REAL 1
Phase 3 Treatment-naïve Adults with Growth Hormone Deficiency (GHD)

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

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 1 was the pivotal phase 3, randomized, parallel-group, placebo-controlled (double-blind) and active-controlled (open-label) trial in treatment naïve patients with AGHD.

Study Design

The study included a 34-week main phase (open-label only with respect to once-daily Norditropin® FlexPro® (somatropin) injection) and a 52-week extension phase (open-label).[2] Patients were randomized 2:1:2 to treatment with once-weekly Sogroya®, once-weekly placebo, or once-daily Norditropin® (**Figure 1**).[2]

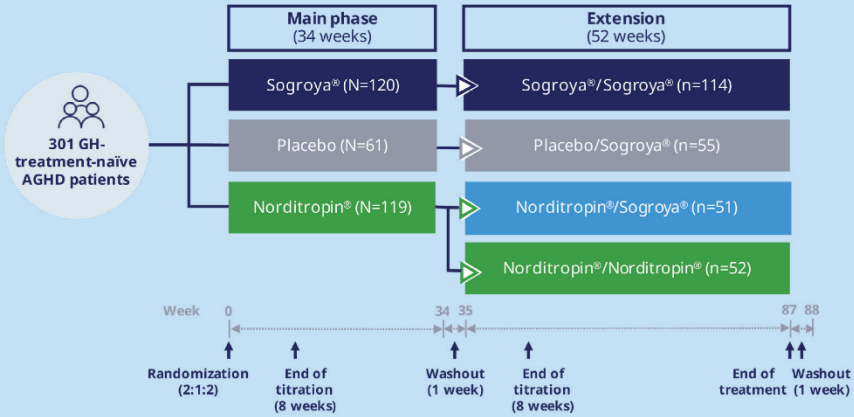
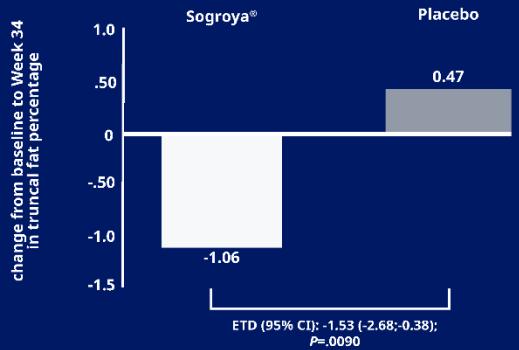


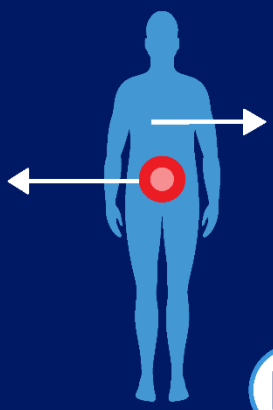
Figure 1. Trial Design
Numbers in the treatment boxes show patients exposed to treatment. One patient in the Sogroya® group did not receive any treatment and was not included in any analyses.
Adapted from Johannsson et al.[2]
Abbreviations: GH: growth hormone; AGHD: adult-growth hormone deficiency

Efficacy

Primary Endpoint

Sogroya® was superior to placebo for the primary endpoint of change from baseline to Week 34 in truncal fat percentage:[2]





Supportive Secondary Endpoints

At Week 34, Sogroya® was associated with desired changes from baseline for the following body composition parameters with a statistically significant difference compared to placebo (**Table 1**):[2,3]

- *Visceral adipose tissue*
- *Android fat mass*
- *Lean body mass*
- *Truncal lean body mass*
- *Appendicular skeletal muscle mass*

The desired changes in overall body composition were observed and maintained after 86 weeks of treatment with both once-weekly Sogroya® and Norditropin®.[2]

Safety

- Incidence of adverse events (AEs) in patients treated with once-weekly Sogroya® were similar to those with once-weekly placebo or once-daily Norditropin®. Majority of the AEs were of mild or moderate severity and considered unlikely related to study drugs by the investigator in both main and extension phase.
- All injection-site reactions were mild or moderate in severity. For additional safety results, please see below.[2-4]
- No anti-somapacitan-beco antibodies were detected.[2]

References: 1. Sogroya® Prescribing Information. Plainsboro, NJ: Novo Nordisk Inc. **2.** Johannsson G, Gordon MB, Højby Rasmussen M, et al. Once-weekly Somapacitan is Effective and Well Tolerated in Adults with GH Deficiency: A Randomized Phase 3 Trial. J Clin Endocrinol Metab. 2020;105(4) Link to Access the Full Text. **3.** Data on File at Novo Nordisk Inc. Plainsboro, NJ. NN8640-4054 (REAL 1), November 2017. **4.** Data On File at Novo Nordisk Inc. Plainsboro, NJ. NN8640-4054 (REAL 1 Ext.), December 2018.

Medical Information Response

Sogroya® (somapacitan-beco) injection – Treatment-naïve Adults with GHD – REAL 1

Summary

- REAL 1 was the pivotal phase 3, randomized, parallel-group, placebo-controlled (double-blind) and active-controlled (open-label) trial in treatment naïve patients with AGHD, which included a 34-week main phase (open-label only with respect to once-daily Norditropin® FlexPro® (somatropin) injection) and a 52-week extension phase (open-label).[2]
    - Patients were randomized 2:1:2 to treatment with once-weekly Sogroya®, once-weekly placebo, or once-daily Norditropin® (**Figure 1**).[2]

Primary Endpoint

- Sogroya® was superior to placebo for the primary endpoint of change from baseline to Week 34 in truncal fat percentage: Sogroya® –1.06% and placebo 0.47% (estimated treatment difference [ETD] –1.53% [95% CI: –2.68 to –0.38]; *P*=.0090) (**Table 1**).[2]

Supportive Secondary Efficacy Endpoints

- At Week 34, Sogroya® was associated with desired changes from baseline for the following body composition parameters with a statistically significant difference compared to placebo: visceral adipose tissue, android fat mass, lean body mass, truncal lean body mass, and appendicular skeletal muscle mass.[2,3]
- The desired changes in overall body composition were observed and maintained after 86 weeks of treatment with both once-weekly Sogroya® and Norditropin®.[2]

Supportive Secondary Safety Endpoints

- Incidence of adverse events (AEs) in patients treated with once-weekly Sogroya® were similar to those with once-weekly placebo or once-daily Norditropin®. Majority of the AEs were of mild or moderate severity and considered unlikely related to study drugs by the investigator in both main and extension phase. All injection-site reactions were mild or moderate in severity. For additional safety results, please see below.[2,4]
- No anti-somapacitan-beco antibodies were detected.[2]

REAL 1

REAL 1 was the pivotal phase 3, randomized, parallel-group, placebo-controlled (double-blind) and active-controlled (open-label) trial in treatment naïve patients with AGHD, which included a 34-week main phase and a 52-week extension phase. The main phase was double-blind with respect to once-weekly Sogroya® and once-weekly placebo, and open-label only with respect to once-daily Norditropin®. The extension phase was open-label. Patients were randomized 2:1:2 to treatment with once-weekly Sogroya®, once-weekly placebo, or once-daily Norditropin® (**Figure 1**).[2]

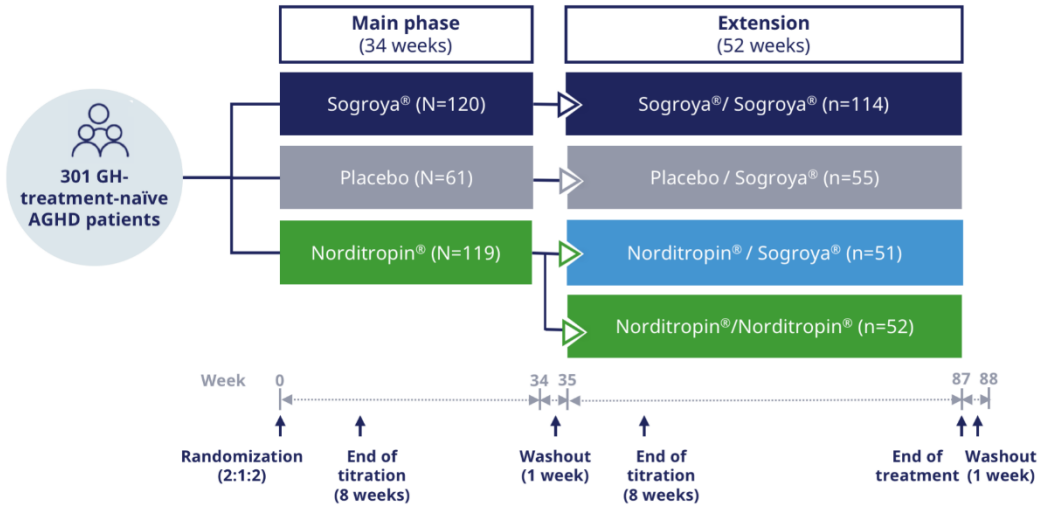


Figure 1. Trial Design

Numbers in the treatment boxes show patients exposed to treatment. One patient in the Sogroya® group did not receive any treatment and was not included in any analyses.

Adapted from Johannsson et al.[2]

Abbreviation: GH: growth hormone; AGHD: adult-growth hormone deficiency

Efficacy

Sogroya® was superior to placebo for the primary endpoint of change from baseline to week 34 in truncal fat percentage: Sogroya® –1.06% and placebo 0.47% (ETD Sogroya®-placebo, –1.53% [95% CI: –2.68 to –0.38]; *P*=.0090) (**Table 1**).[2]

- At Week 34, Sogroya® was associated with desired changes from baseline for the following body composition parameters with a statistically significant difference compared to placebo: visceral adipose tissue, android fat mass, lean body mass, truncal lean body mass, and appendicular skeletal muscle mass (**Table 1**).[2,3]
- At Week 34, mean serum insulin-like growth factor 1 (IGF-1)-SDS increased markedly for both Sogroya® and Norditropin® to similar values (ETD Sogroya®-Norditropin®, 0.02 [95% CI: -0.23;0.28]), but no increase was seen with placebo (ETD Sogroya®-placebo, 2.40 [95% CI: 2.09, 2.72]). A similar pattern was observed for serum insulin-like growth factor binding protein 3 (IGFBP-3) SDS.[2]

In the 52-week extension phase of REAL 1, patients receiving Sogroya® continued treatment, while those receiving placebo were switched to Sogroya®. Those that received Norditropin® in the main phase were randomized 1:1 to continue receiving Norditropin® or receive Sogroya®.[2]

- The desired changes in overall body composition were observed and maintained after 86 weeks of treatment with both once-weekly Sogroya® and Norditropin® (**Table 1**). No statistically significant difference was observed between the active treatment groups.[2]
- No treatment differences in change from baseline to 86 weeks in IGF-1 SDS and IGFBP-3 SDS were observed between Sogroya® and Norditropin®. Transient elevations of IGF-1 SDS above +2 were observed in the fixed-dose treatment period of both the main and extension phases of the trial.[2]

Safety

Incidence of AEs in patients treated with once-weekly Sogroya® were similar to those with once-weekly placebo or once-daily Norditropin®. Majority of the adverse events (AEs) were of mild or moderate severity and considered unlikely related to study drugs by the investigator in both main and extension phase.[2,4]

- All injection-site reactions were mild or moderate in severity.[2]
- In the main phase, the most frequently reported AEs (≥5% of patients) were upper respiratory tract infections (URTI), headache, back pain, and arthralgia across treatment groups.[4]
- The most frequently reported AEs with start date in the extension phase were nasopharyngitis, headache, gastroenteritis, and URTIs.[2]
- In both phases, only minor changes in mean plasma glucose or HbA_{1C} were observed from baseline to end of trial in any treatment arm. No new case of diabetes mellitus amongst patients treated with Sogroya®.[2]
- No anti-somapacitan-beco antibodies or neutralizing anti-GH antibodies were detected. At the 4-week visit only, transient non-neutralizing anti-GH antibodies were detected in one patient from the Norditropin® group.[2]

Additional safety and efficacy results are provided below in **Table 1.**

Table 1. Overview of REAL 1 Clinical Trial[2-4]

STUDY DESIGN							
Methods	Phase 3, 34-week, randomized, multicenter, placebo-controlled (double blind) and active-controlled (open-label), main phase with once-weekly (QW) Sogroya®, placebo, & once-daily Norditropin®; 52-week ext. phase, active-controlled (open label) with QW Sogroya® vs. once-daily Norditropin®						
Patient population	Adults with GHD who were naïve to GH treatment or were not recently taking GH (≥180 days prior to randomization)						
Enrolled (N)	300[a] – main phase; 272-ext. phase						
Duration (weeks)	34 main phase + 52 ext. phase						
	REAL 1 Main Phase			**REAL 1 Ext. Phase**			
Treatment groups	**Sogroya® (N=120)**	**Placebo (N=61)**	**Norditropin® (N=119)**	**Placebo/ Sogroya® (N=61)**	**Sogroya®/ Sogroya® (N=120)**	**Norditropin®/ Norditropin® (N=52)**	**Norditropin®/ Sogroya® (N=51)**
Mean dose (SD) in fixed-dose treatment period	2.52 (1.44) mg/wk	2.18 (0.72) mg/wk	0.33 (0.19) mg/day	2.56 (1.35) mg/wk	2.33 (1.27) mg/wk	0.27 (0.15) mg/day	2.61 (1.31) mg/wk
EFFICACY	**ETD[b] (95% CI): Sogroya®-Placebo**	**ETD[b] (95% CI): Sogroya®-Norditropin®**	**ETD[c] (95% CI): Sogroya®-Norditropin®**				
Truncal fat %[d]	-1.53 (-2.68; -0.38) *P*=.0090	+1.17 (0.23; 2.11)[e]	1.15 (-0.10; 2.40) *P*=.0715				
Percentage change in visceral adipose tissue[f]	-15.7 (-23.4; -8.0) *P*<.0001	-1.7 (-8.0; 4.5) *P*=.5817	2.16 (-9.68; 13.990) *P*=.7197				
Total fat mass, kg	-0.27 (-1.20; 0.66) *P*=.5746	+0.72 (-0.04; 1.49) *P*=.0629	0.98 (-0.25; 2.21) *P*=.1176				
Truncal fat mass, kg	-0.50 (-1.05; -0.06) *P*=.0786	+0.41 (-0.04; 0.86) *P*=.0749	0.61 (-0.09; 1.30) *P*=.0876				
Gynoid fat mass, kg	+0.02 (-0.14; 0.17) *P*=.8511	+0.15 (0.02; 0.28) *P*=.0276	0.14 (-0.07; 0.35) *P*=.1839				
Android fat mass, kg	-0.12 (-0.22 ;-0.01) *P*=.0326	+0.07 (-0.01; 0.16) *P*=.0923	0.10 (-0.04; 0.24) *P*=.1679				
Total lean body mass, kg	1.14 (0.46; 1.83) *P*=.0011	0.05 (-0.51; 0.61) *P*=.8653	0.43 (-0.40; 1.27) *P*=.3092				
Truncal lean body mass, kg	0.45 (0.03; 0.88) *P*=.0380	-0.04 (-0.39; 0.31) *P*=.8295	0.27 (-0.18; 0.72) *P*=.2421				
Appendicular skeletal muscle mass, kg	0.68 (0.34; 1.02) *P*=.0001	0.10 (-0.18; 0.37) *P*=.4996	0.10 (-0.36; 0.56) *P*=.6778				
SAFETY	**Main Phase + Ext. Phase**						
Treatment groups: main/extension	**Placebo/Sogroya® N=61**	**Sogroya®/Sogroya® N=120**	**Norditropin®/ Norditropin® N=52**	**Norditropin®/ Sogroya® N=51**	**Norditropin®/-- N=16**		
AEs (including injection site reactions), n (%)	49 (80.3)	101 (84.2)	46 (88.5)	46 (90.2)	12 (75.0)		
Injection site reactions, n (%)	6 (9.8)	8 (6.7)	5 (9.6)	6 (11.8)	0		
Serious AEs, n (%)	8 (13.1)	13 (10.8)	5 (9.6)	7 (13.7)	4 (25.0)		

a. In REAL 1, 301 patients were randomized, but one patient did not receive treatment and 300 were evaluated.
b. Adjusted values based on analysis of covariance model. ETD from baseline to week 34.
c. Adjusted data based on mixed model for repeated measurements. ETD from baseline to week 86. Subjects from treatment group Norditropin®/-- contribute to the analysis with measurements from the main trial period.
d. The primary endpoint was change in truncal fat percentage to Week 34. The remainder efficacy endpoints are supportive secondary endpoints.
e. This was not designed as a confirmatory test and no hierarchical test strategy was constructed; therefore, no p-value was calculated.
f. *Post hoc*-defined endpoint.

Please see **Appendix A** for starting doses and dose titration algorithm.

Abbreviations: QW: once weekly; ext: extension; GHD: growth hormone deficiency; AGHD: adult-growth hormone deficiency; ETD: estimated treatment difference; AE: adverse event; n=number of subjects.

Appendix A: Starting Doses Dose Titration for REAL 1

Starting Sogroya® doses in REAL 1 for patients aged 23 to 60 years, aged >60 years, and females on oral estrogen were 1.5, 1.0, and 2.0 mg/week, respectively. Corresponding Norditropin® doses were 0.2, 0.1, and 0.3 mg/day, respectively.[2]

Dose titrations based on IGF-1 SDS for REAL 1 are described below in **Table 2**. Timing of blood sampling for IGF-1 SDS based dose titrations was 1 week and 3 days after last dose adjustment.[2]

Table 2. Dose Titration Algorithm

REAL 1 Main and Extension Phase[2]				
IGF-1 SDS Interval	**Sogroya® or Placebo Increment/Reduction of Weekly Dose**		**Norditropin® Increment/Reduction of Daily Dose**	
	Δ IGF-1 SDS > 1	**Δ IGF-1 SDS ≤ 1**	**Δ IGF-1 SDS > 1**	**Δ IGF-1 SDS ≤ 1**
IGF-1 SDS > 3	-1 mg		-0.1 mg/day	
1.75 < IGF-1 SDS ≤ 3	-0.5 mg		-0.05 mg/day	
-0.5 < IGF-1 SDS ≤ 1.75	-	+0.5 mg	-	+0.05 mg/day
-2 < IGF-1 SDS ≤ -0.5	+0.5 mg	+0.5 mg	+0.05 mg/day	+0.05 mg/day
IGF-1 SDS ≤ -2	+1 mg	+1.5 mg	+0.1 mg/day	+0.2 mg/day

Titration period in REAL 1 (for both main and extension phase) consisted of 8 weeks. After titration, fixed dose regimens were given for individuals, but dose reduction was allowed based on investigator's discretion for safety concerns.[2,4]
Abbreviation: IGF-1: Insulin-like growth factor 1; SDS: standard deviation score

References

1. Sogroya® Prescribing Information. Plainsboro, NJ: Novo Nordisk Inc.
2. Johannsson G, Gordon MB, Hojby Rasmussen M, et al. Once-weekly Somapacitan is Effective and Well Tolerated in Adults with GH Deficiency: A Randomized Phase 3 Trial. *J Clin Endocrinol Metab.* 2020;105(4) Link to Access the Full Text
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