REAL 3
Phase 2 Pediatric Growth Hormone Deficiency (GHD)

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

This letter contains information on the use of Sogroya® that is not currently an approved indication.

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Sogroya® is a once-weekly human growth hormone analog indicated for replacement of endogenous GH in adults with GHD.[1]

REAL 3 is a phase 2, randomized, multinational, active-controlled, open-label, double-blinded (Sogroya® doses), dose-finding trial **investigating efficacy and safety of once-weekly Sogroya® compared to once daily Norditropin® FlexPro® (somatropin) injection (Figure 1).** ⊕

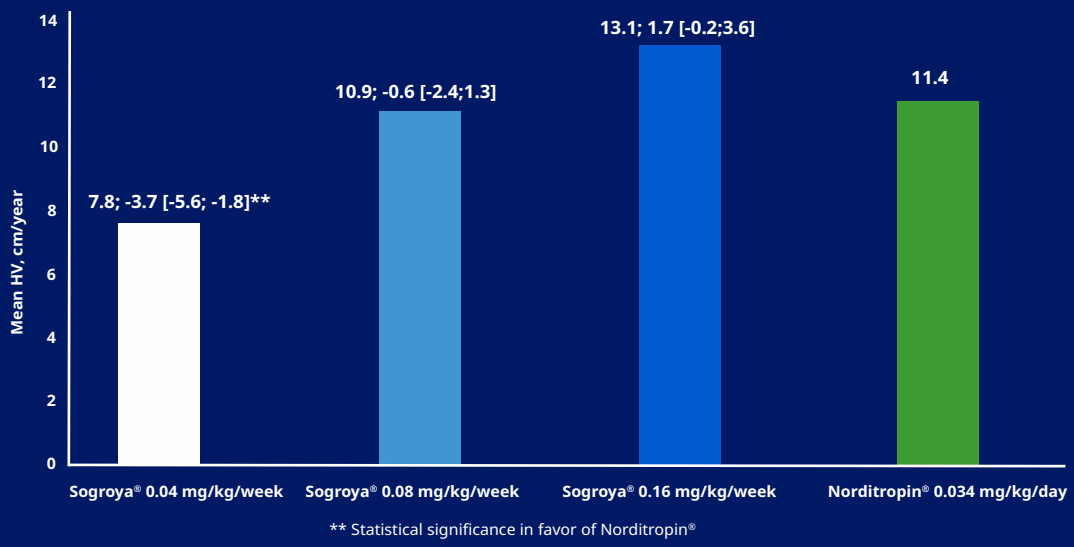
Eligibility and Baseline Criteria

Children were eligible if they were GH treatment-naïve, prepubertal children with a confirmed diagnosis of GHD within 12 months before screening, Tanner stage 1 for boys and girls, and height ≤2 standard deviation score (SDS) below the mean (corresponding to below 3rd percentile) for age and gender according to Centers for Disease Control and Prevention (CDC) growth chart for ages 2 to 20 years.[2] Baseline characteristics are described in **Table 1.** ⊕

Week 26 and Week 52

Primary Endpoint[2]

The primary endpoint was height velocity (HV) at 26 weeks. The HV difference at Week 26 was not statistically significant between Norditropin® 0.034 mg/kg/day and Sogroya® 0.08 or 0.16 mg/kg/week; however, HV was significantly greater with Norditropin® 0.034 mg/kg/day vs Sogroya® 0.04 mg/kg/week.



** Statistical significance in favor of Norditropin®

Figure 2. Mean HV (cm/year) at 26 Weeks[2]

Reported as HV (cm/year); Estimated Treatment Difference (ETD) [95% Confidence Interval]

Results in the figure are estimated means. ETD for Sogroya® in comparison with Norditropin®.

Supportive Secondary Endpoints[2] ⊕

Included changes from baseline to end of Week 26 and Week 52 in height SDS, HV SDS, and insulin-like growth factor 1 (IGF-1) SDS described in **Table 2.**

- Height SDS
- HV SDS
- IGF-1 SDS

Safety[2]

- Sogroya® was well-tolerated at all dose levels up to 52 weeks, and adverse events (AEs) were mild to moderate.
- The most common AEs occurring in 10% or more of patients in any patient group were nasopharyngitis, anemia, tonsilitis, constipation, diarrhea, influenza, pyrexia, rhinitis, upper respiratory tract infection, urticaria, head injury, lipoatrophy, cough, and hematology test abnormal.
- One child treated with Sogroya® 0.04 mg/kg/week experienced two injection-site reactions: injection-site hematoma and lipoatrophy.
- There were no neutralizing anti-GH antibodies or anti-somapacitan-beco antibodies detected.
- Non-neutralizing GH (n=1) and anti-somapacitan-beco antibodies (n=6) were observed, but these did not appear to have an affect on pharmacokinetic/pharmacodynamic (PK/PD) profiles or annualized HV.

Additional Efficacy Analysis

3-Year (156-weeks total treatment)[4]

- Height-based outcomes (HV, changes in HV SDS, height SDS) and changes in IGF-1 SDS are reported in **Table 3**. ⊕ Mean IGF-1 SDS values for both Sogroya® and Norditropin® treatment groups reached within normal range. IGF-1 SDS values were occasionally >2 in a total of 17 children treated with Sogroya® and 4 children treated with Norditropin®.

4-Year (208-weeks total treatment)[3,5]

- HV between groups at year 4 was similar, when compared with year 3. Mean change in HV SDS and height SDS, as well as mean IGF-1 SDS values at year 4 are reported in **Table 4**. ⊕

Safety

3-Year Safety Analysis (156-weeks total treatment)[4]

- No new significant safety issues were identified. Two SAEs (generalized edema and vomiting) in one child receiving Sogroya® 0.16/0.16 mg/kg/week were evaluated by the investigators and deemed to be likely related to trial product.
- Four children (Sogroya®, n=3; Norditropin®, n=1) experienced six mild injection site related AEs after the first year.
- Over the 3-year trial period, low titer non-neutralizing antibodies were observed in 10 children treated with Sogroya®. These antibodies did not appear to affect the PK or PD profiles for Sogroya® or annualized HV.

4-Year Safety Analysis (208-weeks total treatment)[3,5]

- Eighty-four AEs were reported in 20 patients (51.3%) in the Sogroya®/Sogroya® group from weeks 0 to 208 and 12 AEs were reported in 8 patients (72.7%) in the Norditropin®/Sogroya® group from weeks 156 to 208.[5]
- Reported AEs were considered mild (89%) or moderate (10%) with 91% considered unlikely related to treatment with growth hormone.[5]
- There were no serious AEs reported in year 4; in the Sogroya®/Sogroya® group, 1 severe AE (elbow fracture surgery) was reported.
- One patient in the Sogroya®/Sogroya® group experienced 5 injection site reactions; none were reported in the Norditropin®/Sogroya® group.
- Ten patients (26%) in the Sogroya®/Sogroya® group and 1 patient (10%) in the Norditropin®/Sogroya® group developed low titer, non-neutralizing antibodies.

Please note, if you are receiving this document by fax, it may contain icons and/or hyperlinks to websites/publications to expand on information. If you would like to receive this content via e-mail please contact Novo Nordisk Medical Information at (800) 727-6500 or scientific-exchange.com.

References

1. Sogroya® Prescribing Information. Plainsboro, NJ: Novo Nordisk Inc.
2. Savendahl L, Battelino T, Brod M, et al. Once-Weekly Somapacitan vs Daily GH in Children With GH Deficiency: Results From a Randomized Phase 2 Trial. *J Clin Endocrinol Metab*. 2020;105(4)
3. Savendahl L, Battelino T, Rasmussen M, et al. Once-weekly somapacitan in growth hormone deficiency: 4-year efficacy and safety results from REAL 3, a randomized controlled phase 2 trial. 2022. P1001 presented at the Endocrine Society Annual Meeting (ENDO) 2022, Atlanta, GA, USA, June 11-14, 2022.
4. Sävendahl L, Battelino T, Rasmussen M, et al. Once-weekly somapacitan versus daily growth hormone in growth hormone deficiency: 3-year efficacy and safety results from REAL 3, a randomised controlled phase 2 trial. FC9.3. *Hormone Research in Paediatrics*. 2021;82:s57-58.
5. Data on File at Novo Nordisk Inc. Plainsboro, NJ. NN8640-4172 (REAL 3; Up to 208 weeks), February 2022.
6. Savendahl L, Battelino T, Rasmussen MH, et al. Effective GH replacement with once-weekly somapacitan vs daily GH in children with GHD: 3-year results from REAL 3. *J Clin Endocrinol Metab*. 2021

Medical Information Response

Sogroya® (somapacitan-beco) injection vs once-daily growth hormone (GH) in Pediatric Growth Hormone Deficiency (GHD) (REAL 3)

This letter contains information on the use of Sogroya that is not currently an approved indication. Sogroya® is a once-weekly human growth hormone analog indicated for replacement of endogenous GH in adults with GHD.[1]

Study Design

REAL 3 is a phase 2, randomized, multinational, active-controlled, open-label, double-blinded (Sogroya® doses), dose-finding trial investigating efficacy and safety of once-weekly Sogroya® compared to once daily Norditropin® FlexPro® (somatropin) injection. Children were eligible if they were GH treatment-naïve, prepubertal children with a confirmed diagnosis of GHD within 12 months before screening, Tanner stage 1 for boys and girls, and height ≤2 standard deviation score (SDS) below the mean (corresponding to below 3rd percentile) for age and gender according to Centers for Disease Control and Prevention (CDC) growth chart for ages 2 to 20 years.[2] Baseline characteristics are described in **Table 1**.

Fifty-nine eligible children were randomized 1:1:1:1 to Sogroya® 0.04 mg/kg/week, 0.08 mg/kg/week, 0.16 mg/kg/week, and Norditropin® 0.034 mg/kg/day during the 26-week main and 26-week extension phases. After the initial 52 weeks, patients were allocated 3:1 with all patients previously in Sogroya® treatment groups switched to Sogroya® 0.16 mg/kg/week and those previously in the Norditropin® treatment group continued treatment with 0.034 mg/kg/day for the 104-week safety extension phase (**Figure 1**).[2] After 3 years, all patients entering the long-term 208 week safety extension phase continued or were switched to Sogroya® 0.16 mg/kg/wk; those previously on Sogroya® (N=39, Sogroya®/Sogroya®) were compared to those previously on Norditropin® (N=11, Norditropin®/Sogroya®).[2,3]

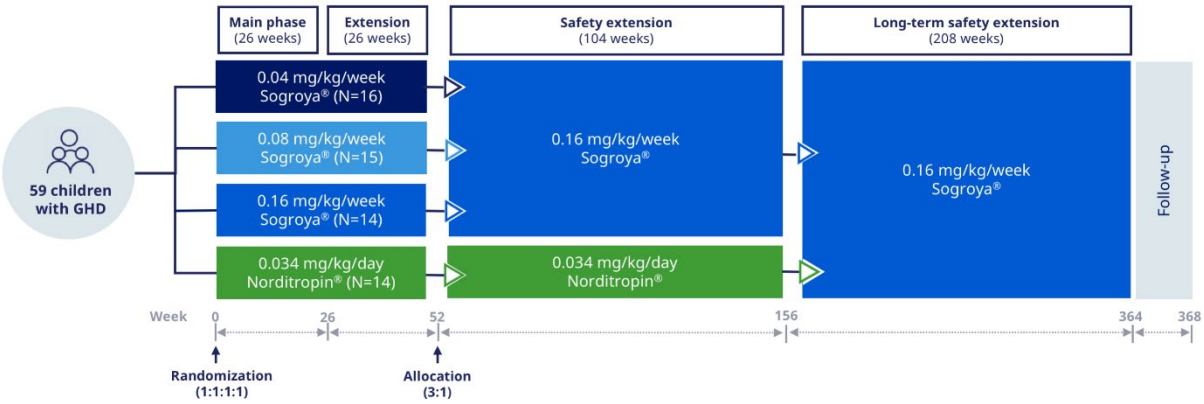


Figure 1. Study Design
Adapted from Savendahl et al.[2]
Abbreviation: GHD: growth hormone deficiency

Table 1: Baseline characteristics[a]

Treatment groups[b]	Sogroya® 0.04 mg/kg/week N=14	Sogroya® 0.08 mg/kg/week N=15	Sogroya® 0.16 mg/kg/week N=14	Norditropin® 0.034 mg/kg/day N=14
Age, years	5.8 (1.8)	5.9 (1.8)	6.1 (2.3)	6.0 (2.0)
Weight, kg	14.2 (4.22)	14.0 (3.54)	14.9 (5.23)	15.5 (5.03)
Height SDS	−4.1 (1.9)	−3.5 (1.5)	−3.8 (2.0)	−3.4 (1.1)
HV SDS	−2.9 (1.9)	−1.8 (1.7)	−2.9 (1.8)	−3.1 (2.1)
GH peak, mcg/L	2.9 (2.2)	3.6 (2.1)	4.1 (2.4)	4.0 (2.0)
IGF-1 SDS	−2.5 (1.0)	−2.5 (0.8)	−2.0 (1.0)	−2.1 (0.7)

a. Mean values (standard deviation), unless otherwise indicated
b. Please note these are treatment groups at baseline; treatment changed at weeks 52 and 156, per study design
Abbreviations: n: number of patients; SDS: standard deviation score; HV: height volume; GH: growth hormone; IGF-1: insulin-like growth factor-1

REAL 3 Results

Efficacy and Safety from 26-week main and 26-week extension phase[2]

The primary endpoint was height velocity (HV) at 26 weeks. The HV difference at week 26 was not statistically significant between Norditropin® 0.034 mg/kg/day and Sogroya® 0.08 or 0.16 mg/kg/week; however, HV was significantly greater with Norditropin® 0.034 mg/kg/day vs Sogroya® 0.04 mg/kg/week (**Figure 2**). Supportive secondary efficacy endpoints included changes from baseline to end of week 26 and week 52 in height SDS, HV SDS, and insulin-like growth factor 1 (IGF-1) SDS (**Table 2**).

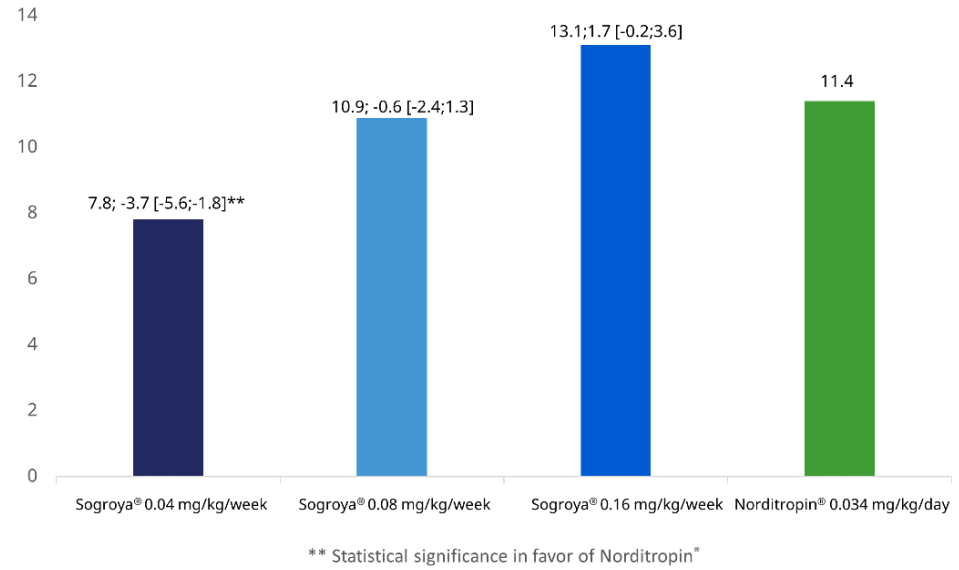


Figure 2. Mean HV (cm/year) at 26 Weeks[2]
Reported as HV (cm/year); Estimated Treatment Difference (ETD) [95% Confidence Interval]
Results in the figure are estimated means. ETD for Sogroya® in comparison with Norditropin®

Sogroya® was well-tolerated at all dose levels up to 52 weeks, and adverse events (AEs) were mild to moderate. The most common AEs occurring in 10% or more of patients in any group were nasopharyngitis, anemia, tonsilitis, constipation, diarrhea, influenza, pyrexia, rhinitis, upper respiratory tract infection, urticaria, head injury, lipoatrophy, cough, and hematology test abnormal. One child treated with Sogroya® 0.04 mg/kg/week experienced two injection-site reactions: injection-site hematoma and lipoatrophy. There were no neutralizing anti-GH antibodies or anti-somapacitan-beco antibodies detected. Non-neutralizing GH (n=1) and anti-somapacitan-beco antibodies (n=6) were observed, but these did not appear to have an affect on pharmacokinetic/pharmacodynamic (PK/PD) profiles or annualized HV.

Table 2. Supportive Secondary Efficacy Endpoints at Week 26 and Week 52[2]

Week (Wk)	Sogroya® 0.04 mg/kg/week N=14	Sogroya® 0.08 mg/kg/week N=15	Sogroya® 0.16 mg/kg/week N=14	Norditropin® 0.034 mg/kg/day N=14
Mean Change in Height SDS; ETD (95%CI)[a]				
Wk 26[b]	0.27; -0.44 (-0.66;-0.22)**	0.63; -0.08 (-0.30;0.14)	0.87; 0.16 (-0.06;0.38)	0.71
Wk 52[c]	0.49; -0.58 (-0.88;-0.28)**	0.98; -0.10 (-0.39;0.20)	1.42; 0.35 (0.05;0.65)*	1.07
Mean Change in HV SDS; ETD (95% CI)[a]				
Wk 26[b]	4.59; -3.65 (-6.23;-1.07)*	8.49; 0.25 (-2.42;2.93)	9.85; 1.61 (-0.97;4.19)	8.23
Wk 52[c]	4.39; -2.34 (-4.01;-0.67)*	7.29; 0.55 (-1.18;2.29)	8.38; 1.64 (-0.02;3.31)	6.73
Mean Change in IGF-1 SDS; ETD (95%CI)[a]				
Wk 26[b]	1.07; −0.99 (−1.76;−0.22)**	2.01; –0.10 (–0.88;0.69)	3.28; 1.13 (0.38; 1.89)*	2.11
Wk 52[c]	0.96; −0.85 (−1.78;−0.08)	1.87; –0.05 (–0.86;0.97)	3.37; 1.56 (0.66; 2.46)*	1.81

a. Week 26 and Week 52 results presented in the table are estimated means.
b. Change from baseline after 26 weeks of treatment
c. Change from baseline after 52 weeks of treatment
* Denotes statistical significance in favor of Sogroya®; ** Denotes statistical significance in favor of Norditropin®
Abbreviations: Wk: week; SDS: standard deviation score; ETD: estimated treatment difference; HV: height velocity; IGF-1: insulin-like growth factor 1

3-Year Efficacy and Safety (156-weeks total treatment)[4]

Height-based outcomes (HV, changes in HV SDS, height SDS) and changes in IGF-1 SDS are reported in **Table 3.** Mean IGF-1 SDS values for both Sogroya® and Norditropin® treatment groups reached within normal range. IGF-1 SDS values were occasionally >2 in a total of 17 children treated with Sogroya® and 4 children treated with Norditropin®.

No new significant safety issues were identified. Two SAEs (generalized edema and vomiting) in one child receiving Sogroya® 0.16/0.16 mg/kg/week were evaluated by the investigators and deemed to be likely related to trial product. Four children (Sogroya®, n=3; Norditropin®, n=1) experienced six mild injection site related AEs after the first year. Over the 3-year trial period, low titer non-neutralizing antibodies were observed in 10 children treated with Sogroya®. These antibodies did not appear to affect the PK or PD profiles for Sogroya® or annualized HV.

4-Year Efficacy and Safety (208-weeks total treatment)[3,5]

HV between groups at year 4 was similar, when compared with year 3. Mean change in HV SDS and height SDS, as well as mean IGF-1 SDS values at year 4 are reported in **Table 4**.

Eighty-four AEs were reported in 20 patients (51.3%) in the Sogroya®/Sogroya® group from weeks 0 to 208 and 12 AEs were reported in 8 patients (72.7%) in the Norditropin®/Sogroya® group from weeks 156 to 208.[5] Reported AEs were considered mild (89%) or moderate (10%) with 91% considered unlikely related to treatment with growth hormone.[5] There were no serious AEs reported in year 4; in the Sogroya®/Sogroya® group, 1 severe AE (elbow fracture surgery) was reported. One patient in the Sogroya®/Sogroya® group experienced 5 injection site reactions; none were reported in the Norditropin®/Sogroya® group. Ten patients (26%) in the Sogroya®/Sogroya® group and 1 patient (10%) in the Norditropin®/Sogroya® group developed low titer, non-neutralizing antibodies.

Table 3. 3-Year (156-Weeks Total Treatment) Efficacy and Safety[6,a]

	Sogroya® 0.04/0.16 mg/kg/week[b] (N=14)	Sogroya® 0.08/0.16 mg/kg/week[b] (N=15)	Sogroya® 0.16/0.16 mg/kg/week[b] (N=14)	Norditropin® 0.034 mg/kg/day (N=14)
Mean HV (cm/year) at Week 156b[c,4]	8.9 (1.7)	7.8 (1.5)	8.4 (1.7)[d]	7.6 (2.0)
Mean Change in HV SDS from Baseline[d]	5.4 (2.5)	4.2 (2.8)	5.3 (3.0)	5.3 (3.9)
Mean Change in Height SDS from Baseline[d]	2.4 (1.0)	2.4 (1.0)	2.7 (1.4)	2.1 (0.9)
Mean Change in IGF-1 SDS from Baseline[d]	3.3 (1.0)	3.5 (1.4)	3.7 (1.3)	3.4 (1.6)

a. Analysis conducted using full analysis set (FAS)
b. The Sogroya® treatment groups are referred as 0.04/0.16 mg/kg/week, 0.08/0.16 mg/kg/week, and 0.16/0.16 mg/kg/week to represent the Sogroya® dose patients were treated with during the initial 52 weeks.
c. Data presented as observed mean
d. Based on a post-hoc analysis, the estimated treatment difference in HV between 0.16/0.16 mg/kg/week Sogroya® group and 0.034 mg/kg/day Norditropin® group was 0.8 cm/year (95% CI: -0.4;2.1).
e. Data presented as mean (SD)
Abbreviations: HV: height velocity; IGF-1: insulin-like growth factor 1; SD: standard deviation; SDS: standard deviation score

Table 4. 4-Year (208-Weeks Total Treatment) Efficacy and Safety[3,5,a]

	Sogroya® pooled/0.16 mg/kg/week (N=39)	Norditropin®/0.034 mg/kg/day Sogroya®/0.16 mg/kg/week (N=11)
Mean HV (cm/year) at Week 208[b.c]	7.4 (1.6)	6.6 (1.6)
Mean Change in HV SDS from Baseline[c]	4.0 (2.9)	4.1 (3.2)
Mean Change in Height SDS from Baseline[c]	2.9 (1.3)	2.3 (1.0)
Mean IGF-1 SDS[c]	1.3 (1.2)	1.0 (1.6)

a. All data are observed data and presented as descriptive statistics
b. HV at year 4 is based on height measurements at year 4
c. Data presented as mean (SD)
Abbreviations: HV: height velocity; IGF-1: insulin-like growth factor 1; SD: standard deviation; SDS: standard deviation score

Additional Resources

Please refer to the cited publications and congress materials for additional information on efficacy and safety for the 26-week main, 26-week, 156-week, and 208-week extension phases.

References

1. Sogroya® Prescribing Information. Plainsboro, NJ: Novo Nordisk Inc.
2. Savendahl L, Battelino T, Brod M, et al. Once-Weekly Somapacitan vs Daily GH in Children With GH Deficiency: Results From a Randomized Phase 2 Trial. *J Clin Endocrinol Metab.* 2020;105(4) Link to Access the Full Text
3. Savendahl L, Battelino T, Rasmussen M, et al. Once-weekly somapacitan in growth hormone deficiency: 4-year efficacy and safety results from REAL 3, a randomized controlled phase 2 trial. 2022. P1001 presented at the Endocrine Society Annual Meeting (ENDO) 2022, Atlanta, GA, USA, June 11-14, 2022.
4. Sävendahl L, Battelino T, Rasmussen M, et al. Once-weekly somapacitan versus daily growth hormone in growth hormone deficiency: 3-year efficacy and safety results from REAL 3, a randomised controlled phase 2 trial. FC9.3. *Hormone Research in Paediatrics.* 2021;82:s57-58.
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