Continued Safety and Efficacy of Weekly Lonapegsomatropin (TransCon hGH) for up to Two Years in Children with Growth Hormone Deficiency (GHD)

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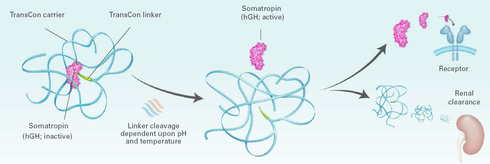
BACKGROUND

- Once-weekly 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. 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, TransCon hGH 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 TransCon hGH 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 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 TransCon hGH 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 TransCon hGH 0.24 mg hGH/kg/week via vial/syringe

Phase 3 enliGHten Open-Label Extension Trial

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

Figure 2. TransCon hGH Phase 3 Clinical Program

OUTCOMES

EFFICACY

- Growth outcomes were evaluated approximately every 13 weeks
- Three groups were analyzed:
  - Treatment-naive subjects treated with TransCon hGH in heiGHt, followed by continuation of TransCon hGH in enliGHten
  - Treatment-naive subjects treated with daily somatropin in heiGHt, followed by TransCon hGH in enliGHten
  - Subjects previously treated with daily somatropin who switched to TransCon hGH in fliGHt, followed by continuation of TransCon hGH 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 TransCon hGH was esimated 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
- 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 2)
- The mean dose of TransCon hGH 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

Table1. Subject Disposition

	heiGHt		fliGHt
	TransCon hGH N (%)	Daily somatropin N (%)	TransCon hGH 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]Denominator for percentage based on subjects enrolled and dosed in enliGHten.
[b]A designation of subject "completion" reflected that (based on Investigator judgement) the subjects had reached satisfactory height, and it was no longer necessary for the subject to continue in the trial and receive treatment for childhood GHD. Additionally, trial completion was required when there was evidence of closed epiphyses (bone age > 14.0 years for females and > 16.0 years for males).

Table 2. Demographics and Disease Characteristics at Start of enliGHten

	heiGHt Subjects		fliGHt Subjects
	TransCon hGH (N = 103)	Daily somatropin (N = 55)	TransCon hGH (N = 140)
Age (years), n			
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)[†]	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)

[†]calculated using a pharmacodynamic model

Height and Pharmacodynamic Outcomes

- For heiGHt subjects, AHV increased from an untreated baseline of 3.93 cm/year with a greater increase observed in subjects initially treated with TransCon hGH (Figure 3)
- In heiGHt, average IGF-1 SDS values were higher for TransCon hGH-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 TransCon hGH generally remained stable without further increase; for heiGHt subjects who switched from daily somatropin to TransCon hGH, an initial increase in average IGF-1 SDS with subsequent stabilization was observed
- heiGHt TransCon hGH subjects continued to approach their average parental height, with height SDS improving from –2.89 at baseline to –1.37 at week 104. Subjects who switched from daily somatropin to TransCon hGH at the start of enliGHten also continued to approach their average parental height, with height SDS improving from –3.0 at baseline to –1.52 at week 104 (Figure 5)
- 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]
- For fliGHt subjects, observed mean (SD) average IGF-1 SDS increased from 0.85 (1.3) at fliGHt baseline (reflecting prior daily somatropin treatment) to 1.62 (1.3) at Week 26 and 1.81 (1.1) at Week 78 (not shown)

Figure 3. AHV Over 104 Weeks for heiGHt Subjects

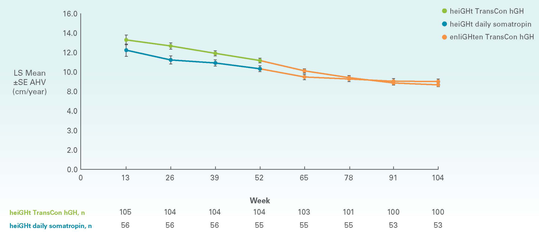
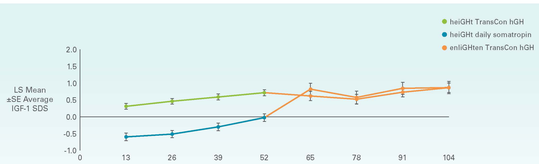
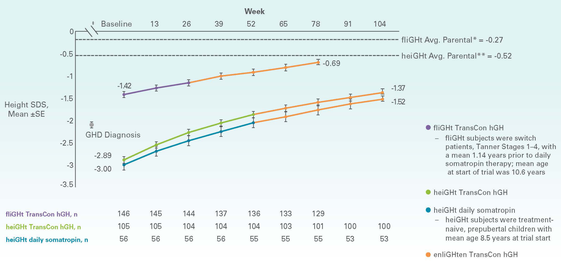


Figure 4. Average IGF-1 SDS Over 104 Weeks for heiGHt Subjects



Dose adjustments per investigator judgement were allowed in enliGHten.

Figure 5. Continuing Improvement in Height SDS During enliGHten for heiGHt and fliGHt Subjects



†from GHD diagnosis to start of fliGHt trial is mean 1.14 years
*Based on N=146 at fliGHt baseline
**Based on N=159 at heiGHt baseline

Safety Outcomes

- The adverse event (AE) profile of TransCon hGH 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 3)
  - 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]
- Across the three Phase 3 trials in pediatric patients with GHD, there were 6.3% showed detectable antibodies to TransCon hGH at any time, however, there was no apparent correlation of anti-TransCon hGH antibodies to adverse events or loss of efficacy (not shown)
- Hemoglobin A1c, cortisol, and free thyroxine were stable and generally remained within the normal range throughout the trials (not shown)
- Between the TransCon hGH and daily somatropin groups, there was a similar change in bone age delay over 104 weeks (Table 4). The bone age/chronological age ratios at Week 52 and Week 104 remained less than 1. Overall, this suggests that the longer-term effects of TransCon hGH (up to 104 weeks) did not occur at the expense of accelerated skeletal maturation

Table 3. Summary of Adverse Events Across All Trials

	heiGHt Trial (52 weeks)		fliGHt Trial (26 weeks)	enliGHten Trial (up to 52 weeks)
Category, n (%)	TransCon hGH (N = 105)	Daily somatropin (N = 56)	TransCon hGH (N = 146)	TransCon hGH (N = 298)
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

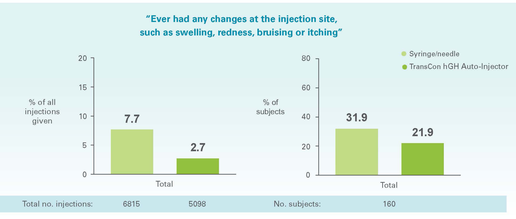
Table 4. Similar Change in Bone Age Over 104 Weeks For heiGHt Subjects

		TransCon hGH (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 (0.1)

Switching to the TransCon hGH Auto-Injector

- As of 01-Jun-2020, 160 subjects were using the GH Auto-Injector in enliGHten
- Overall, fewer injection site reactions were reported with the TransCon hGH Auto-Injector (Figure 6)

Figure 6. 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.

Right graph: Of all subjects who switched to the TransCon hGH Auto-Injector in enliGHten, the % of subjects who ever reported abnormal injection site reactions (i.e., "ever had any changes" etc) in the subject diary is depicted.

CONCLUSIONS

- Across the broad population of the phase 3 program, subjects treated with TransCon hGH 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 TransCon hGH, a lower-than-expected attenuation in 2nd year AHV suggested an improved treatment effect of TransCon hGH relative to the previous daily somatropin
- High retention rates were observed across the phase 3 program, with > 98% of subjects continuing from heiGHt and fliGHt into enliGHten
- Subjects who were using TransCon hGH Auto-Injector had fewer injection site reactions than subjects who were using syringe/needle

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