PHASE 3 CLINICAL PROGRAM

CLINICAL COMMITMENT

Once-weekly Skytrofa® lonapegsomatropin-tcgd

SKYTROFA® has been studied in treatment-naïve and -experienced children with GHD, totaling more than 300 patients[1-4]

Pivotal

heiGHt TRIAL

Supportive trials in switch patients as well as long-term follow-up of participating patients, with up to 6 years of data

fliGHt TRIAL

enliGHten TRIAL

heiGHt: A 52-week open-label, active-controlled trial of treatment-naïve, prepubertal children aged 3 years and older with GHD (N = 161) randomized to SKYTROFA or daily somatropin.[1,2]

fliGHt: A 26-week open-label, single-arm trial of children with GHD who switched to SKYTROFA after having been treated with daily somatropin for ≤ 130 weeks (n = 143).[3]

enliGHten: Long-term open-label extension trial of children with GHD who completed the heiGHt (n = 158) and fliGHt (n = 140) trials (N = 298). Mean duration of treatment was 3.5 years (maximum 5 years).[4,5]

See full study designs throughout.

GHD = growth hormone deficiency.

Learn more about the clinical commitment to pediatric GHD

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
- 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

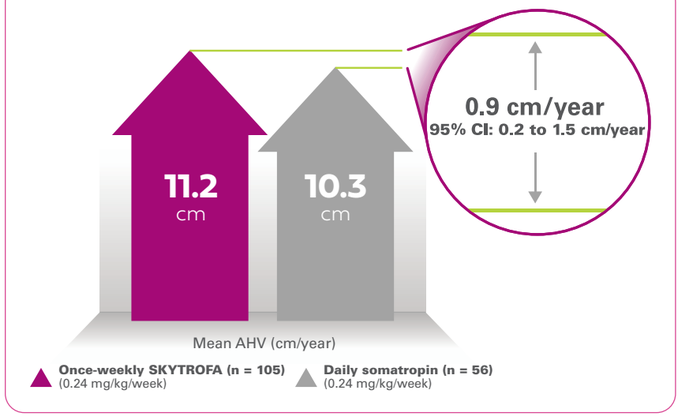
Please see Important Safety Information throughout and accompanying full Prescribing Information for SKYTROFA.

INCREASED GROWTH WITH FEWER INJECTIONS[1]

Pivotal heiGHt TRIAL

SKYTROFA demonstrated higher mean AHV versus daily somatropin[1,2]

Mean AHV* at week 52: once-weekly SKYTROFA versus daily somatropin[1,2]



- The treatment difference in AHV with SKYTROFA compared with daily somatropin at week 52 (11.2 cm/year versus 10.3 cm/year, respectively) was 0.9 cm/year (95% CI: 0.2 to 1.5 cm/year)[1,2]

heiGHt: A 52-week, randomized, open-label, active-controlled, parallel-group phase 3 study of 161 treatment-naïve, prepubertal (Tanner stage I) pediatric patients with GHD aged 3 years and older. Patients were randomized in a 2:1 ratio to receive either SKYTROFA 0.24 mg/kg/week (n = 105) or daily somatropin using Genotropin® 0.24 mg/kg/week (n = 56). The primary endpoint was AHV at 52 weeks.[1,2]

*LS mean by ANCOVA.[2]

Secondary endpoint: height SDS

At week 52, SKYTROFA had a greater increase from baseline in height SDS† compared with daily somatropin: 1.10 versus 0.96 from baseline of –2.9 and –3.0 respectively[1‡]

†LS mean by ANCOVA.[2]

‡Patients treated with SKYTROFA and daily somatropin had an increase in height SDS from baseline (SE) of 1.10 (0.04) and 0.96 (0.05) at week 52, respectively. Estimated difference = 0.14 SDS.[2]

IMPORTANT SAFETY INFORMATION (continued)

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

ESTABLISHED SAFETY PROFILE

Pivotal heiGHt TRIAL

Once-weekly Skytrofa® lonapegsomatropin-tcgd

The safety profile of SKYTROFA has been established in pediatric patients who weigh at least 11.5 kg[1]

AEs reported in ≥ 5% of SKYTROFA-treated pediatric patients and more frequently than in daily somatropin-treated§ pediatric patients (52 weeks of treatment)[1]

AEs	SKYTROFA (n = 105) n (%)	Daily somatropin (n = 56) n (%)
Viral infection	16 (15%)	6 (11%)
Pyrexia	16 (15%)	5 (9%)
Cough	11 (11%)	4 (7%)
Nausea and vomiting	11 (11%)	4 (7%)
Hemorrhage‖	7 (7%)	1 (2%)
Diarrhea	6 (6%)	3 (5%)
Abdominal pain	6 (6%)	2 (4%)
Arthralgia and arthritis¶	6 (6%)	1 (2%)

- Some patients taking SKYTROFA experienced mild injection-site reactions[2]

Low immunogenicity, with no neutralizing antibodies detected[1,2]

Only **6.7%** (7 of 105) of patients showed detectable binding antibodies through week 52 of the heiGHt trial[2]

§Daily somatropin used was Genotropin®.[2]

‖Hemorrhage in the SKYTROFA treatment group included epistaxis (n = 3), contusion (n = 2), petechiae (n = 1), and eye hemorrhage (n = 1).[1]

¶Arthralgia and arthritis in the SKYTROFA treatment group included arthralgia (n = 5) and reactive arthritis (n = 1).[1]

AE = adverse event; AHV = annualized height velocity; ANCOVA = analysis of covariance; CI = confidence interval; GHD = growth hormone deficiency; LS = least squares; SDS = standard deviation score; SE = standard error.

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

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

SAFETY AND TOLERABILITY IN CHILDREN WHO SWITCHED TO SKYTROFA FROM DAILY SOMATROPIN

In the fliGHt trial, once-weekly SKYTROFA demonstrated a safety profile consistent with heiGHt[3]

Adverse events	• Most AEs were mild (45%) or moderate (12%) in severity, and 2 SAEs were reported in 1 patient[3]* • Most common AEs were pyrexia (12%), nasopharyngitis (10%), upper respiratory tract infection (10%), headache (8%), and oropharyngeal pain (5%)[3]
Tolerability	• Once-weekly injections of SKYTROFA were well tolerated[3] ◦ Throughout the trial, the majority of patients (> 95%) did not experience bruising, swelling, or itching[3]

fliGHt: A multicenter, phase 3, open-label, single-arm, 26-week trial investigating the safety, tolerability, and efficacy of SKYTROFA administered once weekly in children with GHD. The trial included 3 treatment-naïve and 143 treatment-experienced patients previously treated with daily somatropin for ≤ 130 weeks. The mean daily somatropin dose was 0.29 mg/kg/week upon entering the trial. Safety and tolerability were the primary endpoints. Patients aged 6 months to 3 years could be treatment naïve and were included only in the safety and tolerability analyses.[3]

Limitations: Short-duration, single-arm study that was not designed or powered to evaluate the efficacy of SKYTROFA. Patients who had had prior daily somatropin and SKYTROFA dose adjustments based on IGF-1 levels instead of clinical response may have confounded outcomes or interpretation of treatment effects. Data should be interpreted with caution; no conclusions can be drawn.

*Both events were assessed by the investigator as unrelated to the study drug.[3]

IMPORTANT SAFETY INFORMATION (continued)

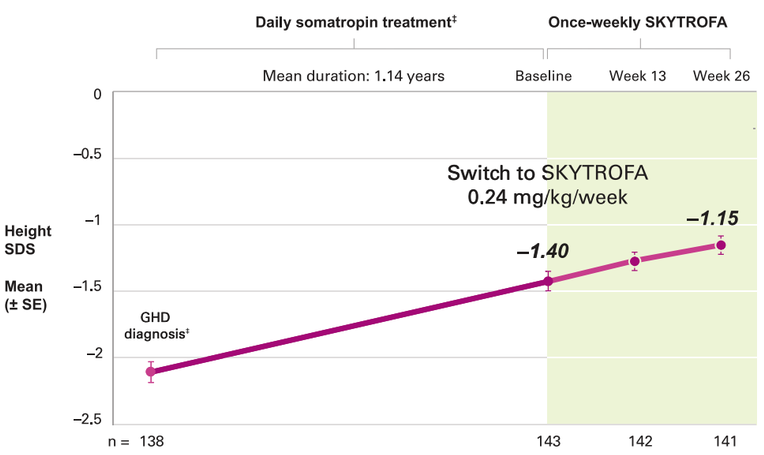
WARNINGS AND PRECAUTIONS (continued)

- **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
- **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

GROWTH AFTER SWITCHING TO SKYTROFA

Continued growth data through week 26 in patients who switched from daily somatropin[3†]

Height SDS from GHD diagnosis to week 26 of the fliGHt trial



Reprinted with permission from S. Karger AG, Basel.[3]

- The change in mean height SDS from baseline through 26 weeks was +0.25[3]
  - Mean (SD) height SDS at baseline was –1.40 (0.83)[3]
- Mean AHV was 8.72 cm/year throughout the 6-month fliGHt trial[3]

Limitations: Short-duration, single-arm study that was not designed or powered to evaluate the efficacy of SKYTROFA. Patients who had had prior daily somatropin and SKYTROFA dose adjustments based on IGF-1 levels instead of clinical response may have confounded outcomes or interpretation of treatment effects. Data should be interpreted with caution; no conclusions can be drawn.

†Values in graph are observed means.[3]

‡The mean (SD) most recent height SDS before diagnosis = –2.1 (0.9) (n = 135).[3]

AE = adverse event; AHV = annualized height velocity; GHD = growth hormone deficiency; IGF-1 = insulin-like growth factor-1; SAE = serious adverse event; SD = standard deviation; SDS = standard deviation score; SE = standard error.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

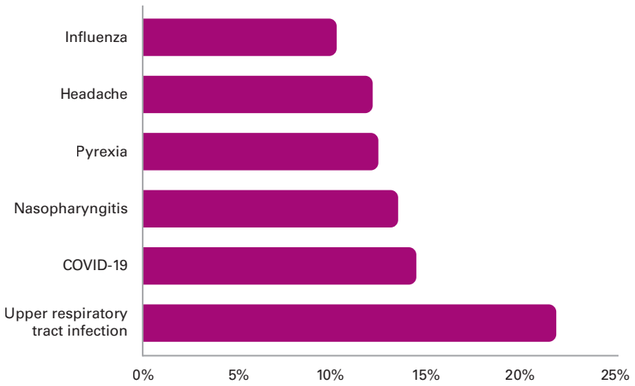
- **Hypoadrenalism:** Patients receiving somatropin therapy who have or are at risk for pituitary hormone deficiency(s) may be at risk for reduced serum cortisol levels and/or unmasking of central (secondary) hypoadrenalism. Patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism 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
- **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

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

LONG-TERM SAFETY DATA

Follow-up for up to 6 years* demonstrated a safety profile consistent with heiGHt and fliGHt[4]

TEAEs experienced by ≥ 10% of patients[4†‡]



enliGHten: An open-label extension study of pediatric patients with GHD who had previously participated in phase 3 SKYTROFA trials, heiGHt (n = 158) or fliGHt (n = 140) (N = 298). The mean age at baseline of the enliGHten trial was 10.3 years. At the start of the enliGHten trial, patients received either SKYTROFA 0.24 mg/kg/week or the most recent dose they had received in the earlier study. Long-term safety was the primary endpoint.[4,5]

Limitations: An open-label, single-arm extension study that enrolled patients previously treated with either daily somatropin or once-weekly SKYTROFA, which had not been designed or powered to evaluate the efficacy of SKYTROFA. Different SKYTROFA baseline starting doses among patients and dose adjustments based on IGF-1 levels, as opposed to clinical response, may have confounded outcomes. Data should be interpreted with caution; no conclusions can be drawn.

- Most TEAEs were mild (40.9%) or moderate (31.2%), and none resulted in treatment discontinuation[4]
- Patients experienced a low rate of injection-site reactions[4]
  - Exposure-adjusted rates for local reactions (swelling, redness, bruising, itching) were 7.1% and 1.3% with vial/syringe and SKYTROFA Auto-Injector injections, respectively[4]
- No neutralizing antibodies were detected[4]

*Mean duration of treatment across heiGHt or fliGHt plus enliGHten was 4.1 years (maximum 6 years).[4]

†Mean duration of treatment in enliGHten was 3.5 years (maximum 5.0 years).[4]

‡TEAEs experienced by ≥ 5% and ≤ 10% in order of increasing frequency were viral upper respiratory tract infection, bronchitis, SARS-CoV-2 test positive, gastroenteritis, ear infection, seasonal allergy, respiratory tract infection viral, vomiting, pharyngitis streptococcal, and cough.[4]

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

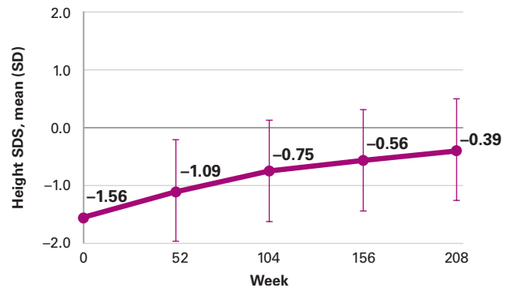
- **Progression of Preexisting Scoliosis in Pediatric Patients:** Monitor patients with a history of scoliosis for disease progression
- **Pancreatitis:** Cases of pancreatitis have been reported in pediatric patients receiving somatropin. The risk may be greater in pediatric patients than in adults. 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
- **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

LONG-TERM GROWTH DATA

Once-weekly Skytrofa® lonapegsomatropin-tcgd

Full analysis set§

Mean height SDS approached 0 (population norm) at year 4[4]

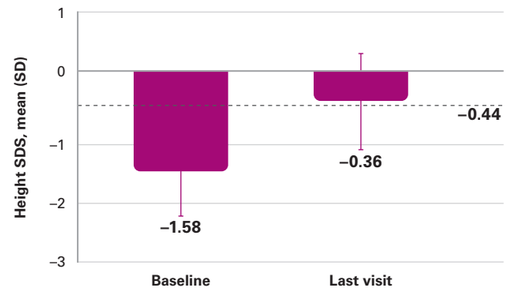


- Mean height SDS increased to –0.39 at week 208 from –1.56 at baseline[4]

§All participants who signed informed consent for the extension trial and received at least one dose of SKYTROFA.[4]

Treatment-completer subset

Mean height SDS for treatment completers at baseline and at last visit[4‖]



- At their last visit, 59.3% of treatment completers met or exceeded their individual average parental height SDS[4]

‖Dashed line indicates mean average parental height SDS (average parental height = height SDS_{mother} + height SDS_{father}]/2).[4]

Limitations: An open-label, single-arm extension study that enrolled patients previously treated with either daily somatropin or once-weekly SKYTROFA, which had not been designed or powered to evaluate the efficacy of SKYTROFA. Different SKYTROFA baseline starting doses among patients and dose adjustments based on IGF-1 levels, as opposed to clinical response, may have confounded outcomes. Data should be interpreted with caution; no conclusions can be drawn.

Treatment-completer subset

Patients who completed SKYTROFA treatment¶ (n = 81) because it was determined by the physician that patients achieved near-adult height or that treatment for pediatric GHD was no longer necessary[4]

¶Mean duration of treatment across heiGHt or fliGHt plus enliGHten was 3.2 years (maximum 5.3 years).[4]

GHD = growth hormone deficiency; IGF-1 = insulin-like growth factor-1; SD = standard deviation; SDS = standard deviation score; TEAE = treatment-emergent adverse event.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **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

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

Once-weekly
Skytrofa®
lonapegsomatropin-tcgd

SKYTROFA Is the First FDA-approved
Once-weekly Treatment for Pediatric GHD

DISCOVER ALL THAT SKYTROFA HAS TO OFFER YOUR PEDIATRIC PATIENTS WITH GHD

Visit **Skytrofahcp.com**

GHD = growth hormone deficiency.

IMPORTANT SAFETY INFORMATION (continued)

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

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.

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

References: 1. SKYTROFA. Prescribing information. Ascendis Pharma Endocrinology, Inc.; 2025. **2.** 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 **3.** Maniatis AK, Nadgir U, Saenger P, et al. Switching to weekly lonapegsomatropin from daily somatropin in children with growth hormone deficiency: the fliGHt trial. *Horm Res Paediatr.* 2022;95(3):233-243. doi:10.1159/000524003 **4.** 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 **5.** Maniatis AK, Casella SJ, Nadgir UM, et al. Safety and efficacy of lonapegsomatropin in children with growth hormone deficiency: enliGHten trial 2-year results. *J Clin Endocrinol Metab.* 2022;107(7):e2680-e2689. doi:10.1210/clinem/dgac217

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