Æterna Zentaris

Macimorelin

Evaluation of Adult Growth Hormone Deficiency (AGHD)

Macimorelin is an oral growth hormone secretagogue (GHS) receptor agonist used to test for Adult Growth Hormone Deficiency, a rare endocrine disorder.

Therapeutic Area

Endocrinology

Indication/Target Disease

AGHD may occur in an adult subject who has a history of childhood onset GHD or may occur during adulthood as an acquired condition.

About 6,000 cases of AGHD are reported each year in the United States, with an estimated 50,000 diagnosed adults. The prevalence after traumatic brain injury is estimated at 12%.[1] In general, the prevalence and incidence of AGHD is not well investigated in Europe by epidemiological studies. However, the NHS has estimated the number of subjects with AGHD in England and Wales with 12,600 and the prevalence in UK with 1 case in 10,000 of the adult population.[2] The prevalence in France was estimated by Sassiolas et al. with 2,638 cases, based on a ratio of 4.6 cases per 100,000 inhabitants. In the same study, a disease incidence was reported with 1.2 new cases per 100,000 inhabitants.[3] Regal et al. published data for Spain with an incidence of 4.44 cases per 100,000 female inhabitants and of 4.08 for male inhabitants.[4] Figures for Denmark taken from a publication from Stochholm et al. show an incidence of 1.42 new cases per 100,000 for females and of 1.9 cases for males. Considering a total population of 510 million for the European countries (EU-28), about 51,000 adults are estimated to be diagnosed with GHD.[5]

In other areas of the world, the incidence and prevalence of AGHD are not known, and awareness and diagnosis remains low. Growth hormone (GH) not only plays an important role in growth from childhood to adulthood, but also helps promote a hormonally-balanced health status. AGHD mostly results from damage to the pituitary gland, which can be caused by tumors, traumatic brain injury, brain infarction, radiation or infections. It is usually characterized by a reduction in bone mineral density, lean body mass, exercise capacity, and overall quality of life as well as an increase of cardiovascular risks.

Mechanism of Action

GHS are potent regulators of lipid, sugar and protein metabolism that directly stimulate growth hormone secretion from the pituitary gland without the involvement of Growth Hormone-Releasing Hormone or somatostatin.

How Macimorelin Works

- Macimorelin stimulates the secretion of GH from the pituitary gland into the circulatory system.
- Stimulated GH levels are measured in only four blood samples over ninety minutes after oral administration of macimorelin (no intravenous infusions or intramuscular injections).
- No healthcare personnel supervision is required.

Development Milestones

Macimorelin was invented and first synthesized by the research group of Professor Martinez at the University of Montpellier, Centre National de la Recherche Scientitifique (CNRS). This transpired from a long-lasting research collaboration with Aeterna Zentaris. Aeterna Zentaris later in-licensed macimorelin as a development candidate from the CNRS* and proceeded with the pre-clinical and clinical development of the compound. The following are developmental milestones.

January 17, 2018 Aeterna Zentaris announced that through a wholly-owned subsidiary, it entered into a license and assignment agreement with Strongbridge Ireland Ltd. to carry out development, manufacturing registration and commercialization of Macrilen™ (macimorelin) in the United States and Canada.

December 20, 2017 Aeterna Zentaris announced that the U.S. Food and Drug Administration (FDA) granted marketing approval for Macrilen™ (macimorelin). For information about Macrilen™ the first and only FDA-approved oral drug for the diagnosis of Adult Growth Hormone Deficiency including Important Safety Information and Full Prescribing information, visit: http://www.strongbridgebio.com/products/.

November 27, 2017 Aeterna Zentaris announced that the Marketing Authorization Application (MAA) for the use of macimorelin for the evaluation of AGHD was accepted by the European Medicines Agency (EMA) for regulatory review.

October 5, 2017 Macimorelin granted orphan drug designation by the FDA for diagnosis of AGHD. Aeterna Zentaris proposed, subject to FDA approval, to market macimorelin under the name Macrilen™.

July 18, 2017 Aeterna Zentaris announced that it had been notified by the FDA that its NDA seeking approval of Macrilen™ for the evaluation of AGHD had been accepted as a complete response to the FDA's November 5, 2014 Complete Response Letter and granted a PDUFA date of December 30, 2017.

June 30, 2017 Aeterna Zentaris announced that the new drug application (NDA) seeking approval of macimorelin was resubmitted to the FDA.

April 2, 2017 Jose M. Garcia M.D., Ph.D., an Associate Professor of Medicine at the Puget Sound Veterans Administration Hospital and the University of Washington, presented an abstract at the 99th Annual Meeting of the Endocrine Society in Orlando, Florida, entitled "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)." To view the poster, click here.

March 30, 2017 Aeterna Zentaris announced that following its meeting with the FDA on March 29, 2017 it intends to file an NDA seeking approval for macimorelin for the evaluation of growth hormone deficiency in adults.

February 13, 2017 Aeterna Zentaris announced that following a comprehensive review of data obtained from the confirmatory Phase 3 clinical trial of macimorelin for the evaluation of AGHD using the Insulin Tolerance Test (ITT) as a comparator, it concluded that macimorelin demonstrated performance supportive of achieving registration with the FDA. The FDA agreed to consider its conclusion during a Type A meeting. The Company's comprehensive analysis of the data presented to the FDA concluded as follows:

Macimorelin was shown to diagnose AGHD accurately comparing the diagnostic agreement between macimorelin and the benchmark, ITT.

- The clinical trial was an open-label, randomized, cross-over study (N=154).
- Overall, macimorelin and the ITT were in complete agreement among 84% of all subjects.
- Among those with a high likelihood of AGHD prior to testing, macimorelin and the ITT were in complete agreement among 89% of subjects.
- Macimorelin was evaluable in >99% of tests at first try, compared to 83% evaluable with the ITT.
- Repeatability was observed in 91% of the patients (N=34) who underwent two macimorelin tests.

Macimorelin Has a Favorable Safety Profile

- Only 25% of subjects reported any adverse event (AE) after receiving macimorelin compared with 96% reporting an AE during the ITT.
- The most common side effects were changed sense of taste, dizziness, headache, fatigue, nausea, hunger, diarrhea, upper respiratory tract infection, feeling hot, excessive sweating, sore nose and throat, and decreased heart rate. These were seen in less than 5% of clinical trial participants who took macimorelin.
- There are no contraindications based on the U.S. approved label.

For more information about the Phase 3 clinical trial of macimorelin, visit:

https://www.clinicaltrials.gov/ct2/show/NCT02558829?term=macimorelin

January 4, 2017 Aeterna Zentaris announced that the confirmatory Phase 3 clinical trial of macimorelin failed to achieve its objective of validating a single oral dose of macimorelin for the evaluation of growth hormone deficiency in adults using the Insulin Tolerance Test as a comparator.

Partnership Status

Aeterna Zentaris, through a wholly-owned subsidiary, entered into a licensing and assignment agreement with Strongbridge Ireland Ltd. to carry out development, manufacturing, registration and commercialization of (macimorelin) to be marketed under the name Macrilen™ in the United States and Canada. To learn more about the agreement, click here.

For partnership opportunities outside of the United States and Canada, please contact our Business Development Department at BD@aezsinc.com.

1.2016 Endocrine Society 'Hormonal Replacement in Hypopituitarism in Adults' Guideline
2.NHS Technology Appraisal 64, August 2003
3.Sassiolas et al., European Journal of Endocrinology, 1999, 595-600
4.Regal et al., Clinical Endocrinology, 2001, 735-740
5.Stochholm et al., European Journal of Endocrinology, 2006, 61-71