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

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**FINANCIAL DISCLOSURE**

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Oramed Pharmaceuticals: Scientific advisory board member

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Integrium: Clinical Research Organization for this study

**Kenneth Homer**  
Integrium: Clinical Research Organization for this study

**Miriam Kidron**  
Oramed Pharmaceuticals: Chief Scientific Officer

**Julio Rosenstock**  
Oramed Pharmaceuticals: Scientific advisory board member
FATE OF PROTEIN/PEPTIDES IN THE GIT

- Harsh pH
- Mechanical challenges
- Protease threat
- Absorption barrier

Protein breakdown, low bioavailability
ORAMED TECHNOLOGY

Making needles needless

- Protease inhibitors
- Enteric coating
- Emulsifier
- Absorption enhancer

PROTEIN/PEPTIDE
20% of secreted insulin reaches the bloodstream

Portal/peripheral ratios are retained ➔ lower risk of hypoglycemia
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.

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

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 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/kg²
- Renal function eGFR > 30 ml/min/1.73 m²
- 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

**RUN-IN**
- Single-blind, 2-week placebo run-in. Patients hooked up to blinded continuous glucose monitor (CGM) for entire run-in period.

**DOSE ESCALATION**
- ONLY FOR PATIENTS RANDOMIZED TO RECEIVE 32 mg ORMD-0801:
  - Double-blind, 2 weeks, with dose escalation from 16 mg to 24 mg ORMD-0801 or placebo, QD, BID or TID

**MAINTENANCE**
- Double-blind, 10 weeks (for 32 mg cohorts) or 12 weeks (for 8 and 16 mg cohorts) ORMD-0801 or placebo, QD, BID or TID. Last 2 wks: patients hooked up to blinded CGM.

**FOLLOW UP**
- 2 wks after last dose

**DOSAGE**
- QD: At bedtime
- BID: At bedtime and 30-45 min before breakfast
- TID: At bedtime and 30-45 min before breakfast and lunch
### Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>POOLED PLACEBO N=82</th>
<th>QD 8 mg N=15</th>
<th>QD 16 mg N=18</th>
<th>QD 32 mg N=69</th>
<th>BID 8 mg N=17</th>
<th>BID 16 mg N=15</th>
<th>BID 32 mg N=68</th>
<th>TID 32 mg N=69</th>
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</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
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<tr>
<td>Male</td>
<td>49 (59.8)</td>
<td>10 (66.7)</td>
<td>11 (61.1)</td>
<td>42 (60.9)</td>
<td>10 (58.8)</td>
<td>11 (73.3)</td>
<td>45 (66.2)</td>
<td>40 (58.0)</td>
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<tr>
<td>Female</td>
<td>33 (40.2)</td>
<td>5 (33.3)</td>
<td>7 (38.9)</td>
<td>27 (39.1)</td>
<td>7 (41.2)</td>
<td>4 (26.7)</td>
<td>23 (33.8)</td>
<td>29 (42.0)</td>
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<td><strong>Race, n (%)</strong></td>
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<tr>
<td>White</td>
<td>69 (84.1)</td>
<td>12 (80.0)</td>
<td>16 (88.9)</td>
<td>59 (85.5)</td>
<td>11 (64.7)</td>
<td>11 (73.3)</td>
<td>57 (83.8)</td>
<td>58 (84.1)</td>
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<tr>
<td>Black or African-Am</td>
<td>11 (13.4)</td>
<td>3 (20.0)</td>
<td>1 (5.6)</td>
<td>0 (3.4)</td>
<td>4 (23.5)</td>
<td>1 (6.7)</td>
<td>2 (2.9)</td>
<td>1 (1.4)</td>
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<tr>
<td>Asian</td>
<td>0 (1.2)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (4.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.5)</td>
<td>0 (0.0)</td>
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<tr>
<td>Other</td>
<td>1 (1.2)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.5)</td>
<td>1 (1.4)</td>
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<tr>
<td><strong>Age, (y)</strong></td>
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<tr>
<td>Mean [Std]</td>
<td>55.8 (9.9)</td>
<td>53.7 (8.3)</td>
<td>55.0 (11.2)</td>
<td>56.7 (10.8)</td>
<td>56.9 (9.1)</td>
<td>55.0 (11.8)</td>
<td>55.7 (10.6)</td>
<td>55.2 (11.7)</td>
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<tr>
<td><strong>BMI, (m/kg²)</strong></td>
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<tr>
<td>Mean [Std]</td>
<td>31.1 (4.8)</td>
<td>31.8 (4.4)</td>
<td>31.8 (6.1)</td>
<td>31.7 (4.9)</td>
<td>31.0 (5.0)</td>
<td>30.8 (5.4)</td>
<td>30.4 (4.8)</td>
<td>31.2 (4.0)</td>
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<tr>
<td><strong>HbA1c, (%)</strong></td>
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<tr>
<td>Mean [Std]</td>
<td>9.5 (1.4)</td>
<td>9.8 (1.8)</td>
<td>9.0 (1.4)</td>
<td>9.0 (1.3)</td>
<td>8.5 (1.1)</td>
<td>9.2 (1.7)</td>
<td>9.4 (1.7)</td>
<td>9.7 (1.6)</td>
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<tr>
<td><strong>Diabetes Meds, n (%)</strong></td>
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<tr>
<td>Metformin (M) only</td>
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<td></td>
</tr>
<tr>
<td>M+OAD, not SU</td>
<td>22 (26.8)</td>
<td>6 (40.0)</td>
<td>7 (38.9)</td>
<td>20 (29.0)</td>
<td>5 (29.4)</td>
<td>5 (33.3)</td>
<td>20 (29.4)</td>
<td>12 (17.4)</td>
</tr>
<tr>
<td>M+SU</td>
<td>13 (15.9)</td>
<td>1 (6.7)</td>
<td>1 (5.6)</td>
<td>10 (14.5)</td>
<td>0 (0.0)</td>
<td>2 (13.3)</td>
<td>8 (11.8)</td>
<td>12 (17.4)</td>
</tr>
<tr>
<td>M+SU+Other</td>
<td>33 (40.2)</td>
<td>7 (46.7)</td>
<td>8 (44.4)</td>
<td>30 (43.5)</td>
<td>7 (41.2)</td>
<td>3 (20.0)</td>
<td>26 (38.2)</td>
<td>33 (47.8)</td>
</tr>
</tbody>
</table>
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

ALL DAY

PL
QD
BID
TID
8 mg 16 mg 32 mg 8 mg 16 mg 32 mg 32 mg

24.1
-30.8
-100.7
-247
-487

-452

195.6

QD
BID
TID
8 mg 16 mg 32 mg 8 mg 16 mg 32 mg 32 mg

8.4
-50.3
-106.0
-362.8
-773.4

137.8

QD
BID
TID
8 mg 16 mg 32 mg 8 mg 16 mg 32 mg 32 mg

27.1
-170.4
-373.4
-773.4

7.9

7.1

NIGHT

PL
QD
BID
TID
8 mg 16 mg 32 mg 8 mg 16 mg 32 mg 32 mg

-147.5
-77.6
-102.5
-7.4
-31.1

28.7

QD
BID
TID
8 mg 16 mg 32 mg 8 mg 16 mg 32 mg 32 mg

7.1

-102.5
-77.6
-102.5

-31.1

-7.4

-452
## Results – Body Weight (Kg)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>QD</th>
<th>Bid</th>
<th>TID</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>8 mg</strong></td>
<td>109.3 ± 6.5</td>
<td>95.4 ± 6.6</td>
<td>100.9 ± 6.4</td>
<td>97.2 ± 5.1</td>
</tr>
<tr>
<td><strong>16 mg</strong></td>
<td>95.4 ± 6.6</td>
<td>97.0 ± 6.9</td>
<td>96.7 ± 6.5</td>
<td>96.0 ± 5.2</td>
</tr>
<tr>
<td><strong>32 mg</strong></td>
<td>96.3 ± 5.1</td>
<td>95.8 ± 5.3</td>
<td>94.0 ± 4.9</td>
<td>95.6 ± 5.0</td>
</tr>
</tbody>
</table>

**Baseline**

|                  | 95.7 ± 5.3 | 92.8 ± 5.5 |

**Week 12**

|                  | 110.3 ± 6.9 | 97.0 ± 6.9 |

**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 |

**N (BL/W12)**

|                  | 51/44 | 14/13 | 14/13 | 62/59 | 13/12 | 14/10 | 62/55 | 58/52 |

Least Square Means ± Standard Error are presented. The number of subjects at baseline and at 12-weeks differ.
All patients experiencing hypoglycemia were concomitantly taking sulfonylurea.
<table>
<thead>
<tr>
<th><strong>DRAE</strong></th>
<th><strong>PL</strong></th>
<th><strong>8 mg QD</strong></th>
<th><strong>16 mg QD</strong></th>
<th><strong>32 mg QD</strong></th>
<th><strong>8 mg BID</strong></th>
<th><strong>16 mg BID</strong></th>
<th><strong>32 mg BID</strong></th>
<th><strong>32 mg TID</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>** Events**</td>
<td>Hypoglycemia, papules on fingers and toes, dry throat</td>
<td>Abdominal cramping, nausea, constipation, loose stools</td>
<td></td>
<td>Diarrhea, headache, loss of appetite, dry mouth, anxiety, nausea, epigastric pain</td>
<td></td>
<td>Headache, abdominal bleeding</td>
<td>Intermittent diarrhea, gastroesophageal reflux, pruritis, weight gain</td>
<td>Diarrhea, intermittent abdominal pain, loose stools, increased stool frequency, vomiting, soft stools</td>
</tr>
</tbody>
</table>

*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.