1C≥7.5%
- Stable metformin dose ≥1500 mg or maximal tolerated dose for at least 3 months
- Taking up to two oral antidiabetics (SU, DPP-4, SGLT-2, or TZD), with stable dose for at least 3 months
- BMI ≤40 mg/kg^2
- Renal function eGFR >30 ml/min/1.73 m^2
- Women not pregnant, use of effective contraceptive required, when relevant

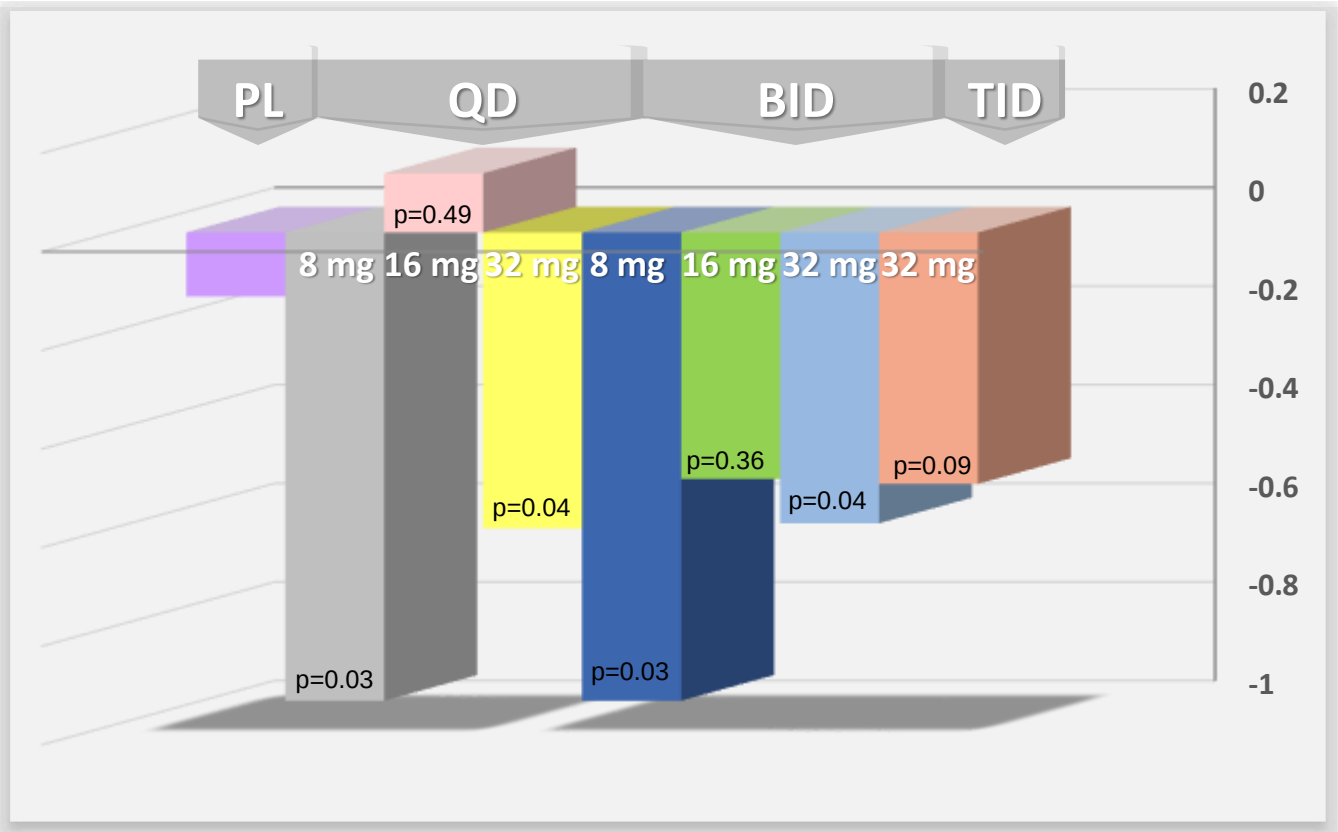
EXCLUSION CRITERIA

- Use of GLP-1 agonist within 3 months of study
- Use of basal, pre-mix, or prandial insulin for more than 7 days within 6 months of study
- >2 episodes of hypoglycemia within 6 months of study
- History of hypoglycemic unawareness
- Uncontrolled or untreated severe hypertension

Demographics and Baseline Characteristics

	POOLED PLACEBO N=82	QD 8 mg N=15	QD 16 mg N=18	QD 32 mg N=69	BID 8 mg N=17	BID 16 mg N=15	BID 32 mg N=68	TID 32 mg N=69
Sex, n (%)								
Male	49 (59.8)	10 (66.7)	11 (61.1)	42 (60.9)	10 (58.8)	11 (73.3)	45 (66.2)	40 (58.0)
Female	33 (40.2)	5 (33.3)	7 (38.9)	27 (39.1	7 (41.2)	4 (26.7)	23 (33.8)	29 (42.0)
Race, n (%)								
White	69 (84.1)	12 (80.0)	16 (88.9)	59 (85.5)	11 (64.7)	11 (73.3)	57 (83.8)	58 (84.1)
Black or African-Am	11 (13.4)	3 (20.0)	1 (5.6)	7 (10.1)	4 (23.5)	1(6.7)	8 (11.8)	8 (11.6)
Asian	0	0	1 (5.6)	0	0	2 (13.3)	2 (2.9)	1 (1.4)
Other	1 (1.2)	0	0	3 (4.3)	0	0	1 (1.5)	2 (2.8)
Age, (y) Mean [Std]	55.8 (9.9)	53.7 (8.3)	55.0 (11.2)	56.7 (10.8)	56.9 (9.1)	55.0 (11.8)	55.7 (10.6)	55.2(11.7)
BMI, (m/kg^2) Mean [Std]	31.1 (4.8)	31.8 (4.4)	31.8 (6.1)	31.7 (4.9)	31.0 (5.0)	30.8 (5.4)	30.4 (4.8)	31.2 (4.0)
HbA1c, (%) Mean [Std]	9.5 (1.4)	9.8 (1.8)	9.0 (1.4)	9.0 (1.3)	8.5 (1.1)	9.2 (1.7)	9.4 (1.7)	9.7 (1.6)
Diabetes Meds, n (%)								
Metformin (M) only	22 (26.8)	6 (40.0)	7 (38.9)	20 (29.0)	5 (29.4)	5 (33.3)	20 (29.4)	12 (17.4)
M+OAD, not SU	13 (15.9)	1 (6.7)	1 (5.6)	10 (14.5)	0	2 (13.3)	8 (11.8)	12 (17.4)
M+SU	33 (40.2)	7 (46.7)	8 (44.4)	30 (43.5)	7 (41.2)	3 (20.0)	26 (38.2)	33 (47.8)
M+SU+Other	10 (12.2)	0 (0)	1 (5.6)	5 (17.2)	1 (5.9)	3 (20.0)	8 (11.8)	6 (8.7)

RESULTS – HBA1C CHANGE FROM BASELINE – INTENT TO TREAT (ITT) POPULATION

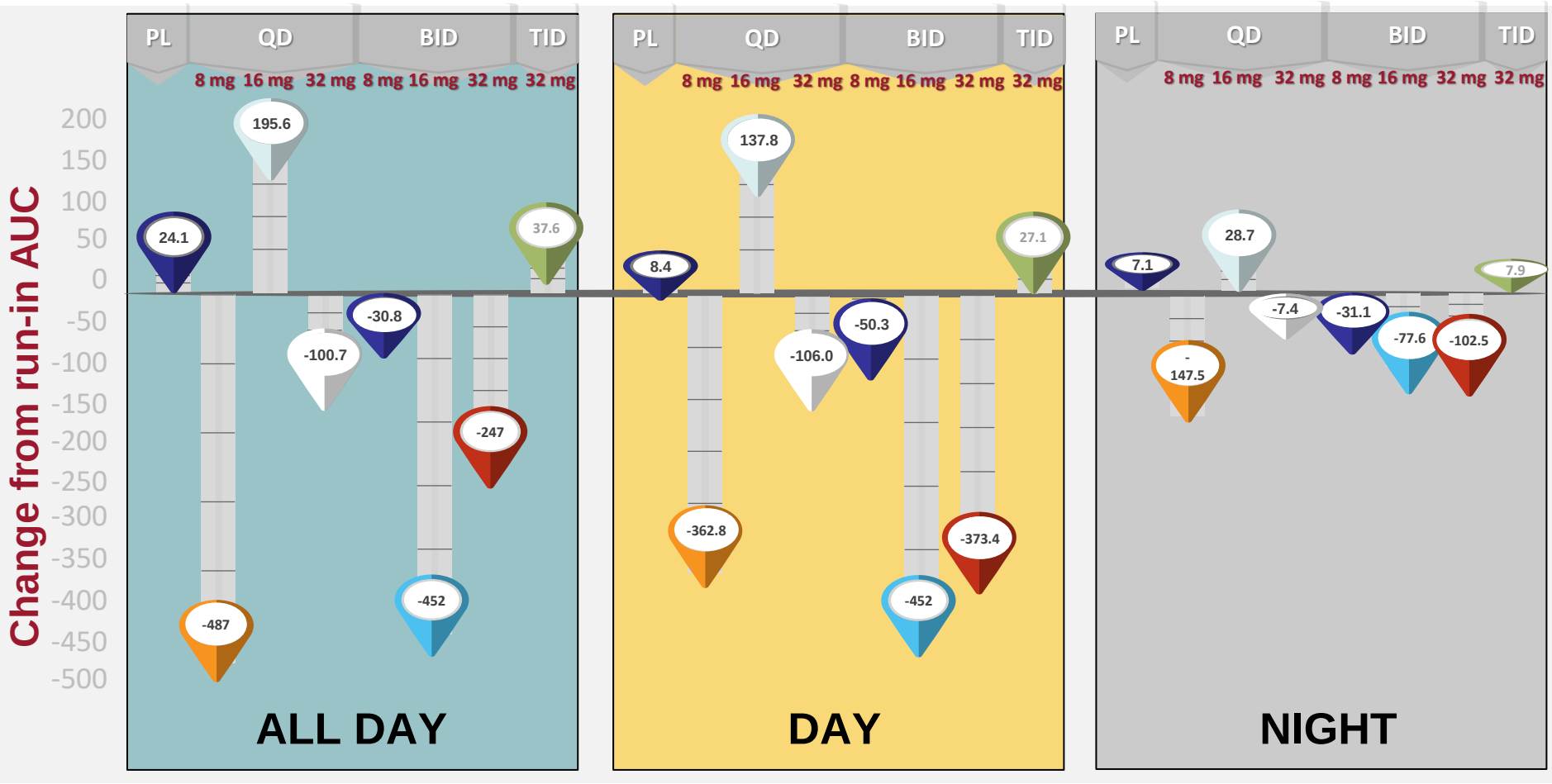


**** Least square means are presented.*** ********

***The number of subjects at baseline and at 12-weeks differ.*

p-values obtained using Analysis of Covariance model with treatment as the primary effect and site, baseline value, metformin usage, sulfonylureas usage, and number of additional diabetes medications used as covariates.

Results – Weeks 10-12 Continuous Glucose Area Under the Curve (mg*h/dL) - ITT

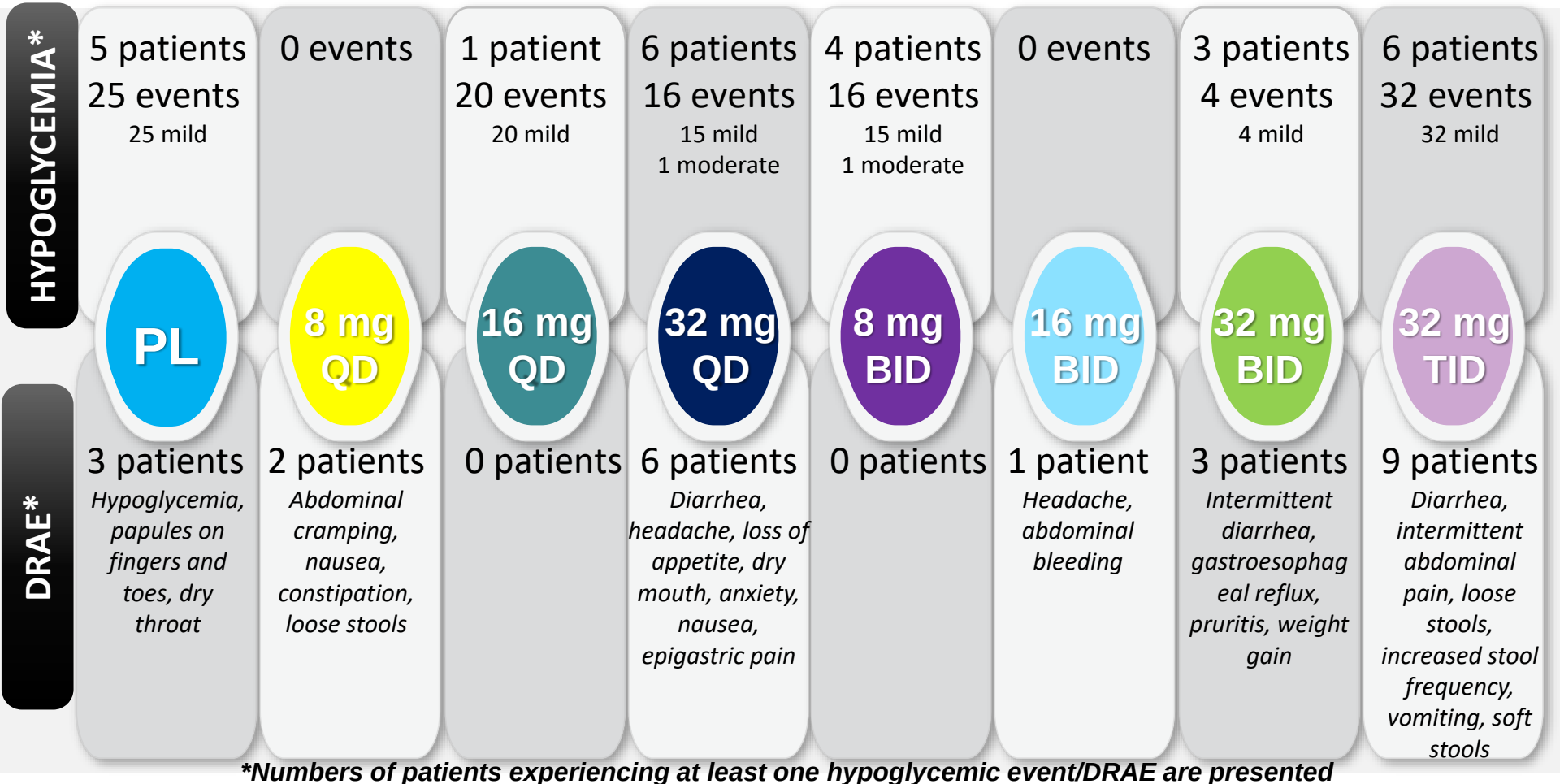


Results – Body Weight (Kg)

	PLACEBO	QD			BID			TID
		8 mg	16 mg	32 mg	8 mg	16 mg	32 mg	32 mg
Baseline	95.7±5.3	109.3±6.5	95.4±6.6	96.3±5.1	100.9±6.4	96.7±6.5	94.0±4.9	97.2±5.1
Week 12	92.8±5.5	110.3±6.9	97.0±6.9	95.8±5.3	99.7±6.9	92.5±7.3	92.8±5.0	96.6±5.2
Change from baseline	-0.3±0.8	-1.4±1.0	0.5±1.0	0.1±0.8	-0.6±1.0	0.8±1.0	-0.4±0.7	-0.5±0.8

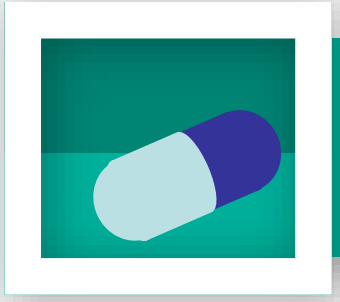
Least Square Means ± Standard Error are presented. The number of subjects at baseline and at 12-weeks differ.

Safety – Hypoglycemia and Drug-related Adverse Events* (DRAEs)



*Numbers of patients experiencing at least one hypoglycemic event/DRAE are presented

Conclusion And Discussion



The 12-week 8-32 mg ORMD-0801 QD and BID treatments elicited clinically significant HbA1c reductions among T2DM patients inadequately controlled on standard therapies and with mean HbA1c levels >8%. CGM and serum glucose measures showed similar trends.

ORMD-0801 was not associated with an increased risk of hypoglycemia or with severe or serious side effects. No significant weight gain or postprandial glucose parameters (not shown) were recorded over the 12-week treatment period.

This study clearly demonstrated that when considering changes in 12-week HbA1c levels, there is no significant benefit to be derived from dosing more than once daily, at night. QD dosing will certainly enhance subject compliance and reduce treatment costs.