24 February 2022
EMA/153951/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sogroya

International non-proprietary name: somapacitan

Procedure No. EMEA/H/C/005030/X/0001/G

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AGHD:	adult growth hormone deficiency
AUC:	area under the curve
Cps:	counts per second
C_{max}:	maximum concentration
CLIA:	chemiluaminescent immunoassay
CRO:	Clinical Research Organisation
CV:	coefficient of variation
ELISA:	enzyme-linked immunosorbent assay
EMA:	European Medicines Agency
GCP:	Good Clinical Practice
GH:	growth hormone
GHD:	growth hormone deficiency
GLP-1:	glucagon-like peptide 1
hGH:	human growth hormone
hGHBP:	human growth hormone binding protein
IEC:	Independent Ethical Committee
IGF-I:	insulin-like growth factor
ISR:	incurred sample re-analysis
LLOQ:	lower limit of quantification
LOCI:	luminescent Oxygen Channelling Immunoassay
4PL:	4-parameter logistic
PD:	pharmacodymamic
PK:	pharmacokinetic
QC:	quality control
q.s.:	quantum satis
RE:	relative error
RLU:	relative light units
s.c.	subcutaneous
s.d.:	standard deviation
SDS:	standard deviation score
SGA:	small for gestational age
t½:	half-life
ULOQ:	upper limit of quantification

1. Background information on the procedure

1.1. Submission of the dossier

Novo Nordisk A/S submitted on 27 May 2021 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
B.II.d.1.a	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	IA
B.II.b.1.c	B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes	II

The MAH applied for extension application to add a new strength of 5 mg/1.5 mL (3.3 mg/mL) grouped with a Type II Quality variation for a new finished product facility and a Type IA variation, tightening of specification limit. RMP was updated (version 2.0) accordingly.

Type II variation (B.II.b.1.c) to transfer the formulation, filling and inspection activities for Sogroya finished product (cartridges) from Novo Nordisk A/S, Hagedornsvej 1, DK-2820 Gentofte, Hovedstaden, Denmark to Novo Nordisk A/S, Hallas Allé, DK-4400 Kalundborg, Denmark. The activities at the Kalundborg site will also include finished product QC testing (microbiological; sterility). The site in Gentofte will also be maintained as a finished product QC testing site (microbiological; sterility). The changes apply to the approved Sogroya 10 mg strength as well as to the Sogroya 5 mg strength currently applied for via line extension. The following consequential changes are included:
- Introduction of an optimized one-step manufacturing process
- Change in process controls limits for mixing speed and time
- Upscale of the batch size range
- Expansion of sterile filtration time
- New silicone emulsion for siliconization of the glass cartridges.

Type IA variation (B.II.d.1.a) to align the Endotoxin release acceptance for Sogroya 10 mg, to the narrower limit proposed limit for the 5 mg strength (<16 EU/ml). At the same time, the units for Endotoxin are changed from EU/mg to EU/ml.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: N/A

The application was received by the EMA on	27 May 2021
The procedure started on	17 June 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	6 September 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	10 September 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 September 2021
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	14 October 2021
The MAH submitted the responses to the CHMP consolidated List of Questions on	19 November 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	4 January 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report to all CHMP and PRAC members on	20 January 2022
The CHMP agreed on a List of outstanding issues in writing to be sent to the MAH on	27 January 2022
The MAH submitted the responses to the CHMP List of Outstanding Issues on	31 January 2022
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	9 February 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report to all CHMP and PRAC members on	17 February 2022

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Sogroya on	24 February 2022
The CHMP adopted a report on similarity of Sogroya with name of the authorised orphan medicinal product(s) on (see Appendix on similarity)	24 February 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Growth hormone (GH) deficiency is a rare disorder which affects both children and adults. It is characterised by inadequate systemic availability of GH due to inadequate secretion from the anterior pituitary gland or destruction of the gland.

The diagnosis of adult growth hormone deficiency (AGHD) is defined according to the consensus guidelines for the diagnosis and treatment of AGHD.[1]

Clinical studies using biosynthetic GH have confirmed that GH continues to play a vital role in optimising health even after attainment of final adult height and has demonstrated that adults with long-standing GH deficiency derive substantial benefit from GH replacement.

Somapacitan growth hormone product Sogroya is proposed for the replacement of endogenous GH in AGHD.

2.2. About the product

Somapacitan is a long-acting recombinant human GH derivative with a single substitution in the peptide backbone (leucine [L] at position 101 substituted with cysteine [C]) to which an albumin binding moiety has been attached (see Figure 1). The albumin binding moiety (side-chain) consists of a C16 fatty acid moiety and a hydrophilic spacer attached to position 101 of the protein by chemical conjugation. The non-covalent, reversible binding to endogenous albumin delays the elimination of somapacitan and thereby prolongs the in vivo half-life (t½ and duration of action). Similar techniques have previously been used to prolong the half-life of insulin and GLP-1 molecules, such as Levemir, Victoza and Ozempic.

[1] Ho KK, GH Deficiency Consensus Workshop Participants. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Paediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. Eur J Endocrinol. 2007;157(6):695-700.

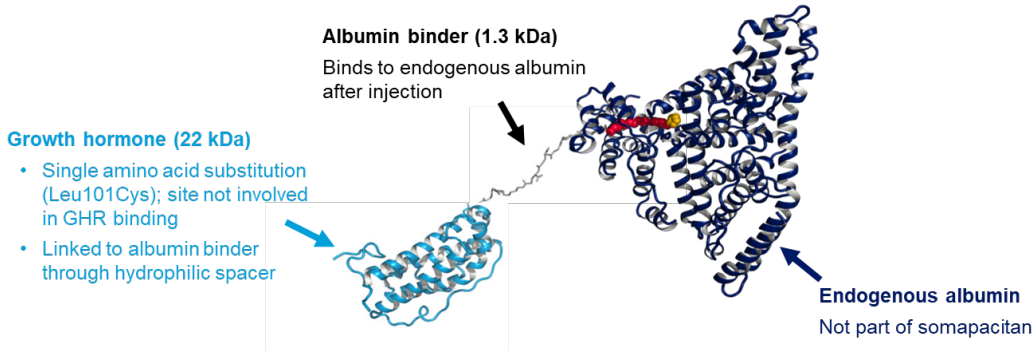


Figure 1. Somapacitan bound to albumin

The pharmacological effects of somapacitan are like those of human GH. These include stimulation of somatic growth, especially skeletal and muscle growth and maintenance. In addition, human GH has many other effects on the body including increasing lipolysis, protein synthesis, muscle mass, and gluconeogenesis in the liver, and reducing glucose uptake in the liver. As for human GH, the mechanism of action of somapacitan is either direct via the GH receptor or indirect via stimulation of IGF-I expression and release.

The approved product is a ready-to-use liquid formulation of 10 mg in a 1.5 ml cartridge (somapacitan 10 mg/1.5 ml strength). Novo Nordisk applies for an additional strength of a ready-to-use liquid formulation of 5 mg in a 1.5 ml cartridge (somapacitan 5 mg/1.5 ml strength).

As indicated by the applicant, the clinical development programme for somapacitan in AGHD was conducted with the somapacitan 10 mg/1.5 ml strength in the PDS290 pen-injector. The in-use time for somapacitan is 6 weeks. As the maintenance/treatment dose of somapacitan is individualised, patients with low somapacitan dose would not use the total amount of the 10 mg/1.5 ml product within 6 weeks. In clinical practice, somapacitan will be individually titrated to the individual patient needs, according to clinical response, IGF-I SDS and tolerability. No additional dosing adjustments are proposed to support the safe and effective use of somapacitan 5 mg/1.5 ml. Therefore, there will be no need to differentiate in the prescriptions for the somapacitan 5 mg/1.5 ml and 10 mg/1.5 ml strengths. A somapacitan product strength of 5 mg/1.5 ml would enable the patients/physicians to choose an appropriate somapacitan formulation depending on required dose of somapacitan and hence, the somapacitan 5 mg/1.5 ml strength offers an additional valuable choice with a similar safety profile in the armamentarium for patients and physicians in treatment of patients with AGHD.

To support the application, the applicant has submitted a bioequivalence study (study number NN86409-4491) in healthy volunteers.

The primary objective of the study was to confirm bioequivalence of two different strengths of somapacitan (5 mg/1.5 ml and 10 mg/1.5 ml) administered subcutaneously in equimolar doses by assessing the total somapacitan exposure (AUC_{0-t}) and C_{max}.

The secondary objectives was to investigate other pharmacokinetic properties of somapacitan in subjects dosed with two different strengths (5 mg/1.5 ml and 10 mg/1.5 ml) at equimolar doses, and to investigate the pharmacodynamic properties of somapacitan in subjects dosed with the two different strengths at equimolar doses.

2.3. Type of Application and aspects on development

This line extension concerns one strength for which a bioequivalence study is submitted. A biowaiver is not applicable.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a pre-filled pen (solution for injection) containing 10 mg/ 1.5 ml (already marketed) or 5 mg/1.5ml (subject of this line extension) of somapacitan as active substance.

Other ingredients are

Histidine

Mannitol

Poloxamer 188

Phenol

Water for injections

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment).

These are the same for both strengths and were also listed in the application for the 10 mg strength. The new strength is presented in its own pen injector that is distinguishable from but equivalent to the injector used for the already marketed 10 mg strength.

2.4.2. Active Substance

2.4.2.1. General Information

No changes are made to the active substance, which means it remains identical to the already approved active substance for Sogroya (somapacitan).

However, CTD 3.2.S.4. Control of Drug Substance has been updated to include the validation of analytical methods common to active substance and finished product for the 5 mg strength.

2.4.2.2. Manufacture, process controls and characterisation

Updated method validation reports have been provided. The following is noted:

AIE-HPLC (M 118) The validation of this method for the 5 mg strength is accepted.

RP-UHPLC (M120) For Related Impurities and Hydrophilic forms 2, specificity and precision of the method has been confirmed with somapacitan 5 mg and aged somapacitan 5 mg drug product samples.

SE-HPLC (M122) For determination of HMWP and Content of somapacitan, specificity and precision of this method are sufficiently validated for somapacitan 5 mg drug product.

2.4.3. Finished medicinal product

2 . 4 . 3 . 1 . Description of the product and Pharmaceutical Development

Description and composition of the finished product

The composition of the somapacitan 5mg/1.5ml (new strength) and 10mg/1.5ml (existing strength) solution for injection is shown in **Table 1**.

Table 1: composition of finished product (somapacitan 5mg and somapacitan 10 mg.)

Component	Function	Reference to standards
Active substance		
Somapacitan	Active ingredient	Novo Nordisk A/S
Excipients		
Histidine	Buffering agent	Ph. Eur., USP, JP
Mannitol	Tonicity agent	Ph. Eur., USP, JP
Poloxamer 188	Stabiliser	Ph. Eur., USP, JPE
Phenol	Preservative	Ph. Eur., USP, JP
Hydrochloric acid	pH adjustment	Ph. Eur., USP, JP
Sodium hydroxide	pH adjustment	Ph. Eur., USP, JP
Water for injections	Solvent	Ph. Eur., USP, JP

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in the table above.

No overage or overfill is mentioned in the CTD.

This line extension concerns 1 strength for which a bioequivalence study is submitted (number NN8640—4491). A biowaiver is not applicable. Based on the presented bioequivalence study NN8640-4491, the somapacitan 5 mg/1.5 ml is considered bioequivalent with the somapacitan 10 mg/1.5 ml, based on the IGF-I levels.

Container closure system

The primary packaging as stated in the SmPC is:

"1.5 mL solution in a glass cartridge (Type I colourless glass) with a plunger made of chlorobutyl rubber and a stopper made of bromobutyl/isoprene rubber sealed with an aluminium cap.

The cartridge is contained in a multidose disposable pen made of polypropylene, polyacetal, polycarbonate and acrylonitrile butadiene styrene and in addition two metal springs.

The cartridge is permanently sealed in a pen-injector.

Pack sizes of 1 pre-filled pen and multipack of 5 (5 packs of 1) pre-filled pen."

The introduction of a new silicone oil emulsion for siliconisation of the cartridges is described. No other changes are reported in the container closure system.

The MAH's approach to the safety evaluation of the new silicone oil emulsion is confirmed to be in line with the ICH M7, and acceptable.

The new silicone oil emulsion is compliant to Ph.Eur., and no other changes are reported. A new leachable study is initiated. The MAH has made a commitment to provide the results of this study once available (Recommendation).

The product is available in a pre-filled pen. The PDS290 pen-injectors with integrated 1.5 ml cartridge for somapacitan 10 mg or 5 mg are compliant to ISO 13485:2016. The description of the device and its mechanistic aspects have been provided in sufficient detail. Dose accuracy has been verified for various dose settings and at various environmental conditions as per ISO 11608-1. ISO certificates and a notified body report are provided and do not raise any issues. The NB opinion report is sufficiently detailed and conformity to general safety and performance requirements as intended in Annex 1 of EU regulation 2017/745 is systematically reported. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Pharmaceutical development

This section has been updated to encompass the 5 mg strength. In fact the only adaptation is the 5 mg strength is mentioned in the documents next to the already approved 10 mg strength. Also a clinical bioequivalence study of the 5 mg strength has been added to the table of formulations tested in P.2.2.

The MAH has formulated the 5 mg product with exactly the same composition as the 10 mg product except for the lower content of somapacitan based on "formulation development work performed with somapacitan drug product in a matrix covering drug product strengths from 5 mg to 15 mg in a 1.5 ml cartridge", as mentioned with this same phrase in the application for the 10 mg strength. However, no further description of this matrix and its development are provided, and the optimisation studies described are all performed with 6.7 mg/mL (corresponding to the 10 mg product). As no significant detectable changes are expected by the lower somapacitan concentration there is no need for additional optimisation studies.

The critical quality attributes identified were defined in eCTD section 3.2.P.5.6. Control Strategy for Drug Product.

The manufacturing development have been evaluated through the use of risk assessment to identify the critical product quality attributes and critical process parameters. A risk analysis was performed using the failure mode effect analysis (FMEA method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. The critical process parameters have been adequately identified.

2.4.3.2. Manufacture of the product and process controls

The line extension submission also included a type II variation to transfer the formulation, filling and inspection activities for the finished product (cartridges) from Novo Nordisk A/S, Hagedornsvej 1, DK-2820 Gentofte, Hovedstaden, Denmark to Novo Nordisk A/S, Hallas Allé, DK-4400 Kalundborg, Denmark. The activities at the Kalundborg site will also include finished product QC testing (microbiological; sterility). The site in Gentofte will also be maintained as a finished product QC testing site (microbiological; sterility). The changes apply to the approved Sogroya 10 mg strength as well as to the Sogroya 5 mg strength currently applied for via line extension. In connection with the manufacturing site transfer, some changes were introduced in the manufacturing process, i.e. an optimized

manufacturing process as well as an upscaled batch size range and a new silicone emulsion for siliconization of the glass cartridges.

The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Information on in-process controls has been provided.

2.4.3.3. Product specification, analytical procedures, batch analysis

The finished product release and shelf specifications are considered acceptable, and include relevant tests to control general parameters, identity, specific bioactivity, content, product-related impurities, process-related impurities, microbial controls and device functionality.

The content of the 5 mg strength is added to the specifications.

Further, the specification for Bacterial endotoxins has been amended (i.e. now based on volume instead of protein mass). The new specification is slightly tighter for the 10 mg product and clearly tighter for the 5 mg product. This amended specification is acceptable.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) validated. The respective summaries have been provided for the verification of the analytical procedures for the 5 mg strength of the finished product in accordance with ICH guidelines.

Batch analyses

For the 5 mg (new) strength, data for commercial scale batches and laboratory scale batches were provided. Some of the batches are manufactured at the new site and commercial scale. These are the batches that have been used to validate the process at the new site.

For the 10 mg (existing) strength, and for the 15 mg strength (subject to a future application) data from commercial scale batches are added to the dossier.

The acceptance criteria for each batch are presented with the corresponding test results. All of the batches listed, comply to the acceptance criteria, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Reference standard

The reference materials used for testing and release of the finished product are the same as the ones used for the active substance. No change to the reference materials is proposed as part of this application.

Container closure system

A picture of the somapacitan 5 mg PDS290 pen-injector is added. As shown in **Figure 2** and **Figure 3** below, it is distinguishable from the 10 mg product by its colour and the numbering of the dose increments, which are half of those of the 10 mg product.

Figure 2. Somapacitan 5 mg in a 1.5 ml cartridge assembled in a PDS290 pen-injector

Figure 3. Somapacitan 10 mg in a 1.5 ml cartridge assembled in a PDS290 pen-injector

The summary of human factors validation has been updated to encompass the 5 mg strengths. The MAH has experience with several similar pens that are on the market and has evaluated the Somapacitan 5 mg pen in comparison with these. Clinical experience also confirms its adequate handling by patients in practice. No concerns are raised from this information.

The somapacitan PDS290 pen-injector used in clinical trial (see **Figure 4**) have two features that differentiate it from the to-be-marketed device :

- coloured components:
    - green or brown cartridge holder (with markings but no imprints)
    - green cap
    - brown dose button
- dose indicator:
    - sequential numbers shown on the scale drum instead of 'mg' values
    - "mg" imprint next to the pointer is absent

Figure 4. Somapacitan PDS290 pen-injector used in clinical trials

The mechanism responsible for dialling and dosing are identical in the clinical and to-be-marketed PDS290 pen-injectors. The difference between them have no influence on the dose delivery mechanism.

It is noted that the pens used in clinical trials differ from the pens to be marketed or already marketed. This makes the experience in pen handling by patients reported in clinical trials less convincing as evidence for the commercial pen injector. However, the differences are small and not expected to complicate handling by patients.

The description of the device and its mechanistic aspects have been provided in sufficient detail and is acceptable.

2.4.3.4. Stability of the product

The proposed storage and shelf life for somapacitan 5 and 10 mg is 24 months at 2-8 °C including an in-use period of 6 weeks at 2-8 ºC and 72 hours (3 days) at or below 30 ºC.

Stability studies for the 5 mg strength and finished product manufactured at the Kalundborg site are added.

Based on the data, the MAH's proposal of a shelf life of 24 months at 2-8 °C for somapacitan 5 mg and somapacitan 10 mg drug product and in-use period of 6 weeks at 2-8 ºC including the possibility of storage at or below 30 ºC for a maximum of 72 hours (3 days) are justified and acceptable.

Real time/real condition stability data of somapacitan 5 mg and somapacitan 10 mg full scale manufacturing validation batches of finished product from the Gentofte site for 24 months at 5 °C ± 3 °C/ambient humidity/protected from light and for up to 6 months under accelerated conditions at 25 ºC± 2 °C/ambient humidity/protected from light according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing. The parameters tested are the same as for release.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

In addition, somapacitan 5 mg and somapacitan 10 mg were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. It is also agreed that data from the photostability study show that both strengths of somapacitan drug product are photostable when stored in the PDS290 pen-injector.

Real time/real condition stability data of somapacitan 5 mg and somapacitan 10 mg full scale manufacturing validation batches of finished product from the Kalundborg site for up to 18 months at 5 °C ± 3 °C/ambient humidity/protected from light and for up to 6 months under accelerated conditions at 25 ºC± 2 °C/ambient humidity/protected from light according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing. The parameters tested are the same as for release.

The long-term stability study of the process validation batches for full-scale manufacturing at the Kalundborg site is still ongoing, and data are provided for up to 18 months. The study will be finalised according to design and provide the final report once available (Recommendation). The data for up to 18 months do not give rise to concerns.

2.4.3.5. Adventitious agents

Not applicable (no changes reported with this line extension).

2.4.4. Discussion on chemical, and pharmaceutical aspects

The active substance is identical to the approved presentation.

The finished product intended for the market is a line extension to the currently marketed Sogroya 10 mg (somapacitan 6,6 mg/ml). Compared to Sogroya 10 mg only the concentration of the active substance is decreased to 3,3 mg/ml. Overall, sufficient quality of the new 5 mg strength of Sogroya (somapacitan) is reasonably justified and comparable to the 10 mg strength.

In combination with the introduction of the new strength, the MAH proposes a transfer of the manufacture of Sogroya to a site in Kalundborg, a change in the manufacturing process and an upscale of the maximum batch size. The information provided supports the MAH's claim that these changes do not negatively impact the quality of the product.

In general, the Quality related documentation on development, manufacture and control of the active substance and finished product has been sufficiently presented. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics.

No Major Objections were identified during the procedure. The Applicant has made commitments to keep the Agency updated about the data from ongoing studies (leachable and stability studies), please refer to the section on recommendations for future quality development below.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC.

2.4.6. Recommendation(s) for future quality development

- To provide the results of the new leachable study, initiated to qualify the new silicone oil emulsion, once available.
- To provide the stability data covering the process validation batches for full-scale manufacturing at the Kalundborg site when the results are available.

2.5. Non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Somapacitan are known. As the current application is a line-extension for a new strength of the same pharmaceutical form, the applicant has not provided additional studies and further studies are not required. No overview based on literature review is considered necessary.

2.5.1. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of the Line extension of an additional strength, Sogroya 5 mg, and transfer to the new facility in Kalundborg (FF), no increase in environmental exposure in the use of the product is expected as the changes do not affect the maximum daily dose or the predicted forecast of amount of somapacitan API to be placed on the market. Thus, the ERA is expected to be similar.

2.5.2. Discussion on non-clinical aspects

Application is a line-extension, from a non-clinical point of view, the pharmacology, safety pharmacology, pharmacokinetics and toxicological properties are considered known.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, somapacitan is not expected to pose a risk to the environment.

2.5.3. Conclusion on the non-clinical aspects

There are no objections to approval of Sogroya 5 mg/1.5 ml from a non-clinical point of view.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

To support the application, the applicant has submitted 1 bioequivalence study, number NN8640—4491.

2.6.2. Clinical pharmacology

This line extension concerns 1 strength for which a bioequivalence study is submitted (see below). A biowaiver is not applicable.

2.6.2.1. Pharmacokinetics

Study NN8640-4491: A randomised, double-blind, single dose, three period, complete cross over trial in healthy subjects investigating the pharmacokinetics of subcutaneous injections of somapacitan 5 mg/1.5 ml and 10 mg/1.5 ml.

Methods

- **Study design**

This was a randomised, three-treatment, three-period, single dose, crossover bioequivalence study. Thirty-three healthy subjects were dosed in this study. Each subject received after an overnight fast, subcutaneously a single dose in equimolar doses of 0.04 mg/kg body weight using the PDS290 pen-injector of the Test (5 mg/1.5 ml strength) or the Reference somapacitan formulations (10 mg/1.5 ml strength). The Reference was administered twice (semi-replicate study design).

According to the SmPC, the starting dose in adults is 1.5 mg/week. The administered dose of 0.04 mg/kg in this bioequivalence study is approximately in the range of this starting dose. Moreover, linear pharmacokinetics was shown in the clinically relevant dose range.

The washout period was 3 weeks. Blood samples were taken for pharmacokinetics and pharmacodynamic assessment were taken up to 504 h after injection. It is indicated in the study report that the procedures for sampling, handling of samples, labelling, storage and shipment will be carried out in accordance with the laboratory manual. This manual has been provided on request.

- **Test and reference products**

Somapacitan 5 mg/1.5ml, solution for injection has been compared to Somapacitan 10 mg/1.5 ml, solution for injection. Both solutions were administered using the PDS290 pen injector.

The composition of the Test 5 mg/1.5 ml solution for injection and 10 mg/1.5 ml solution for injection are identical, except for the content of the active ingredient.

The Reference product is the companies own innovator product.

The potency of the used Test and Reference formulation has been provided on request. The difference in somapacitan potency between the 5 mg/1.5 ml. Test batch and the 10 mg/1.5 ml Reference batch is 7.8% based upon biological activity. For BE studies no correction needs to be applied in case the potency difference is within 5%. However, considering that somapacitan Test/Reference ratio's in the BE study were lower (see below), i.e. 0.95 for AUC and 0.77 for Cmax, in case of potency correction based upon the biological activity would be in favour of the Test (i.e. being more comparable). Moreover, 95% CI for the pharmacodynamic parameters IGF-I AUC and Cmax were applied to support comparability between Test and Reference, showing comparability of both products.

The batch size of the Test formulation has been provided on request, and were within the commercial batch size range.

- **Population(s) studied**

Thirty-three healthy subjects were randomised in this study. One subject in the treatment sequence Reference/Test/Reference withdrew from the trial before receiving the third treatment resulting in a total of 32 completers in the trial. In accordance with the protocol, the 32 subjects completing the trial were included in the statistical analysis.

- **Analytical methods**

For the analysis of somapacitan in human serum a specific LOCI assay was applied. The method proved to be sensitive and robust for analysis of somapacitan. Validation results showed acceptable performance within the normal standard criteria. In addition, somapacitan is stable in plasma during a sufficient long period. The method is similar to the method applied previous for the original application of the 10mg/1.5 ml solution for injection. Incurred sample reanalysis showed good performance of the method during study sample analysis.

The analytical method of IGF-I in serum showed acceptable performance of the method. It was indicated that the method has been validated. The applicant has confirmed on request, that the method is similar to the method applied previous for the original application of the 10mg/1.5 ml solution for injection.

Incurred sample reanalysis showed good performance of the method during study sample analysis.

- **Pharmacokinetic Variables**

Somapacitan AUC_{0-t} and C_{max} were considered the primary pharmacokinetic endpoints. AUC_{0-168h}, AUC_{0-inf}, t_{max} and $t_{½}$ were considered secondary pharmacokinetic endpoints.

Supportive secondary PD endpoints, i.e. AUC_{0-168h}, C_{max} and t_{max}, will be derived from the serum insulin-like growth factor I (IGF-I) concentration time curve.

- **Statistical methods**

The primary endpoints AUC_{0-t} and C_{max} will be log-transformed prior to analysis using an analysis of covariance model (ANOVA). The model will include product, period, sequence and subject within sequence as fixed effects. The variance will be allowed to depend on product. From this model, the product difference will be estimated and the estimate will be back-transformed to original scale and presented as ratios with corresponding 90% CIs. The estimated within-subject deviation s(C_{max}, Reference) for the Reference product from this model will be used when determining the width of the acceptance range for C_{max}.

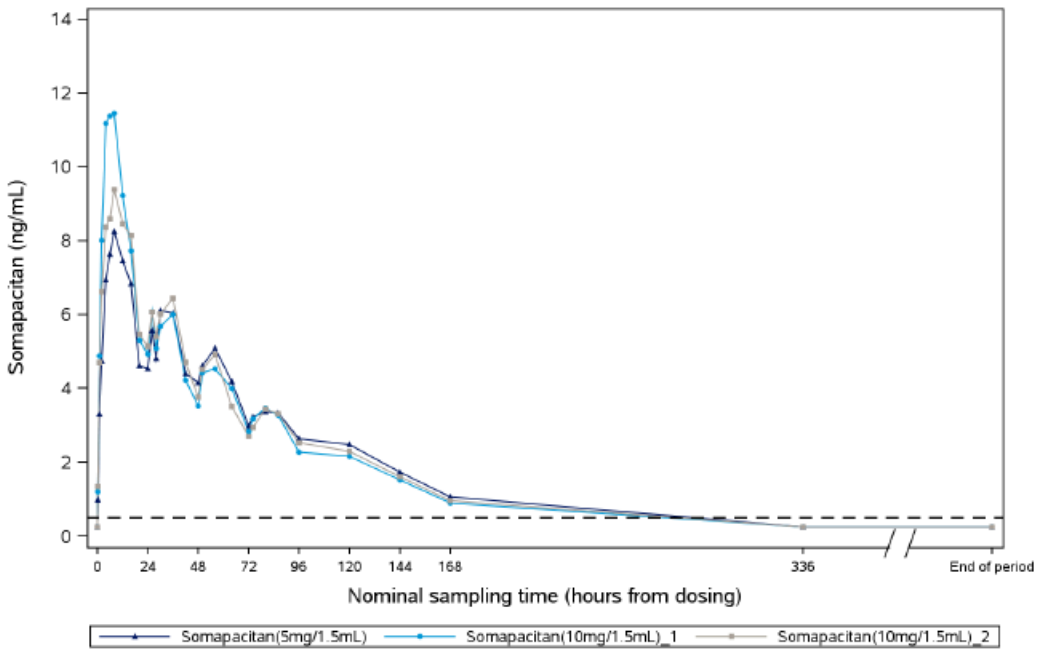
If within-subject CV (C_{max}, Reference) >30% then for the EMA guideline-based method: [U, L] = exp [±k·s (C_{max}, Reference)], where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760. The two products will be confirmed as bioequivalent (EMA-based method) if the 90% CI of C_{max} lies completely within [U,L] as defined above, the point estimate of the ratio lies within [0.8;1.25] and the 90% CI of AUC_{0-t} lies completely within the standard acceptance range [0.8;1.25]. If the within-subject CV (C_{max}, Reference) ≤30% then the 90% CI for C_{max} also needs to lie completely within the standard acceptance range [0.8;1.25]. The [U, L] cannot be extended beyond the range determined by a within-subject standard deviation corresponding to a within-subject CV of 50%.

Results

Somapacitan:

The mean concentration-time curves and the pharmacokinetic variables of somapacitan of the Test and the Reference product are shown in Figure 6 and Table 7.

Figure 5. Somapacitan geometric mean concentration-time curves after administration of somapacitan 5 mg/1.5ml, solution for injection, and somapacitan 10 mg/1.5ml, solution for injection, at a dose of 0.04 mg/kg to healthy volunteers.



Values below lower limit of quantification are imputed.
Reference line for lower limit of quantification.
End of period is the sample taken just before the next dosing, or at the follow-up visit (Visit 17) if the treatment is the last in the subject's treatment sequence.

Table 2. Pharmacokinetic variables of somapacitan of the Test and Reference (as geometric mean, CV, median and minimum and maximal values).

PK parameter	Treatment	N	Geometric Mean	CV (%)	Min	Median	Max
AUC (0-t) (ng*h/mL)	Somapacitan(5mg/1.5mL)	32	820	40.2	456	823	2155
	Somapacitan(10mg/1.5mL)_1	32	839	41.0	366	799	2210
	Somapacitan(10mg/1.5mL)_2	32	894	50.4	449	790	3773
AUC (0-168h) (ng*h/mL)	Somapacitan(5mg/1.5mL)	32	641	43.5	323	628	1924
	Somapacitan(10mg/1.5mL)_1	32	677	47.4	282	695	2032
	Somapacitan(10mg/1.5mL)_2	32	705	58.1	318	649	3689
AUC (0-inf) (ng*h/mL)	Somapacitan(5mg/1.5mL)	32	825	40.1	456	827	2155
	Somapacitan(10mg/1.5mL)_1	32	844	40.8	366	806	2210
	Somapacitan(10mg/1.5mL)_2	32	898	50.1	449	790	3775
Cmax (ng/mL)	Somapacitan(5mg/1.5mL)	32	10.61	56.9	3.15	9.87	34.80
	Somapacitan(10mg/1.5mL)_1	32	14.09	76.8	4.39	15.25	57.00
	Somapacitan(10mg/1.5mL)_2	32	13.18	94.0	3.94	11.60	165.00
Terminal half-life (hrs)	Somapacitan(5mg/1.5mL)	32	52.7	40.5	29.5	49.7	117.3
	Somapacitan(10mg/1.5mL)_1	32	53.9	45.5	26.2	57.2	99.2
	Somapacitan(10mg/1.5mL)_2	32	50.5	42.3	23.5	46.4	117.5
Tmax (hrs)	Somapacitan(5mg/1.5mL)	32	13.0	8.8	4.0	10.0	36.0
	Somapacitan(10mg/1.5mL)_1	32	11.3	13.4	2.0	8.0	64.0
	Somapacitan(10mg/1.5mL)_2	32	16.8	18.5	0.3	8.0	80.0

The results of the statistical analysis of the primary pharmacokinetic endpoints AUC_{0-t} and C_{max} are listed in Table 8.

For AUC_{0-168h} and AUC_{0-inf} bioequivalence was shown within the 80 – 125% criteria.

Table 3. Statistical evaluation on somapacitan primary pharmacokinetic endpoints AUC0-t and Cmax.

Endpoint	Bioequivalence acceptance criteria	Results Ratio[a] [90% CI]	Results Critical bound Point estimate	Bioequivalence criteria met
AUC_{0-t}	90% CI of ratio within [0.80; 1.25]	0.95 [0.89; 1.01]	Not applicable	Yes
C_{max}	*EMA approach* 90% CI of ratio within [0.70; 1.43] Point estimate within [0.80; 1.25]	0.77 [0.68; 0.89]	Not applicable	No
	FDA approach Critical bound ≤ 0 Point estimate within [0.80; 1.25]		-0.04 0.77	

[a] The 90%CI was not used in the assessment of bioequivalence for C_{max} in the FDA approach.

Abbreviations: AUC_{0-t} = area under the somapacitan serum concentration time curve from time 0 to the time of the last quantifiable concentration after dosing; CI = confidence interval; C_{max} = maximum somapacitan serum concentration; EMA = Europeans Medicines Agency; FDA = Food and Drug Administration;

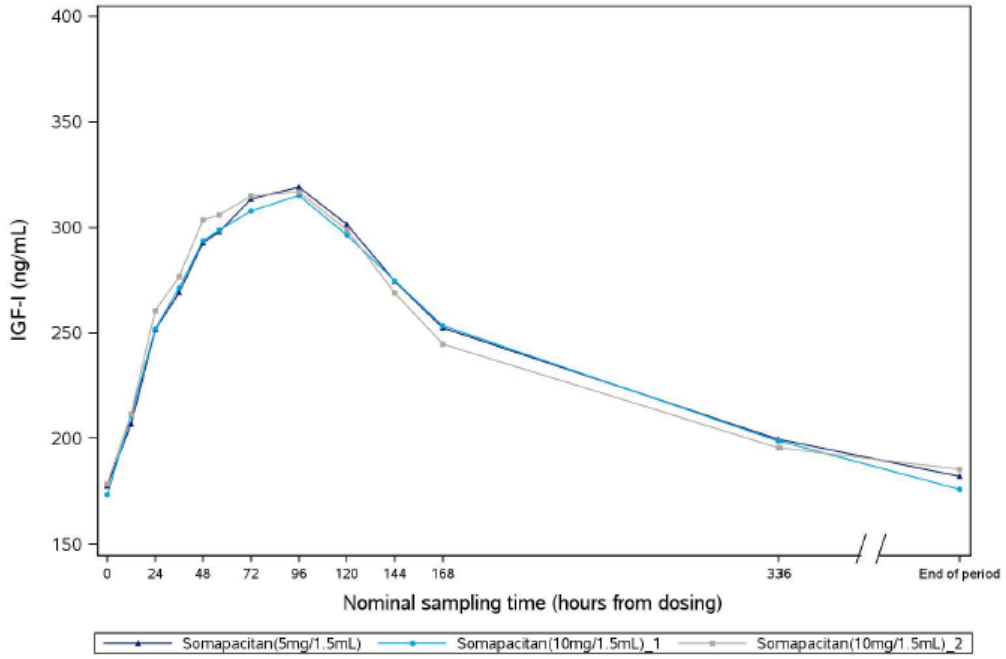
A pharmacokinetic report, including individual data summarised and tabulated with arithmetic mean and s.d. data could not be retrieved from the study report. However it appeared that the data were tabulated in appendices to the report.

A statistical report could not be retrieved from the study report. However it appeared that the data were integrated in the stud report.

IGF-I:

The mean IGF-I concentration-time curves and the pharmacokinetic variables of IGF-I of the Test and the Reference product are shown in Figure 7 and Table 9, respectively.

Figure 6. IGF-I mean concentration-time curves after administration of somapacitan 5 mg/1.5ml, solution for injection, and somapacitan 10 mg/1.5ml, solution for injection, at a dose of 0.04 mg/kg to healthy volunteers.



IGF-I: Insulin-like growth factor I
End of period is the sample taken just before the next dosing, or at the follow-up visit (Visit 17) if the treatment is the last in the subject's treatment sequence.

Table 4. IGF-I pharmacokinetic variables of the Test and Reference (as geometric mean, CV, median and minimum and maximal values).

PD parameter	Treatment	N	Geometric Mean	CV (%)	Min	Median	Max
AUC (0-168h) (ng*h/mL)	Somapacitan(5mg/1.5mL)	32	46400	17.8	34113	46089	63338
	Somapacitan(10mg/1.5mL)_1	32	46118	18.2	34335	44540	67248
	Somapacitan(10mg/1.5mL)_2	32	46520	18.4	31596	46155	66983
Cmax (ng/mL)	Somapacitan(5mg/1.5mL)	32	322.1	19.1	220.0	322.9	440.6
	Somapacitan(10mg/1.5mL)_1	32	316.4	18.7	237.1	307.7	471.4
	Somapacitan(10mg/1.5mL)_2	32	323.8	20.1	205.9	331.9	445.4
Tmax (hrs)	Somapacitan(5mg/1.5mL)	32	85.8	21.4	48.0	96.0	145.0
	Somapacitan(10mg/1.5mL)_1	32	88.3	19.6	48.0	96.0	120.5
	Somapacitan(10mg/1.5mL)_2	32	79.3	27.5	24.0	96.0	145.6

The results of the statistical analysis of the supportive secondary endpoints of IGF-I $AUC_{0\text{-}168h}$ is listed in Table 10.

Table 5. Statistical evaluation on IGF-I secondary pharmacokinetic endpoints $AUC_{0\text{-}168h}$.

	Number of subjects in full analysis set	N	Estimate	90% CI
AUC (0-168h) (ng*h/mL) of IGF-I				
Geometric mean				
Somapacitan(5mg/1.5mL)	32	32	46373	
Somapacitan(10mg/1.5mL)	32	32	46296	
Ratio				
Somapacitan(5mg/1.5mL) / Somapacitan(10mg/1.5mL)			1.00	[0.98 ; 1.02]

- ***Safety data***

A total of 17 subjects had 34 AEs during the trial. The majority of the AEs (30 AEs in 16 subjects) were mild in severity and a few AEs (4 AEs in 4 subjects) were moderate in severity. No subject had severe AEs. A total of 22 AEs in 9 subjects were reported to be either possibly or probably related to somapacitan and 12 AEs in 10 subjects were unlikely to be related to somapacitan according to the investigator. No action with somapacitan was taken upon development of the AEs. At the end of trial, all but 2 subjects recovered from their AEs, however later during the reporting of the trial, it was confirmed by the site that the 2 subjects had recovered from their AEs.

The most frequently reported AEs (≥5% of the subjects) by PTs were headache (8 AEs in 5 subjects [15.2%]), back pain (3 AEs in 3 subjects [9.1%]) and vomiting (2 AEs in 2 subjects [6.1%]). There was no apparent pattern of difference in the distribution of AEs between the two strengths of somapacitan.

2.6.2.2. Pharmacokinetic Conclusion

Based on the primary pharmacokinetic endpoints of somapacitan, the new 5mg/1.5 ml solution for injection is not bioequivalent to the Reference 10mg/1.5 ml solution for injection. Bioequivalence is shown for AUC_{0-t}, as the 90% CI was within the normal 80 – 125% criteria. Although the observed within-subject variability for C_{max} was 54.30% and in accordance with EMA's Guideline on the investigation of bioequivalence, the 90% CI could be widened to 0.70 – 1.43, bioequivalence was not shown for C_{max}, as the 90% CI was 0.68 – 0.89 and thus outside the widened CI.

Based on the secondary IGF-I endpoint AUC_{0-168h}, the new 5mg/1.5 ml solution for injection is comparable to the Reference 10mg/1.5 ml solution for injection. However, as IGF-I can be considered a pharmacodynamic endpoint, 95% CI should be applied, instead of 90% CI. In addition, to further support the comparability in IGF-I levels, the applicant was requested to provide data on C_{max} levels, including a statistical analysis and providing the 95% CI. This has been raised as a major objection.

2.6.2.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application. However, IGF-I was evaluated in the bioequivalence study NN8640-4491.

2.6.3. Discussion on clinical pharmacology

Based on the submitted bioequivalence study NN8640—4491 with a semi-replicate design, the new 5mg/1.5 ml solution for injection is not bioequivalent to the Reference 10mg/1.5 ml solution for injection.

Bioequivalence is shown for the somapacitan primary endpoint AUC_{0-t}, as the 90% CI was within the normal 80 – 125% criteria. Although the observed within-subject variability for C_{max} was 54.30% and in accordance with EMA's Guideline on the investigation of bioequivalence, the 90% CI could be widened to 0.70 – 1.43, bioequivalence was not shown for the somapacitan primary endpoint C_{max}, as the 90% CI was 0.68 – 0.89 and thus outside the widened CI. From these pharmacokinetic results of somapacitan it can be concluded that the performance of the two formulations differ. It should therefore be justified that the difference in somapacitan concentration levels for these formulations is not affecting the safety and efficacy of somapacitan itself. Based on the applicant's response it can be considered that in the BE study, comparable somapacitan AUC values were observed. Cmax levels were lower, however, these are considered not relevant for the efficacy. This is confirmed by the pharmacodynamic/efficacy parameters AUC0-504h, IGF-I and Cmax, IGF-I, being comparable between Test and Reference.

Safety concerns due to lower Cmax levels are not anticipated. In study NN86409-4491, no new safety issues were identified, although it should be taken into account that the number of subjects in the bioequivalence study is limited (n=32).

Although the observed difference in somapacitan pharmacokinetics, IGF-1 levels were used to further support the safety and efficacy of the new somapacitan formulation. Based on the IGF-I endpoint AUC_{0-168h}, the new 5mg/1.5 ml solution for injection is comparable to the Reference 10mg/1.5 ml solution for injection, as the 90% CI was within 80 – 125%, i.e. 0.98 – 1.02. However, as IGF-I can be considered a pharmacodynamic endpoint, 95% CI should be applied, instead of 90% CI. In addition, no statistical data on Cmax were provided. To further support the comparability in IGF-I levels, on request, data on Cmax levels were provided, including a statistical analysis and the 95% CI. The 95% CI for IGF-I AUC and Cmax, i.e. 0.98 - 1.03 and 0.97 - 1.04, respectively, show that the 95% CI are within the normal acceptance criteria for bioequivalence (i.e. 80 – 125%), but also within the narrowed 90% CI for narrow therapeutic index drugs (i.e. 90 – 111%), indicating that the profiles are very similar. Furthermore, the relevance of the applied bioequivalence criteria, i.e. 95% CI 80 – 125%, has been further justified with regard to the support of the safety and efficacy.

In clinical practise, and as can be observed from the SmPC, initiation of somapacitan treatment and subsequent monitoring will be carried out by experienced specialist qualified in diagnosing and treatment of patients with growth hormone deficiency (e.g. endocrinologists). Of importance, IGF-I levels are used as a guidance for the dose titration apart from an evaluation of the clinical response and adverse events. The target range of the IGF-I standard deviation score (SDS) should not exceed +2 SDS. Dosing and titration (in small steps) will be done per individual patient. IGF-I SDS scores as biomarker will be used for dose titration. After reaching the desired IGF-I SDS level, the efficacy and safety of treatment will be continuously evaluated; IGF-I levels is one of the control parameters/biomarkers. Considering this and

- Considering the fact that the dosing recommendation for proposed Sogroya 5 mg/1.5 ml solution for injection is similar to that of the reference Sogroya 10 mg/1.5 ml solution for injection
- and considering that the IGF-I AUC and Cmax for the new formulation is very similar to the reference,
- and considering that IGF-I levels concern one of the control parameters/biomarkers,

a difference in safety and efficacy is not foreseen. Moreover, as indicated in the SmPCs for both products, after reaching the desired IGF-I SDS level, the efficacy and safety of treatment need to be continuously evaluated, which will limit, although not expected, possible differences between both products.

Therefore it is considered that the lower somapacitan C_{max} can be waived by the comparability in IGF-I exposure.

All outstanding issues are considered resolved.

2.6.4. Conclusions on clinical pharmacology

The CHMP considers clinical pharmacology sufficiently described.

2.6.5. Clinical efficacy

Not applicable.

2.6.6. Clinical safety

Not applicable.

2.6.6.1. Post marketing experience

No post-marketing data are available. The 5 mg/1.5 ml medicinal product has not been marketed in any country.

2.6.7. Discussion on clinical safety

Not applicable.

2.6.8. Conclusions on the clinical aspects

Based on the presented bioequivalence study NN8640-4491, the somapacitan 5 mg/ml is considered bioequivalent with the somapacitan 10 mg/1.5 ml, based on the IGF-I levels.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Neoplasms • Diabetes mellitus type 2 • Medication errors (Incorrect dose administration rate) • Off-label paediatric use
Missing information	• Patients with heart failure, NYHA class >2 • Patients with severe hepatic impairment • Long-term safety

2.7.2. Pharmacovigilance plan

Ongoing and planned additional pharmacovigilance activities

Study (study short name and title) Status (planned/ongoing)	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit–risk)				
None	N/A	N/A	Protocol submission	N/A
			Final report	N/A
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit–risk)				
None	N/A	N/A	Protocol submission	N/A
			Final report	N/A
Category 3 – Required additional pharmacovigilance activities				
A multinational, multicentre, prospective, open label, single-arm, observational, non-interventional post-authorisation safety study to investigate long-term safety of somapacitan in adults with growth hormone deficiency (AGHD) under normal clinical practice conditions (NN8640-4515) Planned	**Primary objective:** To assess safety of somapacitan therapy in AGHD under normal clinical practice conditions. **Secondary objectives:** Under normal clinical practice conditions to: • characterise the somapacitan titration schemes in subgroups[a] • characterise effectiveness in subgroups[a] • evaluate effect of somapacitan by patient-reported outcome (PRO) measures.	• Neoplasms • Diabetes mellitus type 2 • Medication errors (Incorrect dose administration rate) • Patients with heart failure, NYHA class >2 • Patients with severe hepatic impairment • Long-term safety	Protocol submission	Within 2 months of obtaining marketing authorisation
			Final report	One year after the end of the study

[a]Subgroups are defined as female patients on oral oestrogen therapy, adult-onset GHD patients, patients in the transition phase from 18 to 25 years and childhood-onset AGHD patients.

Abbreviations: AGHD = adults with growth hormone deficiency; GHD = growth hormone deficiency; N/A = not applicable; NYHA = New York Heart Association.

2.7.3. Risk minimisation measures

Safety concerns	Routine risk minimisation measures
Important identified risks	
None	N/A
Important potential risks	
Neoplasms	Routine risk communication: • SmPC Section 4.3, where a contraindication concerning any evidence of activity of a tumour is included. Risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4, where a special warning is included on neoplasms. • PL Section 2, where information is included on tumours. Other risk minimisation measures beyond the Product Information: • Medicine's legal status: • Somapacitan is a restricted prescription-only medicine, prescribed by specialists.
Diabetes mellitus type 2	Routine risk communication: • SmPC Section 4.2, where information is included concerning individual dose requirements based on the clinical response and serum IGF-I concentration. Risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4, where a special warning is included on glucose metabolism impairment.

Safety concerns	Routine risk minimisation measures
	• PL Section 2, where information is included on high blood sugar. <u>Other risk minimisation measures beyond the Product Information:</u> • Medicine's legal status: • Somapacitan is a restricted prescription-only medicine, prescribed by specialists.

Safety concerns	Routine risk minimisation measures
Medication errors (Incorrect dose administration rate)	Routine risk communication: • SmPC Section 4.2, where information is included concerning the appropriately qualified and experienced physicians to initiate and monitor somapacitan treatment. In addition, Section 4.2 gives clear instructions regarding once-weekly dose, how to change the dosing day and the steps to follow when a dose is missed. • SmPC Section 5.1, where information regarding maintenance dose is included. Risk minimisation activities recommending specific clinical measures to address the risk: • Labelling Section 5, where the term 'Once weekly' is printed on the carton (on the inner and outer package in multi-package) and preload pen label. • PL Section 3, where information is included concerning how and when to use somapacitan. Other risk minimisation measures beyond the Product Information: • Medicine's legal status: • Somapacitan is a restricted prescription-only medicine, prescribed by specialists.
Off-label paediatric use	Routine risk communication: • SmPC Section 4.1, where information is included concerning the therapeutic indication. • SmPC Section 4.2, under 'Special population', where information is included on paediatric population below 18 years of age. Risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4, where a special warning is included on paediatric population below 18 years of age. • PL Section 2, where information is included on paediatric population below 18 years of age. Other risk minimisation measures beyond the Product Information: • Medicine's legal status: • Somapacitan is a restricted prescription-only medicine, prescribed by specialists.
Missing information	
Patients with heart failure, NYHA class >2	Routine risk communication: • SmPC Section 4.2, where information is included concerning individual dose requirements based on the clinical response and serum IGF-I concentration. Risk minimisation activities recommending specific clinical measures to address the risk: • None proposed Other risk minimisation measures beyond the Product Information: • Medicine's legal status: • Somapacitan is a restricted prescription-only medicine, prescribed by specialists.

Safety concerns	Routine risk minimisation measures
Patients with severe hepatic impairment	Routine risk communication: • SmPC Section 4.2, where information is included concerning individual dose requirements based on the clinical response and serum IGF-I concentration. • SmPC Section 4.2, under 'Special population', where information is included on patients with severe hepatic impairment. Risk minimisation activities recommending specific clinical measures to address the risk: • None proposed Other risk minimisation measures beyond the Product Information: • Medicine's legal status: • Somapacitan is a restricted prescription-only medicine, prescribed by specialists.
Long-term safety	Routine risk communication: • None proposed Risk minimisation activities recommending specific clinical measures to address the risk: • None proposed Other risk minimisation measures beyond the Product Information: • Medicine's legal status: • Somapacitan is a restricted prescription-only medicine, prescribed by specialists.

Abbreviations: IGF-I = insulin-like growth factor-I; N/A = not applicable; NYHA = New York Heart Association; PL = package leaflet; SmPC = Summary of Product Characteristics.

2.7.4. Conclusion

The CHMP considered that the risk management plan version 2.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: This patient leaflet is similar to the already approved patient leaflet for the Sogroya 10 mg/1.5 mL.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Sogroya (somapacitan) is included in the additional monitoring list as it is a biological product.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

This application concerns a line extension of somapacitan 10 mg/1.5 ml solution for injection, i.e. somapacitan 5 mg/1.5 ml solution for injection.

The reference product somapacitan 10 mg/1.5 ml solution for injection, is indicated for the replacement of endogenous GH in adults with growth hormone deficiency.

No nonclinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient.

From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature is considered sufficient.

The bioequivalence study NN8640-4491 forms the pivotal basis with a randomised, three-treatment, three-period, single dose, crossover design, in which the 10 mg/5 ml reference formulation was administered twice. The study design is considered adequate to evaluate the bioequivalence of the 5 mg/1.5 ml solution for injection and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied are adequate.

The 5 mg/1.5 ml test formulation of somapacitan met the protocol-defined criteria for bioequivalence when compared with the 10 mg/1.5 ml reference formulation, with regard to somapacitan AUC_{0-t}. The point estimate and the 90% confidence interval, i.e. 0.95 and 0.89 – 1.01, respectively, were contained within the protocol-defined acceptance range of 80.00 to 125.00%. With regard to somapacitan C_{max}, the protocol-defined criteria for bioequivalence were not met, as the point estimate and the 90% confidence interval, i.e. 0.77 and 0.68 – 0.89, respectively, were not contained within the protocol-defined widened acceptance range of 70.00 to 143.00%. This widened acceptance criteria was based upon the proven high within-subject variability in this study and in accordance with EMA's Guideline on the investigation of bioequivalence.

However, although this observed difference in somapacitan pharmacokinetics, based on the IGF-I endpoint $AUC_{0\text{-}168h}$ (and C_{max}), the new 5mg/1.5 ml solution for injection is comparable to the Reference 10mg/1.5 ml solution for injection, as the 90% CI was within the protocol-defined criteria for bioequivalence of 80.00 – 125.00%, i.e. 0.98 – 1.02. Moreover, as IGF-I can be considered a pharmacodynamic endpoint, by applying the 95% CI, the CI was still within normal criteria for $AUC_{0\text{-}168h}$ and C_{max}, i.e. 0.98 - 1.03 and 0.97 - 1.04, respectively.

In clinical practise, initiation of somapacitan treatment and subsequent monitoring will be carried out by experienced specialist qualified in diagnosing and treatment of patients with growth hormone deficiency. Dosing and titration (in small steps) will be done per individual patient. IGF-I SDS scores as biomarker will be used for dose titration. After reaching the desired IGF-I SDS level, the efficacy and safety of treatment will be continuously evaluated; IGF-I levels is one of the control parameters/biomarkers. Considering this and the fact that after administration of the somapacitan 5 mg/1.5 ml and 10 mg/1.5 ml solution for injection a comparable IGF-I exposure ($AUC_{0\text{-}168h}$) and IGF-I concentration-time curve is observed, a difference in safety and efficacy is not expected. Therefore it is considered that the lower somapacitan C_{max} can be waived by the comparability in IGF-I exposure.

There are no outstanding issues.

3.1. Conclusions

The overall benefit/risk balance of Sogroya is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Sogroya is not similar to Lonapegsomatropin Ascendis Pharma and Ngenla within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix 1. on similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Sogroya new strength is favourable in the following indication(s):

Sogroya is indicated for the replacement of endogenous growth hormone (GH) in adults with growth hormone deficiency (AGHD).

The CHMP therefore recommends the extension(s) of the marketing authorisation for Sogroya subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive

2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

Variations requested		**Type**	**Annexes affected**
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, IIIA, IIIB and A
B.II.d.1.a	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	Type IA	None
B.II.b.1.c	B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes	Type II	None

Extension application to add a new strength of 5 mg/1.5 mL (3.3 mg/mL) grouped with a Type II Quality variation for a new finished product facility and a Type IA variation, tightening of specification limit. RMP was updated (version 2.0) accordingly.

Type II variation (B.II.b.1.c) to transfer the formulation, filling and inspection activities for Sogroya finished product (cartridges) from Novo Nordisk A/S, Hagedornsvej 1, DK-2820 Gentofte, Hovedstaden, Denmark to Novo Nordisk A/S, Hallas Allé, DK-4400 Kalundborg, Denmark. The activities at the Kalundborg site will also include finished product QC testing (microbiological; sterility). The site in Gentofte will also be maintained as a finished product QC testing site (microbiological; sterility). The changes apply to the approved Sogroya 10 mg strength as well as to the Sogroya 5 mg strength currently applied for via line extension. The following consequential changes are included:
- Introduction of an optimized one-step manufacturing process
- Change in process controls limits for mixing speed and time
- Upscale of the batch size range

- Expansion of sterile filtration time
- New silicone emulsion for siliconization of the glass cartridges.

Type IA variation (B.II.d.1.a) to align the Endotoxin release acceptance for Sogroya 10 mg, to the narrower limit proposed limit for the 5 mg strength (<16 EU/ml). At the same time, the units for Endotoxin are changed from EU/mg to EU/ml.