TransCon hGH as a Long-Acting Growth Hormone for the Treatment of Pediatric Growth Hormone Deficiency

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BACKGROUND

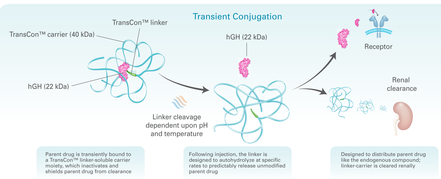
- The fundamental challenge of developing a Long-Acting Growth Hormone (LAGH) is to create a more convenient GH dosing profile while retaining the excellent safety, efficacy, and tolerability profile of daily hGH. With GH receptors in essentially all tissues, replacement therapy should achieve the same tissue distribution and effects of endogenous (and daily) GH while maintaining levels of GH and resulting IGF-1 within the physiologic range
- To create a LAGH that extends the GH half-life thereby allowing less frequent dosing, two basic approaches have been followed (Table 1): (a) combine unmodified GH with a prolongation technology (a depot, crystal, or prodrug) or (b) modify GH in such a way (protein enlargement or albumin binding) that the GH analogue has a longer half-life
- TransCon™ hGH is a LAGH prodrug in development for patients with pediatric growth hormone deficiency (GHD) with hGH transiently bound to an inert carrier. It was designed to release unmodified hGH over 7 days to achieve the same exposure, safety, efficacy, and tolerability as daily hGH with more convenient once weekly dosing. This profile was successfully demonstrated in the Phase 2 trial in pediatric GHD[1]
- TransCon™ hGH is also being developed with an auto-injector for ease of administration and improved adherence

Table 1: Summary of Long-Acting Growth Hormones Categorized by Development Approach

Approach	Company	Product/Formulation	Pediatric GHD Development Status
Unmodified GH: Half-life extension achieved by the slow release of somatropin from polymeric depot, crystal, or prodrug	Genentech, Inc.	**Nutropin Depot** GH encapsulated in polylactide-coglycolic acid microparticles	Approved in the US 1999, withdrawn 2004
	LG Life Sciences, Ltd.	**LB03002** GH encapsulated in sodium hyaluronate microparticles	Approved but not marketed in Europe; available in South Korea
	Altus Pharmaceuticals, Inc.	**ALTU-238** GH crystallization	Discontinued
	Ascendis Pharma A/S	**TransCon™ hGH** Transiently PEGylated hGH prodrug	Phase 3
	GeneScience Pharmaceuticals Co., Ltd.	**Jintrolong** Permanently PEGylated GH	Available in China
	Pfizer, Inc.	**PHA-794428** Permanently PEGylated GH	Discontinued
Modified GH: Half-life achieved by increasing molecular size (except sompapacitan, which is modified with a small albumin affinity tag)	Novo Nordisk A/S	**NNC126-0083** Permanently PEGylated GH	Discontinued
	Ambrx, Inc.	**ARX201** Permanently PEGylated and mutated GH	Discontinued
	Teva Pharmaceutical Industries, Ltd.	**TV-1106** GH fused to albumin	Discontinued
	Versartis, Inc.	**VRS-317** GH fused to XTEN	Discontinued
	OPKO Health, Inc.	**MOD-4023** GH fused to carboxyterminal peptides	Phase 3
	Novo Nordisk A/S	**Somapacitan** Mutated GH attached to an albumin affinity tag	Phase 3
	Genexine, Inc., and Handok, Inc.	**GX-H9** GH fused to an Fc fragment	Phase 2
	Hanmi Pharmaceutical Co., Ltd.	**LAPS-rhGH/HM10560A** GH fused to an Fc fragment	Phase 2

To date, nearly 20 LAGHs have reached various stages of development. Most have failed, some were successfully launched but failed to gain commercial success, two are currently only available in narrow geographic regions, and the remaining are in various stages of clinical development (Table 1).

Figure 1: TransCon™ Growth Hormone Releases Unmodified hGH



TransCon™ hGH is a long-acting prodrug consisting of parent drug, unmodified hGH, transiently bound to a carrier, mPEG (40 kDa), via a proprietary TransCon™ linker. Based on physiologic pH and temperature, the TransCon™ linker autohydrolyzes following first-order kinetics, releasing fully active, unmodified hGH over a one-week period designed to allow the same tissue distribution and receptor activation as endogenous GH. The release of hGH liberates the inert carrier, allowing elimination from the body. The carrier and linker are cleared primarily by renal filtration and to a minor extent by hepatobiliary excretion.

Once-weekly prodrug designed to release unmodified hGH and mimic daily hGH:

- Tissue distribution
- Physiological levels
- Therapeutic effects: safety, efficacy, and tolerability

METHODS

- heiGHt was a global, pivotal, phase 3 randomized, open-label, active-controlled trial comparing once-weekly TransCon™ hGH to daily Genotropin® at equivalent doses (Figure 2)
- Males and females (aged 3-12 or 3-11 years, respectively) in Tanner stage 1 diagnosed with isolated GHD (or as part of multiple pituitary deficiency on stable replacement therapy) via 2 different GH stimulation tests (peak GH ≤ 10 ng/mL) were eligible
- Subjects deemed eligible for the trial were randomly assigned to one of two treatment groups, either TransCon™ hGH 0.24 mg/kg/wk administered subcutaneously (SC) once weekly or daily Genotropin® administered SC once per day in a dose equivalent to 0.24 mg/kg/wk (ie, 0.034 mg/kg/d) for 52 weeks
- Randomization (2:1, TransCon™ hGH to Genotropin®) was stratified by age (≤ 6 years vs > 6 years), gender, and peak stimulated GH level (≤ 5 ng/mL vs > 5 ng/mL)
- TransCon™ hGH and Genotropin® were administered to the thigh, buttocks, or abdomen in a rotating fashion
- Subjects were treated and followed for 52 weeks
- Topline results are reported

Figure 2: Phase 3 heiGHt Trial Design

Key Inclusion Criteria

- Prepubertal children with GHD
- Height SDS ≤ -2.0
- IGF-1 SDS ≤ -1.0
- 2 GH stimulation tests (GH ≤ 10 ng/mL)
- Bone age ≥ 6 months behind chronological

Objective:

- Demonstrate non-inferiority

Key Endpoints

- Annualized Height Velocity (AHV) at 52 weeks (primary endpoint)
- AHV at earlier time points
- Change in HT SDS over 52 weeks
- Change in serum IGF-1 and IGFBP-3 levels
- Change in IGF-1 SDS and IGFBP-3 SDS
- Normalization of IGF-1 SDS
- hGH and IGF-1 levels over 168 hours at week 13 (PK/PD subset)

RESULTS

Table 2: Demographics and Baseline Characteristics

	TransCon™ hGH (n=105) Mean	Genotropin® (n=56) Mean	Total (N=161) Mean
Chronological Age (CA)(years)	8.51	8.48	8.50
Bone Age (BA)(years)	5.84	5.98	5.88
BA/CA	0.69	0.70	0.69
Height SDS	-2.89	-3.00	-2.93
BMI	16.06	16.46	16.20
BMI SDS	-0.32	-0.14	-0.25
Delta Mid-Parental Height SDS	-2.32	-2.55	-2.40
IGF-1 SDS	-2.08	-1.96	-2.04
Peak GH (ng/mL)	5.89	5.48	5.75
Caucasian (%)	95.2	92.9	94.4
Male (%)	81.9	82.1	82.0

A total of 161 subjects from 54 sites were randomized and dosed. In the intention-to-treat population, 158/161 (98.8%) completed the trial, while 2 subjects withdrew. One of 105 (1.0%) in the TransCon™ hGH cohort grew fatigued with the medical system following unrelated acute appendicitis and an appendectomy, while 1/56 (1.8%) in the daily Genotropin® cohort was lost to follow-up prior to the final visit. The cohorts were well-balanced with respect to demographics and baseline characteristics across all parameters.

Table 3: TransCon™ hGH Met Its Primary Endpoint of Non-inferiority and Was Superior to Genotropin® in AHV at Week 52

	TransCon™ hGH (n=105)	Genotropin® (n=56)	Estimate of Treatment Difference	*P*-value
LS Mean AHV at Week 52 (cm/year)	11.2	10.3	0.86	0.0088
Standard Error	0.23	0.30	0.33	
95% Confidence Interval (cm/year)	10.71 – 11.62	9.73 – 10.89	0.22 – 1.50	

LS Mean=Least Squares Mean; ANCOVA model was applied after missing data were imputed by multiple imputation method.

At Week 52, the AHV for TransCon™ hGH was 11.2 cm while that for Genotropin® was 10.3 cm. The treatment difference was 0.86 cm in favor of TransCon™ hGH with a 95% confidence interval of 0.22 to 1.50, which demonstrates not only non-inferiority but also superiority (p=0.0088) over Genotropin®. Further analysis of the AHV revealed that the treatment difference reached statistical significance at Weeks 26 (p=0.0017) (not shown), 39 (p=0.0061) (not shown) and 52 (p=0.0088).

Figure 3: Schematic of Possible Outcomes of the heiGHt Trial

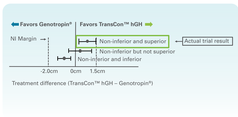


Table 4: Numerically Lower Incidence of Poor Responders with TransCon™ hGH

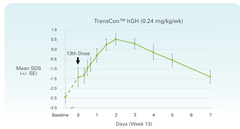
Poor responders defined as AHV < 8.0 cm/year[2]

At Week 52	TransCon™ hGH (n=104)* n (%)	Genotropin® (n=55)* n (%)
Responder	100 (96.2)	49 (89.1)
Poor Responder	4 (3.8)	6 (10.9)

*Excludes one subject/group with missing Week 52 data (98.8% subjects completed study).

In a post-hoc analysis, the proportion of responders in each group was evaluated, defined as achieving at least 8.0 cm/year in AHV. Of those subjects administered TransCon™ hGH, 4/104 (3.8%) were poor responders as compared to 6/55 (10.9%) administered daily Genotropin®.

Figure 4: IGF-1 Profile Over 1 Week of Testing at Week 13 (n=11)



In the subset of subjects (n=11) with intensive PK and PD monitoring during Week 13, results were similar to those reported in the TransCon™ hGH pediatric phase 2 trial (Chatelain, 2017). Mean peak IGF-1 SDS was achieved on Day 2 post-dose. At the end of the week, IGF-1 SDS returned to steady-state baseline (Hours recorded = baseline, 0, 8, 12, 16, 24, 36, 48, 72, 96, 120, 168).

Figure 5: IGF-1 SDS Over 52 Weeks for Equivalent Doses of TransCon™ hGH and Daily Genotropin® (N=161)

Mean IGF-1 SDS levels for TransCon™ hGH were lower at trough and higher at peak than IGF-1 levels for daily Genotropin®; all 3 parameters trended upward with time and generally remained within normal range (ie, under 2.0 SDS). The mean observed TransCon™ hGH IGF-1 SDS at baseline was -2.08, increasing to -0.7 at Week 52 compared to 0 for daily Genotropin®.

Table 5: Change in Bone Age and BA/CA Over 52 Weeks

Bone Age, years	TransCon™ hGH n=105 Mean (SD)	Genotropin® n=56 Mean (SD)
Baseline	5.84 (2.60)	5.98 (2.68)
Week 52	7.16 (2.72)	7.35 (2.94)
Change from Baseline	**1.36 (0.87)**	**1.35 (0.72)**

BA/CA Ratio	TransCon™ hGH n=105 Mean (SD)	Genotropin® n=56 Mean (SD)
Baseline	0.69 (0.16)	0.70 (0.14)
Week 52	0.75 (0.15)	0.76 (0.14)
Change from Baseline	**0.06 (0.10)**	**0.05 (0.08)**

Over 52 weeks, the mean bone age advanced by 1.36 and 1.35 years in the TransCon™ hGH and daily Genotropin® cohorts. The BA/CA ratio increased to 0.75 and 0.76, for TransCon™ hGH and Genotropin®, respectively, for a BA/CA ratio increase of 0.06 over the trial.

Table 6: Summary of Adverse Events: Safety Population

	TransCon™ hGH n=105 n (%)	Genotropin® n=56 n (%)	Total N=161 n (%)
Treatment-emergent Adverse Events (TEAE)	81 (77.1%)	39 (69.6%)	120 (74.5%)
TEAEs Related to Study Drug	12 (11.4%)	10 (17.9%)	22 (13.7%)
Serious Adverse Events (AEs)	1 (1.0%)	1 (1.8%)	2 (1.2%)
Serious AEs Related to Study Drug	0	0	0
TEAEs Leading to Any Action on Study Drug	2 (1.9%)	1 (1.8%)	3 (1.9%)
TEAEs Leading to Discontinuation of Study Drug	0	0	0

Treatment-emergent AEs were common in both groups (77.1% on TransCon™ hGH and 69.6% on Genotropin®). For those related to study drug, values were 11.4% and 17.9% for TransCon™ hGH and Genotropin®, respectively. Two SAEs were reported during the trial, one on TransCon™ hGH (an appendectomy rated as unrelated to study drug), and one on Genotropin® (a concussion rated as unrelated to study drug). Two AEs in the TransCon™ hGH group resulted in a reduction of dose, due to elevations in IGF-1, while one subject on Genotropin® had a dose reduction due to facial swelling, with a normal IGF-1 value.

Figure 6: Safety Analyses

- Low titer anti-hGH binding antibodies were detected with a similar incidence in both TransCon™ hGH and Genotropin® groups in less than 10% of subjects
  - All were non-neutralizing and antibodies all resolved over time
- Mean fasting glucose (Figure 6a) and hemoglobin A1c (Figure 6b) values were stable and within the normal range for both arms:

Figure 6a

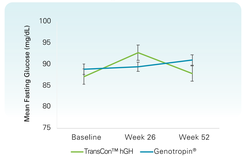
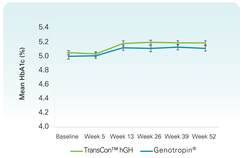
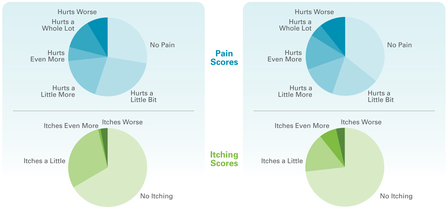


Figure 6b



Safety Analyses Figure 7: Similar Tolerability: Pain and Itching



Pain and itching were assessed using a Subject Diary, where each dose was logged and rated for injection-site reactions by the subject or caregiver (for Pain assessment, using the Wong-Baker FACES Pain Rating Scale). Proportion of responses are represented for the categories of Pain and Itching, for those receiving TransCon™ hGH and those receiving Genotropin®. The pie charts reflect each subject's worst rating for either Pain or Itching over 52 weeks of receiving TransCon™ hGH or Genotropin®. Responses were similar between treatment groups for each score. Two subjects in each treatment arm experienced mild injection-site reactions that were considered adverse events.

CONCLUSIONS

- Treatment with TransCon™ hGH achieved the primary objective of non-inferiority in AHV at 52 weeks, and further showed superiority over Genotropin® (*p*=0.0088)
  - TransCon™ hGH: 11.2 cm/year
  - Genotropin®: 10.3 cm/year
- IGF-1 SDS scores were generally within the normal range following treatment for both groups
- Safety and tolerability of TransCon™ hGH was consistent with daily Genotropin®

CLINICAL IMPLICATIONS

- Availability of a safe and well-tolerated long-acting hGH therapy has been long awaited and elusive
- The standard of care for pediatric GHD for over the past 30 years has been recombinant hGH administered daily. While daily hGH has both an excellent safety profile and satisfactory efficacy, the frequency of its administration causes a significant burden on daily life for both children with GHD and their caregivers
- The heiGHt Trial results represent another step closer to development of a safe, well-tolerated, and effective long-acting treatment for pediatric GHD

Figure 8: TransCon™ hGH Phase 3 Program

Figure 9: Auto-Injector Designed to Improve Adherence

Key Features

- Simple operation with few user steps
- Single low-volume (<0.60 mL) injection for patients ≤60 kg
- Small needle, comparable to daily hGH (31G, 4 mm)
- Room temperature storage
- No waste due to empty-all design
- Device lifetime at least 4 years

Auto-injector introduction during extension study and for commercial launch

REFERENCES:

[1]Chatelain P et al. A randomized phase 2 study of long-active TransCon GH vs daily GH in childhood GH deficiency. *J Clin Endocrinol Metab*. 2017;102(5):1673-1682.

[2]Bakker B, et al. Height velocity targets from the National Cooperative Growth Study for first-year growth hormone responses in short children. *J Clin Endocrinol Metab*. 2008;93(2):352-357.