Design of the foresiGHt Trial: A Multicenter, Randomized, Placebo- and Active-Controlled Trial to Compare Once-Weekly TransCon hGH (lonapegsomatropin) to Placebo and Daily Somatropin in Adults with Growth Hormone Deficiency (GHD)

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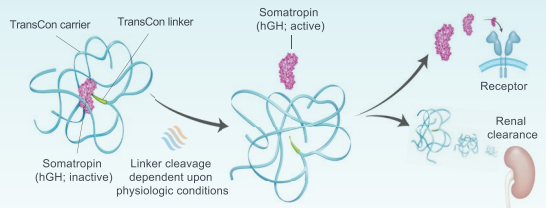
BACKGROUND

- In adults, GHD is characterized by central adiposity, decreased lean muscle mass, increased fat mass, decreased bone mineral density, reduced quality of life, and premature cardiovascular morbidity and mortality[1-3]
- GH replacement for adults with GHD has been shown to improve body composition, quality of life, insulin sensitivity, and bone mineral density[4-5]; currently adults with GHD are treated with daily injections of GH[6]
- GHD in adults frequently goes untreated; in a single-center cross-sectional survey-based study, 34% of participants with GHD were not receiving any GH treatment, with 75% of those having no clear medical reason for discontinuation of their treatment (reasons included lack of information about GHD and GH replacement therapy)[7]
- Nonadherence of subjects who are undergoing GH replacement therapy can impact treatment outcomes[4]; one study reported 35% of adult participants with GHD were "noncompliant and skeptical[8]" and another reported a median of only 80% adherence[9]

LONAPEGSOMATROPIN

- Once-weekly lonapegsomatropin (TransCon hGH) is an investigational prodrug of somatropin for the treatment of growth hormone deficiency (GHD) that consists of 3 components: unmodified somatropin, an inert carrier that protects it, and a linker that temporarily joins the two[10] (Figure 1)

Figure 1. Lonapegsomatropin (TransCon hGH) Design

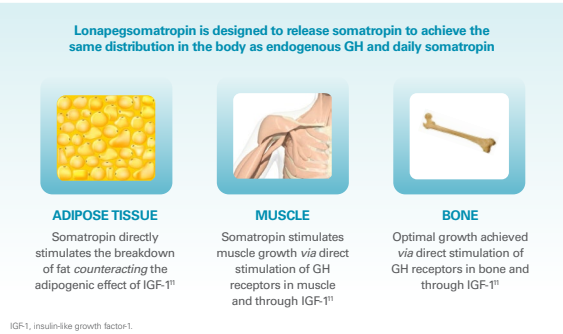


Once-weekly prodrug releases unmodified hGH designed to mimic daily hGH:

- Tissue distribution
- Physiological levels
- Therapeutic effects: efficacy, safety and tolerability

- Lonapegsomatropin is designed to release somatropin to achieve the same distribution in the body as endogenous GH and daily somatropin therapy[10] (Figure 2)

Figure 2. Growth Hormone Supports Overall Endocrine Health



IGF-1, insulin-like growth factor-1.

- A phase 2 dose-finding study in adults with GHD demonstrated that ACP-001 (bioequivalent to lonapegsomatropin) had a pharmacokinetic, pharmacodynamic, and adverse event profile comparable to daily somatropin (Omnitrope®), but with a once-weekly dosing regimen[12]
  - ACP-001 demonstrated a linear, dose-dependent increase in GH exposure without accumulation
  - No lipoatrophy or nodule formation occurred at injection sites and no treatment-emergent anti-GH antibodies were detected
- The safety and efficacy of lonapegsomatropin has also been evaluated in two phase 3 trials and one ongoing long-term extension enliGHten trial in children with GHD
  - In the pivotal phase 3 heiGHt Trial evaluating treatment-naïve children with GHD, lonapegsomatropin demonstrated superior annualized height velocity at 52 weeks compared to daily somatropin therapy (Genotropin®) while maintaining a similar safety and tolerability profile[13]
  - In the phase 3 fliGHt Trial evaluating primarily treatment-experienced children with GHD, lonapegsomatropin was well-tolerated and demonstrated an adverse event profile consistent with the known profile of daily somatropin; growth outcomes were consistent with clinical expectations for this broad pediatric population[14]

METHODS

FORESIGHT STUDY DESIGN

- foresiGHt is a multicenter, randomized, parallel-arm, placebo-controlled (double-blind) and active-controlled (open-label) trial to compare the efficacy and safety of once-weekly lonapegsomatropin with placebo and a daily somatropin product in adults with growth hormone deficiency for 38 weeks, with a 52-week open-label extension period (ClinicalTrials.gov: NCT04615273)
- The primary objective of foresiGHt is to evaluate the efficacy of once-weekly lonapegsomatropin compared to placebo at 38 weeks in adults with GHD
- The trial will be conducted at approximately 120 sites in North America, Europe, Asia, and Oceania

Subject Population

- Adults with GHD treatment-naïve or without GH therapy for at least 12 months. Other key inclusion/exclusion criteria are listed in Table 1

Treatment

- Approximately 240 subjects will be randomized 1:1:1 to once-weekly lonapegsomatropin, once-weekly placebo, or daily somatropin (Norditropin®)
  - The daily somatropin product arm is included as a calibration arm to assist clinical judgement of the trial results

METHODS

- Following screening, the 38-week treatment period will consist of a 12-week gradual dose titration period and 26-week fixed- dose maintenance period (Figure 3)
  - Fixed dosing will be used to ensure maximal comparability across the treatment arms in the trial
  - Three dosing groups per arm will be established to account for different dosing requirements based on age and oral estrogen intake
- For Japan, there will be an additional arm enrolling subjects previously treated with a commercially available daily somatropin for switch to treatment with open-label lonapegsomatropin

Figure 3. foresiGHt Trial Design

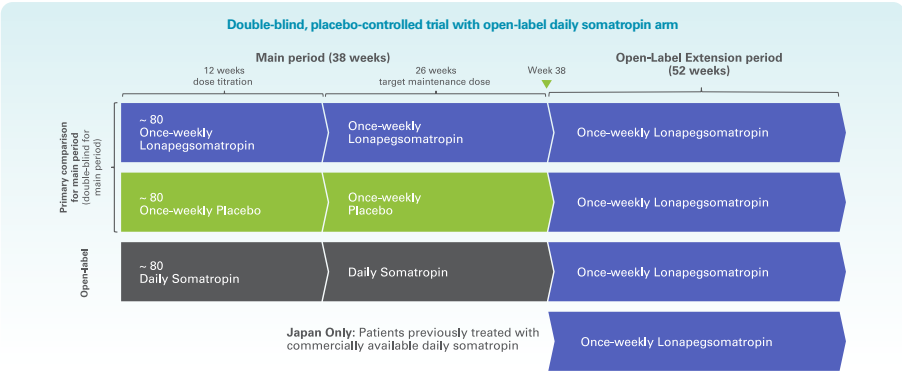


Table 1. Key Inclusion/Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Age 23 – 75 years old	• Diabetes mellitus at screening if poorly controlled (hbA1c > 7.5%) or unstable, or if treated with anti-diabetic drugs other than metformin and/or DPP-4 inhibitors; or significant diabetes complications
• Documented history of structural hypothalamic-pituitary disease, hypothalamic-pituitary surgery, cranial irradiation, 1 – 4 non-GH pituitary hormone deficiencies, or a proven genetic cause of GHD; subjects with childhood onset with growth hormone axis re-tested at end of final height	• Active malignant disease or history of malignancy, with some exceptions
• GHD confirmed by stimulation test (insulin tolerance test, glucagon, macimorelin, growth hormone-releasing hormone + arginine) OR diagnosis of 3 – 4 hypothalamic-pituitary axis deficiencies with IGF-1 SDS ≤ -2.0	• Evidence of growth of pituitary adenoma or other benign intracranial tumor within the last 12 months before screening
• IGF-1 SDS ≤ -1.0 measured by central laboratory	• Anabolic steroids (other than gonadal steroid replacement therapy) or oral/ intravenous/intramuscular corticosteroids (other than in replacement doses) within 90 days prior to or throughout screening
• hGH treatment naïve or no exposure to hGH or GH secretagogue for at least 12 months prior to screening	• eGFR < 60 ml/min/1.73m² as determined by the Modification of Diet in Renal Disease equation
• Stable and adequate hormone replacement therapies for any hormone deficiencies other than growth hormone	• AST or ALT > 3 times the upper limit of normal
• Stable diet and exercise regime with no intention to modify; no plans to undergo bariatric surgery during trial	• Heart failure: New York Heart Association class ≥ 3
	• 12-lead ECG: QTcF ≥ 451 milliseconds
	• Poorly controlled hypertension (blood pressure > 150/95 mmHg)
	• Cerebrovascular accident within prior 5 years

ALT, alanine transaminase; AST, aspartate transaminase; DPP-4, dipeptidyl peptidase-4; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate.

Table 2. Trial Endpoints

Primary Efficacy Endpoint	• Change from baseline in trunk percent fat at Week 38 (assessed by DXA)
Secondary Efficacy Endpoints	• Change from baseline in trunk fat mass (kg) at Week 38 (assessed by DXA) • Change from baseline in total body lean mass (kg) at Week 38 (assessed by DXA)
Safety Endpoints	• Incidence of adverse events • Laboratory values • Vital signs • Anti-drug antibodies • ECG • Fundoscopy
PK/PD Endpoints	• hGH • Lonapegsomatropin • mPEG • IGF-1 • IGFBP-3
Exploratory Efficacy Endpoints	• Additional parameters of body composition • Measures of quality of life

IGFBP-3, insulin-like growth factor-binding protein 3; mPEG. Methoxypolyethelene glycol.

CONCLUSIONS

- The ongoing global phase 3 foresiGHt trial is designed to assess the efficacy, safety, and tolerability of lonapegsomatropin by weekly administration, compared to weekly placebo and daily somatropin replacement therapy in adults with GHD
- Once-weekly lonapegsomatropin may represent a convenient GH replacement option that may optimize adherence and interest in therapy among adults with GHD

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