Albumin Interactions with Sogroya® (somapacitan-beco) injection

Sogroya® is extensively bound (>99%) to plasma proteins.[1]

Since only a small portion of serum albumin is bound at any point in time, **it is considered unlikely that the albumin-binding capability of Sogroya® can interfere with binding to albumin for other albumin-binding medications.[2]**

- Albumin is present [in the circulation] at 35-50 mg/mL whereas C_{max} of Sogroya after first or fourth dose was between 14 and 142 ng/mL
- There is an excess of albumin binding sites available to each drug molecule (by approx 400,000-fold)

Certain medical conditions, such as hepatic or renal impairment, may be associated with hypoalbuminemia.[3,4] It is not anticipated that Sogroya® effects will be materially altered by any changes in plasma albumin levels that are likely to occur in clinical practice.[1,5]

Hepatic Impairment

Based on a phase 1 study in which adult patients with mild or moderate hepatic impairment received Sogroya® at 0.08 mg/kg at steady state, subjects in the moderate hepatic impairment group had a greater exposure to Sogroya® as compared to the mild hepatic impairment group and normal hepatic function group; however, the moderate hepatic impairment group exhibited lower insulin-like growth factor-1 (IGF-1) level than the other two groups.

Dosage Adjustments[1]

Population		Initiation Dose	Titration
Mild Hepatic Impairment	Adult Patients	No dosage adjustments recommended	
	Pediatric Patients		
Moderate Hepatic Impairment	Adult Patients	1 mg once weekly	Use smaller dose increment increases when titrating dosage. Maximum recommended dosage is 4 mg once weekly
	Pediatric Patients	Use is not recommended	
Severe Hepatic Impairment	Adult Patients	Use is not recommended	
	Pediatric Patients		

Renal Impairment

Based on a phase 1 study in adult patients with severe renal impairment and patients requiring hemodialysis, a Sogroya® dose of 0.08 mg/kg at steady state resulted in higher exposures; however, **there are no specific dose adjustments recommended for patients with renal impairment since Sogroya® is individually dose titrated.**[1,6]

Drug-Drug Interactions

Protein binding studies evaluating the concomitant administration of Sogroya® with other protein bound drugs have not been conducted. There is a large excess of albumin in human serum compared to Sogroya® that displacement drug-drug interaction on albumin is considered highly unlikely. **Table 1** provides an overview of clinically significant drug interactions with Sogroya®.[7]

Medical Information Response

Albumin Interactions with Sogroya® (somapacitan-beco) injection

Summary

- Sogroya® is extensively bound (>99%) to plasma proteins.[1]
- Since only a small portion of serum albumin is bound at any point in time, it is considered unlikely that the albumin-binding capability of Sogroya® can interfere with binding to albumin for other albumin-binding medications.[2]

Hypoalbuminemia

- Certain medical conditions, such as hepatic or renal impairment, may be associated with hypoalbuminemia.[3,4]
- It is not anticipated that Sogroya® effects will be materially altered by any changes in plasma albumin levels that are likely to occur in clinical practice.[1,5]

Hepatic impairment

- Based on a phase 1 study in which adult patients with mild or moderate hepatic impairment received Sogroya® at 0.08 mg/kg at steady state, subjects in the moderate hepatic impairment group had a greater exposure to Sogroya® as compared to the mild hepatic impairment group and normal hepatic function group; however, the moderate hepatic impairment group exhibited lower insulin-like growth factor-1 (IGF-1) level than the other two groups.[6] See below **Table 1** for dosage adjustments in adult and pediatric patients with hepatic impairment.

Renal impairment

- Based on a phase 1 study in adult patients with severe renal impairment and patients requiring hemodialysis, a Sogroya® dose of 0.08 mg/kg at steady state resulted in higher exposures; however, there are no specific dose adjustments recommended for patients with renal impairment since Sogroya® is individually dose titrated.[1,6]

Drug-drug interactions

- Protein binding studies evaluating the concomitant administration of Sogroya® with other protein bound drugs have not been conducted. There is a large excess of albumin in human serum compared to Sogroya® that displacement drug-drug interaction on albumin is considered highly unlikely. **Table 2** provides clinically important drug interactions with Sogroya®.[7]

Albumin Binding Sites

Sogroya® is extensively bound to plasma protein (>99%) and expected to distribute in tissues with high albumin concentration such as serum/plasma.[1,8] It has been reported in published literature that changes in plasma protein binding rarely affect the clinical exposure to a drug, because there is typically a vast excess of plasma albumin binding sites (approximately 400,000-fold) available to each drug molecule.[9,10] It is considered unlikely that the albumin-binding capability of Sogroya® can interfere with binding to albumin for other albumin-binding medications. This is because albumin is present at 35-50 mg/mL, where as the C_{max} of Sogroya® in clinical trial after the first or fourth dose was between 14 and 142 ng/mL. At the lowest normal albumin concentration and the highest Sogroya® concentration, the albumin to

Sogroya® molar ratio is approximately 88,000, suggesting albumin occupancy of approximately 0.001%. Since a small portion of serum albumin is bound at any point in time, displacement of albumin-binding moieties, including other drugs, is unlikely to be of clinical relevance.[2]

Additional information on specific binding sites of Sogroya® on human serum albumin and binding affinity for those sites is cited for your reference.[11]

Hypoalbuminemia

Certain medical conditions, such as hepatic or renal impairment, may be associated with hypoalbuminemia.[3,4] It is not anticipated that Sogroya® effects will be materially altered by any changes in plasma albumin levels that are likely to occur in clinical practice.

Hepatic Impairment

In a phase 1, open-label, parallel-group study, Sogroya® 0.08 mg/kg dosing at steady state was evaluated in adult subjects with mild (Child-Pugh Grade A) or moderate (Child-Pugh Grade B) hepatic impairment. The study evaluated pharmacokinetics, pharmacodynamics, safety and tolerability of multiple Sogroya® doses in subjects with hepatic impairment (n=18) compared to subjects with normal hepatic function (n=16). Of the eighteen subjects with hepatic impairment, nine subjects had mild and the other nine subjects had moderate hepatic impairment. All subjects had albumin values within normal range, except for two subjects in the moderate hepatic impairment group. These two subjects had albumin values of 34.8 g/L and 33.8 g/L during visit 1 (screening). Subjects in the moderate hepatic impairment group had a greater exposure to Sogroya® as compared to the mild hepatic impairment group and normal hepatic function group; however, the moderate hepatic impairment group exhibited lower IGF-1 level than the other two groups. In the mild hepatic impairment group, subjects also had a lower IGF-1 level compared with the normal hepatic function group. Subjects in both mild and moderate hepatic impairment group had lower levels of insulin-like growth factor binding protein-3 (IGFBP-3) compared to subjects in the normal hepatic function group. GH resistance is associated with hepatic impairment, which may explain the low response from IGF-1 and IGFBP-3. Since albumin values in this study were mostly within normal range, and Sogroya® occupancy of albumin is very low, it is unlikely that the cause of increased Sogroya® exposure was due to decreased albumin concentrations. Majority of the adverse events (AEs) were mild and occurring in five subjects (n=1 in normal hepatic function group; n=2 each in mild and moderate hepatic function group).[1,5,6,12]

Based on the Prescribing Information, the following in **Table 1** is recommended in adult and pediatric patients with hepatic impairment.

Table 1. Dosage Adjustments in Patients with Hepatic Impairment[1]

Population		Initiation Dose	Titration
Mild Hepatic Impairment	**Adult Patients**	No dosage adjustments recommended	
	Pediatric Patients		
Moderate Hepatic Impairment	**Adult Patients**	1 mg once weekly	Use smaller dose increment increases when titrating dosage. Maximum recommended dosage is 4 mg once weekly
	Pediatric Patients	Use is not recommended	
Severe Hepatic Impairment	**Adult Patients**	Use is not recommended	
	Pediatric Patients		

Renal Impairment

Pharmacokinetic, pharmacodynamic, and safety of Sogroya® was assessed in a phase 1 study in adult subjects with normal renal function (n=15); mild (n=8), moderate (n=8), or severe renal impairment (n=5); and in subjects requiring hemodialysis (n=8). Patients received a Sogroya® dose of 0.08 mg/kg. The degree of renal impairment resulted in higher exposure to Sogroya® at steady state; however, there are no specific dose adjustments recommended for patients with renal impairment since Sogroya® is individually dose-titrated. Most AEs observed in the study were mild in severity and observed in the severe renal impairment group.[1,6,13]

Drug-Drug Interactions

Protein binding studies evaluating the concomitant administration of Sogroya® with other protein bound drugs have not been conducted. The molar concentration of albumin in human serum is >100,000 times higher than that of Sogroya® at steady state. With this large excess of albumin compared to Sogroya®, a displacement drug-drug interaction on albumin is considered highly unlikely. See **Table 2** for an overview of clinically significant drug interactions with Sogroya®.[7]

Table 2: Clinically Important Drug Interactions with Sogroya®[1]

Replacement Glucocorticoid Treatment	
Drugs:	Microsomal enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1) is required for conversion of cortisone to its active metabolite, cortisol, in hepatic and adipose tissue. Growth hormone (GH) inhibits 11βHSD-1. Consequently, individuals with untreated GH deficiency have relative increases in 11βHSD-1 and serum cortisol. Initiation of Sogroya® may result in inhibition of 11βHSD-1 and reduced serum cortisol concentrations.
Intervention:	Patients treated with glucocorticoid replacement for hypoadrenalism may require an increase in their maintenance or stress doses following initiation of Sogroya®
Examples:	Cortisone acetate and prednisone may be affected more than others because conversion of these drugs to their biologically active metabolites is dependent on the activity of 11βHSD-1.
Cytochrome P450-Metabolized Drugs	
Clinical Impact:	Limited published data indicate that GH treatment increases cytochrome P450 (CP450)-mediated antipyrine clearance. Sogroya® may alter the clearance of compounds known to be metabolized by CP450 liver enzymes.
Intervention:	Careful monitoring is advisable when Sogroya® is administered in combination with drugs metabolized by CP450 liver enzymes.
Oral Estrogen	
Clinical Impact:	Oral estrogens may reduce the serum IGF-1 response to Sogroya®.
Intervention:	Patients receiving oral estrogen replacement may require higher Sogroya® dosages.
Insulin and/or Other Hypoglycemic Agents	
Clinical Impact:	Treatment with Sogroya® may decrease insulin sensitivity, particularly at higher doses.
Intervention:	Patients with diabetes mellitus may require adjustment of their doses of insulin and/or other hypoglycemic agents.

Abbreviations: 11βHSD-1: 11β-hydroxysteroid dehydrogenase type 1; GH: growth hormone; CP450: cytochrome P450; IGF-I: insulin-like growth factor I.

References

1. Sogroya® Prescribing Information. Plainsboro, NJ: Novo Nordisk Inc.
2. Rasmussen MH, Janukonyté J, Klose M, et al. Reversible Albumin-Binding GH Possesses a Potential Once-Weekly Treatment Profile in Adult Growth Hormone Deficiency. *J Clin Endocrinol Metab.* 2016;101(3):988-98. Link to Access the Full Text
3. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: Pathogenesis and Clinical Significance. *JPEN J Parenter Enteral Nutr.* 2019;43(2):181-193. Link to Access the Full Text
4. Haller C. Hypoalbuminemia in renal failure: pathogenesis and therapeutic considerations. *Kidney Blood Press Res.* 2005;28(5-6):307-10. Link to Access the Full Text
5. Data on File at Novo Nordisk Inc., Plainsboro, NJ. NN8640-4298, September 2018.
6. Damholt BB, Dombernowsky SL, Bendtsen MD, et al. Effect of Kidney or Hepatic Impairment on the Pharmacokinetics and Pharmacodynamics of Somapacitan: Two Open-Label, Parallel-Group Trials. *Clin Pharmacokinet.* 2021 Link to Access the Full Text
7. Data on File at Novo Nordisk Inc. Plainsboro, NJ. NN8640-Clinical Overview, August 2019.
8. Data on File at Novo Nordisk Inc. Plainsboro, NJ. NN8640 - Summary of Clinical Pharmacology Studies. 2019.
9. Benet LZ, Hoener BA. Changes in plasma protein binding have little clinical relevance. *Clin Pharmacol Ther.* 2002;71(3):115-21. Link to Access the Full Text
10. Kurtzhals P, Havelund S, Jonassen I, et al. Effect of fatty acids and selected drugs on the albumin binding of a long-acting, acylated insulin analogue. *J Pharm Sci.* 1997;86(12):1365-8. Link to Access the Full Text
11. Johansson E, Nielsen AD, Demuth H, et al. Identification of Binding Sites on Human Serum Albumin for Somapacitan, a Long-Acting Growth Hormone Derivative. *Biochemistry.* 2020;59(14):1410-1419. Link to Access the Full Text
12. Damholt BB, Bendtsen MD, Hollensen C, et al. Pharmacokinetics of somapacitan in individuals with hepatic impairment: an open-label, parallel group, phase 1 study [Abstract]. *Endocrine Abstracts.* 2019;63:OC13.4.
13. Damholt BB, Bisgaard C, Dombernowsky SL, et al. Pharmacokinetics of somapacitan in individuals with renal impairment: an open-label, parallel group, phase 1 study. *Endocrine Abstracts.* 2019;63:GP49.