Taiwan Food and Drug Administration

Assessment Report

Trade Name：諾和高注射劑 10 毫克/1.5 毫升
Sogroya solution for injection 10mg/1.5mL

Active Ingredient：Somapacitan

License Number：MOHW-BI 001229

Applicant：台灣諾和諾德藥品股份有限公司

Approval Date：2023/02/21

Indication：適用於成人生長激素缺乏症(AGHD)之補充療法。
For replacement therapy of adults with growth hormone deficiency (AGHD).

1. Background Information

Trade Name	諾和高注射劑 10 毫克/1.5 毫升 Sogroya solution for injection 10mg/1.5mL
Active Ingredient(s)	Somapacitan
Applicant	台灣諾和諾德藥品股份有限公司
Dosage Form & Strengths	注射液劑 6.7 mg/mL
Indication	適用於成人生長激素缺乏症(AGHD)之補充療法。 For replacement therapy of adults with growth hormone deficiency (AGHD).
Posology	詳見仿單
Pharmacological Category **ATC Code**	H01ACX07

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug Substance

The active ingredient in Sogroya, somapacitan, is a long-acting recombinant human growth hormone derivative with a single substitution in the amino acid backbone (leucine at position 101 substituted with cysteine) to which an albumin binding moiety is attached. Binding of endogenous albumin to the side chain delays elimination of somapacitan and thereby prolongs the *in vivo* half-life and duration of action. The pharmacological effects of somapacitan are like those of human growth hormone, which include regulation of somatic growth and metabolism. The mechanism of action is mediated either through binding to the growth hormone receptor or through activation of insulin-like growth factor I.

Somapacitan is produced in *Escherichia coli*. The manufacturing process is sufficiently described. The in-process control tests and limits are acceptable. The overall control strategy for somapacitan drug substance is considered adequate. The structural, physiochemical and biological characterization of somapacitan is considered sufficient. The characterization of the product variants and relevant controls introduced are considered acceptable. Removal of process related impurities has been sufficiently demonstrated. The release tests for somapacitan drug substance are acceptable. A reference standard system has been established for commercial use. The container closure system is acceptable. The data provided are sufficient to support the proposed shelf life for somapacitan drug substance.

2.1.2 Drug Product

Sogroya is a clear to slightly opalescent and colorless to slightly yellow solution for subcutaneous injection, provided in a 1.5 mL cartridge assembled in a pen-injector. The prefilled pen contains the drug product somapacitan at a concentration of 10 mg/1.5 mL.

The drug product manufacturing process is sufficiently described and in-process controls are considered adequate. The release and stability specifications for somapacitan drug product are acceptable. The extractables and leachables studies support the use of the primary container closure system. Sufficient information has been provided on the medical device. The stability data provided are sufficient to support the proposed shelf life for Sogroya of 24 months when stored at 2°C to 8°C.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Somapacitan is a long-acting recombinant human growth hormone (hGH) derivative with a single substitution in the amino acid backbone (L101C) to which an albumin-binding moiety has been attached. The non-covalent, reversible binding to endogenous albumin delays the elimination of somapacitan and thereby prolongs the *in vivo* half-life and duration of action. The surface plasmon resonance analysis indicated that the binding kinetics of somapacitan of fresh batch and end-of-shelf-life batch to growth hormone binding protein (GHBP) or human serum albumin (HSA) were similar. In the primary rat hepatocytes or human hepatoma HuH-7 cell line, somapacitan induced a dose-dependent phosphorylation of STAT5. In the *in vivo* pharmacology study, somapacitan increased body weight gain and plasma IGF-1 in the hypophysectomized rats. Somapacitan with SC or IV administration also increased plasma IGF-1 in monkeys and minipigs. The safety pharmacology studies indicated that SC administration of somapacitan did not affect CNS, cardiovascular, and respiratory systems at up to 9 mg/kg in monkeys.

2.2.2 Toxicological Studies

The pivotal toxicity studies included 2-, 13-, and 26-week repeated-dose studies in both rats and monkeys. Most findings in the toxicity studies were related to the pharmacological effects of growth hormone, e.g., increase in body weight gain and food consumption and the changes in hematology, clinical chemistry, and urinalysis. Swollen mammary glands with increasing secretory activity were attributed to the binding of growth hormone at the prolactin receptor and/or increased IGF-1 levels. The excess growth hormone produced an antagonistic effect on insulin. Dose-dependent increase of insulin, islet cell hypertrophy, and diabetes mellitus-related symptoms were observed in the high-dose (9 mg/kg SC QD) group in rats. Bilateral cataract was observed in all animals presenting diabetes. In the 13-week study, chronic progressive nephropathy was observed in rats of both sexes at 9 mg/kg and two males at 2 mg/kg. The NOAELs of the 26-week toxicity studies were 4 mg/kg SC BIW in rats and 9 mg/kg SC BIW in monkeys. The 4 mg/kg SC BIW also did not affect reproductive performance in male and female rats. Somapacitan did not exhibit significant teratogenicity in both rats and rabbits. Increased incidences of short/bent/thickened long bone and thickened ribs were observed in the high-dose (18 mg/kg SC QD) group in rats, and decreased fetal weight was

found in the groups of 3 and 9 mg/kg SC Q2D in rabbits. However, these findings are expected to resolve after birth. The dose of up to 18 mg/kg SC BIW of somapacitan did not affect the pre- and post-natal development in rats.

All the *in vitro* and *in vivo* genotoxicity studies presented negative results. No carcinogenicity study was conducted. A mammary adenocarcinoma, a sebaceous gland adenoma, and a pituitary adenoma were found separately at different doses and periods in the toxicity studies. They were not dose-dependent and considered incidental and not related to somapacitan. The carcinogenicity of somapacitan is expected to be similar to the existing GH products. The supplementary study indicated that somapacitan did not increase the proliferation ratio of hepatocytes with the most growth hormone receptors.

After comparing the exposure of the NOAEL in the nonclinical toxicity studies to the exposure of maximum clinical dose (0.12 mg/kg QW), the safety margins were 5.62 to 11.4 between rats and humans and more than 1000 between monkeys and humans.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The PK and PD properties of somapacitan following s.c. administration was characterized after a single dose or after multiple once-weekly doses of somapacitan in healthy subjects and AGHD patients. Absolute bioavailability of somapacitan has not been investigated. In AGHD patients, the median t_{max} of somapacitan ranged from 4.0 to 24 hours at doses from 0.02 to 0.12 mg/kg/week. Steady state was reached after 1−2 doses of once-weekly administrations, and the mean accumulation ratio was between 1 and 2. Somapacitan displayed approximately linear PK in the clinically relevant dose range (0.02 to 0.12 mg/kg). Somapacitan is extensively bound to plasma proteins (>99%) and is expected to be distributed like albumin. Based on population PK analyses, the estimated volume of distribution (V/F) was 14.6 L. Somapacitan was extensively metabolized before excretion of its metabolites, and no intact somapacitan was found neither in urine, which was the main excretion route (80.9%), nor in feces where 12.9% of somapacitan-related material was excreted. The terminal half-life was estimated with geometric means ranging from approximately 2 to 3 days at steady state in AGHD patients. A high inter-subject variability is observed in AGHD patients at steady state, ranging from about 62 - 102% for $AUC_{0\text{-}168h}$ and from 113 – 201% in C_{max}.

IGF-1 was measured to assess the PD properties of somapacitan. Maximum IGF-1 concentrations were observed within 2 to 4 days after dosing. A steady state IGF-1 response was reached after 1 to 2 weekly doses with limited cumulative IGF-1 response. Somapacitan induces a less than dose proportional IGF-1 response at steady state in AGHD patients.

2.3.2 Interaction Studies

A dedicated drug-drug interaction (DDI) study was not conducted. The DDI potential is expected to be similar to other marketed GH products.

2.3.3 Special Populations

The potential impact of intrinsic and extrinsic factors on the PK and PD properties of somapacitan was evaluated based on the clinical pharmacology trials and based on the modelling analyses of data from the phase 3 trials. The dose-response for somapacitan was independent of body weight. The modelling analysis showed higher exposure in elderly (≥65 years) compared to younger subjects (<65 years). Elderly subjects were, however, found to be less responsive to somapacitan, but may still require slightly lower doses to reach the IGF-I target than younger subjects. The pooled PK data showed lower somapacitan exposure ($AUC_{0\text{-}168h}$ and C_{max}) in females than in males. The modelling analysis also showed lower somapacitan exposure in females, particularly females on oral oestrogen, as compared to males; and that this was independent of body weight.

The impact of renal and hepatic function on the somapacitan exposure and IGF-I response were evaluated in dedicated trials 4297 and 4298, respectively after 3 doses of 0.08 mg/kg administered once-weekly for 3 weeks. Somapacitan exposure tended to increase with decreasing GFR. Higher IGF-I $AUC_{0\text{-}168h}$ levels were observed in subjects with moderate and severe renal impairment and in subjects requiring hemodialysis, with ratios to normal renal function of 1.35, 1.40 and 1.24 respectively. Hepatic impairment resulted in higher exposure in subjects with moderate (Child-Pugh B) hepatic impairment with ratios to normal hepatic function of 4.69 for $AUC_{0\text{-}168h}$ and 3.52 for C_{max}. Lower somapacitan stimulated IGF-I levels were observed in subjects with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment compared to subjects with normal hepatic function.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The Applicant provided a pivotal study (Trial ID: NN8640-4054) to claim the efficacy of somapacitan for treatment in adult patients with GHD (growth hormone deficiency). It was a Phase 3, randomized, placebo-controlled (double-blind) and active-controlled (open-label) study to compare once weekly dosing of somapacitan with placebo and daily norditropin. A total of 300 subjects were exposed to study treatment.

When comparing efficacy of primary endpoint, truncal fat percentage change from baseline evaluated at Week 34 (comparison to placebo arm only), superior efficacy trend was found in somapacitan arm, with estimated mean difference = -1.53%, 95% CI = [-2.68, -0.38], and p-value = 0.009. Sensitivity and supportive analyses mostly coincided with the main analyses

result. Somapacitan also showed beneficial effects compared to placebo on several body composition parameters.

2.4.2 Safety Results

The AE reporting rates of somapacitan were similar or slightly lower than norditropin and placebo. The majority of AEs were mild-to-moderated in severity and non-serious. The AE profile of once weekly somapacitan was overall similar to that of existing growth hormone (GH) products for daily administration and included the class effects of GH products.

2.5 Bridging Study Evaluation

In trial 3915, the PK and PD of somapacitan were compared in Japanese (N=32) and non-Asian subjects. In addition, population PK analysis on data from the three phase 3 trials (trials 4054, 4043 and 4244) in AGHD patients evaluated the effect of race on somapacitan exposure and IGF-I response. Modelling analysis assessed the impact of three race categories: White (63.0%), Japanese (28.2%) and Asian non-Japanese (8.8%).

In trial 3915, healthy Japanese subjects had similar somapacitan exposure ($AUC_{0\text{-}168h}$ and C_{max}) and similar IGF-I response as healthy non-Asian subjects at the same dose per kg. The predicted dose-exposure across the dose range 0.1−8 mg indicated that Japanese patients had slightly higher exposures (~18%) than White subjects. However, the IGF-I response was similar across race groups across the entire dose range. Overall, similar doses are needed to reach the IGF-I target for Japanese and White AGHD patients, when accounting for effects of sex and oral oestrogen intake.

A total of 46 Japanese subjects were enrolled in Study 4054, consisted of 15% of total population. The estimated mean treatment difference between somapacitan and placebo in change from baseline of truncal fat % in Japanese subjects (-1.76%) was similar to that of the overall population (-1.53%). The safety profile of Japanese subjects was consistent with that of the overall population. In conclusion, the ethnic difference of clinical efficacy and safety was minimal, and the bridging study could be waived.

2.6 Conclusion

This multidisciplinary review recommends approval for Sogroya solution for injection (Somapacitan) for the indication of replacement therapy for adults with growth hormone deficiency.

3. Post-Marketing Requirements

No post-marketing requirement is needed.