enliGHten Trial Final Results

Rationale

Growth Hormone Deficiency (GHD)

- GHD is a complex endocrine disorder characterized by inadequate secretion of GH from the pituitary gland, **leading to impaired linear growth in children & various physiological and metabolic disturbances in both children and adults**[1]
- Although daily somatropin has been the standard of care for decades, **registry data and surveys suggest that patients may have poor adherence to daily somatropin, which is associated with suboptimal growth outcomes**[2]
- **LAGH therapies offer a less frequent administration**[2]

Lonapegsomatropin

Lonapegsomatropin (TransCon® hGH; SKYTROFA®) is a prodrug of somatropin administered subcutaneously once-weekly[3]

- Lonapegsomatropin is designed to provide sustained release of active, unmodified somatropin with the identical 191 amino acid sequence and size (22 kDa) as endogenous growth hormone[3,4]
- Approved in the US by the FDA for pediatric patients aged 1 year & older, weighing at least 11.5 kg for treating growth failure due to GHD, and for adults with GHD[5]
- European Commission approved for children and adolescents aged 3 to 18 years for treating growth failure due to GHD[6]

Lonapegsomatropin Clinical Phase 3 Results

heiGHt

heiGHt trial was a 52-week, open-label, active-controlled, pivotal phase 3 trial evaluating treatment-naive, prepubertal children (males aged 3–12 years; females aged 3–11 years) with GHD[3]

- In the pivotal phase 3 heiGHt trial, lonapegsomatropin demonstrated non-inferiority and superiority in AHV at Week 52 compared with daily somatropin in treatment-naive children with GHD[3]

fliGHt

The fliGHt trial was a 26-week, open-label phase 3 trial evaluating treatment-experienced children (aged 6 months to 17 years; participants <3 years old could be treatment-naive) with GHD[7]

- Children previously treated with daily somatropin could be successfully transitioned to lonapegsomatropin, with continued linear growth & a comparable safety profile to daily somatropin[7]

enliGHten

Participants who completed the heiGHt or fliGHt trial and met all other eligibility criteria for the enliGHten trial were invited to participate[8]

The enliGHten trial was a phase 3 open-label extension trial designed to evaluate the longer-term efficacy and safety of once-weekly lonapegsomatropin in children with GHD[8]

Lonapegsomatropin Phase 3 Clinical Trials Overview

enliGHten – Materials & Methods

The trial was conducted across 63 specialized clinical sites in 15 countries from December 2017 to February 2023[8]

All participants were assigned to receive lonapegsomatropin at a dose of 0.24 mg hGH/kg/week, the same starting dose used in the parent trials heiGHt or fliGHt[8]

- If the lonapegsomatropin dose had been adjusted during the previous trial, the most recent dose was continued at the beginning of the enliGHten trial[8]

An auto-injector developed specifically to deliver once-weekly lonapegsomatropin was made available to participants in the United States[8]

Safety assessments at each 13-week visit included AEs, local tolerability, hormone levels, parameters of glucose and lipid metabolism, immunogenicity, fundoscopy, pubertal status, bone age, and vital sign measurements[8]

Bone age x-ray was required to be completed once every 12 months but may have been performed at any time if clinically indicated[8]

Efficacy was evaluated through AHV, IGF-1 SDS, and the change from baseline in height SDS[8]

Serum IGF-1 measurements were collected in the morning at baseline and 5 days (±1 day) after dosing at all visits (±2 weeks)[8]

AEs, adverse events; AHV, annualized height velocity; GH, growth hormone; GHD, growth hormone deficiency; IGF-1, insulin-like growth factor 1; FDA, Food and Drug Administration; LAGH, long-acting growth hormone; SDS, standard deviation score.

1. Tidblad A. Acta Paediatr. 2022 Feb;111(2):215-24. 2. Christiansen JS et al. Eur J Endocrinol. 2016 Jun;174(6):C1-8. 3. Thornton PS et al. *J Clin Endocrinol Metab.* 2021;106(11):3184-3195. 4. Sprogoe K, et al. Endocr Connect. 2017 Nov;6(8):R171-R81. 5. SKYTROFA® [Prescribing Information]. Palo Alto, CA: Ascendis Pharma. July 2025. 6. Ascendis Pharma Endocrinology Division A/S (2022). SKYTROFA EPAR - Product Information. 7. Maniatis AK et al. *Horm Res Paediatr.* 2022;95(3):233-243. 8. Maniatis AK, et al. *Horm Res Paediatr.* Published online March 6, 2025.

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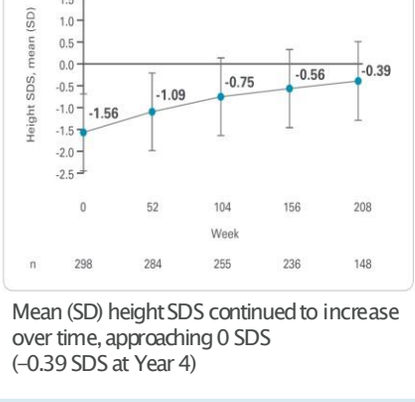
Results - Demographics, Exposure, Outcomes, Efficacy & Safety[1]

Baseline Demographics in enliGHten	Variable	Total (N = 298)
Age, years	Mean (SD)	10.3 (3.4)
	Min, max	1.7, 17.8
Sex, n (%)	Male	235 (78.9)
Height SDS	Mean (SD)	-1.6 (0.88)
IGF-I SDS	Mean (SD)	1.0 (1.30)
Tanner Stage, n (%)	Stage I	214 (71.8)
	Stage II	40 (13.4)
	Stage III	25 (8.4)
	Stage IV	16 (5.4)
	Stage V	3 (1.0)

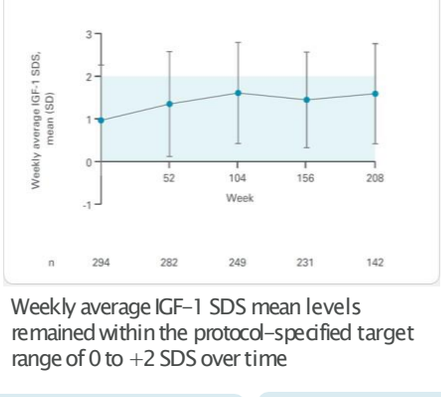
Key Data at Last Visit	Variable	Total (N = 298)
Age, years	Mean (SD)	13.8 (3.0)
	Min, max	5.5, 18.6
	Male	14.0 (3.0)
	Female	12.6 (2.7)
Tanner Stage, n (%)	Stage I	89 (29.9)
	Stage II	32 (10.7)
	Stage III	28 (9.4)
	Stage IV	63 (21.1)
	Stage V	86 (28.9)
Duration of lonapegsomatropin treatment during the enliGHten trial, years	Mean (SD)	3.5 (1.0)
	Min, max	0.1, 5.0
Duration of total lonapegsomatropin treatment (heiGHt or fliGHt plus enliGHten), years	Mean (SD)	4.1 (1.1)
	Median	4.3
	Min, max	0.5, 6.0

Across the heiGHt, fliGHt, and enliGHten trials, total lonapegsomatropin treatment duration was up to 6.0 years, with a median of 4.3 years

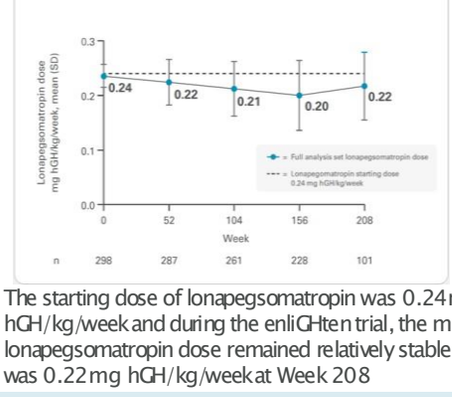
Full Analysis Set[1]



Mean (SD) height SDS continued to increase over time, approaching 0 SDS (–0.39 SDS at Year 4)



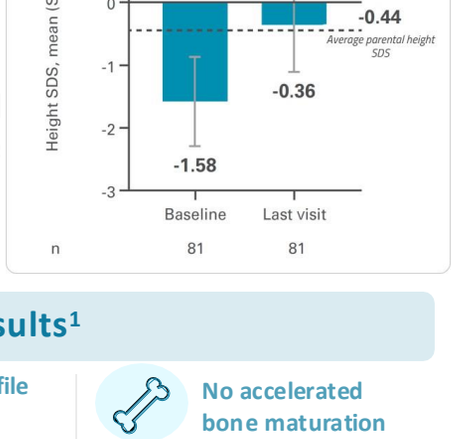
Weekly average IGF–1 SDS mean levels remained within the protocol–specified target range of 0 to +2 SDS over time



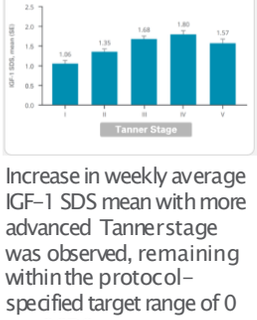
The starting dose of lonapegsomatropin was 0.24 mg hGH/kg/week and during the enliGHten trial, the mean lonapegsomatropin dose remained relatively stable and was 0.22 mg hGH/kg/week at Week 208

Treatment Completers[1]

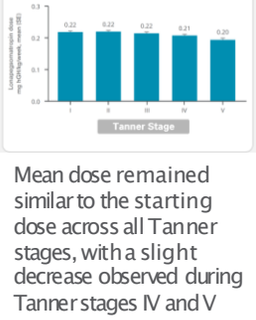
At participants' last visit, **59.3%** of treatment completers (n=81) met or exceeded their individual average parental height SDS



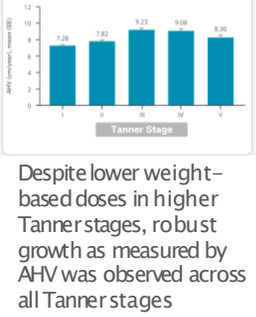
Post hoc analysis – Tanner Stage[1]



Increase in weekly average IGF–1 SDS mean with more advanced Tanner stage was observed, remaining within the protocol–specified target range of 0 to +2 SDS



Mean dose remained similar to the starting dose across all Tanner stages, with a slight decrease observed during Tanner stages IV and V



Despite lower weight–based doses in higher Tanner stages, robust growth as measured by AHV was observed across all Tanner stages

Key Safety Results[1]

Well-tolerated Safety Profile

TEAEs were reported in 75.8% of participants (n=226)

Most TEAEs were mild (40.9%) or moderate (31.2%)

Severe TEAEs were rare (3.7%, n=11) and were assessed as not related to study drug

No TEAE led to discontinuation of lonapegsomatropin treatment

No accelerated bone maturation

Low rate of injection site reactions

Low incidence of anti-drug antibodies & absence of anti-hGH neutralizing antibodies

The enliGHten trial demonstrated longer term safety and efficacy for lonapegsomatropin for the treatment of pediatric GHD[1]

Lonapegsomatropin's sustained efficacy, safety profile consistent with somatropin, and the potential for improved treatment outcomes with increased adherence with a once–weekly injection make lonapegsomatropin a promising option for enhancing growth outcomes and quality of life for children with GHD[1]

AHV, annualized height velocity; anti-hGH, anti-human growth hormone; GHD; growth hormone deficiency; IGF–1, insulin-like growth factor 1; LAGH, long–acting growth hormone; SD, standard deviation; SDS, standard deviation score; TEAEs, treatment emergent adverse events.

1. Maniatis AK, et al. *Horm Res Paediatr*. Published online March 6, 2025.

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