Validation of Macimorelin as a Diagnostic Test for Adult Growth Hormone Deficiency (AGHD): A Phase 3 Study in Comparison with the Insulin Tolerance Test (ITT)

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Background


Conclusions

Macimorelin stimulates the pituitary effectively to secret growth hormones. This stimulation was considerably more pronounced than the stimulation achieved with the ITT (in about 90% of all subjects, GH levels following macimorelin were higher or equal than observed during the ITT). The macimorelin test performed well:

- Sensitivity (92.9%) and Specificity (96.0%) of the macimorelin test were very good.
- The endpoint "negative agreement", which is considered as the more relevant of the two co-primary endpoints, was met, demonstrating that the macimorelin test provides a medical benefit.
- The repeatability 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.

The macimorelin test is safe:

- 30 subjects (20%) reported ITT adverse events after macimorelin test, while 101 subjects (66%) reported ITT adverse events after ITT. Differences and TII were the most reported possible drug-related adverse events for macimorelin.

Study results can be further optimized by modification of the predefined cut-off points of 2.8 ng/mL.

Results

- For the macimorelin test, possibly drug-related AEs reported in more than 2% of the subjects included nausea, vomiting, fatigue, headache, and tremor (2.6% each). Majority of cases were of mild intensity, none of severe intensity.

- For the macimorelin test (upper limb fracture due to fall from a ladder).

- Reproducibility per protocol

- The second co-primary endpoint "positive agreement" was not met.

- For macimorelin cut-off points between 4.5 ng/mL and 8.2 ng/mL, would have resulted in positive and negative agreement with the ITT within the pre-defined success criteria. Increasing the cut-off point above a justified by the more powerful stimulation of macimorelin as compared to the ITT.

- The ITT demonstrated excellent sensitivity and specificity.

- The second co-primary endpoint "positive agreement" was not met.

- In 32 out of 34 (94%) planned macimorelin repeat tests, the second test result matched with the first result.

- In all groups, macimorelin induced higher GH concentrations than the ITT.

- In about 60% of all cases peak GH levels after macimorelin were equal or higher than during the ITT.

- The higher provocative potential of macimorelin as compared to the ITT resulted in a positive study outcome in that both protocol-defined co-primary endpoints would have been met.

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- The ITT demonstrated excellent sensitivity and specificity.

- The ITT was associated with a broad spectrum of signs and symptoms related to hypogonadism. A total of 229 moderate TEAEs during/after the ITT were reported for 64 (40.8%) subjects. Most reported possibly drug-related adverse events for macimorelin included: 5 (3.2%) subjects each with somnolence, hyperhidrosis; 4 (2.5%) with asthenia; 3 (1.9%) with hunger; 2 (1.3%) with malaise, weight gain; 2 (1.3%) with nightmares, and 2 (1.3%) with headache. Fewer subjects included dysgeusia (4.5%), headache (3.2%), nausea (2.6%), and dizziness (2.6%).

- Total of 25 severe TEAEs were reported for 11 (7%) subjects including: 5 (3.2%) subjects each with somnolence, hyperhidrosis; 4 (2.5%) with asthenia; 3 (1.9%) with hunger; 2 (1.3%) with malaise, weight gain; 2 (1.3%) with nightmares, and 2 (1.3%) with headache. Fewer subjects included dysgeusia (4.5%), headache (3.2%), nausea (2.6%), and dizziness (2.6%).

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