SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Sogroya 5 mg/1.5 mL solution for injection in pre-filled pen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of solution contains 3.3 mg of somapacitan*
Each pre-filled pen contains 5 mg of somapacitan in 1.5 mL solution

*Produced by recombinant DNA technology in *Escherichia coli* followed by attachment of an albumin binding moiety.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).
Clear to slightly opalescent, colourless to slightly yellow liquid, essentially free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Sogroya is indicated for the replacement of endogenous growth hormone (GH) in children aged 3 years and above, and adolescents with growth failure due to growth hormone deficiency (paediatric GHD), and in adults with growth hormone deficiency (adult GHD).

4.2 Posology and method of administration

Somapacitan should be initiated and monitored by physicians who are appropriately qualified and experienced in the diagnosis and management of patients with growth hormone deficiency (e.g. endocrinologists).

Posology

Table 1: Dose recommendation

Paediatric GHD	Recommended starting dose
Treatment-naïve paediatric patients and paediatric patients switching from other GH medicinal products	0.16 mg/kg/week
Adult GHD	Recommended starting dose
Naïve patients Adults (≥18 to <60 years) Women on oral oestrogen therapy (irrespective of age) Elderly (60 years or older)	 1.5 mg/week 2 mg/week 1 mg/week
Patients switching from daily GH medicinal products Adults (≥18 to <60 years) Women on oral oestrogen therapy (irrespective of age) Elderly (60 years or older)	 2 mg/week 4 mg/week 1.5 mg/week

Paediatric GHD

Dose titration

Somapacitan dose may be individualised and adjusted based on growth velocity, adverse reactions, body weight and serum insulin-like growth factor I (IGF-I) concentrations.

Average IGF-I standard deviation score (SDS) levels (drawn 4 days after dosing) can guide dose titration. Dose adjustments should be targeted to achieve average IGF-I SDS levels in the normal range, i.e. between -2 and +2 *(preferable close to 0 SDS)*.

If the IGF-I (SDS) is > 2, it should be reassessed after a subsequent somapacitan administration. If the value remains > 2, reducing the dose by 0.04 mg/kg/week is recommended. More than one dose reduction may be required in some patients.

In patients who have had the dose reduced but are not growing well, the dose may be gradually increased as tolerated up to a maximum dose of 0.16 mg/kg/week. Dose increments should not exceed 0.02 mg/kg per week.

Treatment evaluation

Evaluation of efficacy and safety should be considered at approximately 6- to 12-month intervals and may be assessed by evaluating auxological parameters, biochemistry (IGF-I, hormones, glucose, and lipid levels) and pubertal status. More frequent evaluations should be considered during puberty.

Treatment should be discontinued in patients having achieved final height or near final height, i.e. an annualised height velocity < 2 cm/year and a bone age > 14 years in girls or > 16 years in boys which corresponds to the closure of the epiphyseal

growth plates, see section 4.3. Once the epiphyses are fused, patients should be clinically re-evaluated for the need for growth hormone treatment.

When GHD persists after growth completion, growth hormone treatment should be continued to achieve full somatic adult development including lean body mass and bone mineral accrual (for guidance on dosing see recommended dose for adults (Table 1)).

Adult GHD
Dose titration
The somapacitan dose must be individually adjusted for each patient. It is recommended to increase the dose gradually with 2-4 weeks intervals in steps from 0.5 mg to 1.5 mg based on the patients' clinical response and experience of adverse reactions up to a dose of 8 mg somapacitan per week.
Serum insulin like growth factor-I (IGF-I) levels (drawn 3-4 days after dosing) can be used as guidance for the dose titration. The IGF-I standard deviation score (SDS) target should aim for the upper normal range not exceeding 2 SDS. IGF-I SDS levels in the target range are usually achieved within 8 weeks of dose titration. Longer dose titration may be necessary in some adult GHD patients (see below and section 5.1).

Treatment evaluation
Using IGF-I SDS as a biomarker for dose titration, the aim is to reach IGF-I SDS levels within the age-adjusted upper reference range (IGF-I SDS upper reference range: 0 and +2) within 12 months of titration. If this target range cannot be achieved within this period, or the patient does not obtain the desired clinical response, other treatment options should be considered.

During somapacitan maintenance treatment, evaluation of efficacy and safety should be considered at approximately 6- to 12-month intervals and may be assessed by evaluating biochemistry (IGF-I-, glucose-, and lipid levels), body composition, and body mass index.

Paediatric and adult GHD
Switching from other growth hormone products
Patients switching from a weekly growth hormone to somapacitan are recommended to continue administration at their once weekly dosing day.
Patients switching from daily human growth hormone to once-weekly somapacitan should choose the preferred day for the weekly dose and inject the final dose of daily treatment the day before (or at least 8 hours before) injecting the first dose of once-weekly somapacitan. Patients should follow the instructions for the dose presented in Table 1.

Oral oestrogen therapy
Females on oral oestrogen-containing therapy may have reduced IGF-I levels and may require dose adjustment of growth hormone to achieve the treatment goal (see section 4.4).
In paediatric GHD doses above 0.16 mg/kg/week have not been studied and are not recommended.

Missed dose
Patients who miss a dose are advised to inject once-weekly somapacitan upon discovery as soon as possible, within 3 days after the missed dose, and then resume their usual once-weekly dosing schedule. If more than 3 days have passed, the dose should be skipped and the next dose should be administered on the regularly scheduled day. If two or more doses have been missed, the dose should be resumed on the regularly scheduled day.

Changing the dosing day
The day of weekly injection can be changed as long as the time between two doses is at least 4 days. After selecting a new dosing day, the once weekly dosing should be continued.

Flexibility in dosing time
On occasions when injection at the scheduled dosing day is not possible, once-weekly somapacitan can be administered up to 2 days before or 3 days after the scheduled weekly dosing day as long as the time between two doses is at least 4 days (96 hours). Once-weekly dosing for the next dose could be resumed at the regularly scheduled dosing day.

Special populations
Elderly (60 years or older)
Generally, lower doses of somapacitan may be necessary in older patients. For further information, see section 5.2.

Paediatric population
Limited data on the clinical effects of somapacitan are available in paediatric GHD patients under 3 years of age. Currently available data are described in section 5.1, but no recommendation on a posology can be made.

Gender
Men show an increasing IGF-I sensitivity over time. This means that there is a risk that men are overtreated. Women, especially those on oral oestrogen, may require higher doses and a longer titration period than men, see sections 5.1 and 5.2. In females using oral oestrogen, it should be considered to change the route of oestrogen administration (e.g. transdermal, vaginal) see section 4.4.

Renal impairment
No adjustment of the starting dose is required for patients with renal impairment. Patients with renal impairment may need lower doses of somapacitan, but since the dose of somapacitan is individually adjusted according to the need of each patient, no further dose adjustment is required, see section 5.2.

Hepatic impairment
No adjustment of the starting dose is required for patients with hepatic impairment. Patients with moderate hepatic impairment may need higher doses of somapacitan, but since the dose of somapacitan is individually adjusted according to the need of each patient, no further dose adjustment is required. No information regarding the use

of somapacitan in patients with severe hepatic impairment is available. Caution should be exercised if treating these patients with somapacitan, see section 5.2.

Method of administration

Somapacitan is to be administered once-weekly at any time of the day.

Somapacitan is to be injected subcutaneously in the abdomen, thighs, buttocks or upper arms without dose adjustment.

The injection site should be rotated every week to prevent local lipoatrophy.

The pen delivers doses from 0.025 mg (0.0075 mL) to 2 mg (0.6 mL) in increments of 0.025 mg.

For instructions of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Somapacitan must not be used when there is any evidence of activity of a tumour. Intracranial tumours must be inactive and antitumour therapy must be completed prior to starting somapacitan therapy. Treatment should be discontinued if there is evidence of tumour growth, see section 4.4.

Somapacitan must not be used for longitudinal growth promotion in children with closed epiphyses, see section 4.2.

Patients with acute critical illness suffering from complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions must not be treated with somapacitan (regarding patients undergoing substitution therapy, see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Adrenocortical insufficiency

Introduction of growth hormone treatment may result in inhibition of 11βHSD-1 and reduced serum cortisol concentrations. In patients treated with growth hormone, previously undiagnosed central (secondary) hypoadrenalism may be unmasked and glucocorticoid replacement may be required. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress

doses following initiation of growth hormone treatment. It is necessary to monitor patients with known hypoadrenalism for reduced serum cortisol levels and/or for the need of increased doses of glucocorticoid, see section 4.5.

Glucose metabolism impairment

Treatment with growth hormone may decrease insulin sensitivity, particularly at higher doses in susceptible patients and consequently hyperglycaemia may occur in subjects with inadequate insulin secretory capacity. As a result, previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during growth hormone treatment. Therefore, glucose levels should be monitored periodically in all patients treated with growth hormone, especially in those with risk factors for diabetes mellitus, such as obesity, or a family history of diabetes mellitus. Patients with pre-existing type 1 or type 2 diabetes mellitus or impaired glucose tolerance should be monitored closely during growth hormone therapy. The doses of antihyperglycaemic medicinal products may require adjustment when growth hormone therapy is instituted in these patients.

Neoplasms

There is no evidence for increased risk of new primary cancers in patients treated with growth hormone.

In patients in complete remission from malignant diseases or who have been treated for benign tumours, growth hormone therapy has not been associated with an increased relapse rate.
Patients who have achieved complete remission of malignant diseases or who have been treated for benign tumours should be followed closely for relapse after commencement of growth hormone therapy. Growth hormone treatment should be interrupted in case of any development or reoccurrence of malignant or benign tumour.
An overall slight increase in second neoplasms has been observed in childhood cancer survivors treated with growth hormone, with the most frequent being intracranial tumours. The dominant risk factor for secondary neoplasms seems to be prior exposure to radiation.

Benign intracranial hypertension

In the event of severe or recurrent headache, visual symptoms, nausea, and/or vomiting, a fundoscopy for papilloedema is recommended. If papilloedema is confirmed, a diagnosis of benign intracranial hypertension should be considered and if appropriate the growth hormone treatment should be discontinued. At present there is insufficient evidence to guide clinical decision making in patients with resolved intracranial hypertension. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

Thyroid function

Growth hormone increases the extrathyroidal conversion of T4 to T3 and may as such unmask incipient hypothyroidism. As hypothyroidism interferes with the response to growth hormone therapy, patients should have their thyroid function tested regularly and should receive replacement therapy with thyroid hormone when indicated, see sections 4.5 and 4.8.

Use with oral oestrogen

Oral oestrogen influences the IGF-I response to growth hormone including somapacitan. Female patients taking any form of oral oestrogen (hormone therapy or contraception) should consider changing the route of oestrogen administration (e.g. transdermal-, vaginal hormone products) or use another form of contraception. If a woman on oral oestrogen is starting somapacitan therapy, higher starting doses and a longer titration period may be required (see section 4.2).

If a female patient taking somapacitan begins oral oestrogen therapy, the dose of somapacitan may need to be increased to maintain the serum IGF-I levels within the normal age-appropriate range. Conversely, if a female patient on somapacitan discontinues oral oestrogen therapy, the dose of somapacitan may need to be reduced to avoid excess of somapacitan and/or undesirable effects, see sections 4.2 and 4.5.

Skin and subcutaneous tissue disorders

When somapacitan is administered at the same site over a longer period of time, local changes in the subcutaneous tissue such as lipohypertrophy, lipoatrophy, and acquired lipodystrophy might occur. The injection site should be rotated to minimise the risk, see sections 4.2 and 4.8.

Antibodies

Antibodies to somapacitan were not observed in adult GHD patients. Few paediatric GHD patients tested positive for somapacitan binding antibodies. None of these antibodies were neutralising and no impact on the clinical effects was observed. Testing for presence of anti-somapacitan antibodies should be carried out in patients who fail to respond to therapy.

Acute critical illness

The effect of growth hormone on recovery was studied in two placebo controlled trials involving 522 critical ill adult patients suffering from complications following open heart surgery, abdominal surgery, multiple accidental trauma or acute respiratory failure. Mortality was higher in patients treated with 5.3 or 8 mg growth hormone daily compared to patients receiving placebo, 42% vs 19%. Based on this information, these types of patients should not be treated with somapacitan. As there is no information available on the safety of growth hormone substitution therapy in acutely critical ill patients, the benefits of continued treatment in this situation should be weighed against the potential risks involved.

Growth hormone deficiency in adults is a lifelong disease and needs to be treated accordingly, however, experience in patients older than 60 years and in patients with more than five years of treatment in adult growth hormone deficiency is still limited.

Pancreatitis

There have been few reports of pancreatitis during treatment with other growth hormone medicinal products. It should therefore be considered in somapacitan treated patients who develop unexplained abdominal pain.

Slipped capital femoral epiphysis

In fast growing children and patients with endocrine disorders, including GHD, slipped epiphyses of the hip may occur more frequently than in the general population. Children with

persistent hip/knee pain and/or limping during treatment with somapacitan should be examined clinically.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

Cytochrome P450 metabolised drugs

Data from an interaction study performed in growth hormone deficient adults suggests that growth hormone administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes. The clearance of compounds metabolised by cytochrome P450 (e.g. sex steroids, corticosteroids, anticonvulsants and cyclosporine) may be especially increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown.

Glucocorticoids

Growth hormone decreases the conversion of cortisone to cortisol and may unmask previously undiscovered central hypoadrenalism or render low glucocorticoid replacement doses ineffective, see section 4.4.

Oral oestrogens

In females on oral oestrogen therapy, a higher dose of somapacitan may be required to achieve the treatment goal, see sections 4.2 and 4.4.

Antihyperglycaemic products

Antihyperglycaemic treatment including insulin may require dose adjustment in case of somapacitan co-administration since somapacitan may decrease insulin sensitivity, see sections 4.4 and 4.8.

Other

The metabolic effects of somapacitan can also be influenced by concomitant therapy with other hormones, e.g. testosterone and thyroid hormones, see section 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of somapacitan in pregnant women.
Studies in animal have shown reproductive toxicity, see section 5.3.
Sogroya is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether somapacitan/metabolites are excreted in human milk.
Available pharmacodynamic/toxicological data in animals have shown excretion of somapacitan in milk, see section 5.3.
A risk to the breastfed newborns/infants cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Sogroya therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There is no clinical experience with somapacitan use and its potential effect on fertility. No adverse effects were observed on male and female fertility in rats, see section 5.3.

4.7 Effects on ability to drive and use machines

Sogroya has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile

The commonly most frequently reported adverse drug reactions (ADRs) are (in decreasing order [paediatric GHD, adult GHD]) headache (12%, 12%), pain in extremity (9%, NA), hypothyroidism (5%, 2%), injection site reactions (5%, 1%), peripheral oedema (3%, 4%), arthralgia (2%, 7%), hyperglycaemia (2%, 1%), fatigue (2%, 6%) and adrenocortical insufficiency (1.5%, 3%).

Tabulated list of adverse reactions

The ADRs listed in Table 2 are based on the safety data from one ongoing pivotal phase 3 trial (52 weeks) in paediatric patients with GHD (baseline age: 2.5 to 11 years) and adverse reactions from somapacitan treatment. The frequencies of the ADRs have been calculated based on the frequencies in the pivotal phase 3 trial.
The adverse reactions listed in Table 3 are based on the compiled safety data from three completed phase 3 trials in adult patients with GHD (baseline age: 19 to 77 years).

The ADRs are listed by MedDRA system organ class and frequency category defined as: Very common (≥1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 2: Adverse reactions from phase 3 clinical trial in paediatric GHD

MedDRA system organ class	Very common	Common
Endocrine disorders		Hypothyroidism*

		Adrenocortical insufficiency
Metabolism and nutrition disorders		Hyperglycaemia
Nervous system disorders	Headache*	
Musculo-skeletal and connective tissue disorders		Arthralgia Pain in extremity**
General disorders and administration site conditions		Peripheral oedema* Injection site reactions*[#] Fatigue

*In general, these adverse reactions were non-serious, of mild severity and transient
[#]The injection site reactions included injection site bruising (1.5%), injection site pain (1.5%), injection site haematoma (1.5%), and injection site swelling (0.8%).
**Primarily mild leg pain

Table 3: Adverse reactions from three completed phase 3 trials in adult patients with GHD

MedDRA system organ class	**Very common**	**Common**	**Uncommon**
Endocrine disorders		Adrenocortical insufficiency Hypothyroidism	
Metabolism and nutrition disorders		Hyperglycaemia*	
Nervous system disorders	Headache	Paraesthesia	Carpal tunnel syndrome
Skin and subcutaneous tissue disorders		Rash* Urticaria*	Lipohypertrophy* Pruritus*
Musculoskeletal and connective tissue disorders		Arthralgia Myalgia Muscle stiffness*	Joint stiffness
General disorders and administration site conditions		Peripheral oedema Fatigue Asthenia Injection site reactions*	

*In general, these adverse reactions were non-serious, mild or moderate severity and transient

Description of selected adverse reactions

Peripheral oedema
Peripheral oedema was commonly observed (3% in paediatric GHD and 4% in adult GHD). Growth hormone deficient patients are characterised by extracellular volume deficit. When

treatment with growth hormone products is initiated, this deficit is corrected. Fluid retention with peripheral oedema may occur. The symptoms are usually transient, dose dependent and may require transient dose reduction.

Adrenocortical insufficiency
Adrenocortical insufficiency was commonly observed (1.5% in paediatric GHD and 3% in adult GHD), see section 4.4.

Paediatric population

The safety of somapacitan has been established in children and adolescents aged 3 years and above with growth failure due to GHD. The safety profile of somapacitan in GHD patients under 3 years of age is not established.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

Yellow Card Scheme
Website: https://yellowcard.mhra.gov.ukor search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

There is limited clinical experience with overdose of somapacitan.

Based on experience with daily growth hormone treatment, short term overdose with low blood glucose levels initially, followed by high blood glucose levels can occur. These decreased glucose levels have been detected biochemically, but without clinical signs of hypoglycaemia.

Long-term overdosage could result in signs and symptoms consistent with the known effects of human growth hormone excess.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, somatropin and somatropin agonists, ATC code: H01AC07.

Mechanism of action

Somapacitan is a long-acting recombinant human growth hormone derivative. It consists of 191 amino acids similar to endogenous human growth hormone, with a single substitution in the amino acid backbone (L101C) to which an albumin binding moiety has been attached.

The albumin binding moiety (side-chain) consists of a fatty acid moiety and a hydrophilic spacer attached to position 101 of the protein.
The mechanism of action of somapacitan is either directly via the GH-receptor and/or indirectly via IGF-I produced in tissues throughout the body, but predominantly by the liver. When growth hormone deficiency is treated with somapacitan a normalisation of body composition (i.e., decreased body fat mass, increased lean body mass) and of metabolic action is achieved.

Somapacitan stimulates skeletal growth in paediatric patients with GHD as a result of effects on the growth plates (epiphyses) of bones, see section 5.3.

Pharmacodynamic effects

IGF-I
IGF-I is a generally accepted biomarker for efficacy in GHD.
A dose-dependent IGF-I response is induced following somapacitan administration.

A steady state pattern in IGF-I responses is reached after 1-2 weekly doses.
The IGF-I levels fluctuate during the week. The IGF-I response is maximal after 2 to 4 days. Compared with daily GH treatment, the IGF-I profile of somapacitan differs, see Figure 1.

In paediatric GHD patients somapacitan produces a dose linear IGF-I response, with a change of 0.02 mg/kg on average resulting in a change in IGF-I standard deviation score (SDS) of 0.32.

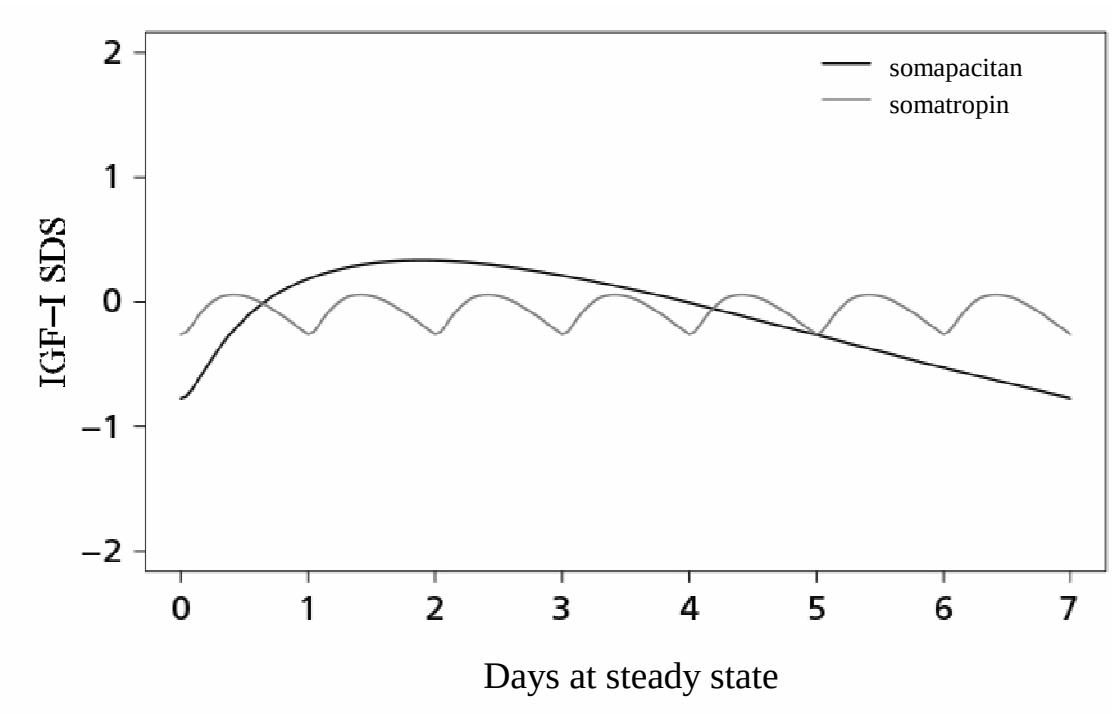

Figure 1: Model-derived IGF-I profiles during steady state of somapacitan and somatropin (based on data from adult GHD)

Clinical efficacy and safety

Paediatric GHD
REAL 4 (phase 3)
The efficacy and safety of once weekly somapacitan was evaluated in a 52 weeks randomised, multi-center, open-label, active-controlled, parallel-group phase 3 trial (REAL 4) in 200 treatment-naïve, paediatric patients with GHD. Patients were randomised to 0.16 mg/kg/week once weekly somapacitan (N=132) or 0.034 mg/kg/day once daily somatropin (N=68).

At baseline, the 200 patients had a mean age of 6.4 years (range: 2.5 to 11 years). 74.5% of the patients were male.

The annualised height velocity at week 52 was similar for somapacitan and somatropin (Table 4).

Table 4: Growth results at week 52 in paediatric patients with GHD

	Once-weekly somapacitan (N=132)	Once-daily somatropin (N=68)	Estimate of treatment difference (95% CI) (somapacitan-minus somatropin)
Annualised height velocity (cm/year)	11.2	11.7	-0.5 [-1.1; 0.2]

In accordance with this, changes at week 52 compared to baseline with respect to the height SDS and IGF-I SDS were also similar for somapacitan and somatropin (Table 5).

Table 5: Height SDS and IGF-I SDS in paediatric patients with GHD – 52 weeks treatment

	Once-weekly somapacitan (N=132)	Once-daily somatropin (N=68)	Estimate of treatment difference (95% CI) (somapacitan minus somatropin)
Height SDS, baseline[a]	-2.99	-3.47	
Height SDS, change from baseline	1.25	1.30	-0.05 [-0.18; 0.08]
IGF-I SDS, baseline[a]	-2.03	-2.33	
IGF-I SDS, week 52[a]	0.28	0.10	
IGF-I SDS level change from baseline	2.36	2.33	0.03 [-0.30; 0.36]

[a] Observed mean

The vast majority of paediatric patients (96.9%) in the trial achieved an average IGF-I SDS level within normal range (-2 to +2) after 52 weeks of treatment with once weekly somapacitan (Table 6). A low number of patients had average IGF-I SDS above +2 (2.3%) and no patients had average IGF-I SDS above +3.

Table 6: Average IGF-I SDS values after 52 weeks of treatment of paediatric patients with GHD with once weekly somapacitan

IGF-I SDS category	Week 52 average (N=132)
<-2	0.8%
-2 to 0	21.2%
0 to +2	75.8%
+2 to +3	2.3%
>+3	0

REAL 3 (phase 2)
A total of 59 GH treatment-naïve GH-deficient paediatric patients completed a 26-week main period and a 26-week extension in a 4-arm parallel group trial with once weekly somapacitan at dose levels of 0.04, 0.08 and 0.16 mg/kg/week and active control arm of 0.034 mg/kg/day daily somatropin. The patients continued in a 104-week open-label safety extension parallel arms with somapacitan 0.16 mg/kg/week and daily somatropin 0.034 mg/kg/day. All patients were afterwards transferred to once weekly somapacitan 0.16 mg/kg/week in a 208-week long-term safety extension.

Treatment with once weekly somapacitan led to continuous treatment benefits up to at least week 208. Height SDS was -1.06 (change from baseline: 2.85) in 38 patients.

Height outcome obtained at week 208 in patients switching from 0.034 mg/kg/day daily somatropin to 0.16 mg/kg/week once weekly somapacitan at week 156 indicated that treatment benefits with daily GH treatment are maintained after switching to once weekly somapacitan.

Mean IGF-I SDS remained within the normal range for all groups.

Adult GHD
In a 34-week placebo-controlled (double-blind) and active-controlled (open) trial, 301 treatment-naïve adult patients with GHD were randomised (2:1:2) and 300 were exposed to once-weekly somapacitan or to placebo or to daily somatropin for a 34-week treatment period (main phase of the trial). The patient population had a mean age of 45.1 years (range 23-77 years; 41 patients were 65 years or above), 51.7% were females, and 69.7% had adult onset GHD.
A total of 272 adult GHD patients who completed the 34-week main phase continued in a 53-week open-label extension period. Subjects on placebo were switched to somapacitan and patients on somatropin were re-randomised (1:1) to either somapacitan or somatropin.

Observed clinical effects for the main endpoints in the main treatment phase (Table 7) and extension treatment phase (Table 8) are presented below.

Table 7: Results at 34 weeks

Change from baseline at 34 weeks[a]	somapacitan	somatropin	placebo	Difference somapacitan - placebo [95% CI] p-value	Difference somapacitan-somatropin [95% CI]
Number of subjects (N)	120	119	61		
Truncal fat % (Primary endpoint)	-1.06	-2.23	0.47	-1.53 [-2.68; -0.38] 0.0090[b]	1.17 [0.23; 2.11]
Visceral adipose tissue (cm^2)	-10	-9	3	-14 [-21; -7]	-1 [-7; 4]
Appendicular skeletal muscle mass (g)	558	462	-121	679 [340; 1,019]	96 [-182; 374]
Lean body mass (g)	1,394	1,345	250	1144 [459; 1,829]	49 [-513; 610]
IGF-I SDS level	2.40	2.37	-0.01	2.40 [2.09; 2.72]	0.02 [-0.23; 0.28]

Abbreviations: N = Number of subjects in full analysis set, CI = Confidence interval, DM=Diabetes mellitus. IGF-I SDS: Insulin-like growth factor-I standard deviation score.

[a] Body composition parameters are based on dual-energy X-ray absorptiometry (DXA) scanning.

[b] The primary analysis was a comparison of changes from baseline for somapacitan and placebo in truncal fat %. Changes in truncal fat % from baseline to the 34 week's measurements was analysed using an analysis of covariance model with treatment, GHD onset type, sex, region, DM and sex by region by DM interaction as factors and baseline as a covariate incorporating a multiple imputation technique where missing week 34 values were imputed based on data from the placebo group.

Post-hoc subgroup analysis of changes from baseline in truncal fat percentage (%) compared to placebo at week 34 showed an estimated treatment difference (somapacitan-placebo) of -2.49% [-4.19; -0.79] in men, -0.80% [-2.99; 1.39] in women not on oral oestrogen, -1.44% [-3.97; 1.09] in women on oral oestrogen.

Table 8: Results at 87 weeks

Change from baseline at 87 weeks[a]	somapacitan/ somapacitan	somatropin/ somatropin	placebo/ somapacitan	somatropin/ somapacitan	Difference somapacitan/ somapacitan vs somatropin/somatropin [95% CI]
Number of subjects (N)	114	52	54	51	
Truncal fat %	-1.52	-2.67	-2.28	-1.35	1.15 [-0.10; 2.40]
Visceral adipose tissue (cm^2)	-6.64	-6.85	-10.21	-8.77	0.22 [-10; 10]
Appendicular skeletal muscle mass (g)	546.11	449.09	411.05	575.80	97.02 [-362; 556]
Lean body mass (g)	1,739.05	1,305.73	1,660.56	1,707.82	433.32 [-404; 1271]

[a] Body composition parameters are based on DXA scanning.

Observed and simulated IGF-I SDS levels in the clinical study

In the main phase of the clinical study IGF-I SDS values of 0 and above were overall achieved in 53% of somapacitan-treated adult GHD study patients after an 8-week dose titration period. This proportion was however lower in particular subgroups such as women on oral oestrogen (32%) and patients with childhood-onset (39%) (Table 9). *Post-hoc* simulation analyses indicated that the proportions of adult GHD patients achieving IGF-I SDS levels above 0 are expected to be higher in case somapacitan dose titration beyond 8 weeks would be allowed. In this simulation analysis, it was assumed that somapacitan dose titration was well-tolerated in all patients until the IGF-I SDS target range or a somapacitan dose of 8 mg per week would be achieved.

Table 9 Proportions of somapacitan-treated adult GHD patients with IGF-I SDS levels above 0

Subgroups	Men	Women not on oral oestrogen	Women on oral oestrogen	Childhood-onset adult GHD	Adult-onset adult GHD	All
Observed[a]	71%	46%	32%	39%	60%	53%
Post-hoc simulations	100%	96%	70%	84%	92%	90%

[a] The trial was designed to titrate towards a IGF-I SDS level above -0.5

Maintenance dose

Maintenance dose varies from person to person and between male and female patients. The average somapacitan maintenance dose observed in the phase 3 clinical trials was 2.4 mg/week.

Paediatric and adult GHD

Clinical safety

The safety profile of somapacitan was similar to the well-known safety profile of somatropin. No new safety issues were identified, see section 4.8.

Immunogenicity
Anti-drug antibodies (ADA) were uncommonly detected in paediatric patients (16/132). None of these antibodies were neutralising. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed. No anti-drug antibodies were detected in adult patients.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Sogroya in all subsets of the paediatric population in growth hormone deficiency (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Somapacitan has pharmacokinetic properties compatible with once weekly administration. The reversible binding to endogenous albumin delays elimination of somapacitan and thereby prolongs the *in vivo* half-life and duration of action.
The pharmacokinetics of somapacitan following subcutaneous administration have been investigated at dose levels from 0.02 to 0.16 mg/kg/week in paediatric population (2.5 to 14 years), at dose levels from 0.01 to 0.32 mg/kg in healthy adults, and in doses up to 0.12 mg/kg in patients with adult GHD.
Overall, somapacitan displays non-linear pharmacokinetics across the investigated dose range. However, in the clinically relevant dose range of somapacitan in adult GHD, somapacitan pharmacokinetics are approximately linear.
In paediatric GHD, a somapacitan dose of 0.16 mg/kg/week corresponds to an average concentration of 80.2 ng/mL and in adult GHD, somapacitan doses in the clinically relevant range correspond to average concentrations of 0.1-36.2 ng/mL.

Absorption

In adult and paediatric patients with GHD median t_{max} ranged from 4 to 25.5 hours at doses from 0.02 mg/kg/week to 0.16 mg/kg/week.
Steady state exposure was achieved following 1-2 weekly administration.
Absolute bioavailability of somapacitan in humans has not been investigated.

Distribution

Somapacitan is extensively bound (>99%) to plasma proteins and is expected to be distributed like albumin. Based on population PK analyses, the estimated volume of distribution (V/F) was 1.7 L in paediatric GHD patients and 14.6 L in adult GHD patients.

Elimination

Following a single dose and repeated dosing of 0.16 mg/kg/week the terminal half-life was approximately 34 hours in paediatric GHD patients.
The terminal half-life was estimated with geometric means ranging from approximately 2 to 3 days at steady state in paediatric and adult GHD patients (doses: 0.02 to 0.12 mg/kg).
Somapacitan will be present in circulation for approximately 2 weeks after the last dose. Little to no accumulation (mean accumulation ratio: 1-2) of somapacitan following multiple dosing has been observed.

Biotransformation

Somapacitan is extensively metabolised by proteolytic degradation and cleavage of the linker sequence between the peptide and albumin binder.

Somapacitan was extensively metabolised before excretion and no intact somapacitan was found neither in urine, which was the main excretion route (81%), nor in faeces where 13% of somapacitan related material was found, indicating full biotransformation before excretion.

Special populations

Paediatric GHD patients
Based on population pharmacokinetic analysis gender, race and body weight do not have a clinically meaningful effect on the pharmacokinetics following weight-based dosing.

Adult GHD patients
Age
Subjects older than 60 years have higher exposure (29%) than younger subjects at the same somapacitan dose. A lower starting dose for subjects above 60 years is described in section 4.2.

Gender
Female subjects and in particular female subjects on oral oestrogen, have lower exposure (53% for females on oral oestrogen and 30 % for females not on oral oestrogen) than male subjects at the same somapacitan dose. A higher starting dose for females on oral oestrogen is described in section 4.2.

Race
There was no difference in somapacitan exposure and IGF-I response between Japanese and White subjects. Despite a higher exposure in Asian Non-Japanese compared to White at the same somapacitan dose, White, Japanese and Asian Non-Japanese needed the same doses to reach similar IGF-I levels. Therefore, there is no dose adjustment recommendation based on race.

Ethnicity
Ethnicity (Hispanic or Latino 4.5% (15 subjects received somapacitan)) was not investigated due to small sample size in the development programme.

Body weight
Despite a higher exposure in subjects with low body weight as compared to subjects with high body weight at the same somapacitan dose, subjects needed the same doses to reach similar IGF-I levels across the body weight range 35 kg to 150 kg. Therefore, there is no dose adjustment recommendation based on body weight.

Renal impairment
A somapacitan dose of 0.08 mg/kg at steady state resulted in higher exposures in subjects with renal impairment, most pronounced in subjects with severe renal impairment and in subjects requiring haemodialysis, where $AUC_{0\text{-}168h}$ ratios to

normal renal function were 1.75 and 1.63, respectively. In general, somapacitan exposure tended to increase with decreasing GFR.
Higher IGF-I $_{AUC0\text{-}168h}$ levels were observed in subjects with moderate and severe renal impairment and subjects requiring haemodialysis, with ratios to normal renal function of 1.35, 1.40 and 1.24 respectively.
Due to the modest increase observed in IGF-I combined with the low recommended starting doses and the individual dose titration of somapacitan, there is no dose adjustment recommendation in patients with renal impairment.

Hepatic impairment
A somapacitan dose of 0.08 mg/kg at steady state resulted in higher exposure in subjects with moderate 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 and moderate hepatic impairment compared to subjects with normal hepatic function (ratio to normal was 0.85 for mild and 0.75 for moderate).
Due to the modest decrease observed in IGF-I combined with the individual dose titration of somapacitan, there is no dose adjustment recommendation in patients with hepatic impairment.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity or pre- and postnatal development.

No carcinogenicity studies have been performed with somapacitan.

No adverse effects were observed on male and female fertility in rats at a dose resulting in exposure at least 13 and 15-times greater than the expected maximum clinical exposure at 8 mg/week for males and females, respectively. However, irregular female oestrus cycle was seen at all doses treated.

No evidence of foetal harm was identified when pregnant rats and rabbits were administered subcutaneous somapacitan during organogenesis at doses leading to exposures well above expected exposure at the maximum clinical dose of 8 mg/week (at least 18-fold). At high doses leading to exposure at least 130-fold above the expected maximum clinical exposure at 8 mg/week, short/bent/thickened long bones were found in pups from female rats receiving somapacitan. Such findings in rats are known to resolve after birth and should be regarded as minor malformations, not permanent abnormalities.
Foetal growth was reduced when pregnant rabbits were dosed with somapacitan subcutaneously at exposures at least 9-fold above the expected exposure at the maximum clinical dose of 8 mg/week.

In lactating rats, somapacitan related material was secreted into milk but to a lower level than observed in plasma (up to 50% of level in plasma).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Mannitol
Poloxamer 188
Phenol
Water for injections
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment).

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

After first opening
6 weeks. Store in a refrigerator (2°C - 8°C).
Do not freeze. Keep away from the freezing element.
Keep Sogroya in the outer carton with the pen cap on to protect from light.

Before and after first opening
If refrigeration is not possible (e.g. during travelling), Sogroya may be kept temporarily at temperatures up to 30°C for up to a total of 72 hours (3 days). Return Sogroya to the refrigerator again after storage at this temperature. If stored out of refrigeration and then returned to refrigeration, the total combined time out of refrigeration should not exceed 3 days, monitor this carefully. The Sogroya pen should be discarded, if it has been kept up to 30°C for more than 72 hours (3 days) or for any period of time kept above 30°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze. Keep away from the freezing element.
Keep Sogroya in the outer carton with the pen cap on to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

The pre-filled pen consists of 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.

Sogroya 5 mg/1.5 mL solution for injection in pre-filled pen is a colour-coded pre-filled pen with the dose button on the pen-injector coloured teal.

Pack sizes of 1 pre-filled pen and multipack of 5 (5 packs of 1) pre-filled pens. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The pen is for use by one person only.

Sogroya should not be used if the solution does not appear clear to slightly opalescent, colourless to slightly yellow and free from visible particles.

Sogroya must not be used if it has been frozen.

The cartridge must not be taken out of the pre-filled pen and refilled.

A needle must always be attached before use. Needles must not be re-used. The injection needle should be removed after each injection and the pen should be stored without a needle attached. This may prevent blocked needles, contamination, infection, leakage of solution and inaccurate dosing.
In the event of blocked needles, patients must follow the instructions described in the instructions for use accompanying the package leaflet.

Needles are not included. Sogroya pre-filled pen-injector is designed to be used with disposable needles of a length between 4 mm and 8 mm and a gauge between 30G and 32G.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé

DK-2880 Bagsværd
Denmark

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