Lonapegsomatropin (TransCon™ hGH) in Children with Growth Hormone Deficiency: Efficacy and Safety of up to 2 Years of Treatment

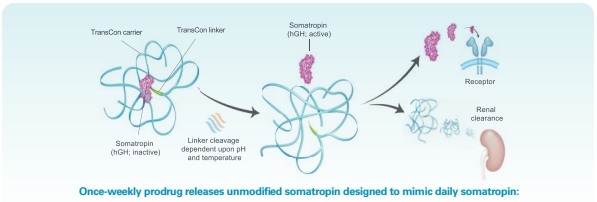
Aristides K. Maniatis[1], Ulhas M. Nadgir[2], Paul Hofman[3], Paul Saenger[4], Elena D. Chertok[5], Elena. M. Aghajanova[6], Wenjie Song[7], Meng Mao[7], Steven Chessler[7], Allison Komirenko[7], Michael Beckert[7], Aimee D. Shu[7], Paul S. Thornton[8]

[1]Rocky Mountain Pediatric Endocrinology, Centennial, CO, USA; [2]Center of Excellence in Diabetes and Endocrinology, Sacramento, CA; [3]Liggins Institute, University of Auckland, Auckland, New Zealand; [4]NYU Langone Health, New York, NY; [5]Voronezh State Medical University, Voronezh, Russia; [6]Yerevan State Medical University, Yerevan, Armenia; [7]Ascendis Pharma, Palo Alto, CA USA. [8]Cook Children's Health Care System, Fort Worth, TX

BACKGROUND

- Once-weekly lonapegsomatropin (TransCon hGH) is an investigational prodrug for 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[1,2] (Figure 1)

Figure 1. Lonapegsomatropin (TransCon hGH) Design



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

• Tissue Distribution • Physiological levels • Therapeutic effects: efficacy, safety and tolerability

- In the pivotal phase 3 heiGHt Trial evaluating treatment-naïve children with GHD, lonapegsomatropin demonstrated superior annualized height velocity (AHV) and statistically greater change from baseline in height standard deviation score (Δ height SDS) at 52 weeks compared to daily somatropin therapy (Genotropin) and had a similar safety and tolerability profile[3]
- In the phase 3 fliGHt Trial, children who switched from daily somatropin to lonapegsomatropin continued to grow well and maintained a good safety profile[4]
- Results are reported from heiGHt and fliGHt subjects who continued into the phase 3 enliGHten open-label long-term extension (OLE) Trial for up to 52 weeks (data cut: June 1st 2020)

METHODS

TRIAL DESIGN

Phase 3 heiGHt Trial

- heiGHt was a 52-week, open-label, active-controlled, pivotal phase 3 trial in which treatment-naïve, prepubertal subjects (males 3-12; females 3-11 years old) with GHD were randomized 2:1 to receive once-weekly lonapegsomatropin 0.24 mg hGH/kg/week via vial/syringe or an equivalent weekly dose of daily somatropin via pen device

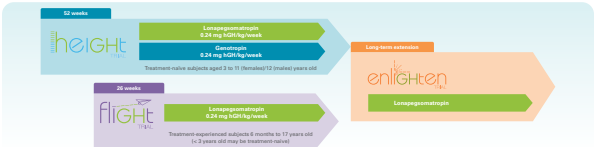
Phase 3 fliGHt Trial

- fliGHt was a 26-week, open-label phase 3 trial in which treatment-experienced subjects (6 months to 17 years old; subjects < 3 years old could be treatment-naïve) with GHD switched from their previous daily somatropin to lonapegsomatropin 0.24 mg hGH/kg/week via vial/syringe

Phase 3 enliGHten OLE Trial

- All subjects who enrolled into the long-term extension trial received lonapegsomatropin at their previous dose via vial/syringe (somatropin subjects from heiGHt started lonapegsomatropin 0.24 mg hGH/kg/week) (Figure 2)
- Subjects in the US switched to the TransCon hGH Auto-Injector when available

Figure 2. Lonapegsomatropin Phase 3 Clinical Program



OUTCOMES

Efficacy

- Growth outcomes were evaluated approximately every 13 weeks
- Three groups were analyzed:
  - Treatment-naïve subjects treated with lonapegsomatropin in heiGHt, followed by continuation of lonapegsomatropin in enliGHten
  - Treatment-naïve subjects treated with daily somatropin in heiGHt, followed by lonapegsomatropin in enliGHten
  - Subjects previously treated with daily somatropin who switched to lonapegsomatropin in fliGHt, followed by continuation of lonapegsomatropin in enliGHten
- Comparisons between the two heiGHt treatment groups allowed for the evaluation of safety and efficacy outcomes as they had similar baseline demographics and comparable treatment histories
- IGF-1 was obtained on post-dose Day 5 (±1) in fliGHt and enliGHten; in heiGHt, average IGF-1 for lonapegsomatropin was calculated based on a population pharmacodynamic model

SAFETY

- Safety was evaluated throughout the trial periods and is summarized by trial

STATISTICAL ANALYSIS

- A by-visit ANCOVA model was used to analyze numeric endpoints

RESULTS

Disposition, Demographics, and Baseline Characteristics

- Nearly all subjects who completed heiGHt (158/159) and fliGHt (140/144) continued into enliGHten (Table 1)
  - Eight (2.7%) subjects have prematurely withdrawn from the trial for the following reasons: 4 subjects (1.3%) due to withdrawn consent, 2 (0.7%) for protocol violation, and 2 for "other" reasons
  - As of the data cut, 2 subjects have achieved near adult height (AHV <2 cm/year over the last 9 months or bone age >14 [females] or >16 [males]) and thus have completed the trial
- Baseline demographics were balanced between groups in heiGHt (Table 2). Subjects enrolled in fliGHt were primarily treatment-experienced (98%) and ranged from 1.2 to 17.4 years old
- Upon entry into enliGHten, subjects from fliGHt were generally older and more advanced in Tanner Stage compared to those entering from heiGHt (Table 3)
- The mean dose of lonapegsomatropin remained approximately 0.24 mg hGH/kg/wk for subjects from heiGHt at Week 104 and was 0.20 mg hGH/kg/wk for subjects from fliGHt at Week 78

Table 1. Subject Disposition

	heiGHt		fliGHt
	Lonapegsomatropin N (%)	Daily somatropin N (%)	Lonapegsomatropin N (%)
Enrolled and dosed in parent trial	105	56	146
Completed parent trial	104 (99.0)	55 (98.2)	144 (98.6)
Enrolled and dosed in enliGHten	103 (98.1)	55 (98.2)	140 (95.9)
Withdrew from enliGHten[a]	3 (2.9)	1 (1.8)	4 (2.9)
Completed enliGHten[b]	0	0	7 (5.0)

[a]Demonstrator based on subjects enrolled and dosed in enliGHten.
[b]Each subject's participation is expected to last up until the product is approved and commercially available, alternative arrangements have been made for continued subject access to hGH treatment, or treatment for pediatric growth hormone deficiency is no longer considered appropriate (including – but not limited to – when there is evidence of closed epiphysis [bone age >16.0 years for females; >16.5 years for males]). When any of the 3 criteria is met, the subject will be considered to have completed the extension trial. The total duration of participation for each subject in the trial will therefore depend on the conditions listed above and may be different in different countries and regions.

Table 2. Demographics and Baseline Characteristics

	heiGHt		fliGHt[1]
	Lonapegsomatropin (N = 105)	Daily somatropin (N = 56)	Lonapegsomatropin (N = 146)
Age			
Mean (SD)	8.5 (2.7)	8.5 (2.8)	10.6 (3.9)
Min, max	3.3, 13.1	3.2, 12.9	1.2, 17.4
Gender, Males, n (%)	86 (81.9)	46 (82.1)	110 (75.3)
Height SDS, Mean (SD)	-2.9 (0.8)	-3.0 (0.9)	-1.4 (0.8)
Δ Average Parental Height, Mean (SD)	-2.3 (1.1)	-2.6 (1.3)	-1.1 (1.0)
IGF-1 SDS, Mean (SD)	-2.1 (0.9)	-2.0 (1.0)	0.9 (1.3)
Peak stimulated GH level prior to initiating GH therapy			
Mean (SD)	5.9 (2.8)	5.5 (3.0)	5.9 (2.6)
≤5 ng/mL, n (%)	37 (35.2)	21 (37.5)	52 (35.6)
>5 ng/mL, n (%)	68 (64.8)	35 (62.5)	91 (62.3)

[1]Demographics and baseline characteristics are presented for the time of enrollment into fliGHt; subjects had been previously treated for an average of 1.18 years of daily somatropin therapy.

Table 3. Demographics and Disease Characteristics at Start of enliGHten

	heiGHt		fliGHt
	Lonapegsomatropin (N = 103)	Daily somatropin (N = 55)	Lonapegsomatropin (N = 140)
Age			
Mean (age)	9.5 (2.7)	9.5 (2.8)	11.1 (3.9)
Min, max	4.4, 14.1	4.2, 13.9	1.7, 17.8
Height SDS, Mean (SD)	-1.9 (0.7)	-2.1 (0.8)	-1.1 (0.8)
Average IGF-1 SDS, mean (SD)	0.6 (0.9)[1]	0.01 (1.1)	1.6 (1.3)
Tanner Stage			
Stage I, n (%)	92 (89.3)	45 (81.8)	77 (55.0)
Stage II, n (%)	11 (10.7)	8 (14.5)	21 (15.0)
Stage III, n (%)	0	2 (3.6)	22 (15.7)
Stage IV, n (%)	0	0	17 (12.1)
Stage V, n (%)	0	0	3 (2.1)

[1]calculated using a pharmacodynamic model

Height and Pharmacodynamic Outcomes

- For heiGHt subjects, AHV increased from an untreated baseline of 3.93 cm/year in favor of subjects initially treated with lonapegsomatropin (Figure 3)
- In heiGHt, average IGF-1 SDS values were higher for lonapegsomatropin-treated subjects compared with daily somatropin-treated subjects, paralleling the observed improved growth outcomes (Figure 4)
- Beyond 52 weeks, average IGF-1 SDS for heiGHt subjects who started on lonapegsomatropin generally remained stable without further increase; for heiGHt subjects who switched from daily somatropin to lonapegsomatropin, an initial increase in average IGF-1 SDS with subsequent stabilization was observed (Figure 4)

Figure 3. AHV over 104 Weeks for heiGHt subjects

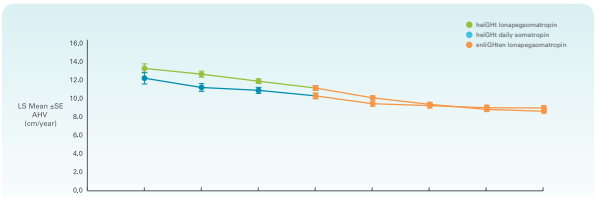
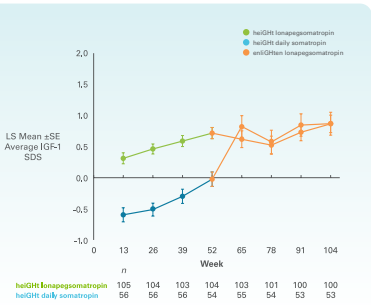
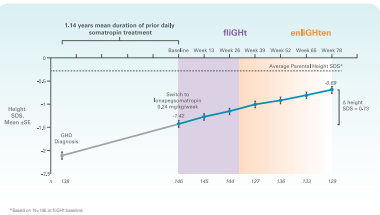


Figure 4. Average IGF-1 SDS Over 104 Weeks For heiGHt Subjects



- fliGHt subjects continued to approach their average parental height, with height SDS improving from –1.42 at fliGHt baseline to –0.69 at Week 78 (Figure 5); LS mean (SE) AHV at Week 78 was 8.3 cm/year and was consistent with clinical expectations given the characteristics of the enrolled subjects[5]

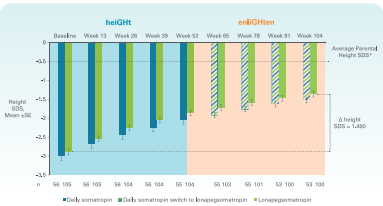
Figure 5. Sustained Improvement in Height SDS For fliGHt Subjects



*Based on N=138 at fliGHt baseline.

- heiGHt subjects starting lonapegsomatropin continued to approach their average parental height, with height SDS improving from -2.89 at baseline to -1.37 at week 104. For those subjects starting on daily somatropin switching to lonapegsomatropin also continued to approach their average parental height, with height SDS improving from -3.0 at baseline to -1.52 at week 104 (Figure 6).

Figure 6. Sustained Improvement in Height SDS For heiGHt Subjects



*Based on N=56 at heiGHt baseline.

- As of this data cut, a total of 5 subjects have met or exceeded their target height (Table 4). All 5 subjects were from the fliGHt trial. Prior exposure to somatropin varied (range 0.6-2.4 years) but all received lonapegsomatropin for approximately 2 years (range 1.7-2.0 years). All 5 exceeded their average parental height SDS.
- For fliGHt subjects, observed mean (SD) average IGF-1 SDS increased from 0.85 (1.3) at fliGHt baseline to 1.62 (1.3) at Week 26 and 1.81 (1.1) at Week 78 (not shown)

Table 4. Subjects Who Met or Exceeded Target Height

Subject age[1] (male)	Duration of Prior somatropin (years)	Duration on lonapeg-somatropin (years)	Height SDS at Baseline[2]	Most Recent[3] Height SDS	Avg Parental Height SDS[4]	Height at Baseline (cm)[2]	Most Recent[3] Height (cm)	Target Height[4] (cm)	Most Recent[3] AHV[5] (cm/yr)
14.9	0.6	2.0	-1.6	-0.04	-0.37	156.5	174.9	174.0	8.8
15.4	2.1	1.8	-0.33	0.26	-0.97	169.2	177.3	170.3	2.8
15.6	0.5	1.8	-0.67	0.61	-0.83	167.2	180.0	171.0	5.8
14.4	2.4	1.7	-0.89	0.08	-0.54	159.6	173.9	172.9	9.3
15.6	1.0	2.0	-1.64	-0.23	-0.56	159.2	174.2	172.9	5.4

[1]at start of fliGHt
[2]as of the 01-June-2020 data cut
[3]Target height = (mother's height in cm + father's height in cm + 6.5 if male)/2
[4]52-week rolling baseline
AHV, Annualized height velocity

Safety Outcomes

- The adverse event (AE) profile of lonapegsomatropin was consistent across the phase 3 studies; treatment emergent AEs (TEAEs) were generally mild and no serious TEAEs were considered to be related to study drug (Table 5)
  - In enliGHten, the most common TEAEs were upper respiratory tract infection (21.1%), nasopharyngitis (11.1%), cough (8.7%), and pyrexia (8.4%); these are consistent with other clinical trials evaluating daily somatropin in children with GHD[6,7]
- Low titer non-neutralizing anti-drug binding antibodies were detected in <10% of lonapegsomatropin-treated subjects (not shown)
- Hemoglobin A1c, cortisol, and free thyroxine were stable and generally remained within the normal range throughout the trials (not shown)

Table 5. Summary of Adverse Events Across All Trials

	heiGHt Trial (52 weeks)		fliGHt Trial (26 weeks)	enliGHten Trial (up to 52 weeks)
Category, n (%)	Lonapegsomatropin (N = 105)	Daily somatropin (N = 56)	Lonapegsomatropin (N = 146)	Lonapegsomatropin (N = 238)
Treatment-emergent Adverse Events (TEAEs)	81 (77)	39 (70)	83 (57)	195 (65.4)
TEAEs Related to Study Drug	12 (11)	10 (18)	6 (4.1)	13 (4.4)
Serious Adverse Events (SAEs)	1 (1.0)	1 (1.8)	1 (0.7)	10 (3.4)
SAEs Related to Study Drug	0	0	0	0
TEAEs Leading to Any Action on Study Drug	2 (1.9)	1 (1.8)	2 (1.4)	5 (1.7)
TEAEs Leading to Discontinuation of Study Drug	0	0	0	0

- Over time, treatment with lonapegsomatropin was associated with mean BMI SDS that stabilized towards 0 (Figure 7)
- Between the lonapegsomatropin and daily somatropin groups, there was a similar change in bone age over 104 weeks (Table 6). The bone age/chronological age ratios at Week 52 and Week 104 remained less than 1, representing normal skeletal maturation. Overall, this suggests that the longer-term effects of lonapegsomatropin (up to 104 weeks) did not occur at the expense of accelerated skeletal maturation.

Figure 7. BMI SDS Across All Trials

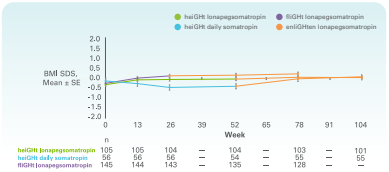


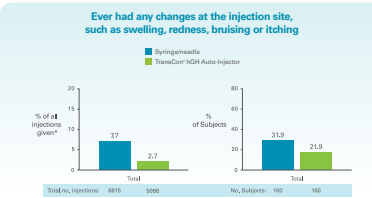
Table 6. Similar Change in Bone Age Over 104 Weeks For heiGHt Subjects

		Lonapegsomatropin (N = 105)		Daily somatropin (N = 56)	
	n	Mean (SD)	Δ Baseline Mean (SD)	Mean (SD)	Δ Baseline Mean (SD)
Bone age/chronological age ratio					
Baseline	105	0.7 (0.2)	–	0.7 (0.1)	–
Week 52	104	0.7 (0.1)	0.1 (0.1)	0.8 (0.1)	0.1 (0.1)
Week 104	98	0.8 (0.1)	0.1 (0.1)	0.8 (0.1)	0.1 (0.1)
Delay in bone age (years)					
Baseline	105	2.5 (1.3)	–	2.3 (1.1)	–
Week 52	104	2.3 (1.4)	-0.2 (0.9)	2.1 (1.1)	-0.2 (0.7)
Week 104	98	2.1 (1.5)	-0.4 (1.0)	2.0 (1.2)	-0.4 (1.0)

Switching to the TransCon hGH Auto-Injector

- Once available, subjects in enliGHten at select sites in the US were switched from vial and syringe to the TransCon hGH Auto-Injector; currently, 160 subjects are using the GH Auto-Injector in enliGHten
- Overall, fewer local tolerability reactions were reported with the TransCon hGH Auto-Injector compared with syringe/needle (Figure 8)

Figure 8. Local Tolerability from Subject Diary During The enliGHten Trial



Local tolerability was defined as an injection site reaction deemed abnormal from those ordinarily observed in SC injections (including pain, intensity, or duration). Between visits, local tolerability will be evaluated and documented by the subject/parent/legal guardian/caregiver in the subject diary. At clinic visits, assessment of local tolerability was performed by injection site examination by trial staff (documented as part of the physical exam), in conjunction with subject diary review.

Left graph: Of all subjects who switched to the TransCon hGH Auto-Injector in enliGHten, the % of total injections given which were recorded in the patient diary as "ever had any changes at the injection site, such as swelling, redness, bruising or itching" is depicted. Overall, fewer injections given by the TransCon hGH Auto-Injector were rated as such.

Right graph: Of all subjects who switched from vial/syringe to the TransCon hGH Auto-Injector in enliGHten (n=160), the % of subjects who ever reported abnormal injection site reactions (i.e., "ever had any changes" etc) in the patient diary is depicted. Overall, fewer subjects responded that injections given by the TransCon hGH Auto-Injector caused local tolerability reactions.

CONCLUSIONS

- Across the broad population of the phase 3 program, subjects treated with lonapegsomatropin for up to 2 years continued to grow well, with a safety profile comparable to daily growth hormone, including a similar AE profile, stable BMI, stable laboratory parameters, and low immunogenicity
- Among subjects who switched from daily somatropin to lonapegsomatropin, a lower-than-expected attenuation in 2nd year AHV suggested an improved treatment effect of lonapegsomatropin relative to the previous daily somatropin
- As of this data cut, 5 subjects have met or exceeded their target height and have also exceeded their average parental height SDS
- High retention rates were observed across the phase 3 program, with >98% of subjects continuing from heiGHt and fliGHt into enliGHten
- The TransCon hGH Auto-Injector was well-tolerated

REFERENCES:
1. Sprogøe K et al. *Endocr Connect.* 2017;6(8):R171-R181. 2. Chatelain P et al. *J Clin Endocrinol Metab.* 2017;102(5):1673-1682. 3. Thornton P et al. *Transcon Growth Hormone In The Treatment Of Pediatric Growth Hormone Deficiency: Results Of The Phase 3 Height Trial.* Presented at ENDO March 2019; New Orleans, LA. 4. Maniatis A et al. *Phase 3 fliGHt Trial: Experience of Switching from Daily Growth Hormone Therapy to Once-Weekly TransCon hGH in Children with Growth Hormone Deficiency.* Presented at ENDO June 2020. 5. Bakker B et al. *J Clin Endocrinol Metab.* 2018;103(2):352-357. 6. Cohen GM et al. *J Clin Endocrinol Metab.* 2002;87(1):90-98. 7. Peterkova V et al. *Horm Res.* 2007;68(6): 288-293.

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