RFC 4.5

# 12-Month effects of once-weekly and twice monthly Administration of hybrid Fc-fused human growth hormone, GX-H9, treatment in pediatric patients with GHD

*Oleg Malievskiy, MD, PhD, Bashkir State Medical University, Ufa, Russian Federation; Aryaev Mykola, MD, Odessa National Medical University, Odessa, Ukraine; Zelinska Nataliya, MD, PhD, Ukrainian Scientifically Practical Center of Endocrine Surgery and Transplantation of Endocrine Organs and Tissues, Kyiv, Ukraine; Elena V. Bolshova, MD, Institute of Endocrinology and Metabolism named after Komisarenko NAMS of Ukraine, Kyiv, Ukraine; Ganna Senatorova, MD, Kharkiv National Medical University, Kharkiv, Ukraine; György Oroszlán, MD, Markusovszky University Hospital, Szombathely, Hungary; Julia Skorodok, MD, St. Petersburg State Pediatric Medical University, St. Petersburg, Russian Federation; Valentina Peterkova, MD, PhD, Institute of Pediatric Endocrinology, Moscow, Russian Federation; Chorna Nataliya, MD, Regional Clinical Children's Hospital, Ivano-Frankivsk, Ukraine; Tamila Sorokman, MD, PhD, Bukovinian State Medical University, Chernivtsi, Ukraine; Seung Yang, MD, Kangdong Sacred Heart Hospital, Seoul, Korea, Republic of; Ji Eun Lee, MD, PhD, Inha University Hospital, Incheon, Korea, Republic of; Agota Muzsnai, MD, PhD, St. John's Hospital and United Hospitals of Northern Buda, Budapest, Hungary; Jin Soon Hwang, MD, PhD, Ajou University School of Medicine, Ajou University Hospital, Suwon, Korea, Republic of; Sang Yoon Lee, MD, HANDOK Inc., Seoul, Korea, Republic of; Yun Jung Choi, RPh, PhD, Genexine, Inc., Seongnam, Korea, Republic of; Hyi-Jeong Ji, PhD, Genexine, Inc., Seongnam, Korea, Republic of; Jungwon Woo, PhD, Genexine, Inc., Seongnam, Korea, Republic of; Young-Chul Sung, PhD, Genexine, Inc., Seongnam, Korea, Republic of;*

## Introduction

### Background

Recombinant human growth hormone (rhGH) is a standard treatment for children with growth hormone deficiency (GHD). However, current rhGH therapy involves daily subcutaneous injections with years of treatment. The challenge of daily rhGH injections has proven to limit compliance, often reducing the ability to maintain height velocity (HV) or optimal clinical outcomes. Thus, long-acting rhGH could improve ease of use, compliance, and real-world efficacy.

**GX-H9 (rhGH-hyFc$^{TM}$)**

- **GX-H9** is a long-acting recombinant human growth hormone fused to hybrid Fc (hyFc) with a proposed weekly and every other week (EOW) dosing schedule for patients with GHD.
- A novel Fc-based platform technology, hyFc$^{TM}$, is constructed to produce long-acting Fc fusion proteins with a hybrid of IgD and IgG4, which extends half-life and increases bioactivity of fused proteins.

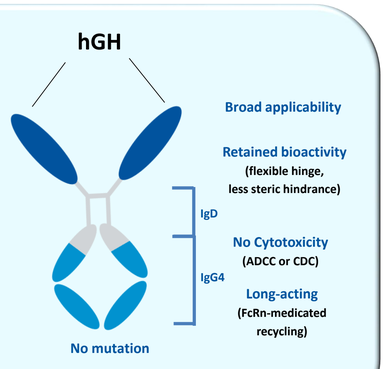


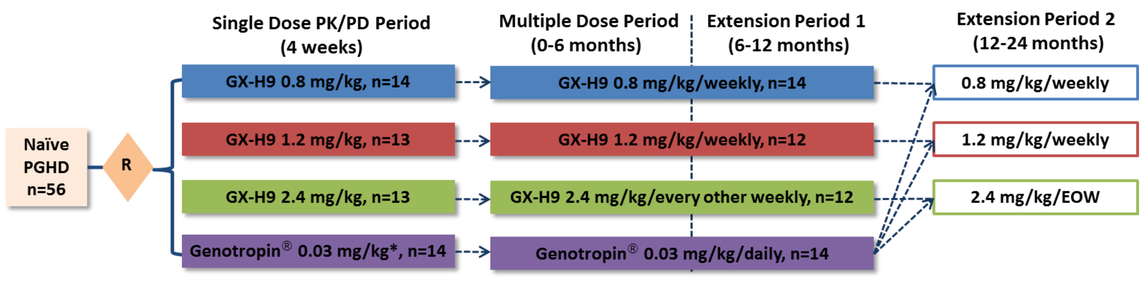

**Figure 1. Structure of GX-H9.**

### Objectives

GX-H9 is a long-acting form of recombinant human GH under clinical development for both adults and children with GH deficiency (GHD). This study was designed to compare 12-month effects of once-weekly and twice-monthly (every other week; EOW) administration of GX-H9 treatment to that of daily GH, Genotropin®, in pediatric patients with GHD.

### Methods

A Phase 2, randomized, open-label, active-controlled, parallel, dose finding study of GX-H9 is being conducted at 27 endocrinology centers in 10 countries (Europe, Middle East and Republic of Korea) for pre-pubertal treatment-naïve children with GHD. (EudraCT Number: 2015-001939-21, ClinicalTrials.gov Identifier: NCT03309891)




* Genotropin® 0.03 mg/kg/daily: seven doses on seven consecutive days during single dose PK/PD period.

**Figure 2. Overall Study Design**

## Subject Disposition and Characteristics

- 56 subjects were randomized and 2 out of 56 subjects withdrew before dosing. Afterward, 4 subjects dropped out during multiple dose period.
- A total of 50 subjects completed 12 months of treatment.

**Table 1. Demographic and Baseline Characteristics (N=54)**

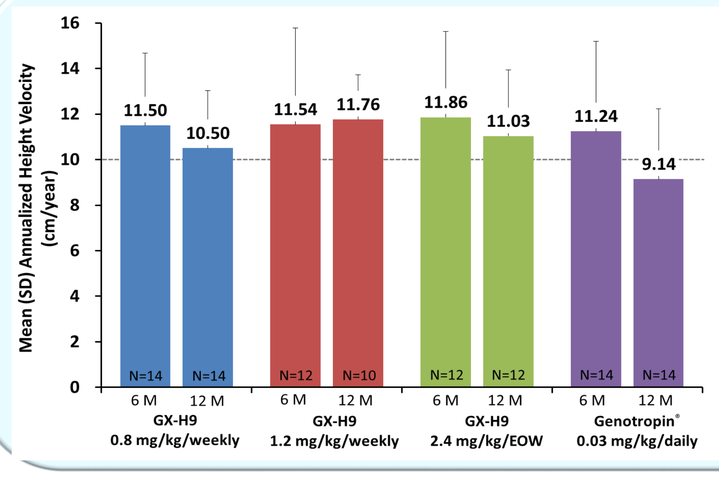
| | GX-H9 | | | Genotropin® |
|---|---|---|---|---|
| | 0.8 mg/kg/weekly (n=14) | 1.2 mg/kg/weekly (n=13) | 2.4 mg/kg/EOW (n=13) | 0.03 mg/kg/daily (n=14) |
| Baseline Age [years], mean (SD) | 6.81 (2.28) | 6.70 (2.03) | 6.97 (2.61) | 6.89 (1.92) |
| Gender(Male/Female), n (%) | 8 (57.14) / 6 (42.86) | 11 (84.62) / 2 (15.38) | 12 (92.31) / 1 (7.69) | 9 (64.29) / 5 (35.71) |
| Race (Caucasian/Asian), n (%) | 12 (85.71) / 2 (14.29) | 11 (84.62) / 2 (15.38) | 12 (92.31) / 1 (7.69) | 13 (92.86) / 1 (7.14) |
| BMI SDS, mean (SD) | -0.44 (1.37) | -0.32 (1.08) | -0.19 (0.92) | -0.28 (1.17) |
| Height SDS, mean (SD) | -3.66 (1.05) | -3.43 (0.61) | -3.09 (0.62) | -4.25 (1.19) |
| aHV SDS, mean (SD) | -1.99 (1.85) | -3.43 (1.87) | -1.85 (1.08) | -3.16 (2.25) |
| IGF-1 SDS, mean (SD) | -2.49 (1.14) | -2.22 (1.15) | -2.37 (1.15) | -2.23 (1.07) |
| Stimulated $GH_{max}$ [ng/mL], mean (SD) | 5.17 (3.50) | 4.16 (2.83) | 4.49 (3.15) | 4.73 (3.06) |
| Peak GH concentration during stimulation test > 5 ng/mL, n (%) | 7 (50.00) | 5 (38.46) | 6 (46.15) | 6 (42.86) |

## Results – Safety (12 months)

- All treatment-emergent adverse drug reactions were mild to moderate and mostly transient.
- No lipoatrophy, injection site nodule formation nor insulin resistance was observed.

## Results – Efficacy (12 months)

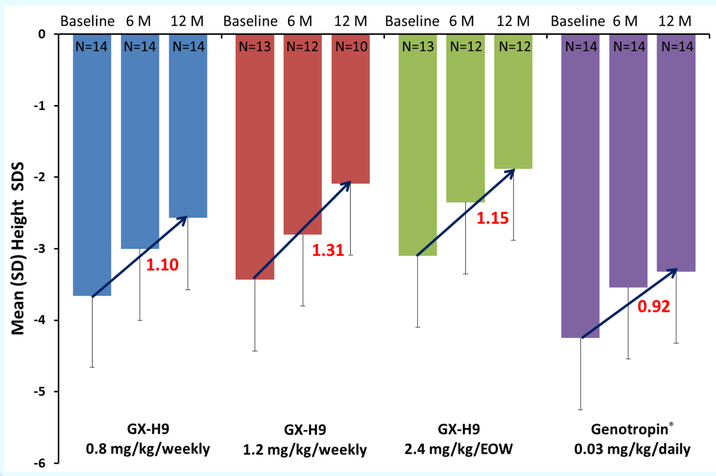
### Annualized Height Velocity at 6 and 12 months




The height velocity at 12 months indicated comparable growth rates between all doses of GX-H9 (both weekly and EOW schedules) and the active comparator, Genotropin®.

**Figure 3. Mean (SD) annualized height velocity at 6 months and 12 months after treatment.**

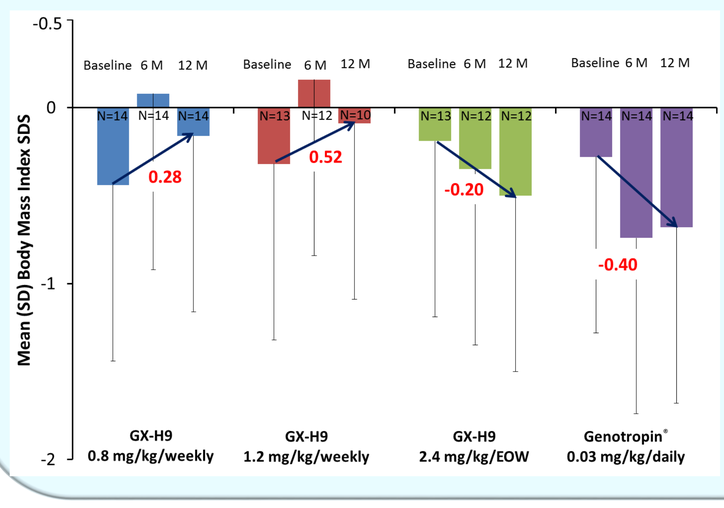
### Height SDS at 6 and 12 months




Changes in height SDS from baseline to 6 months and 12 months of treatment were comparable between all doses of GX-H9 (both weekly and EOW schedules) and the active comparator, Genotropin®.

**Figure 4. Mean (SD) height SDS at baseline, 6 months and 12 months after treatment.**

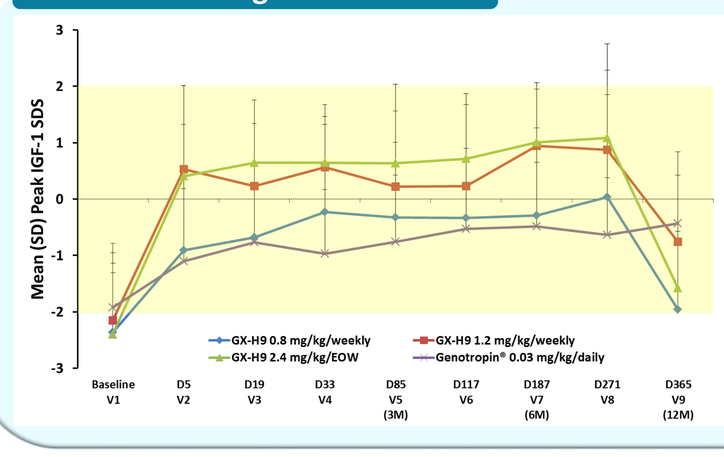
### Body Mass Index (BMI) SDS at 6 and 12 months




Pre and post BMI SDS were comparable between all doses of GX-H9 (both weekly and EOW schedules) and the active comparator, Genotropin® throughout the 12 months of treatment.

**Figure 5. Mean (SD) BMI SDS at baseline, 6 months and 12 months after treatment.**

### IGF-1 SDS throughout 12 months




Average peak IGF-1 SDS were within range of -2 SDS to +2 SDS for 12 months in subjects with all doses of GX-H9 (both weekly and EOW treatment) and the active comparator, Genotropin®.

**Figure 6. Mean (SD) peak IGF-1 SDS throughout 12 months of treatment.**

## Conclusions

- Height velocity and Height SDS at 12 months were comparable across GX-H9 treatment groups and the active comparator Genotropin® group.
- GX-H9 treatment for 12 months was safe and well-tolerated as Genotropin®, for GH-naïve patients with PGHD.
- GX-H9 showed potential for both weekly and twice-monthly administration in children with GHD.

**ACKNOWLEDGEMENTS** This study was sponsored by Genexine, Inc. and Handok Inc. This research was supported by Korea Drug Development Fund (KDDF) funded by MSIP, MOTIE and MOHW (Grant No. KDDF-201308-07 for Phase I Study, KDDF-201502-11 for Phase II AGHD Study, & KDDF-201509-12 for Phase II PGHD Study).

**DISCLOSURE** SY Lee is an employee and shareholder of HANDOK Inc. YJ Choi, HJ Ji, J Woo, YC Sung are employees and stockholders of Genexine, Inc.