Treatment With Oral Octreotide Capsules May Not Adversely Affect Glycemic Control in Patients With Acromegaly: Results From the Phase 3 CHIASMA OPTIMAL Study

Disclosures

• Dr. Samson is a consultant for Chiasma; is an advisory board member for Novartis and Chiasma; has received grants from Novartis; and is a research investigator for Chiasma, Corcept, Novartis, and OPKO.
Octreotide Specificity for SSTs May Offer Balanced Glycemic Control


Safety, including measures of glucose homeostasis, of oral octreotide capsules was evaluated in CHIASMA OPTIMAL, a prospective phase 3 study in patients whose acromegaly was controlled by injectable SRL treatment.

- In trials involving patients previously on somatostatin receptor ligands (SRLs), hyperglycemia occurred in 15% receiving long-acting octreotide.
- Glucagon-producing α cells mostly express SST2, whereas SST5 and SST2 are found in insulin-producing β cells.
- The ratio of affinity to SSTs mediates the balance of glucose production and thus potential hyperglycemia risk.

Octreotide binds with a high affinity for both SST5 and SST2.

Overall Glucose Homeostasis

- Glucagon
- Insulin
- SST2
- SST5

α cells

β cells

OOC, oral octreotide capsule; SRL, somatostatin receptor ligand; SST, somatostatin receptor.
The Mechanism of Oral Octreotide Capsules

• MYCAPSSA® is an investigational oral octreotide formulation designed for intestinal absorption using an excipient mixture (TPE®), in an enteric-coated hard gelatin capsule

• TPE induces local, transient, and reversible paracellular permeation, enabling orally administered octreotide to be absorbed into systemic circulation

• This formulation is designed to prevent early gastric release

Mechanism of Oral Octreotide Capsules

Unmodified octreotide peptide and TPE® (medium chain fatty acid C₈, inert excipients) in enteric-coated capsule

TPE® transiently and reversibly opens tight junctions in the intestinal barrier

Figure adapted from Melmed S. Nat Rev Endocrinol. 2016;12(2):90-98.


*conditional trade name. TPE, transient permeability enhancer.
CHIASMA OPTIMAL: Inclusion/Exclusion Criteria

Key Inclusion criteria

- Adults aged ≥18 years at first screening
- Evidence of active disease (IGF-I ≥1.3 × ULN following the most recent pituitary surgery)
- Received injectable SRL therapy for ≥6 months
- On a stable dose of injectable SRL therapy for ≥3 months
- Average IGF-I ≤1.0 × ULN of 2 screening assessments

Key Exclusion criteria

- Receiving off-label doses of injectable SRLs
- Undergone radiotherapy any time in the past or pituitary surgery within 6 months prior to screening

IGF-I, insulin growth factor-1; ULN, upper limit of normal.
CHIASMA OPTIMAL: Study Design

**Early study medication discontinuations (both arms), to be followed ≤36 wks, per protocol.**

- Discontinuations were considered nonresponders regardless of clinical response at the time of discontinuation (nonresponse imputation). Exploratory analyses were performed utilizing the last observation carried forward analysis, as well as a completer analysis of response among the subgroup that completed the entire 36 weeks on study drug.

**DPC (36 weeks)**

- **Primary endpoint**
- **OLE**

---

**Screening**

- The last SRL injection can be within the screening period as long as baseline is the end of the injection interval.
- Screening Visit 2 is within 2 weeks from baseline/randomization.

**Pre-defined withdrawal criteria (both arms)**

- IGF-I ≥1.3 x ULN for 2 consecutive visits on the highest dose and exacerbation of clinical signs/symptoms.
- Early terminated patients followed ≤36 weeks on injections, per protocol.

---

**Last SRL injection**

**Screening**

**Baseline**

**Placebo N=28**

**Withdrawal**

**OOC 40 mg → 60 mg → 80 mg**

**34 36 weeks**

**OOC 60 mg → 80 mg → 40 mg**

---

*a* Early study medication discontinuations (both arms), to be followed ≤36 wks, per protocol. 
*b* Per study protocol, discontinuations were considered nonresponders regardless of clinical response at the time of discontinuation (nonresponse imputation). Exploratory analyses were performed utilizing the last observation carried forward analysis, as well as a completer analysis of response among the subgroup that completed the entire 36 weeks on study drug.

DPC, double-blind placebo-controlled; OLE, open-label extension.
CHIASMA OPTIMAL: Efficacy Endpoints

Mean IGF-I at Baseline and end of DPC period

Mean IGF-I for the OOC cohort was maintained within the normal range.

*Mean calculated from average of 2 assessments within 2 weeks prior to randomization.
# CHIASMA OPTIMAL: Efficacy Endpoints

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>OOC (N=28)</th>
<th>Placebo (N=28)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion maintaining IGF-I response, %</td>
<td>58</td>
<td>19&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.008</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion maintaining GH response, %</td>
<td>78</td>
<td>30</td>
<td>0.001</td>
</tr>
<tr>
<td>Median time to IGF-I &gt;1.0 x ULN, wk</td>
<td>Not met</td>
<td>16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median time to IGF-I &gt;1.3 x ULN, wk</td>
<td>Not met</td>
<td>16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rescued to prior injectable, %</td>
<td>25</td>
<td>68</td>
<td>0.003</td>
</tr>
</tbody>
</table>

<sup>a</sup> All 19% of the placebo responders (n=5) continued in the OLE based on PI discretion, because they either had lost response at some point in the study, or had continuing acromegaly symptoms.
## CHIASMA OPTIMAL: Safety Results

<table>
<thead>
<tr>
<th>Subjects with:</th>
<th>OOC</th>
<th></th>
<th>Placebo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>≥1 TEAE</td>
<td>28</td>
<td>100.0</td>
<td>27</td>
<td>96.4</td>
</tr>
<tr>
<td>≥1 Treatment-related TEAE</td>
<td>18</td>
<td>64.3</td>
<td>15</td>
<td>53.6</td>
</tr>
<tr>
<td>≥1 SAE</td>
<td>2</td>
<td>7.1</td>
<td>1</td>
<td>3.6</td>
</tr>
<tr>
<td>≥1 Treatment-related SAEs</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>≥1 Maximum severity severe TEAE</td>
<td>3</td>
<td>10.7</td>
<td>7</td>
<td>25.0</td>
</tr>
<tr>
<td>≥1 TEAE leading to study drug discontinuation</td>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.1</td>
<td>1</td>
<td>3.6</td>
</tr>
<tr>
<td>≥1 TEAE of special interest (acromegaly symptoms)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>15</td>
<td>53.6</td>
<td>26</td>
<td>92.9</td>
</tr>
</tbody>
</table>

- Most TEAEs were mild or moderate
- GI AEs were transient
- No deaths were reported during the DPC period
- Overall, OOCs were well tolerated; no new/unexpected safety signals were observed
- Three patients in the OOC group experienced severe TEAEs:
  - Gastrointestinal (abdominal discomfort, dyspepsia, nausea, vomiting)
  - Nervous system disorders (headache)

<sup>a</sup>TEAEs leading to study drug discontinuation in two patients the OOC group were nausea, vomiting, abdominal discomfort, heartburn and headache.

<sup>b</sup>TEAEs of special interest includes: headache, fatigue, perspiration, soft tissue swelling, arthralgia, dysglycemia, hypertension, or other signs in view of investigator as related to acromegaly. SAE, serious adverse event; TEAE, treatment-emergent adverse event.
AEs Related To Blood Glucose Control

Minimal shifts in glucose control were consistent with class effect for first-generation SRLs.

<table>
<thead>
<tr>
<th>MedDRA Listing</th>
<th>OOC (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>1</td>
</tr>
<tr>
<td>Blood glucose increased^a</td>
<td>3</td>
</tr>
<tr>
<td>Hyperglycemia^b</td>
<td>1</td>
</tr>
</tbody>
</table>

\^1 of these AEs was deemed related to study drug by the investigator. \^bDeemed possibly related to study drug.
Glucose Control Throughout the DPC Period

In the OOC group (n=28)

• 19 patients had normal glucose levels at baseline and EOT (67.9%)

• 3 patients stayed within the same elevated range at EOT as they were at baseline (10.7%)

• 1 patient was in a lower range by EOT (3.6%)
  • Shifted from mild elevation to normal range

• 5 patients were in a higher range by EOT (17.9%)
  • All shifted from normal range to a mild elevation
  • 4 remained on OOC throughout the DPC, 1 discontinued due to treatment failure

EOT, end of treatment.
Serum Glucose From Baseline to End of Treatment Was Consistent

- Glycemic control from baseline to EOT shifted from normal to high HbA1c in 1 patient in OOC group

Glucose levels in OOC group during the DPC period

Mean serum glucose and HbA1c remained consistent from baseline to EOT in the study

HbA1c, hemoglobin A1c.
Conclusions

• OOCs showed maintenance of glycemic control and an excellent safety profile for patients previously treated with injectable SRLs

• Minimal shifts in glucose control were consistent with class effect for first generation SRLs

• Mean serum glucose and HbA1c levels in patients with acromegaly receiving OOC treatment were consistent from baseline to EOT

Glycemic control in patients receiving OOC treatment is consistent with the class effect observed in first generation injectable SRLs