Pivotal foreSIGHt TRIAL

Once-weekly Skytrofa® lonapegsomatropin-tcgd

Phase 3 foresiGHt Trial

Efficacy, safety, and tolerability of once-weekly SKYTROFA® in adults with GHD

This study was sponsored by Ascendis Pharma Endocrinology Division A/S.

GHD = growth hormone deficiency.

IMPORTANT SAFETY INFORMATION

INDICATIONS AND USAGE

SKYTROFA® (lonapegsomatropin-tcgd) injection is a human growth hormone (GH) indicated for the:

- Treatment of pediatric patients aged 1 year and older who weigh at least 11.5 kg and have growth failure due to inadequate secretion of endogenous GH
- Replacement of endogenous GH in adults with growth hormone deficiency (GHD)

CONTRAINDICATIONS

SKYTROFA is contraindicated in patients with:

- Acute critical illness after open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure due to risk of increased mortality with use of somatropin
- Hypersensitivity to somatropin or any of the excipients in SKYTROFA
- Pediatric patients with closed epiphyses
- Active malignancy

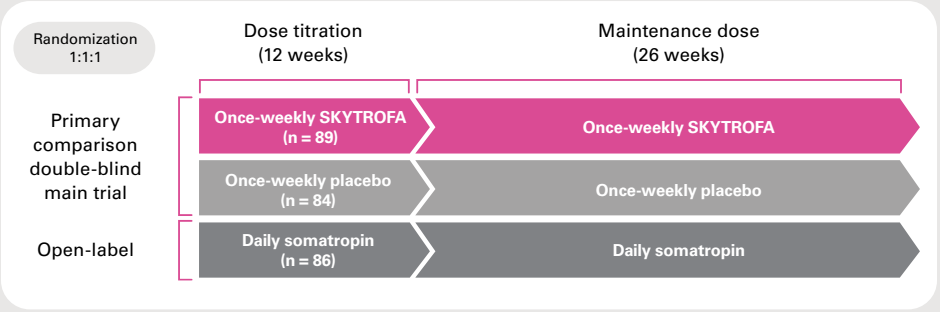
Please see Important Safety Information throughout and click here for full Prescribing Information for SKYTROFA.

Background

- SKYTROFA is a once-weekly prodrug of somatropin that was FDA approved in 2021 for the treatment of children with GHD aged 1 year and older weighing at least 11.5 kg[1,2]
- SKYTROFA provides predictable release of active unmodified somatropin over the course of a week[2,3]*
- In July 2025, the FDA approved SKYTROFA for the replacement of endogenous GH in adults with GHD[2]

foresiGHt study design

A pivotal, phase 3, 38-week, multicenter, randomized, placebo-controlled (double-blind) trial that investigated efficacy, safety, and tolerability of SKYTROFA in adults with GHD (N = 259)[2,4]



- The daily somatropin arm (open-label) was included for calibration purpose to assist with clinical judgment of the trial results[5]
- The study population consisted of 259 adults with GHD who were GH-treatment naïve or had not received GH treatment in the prior 12 months[4]
- Doses were titrated over 12 weeks to reach the target maintenance dose by subgroup based on age and oral estrogen intake, with a fixed maintenance dose for the remaining 26 weeks of treatment[4]
- The primary efficacy endpoint was the change from baseline in trunk percent fat compared with placebo at week 38[2]

*SKYTROFA is a prodrug that releases active somatropin with the same molecular weight and amino acid sequence as endogenous GH.[2,3]

GH = growth hormone; GHD = growth hormone deficiency.

IMPORTANT SAFETY INFORMATION (continued)

CONTRAINDICATIONS (continued)

- Active proliferative or severe non-proliferative diabetic retinopathy
- Pediatric patients with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment due to the risk of sudden death

WARNINGS AND PRECAUTIONS

- **Increased Mortality in Patients with Acute Critical Illness:** Increased mortality has been reported after treatment with somatropin in patients with acute critical illness due to complications following open-heart surgery, abdominal surgery, multiple accidental trauma, and in patients with acute respiratory failure
- **Severe Hypersensitivity:** Serious systemic hypersensitivity reactions including anaphylaxis and angioedema have been reported with post-marketing use of somatropin products, including SKYTROFA. Inform patients and/or caregivers that such reactions are possible and that prompt medical attention should be sought if an allergic reaction occurs

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Study population

Once-weekly Skytrofa® lonapegsomatropin-tcgd

Demographics and baseline characteristics[4]

Baseline demographics and clinical characteristics	SKYTROFA (n = 89)	Placebo (n = 84)	Somatropin (n = 86)
Age, mean (SD)	43.0 (13.4)	44.1 (14.7)	41.3 (14.3)
> 60 years, n (%)	12 (13.5)	11 (13.1)	11 (12.8)
Female, n (%)	42 (47.2)	39 (46.4)	38 (44.2)
GHD onset			
Adulthood, n (%)	50 (56.2)	46 (54.8)	49 (57.0)
Childhood, n (%)	39 (43.8)	38 (45.2)	37 (43.0)
BMI (kg/m^2), mean (SD)	27.0 (5.0)	28.5 (6.5)	28.6 (7.2)
IGF-1 SDS, mean (SD)	–2.6 (1.0)	–2.7 (1.2)	–2.8 (1.0)

BMI = body mass index; GHD = growth hormone deficiency; IGF-1 = insulin-like growth factor-1; SD = standard deviation; SDS = standard deviation score.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Increased Risk of Neoplasms:** There is an increased risk of malignancy progression with somatropin treatment in patients with active malignancy. Any preexisting malignancy should be inactive, and its treatment complete prior to instituting SKYTROFA. In childhood cancer survivors treated with radiation to the brain/head for their first neoplasm who developed subsequent GHD and were treated with somatropin, an increased risk of a second neoplasm has been reported. Children with certain rare genetic causes of short stature have an increased risk of developing malignancies and should be carefully monitored for development of neoplasms. Monitor patients with a history of GHD secondary to an intracranial neoplasm for progression/recurrence of the tumor. Monitor patients carefully for development of neoplasms and/or increased growth/potential malignant changes of preexisting nevi. Advise patients/caregivers to report changes in the appearance of preexisting nevi
- **Glucose Intolerance and Diabetes Mellitus:** Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses. Previously undiagnosed impaired glucose tolerance and overt type 2 diabetes mellitus may be unmasked. Monitor glucose levels in all patients, especially those with risk factors for type 2 diabetes mellitus, such as obesity or a family history of type 2 diabetes mellitus. When initiating SKYTROFA, monitor patients with preexisting type 1 or type 2 diabetes mellitus or impaired glucose tolerance closely, and adjust the doses of antihyperglycemic drugs as needed

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SKYTROFA demonstrated significant improvement in trunk percent fat compared with placebo

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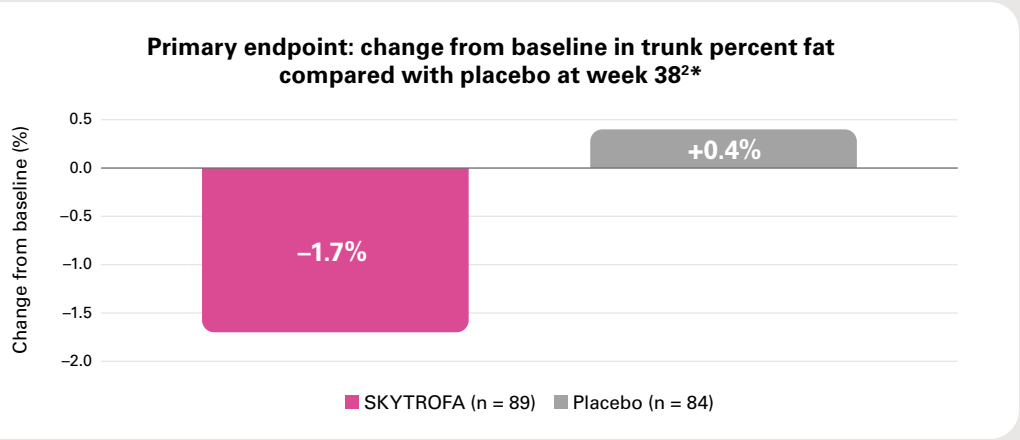

- SKYTROFA demonstrated a statistically significant greater reduction in trunk percent fat compared with placebo[2]
  - LS mean difference was –2.0% (95% CI: –2.9 to –1.1; $P < 0.0001$)[2]
- Patients treated with daily somatropin achieved a change in trunk percent fat of –3.1% after 38 weeks. No formal statistical comparison between SKYTROFA and daily somatropin was conducted[2]

Secondary efficacy endpoints

- Greater increase in total body lean mass compared with placebo (+1.6 kg versus –0.1 kg, respectively; LS mean difference: 1.7 kg; 95% CI: 1.0 to 2.5; $P < 0.0001$)[2]
- Greater reduction in trunk fat mass compared with placebo (–0.5 kg versus +0.2 kg, respectively; LS mean difference: –0.7 kg; 95% CI: –1.2 to –0.2; $P = 0.005$)[2]

*As measured by DXA.[2]

CI = confidence interval; DXA = dual-energy X-ray absorptiometry; LS = least squares.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Intracranial Hypertension:** Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported in a small number of patients treated with somatropin. Symptoms usually occurred within 8 weeks of the initiation of somatropin and resolved rapidly after cessation of therapy/reduction of the dose. Perform fundoscopic examination prior to initiation of treatment and periodically thereafter. If papilledema is observed, stop the treatment. If somatropin-induced IH is confirmed, restart SKYTROFA treatment at a lower dose after IH-associated signs and symptoms have resolved
- **Fluid Retention:** May occur during somatropin therapy. Clinical manifestations of fluid retention (eg, edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/paresthesia) are usually transient and dose dependent
- **Hypoadrenalism:** Patients receiving somatropin therapy who have or are at risk for pituitary hormone deficiency(s) may be at risk for reduced serum cortisol levels and/or unmasking of central (secondary) hypoadrenalism. Patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance/stress doses following initiation of SKYTROFA therapy. Monitor patients with known hypoadrenalism for reduced serum cortisol levels and/or need for glucocorticoid dose increases

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SKYTROFA normalized IGF-1 SDS level at week 38

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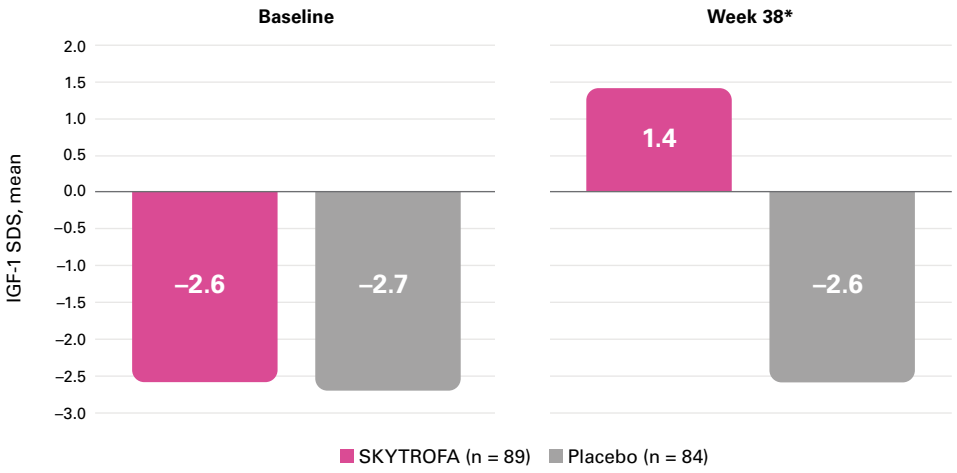
IGF-1 SDS at baseline and after 38 weeks of treatment in adults with GHD[2]



*Sampling time corresponded to weekly average IGF-1 SDS for SKYTROFA.[2]

- At week 38, treatment with SKYTROFA resulted in normalization of IGF-1 SDS to 1.4, compared with minimal change shown with placebo from a baseline of –2.7 to –2.6[2]

IGF-1 = insulin-like growth factor-1; SDS = standard deviation score.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Hypothyroidism:** Undiagnosed/untreated hypothyroidism may prevent an optimal response to SKYTROFA. Monitor thyroid function periodically as hypothyroidism may occur or worsen after initiation of SKYTROFA
- **Slipped Capital Femoral Epiphysis in Pediatric Patients:** Slipped capital femoral epiphysis may occur more frequently in patients undergoing rapid growth and may lead to osteonecrosis. Evaluate pediatric patients receiving SKYTROFA with the onset of a limp or complaints of persistent hip or knee pain for slipped capital femoral epiphysis and osteonecrosis, and manage accordingly
- **Progression of Preexisting Scoliosis in Pediatric Patients:** Monitor patients with a history of scoliosis for disease progression
- **Pancreatitis:** Cases of pancreatitis have been reported in pediatric patients receiving somatropin. The risk may be greater in pediatric patients than in adults. Consider pancreatitis in patients with persistent severe abdominal pain
- **Lipoatrophy:** Lipoatrophy may result when somatropin is administered at the same site over a long period of time. Rotate injection sites to reduce this risk

Please see Important Safety Information throughout and click here for full Prescribing Information for SKYTROFA.

Established safety profile

Once-weekly Skytrofa® lonapegsomatropin-tcgd

AEs occurring in ≥ 5% of SKYTROFA-treated adults and more frequently than in placebo-treated adults (38 weeks of treatment)[2]

AEs	SKYTROFA (n = 89) n (%)	Placebo (n = 84) n (%)
Edema*	7 (8%)	1 (1%)
Central (secondary) hypothyroidism†	6 (7%)	1 (1%)

AEs that are medically related were grouped to a single preferred term.

*Edema in the SKYTROFA treatment group included edema peripheral (6) and peripheral swelling (1).
†Central (secondary) hypothyroidism in the SKYTROFA treatment group included thyroxine free decreased (3), central hypothyroidism (2), thyroxine decreased (1), blood thyroid-stimulating hormone decreased (1), tri-iodothyronine free decreased (1). Preexisting central hypothyroidism in 5 of 6 SKYTROFA-treated patients.

- More SKYTROFA-treated patients shifted from normal or low baseline levels to elevated alkaline phosphatase levels at the end of the trial compared with those in the placebo group (14% versus 6%)[2]
- The incidence of injection-site reactions was similarly low with SKYTROFA and placebo (4.5% and 4.8%, respectively)[4]

AE = adverse event.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Sudden Death in Pediatric Patients With Prader-Willi Syndrome:** There have been reports of fatalities after initiating therapy with somatropin in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnea, or unidentified respiratory infection. Male patients with one or more of these factors may be at greater risk than female patients. SKYTROFA is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome
- **Laboratory Tests:** Serum levels of alkaline phosphatase and phosphate may increase after SKYTROFA therapy. Serum levels of parathyroid hormone may increase after somatropin treatment. If a patient is found to have abnormal laboratory tests, monitor as appropriate

ADVERSE REACTIONS

- Pediatric patients with GHD: the most common adverse reactions (≥ 5%) in patients treated with SKYTROFA and more frequently than in those treated with daily somatropin were viral infection, pyrexia, cough, nausea and vomiting, hemorrhage, diarrhea, abdominal pain, and arthralgia and arthritis
- Adult patients with GHD: the most common adverse reaction (≥ 5%) in patients treated with SKYTROFA and more frequently than in those treated with placebo were edema and central (secondary) hypothyroidism

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Visit Skytrofahcp.com/aghd to learn more about SKYTROFA

References: 1. Maniatis AK, Thornton PS, Nadgir UM, et al. Children with growth hormone deficiency treated with lonapegsomatropin demonstrated sustained height improvements for up to 6 years: enliGHten trial final results. *Horm Res Paediatr.* Published online March 6, 2025. doi:10.1159/000545064 **2.** SKYTROFA. Prescribing information. Ascendis Pharma, Inc.; 2025. **3.** Thornton PS, Maniatis AK, Aghajanova E, et al. Weekly lonapegsomatropin in treatment-naïve children with growth hormone deficiency: the phase 3 heiGHt trial. *J Clin Endocrinol Metab.* 2021;106(11):3184-3195. doi:10.1210/clinem/dgab529 **4.** Gilis-Januszewska A, Biller BMK, Doknic M, et al. Results of the foresiGHt trial support the efficacy and safety of once-weekly lonapegsomatropin in adults with growth hormone deficiency (GHD). Abstract/poster presented at: Joint Congress of European Society for Paediatric Endocrinology and European Society of Endocrinology; May 10-13, 2025; Copenhagen, Denmark. **5.** Fleseriu M, Jørgensen JOL, Yuen KCJ, et al. 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). Poster presented at: Annual Meeting of the Endocrine Society; March 20-23, 2021.

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IMPORTANT SAFETY INFORMATION (continued)

DRUG INTERACTIONS

- **Glucocorticoids:** Patients treated with glucocorticoid replacement for hypoadrenalism may require an increase in their maintenance or stress doses following initiation of SKYTROFA
- **Pharmacologic Glucocorticoid Therapy and Supraphysiologic Glucocorticoid Treatment:** Adjust glucocorticoid dosing in pediatric patients to avoid both hypoadrenalism and an inhibitory effect on growth
- **Cytochrome P450-Metabolized Drugs:** SKYTROFA may alter the clearance. Monitor carefully if used with SKYTROFA
- **Oral Estrogen:** Patients receiving oral estrogen replacement may require higher SKYTROFA dosages
- **Insulin and/or Other Antihyperglycemic Agents:** Dose adjustment of insulin and/or antihyperglycemic agent may be required for patients with diabetes mellitus

You are encouraged to report side effects to FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Ascendis Pharma at 1-844-442-7236.

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