REAL 4
Phase 3 Pediatric Growth Hormone Deficiency (GHD)

Sogroya® (somapacitan-beco) injection vs. once-daily growth hormone (GH)

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Sogroya® is a human growth hormone analog indicated for the treatment of pediatric patients aged 2.5 years and older who have growth failure due to inadequate secretion of endogenous growth hormone (GH) and for the replacement of endogenous growth hormone in adults with growth hormone deficiency.[1]

REAL 4 is an ongoing phase 3, randomized, multinational, open-label, and active-controlled parallel group trial **investigating efficacy and safety of once-weekly Sogroya® compared to once daily Norditropin®** in GH-naïve pre-pubertal children with GHD **(Figure 1)**. ⊕

Eligibility Criteria

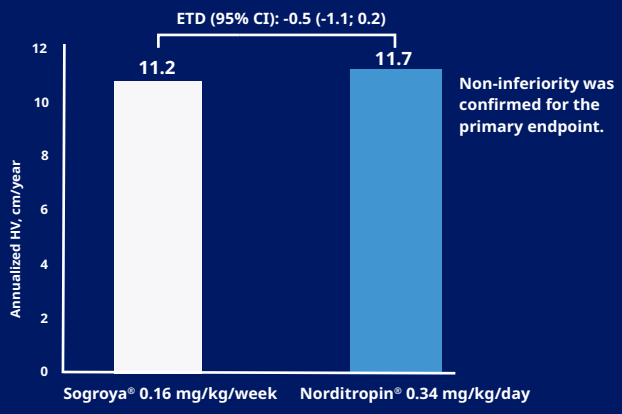
Inclusion criteria included treatment-naïve prepubertal children with a confirmed diagnosis of GHD within 12 months before randomization, impaired height (defined as ≥2 standard deviations below mean for age and sex), height velocity ([HV], defined as <25th percentile for age and sex according to the standards of Prader calculated over 6-18 months prior to screening), and IGF-1< -1 SDS at screening.[2,3]

Exclusion criteria included children born short for gestational age, diabetes mellitus or attention deficit hyperactivity disorder, current or past history of malignancies, concomitant treatments affecting growth, or other abnormalities that may affect growth or standard growth measurements.[2] Baseline characteristics are described in **Table 1**. ⊕

52-week Main Phase

Primary Endpoint[2]

The primary endpoint was the effect of Sogroya® versus Norditropin® on annualized HV with a non-inferiority margin of -1.8 cm/year at Week 52.



Non-inferiority was confirmed for the primary endpoint.

Figure 2: Annualized HV at Week 52[2]
Results in the figure are estimated means.

Supportive Secondary Endpoints ⊕

- Height SDS
- IGF-1 SDS
- HV SDS
- BA vs CA ratio

Patient-reported Outcomes (PROs)[2]

Reduction in disease burden from Week 0 to Week 52 was similar between treatment groups based on scores from the GHD-Child Impact Measure (GHD-CIM).[2] Treatment burden was assessed at Week 52 using the GHD-Child Treatment Burden (GHD-CTB) and GHD-Parent Treatment Burden (GHD-PTB) tools and demonstrated significant findings specifically in the GHD-PTB questionairre results.[2] A survey tool given at Week 26 to evaluate use of Sogroya® and Norditropin® pens indicated the pens were considered "easy or very easy to use" and "easy or very easy to learn to use" by 96% and >90% of respondents, respectively.[2,4]

Safety

- A total of 94 patients (71.2%) and 41 patients (60.3%) reported adverse events (AEs) in the Sogroya® and Norditropin® groups, respectively.[2]
- The majority of AEs were mild/moderate in severity and unlikely related to trial product.[2] The most common (≥5%) AEs observed were headache, nasopharyngitis, pyrexia, pain in extremity, bronchitis, and vomiting.
- Injection site reactions (ISRs) were reported in 5.3% of the Sogroya® group and 5.9% of the Norditropin® group. The ISRs occurred in seven children (nine events) and four children (four events) in the Sogroya® and Norditropin® groups, respectively.[2,4]
- There were no neutralizing anti-drug antibodies detected in either treatment group, nor any clinically relevant findings related to glucose metabolism.[2]

References: 1. Sogroya® Prescribing Information. Plainsboro, NJ: Novo Nordisk Inc. **2.** Miller BS, Blair JC, Rasmussen MH, et al. Weekly Somapacitan is Effective and Well Tolerated in Children with GH Deficiency: The Randomized Phase 3 REAL4 Trial. J Clin Endocrinol Metab. 2022 **3.** Miller B, Blair J, Hojby M, et al. Once-weekly Somapacitan is Effective and Well Tolerated in Children with GHD: a Randomized Phase 3 Trial. Poster LBMON195 presented at the Endocrine Society Annual Meeting (ENDO) 2022, Atlanta, GA, USA, June 11-14, 2022. **4.** Data On File at Novo Nordisk Inc. Plainsboro, NJ. NN8640-4263 (REAL 4; 52-Week). March 2022. **5.** Juul RV, Rasmussen MH, Agerso H, et al. Pharmacokinetics and Pharmacodynamics of Once-Weekly Somapacitan in Children and Adults: Supporting Dosing Rationales with a Model-Based Analysis of Three Phase I Trials. Clin Pharmacokinet. 2019;58(1):63-75. Link to Access the Full Text

Abbreviations: BA: bone age; CA: chronological age; HV: height velocity; IGF-1: insulin-like growth factor-1; SDS: standard deviation score.

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Medical Information Response

Sogroya® (somapacitan-beco) injection vs once-daily growth hormone (GH) in Pediatric Growth Hormone Deficiency (GHD) (REAL 4)

Sogroya® is a human growth hormone (GH) analog indicated for treatment of pediatric patients aged 2.5 years and older who have growth failure due to inadequate secretion of endogenous GH and replacement of endogenous GH in adults with growth hormone deficiency (GHD).[1]

Study Design[2]

REAL 4 (**Figure 1**) is an ongoing phase 3, randomized, multinational, open-label, and active-controlled parallel group trial investigating efficacy and safety of once-weekly Sogroya® compared to once daily Norditropin® in GH-naïve pre-pubertal children with GHD. REAL 4 consists of a 52-week main phase where patients are randomized 2:1 to Sogroya® 0.16 mg/kg/week or Norditropin® 0.034 mg/kg/day. A 3-year safety extension phase will follow, where all patients will receive Sogroya® 0.16 mg/kg/week. Of the 200 patients randomized, 199 completed the 52-week main phase, with one patient discontinuing Sogroya® due to violation of study criteria but was included in the full analysis set (FAS) and safety analysis set (SAS).[3]

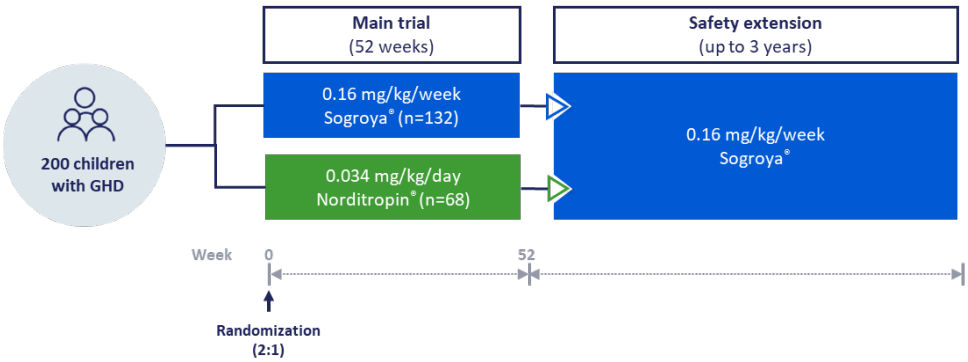

Figure 1. Study Design and Dosing in REAL 4
Adapted from Miller et al.[3]
Abbreviation: GHD: growth hormone deficiency

Inclusion criteria included treatment-naïve prepubertal children with a confirmed diagnosis of GHD within 12 months before randomization, impaired height (defined as ≥2 standard deviations below mean for age and sex), height velocity ([HV], defined as <25th percentile for age and sex according to the standards of Prader calculated over 6-18 months prior to screening), and IFG-I < -1 SDS at screening.[2,3] Exclusion criteria included children born short for gestational age, diabetes mellitus or attention deficit hyperactivity disorder, current or past history of malignancies, concomitant treatments affecting growth, or other abnormalities that may affect growth or standard growth measurements.[2] Baseline characteristics are described in **Table 1**.

Table 1. Baseline Characteristics and Demographics[2,a]

	Sogroya® N=132	Norditropin® N=68
Age, years	6.4 (2.2)	6.4 (2.4)
Sex, number of males (%)	99 (75)	50 (74)
GH peak, mcg/L	4.93 (2.5)	4.1 (2.77)
HV, cm/year	4.3 (1.4)	4.1 (1.4)
Height SDS	-2.99 (1.02)	-3.47 (1.52)
IGF-1	-2.03 (0.97)	-2.33 (1.03)

a. Mean values (standard deviation), unless otherwise indicated.
Abbreviations: n: number of patients; HV: height velocity; SDS: standard deviation score; IGF-1: insulin-like growth factor-1.

The primary endpoint was the effect of Sogroya® versus Norditropin® on annualized HV with a non-inferiority margin of -1.8 cm/year at week 52.[2] Secondary endpoints included height standard deviation score (HSDS), height velocity SDS, bone age vs chronological age ratio, and insulin-like growth factor-1 [IGF-1] SDS. Patient-reported outcome measures (PROs) and safety endpoints were also assessed.

Efficacy and Safety Results (52-week Main Phase)

Non-inferiority was confirmed for the primary endpoint (**Table 2**).[2] Results of the supportive secondary endpoints demonstrate similar mean changes for all endpoints between Sogroya® and Norditropin® in (**Table 2**).[3,4] The observed mean IGF-1 SDS at week 52 for Sogroya® corresponded to the weekly average IGF-1 derived from a population pharmacokinetic/pharmacodynamic model described previously.[2,5]

Table 2. Primary and Supportive Secondary Efficacy Endpoints at Week 52[2,a]

	Sogroya® 0.16 mg/kg/week N=132	Norditropin® 0.034 mg/kg/day N=68[b]	ETD (95% CI)[c,d]
Annualized HV, cm/year	11.2	11.7	-0.5 (-1.1; 0.2)
Estimated Mean Change in Height SDS[e]	1.25	1.30	-0.05 (-0.18; 0.08)
Estimated Mean Change in HV SDS[e]	8.05	8.82	-0.78 (-1.63; 0.08)
Estimated Mean Change in IGF-1 SDS[e]	2.36	2.33	0.03 (-0.30; 0.36)
Estimated Mean Change in BA vs CA	0.06	0.08	-0.02 (-0.06; 0.01)

a. All data from full analysis set (all randomized subjects).
b. Number of patients in Norditropin® group was n=67 for mean change in IGF-1 SDS.
c. Based on estimated mean.
d. HV at week 52 and changes from baseline in height SDS and HV SDS are analyzed using an analysis of covariance model, while change from baseline in IGF-1 SDS is analyzed using a mixed model for repeated measurements, with treatment, gender, age group, region, GH peak group and gender by age group by region interaction term as factors, and baseline value as covariate.
e. Change from baseline after 52 weeks of treatment
Abbreviations: SDS: standard deviation score; ETD: estimated treatment difference; CI: confidence interval; HV: height velocity; IGF-1: insulin-like growth factor-1; BA: bone age; CA: chronological age.

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