IONIS® InBrief
01 Nov 2021

Topline results of Phase 2 clinical study support continued development of Cimdelirsen designed to treat uncontrolled acromegaly

Ionis completed a Phase 2 clinical study evaluating cimdelirsen (IONIS-GHR-L_{Rx}) as an add-on therapy in patients with uncontrolled acromegaly despite stable therapy with long-acting somatostatin receptor ligands (SRL). Based on the results of this Phase 2 study and a preliminary analysis of the ongoing open-label study, proof of mechanism was achieved with a strong indication of proof of concept supporting the continued development of cimdelirsen.

Due to enrollment difficulties associated with the COVID-19 pandemic, the study closed early, resulting in smaller cohort sizes than planned. However, while no longer powered to assess the primary endpoint (% IGF- lowering at Day 141) in accordance with the protocol, the study did permit placebo-controlled evaluation of safety and efficacy.

“Data from the Phase 2 study are encouraging as they showed target reduction without an increase in growth hormone levels, reduction in integrated IGF-1 area under the curve (AUC) response and good safety and tolerability that support ongoing development`. These data bring us one step closer to providing an effective treatment option for patients with uncontrolled acromegaly,” said Sanjay Bhanot, M.D., Ph.D., senior vice president, chief medical officer and cardiometabolic franchise leader at Ionis.

Cimdelirsen is a wholly owned investigational antisense medicine designed to inhibit the production of growth hormone receptor (GHr), thereby inhibiting the downstream effects of growth hormone hypersecretion and consequently reducing circulating levels of insulin-like growth factor-1 (IGF-1) in people living with uncontrolled acromegaly. It was developed using Ionis’ advanced **LI**gand **C**onjugated **A**ntisense (LICA) technology.

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Key objectives achieved in Ionis' Phase 2 study include:

- Demonstrated good safety and tolerability at all doses
- No drug related SAEs or deaths. The most common AEs were UTI and headaches which were unrelated to study drug and not dose-dependent
- Significant target reduction as measured by mean reduction in circulating GHBP (circulating GH receptor) levels of up to -64% (p=0.0001)
- Target reduction was not accompanied by an increase in growth hormone levels
- Integrated area under the curve for IGF-1 demonstrated a significant median reduction in the high dose group (-1229%*day p= 0.05) compared to an increase in the placebo group (+519%*day)
- Preliminary data suggests that Quality of Life scores improved with cimdelirsen treated patients

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"Acromegaly is a rare, serious and life-threatening disease for which there has been limited recent innovation and a clear unmet need. Cimdelirsen could offer tangible hope for a convenient at-home, self-administered treatment if long-term studies extend the current findings of GHBP and IGF-1 reduction without associated GH increases that are also accompanied by improvement in quality of life," said Shlomo Melmed, MB, ChB, executive vice president of academic affairs, dean of the medical faculty and professor of medicine at Cedars-Sinai Medical Center.

KEY TAKEAWAY

The data in this Phase 2 study demonstrate significant and sustained target reduction coupled with good safety and tolerability of cimdelirsen as an add-on therapy to long-acting somatostatin receptor ligands and provide support to continue developing this potentially transformative treatment.

Results: significant target reduction using a biomarker

GHBP in the blood is a cleavage product of membrane bound GHR and was used as a biomarker for the level of hepatic GHR antisense reduction.

In this study, proof of mechanism was demonstrated by a significant, dose-dependent mean percent reduction in GHBP.

The percent change from baseline to Day 141 was –2% placebo, -43% low dose and –64% high dose; p <0.001 and 0.001 for the low dose and high dose groups, respectively.

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Results: no growth hormone increase, an important safety finding

Importantly, significant GHBP reductions were not associated with fasting GH increases. The mean change from baseline to Day 141 was 1ng/mL placebo, 0 ng/mL low dose and 1ng/mL high dose; p= 0.90 and 0.47 for the low dose and high dose groups, respectively.

Results: IGF-1 reduction based on integrated AUC

In this study, an indicator of proof of concept is observed from the integrated AUC for IGF-1 results.

The integrated AUC for IGF-1 percent change from baseline demonstrated dose-dependent reductions that were significant at the high dose, after GHBP had reached near-maximal reductions (Day 57 – Day 141).

The median percent change from baseline was +519 (%*day) in placebo, -519 (%*day) in low dose and –1229 (%*day) in high dose; p=0.21 and 0.05 for the low dose and high dose groups, respectively.

Two once monthly cimdelirsen dosing groups were analyzed:

- **Low Dose Group:** patients from 60 mg + 80 mg
- **High Dose Group:** patients from 120 mg + 160 mg

Next Steps For Ionis' Program:

The open-label extension study and monotherapy study are ongoing and are expected to be completed in 2022. Data from these studies and the Phase 2 study are planned to be presented at a medical meeting.

Ionis' Forward-looking Statement

This Ionis InBrief includes forward-looking statements regarding Ionis' business and the therapeutic and commercial potential of Ionis' technologies, cimdelirsen (IONIS-GHR-L_{Rx}) and other products in development. Any statement describing Ionis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, including those related to the impact COVID-19 could have on our business, and including but not limited to those related to our commercial products and the medicines in our pipeline, and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements.

Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on Form 10-K for the year ended December 31, 2020, and the most recent Form 10-Q quarterly filing, which are on file with the SEC. Copies of these and other documents are available from the Company.