Validation of Macimorelin As a Diagnostic Test for Adult Growth Hormone Deficiency: A Phase 3 Study in Comparison with the Insulin Tolerance Test

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Macimorelin
A potent stimulator of GH release

- **Macimorelin** is an orally-active ghrelin receptor agonist that induces a fasting patient’s GH secretion in a similar way as ghrelin (GH secretion).

- Upon stimulation by **Macimorelin** GH is released from the pituitary gland into the circulation.

- Stimulated GH levels are measured in blood for the assessment of growth hormone deficiency (GHD).
Assessing AGHD with Macimorelin vs. the ITT

**Insulin Tolerance Test (“ITT”)**

Fasted Patient

Initial Blood Draw

**Physician Supervision**

<table>
<thead>
<tr>
<th>2 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia induced via Insulin IV administration</td>
</tr>
<tr>
<td>Multiple blood draws and monitoring of blood glucose levels</td>
</tr>
</tbody>
</table>

Up to several Hours

Continued medical supervision

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**Macimorelin**

Fasted Patient

Initial Blood Draw

Patient Drinks Solution

**No Physician Supervision Required**

1-2 blood draws

1 Hour

No patient restrictions or necessary care
Macimorelin Phase 3 Trial
Trial Design

- **Primary Objective**
  - Validation of macimorelin for the diagnosis of AGHD, using the Insulin Tolerance Test (ITT) as comparator

- **Co-Primary Efficacy Variables**
  - “Percent Negative Agreement” and “Percent Positive Agreement”

- **Patients**
  - Patients with suspected GHD (low ↔ high risk) and healthy subjects
  - Sites: 21 in EU, 5 in US

**Pivotal Phase 3 Study**
Open-label, randomized, 2-way crossover

- ITT → Macimorelin
- Macimorelin → ITT

**Extension Study (EU only)**
N= 30 Patients

- Macimorelin → Macimorelin
- Macimorelin → Macimorelin

Æterna Zentaris
Macimorelin Phase 3 Trial
Recruitment

- Patients enrolled: 157
- Patients withdrawn: 4
- Patients non-evaluable: 13 (due to non-evaluable ITT)
- Patients fully evaluable: 140

- Balance in groups
  - Approx. 25% of the trial population patients with „high likelyhood“ and „low likelyhood“ each
  - Approx. 25% of the evaluable patients to be recruited at US sites
  - 20-25 healthy subjects matching a „high likelyhood“ subject

- ITT test outcome
  - ≥ 55 with positive and ≥ 55 with negative ITT outcome

Æterna Zentaris
### Macimorelin Phase 3 Trial – Results
#### Equivalence Criteria

<table>
<thead>
<tr>
<th>Macimorelin stimulation test outcome</th>
<th>Insulin tolerance test outcome</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Positive</td>
<td>55</td>
<td>39.29</td>
</tr>
<tr>
<td>Negative</td>
<td>19</td>
<td>13.57</td>
</tr>
<tr>
<td>Total</td>
<td>74</td>
<td>52.86</td>
</tr>
</tbody>
</table>

Positive outcome: GH release below pre-defined cut-off point
Negative outcome: GH release above pre-defined cut-off point

### ITT Outcome

<table>
<thead>
<tr>
<th>Macrilen™ Outcome</th>
<th>Positive</th>
<th>Negative</th>
<th>Percent Positive Agreement = 100% x A/(A+C)</th>
<th>Percent Negative Agreement = 100% x D/(B+D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>A</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>C</td>
<td>D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>A+C</td>
<td>B+D</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Macimorelin Phase 3 Trial – Results
Equivalence Criteria not met

Results did not meet the pre-defined equivalence criteria for Macimorelin success

- Negative Agreement: 93.94% (CI: 85.20%, 98.32%) ✔
- Positive Agreement: 74.32% (CI: 62.84%, 83.78%) ☠

Under the study protocol, performance of Macimorelin was considered acceptable if the lower bound of the two-sided 95% confidence interval for the primary efficacy variables is

- 75% or higher for ‘Percent Negative Agreement’ and
- 70% or higher for the ‘Percent Positive Agreement’

➢ Secondary endpoint: (acceptance criteria not defined)
- Overall agreement: 83.57 % (CI: 76.38%, 89.29%)
## Macimorelin Phase 3 Trial – Results

### Sensitivity and Specificity of Macimorelin

<table>
<thead>
<tr>
<th>Macimorelin stimulation test outcome</th>
<th>AGHD group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A. High likelihood of GHD</td>
<td>B. Healthy control</td>
</tr>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Positive</td>
<td>33</td>
<td>86.84</td>
</tr>
<tr>
<td>Negative</td>
<td>5</td>
<td>13.16</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>100.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Lower confidence limit</th>
<th>Upper confidence limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.87</td>
<td>0.72</td>
<td>0.96</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.96</td>
<td>0.80</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Macimorelin Phase 3 Trial – Results
Repeatability of Macimorelin

<table>
<thead>
<tr>
<th>Subject disposition</th>
<th>AGHD likelihood Group</th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A: High</td>
<td>B: Intermediate</td>
<td>C: Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>All subjects</td>
<td>13</td>
<td>12</td>
<td>9</td>
<td></td>
<td>34</td>
</tr>
<tr>
<td>Match between first and second MAC test</td>
<td>13</td>
<td>11</td>
<td>8</td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>

Repeatability per protocol: 32 matching out of 34
Macimorelin Phase 3 Trial – Results
Evaluability of Macimorelin and ITT

**ITT**
- ITT evaluable upon repeat: 9%
- ITT not repeated: 6%
- ITT not evaluable twice: 3%
- ITT evaluable at first try: 82%

**Macimorelin**
- MAC not evaluable at first try, evaluable upon repeat: 1%
- MAC evaluable at first try: 99%
Macimorelin Phase 3 Trial – Results
Peak GH concentrations after Macimorelin and ITT
Macimorelin Phase 3 Trial – Results
Robustness of Macimorelin

- Macimorelin was found to be the more robust test than ITT, since only 1 out 153 Macimorelin tests needed to be repeated to become evaluable (compared to 28 out of 157 for the ITT)
  - Reproducible outcome of the Macimorelin test upon planned repetition in the repeatability study (34 tests) is further evidence of its robustness

- Macimorelin stimulated GH release more powerfully than the ITT
  - in about 80% of all cases peak GH levels following Macimorelin were equal or higher than observed during the ITT
Macimorelin Phase 3 Trial – Results
Neg. and pos. agreement for varying cut-off points of Macimorelin

Primary end point criteria: neg. agreem.
pos. agreem.

Both co-primary endpoints would be met

Favorable cut-off point range

Pre-specified cut-off point

Neg % agree  Pos % agree
Macimorelin Phase 3 Trial
Conclusions (1 of 2)

- Macimorelin stimulates the pituitary gland effectively to secret growth hormone.
  - This stimulation was consistently more pronounced than the stimulation achieved with the ITT (in about 80% of all cases peak GH levels following Macimorelin were equal or higher than observed during the ITT).

- The Macimorelin test performed well in the study:
  - Sensitivity (87%) and Specificity (96%) of the Macimorelin test were very good.
  - Data of the previous study (82% sensitivity, 92% specificity) could be reproduced.
  - The co-primary endpoint “negative agreement”, which is considered as the more relevant endpoint, was met, demonstrating that the Macimorelin test provides medical benefit.
  - The co-primary endpoint “positive agreement” was not met.
In the repeatability extension part of the study, conducted upon request from the EMA, Macimorelin results proved to be highly reproducible.

- 94% reproducibility (32 out of 34 cases at the pre-defined cut-off point)
- Reproducibility of the ITT, which was not investigated in this study, appears worse than the Macimorelin test as demonstrated by a high number of non-evaluable ITTs in the study

Study results can be further optimized by modulation of the pre-defined cut-off point of 2.8 ng/mL.

- Any cut-off point for Macimorelin between 4.6 ng/mL and 8.2 ng/mL would have resulted in a positive study outcome in that both protocol-defined co-primary endpoints would have been met.
- Increasing the cut-off point when comparing to the ITT outcome is justified by the more powerful stimulation of Macimorelin as compared to the ITT (pre-defined cut-off point of 5.1 ng/mL)