



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

28 January 2021  
EMA/95144/2021  
Committee for Medicinal Products for Human Use (CHMP)

## Assessment report

### **Sogroya**

International non-proprietary name: somapacitan

Procedure No. EMEA/H/C/005030/0000

### **Note**

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



# Table of contents

|   |          |
|---|----------|
| <b>1. Background information on the procedure</b> .....                         | <b>6</b> |
| 1.1. Submission of the dossier .....  | 6        |
| 1.2. Steps taken for the assessment of the product .....                        | 7        |
| <b>2. Scientific discussion</b> .....   | <b>9</b> |
| 2.1. Problem statement .....  | 9        |
| 2.1.1. Disease or condition .....   | 9        |
| 2.1.2. Epidemiology .....   | 10       |
| 2.1.3. Aetiology and pathogenesis .....   | 10       |
| 2.1.4. Clinical presentation, diagnosis .....                                   | 10       |
| 2.1.5. Management.....  | 12       |
| 2.2. Quality aspects .....  | 15       |
| 2.2.1. Introduction.....  | 15       |
| 2.2.2. Active Substance.....  | 15       |
| 2.2.3. Finished Medicinal Product.....  | 21       |
| 2.2.4. Discussion on chemical, pharmaceutical and biological aspects.....       | 26       |
| 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects ..... | 27       |
| 2.3. Non-clinical aspects.....  | 27       |
| 2.3.1. Introduction.....  | 27       |
| 2.3.2. Pharmacology .....   | 27       |
| 2.3.3. Pharmacokinetics .....   | 30       |
| 2.3.4. Toxicology .....   | 32       |
| 2.3.5. Ecotoxicity/environmental risk assessment .....                          | 38       |
| 2.3.6. Discussion on non-clinical aspects .....                                 | 38       |
| 2.3.7. Conclusion on the non-clinical aspects .....                             | 40       |
| 2.4. Clinical aspects .....   | 40       |
| 2.4.1. Introduction.....  | 40       |
| 2.4.2. Pharmacokinetics .....   | 45       |
| 2.4.3. Pharmacodynamics.....  | 51       |
| 2.4.4. Discussion on clinical pharmacology.....                                 | 57       |
| 2.4.5. Conclusions on clinical pharmacology.....                                | 58       |
| 2.5. Clinical efficacy .....  | 58       |
| 2.5.1. Dose response study(ies) .....   | 58       |
| 2.5.2. Main study(ies) .....  | 58       |
| 2.5.3. Discussion on clinical efficacy.....                                     | 93       |
| 2.5.4. Conclusions on the clinical efficacy .....                               | 102      |
| 2.6. Clinical safety .....  | 102      |
| 2.6.1. Discussion on clinical safety.....                                       | 110      |
| 2.6.2. Conclusions on the clinical safety .....                                 | 112      |
| 2.7. Risk Management Plan.....  | 113      |
| 2.8. Pharmacovigilance .....  | 117      |

|   |            |
|---|------------|
| 2.9. New Active Substance .....                                     | 118        |
| 2.10. Product information .....                                     | 118        |
| 2.10.1. User consultation.....                                      | 118        |
| 2.10.2. Additional monitoring.....                                  | 118        |
| <b>3. Benefit-Risk Balance .....</b>                                | <b>118</b> |
| 3.1. Therapeutic Context .....                                      | 118        |
| 3.1.1. Disease or condition .....                                   | 118        |
| 3.1.2. Available therapies and unmet medical need.....              | 119        |
| 3.1.3. Main clinical studies .....                                  | 120        |
| 3.2. Favourable effects .....                                       | 121        |
| 3.3. Uncertainties and limitations about favourable effects.....    | 122        |
| 3.4. Unfavourable effects.....                                      | 123        |
| 3.5. Uncertainties and limitations about unfavourable effects ..... | 124        |
| 3.6. Effects Table.....   | 124        |
| 3.7. Benefit-risk assessment and discussion.....                    | 126        |
| 3.7.1. Importance of favourable and unfavourable effects.....       | 126        |
| 3.7.2. Balance of benefits and risks .....                          | 127        |
| 3.7.3. Additional considerations on the benefit-risk balance .....  | 128        |
| 3.8. Conclusions .....  | 128        |
| <b>4. Recommendations.....</b>                                      | <b>128</b> |

## List of abbreviations

|                     |   |
|---------------------|---|
| AE                  | adverse event   |
| AGHD                | adult growth hormone deficiency   |
| AME                 | absorption, metabolism and excretion  |
| ANCOVA              | analysis of covariance  |
| AUC <sub>0–xh</sub> | area under the concentration-time curve from time 0 (dosing) to x hours after dosing                |
| BID                 | twice daily   |
| BMI                 | body mass index   |
| C <sub>avg</sub>    | average concentration   |
| CI                  | confidence interval   |
| CKD                 | chronic kidney disease  |
| CKD-EPI             | Chronic Kidney Disease Epidemiology Collaboration   |
| CL                  | clearance   |
| CLCR                | creatinine clearance  |
| C <sub>max</sub>    | maximum concentration   |
| CV                  | coefficient of variation  |
| DXA                 | dual-energy X-ray absorptiometry  |
| ECG                 | electrocardiogram   |
| EMA                 | European Medicines Agency   |
| EOT                 | end-of-text   |
| ETD                 | estimated treatment difference  |
| FAS                 | full analysis set   |
| FDA                 | US Food and Drug Administration   |
| FHD                 | first human dose  |
| eGFR                | estimated glomerular filtration rate  |
| GCP                 | Good Clinical Practise  |
| GFR                 | glomerular filtration rate  |
| GH                  | growth hormone  |
| HDL                 | high density lipoprotein  |
| hsCRP               | high-sensitivity C-reactive protein   |
| ICH                 | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IGF-I               | insulin-like growth factor I  |
| IGFBP               | insulin-like growth factor binding protein  |
| IL-6                | interleukin 6   |
| LDL                 | low density lipoprotein   |
| MAR                 | missing at random   |
| MD                  | multiple dose   |
| OD                  | once daily  |
| PD                  | pharmacodynamics  |
| PK                  | pharmacokinetics  |
| PMDA                | Pharmaceuticals and Medical Devices Agency  |
| PRO                 | patient reported outcomes   |
| PYE                 | patient years of exposure   |
| QTc                 | corrected QT interval   |

QTcF Fridericia heart rate corrected QT interval  
Racc accumulation ratio  
s.c. subcutaneous  
SD single dose or standard deviation (in a statistical context)  
SF-36 36-Item Short Form Survey  
t<sub>1/2</sub> terminal half-life  
TID three times daily  
TRIM-AGHD Treatment Related Impact Measure - Adult Growth Hormone Deficiency  
tmax time to maximum observed concentration  
TSQM-9 Treatment Satisfaction Questionnaire for Medication  
V/F volume of distribution

# 1. Background information on the procedure

## ***1.1. Submission of the dossier***

The applicant Novo Nordisk A/S submitted on 11 September 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Sogroya, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 September 2019.

Sogroya, was designated as an orphan medicinal product EU/3/18/2068 on 24 August 2018 in the following condition: Treatment of growth hormone deficiency based on the criterion of significant benefit.

The applicant applied for the following indication: Sogroya is indicated for the replacement of endogenous growth hormone (GH) in adults with growth hormone deficiency (AGHD).

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Sogroya as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website:  
<https://www.ema.europa.eu/en/medicines/human/EPAR/Sogroya>

### **The legal basis for this application refers to:**

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

### ***Information on Paediatric requirements***

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMEA-001469-PIP01-13 on the granting of a (product-specific) waiver.

### ***Information relating to orphan market exclusivity***

### **Similarity**

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## New active Substance status

The applicant requested the active substance somapacitan contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

### Scientific Advice

The applicant received the following Scientific Advice on the development relevant for the indication subject to the present application:

| Date             | Reference                    | SAWP co-ordinators              |
|------------------|------------------------------|---------------------------------|
| 21 February 2013 | EMA/H/SA/2492/1/2012/III     | Dr Huemer, Dr Gudmundsson       |
| 27 June 2013     | EMA/H/SA/2492/1/FU/1/2013/II | Dr Huemer, Dr Gudmundsson       |
| 30 March 2014    | EMA/H/SA/2492/1/FU/2/2014/II | Dr Ovelgoenne, Prof. Westermark |
| 22 March 2018    | EMA/H/SA/2492/2/2018/I       | Dr Killalea, Dr Kirisits        |

The Scientific Advice pertained to the following Quality, Non-Clinical and Clinical aspects:

- Characterisation of expression host organism
- Drug substance specifications, impurity profile
- Stability profile of liquid formulation and rationale to support end of shelf life limits
- Comparability exercise between phase 3 and commercial drug substance manufacturing processes
- Requirement for pre-/postnatal toxicity studies
- Requirement for juvenile animal studies
- Carcinogenicity assessment strategy
- Rationale for dose selection for Phase 3 study
- Phase 3 design in AGHD: trial duration, primary efficacy endpoint, safety database, detection and characterisation of anti-drug antibodies
- Rationale to demonstrate improved patient convenience based on PRO data.

### 1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Jean-Michel Race

|  |                   |
|--|-------------------|
| The application was received by the EMA on                                     | 11 September 2019 |
| The procedure started on   | 3 October 2019    |
| The Rapporteur's first Assessment Report was circulated to all CHMP members on | 21 December 2019  |

|   |                   |
|---|-------------------|
| The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on   | 20 December 2019  |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on   | 3 January 2020    |
| The PRAC Rapporteur's Updated Assessment Report was circulated to all PRAC members on   | 15 January 2020   |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on   | 30 January 2020   |
| The applicant submitted the responses to the CHMP consolidated List of Questions on   | 22 April 2020     |
| The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:   |                   |
| <ul style="list-style-type: none"> <li>– A GCP inspection at two investigator sites located in India (dates of inspection: 10-14 February 2020) and in Australia (dates of inspection: 20-24 January 2020) and at the Sponsor site in India (dates of inspection: 17-21 February 2020). The outcome of the inspection carried out was issued on.</li> </ul> | 12 May 2020       |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on   | 3 June 2020       |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on  | 11 June 2020      |
| The Rapporteurs circulated Updated Joint Assessment Report on the responses to the List of Questions to all CHMP members on   | 19 June 2020      |
| The CHMP agreed on a List of outstanding issues in writing and to be sent to the applicant on   | 25 June 2020      |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on   | 14 August 2020    |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on  | 3 September 2020  |
| The Rapporteurs circulated Updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on  | 10 September 2020 |
| The CHMP agreed on 2 <sup>nd</sup> List of outstanding issues in writing and to be sent to the applicant on   | 17 September 2020 |
| The applicant submitted the responses to 2 <sup>nd</sup> CHMP List of Outstanding Issues on   | 9 October 2020    |
| The Rapporteurs circulated the Joint Assessment Report on the   | 28 October 2020   |

|   |                  |
|---|------------------|
| responses to 2 <sup>nd</sup> List of Outstanding Issues to all CHMP members on  |                  |
| Ad hoc Expert group were convened to address questions raised by the CHMP on<br><br>The CHMP considered the views of the AGEH as presented in the minutes of this meeting.              | 29 October 2020  |
| The Rapporteurs circulated Updated Joint Assessment Report on the responses to 2 <sup>nd</sup> List of Outstanding Issues to all CHMP members on  | 6 November 2020  |
| The CHMP agreed on 3 <sup>rd</sup> List of outstanding issues in writing and to be sent to the applicant on   | 12 November 2020 |
| The applicant submitted the responses to 3 <sup>rd</sup> CHMP List of Outstanding Issues on   | 11 December 2020 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to 3 <sup>rd</sup> List of Outstanding Issues to all CHMP members on  | 14 January 2021  |
| The Rapporteurs circulated Updated Joint Assessment Report on the responses to 3 <sup>rd</sup> List of Outstanding Issues to all CHMP members on  | 21 January 2021  |
| 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 | 28 January 2021  |

## 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.<sup>1</sup>

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.

<sup>1</sup> 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 Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. Eur J Endocrinol. 2007;157(6):695-700.

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

### **2.1.2. Epidemiology**

An estimated 6,000 adults are diagnosed with AGHD every year in the United States. AGHD Has been estimated to affect 1 in 100,000 people annually, whereas its incidence is approximately 2 cases per 100,000 population when childhood-onset GH deficiency (GHD) patients are considered. About 15%-20% of the cases represent the transition of childhood GHD into adulthood GHD.

The age of presentation of acquired GHD in adults often coincides with the discovery of pituitary tumours, usually between the fourth and fifth decade of life.

### **2.1.3. Aetiology and pathogenesis**

The aetiology of GH deficiency (GHD) can be congenital (resulting from genetic mutations, or from structural defects in the hypothalamic-pituitary areas of the brain), acquired (e.g. as result of traumatic brain injury, infection, radiation therapy, or tumour growth within the hypothalamic-pituitary areas of the brain) or idiopathic. GHD May occur as an isolated hormonal deficiency or in combination with multiple pituitary hormone deficiencies (hypopituitarism). The most common causes of AGHD are damage to the pituitary gland or hypothalamus caused by a tumour (e.g., pituitary adenoma or craniopharyngioma), or due to surgery or radiotherapy.<sup>2</sup>

As a general rule, the secretion of GH and gonadotropins is more likely to be affected by organic pituitary disease than that of corticotropin (ACTH) and thyroid-stimulating hormone (TSH). The likelihood of GH deficiency in such patients has been estimated to range from approximately 45 percent in patients with no other pituitary hormone deficits to virtually 100 percent in patients with multiple deficits.

When GHD occurs in childhood due to any of the organic causes above, the deficiency will almost always persist into adulthood. In contrast, idiopathic GHD in childhood may not persist.

### **2.1.4. Clinical presentation, diagnosis**

The symptomology can be divided into neuropsychiatric-cognitive, cardiac, metabolic, muscular, and bone symptoms, such as:

- Changes in memory, processing speed and attention
- Lack of well-being
- Depression
- Anxiety
- Social isolation
- Fatigue
- Lack of strength
- Fibromyalgia syndrome
- Neuromuscular dysfunction
- Central adiposity
- Decreased muscle mass
- Decreased bone density
- Impaired cardiac function

---

<sup>2</sup> Vance ML, Mauras N. Growth hormone therapy in adults and children. N Engl J Med. 1999;341(16):1206-16.

- Decreased insulin sensitivity
- Accelerated atherogenesis with increased carotid intima-media thickness
- Increased low-density lipoprotein
- Pro-thrombotic state
- Decreased sweating and thermoregulation.

#### *Neuropsychiatric-cognitive abnormalities*

Patients with GHD frequently complain of low energy levels, emotional lability, and mental fatigue, resulting in a low perceived quality of life.

#### *Cardiovascular morbidity and mortality*

Although a matter of much debate, several authors have demonstrated increased cardiovascular mortality. GH deficiency and insufficiency are associated with higher levels of plasminogen activator inhibitor-I levels (*prothrombotic*), carotid intima-media thickness, and loss of circulating CD34+ cells, suggesting *endothelial dysfunction*. The degree of GHD is directly related to increased total cholesterol, low-density lipoprotein-C (LDL), truncal fat, waist-hip ratio, and risk of hypertension, all responsible for the proposed increased cardiovascular mortality.

#### *Body composition and metabolic abnormalities*

AGHD Patients have reduced lean body mass and increased abdominal adiposity. In a study of 15 healthy adult women, the authors showed that GH secretion was much reduced in patients with high truncal fat compared to those with low truncal fat. Truncal obesity is associated with metabolic syndrome and insulin resistance.

#### *Muscular abnormalities*

AGHD Has been associated with reduced lean muscle mass and impaired neuromuscular function.

#### *Bone abnormalities*

Although GH may act directly on skeletal cells, most of its effects are mediated by IGF-I, which is present in the systemic circulation and is synthesised by peripheral tissues. AGHD Causes low bone turnover osteoporosis with an increase in vertebral and non-vertebral fractures, and low bone mass.

#### *Diagnosis*

According to the current guidelines severe GHD should be defined biochemically within an appropriate clinical context.

In patients with hypothalamic-pituitary disease, the syndrome of AGHD characteristically presents with alterations in body composition, including reduced lean body mass and bone mineral density and increased fat mass with a preponderance of abdominal adiposity (increased waist circumference). The skin is thin and dry, and sweating is reduced. Muscle strength and exercise performance are reduced. An impaired sense of well-being and other psychological complaints are common.

An evaluation for AGHD should be considered only in patients with evidence of hypothalamic-pituitary disease, subjects who have received cranial irradiation, or patients with childhood onset of GH deficiency.

In patients with organic hypothalamic-pituitary disease, the likelihood of AGHD increases with the increasing number of pituitary hormone deficits from approximately 45% if no other deficits are present to nearly 100% if three or four pituitary hormone deficiencies are present.

The diagnosis of AGHD is established by provocative testing of GH secretion. Patients should be receiving stable and adequate hormone replacement for other hormonal deficits before testing.

At present, the insulin tolerance test is the diagnostic test of choice. The test is contra-indicated in patients with electrocardiographic evidence or history of ischemic heart disease or in patients with seizure disorders. Severe AGHD is defined by a peak GH response to hypoglycaemia of less than 3 µg/L.

In patients with contra-indications to the insulin tolerance test, alternative provocative tests of GH secretion must be used with appropriate cut-offs (e.g. combined administration of arginine and GHRH).

Adult patients with hypothalamic-pituitary disease and one or two additional pituitary hormone deficits require only one provocative test of GH secretion for the diagnosis of AGHD. In adult patients with deficiencies in three or more pituitary axes growth hormone deficiency might be assumed, and in this context provocative testing is optional.

Childhood-onset GH deficiency requires reconfirmation in adulthood. To establish the diagnosis of isolated AGHD, it is recommended that, in addition, a second biochemical test of GH status be abnormal.

### **2.1.5. Management**

Once the diagnosis of AGHD is established, an ideal replacement regimen with growth hormone should be instituted and titrated to a clinical response and serum IGF-I level. Several growth hormone medicinal products have been registered within the European Union such as Norditropin Flexpro (e.g. DK/H/0001/015), Norditropin SimpleXx (e.g. DK/H/0001/005), Nutropin Aq (e.g. EU/1/00/164), Omnitrope (e.g. EU/1/06/332), and Genotropin (e.g. DK/H/0012/023). Many of these medicinal products contain somatropin growth hormone as active substance. Growth hormone is to be administered daily for many of these products.

#### Dosing regimens

Growth hormone has to be dosed according to individual requirements of AGHD patients. In general, women require higher doses of GH to achieve the same IGFI response. GH secretion normally decreases with age. In line with this, GH dose requirements are lower in older patients. For patients aged 30–60 years, a starting dose of 300 µg/day is reasonable and is usually not associated with any side effects. Daily dosing should be increased by 100–200 µg every 1–2 months titrated to the IGF-I/IGF-I SDS target range of 0 up to +2, which should generally be kept in the upper half of the reference range, although no published studies offer specific guidance in this regard. Clinical benefits may not become apparent for 6 or more months of treatment. Older (>60 years) patients should be started on lower doses (100–200 µg/day) and increased more slowly. Younger (<30 years) patients may benefit from higher initial doses (400–500 µg/day); for patients transitioning from paediatric treatment, even higher doses may be appropriate. For women on oestrogen treatment both starting dose and maintenance dose appear to be higher. Current growth hormone-containing products provide separate starting regimens for patients with childhood-onset and those with adulthood-onset AGHD.

#### Adverse events

Most adverse effects include fluid retention (5–18%), hypertension, paresthesias, joint stiffness, peripheral oedema, arthralgia, and myalgias, carpal tunnel syndrome (2%). Adult patients who are older, heavier, or female are more prone to develop these complications. Most of these adverse reactions improve with dose

reduction. Insulin resistance and type 2 diabetes can occur or worsen in patients with pre-existing diabetes. Retinopathy, benign intracranial hypertension, and gynecomastia are rare.

Although there might have been some concern with respect to the risk of cancer with the use of GH therapy, an increase in the recurrence rates of either intracranial or extracranial tumours has not been demonstrated in AGHD.

### Interactions

GH treatment can affect the metabolism of other hormones. GH Affects 11BHS-1 (11-betahydroxydehydrogenase-1); hence the initiation of GH may lead to partial cortisol deficiency. GH may also interact with the TSH axis. Patients on thyroxine replacement frequently require an increase in their dose probably because of enhanced peripheral conversion of T4 to T3 mediated via GH. It may also have a central inhibitory effect on TSH. Women require a higher GH dose than men to achieve a similar increment in IGF-I. GH Sensitivity is blunted in females on oral oestrogen. Therefore, a thorough assessment of the pituitary gland in its entirety is required before considering isolated GH therapy.

### Unmet medical need according to the applicant

Current GH treatment for AGHD is administered as daily subcutaneous injections in the vast majority of patients and often necessitates many years or life-long treatment. Although the development of liquid GH formulations and convenient pen devices have simplified the administration process, the daily injections remain a burden for the patients and may affect treatment adherence and thereby treatment effectiveness.

Within GH treatment, studies of AGHD patients have shown poor adherence. For example, a survey of 158 AGHD patients who were receiving or had received GH therapy rated only 34% as 'highly' compliant<sup>3</sup>, and a retrospective single-centre cohort study classified compliance as <20% in approximately 9% of 179 AGHD patients.<sup>4</sup> In addition, frequent pain from injection, bruising and stinging can contribute to the burden associated with daily GH treatment.<sup>5</sup>

A long-acting GH like somapacitan which is suitable for once-weekly administration addresses an important problem with treatment adherence in chronic disease by reducing the number of required injections (from 365 to 52 per year). This reduces the distress associated with daily injections and is likely to improve the patients' treatment adherence. In other chronic diseases, research indicates that reduced treatment frequency directly increases treatment adherence.<sup>6,7,8,9</sup>

In line with the above description of disease characteristics, the clinical part of this overview will focus on changes in body composition, (health-related) quality of life and treatment convenience.

---

<sup>3</sup> Rosenfeld RG, Bakker B. Compliance and persistence in pediatric and adult patients receiving growth hormone therapy. *Endocr Pract.* 2008;14(2):143-54.

<sup>4</sup> Auer MK, Stieg MR, Hoffmann J, Stalla GK. Is insulin-like growth factor-I a good marker for treatment adherence in growth hormone deficiency in adulthood? *Clin Endocrinol (Oxf).* 2016;84(6):862-9.

<sup>5</sup> Kremidas D, Wisniewski T, Divino VM, Bala K, Olsen M, Germak J, et al. Administration burden associated with recombinant human growth hormone treatment: perspectives of patients and caregivers. *J Pediatr Nurs.* 2013;28(1):55-63.

<sup>6</sup> Claxton A, de Klerk E, Parry M, Robinson JM, Schmidt ME. Patient compliance to a new enteric-coated weekly formulation of fluoxetine during continuation treatment of major depressive disorder. *J Clin Psychiatry.* 2000;61(12):928-32.

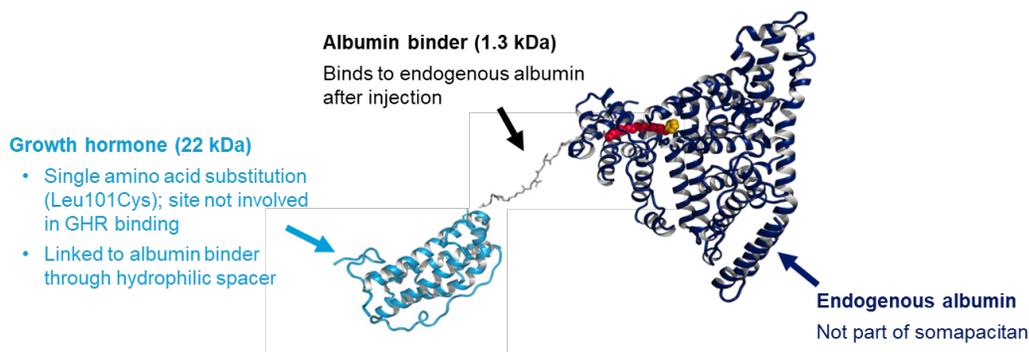
<sup>7</sup> Zoellner Y, Balp MM, Marco AG. The role of galenic innovation in improving treatment compliance and persistence: three case studies. *Clinicoecon Outcomes Res.* 2011;3:109-16.

<sup>8</sup> Kishimoto H, Maehara M. Compliance and persistence with daily, weekly, and monthly bisphosphonates for osteoporosis in Japan: analysis of data from the CISA. *Arch Osteoporos.* 2015;10:231.

<sup>9</sup> Johnston SS, Nguyen H, Felber E, Cappell K, Nelson JK, Chu BC, et al. Retrospective study of adherence to glucagon-like peptide-1 receptor agonist therapy in patients with type 2 diabetes mellitus in the United States. *Adv Ther.* 2014;31(11):1119-33.

## 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. 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 ( $t_{1/2}$  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.



**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 applicant applies for the indication: "Sogroya is indicated for the replacement of endogenous GH in adults with growth hormone deficiency (AGHD)".

## Type of Application and aspects on development

The somapacitan clinical development programme was designed and conducted in accordance with the consensus guidelines for the diagnosis and treatment of adults with GHD treatment guidelines<sup>10,11</sup> and in alignment with scientific advice provided by EMA, FDA and BfArM. FDA guidance with respect to the development of somapacitan for AGHD was not submitted by the applicant.

A detailed evaluation of QTc intervals was performed in trial 4054 (confirmatory phase 3 trial) as advised by FDA, a dedicated QT/QTc trial was not considered needed. Furthermore, no dedicated drug-drug interaction study was performed as agreed with FDA.

<sup>10</sup> 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 Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. *Eur J Endocrinol.* 2007;157(6):695-700.

<sup>11</sup> Molitch ME, Clemmons D, Malozowski S, Merriam GR, Vance ML. Evaluation and Treatment of Adult Growth Hormone Deficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2011;96:1587-609.

## 2.2. Quality aspects

### 2.2.1. Introduction

The finished product is presented as a solution for injection containing 10 mg/1.5 mL of somapacitan as active substance.

Other ingredients are: histidine, mannitol, poloxamer 188, phenol, water for injections, hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment).

The product is available in 1.5 mL 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.

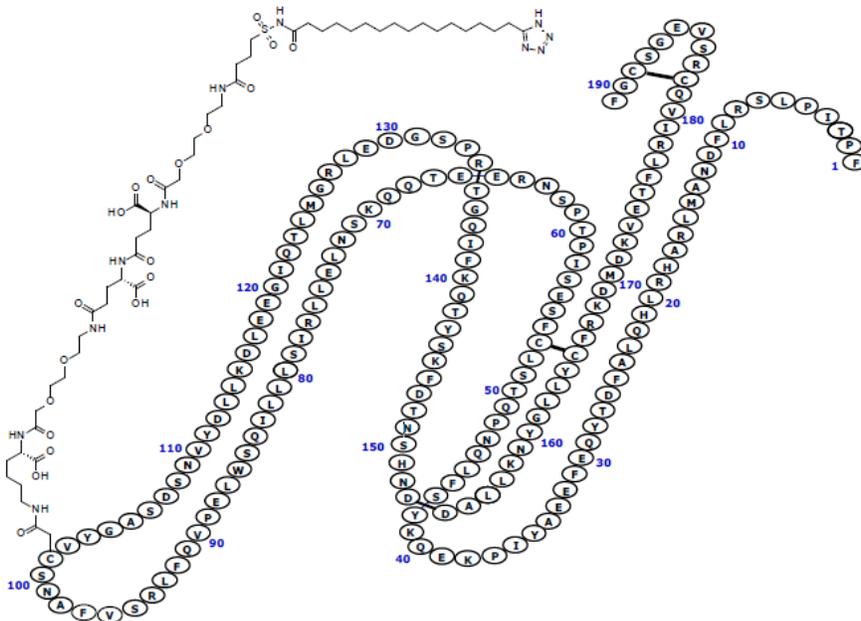
The cartridge is contained in a multidose disposable pen made of polypropylene, polyacetal, polycarbonate and acrylonitrile butadiene styrene and in addition two metal springs. The cartridge is permanently sealed in a pen-injector.

The finished product is available in pack sizes of 1 pre-filled pen and multipack of 5 (5 packs of 1) pre-filled pens.

### 2.2.2. Active Substance

#### General Information

Somapacitan (INN) is a recombinant human growth hormone (hGH) derivative produced in *E. Coli*. The leucine at position 101 of the amino acid backbone is replaced with a cysteine to which an albumin binding moiety consisting of an albumin binder and a hydrophilic spacer is attached (see Figure 1). The protein backbone displays the four-helical bundle structure with an up-up down-down topology as seen for hGH. The structure contains two disulphide bridges, Cys53-Cys165 and Cys182-Cys189, respectively. The albumin binding moiety consists of an albumin binder (16-(1H-tetrazol-5-yl) hexadecanoic acid including a 4-carboxypropyl sulfonamide) and a hydrophilic spacer consisting of six groups. The hydrophilic spacer consists of an acetyl group connected to the  $\epsilon$ -amino group of lysine by an amide bond, two 8-amino-3,6-dioxaoctanoic acid (ADO) groups and two  $\gamma$ -glutamic acid (Glu) residues. Terminally, the sulfonamide group together with the 16-(1H-tetrazol-5-yl) hexadecanoic acid provides the albumin binding function. The molecular mass is 23290.56 Da, of which the albumin binding moiety accounts for 1190.6 Da.



**Figure 2: Schematic presentation of the primary structure of somapacitan (not to scale)**

Somapacitan binds selectively to and activates hGH receptor, the target for native hGH. When somapacitan is injected, the albumin binding moiety binds non-covalently to endogenous albumin resulting in decreased renal clearance and protection from metabolic degradation.

## Manufacture, process controls and characterisation

The active substance is manufactured at Novo Nordisk US Bio Production Inc. (NNUSBPI) in New Hampshire, USA. Three sites of Novo Nordisk A/S in Denmark are involved in the quality control of the active substance.

### ***Description of manufacturing process and process controls***

#### *Active substance*

The manufacturing process is divided into three stages: propagation/fermentation, recovery, and modification/purification (see Figure 2).

The active substance manufacturing process starts with the thawing of one working cell bank (WCB) vial.

In the propagation and fermentation stage, the cells are propagated from the WCB in shake flasks and transferred into a bioreactor for further propagation.

At the end of the production phase, the recovery process starts, consisting of cell harvest, homogenisation, solubilisation, clarification, and a chromatography step.

The purification of the somapacitan precursor includes chromatographic steps and is followed by digestion of somapacitan precursor and alkylation of reduced digested somapacitan precursor with side-chain reagent. At the end of the manufacturing process, the active substance is pre-formulated. It is then filtered through the 0.2 µm filter into bottles, stored and shipped to the finished product manufacturing sites.

The different buffers used at different levels of the upstream and downstream process are well defined. The manufacturing steps are generally well described with the process parameters and the ranges.

No reprocessing is performed.

Pooling of capture batches is supported by the process verification study (also referred to as process performance qualification (PPQ)).

#### *Side chain*

The synthesis of the albumin binding side chain has been described in sufficient detail. The reaction mechanism has been provided, the reagents indicated, and information on reaction conditions (temperatures, durations, and amounts of materials) are provided, for critical and non-critical parameters. A justification of the defined starting materials and a discussion on the carry-over of impurities and incorporation into the active substance have been provided.

A major objection was raised as one of the initially proposed side chain starting materials was not considered suitable in view of its structure, the origin and fate of several impurities and the remainder of the synthesis. The issue was resolved as the applicant agreed to redefine the starting material as requested and to update the dossier accordingly. The redefined starting material is considered suitable in view of its structure, the origin & fate of several impurities and the remainder of the synthesis. The control of the (starting) materials used for manufacturing of the side chain is considered sufficient. Information on the synthesis routes and the names and addresses of the suppliers have been provided. No materials of human or animal origin are used in the synthesis of the side chain.

In response to a major objection raised, a discussion on potential formation of specified impurities has been provided. The applicant provided a quantitative risk assessment using purge factors to evaluate the risk of carry over. However, none of these predicted factors were supported by measured purge factors (experimental data or spiking studies) and the applicant was asked to provide further data. In response, the applicant provided the requested analytical data, demonstrating acceptable levels of the impurities. These results support the risk analysis presented. The justification for the impurity limit at the level of the side chain is considered acceptable based on the limit in the active substance, the yield of the synthesis step and the contribution of the side chain to the total active substance. The analytical method used has been shown to be adequately validated. The major objection is thereby considered fully resolved.

#### **Control of materials**

Overviews of the raw materials used for propagation and fermentation, recovery, modification and purification are provided. With few exceptions, quality control of all raw materials consists of identity testing in accordance with Ph. Eur. methods. The specifications applied to non-compendial raw materials are sufficient. The nature of the filters and membranes has been described. Sufficient information is provided on the chromatography resins. No raw materials of animal origin are used in the somapacitan active substance manufacturing process.

The source, history, and generation of the cell substrate is sufficiently described.

The clone that was used for the generation of the master cell bank (MCB) is derived from an *E. coli* strain transformed with the expression plasmid

The coding sequence was derived from the hGH coding sequence used at Novo Nordisk A/S for production of somatropin product Norditropin. The L101C mutation was introduced by a PCR approach. The applicant analysed the expression construct by sequencing and protein expression.

A brief description of the manufacture of the MCB and WCB cell banks is provided, including a summary of the characterisation results. The testing is in line with expectations. Stability of the cell banks is assessed by viability testing. In addition, the applicant will perform trending of the expression in active substance production batches to confirm stability of the WCB with regard to its ability to produce the protein of interest.

The provided protocol for establishment of future WCBs is acceptable.

### ***Control of critical steps and intermediates***

#### *Active substance*

The applicant provided an overview of process parameters, in-process hold-times, and in-process tests for all steps in the active substance manufacturing process.

The in-process tests are divided in 'critical in process tests', 'in process tests with limits' and 'in process tests without limits'. The applicant explained that the latter tests are intended to gain knowledge and for trend analysis. This is acceptable. For critical in-process tests, out of specification (OOS) results will result in batch rejection.

Controls are in place for OD<sub>600</sub> (end of propagation and end of fermentation), content, purity, product-related impurities, and process-related impurities. An overview of the analytical procedures used for critical in-process tests is provided, including method descriptions and method validation or verification as appropriate.

In process holding times are defined for the different process steps. Supportive data has been provided.

One intermediate is defined in the active substance manufacturing process. A defined shelf life is proposed for this intermediate, which is acceptable based on stability data.

#### *Side chain*

The in-process testing program for the side-chain reagent, including the specification and method descriptions are provided. Test parameters include identity, assay and impurities. The method descriptions are acceptable.

The specification for the side chain has been appropriately justified. The limits for assay, total impurities and specified impurities are acceptable and supported by batch analysis data.

A protocol for a stability study for side chain is provided. Data have been provided, which support the proposed re-test period.

### ***Process validation and/or evaluation***

The process validation of the active substance manufacturing process has three key elements:

- Process design, including process evaluation studies and assessment of impurity reduction.
- PPQ studies comprising of fermentation batches with subsequent modification and purification as defined by the protocols.
- Ongoing process verification, including monitoring and assessment of process performance by yield and selected impurities.

#### *Process evaluation studies*

All process parameters have been evaluated using a risk-based approach with regard to their potential effect on the critical quality attributes (CQAs) and process performance. Based on this, process parameters were selected for further investigation in laboratory scale and/or production scale process characterisation experiments in order to justify limits for the process parameters. The risk assessment is provided. The summaries of the characterisation studies and additional data that was provided upon request sufficiently justify the operational ranges of the process parameters, also taking into account that appropriate controls are in place. The representativeness of the small-scale studies is sufficiently demonstrated.

Removal of the process related impurities is sufficiently demonstrated.

#### *PPQ studies*

Fermentation and recovery: An appropriate number of batches were included. All acceptance criteria were met and results support consistent performance of these process steps.

Modification and purification: The PPQ batches for fermentation and recovery were manufactured into substance batches. Additional testing was performed to address impurity removal. All acceptance criteria were met, with the exception of an OOS results which was attributed to a technical error and not process related. Taken together, the results support consistent performance of these process steps.

Column lifetime and sanitisation procedures are supported by validation data. In addition, an extractable study was performed for each resin. None of the extractable levels were found above their corresponding analytical evaluation threshold.

Sufficient information is provided as regards the extractables and leachables from the materials that are in contact with the active substance.

A summary of the shipping and transportation validation of intermediates is provided and gives no reason for concern.

#### *Ongoing process verification*

Data from the in-process controls and additional testing will be reviewed after manufacture of a defined number of fermentation runs following PPQ. Test results will be evaluated in an internal ongoing process verification report which will use applied statistics to conclude on further monitoring. The approach is considered acceptable.

#### **Manufacturing process development**

Development of the active substance manufacturing process is sufficiently described. The applicant identifies 4 manufacturing processes: the initial non-clinical process, the Phase 1 process, the Phase 3 initial process and the Phase 3 process. Changes implemented between the processes have been described and include changes to process steps, source of materials, manufacturing scale, active substance concentration, container closure and manufacturing facilities.

For each of the manufacturing processes/process stages at least 1 batch was included in the comparability exercise. In addition, batch release results were compared. The characterisation studies performed to assess comparability are considered appropriate. The results of the comparability study did not reveal any differences between batches manufactured according to the different manufacturing process, apart from a tendency of reduced levels of impurities at later stages of process development.

## **Characterisation**

#### *Structural characteristics and physico-chemical properties*

To study its structural characteristics, the applicant analysed somapacitan using a number of analytical methods. The results confirmed the theoretical mass, amino acid sequence, location of disulphide bridges and the albumin binder, and integrity of the N- and C-termini. In addition, the applicant appropriately analysed the physical-chemical properties of somapacitan, including higher order structure, solubility, isoelectric point, UV absorbance spectra, and pH stability.

### *Biological activity*

The applicant has evaluated the binding capacity of somapacitan to growth hormone binding protein, and human serum albumin, and its biological activity. The biological activity is determined using a bioassay in which cell proliferation of a growth-hormone dependent cell line in response to increasing concentrations of somapacitan is measured. Results are calculated using an in-house reference standard and expressed as U/mg monomeric protein.

### *Product-related impurities*

Product-related impurities/substances are appropriately described and characterised. Depending on their biological activity, they are either classified as 'substance' (full bioactivity) or 'impurity' (bioactivity differs from somapacitan). The control strategy for product-related substances/impurities is in general acceptable. In-process controls with limits are in place for impurities. The active substance specification includes acceptance criteria for certain product-related impurities.

### *Process-related impurities*

Removal of process related impurities is sufficiently demonstrated. Active substance release specifications are in place for endotoxin.

## **Specification, analytical procedures, reference standards, batch analysis, and container closure**

The release specifications for somapacitan active substance are in general acceptable and include general parameters, identity, specific bioactivity, content, product-related impurities, process-related impurities, and microbial controls

The applicant briefly described the approach for setting quantitative acceptance criteria, and for each parameter provided an overview of the release method and the data used to set acceptance criteria. Upon request, the proposed acceptance criteria were tightened and further justified to reflect actual current manufacturing experience.

### *Analytical methods*

The description of the test methods is acceptable. All methods have been validated in line with ICH guidelines or, in case of compendial methods, verified in accordance with Ph. Eur.

The Bioassay (U/mL) consists in an *in vitro* cell proliferation assay cells dependent on growth hormone for proliferation. The growth of the cell line is induced in a dose-dependent manner by adding increasing concentrations of somapacitan or recombinant hGH. The bioactivity is calculated by comparison of the dose-response curve of an analytical sample to the dose-response curve for the somapacitan reference material. The Specific bioactivity is defined as 1.00 U/mg for the somapacitan primary reference material, as no external standard exists.

### *Batch analysis*

Batch analysis data were presented for all the active substance batches produced during development for non-clinical studies, clinical trials, reference material, setting of specifications, stability studies, comparability studies, technical use and PPQ. The specifications have been updated throughout development. All data comply

with the active substance acceptance criteria. For PPQ batches, all results met commercial acceptance criteria and demonstrate consistency in the active substance manufacturing process.

#### *Reference standards*

The production and testing of the current primary and secondary material (PRM and SRM) are in general sufficiently described. Both standards are derived from the same active substance batch and tested in accordance with the active substance release specifications.

The PRM and SRM have both been assigned a specific activity of 1 U/mg by default. This is acceptable, as they are derived from the same active substance batch, no international standard is available, and data demonstrating a correlation between content and activity is provided.

New standards will be prepared and qualified as described for the current standards. The issue of potency shifts, which might result from the approach to assign a default specific activity of 1 U/mg to new reference standards, was sufficiently addressed.

The long-term stability is followed by yearly monitoring. Upon request, a stability protocol for the PRM and SRM was provided.

#### *Container closure system*

The active substance is stored in suitable containers. The information provided on the container closure system includes its raw materials, dimensional drawings, manufacturers, compliance with compendial requirements, release specifications and a discussion on extractables and leachables. The information provided for the container closure system is considered acceptable.

## **Stability**

The active substance stability studies are performed in accordance with ICH/CHMP guidelines. A representative version of the proposed container closure system was used in the stability studies. Primary stability studies were performed with batches from the commercial process. Batches were also used for accelerated stability testing.

Results from all batches were comparable and complied with the specifications under long-term storage conditions. No trends were observed.

With regard to the PPQ batches, long term stability and accelerated data are available. Results are in line with the results from the primary stability studies.

Based on the data presented, the proposed shelf life is considered acceptable.

The provided stability commitment is acceptable. For the future stability studies, it is accepted that the test for specific bioactivity is omitted, as biological activity is considered to be controlled by content.

### **2.2.3. Finished Medicinal Product**

## **Description of the product and Pharmaceutical Development**

The finished product composition is provided in Table 1.

**Table 1 Somapacitan 10 mg composition**

| Component            | Function          | Reference to standards |
|----------------------|-------------------|------------------------|
| Somapacitan          | Active ingredient | Novo Nordisk A/S       |
| 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.

There is no overage or overfill.

The applicant provided an outline of the formulation development. The use of a liquid formulation compatible with a dose-adjustable multidose cartridge/pen is sufficiently substantiated.

The chosen formulation is a compromise between several elements. Especially the trade-off between HMWPs and deamidation is noted. The preservative efficacy is justified as being an acceptable compromise providing sufficient microbial reduction for a weekly dosed product as well as adequate chemical stability and acceptable local tolerance. In conclusion, the chosen formulation is considered sufficiently substantiated with data, including the choice of the preservation system.

The primary packaging is a 1.5 ml cartridge made of colourless hydrolytic glass (type 1 glass, Ph. Eur., USP and JP). The closure at one end of the cartridge is a cap that consists of a rubber disc and a seal of aluminium. The rubber disc, in contact with the finished product, is made of laminated bromobutyl rubber (type 1 rubber, Ph. Eur. and USP). The closure at the other end of the cartridge is a plunger made of chlorobutyl rubber (type 1 rubber, Ph. Eur. and USP). The laminated rubber and rubber plunger are not made with natural rubber latex.

Both rubber components used, the laminate rubber components in the cap and the rubber plunger, comply with Ph. Eur. 3.2.9 Rubber Closed for Containers for Aqueous Parenteral Preparations, for Powders and for Freeze-dried Powders (Type I rubber).

The glass barrel complies with Ph. Eur. 3.2.1 Glass containers for Pharmaceutical Use (Type I).

The 1.5 mL cartridge is assembled in a PDS290 pen-injector, which is a multi-dose device, intended for once-weekly subcutaneous injection of somapacitan (see Figure 3). It is an integral device which should be discarded when empty or at the end of the in-use shelf life (6 weeks). The device was also used during the Phase 3 clinical studies.

The PDS290 pen-injector was designed and developed by Novo Nordisk A/S to comply with the relevant requirements of Annex I 'Essential Requirements' of Directive 93/42 EEC. An EU Declaration of Conformity issued by the device manufacturer Novo Nordisk A/S (Novo Allé, DK-2880 Bagsvaerd Hovedstaden, Denmark)

and a Certificate of Conformity issued by a Notified Body (LRQA) for the Novo Nordisk A/S (Novo Allé, DK-2880 Bagsvaerd Hovedstaden, Denmark) have been provided.



**Figure 3 Somapacitan cartridge assembled in a PDS290 pen-injector**

The finished product is enclosed within the cartridge and not in contact with the device. The device is intended to connect to a standard needle thread or a needle with a bayonet coupling prior to finished product administration. Needles are not included. The pen has been tested with 31 Gx6 mm and 32 Gx5 mm disposable needles.

The description of the device and its mechanistic aspects have been provided in sufficient detail. The design is in line with requirements of ISO 11608-1:2015. The device is based on currently registered devices such as the somatropin product Norditropin FlexPro. Biocompatibility is stated as per ISO 10993-1:2018. Design verification results have been provided in order to show dose accuracy at various dose settings and at various environmental conditions as per ISO 11608-1. The usability study (human factors validation study) is based on the PDS290 pen-injector family studies performed on other pen-injectors / products of the applicant. Similarity of the device regarding dose, intended use and user population of somatropin (0.05 mg somatropin per increment with maximum of 80 increments, subcutaneous injection, adults and paediatric population in home or hospital setting) is acceptable. No adverse events related to the device were reported during the clinical trials. This is considered sufficient justification for not performing a new usability study specifically for somapacitan.

## **Manufacture of the product and process controls**

The finished product is manufactured at Novo Nordisk A/S (Gentofte, Denmark).

The finished product manufacturing process consists of successive mixing of two solutions, including formulation steps. Following the mixing steps, the finished product is sterile filtered through two filters in series, filled aseptically in the cartridges, visually inspected then stored protected from light at 2°C-8°C.

Overall the description is clear with identification of the process parameters and their limits.

Critical steps and controls were identified.

A major objection was raised in relation to lack of adequate information around the assembly process and control strategy for the pen-injectors. In response, the applicant provided the requested information in relation to the in-process controls, validation of the assembly process and provided further justification of the parameters to be included in the finished product specifications. The responses were considered satisfactory and therefore the major objection was resolved.

An appropriate validation campaign was executed for the formulation and cartridge filling steps, which comprised PPQ batches of the to-be-marketed 10 mg/1.5 mL product and a supportive batch.

The critical features of the assembly process of the pen-injector have been validated.

## **Product specification, analytical procedures, batch analysis**

The release specifications for somapacitan finished product include general parameters (pH, appearance), identity, content, product-related impurities, particulate matter, osmolality, identity of phenol, phenol poloxamer 188, dose accuracy, extractable volume, and microbial controls (sterility, endotoxin).

In general, the finished product specifications and control strategy are reasonably well described and justified.

During the procedure, a major objection was raised as the proposed specification acceptance criteria (for both active substance and finished product, release and shelf life) were not considered acceptable.

The Applicant was asked to substantiate (with, e.g. biological, immunological and toxicological data) that the proposed levels would not pose a clinical safety concern in cases where the shelf-life criteria were wider than clinical experience. It was also requested that acceptance criteria should be substantiated where they did not reflect actual current manufacturing experience.

In response, the applicant provided an extensive re-evaluation of the data set and improved the justification of specifications. From the presented justification, it can be concluded that the proposed acceptance criteria are in line with manufacturing experience/capability. Upon further request, the applicant also provided a more robust justification based on the available clinical/non-clinical/toxicological data, including considerations relating to immunogenicity. As the responses were found satisfactory, the major objection was considered resolved.

Potential sources and levels of elemental impurities and residual solvents in somapacitan finished product have been evaluated. In alignment with ICH Q3D a risk assessment based on the principles of risk management as described in ICH Q9 has been performed to determine the probability of inclusion of elemental impurities in somapacitan finished product, and to establish appropriate controls to ensure the quality of the finished product. The levels of elemental impurities are well below the threshold of 30% of the permitted daily exposure (PDE) limits stated in ICH Q3D. The levels of residual solvents are well below the PDE limits stated in ICH Q3C. Elemental impurities and residual solvents are therefore not included in the finished product specifications.

A risk evaluation in relation to the potential risk of nitrosamine impurities has been provided covering both the active substance and finished product. A detailed discussion is included in the active substance section. The risk assessment at the level of finished product, concluding that there is no risk for nitrosamine formation relating to the excipients or the rubber closures, is endorsed.

### *Analytical methods*

The following tests are performed in accordance with Ph. Eur.: appearance, osmolality, pH, particulates, sterility, bacterial endotoxins and extractable volume. The non-compendial methods used to determine content and purity/impurity profile are identical to the analytical methods used for the active substance and their suitability has been confirmed in the active substance section. In addition, phenol identity and content are determined and poloxamer 188 content. These tests have been suitably validated.

The absence of determination of the specific bioactivity at the finished product level was justified in the active substance section by the establishment of a correlation between the content and the specific bioactivity.

### *Batch analysis*

An overview of somapacitan 10 mg/1.5 mL batches produced during development is provided as well as supportive data for other somapacitan presentations (not covered by the current application). The batch analyses data demonstrates acceptable batch-to-batch consistency and reproducibility of the manufacturing process proposed for the finished product.

### *Reference standards*

The reference materials used for testing and release of the finished product are the same as the ones used for the active substance. Therefore, reference is made to the active substance section.

## **Stability of the product**

The proposed storage and shelf life for the finished product is 24 months at 2-8 °C including an in-use period of 6 weeks at 2-8 °C and a total of 72 hours (3 days) at room temperature (at or below 30 °C).

The composition, finished product manufacturing process, batch size and container closure system used in the presented studies are identical to the ones intended for the market.

A finalised long-term stability study (24 months at 5 °C ± 3 °C) and a finalised accelerated stability study (6 months at 25 °C ± 2 °C) were performed on the primary stability batches.

For the PPQ batches long-term stability study, 24 months at 5 °C ± 3 °C, has been initiated (12 months data currently available), and an accelerated stability study (6 months at 25 °C ± 2 °C) has been finalised.

The proposed testing program, which mainly comprises the specification/release tests, is exhaustive and can be considered acceptable.

The primary and PPQ batches have similar degradation patterns and rates. It is noted that after 24 months values for several product-related substances/impurities are well below the proposed shelf-life specification. The results of the accelerated stability studies are consistent with the results obtained in the real-time stability studies.

An in-use stability study (5 °C ± 3 °C for 6 weeks including 72 hours (3 days) at 30 °C ± 2 °C) has been performed on the primary stability batches at beginning, middle and end of the proposed shelf life. The results of the in-use studies support the proposed in-use period of 6 weeks at 2-8 °C, including the possibility of storage at or below 30 °C for a maximum of 72 hours (3 days) at or below 30 °C, allowing for patient portability.

A photostability study in line with ICH Q1B was also performed. The finished product in the primary container was shown to be susceptible to chemical degradation when exposed to light. The PDS290 pen-injector provides adequate protection of the somapacitan finished product in the primary container.

In conclusion, the data provided support the proposed shelf life for the finished product of 24 months at 2-8 °C including an in-use period of 6 weeks at 2-8 °C and 72 hours (3 days) at room temperature (at or below 30 °C).

An appropriate commitment to finalise the ongoing studies has been provided.

## Adventitious agents

As no raw materials of human or animal origin are used for the manufacture of somapacitan, the finished product is evaluated to be safe with regards to TSE agents.

The producing host strain is *E. coli*, and since it is not the natural host for mammalian viruses, no testing for endogenous or adventitious viruses has been performed.

A recombinant enzyme is a raw material used during the manufacturing process of somapacitan active substance. This enzyme is expressed in a CHO cell line and produced using a serum-free cell cultivation process. The raw material master cell bank has been tested for endogenous and adventitious viruses according to ICH Q5A. Furthermore, only non-animal derived raw materials are used during the production of the raw material. The risk of TSE is therefore negligible, and the risk of a contamination with adventitious agents is also minimized.

### 2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure four major objections were raised in relation to quality aspects.

A major objection was raised in relation to the choice of starting material for the albumin binding side chain. The proposed starting material was not considered suitable in view of its structure, the origin and fate of several impurities and the remainder of the synthesis. The issue was resolved as the applicant agreed to redefine the starting material as requested and to update the dossier accordingly.

A second major objection was raised as the proposed specification acceptance criteria (for both active substance and finished product, release and shelf life) were not considered acceptable. The Applicant was asked to substantiate that the proposed levels would not pose a clinical safety concern in cases where the shelf-life criteria were wider than clinical experience. It was also requested that acceptance criteria should be substantiated where they did not reflect actual current manufacturing experience. In response, the Applicant provided an extensive re-evaluation of the data set and improved the justification of specifications. This was considered acceptable.

A third major objection related to a lack of information around the assembly process and control strategy for the pen-injectors. In response, the applicant provided the requested information and the major objection was resolved.

Additionally, a major objection was raised in relation to the risk of specified impurities and the absence of a risk assessment and/or control strategy to address this risk. In response, a risk assessment based on predicted/theoretical purge factors was provided to estimate residual impurity levels in the starting material and somapacitan active substance. Upon request, analytical data was also provided to support the risk assessment. Further to some additional clarifications and provision of validation data for the applied method, the major objection was considered resolved.

## **2.2.5. 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. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

## **2.3. Non-clinical aspects**

### **2.3.1. Introduction**

Somapacitan is a long-acting human recombinant growth hormone (GH) analogue with a single substitution in the amino acid backbone (L101C), to which an albumin binding moiety has been attached via a hydrophilic spacer. The hydrophilic spacer ensures sufficient distance between the albumin binding portion and the GHR binding portion of somapacitan so the molecule can activate the GHR while bound to HSA. The albumin binding is non-covalently and serves to prolong the half-life of the compound.

Somapacitan is intended to be used for the treatment of adults with growth hormone deficiency and is suitable for once-weekly administration in humans.

Somapacitan is produced using recombinant DNA technology in *Escherichia coli* (protein backbone) and using chemical conjugation (spacer). Somapacitan has a molecular weight of 23,305.1 g/mol and is soluble in an aqueous solution.

### **2.3.2. Pharmacology**

#### ***Primary pharmacodynamic studies***

Somapacitan is a growth hormone receptor (GHR) agonist. Like human growth hormone (hGH), somapacitan exerts its biological action via binding to and subsequent activation of the GHR. As for growth hormone (GH), the mechanism of action of somapacitan is either directly or indirectly via insulin-like growth factor-I (IGF-I) secretion.

The GHR is expressed as a monomer which forms a ligand-receptor complex consisting of one somapacitan/hGH molecule and two GHR molecules. This results in receptor dimerization and receptor conformational changes in the cell membrane that leads to signal transduction by activation of the JAK/STAT system and a subsequent increase in the production of IGF-I, mainly in the liver, or activation of the MAPK/ERK system leading to stimulation of division and multiplication of chondrocytes. IGF-I has growth-stimulating effects on a number of tissues, including bone tissue thus increased height during childhood and adolescents is the most widely known effect of hGH. In addition to increasing height in children, growth hormone has many other effects on the body, including increasing lipolysis, protein synthesis, muscle mass and gluconeogenesis in the liver and reducing liver uptake of glucose. The effect of somapacitan has been evaluated in several *in vitro* and *in vivo* pharmacology studies.

Surface plasmon resonance (SPR) analysis was used to evaluate the binding kinetics of somapacitan to the growth hormone binding protein (GHBP). The GHBP was used as a surrogate for the GH receptor (GHR),

since affinities are similar due to receptor ectodomain shedding. The binding kinetics to GHBP ( $K_D$ ) was found to be 2.3 and 3.0 nM, for hGH and somapacitan, respectively.

The natural growth hormone (GH) is evolutionarily homologous to prolactin (PRL). Therefore, also, the potency for the PRL receptor was assessed.

The potency of somapacitan and hGH has been compared on the human GHR and human prolactin receptor (PRLR), using bone marrow-derived murine pro-B lymphoid cells (BA/F3) stably overexpressing the human GHR or human PRLR, with cell proliferation as a read-out. The potency ( $EC_{50}$ ) for the GHR was found to be 13 pM for wild-type hGH and 44 pM for somapacitan (range 33 – 54 pM), indicating that the potency of somapacitan was about 0.3-fold hGH. With respect to the hPRLR the potency ( $EC_{50}$ ) of somapacitan was 4.1 nM, which is ~8-fold and ~25-fold lower than the potencies of hGH or hPRL, which were 0.52 nM and 0.16 nM, respectively. Somapacitan has a 93-fold higher potency for the hGHR and hGH 38-fold. Using these assays, no clear differences were found in eight different batches, which were used in different phases of development and also included fresh and an end-of-shelf-life batch.

Primary rat hepatocytes and a human hepatoma cell line HuH-7 were used to determine the GHR activation and immediate down-stream intracellular signalling (JAK2/STAT5) of somapacitan and hGH. Similar time and concentration-dependent GH receptor activation and desensitisation responses are observed in the rat hepatocytes and human HuH-7 cell line for somapacitan and hGH. Using 8 nM, phosphorylation of STAT5 (P-STAT5) was induced, which was maximal after 7.5 – 15 minutes, and declined after 30-60 min. It should be noted, however, that compared to hGH a submaximal somapacitan concentration was used and that no albumin was present in these assays, making the comparison less physiologically relevant.

SPR was also used to assess binding kinetic to HSA (qualitative only). It was found that hGH did not bind to HSA, while somapacitan did bind. In addition, using protein crystallography, size exclusion chromatography and isothermal titration calorimetry, it was found that somapacitan binds to a high-affinity site ( $K_D \sim 0.1$ – $1.0 \mu\text{M}$ ) and two low-affinity sites ( $K_D \sim 1$ – $10 \mu\text{M}$ ) but that at physiological temperature (37°C) only binding to the high-affinity site (hydrophobic interactions) is observed. The binding of somapacitan to plasma proteins in human plasma was further investigated using reconstituted human plasma and immobilised somapacitan. Binding to HSA was most prominent and at least 100 times more abundant than to other plasma proteins.

The pharmacological mechanism of GH agonists is well described in the literature. The *in vivo* pharmacodynamics of somapacitan has been investigated in the hypophysectomised Sprague Dawley (SD) rat, a rodent model of growth hormone deficiency, using single and multiple doses. Upon single dosing (0.2 – 35 mg/kg, sc), a dose-dependent increase was seen in body weight gain and in plasma IGF-I levels, that increased up to 1000 ng/ml after 3 days. Maximal effect was found with ~3.5 mg/kg.

The hypophysectomised SD rat model was also used to evaluate in the pharmacodynamic effect of a “Fresh” (new batch stored at 5°C) as compared to an “end-of-shelf-life” (stored at 30°C for 3 months) somapacitan batches. No significant differences were observed in the pharmacodynamic properties of Fresh or end-of-shelf-life batches.

In a four-week multiple-dose study using hypophysectomised male SD rats, the pharmacodynamic effect of daily hGH (sc, 0.44 mg/kg, 2 nmol/kg) and once weekly somapacitan (sc, 3.26 mg/kg, 14 nmol/kg) administration was compared. Using daily hGH administration, body weight almost linearly increased for two weeks and plateaued thereafter, while the same weekly dose of somapacitan induced a step-wise increase in body weight, which continued to increase for up to four weeks. Differences were also seen on IGF-I levels, which gradually increased using daily hGH and remained constant thereafter. Using once weekly somapacitan dosing, plasma IGF-I rapidly and more prominently increased. The levels declined after four days giving a

weekly fluctuating IGF-I concentration within each dosing interval. The different (stronger) effect on body weight gain seems to be in line with the difference in IGF-I response with somapacitan. Somapacitan also gave a significantly greater increase in nose-tail length, tibia weight and BMC and a similar effect on cortical thickness, muscle mass and body weight normalised lean body mass and fat mass. Blood glucose and insulin levels were evaluated in order to assess the risk of developing hyperinsulinemia and reduced insulin sensitivity, but no difference was observed between the current treatment and vehicle control. The insulin concentrations varied independently of treatment in the range of 50-160 pM, while the blood glucose concentrations were stable within the normoglycaemic levels of 4.5-6.5 nM. In summary, the same cumulative weekly somapacitan dose gave a more prominent (~2-fold) increase in IGF-I exposure and in body weight gain than daily hGH, although somapacitan has a 3-fold lower *in vitro* potency than hGH.

In male cynomolgus monkeys, a single dose of somapacitan (21.5 nmol/kg, 0.5 mg/kg; i.v. or s.c.) was found to increase IGF-I plasma levels 1.5-fold. IGF-I levels started to increase one day after dosing and maximum levels were reached after 5 – 7 days, while ten days after treatment plasma IGF-I levels were returned to pre-treatment levels. Somapacitan exposure was about 30% lower using the s.c. route but this did not influence the extent of the IGF-I response.

In male Göttingen minipigs, a single dose of somapacitan (10 nmol/kg, 0.23 mg/kg; i.v. or s.c.) was found to increase IGF-I plasma levels 3-fold. IGF-I levels started to increase one day after dosing, and maximum levels were reached after 3 – 4 days and declined thereafter to IGF-I levels slightly above pre-treatment levels at days 7 – 14 post-treatment. A similar increase in IGF-I levels was found using s.c. or i.v. administration, although somapacitan exposure was about 3-fold higher using the i.v. route.

## **Secondary pharmacodynamic studies**

A broad profiling screening panel using 68 biochemical receptors, ion-channels and neurotransmitter transporters did not show a clinically relevant competitive interaction with somapacitan (3 µM, 70 µg/mL), which is 1000-fold higher than the C<sub>max</sub> exposure of 62.3 ng/mL (~2.7 nM) at a human dose of 8 mg/week. No secondary pharmacology effects are expected from somapacitan apart from the known GH effects and lower PRL activity.

## **Safety pharmacology programme**

The safety pharmacology studies were designed to investigate the effect of somapacitan on major organ function (central nervous system, respiratory system and cardiovascular system) and have been conducted *in vitro* and as a part of the GLP repeat-dose toxicity studies in monkeys. A maximal plasma concentration (C<sub>max</sub>) of 62.7 ng/ml has been taken as the mean C<sub>max</sub> in humans at the maximum recommended human dose (MRHD) of 8 mg/week for exposure comparison.

*In vitro* studies on the potential for inhibition of the cardiac potassium channel (human ether-a-go-go-related gene, hERG) were used for assessment of the potential for QT prolongation. Treatment with somapacitan (3 µM) produced no inhibition of hERG channel tail current recorded in HEK293 cells stably transfected with hERG cDNA. This indicates that a 1000-fold higher concentration than the mean maximal plasma concentration at the MRHD produced no inhibition of hERG tail current.

The potential effect of somapacitan for QT prolongation was also studied using action potential recordings in isolated female rabbit Purkinje fibres. No effects of somapacitan were detected on action potential

parameters of 0.03 µM up to 3 µM, which corresponds to 1000-fold above the maximal mean plasma concentration at the MRHD.

The effect of somapacitan on cardiovascular function was studied in male and female cynomolgus monkeys dosed for 2, 13 or 26 weeks with 0.4, 2 or 9 mg/kg (sc, biweekly) somapacitan or vehicle. No effects related to somapacitan were observed on blood pressure, heart rate or ECG variables examined (P, PR, QRS, ST, QT, QTc, QTcM). In conclusion, it was found that there were no clinically relevant findings in cynomolgus monkeys in repeated doses up to 9 mg/kg biweekly, corresponding to >2000-fold the mean C<sub>max</sub> at the MRHD of 8 mg/week.

The effect of somapacitan on neurobehavioural function after 3 days of treatment was studied in male and female cynomolgus monkeys dosed for 2 weeks with 0.4, 2 or 9 mg/kg (sc, biweekly) somapacitan or vehicle. No effects related to somapacitan were observed on a.o. locomotor activity, balance, alertness, vocalisation, grooming, tremors, convulsion, unusual behaviour, aggressiveness, piloerection, several reflexes and motor control.

In the same cynomolgus monkeys study the effect of somapacitan on respiratory function was studied. No effects related to somapacitan were observed on respiratory rate or respiratory depth. The NOAEL was considered to be 9 mg/kg, biweekly, corresponding to >2000-fold the mean C<sub>max</sub> at the MRHD of 8 mg/week.

### ***Pharmacodynamic drug interactions***

Nonclinical pharmacodynamic drug interaction studies have not been conducted with somapacitan. Current marketed GH products have been reported to pharmacodynamically interact with eg glucocorticoids, thyroids, oestrogens and other reproductive hormones. These effects are also expected for somapacitan.

### **2.3.3. Pharmacokinetics**

Somapacitan pharmacokinetic profile was characterized following single intravenous (iv) administration in rat, minipig and monkey and subcutaneous (sc) administration to rats, rabbits and cynomolgus monkeys as well as in mouse and minipig. Toxicokinetic profiles following repeated dosing were characterized in rat and monkey following sc dosing for a total duration of up to 26 weeks. In addition, exposure was characterized as part of the Embryo-Foetal Development Studies in rats and rabbits as well as the PPNP studies in rats.

#### Methods of analysis

A luminescent oxygen channelling immunoassay (LOCI [AlphaLISA]) was used to determine the plasma concentration of somapacitan. The provided validation reports demonstrate that the assays were suitable to assess somapacitan concentrations in monkey, rabbit, mouse and rat plasma. The detection range was 60-12000 ng/ml. Incurred sample reanalysis (ISR) was performed in rat, monkey and rabbit and was acceptable.

Distribution of radioactivity in rats was analyzed quantitatively via whole-body autoradiography.

To detect antibodies against somapacitan (ADA), bridging ELISA methods were developed for rat and monkey serum. The assays were selective, and the sensitivity was found to be 160 ng/mL for the assay in rat serum and 625 ng/ml for the assay in monkey serum (it is noted that the values reported in the summary differ from the values in the report). The ADA method has been appropriately validated in accordance with current guidelines. The assay cut point has been specified according to pre-treatment samples allowing a 1% false

positive rate. Drug tolerance was 5000 ng/mL of somapacitan in rat serum and 1250 ng/ml in monkey serum. It should be noted, however, that the levels of somapacitan in monkey serum may be well above the drug tolerance levels and may therefore interfere with the assay sensitivity for ADA detection. No assay was available for measuring the neutralising effect of the ADAs, but the impact of ADA's was analysed by comparing pharmacokinetic and pharmacodynamic data.

### Absorption

Single-dose pharmacokinetic studies following IV administration of somapacitan were performed in rats, Cynomolgus monkeys and minipigs. SC single-dose studies were, in addition to these species, also performed in mice and rabbits.

Somapacitan showed non-linear pharmacokinetics, indicated by a decrease in clearance with increasing dose levels in rats and a plasma decline in several phases in monkeys. T<sub>max</sub> ranged from 8h in rat to 24h in the monkey. The steady-state volume of distribution is low (20-39 ml/kg in all species) and limited to plasma volume. Terminal elimination half-life (T<sub>1/2</sub>) was between 4 and 17 hours via the SC route and did not differ from values observed in the IV studies.

The SC bioavailability of somapacitan was 69, 39 and 36% in monkey, rat and minipig, respectively. Overall, a supraproportional increase in exposure was observed with increasing doses, although this was most pronounced at the lower doses. Multiple-dose toxicokinetic studies were performed in rats, pregnant rabbits and cynomolgus monkeys. In the rat, exposure was reduced after repeated administration. This was less pronounced when the frequency of dosing was reduced from daily to bi-weekly. Also in pregnant rabbits, exposure was reduced after repeated administration of low doses. At higher dose levels, however, some accumulation was observed. Also, in monkeys and humans, slight accumulation was observed (<2-fold). T<sub>1/2</sub> in monkeys after repeated exposure was longer than following single doses (53-64h compared to 17h). The non-linear pharmacokinetics of somapacitan are consistent with the pharmacokinetics of human growth hormone, which is eliminated by a non-saturable renal route and a saturable hepatic route.

Anti-drug antibodies against somapacitan were detected in 33-46% of the rats at the end of the 13 and 26 week study and in only 1 or 2 of the monkeys. Since the levels of somapacitan in monkey serum are well above the drug tolerance levels, this may, therefore, interfere with the assay sensitivity for ADA detection. In both species, no clear impact on exposure levels was observed.

There were no apparent gender differences in exposure.

### Distribution

The extent of plasma protein binding of somapacitan was evaluated in plasma from mouse, rat, rabbit, monkey, pig and human using surface plasmon resonance biosensor technology. Somapacitan was highly protein-bound (>99%) with free concentrations of 0.01 in New Zealand rabbits, 0.1-0.5 in Wistar rats and 0.02 in Cynomolgus monkey, which is in the same low range as with human plasma (0.04%).

Tissue distribution of somapacitan was investigated in albino and pigmented rats using quantitative whole-body autoradiography (QWBA) following a single s.c. administration of 9 mg/kg [<sup>3</sup>H]-somapacitan (two <sup>3</sup>H atoms positioned in the lysine moiety in the linker). Somapacitan was relatively slowly absorbed from the injection site, and widely distributed. Plasma to blood ratio was 1.3-1.6. Somapacitan-related material was detected in the majority of analysed tissues. Highest concentrations were observed between 12 and 36 hours post-dose in bile ducts, kidney cortex, tooth pulp, liver, cerebrospinal fluid, pigmented skin and the urinary bladder wall (tissue-blood (T/B) AUC ratios up to 8). In all other tissues, T/B AUC ratios were <1. Low levels of radioactivity (<2% of that in blood) were observed in the central nervous system. Melanin binding in the

pigmented uveal tract and skin was observed, but this was reversible (no quantifiable radioactivity at 336h post-dosing).

The effects of somapacitan on placental transfer was assessed by QWBA in pregnant rats following a single s.c. dose of 9 mg/kg [<sup>3</sup>H]-somapacitan on gestational day 17. Higher tissue to blood AUC ratios, up to 17.6 were observed in pregnant rats. Somapacitan-related material was found in the majority of analysed foetal tissues. Foetal tissue to maternal blood AUC ratio was 0.542 for the kidney and <0.2 for all other tissues.

Following a single s.c. dose of 8 mg/kg somapacitan to lactating rats on approximately day 10 postpartum, somapacitan-related material was shown to be secreted into milk. The milk/plasma ratios were in the range of 0.175 - 0.496.

### Metabolism

No metabolic turnover of somapacitan was observed in mouse, rat, monkey and human hepatocytes incubated for 48 hours.

The *in vivo* metabolism of somapacitan was investigated in rats, monkeys and humans. Somapacitan was the main component in plasma. Two major metabolites were identified in plasma: M1 and M1B (products from proteolysis of the peptide backbone in somapacitan with intact side chain of Cys101; sum of M1 and M1B 15-28% in rat, 12% in human) and the unidentified metabolite P1 (eluted early in the chromatogram and likely to be tritiated water or another volatile component) (2-4% in rat plasma, 21% in human plasma). Two other metabolites with an exposure <5% of total AUC were identified in human plasma. All human metabolites were also found in rat and monkey plasma. The rat-human exposure ratios of P1 after multiple dosing of the MRHD were 9.1 and 5.2 (C<sub>max</sub> and AUC<sub>0-168h</sub>). The obtained C<sub>max</sub> exposure of M1 and M1B and rat-human exposure ratios was >70.

### Excretion

Excretion of [<sup>3</sup>H]-somapacitan was investigated in faeces and urine of rats (both sexes) and male monkeys as well as in rat bile, up to 120 hours post-dose. Elimination was slow. Urine (cage wash included) was the primary route of excretion (83-86% in rat and 54% in monkey). Faecal excretion accounted for 13-15% of the dose in rats and 1.7% in monkeys. A study in bile duct cannulated rats showed that biliary excretion accounted for 3.3-4.0% of the administered dose. [<sup>3</sup>H]-somapacitan was excreted only as metabolites; no detectable levels of intact somapacitan were observed in urine and faeces. In the monkey, at 120 hours post-dose, 38% of the label was still retained in the carcass and total recovery was 94%. No obvious gender related differences were observed in the rat. Also in humans, urine was the main excretion route (81%), and 13% was excreted via faeces.

### Pharmacokinetic drug interactions

The results of the studies on the pharmacokinetic drug interaction potential will be evaluated in the clinical assessment report.

## **2.3.4. Toxicology**

### ***Single dose toxicity***

No single dose toxicity studies were included in the non-clinical safety programme, this is acceptable.

## ***Repeat dose toxicity***

### Rat

Somapacitan was tested in rat repeat-dose toxicity studies, by daily dosing in a 2-week and 3-month study and by twice-weekly dosing in a half-year study.

Body weight gain, food consumption and IGF-I levels were all increased dose-dependently across all studies. In addition, increased relative organ size was observed for most of the organs at higher doses tested, which was accompanied by hypertrophy, hyperplasia, increased collagen and other histopathological findings related to excessive growth of organs. These effects were part of the expected pharmacological of somapacitan in rats and were partially recovered at the end of the recovery period.

Anti-drug antibodies (ADA) formation of approximately 30-60% was observed in all rat studies. However, this did not seem to have an effect on exposure and pharmacology related outcome (e.g. increased body weight gain). Positive ADAs were observed in 70% of the control animals in the 3-month study. The cause was not identified since there were no quantifiable levels of somapacitan in the control formulations or in the blood plasma at the toxicokinetic investigations, and there were extensive measures in place to avoid cross-contamination.

In both males and females, lactation and mammary changes and feminisation in males only were observed in all studies, often at the lowest dose tested.

Across studies, haematology parameters affected by somapacitan included decreased haematocrit, haemoglobin and erythrocyte count, low mean cell haemoglobin concentration increased reticulocyte counts and high mean cell haemoglobin and mean cell volume.

Clinical chemistry included increased plasma levels of bilirubin, increased platelet count and decreased APT. Total protein was increased, which is related to increased protein synthesis induced by growth hormone. Also, increased cholesterol and triglyceride levels were observed. Calcium values were increased and plasma sodium and chloride was often decreased in males only, which was accompanied by an increased urinary output and low urine pH in males.

In the 3-month study and to a lesser extent the half-year study, signs of diabetes were observed, mainly in males, consisting of excessive water intake, increased urine production, high glucose in urine, body weight loss, dose-related increase of insulin levels, islet cell hypertrophy/hyperplasia in the pancreas, findings in male reproductive organs and bilateral cataract in all animals displaying clinical symptoms of diabetes.

Most of the above-described somapacitan induced findings in rat were also observed in a previous repeat-dose toxicity study in the rat with human growth hormone (Jorgenson, 1988). Findings in the previous study included effects on body weight, food consumption, haematology parameters (haemoglobin and RBC decreases, WBC increases), clinical chemistry parameters (decreases serum cholesterol, beta globulin, phosphate, ALAT, APT, blood glucose levels and albumin), development of anti-drug-antibodies, increased amounts of calcium and phosphate in urine, enlarged mammary glands with lactation in both males and females, hyperplasia of the mammary glands, increased organ weights for all organs except prostate, testes and pituitary, yellow spots and inflammation in the prostate, mucification of the vaginal epithelium, haematopoietic activity in the red pulp of the spleen and fibrosis at the injection sites.

Most findings could be explained by the pharmacological action of human growth hormone in rats. However, administration of hGH and somapacitan to rodents results in an un-physiological receptor activation of both the growth hormone receptor (GHR) and the prolactin receptor (PRLR). In humans and monkeys, endogenous

GH has a high affinity for both the GHR and PRLR. Likewise, in rodents, human GH has a high affinity for both the endogenous GHR and the PRLR, whereas rodent GH only binds to the rodent GH receptor. Due to this known un-physiological binding of somapacitan and hGH to the PRLR receptor, it is difficult to discern which effects observed are relevant for the clinical situation. Based on this, the rat is not considered an appropriate model for testing toxicity of somapacitan.

Although it is recognized that many of the observed effects can be explained by the pharmacological action of somapacitan in rats, these observed effects are still considered to be adverse and have been taken into account to establish the NOAEL. In all studies, adverse effects were observed at the lowest dose tested, including effects on mammary tissue and lactation in both males and females. Therefore, it is considered that a NOAEL was not reached in any of the rat repeat-dose toxicity studies. The exposure (AUC) at the lowest dose tested with daily dosing in the 2-week and 3-month study (0.4 mg/kg/day) was unfortunately not reported for males. In females, this was reported, and an exposure margin was 4.8-22.8 fold MRHD was calculated. The exposure margin at the lowest dose tested for twice-weekly dosing in the half-year study was 3.5 and 3.3 fold MRHD exposure for males and females, respectively.

Additionally, in the 3-month study, some specific adverse findings were observed, including CPN in kidney and diabetes-like symptoms, including cataract formation. The exposure margin at the NOAEL for findings of CPN in the kidneys was 11 fold MRHD exposure, the exposure margin for the NOAEL for cataract formation and diabetes-like symptoms observed in males was approximately 38 fold the MRHD exposure.

#### Cynomolgus monkey

In repeat-dose toxicity studies cynomolgus monkeys were treated with somapacitan for up to 6 months. Somapacitan increased IGF-I plasma concentrations at all doses tested. Mammary swelling and lactation were observed in males and females, together with histopathological changes including acinar dilation and epithelial papillary hyperplasia. These adverse effects were more prominent in females and partially reversible at up to 6 weeks recovery. Haematology findings included decreased haematocrit and haemoglobin count in females and decreased plasma glucose in males. No glucose was detected in urine. In literature, similar effects by human growth hormone on mammary tissue, including lactation, and increased glucose levels were earlier described in a cynomolgus monkey repeat dose study (Jorgensen, 1988). Red areas were observed at the injection site, with scabs and ulcers and necrosis/collagen degeneration with or without oedema and perivascular inflammation was observed around the injection site. Although most effects are considered to be related to the pharmacology of somapacitan, they are considered to be adverse. Therefore, a NOAEL was not reached in these studies. The exposure margin at the lowest doses tested in cynomolgus monkeys compared to exposure at MRHD lies between 67 and 95 fold.

### **Genotoxicity**

Somapacitan was not found to be genotoxic in the reverse mutation test, chromosome aberration test and the in vivo micronucleus test. Somapacitan has no genotoxic potential.

### **Carcinogenicity**

In a CHMP scientific advice procedure it was agreed that a carcinogenicity assessment of somapacitan based on a weight of evidence approach in accordance with the ICH S6 guideline was likely to be sufficient. CHMP also endorsed that the rodent is an unsuitable model for human risk assessment related to the carcinogenic potential of somapacitan, due to differences in receptor activation pattern between human growth hormone

in rodent and human. The CHMP concluded that long-term carcinogenicity studies in the rat are considered not likely to contribute to human risk assessment.

The Applicant provided a weight of evidence approach on the potential for the carcinogenicity of somapacitan using non-clinical data of somapacitan and a literature review of human growth hormone and carcinogenicity.

Repeat-dose toxicity studies showed that the proliferative effects of supra-physiological doses of somapacitan and hGH in the rat included an increase in body weight gain and organ weights as well as hyperplasia in bone and mammary gland and hypertrophy in a large number of organs. In cynomolgus monkey, proliferative effects were only observed in the mammary gland. Difference between rat and monkey can be explained by the activation by hGH of the prolactin receptor (PRLR), which is seen specifically in rats. Genotoxicity studies for somapacitan did not show genotoxic potential. Therefore, the proliferative changes in the repeat-dose toxicity studies are considered to be due to the exaggerated pharmacology of somapacitan. In addition, in vivo proliferative effect on hepatocytes in monkeys was not observed. Also, in vitro proliferation data of somapacitan investigated in a functional Ba/F3 cell proliferation assay showed the potency of somapacitan was approximately 3-4-fold lower and 8-fold lower than the potency of wild-type hGH in activating the human GHR and human prolactin receptor, respectively. These data show that the risk of mitogenic action of somapacitan is similar to wild type hGH related to binding to human GHR and PRLR.

Incidentally, one tumour was observed in each of the three pivotal rat studies. All three tumours were of a different type and observed at different doses without any dose-response relationship.

In literature, it was shown that recombinant rat and mouse GH was not carcinogenic in rat and mouse, respectively. However, transgenic mice for hGH were found to develop mammary gland carcinomas, probably due to un-physiological stimulation of PRLR. In addition, it was shown in bovine growth hormone transgenic mice that 20 fold elevated levels of growth hormone with increased IGF-I levels did not induce tumour growth, whereas stimulation of PRLR without stimulation of GH or IGF-I did induce mammary tumours in these transgenic mice. This data indicate that in the rodent, proliferative and hypertrophic effects are caused through the PRLR.

The provided weight of evidence approach shows the rodent is not a sufficient model to study carcinogenicity of human growth hormone in rodents.

The Applicant shortly described literature on possible carcinogenic effects of hGH in human. In short, in human, it remains inconclusive if there is an association between growth hormone replacement therapy and increased long-term risk of developing a malignancy.

As with human growth hormone products, somapacitan is to be contraindicated for treatment in the presence of active malignancy and any pre-existing malignancy should be inactive and its treatment complete prior to instituting therapy with somapacitan.

## ***Reproduction Toxicity***

### Fertility

Male and female fertility was assessed in rats.

In males, relative organ weight (as percentage of terminal body weight) of epididymis, prostate, seminal vesicles and testes were decreased. This effect can be explained by the somapacitan induced increased body weight of the rats compared to control. In addition, pale areas of the prostate were observed, which was also

described in literature in a repeat-dose toxicity study in rats with hGH (Jorgenson, 1988). However, no effects were observed on pre-coital interval, mating performance and fertility and mean numbers of implantations, resorptions and live embryos. Somapacitan did not have an adverse effect on male fertility at an exposure margin of 13 fold exposure at MRHD.

In females, somapacitan induced irregular oestrous cycles at all doses tested. In addition, number of copulation plugs and sperm count estimates from vaginal smears at mating were lower at all doses. However, these changes did not have any effect on mating performance, fertility, litter size mean numbers of implantations, resorptions and live embryos. Therefore, earlier described effects are not considered adverse in rats. However, the clinical relevance of somapacitan induced disruption of the oestrus cycle is unknown. Female fertility was not adversely affected up to an exposure margin of 15 fold exposure at MRHD.

#### Embryo-foetal development

Effects of somapacitan on embryo-foetal development were assessed in rat and rabbit.

In rat repeat-dose toxicity studies, clearance of somapacitan after daily dosing significantly increased around Days 4-6 of treatment. Therefore, to ensure adequate exposure throughout organogenesis, a split-dose design was employed with exposure from GD6-9, GD10-13 and GD14-17. Maternal animals showed body weight gains at all doses tested for all treatment periods, with a concurrent increase of IGF-I. Mean foetal weights were slightly increased during treatment at GD10-13. In addition, at GD10-13 at the high dose only, an increased incidence of short-, bent-, and/or thickened long bones was observed. In literature, it has been described that these findings are common in rat and resolve within a few weeks after birth. Furthermore, it has recently been suggested by multiple research groups that these effects are to be recognized as variations. Although the severity of these findings can be questioned, the applicant considered these effects as adverse and used these effects to set the NOAEL. The exposure margin for embryo-foetal development at this NOAEL is 18 fold exposure at MRHD.

In the rabbit, somapacitan was given every other day from GD6 through GD18. Maternal body weight gain was increased at the mid and high dose and IGF-I was also increased in a dose-responsive manner. Placental weight was reduced at a high dose. Foetal weight was reduced at all doses, with 9% at low dose and 11% at mid and high doses. Reduced foetal weight was found concurrent with unossified and incomplete ossification of the metacarpals and phalanges at all dose levels. These growth-related effects may be secondary due to the reduced placental weight at high dose and maternal mediated effects, although no major maternal toxicity was observed at any dose. No malformations or embryo-foetal lethality were observed. Based on the significantly reduced foetal body weight of up to 11%, a NOAEL for embryo-foetal development cannot be determined. Exposure at the lowest dose tested was 9 fold exposure at MRHD.

#### Pre-and postnatal toxicity

In a pre-and postnatal study in rats, somapacitan postnatal pup weight gain was increased. In addition, a dilated renal pelvis was observed in offspring. However, this effect was reversible in animals grown to maturity. These effects were not considered adverse. The exposure margin was 310 fold exposure at MRHD.

#### Juvenile toxicity

No juvenile toxicity studies were performed. The PDCO adopted a refusal of the PIP for somapacitan and agreement of a full waiver in all paediatric subsets on the grounds of lack of significant therapeutic benefit and likely lack of safety.

## **Toxicokinetic data**

Overall, plasma concentrations increased in a supra-proportional manner, although this was most pronounced at the lower doses.

Adequate exposure was maintained to evaluate safety in the toxicological studies. Exposure multiples (based on AUC) at lowest doses tested were 2.4-11 in rats and 67-95 in monkeys. Also in reproductive toxicology studies exposure ratios were sufficient ( $\geq 13$  in rats but  $< 9$  in rabbits).

Anti-somapacitan antibodies were detected in 33-46% of the rats at the end of the 13 and 26-week study and in only 1 or 2 of the monkeys (probably an underestimation due to the fact that the levels of somapacitan in monkey serum were above the drug tolerance levels). However, in both species, no clear impact on exposure levels was observed.

### Interspecies comparison

The pharmacokinetics of somapacitan were studied primarily in rats and monkeys. The absorption of somapacitan following SC administration was relatively fast, with a T<sub>max</sub> of 4-24 h in rats, monkeys and humans. Somapacitan displays non-linear pharmacokinetics, but at low doses (as in the clinically relevant dose range), pharmacokinetics are approximately linear. When dose levels increase further, plasma clearance decreases. At low doses, exposure was reduced after repeated administration in rats and rabbits, but at higher doses some accumulation is observed. In all species as well as humans, somapacitan is extensively bound ( $>99\%$ ) to plasma proteins (mainly albumin). The steady-state volume of distribution is low (20-39 ml/kg) in all species. The estimated volume of distribution (V/F) in humans was 14.6 L. In animals and humans, somapacitan is metabolised by proteolytic degradation, and cleavage of the linker sequence between the peptide and albumin binder. Urine is the primary route of excretion. Elimination half-life in animals ranges from 4-17 hours and is similar after s.c. and iv administration. In AGHD patients, a plasma terminal half-life of 2-3 days was estimated. The subcutaneous bioavailability of somapacitan in humans has not been investigated but was 36-69% in rat, monkey and minipig. No obvious gender differences were observed in the pharmacokinetics of somapacitan in animals. In humans, females (especially females on oral oestrogen) have lower exposure than males.

## **Local Tolerance**

Somapacitan produced limited inflammatory effects at the local injection site in rats (inflammatory cell infiltrate), monkeys (limited inflammatory tissue reaction) and rabbits (mild inflammatory changes).

## **Other toxicity studies**

### Antigenicity

Anti-drug antibodies for somapacitan were formed in the rat (30-60%) and were sporadically observed in the monkey. However, adequate exposure was obtained in toxicity studies, and expected pharmacodynamic effects were registered.

### Metabolites

All human metabolites of somapacitan were also found in rat and monkey plasma. The rat–human exposure ratios of P1 after multiple dosing of the MRHD were 9.1 and 5.2 (C<sub>max</sub> and AUC<sub>0-168h</sub>). The obtained C<sub>max</sub> exposure of M1 and M1B and rat–human exposure ratios were >70.

### Impurities

Three different batches of somapacitan were tested in a one-month rat repeat-dose toxicity study. Batches tested were the batch used in pivotal non-clinical repeat-dose studies in rat, a batch with additional impurities (fatty acid loss) and an end of shelf life batch group consisting of two batches tested during the experiment. First end of shelf life batch was stored (to induce deamidation) and used for dosing in weeks 1, and 2 of this study, and second end of shelf life batch was stored (to induce high molecular weight proteins) and used for dosing in weeks 3 and 4. It is unknown why the Applicant tested two different batches in one treatment group. In addition, each of the end of life batches was only tested in serial for 2 weeks, whereas the comparator batch (the one used in pivotal studies) was tested for four weeks. The end of shelf-life batches was taken into account to compare pharmacodynamic endpoints (body weight gain, IGF-I and insulin plasma levels) with the comparator batch. Although body weight gain was assessed throughout the study, IGF-I and insulin levels were only assessed at the start and the end of the study. Adverse effects observed were generally similar between the three batches; however, the end of shelf life batches group showed a marginally lower exposure profile with less severe effects on body weight increase at the end of the study. Impurities present in one batch were sufficiently qualified.

### **2.3.5. Ecotoxicity/environmental risk assessment**

The active substance is a peptide, 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.

### **2.3.6. Discussion on non-clinical aspects**

From a non-clinical point of view, the pharmacology, safety pharmacology, pharmacokinetics and toxicology programs are considered sufficient.

The animal to human exposure ratios have been determined using experimental AUC values of clinical study 3947 at steady state (0.12 mg/kg dose). Although the Exposure Multiple (EM) at the NOAEL is very low for the repeated dose toxicity studies in rat, it is sufficient in the repeated dose toxicity studies in monkey and in the reproduction toxicity studies.

Repeat-dose toxicity studies in rats have been conducted with a daily sc administration in the 2 and 13-week studies. Given the development of diabetes in the 13-week study, the dosing regimen has been changed to twice-weekly administrations for the 26-week study. In rats, most toxicological findings observed could be explained by the pharmacological action of somapacitan via IGF-I. Moreover, the toxicokinetic profile in rats is special with a shorter half-life compared to humans and a decline in exposure after multiple daily administrations. The exposure to somapacitan in rats is also dependent on time, dose and dosing frequency. The toxicokinetic profiles of somapacitan when administered once, twice or three times weekly have been compared in the context of an investigative three-week PK study in rats (study 2122272). An increase of the dosing frequency from twice weekly to three times weekly generally resulted in a reduced exposure. For once-weekly dosing, AUC<sub>0-24hr</sub> was similar to Day 1, for twice-weekly and three times weekly it had decreased to approximately 60% and 40% of Day 1 levels, respectively. Dose-normalised exposure in terms of AUC<sub>0-24hr</sub> and approximate C<sub>max</sub> (6 hours concentration) generally decreased with increasing dose and

with decreasing dosing interval. The time course of IGF-I concentrations was not investigated in this study. However, data from studies performed in hypophysectomised rats with once weekly administration have shown that peak IGF-I concentrations were observed 2-4 days after dosing. Therefore, taking into account both PD and PK aspects, the dose frequency of twice/week was the most appropriate choice to investigate the toxicity of somapacitan in the 26-week study in rats.

The Applicant provided a weight of evidence approach on the potential for the carcinogenicity of somapacitan using non-clinical data of somapacitan and a literature review of human growth hormone and carcinogenicity. In literature, it was shown that recombinant rat and mouse GH was not carcinogenic in rat and mouse, respectively. However, transgenic mice for hGH were found to develop mammary gland carcinomas, probably due to un-physiological stimulation of PRLR as is the case in the rat. In addition, it was shown in bovine growth hormone transgenic mice that 20-fold elevated levels of growth hormone with increased IGF-I levels did not induce tumour growth, whereas stimulation of PRLR without stimulation of GH or IGF-I did induce mammary tumours in these transgenic mice. These data indicate that in the rodent, proliferative and hypertrophic effects are caused through the PRLR.

Regarding the carcinogenic potential of IGF-I, the applicant points out that although the concentration profile of IGF-I is different due to the weekly dosing scheme of their product compared to daily hGH dosing, the physiological IGF-I levels (C<sub>max</sub>, C<sub>min</sub> and AUC) of IGF-I remains within normal levels. Furthermore, from animal studies with IGF-I, it is clear that a tumour promoting effect is only evident at doses that result in higher than physiological IGF-I levels. Clinically, similar average levels of IGF-I are obtained in the pivotal phase 3 trial for somapacitan compared to daily GH treatment. In addition, the deviation between IGF-I response seems similar between the two treatments in this study. Furthermore, the difference in IGF-I response over time within a dosing interval does not seem to appear, and therefore upregulation of the IGF-I receptor seems unlikely. It is, therefore, agreed that the risk of tumour promotion by high peak levels of IGF-I is rather low.

In a female rat fertility study, somapacitan induced irregular oestrous cycles at all doses tested. In addition, number of copulation plugs and sperm count estimates from vaginal smears at mating were lower at all doses. However, these changes did not have any effect on mating performance, fertility, litter size mean numbers of implantations, resorptions and live embryos. Therefore, earlier described effects are not considered adverse in rats. These effects are likely PRL receptor-mediated. However, the clinical relevance of somapacitan induced disruption of the oestrus cycle is low.

Regarding the rat EFD toxicity study, the Applicant could have performed more explorative research and provided a more broad discussion on the rationale of determining an optimal dosing schedule, taking into account the enhanced clearance of somapacitan after 4 days daily exposure in rat and information gathered from the long-term repeat-dose toxicity studies. However, based on the twice-weekly dosing in the 26-week repeat-dose toxicity study in rats, exposure was greatly decreased after 24 hours exposure. Taking into account this information, the four-day-window treatment schedule seems to be the most optimal for the EFD in rats. Although there is no continuous exposure to the embryos from implantation to closure of hard palate, possible somapacitan induced malformations, which are related to exposure at a certain stage of development, should be picked up with this approach. Growth related effects and maybe to a lesser extent embryo foetal death may be more difficult to pick up with this approach. However, exposure at the highest dose tested (18 mg/kg/day) was stable at first and fourth day of exposure for each treatment-window group. In addition, at the highest dose tested the exposure ratio was 130 fold MRHD exposure (which is above the 25-fold exposure level as threshold of concern for EFD toxicity, as described in ICH S5R3).

The treatment-related increase in postimplantation loss reported in the rabbit EFD toxicity study cannot be excluded. However, the exposure margin at the high dose in the rabbit EFD study is approximately 1400 fold exposure at MRHD and therefore, this finding is of limited concern for the human situation.

Three different batches of somapacitan were tested in a one-month rat repeat-dose toxicity study to test for impurities and pharmacodynamic consistency. Batches tested were the batch used in pivotal non-clinical repeat-dose studies in rat, a batch with additional impurities (fatty acid loss) and an end of shelf life batch group consisting of two batches tested during the experiment. First end of shelf life batch was stored (to induce deamidation) and used for dosing in weeks 1, and 2 of this study and batch was stored (to induce high molecular weight proteins) and used for dosing in weeks 3 and 4. It is unknown why the Applicant tested two different batches in one treatment group. In addition, each of the end of life batches was only tested in serial for 2 weeks, whereas the comparator batch (the one used in pivotal studies) was tested for four weeks. The end of shelf life batches were taken into account to compare pharmacodynamic endpoints (body weight gain, IGF-I and insulin plasma levels) with the comparator batch. Although body weight gain was assessed throughout the study, IGF-I and insulin levels were only assessed at the start and end of the study. This testing paradigm was chosen due to limitations of product availability. Based on the toxicological profile of the different batches, there are no increased concerns from a toxicological point of view. However, repeat dose toxicity study 213245 was not adequately designed to make a statement on the efficacy of the EoSL batches. In addition, no conclusions can be drawn on the efficacy of the batch which was tested in the first two weeks of the study only, deamination), since IGF-I and insulin levels were not measured in this part of the study. Further, only limited conclusions on efficacy can be drawn from the second EoSL batch (high molecular weight proteins). It should be noted that although the data are not robust enough to be able to draw conclusions on efficacy, there was a slight difference in body weight gain of the animals between the different batches.

### 2.3.7. Conclusion on the non-clinical aspects

From a non-clinical point of view, there are no points that need to be addressed at this stage. Therefore, currently, somapacitan is considered approvable from a non-clinical point of view.

## 2.4. Clinical aspects

### 2.4.1. Introduction

#### **GCP**

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant 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.

**Table 2 Tabular overview of clinical studies**

| Trial ID (countries) | Trial design and duration of treatment | Subjects exposed (M/F) Age | Dose regimen (and PYE for AGHD) |
|----------------------|--|----------------------------|---------------------------------|
|----------------------|--|----------------------------|---------------------------------|

| Phase 1 (Healthy subjects and special populations) |  |  |   |
|--|--|--|---|
| 3915a (DE)   | Safety, tolerability, First human dose, PK/PD of somapacitan Randomized, single-dose and multiple-dose, dose escalating, double-blinded, placebo-controlled.<br><br>Trial duration: 4 weeks. | 105 healthy subjects<br>Single-dose: 40 healthy subjects.<br><br>(40/0)<br><br>22–43 years   | Somapacitan s.c. 5 single-dose cohorts: 0.01, 0.04, 0.08, 0.16 and 0.32 mg/kg or placebo.         |
|  |  | Multiple-dose: 32 Japanese healthy subjects <sup>b</sup><br><br>(32/0);<br><br>23–38 years<br><br>33 Non-Asian healthy subjects <sup>b</sup><br><br>(33/0)<br><br>22–45 years              | Somapacitan s.c. 4 multiple-dose cohorts: 0.02, 0.08, 0.16 and 0.24 mg/kg or placebo once-weekly. |
| 4237 (NL)  | Absorption, metabolism and excretion (AME) of somapacitan.<br><br>Single-dose, open-labelled.<br><br>Trial duration: 5 weeks.  | 7 healthy subjects<br><br>(7/0)<br><br>45–62 years   | 6 mg somapacitan containing [ <sup>3</sup> H]-somapacitan up to 20 MBq, s                         |
| 4297 (DE)  | PK/PD and safety of somapacitan in subjects with renal impairment Multiple-dose, open-labelled.<br>Trial duration: approx. 6 weeks   | 44 subjects (25/19):<br><ul style="list-style-type: none"> <li>• 15 healthy</li> <li>• 29 renal impaired</li> </ul> (mild: 8; moderate: 8; severe: 5; haemodialysis: 8)<br><br>28–74 years | Somapacitan s.c. once-weekly for 3 weeks: 0.08 mg/kg  |
| 4298 (SK)  | PK/PD and safety of somapacitan in subjects with hepatic impairment Multiple-dose, open-labelled.  | 34 subjects (15/19):<br><ul style="list-style-type: none"> <li>• 16 healthy</li> <li>• 18 hepatic impaired</li> </ul> (mild: 9; moderate: 9).  | Somapacitan s.c. once-weekly for 3 weeks: 0.08 mg/kg  |

|  |  |   |   |
|--|--|---|---|
|  | Trial duration:<br>approx. 6 weeks   | 37-69 years   |   |
| Phase 1 (AGHD patients)  |  |   |   |
| 3947<br>(DK, SE)   | Safety, tolerability,<br>PK/PD Randomized,<br>multiple-dose, dose-<br>escalating, sequential<br>dose group, open-<br>labelled, active-<br>controlled<br>(somatropin).<br><br>Trial duration: 4<br>weeks  | 34 AGHD patients<br>(25/9)<br><br>21–69 years   | <ul style="list-style-type: none"> <li>• Somapacitan s.c. once-weekly for 4 weeks: 0.02, 0.04, 0.08 and 0.12 mg/kg (6-7 patients per group corresponding to 0.4-0.5 PYE) In total, 26 patients, 1.8 PYE</li> <li>• Somatropin s.c. daily: as pre-trial. 8 patients, 0.6 PYE</li> </ul>  |
| Phase 3a (AGHD patients)   |  |   |   |
| 4054a<br>(AU, DE, IN, JP,<br>LV, LT, MY, PL,<br>RO, RU, ZA, SE,<br>TR, UA, UK, US) | Efficacy and safety<br>Randomized, parallel-<br>group, placebo-<br>(double-blinded) and<br>active-controlled<br>(open; somatropin)<br>trial to compare the<br>efficacy and safety of<br>once-weekly<br>somapacitan with<br>once-weekly placebo<br>and daily somatropin<br>for 34 weeks (main),<br>followed by a 52<br>weeks open-labelled<br>extension period <sup>e</sup> .<br><br>Trial duration: 86<br>weeks exposure and<br>88 weeks in trial. | 300 treatment-naïve<br>AGHD patients<br>(including 46<br>Japanese patients)<br>(145/155)<br><br>23–77 years | <p>Main period:</p> <ul style="list-style-type: none"> <li>• Somapacitan s.c. once-weekly (individual dose titration based on IGF-I SDS; starting dose depends on age) or placebo once-weekly.</li> <li>• Somatropin s.c. daily (individual dose titration based on IGF-I SDS; starting dose depends on age).</li> <li>• 8 weeks dose titration and 26 weeks fixed-dose treatment.</li> </ul> <p>Extension period:</p> <ul style="list-style-type: none"> <li>• Somapacitan s.c. once-weekly or somatropin s.c. daily.</li> <li>• 8 weeks dose titration and 44 weeks fixed-dose treatment.</li> </ul> <p>Full trial:</p> <ul style="list-style-type: none"> <li>• Somapacitan, actual mean dose: 0.040 mg/kg. 288.8 PYE.</li> <li>• Somatropin, actual mean dose: 0.005 mg/kg. 123.2 PYE.</li> </ul> |
| 4043a  | Safety Randomized,<br>open-labelled,   | 92 previously GH-<br>treated AGHD patients  | <ul style="list-style-type: none"> <li>• Somapacitan s.c. once-weekly (individual dose titration based</li> </ul>   |

|                          |   |   |   |
|--------------------------|---|---|---|
| (DE, DK, FR, JP, SE, UK) | parallel-group, active controlled (somatropin) to compare safety of once weekly somapacitan with daily somatropin.<br><br>Trial duration: 26 weeks exposure and 27 weeks in trial.  | (including 17 Japanese patients)<br><br>(50/42)<br><br>19–77 years                | on IGF-I SDS; starting dose depends on age <sup>c</sup> ). Actual mean dose: 0.027 mg/kg. 29.6 PYE.<br><br><ul style="list-style-type: none"> <li>Somatropin s.c. daily (individual dose titration based on IGF-I SDS; starting dose depends on aged). Actual mean dose: 0.003 mg/kg. 14.6 PYE.</li> <li>8 weeks dose titration and 18 weeks fixed-dose treatment.</li> </ul> |
| 4244a (JP)               | Safety and efficacy Randomized, open-labelled, parallel-group, active controlled (somatropin) to evaluate safety of once weekly somapacitan and daily somatropin.<br><br>Trial duration: 52 weeks exposure and 53 weeks in trial. | 62 previously GH-treated Japanese AGHD patients<br><br>(33/29)<br><br>20-75 years | <ul style="list-style-type: none"> <li>Somapacitan s.c. once-weekly (individual dose titration; starting dose depends on age<sup>c</sup>) Actual mean dose: 0.029 mg/kg. 45.4 PYE.</li> <li>Somatropin s.c. daily (starting dose depends on aged). Actual mean dose: 0.003 mg/kg. 14.8 PYE</li> </ul>   |

Abbreviations: AGHD = adult growth hormone deficiency; AME = absorption, metabolism and excretion; F = female; GH = human growth hormone; M = male; PYE = patient years of exposure; s.c. = subcutaneous; AU = Australia; DE = Germany; DK = Denmark; FR = France; IN = India; JP = Japan; LV = Latvia; LT = Lithuania; MY = Malaysia; NL = Netherlands; PL = Poland; RO = Romania; RU = Russia; ZA = South Africa; SE = Sweden; SK = Slovakia; TR = Turkey; UA = Ukraine; UK = United Kingdom; US = United States.

a Trial includes Japanese subjects/patients.

b In trial 3915, Japanese passport and Japanese born parents was required for Japanese subjects; non-Asian born parents was required for Non-Asian subjects.

c Somapacitan starting dose: patients between 23-60 years (trial 4054) or 18-60 years (trials 4043 and 4244) of age start at 1.5 mg/week; females on oral oestrogen irrespective of age start at 2.0 mg/week, and patients older than 60 years of age start at 1.0 mg/week.

d Somatropin starting dose: patients between 23-60 years (trial 4054) or 18-60 years (trials 4043 and 4244) of age start at 0.2 mg/day; females on oral oestrogen irrespective of age start at 0.3 mg/day; patients older than 60 years of age start at 0.1 mg/day.

e In the extension period, patients treated with somapacitan continued their once-weekly somapacitan treatment, patients treated with placebo were switched to somapacitan treatment and patients treated with somatropin were re-randomized to continue somatropin treatment or switch to somapacitan treatment

The applicant conducted a *post-hoc* simulation study and an exposure-response analysis based on data from pivotal study 4054. These evaluations and the results thereof will be summarized below.

## **GCP inspection**

GCP inspections (reference number GCP/2019/041) concerning study NN8640-4054 were conducted at an outpatient centre in Hyderabad (India; site 1), a clinical research unit in Melbourne (Australia; site 2), and at the Sponsor site in Bangalore (India; site 3). The inspections at the three sites mentioned above were routine Good Clinical Practice (GCP) inspections. The purpose of the inspections was to verify whether study 4054 was conducted in compliance with GCP and applicable regulations, in particular where it has an impact on the validity of the data or the ethical conduct of the study.

### **Inspection findings**

The most important findings are described below.

The inspectors stated that the regional and local offices of the sponsor had a high level of autonomy or independence (e.g. with respect to documents and forms to be provided, but also on monitoring and direct-line interactions with sites/principal investigators concerning questions and issues). According to the inspectors, the actual structural organisation of the sponsor resulted in a non-uniform conduct of the study at different sites. The management of the study by the sponsor in practice, including monitoring, did not result in adequate sponsor oversight and control over global study issues and collected data. As a consequence, many of the reported inspection findings are relevant for the full study.

According to the inspectors, the source data (e.g. DXA scans) were not or not adequately archived for a substantial number of the investigator sites. For at least two sites in India, most of these source data were permanently lost due to a computer issue. In view of the inspectors, these source data are likely retrievable for most sites. Therefore, according to the inspectors these serious issues are not considered to have a significant impact on the final reliability of the reported data.

The critical finding reported in relation to the ethical conduct (study specific constraints for (potential) trial participants before having signed the informed consent form), which, again, is a very serious issue in need of adequate remedy, is also not considered to have a significant impact on final reliability of the reported data.

### **Conclusion inspectors**

According to the inspectors, the reported critical and major findings do reflect serious shortcomings to, non-compliances with and violations of ICH GCP requirements. As such, they did affect or could have affected the rights, well-being and safety of the participants as well as the quality and integrity of the data.

### ***Interpretability of study data of study 4054***

According to the inspectors, obtained study data may be used despite the lack of sponsor oversight and adequate quality assessment and quality control. This is because of the set-up of the study (primary efficacy parameter and several secondary efficacy parameters calculated by a third party, based on the DXA scans provided), the fact that only a very limited number of serious adverse events occurred, and a number of crucial processes went well. The inspectors could still support a decision by the assessors to use the clinical trial data reported in the evaluation process of this centralised procedure.

### **Discussion on GCP inspection findings**

Taking into account the inspection findings, study 4054 does not meet current GCP requirements. However, the inspectors did not report data manipulation. Instead, the inspectors indicated that the clinical study data may still be interpreted.

Because of this, the results of the study 4054 will be summarised and interpreted below with acknowledgement of the GCP inspection findings.

## 2.4.2. Pharmacokinetics

The completed somapacitan clinical development programme in AGHD is comprised of 8 clinical trials consisting of 5 clinical pharmacology trials, 1 confirmatory phase 3 trial, and 2 supportive phase 3 trials. In addition, pharmacokinetic data were included in a population pharmacokinetic analyses.

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 sufficiently long period. Incurred sample reanalysis data were presented for study 3915 (healthy subjects), study 3947 and 4244 (AGHD patients), study 4297 (patients with various degrees of renal impairment) and study 4298 (patients with hepatic impairment), showing that the method was reproducible.

For the analysis of somatropin in human serum 2 validated analytical methods were applied, i.e., an ELISA and a CLIA. The methods proved to be sensitive and robust for analysis of somatropin. Validation results showed acceptable performance within the normal standard criteria. In addition, somatropin is stable in plasma during a sufficiently long period. It was indicated that for the CLIA selectivity was not validated. Different validated methods were carried out at Novo Nordisk and an additional site, and cross-validation showed that both methods gave comparable results. Incurred sample reanalysis data were presented for the ELISA in study 4054 (AGHD patients), and CLIA in study 3947 (AGHD patients), showing that the method was reproducible.

For the analysis of IGF-I and IGFBP-3 commercial available kits have been applied. The kits have been validated, showing acceptable accuracy, precision, dilution linearity, and parallelism. Moreover, the reproducibility of the method was shown by incurred sample reanalysis.

The anti somapacitan antibody bridging ELISA screening assay was validated for human serum samples. (from healthy subjects and growth hormone deficient patients) The validation data shows that the assay is fit for purpose of measuring anti somapacitan antibodies in human subjects after treatment with somapacitan. Based on the validation results, the cell-based in vitro neutralising assay is considered appropriate. This was further supported by the very low assay variability ( $\leq 10\%$  CV).

Population pharmacokinetic analysis:

A population pharmacokinetic analysis was carried out to describe the release characteristics of somapacitan after s.c. administration. A one-compartment model with dual first and zero-order absorption through a transit compartment, and with saturable elimination was used to describe the somapacitan PK. Goodness-of-fit plots of the final model for somapacitan against the population model prediction and individual model prediction showing a normal random scatter around the identity line and indicated the absence of significant bias. The pcVPC demonstrates that the final model adequately described the time course of somapacitan plasma concentrations and its associated variability after s.c. dosing. Between categories of sex, race and age groups, body weight appeared to be correlated to all three covariate categories. Overall, the popPK model performed well.

PK/PD analysis:

For the PK/PD model of the effect of somapacitan on IGF-I, PK/PD was described using an indirect response model. The model used an error model consisting of an additional and proportional error. Goodness-of-fit plots of the final model showed a normal random scatter around the identity line and indicated the absence of significant bias. Furthermore, the pcVPC demonstrates that the final model adequately described the time course of somapacitan effect on IGF-I plasma concentrations and its associated variability after s.c. dosing.

## **Absorption**

A freeze-dried formulation (6.7 mg/vial) and a liquid formulation (10 mg/1.5 ml) were used in the clinical development of somapacitan. The performed exposure comparison between the freeze-dried formulation and liquid formulation indicates that steady-state exposure ( $AUC_{0-168h}$  and to some degree  $C_{max}$ ) is higher in the trials using the freeze-dried formulation (trials 3915, 3947) compared to the trials using the liquid formulation (trials 4297, 4298). These differences may be attributed to the proportion of females in the trial populations.

Both somapacitan pen-injectors, used in clinical trials and to-be-marketed, are identical in all functional parts. They also are functionally identical to Norditropin-FlexPro pen-injector whereas device constituent of Norditropin NordiFlex is an earlier device design.

After s.c. administration  $t_{max}$  values are observed after about 8 - 20h. Injections sites were abdomen and thigh, and the influence of the injection site was not specifically evaluated. In the Phase III studies, both injection sites were used. For growth hormone, it was reported that absorption is not influenced due to a different injection site. Additional, in the popPK analysis, the injection site was not identified as a significant covariate.

A more than dose proportional increase in AUC and  $C_{max}$  is observed over the dose range of 0.01 – 0.32 mg/kg (about 0.7 – 25 mg/week). This may suggest saturable elimination mechanisms, e.g. receptor mediated clearance. At doses in the more clinically relevant range, i.e. below 0.08 mg/kg (about 6 – 7 mg/week) linear pharmacokinetics are observed for AUC; however,  $C_{max}$  increased still more than dose-proportional (factor 3.5 after doubling the dose at multiple dosing).

To be noted, after the first dose, the somapacitan dose is titrated based upon the clinical response, so possible non-linear pharmacokinetics are considered less relevant. Dosing in mg/week without taking body weight into consideration, followed by individual dose adjustment/titration based on IGF-I SDS and clinical response is considered appropriate.

No unexpected accumulation is observed after applying the SmPC recommended dose scheme. Steady-state was estimated to be reached after 1 – 2 doses, with a low accumulation ratio (<2). Within the dose ranges evaluated, there is no evidence of a dose- and time-dependent PK of somapacitan.

A high intersubject variability is observed in AGHD patients at steady state, ranging from about 62 - 102% for  $AUC_{0-168h}$  and from 113 – 201% in  $C_{max}$ . PopPK simulations confirmed the moderate to high inter-subject variability (estimated 64%). Exclusion of the co-variables decreased inter-subject variability to about 44%. The covariates body weight, sex and oral oestrogen use, race and age, which were included in the popPK modelling, explained 78% of the observed inter-subject variability. This high variability is thus less relevant after dosing, when the specific subject is dosed and titrated, including the different covariates between the subjects.

Pharmacokinetics were in general comparable between healthy subjects and AGHD patients (reference 0.08 mg/kg dose level). PopPK modelling indicated that in the fixed-dose periods after titration, the mean somapacitan dose was 2.4 mg/week, the estimated geometric mean  $C_{avg}$  was 2.7 ng/ml, the geometric mean  $C_{max}$  was 7.4 ng/ml, the  $t_{max}$  was 5.8 h, the approximate half-life 69.2 h and the accumulation ratio ( $R_{acc}$ ) was 1.23. The estimated  $AUC_{0-168h}$  was 448 ng.h/ml.

Delayed and missed doses:

Delaying a dose or missing a dose will result in decreased somapacitan plasma levels. IGF-I levels showed the same pattern. Delaying a dose by 3 days and the next dose is administered as scheduled, resulting in further lower somapacitan plasma levels during the 3 days of delay, slightly decreased peak concentration after next normal scheduled dose and higher trough concentrations after this dose, compared to normal dosing. Two weeks after the delayed dose, the concentrations will be completely restored.

After missing a dose, the concentration of somapacitan will decrease till the next scheduled dose but is expected to be completely restored 2 weeks after the missed dose.

IGF-I levels following the same pattern (see further Pharmacodynamics for dose recommendation).

Bioavailability/bioequivalence:

A freeze-dried powder and a liquid formulation were used in the clinical studies. Considering the formulation is a solution for subcutaneously (s.c.) injection and taking into account the comparability in excipients and that the albumin binding moiety is controlling the release, a difference in bioavailability between the different formulations used is not expected. This is also shown by an inter-study comparison of pharmacokinetics obtained with the freeze-dried powder formulation and the liquid formulation, showing comparable pharmacokinetics.

## ***Distribution***

Somapacitan is highly bound to albumin (>99%) and slowly release from albumin. The popPK model (incorporating rate-limiting absorption) estimated a volume of distribution of 14.6 l, which would be in line with the volume of distribution of albumin (13.6 l).

## ***Elimination***

Metabolism:

After injection, somapacitan is considered metabolised by proteolytic cleavages of the peptide backbone and sequential degradation of the linker sequence. This resulted in 3 main plasma metabolites (named P1, M1 and M1B) and two main urine metabolites (named M4 and M5). Intact somapacitan accounted for 59% of the total exposure of somapacitan-related material in plasma, and P1 accounted for 21% and M1 and M1B accounted for 12%. The remaining plasma metabolites accounted for <10% of the total AUC exposure.

After administration of [3H]-somapacitan, 94% of the administered dose was recovered 28 days after dosing, of which 80.9% was excreted in urine (wet samples), 12.9% was excreted in faeces (wet samples) and 0.19% was excreted in expired air. No intact somapacitan was recovered in urine and faeces.

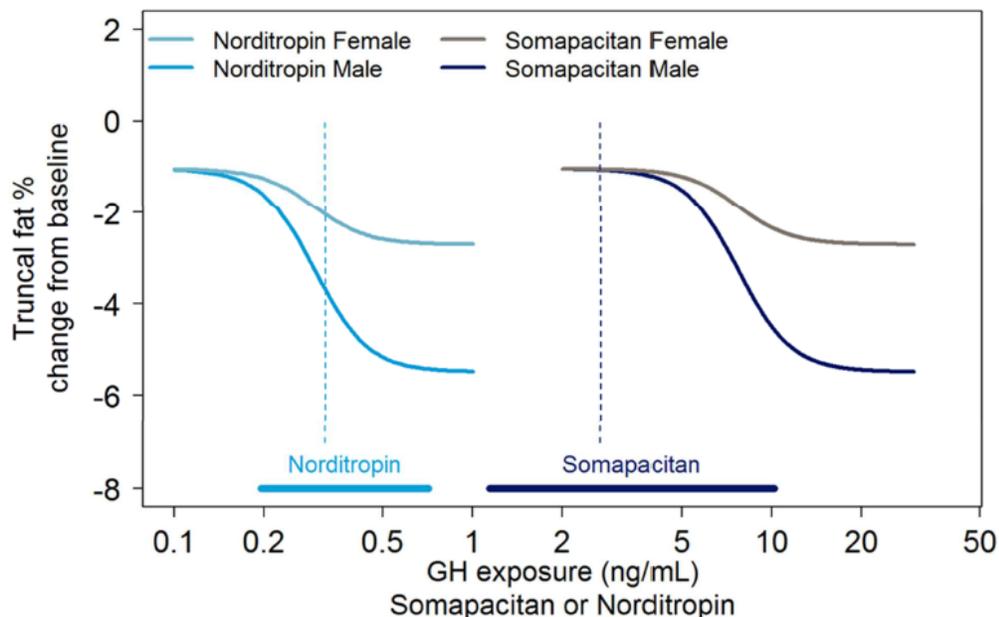
#### Elimination:

At steady state, the elimination half-life of somapacitan in AGHD patients ranged from 49 – 76h. Based on modelling analyses, the terminal half-life was estimated to be 69.2h. More than 80% of somapacitan in the circulation was eliminated within 7 days after dosing at steady-state. The CL/F at steady state ranged from 0.021 to 0.039 l/h/kg with high variability (CV of 62.0 to 99.9%).

With the SPC recommended dosing scheme, somapacitan steady-state exposure is reached after 1 – 2 injections, with limited further accumulation.

The applicant indicated that a subset of patients might not have reached the optimal dose and effect. Using data from study 4054, and applying population PK/PD modelling, based upon exposure-response data it was predicted that a total of 90% of the population reached, or would likely be able to reach, an IGF-I SDS above 0 within the proposed dose range (up to 8 mg) and based on continued titration towards and IGF-I SDS level of 0 to +2.

Furthermore, a post-hoc exposure-response analysis was conducted in order to test the hypothesis that all available exposure-response data in study 4054 were consistent with a similar maximum effect of somapacitan and somatropin, and in order to identify the EC50 for somapacitan and somatropin, i.e. the steepest part of the direct exposure-response relationship to truncal fat percentage. A combined model was fitted to all available exposure-response data in trial 4054. The model described the change in truncal fat percentage with a linear relationship to IGF-I average SDS (indirect effect) and Emax relationships to exposure of somapacitan/somatropin (direct effects). The analysis indicated that the estimated EC50 for somatropin was 0.30 ng/ml, equivalent to the mean exposure observed in the main treatment phase of study 4054 (Figure 4). The estimated EC50 for somapacitan was 7.76 ng/ml equivalent to the exposures in the upper end of the observed range in the main treatment phase of study 4054. This may indicate that a higher response may be expected by increasing the somapacitan dose, however, this could not be supported by clinical data (see further sections Clinical efficacy, Dose-response studies and main clinical studies).



Note: Predictions from the *post-hoc* exposure response model of combined data from trial 4054 main and extension. Prediction of exposure-response with 2.6 SDS change from baseline (e.g. from -2.6 to 0 SDS). Vertical dotted lines display the geometric means of somapacitan and Norditropin<sup>®</sup> exposure leading to same weekly IGF-I average in phase 3. Horizontal lines display 80% exposure range in trial 4054 main phase.

**Figure 4 Prediction of the direct effect of growth hormone (somapacitan or somatropin on truncal fat percentage)**

## ***Dose proportionality and time dependencies***

### ***Special populations***

Exposures in special patient groups were based upon pharmacokinetic data and popPK analysis.

Based upon the existing model, body weight had an impact on exposure with exposure being higher in a subject with a low body weight of 45 kg (3.12-fold) and lower in a heavy subject weighing 115 kg (-39%) as compared to the reference subject weighing 85 kg. As exposure was inversely related to body weight, a dose-normalized to body weight posology would be more adequate. However, it appeared that dosing steps in mg resulted in similar IGF-I levels after titration in all body weight groups, indicating that normalisation to body weight is not required to reach IGF-I target level. Indeed, the correlation between exposure and body weight is not a directly proportional function, and there is substantial variability not related to body weight. Apart from the relationship between somapacitan dose and exposure, the relationship between somapacitan dose and the IGF-I response is also considered: while exposure is inversely related to body weight, the opposite relationship exists between body weight and IGF-I. To evaluate if dosing steps in mg is appropriate for titration to IGF-I target levels, IGF-I levels after titration were compared across body weights. Overall similar IGF-I levels were obtained after titration in all body weight groups, suggesting that normalisation to body weight is not required to reach IGF-I target level. It is thus considered that dosing in mg/week without taking body weight into consideration, followed by individual dose adjustment/titration based on IGF-I SDS and clinical response is appropriate.

No significant or relevant changes in parameters related to weight, gender and race were found between the original PK/PD model and the updated PK/PD model. Neither patients with childhood or adulthood GHD onset, transition age patients (18-25 years), patients by BMI range (<25 kg/m<sup>2</sup>, 25-35 kg/m<sup>2</sup>, 35-40 kg/m<sup>2</sup> and > 40 kg/m<sup>2</sup>) or patients with diabetes were significant covariates at p<0.01 in the population PK and PK/PD models, meaning that no significant impact on dose-response relationships was found when accounting for correlation to factors that were significant in the models (i.e. gender, age, race and body weight).

Age below 25 years was tested as a covariate in the PK and PK/PD models but was not identified as significant in either model. Data indicated no increased risk of bone or cardiac disorders in this subpopulation based on 48 patients in transition age (from 18 to 25 years old), including 41 patients treated by somapacitan.

AGHD Patients in the transition age received higher doses but obtained lower IGF-I levels after titration than older AGHD patients. This could indicate that AGHD patients in the transition age may need higher doses than AGHD patients outside the transition age and is in accordance with the fact that endogenous growth hormone secretion and IGF-I levels are much higher in healthy subjects in this age group as compared to older subjects.

Female subject using no oestrogens has a 30% lower exposure compared to male subjects, while females subjects on oestrogens had a 53% lower exposure. The IGF-I response was lower in females compared to males and lowest in females on oral oestrogen for similar doses of somapacitan (see Pharmacodynamics). Females and especially females on oral oestrogen may thus require higher doses of somapacitan to reach a similar IGF-I target range as compared to males.

Subjects aged ≥65 years had a 35% higher somapacitan exposure compared to subjects aged 18 - 64 years. The IGF-I response was slightly higher in the older subjects (see section Pharmacodynamics) and slightly lower doses may be needed to reach the IGF-I target in elderly compared to younger patients.

Somapacitan exposure was 18% higher in Japanese and 33% lower in Asian non-Japanese compared to White subjects. However, the IGF-I response was comparable across the race groups (see section Pharmacodynamics) and similar doses are needed to reach the IGF-I.

A mild, moderate, severe renal impairment and patients requiring haemodialysis increased exposure by 25, 27, 75 and 63%, respectively. In line with the increase in somapacitan exposure, IGF-I levels were also increased. This is in line with published data indicating decreased clearance of GH due to renal impairment. In line with the increase in somapacitan exposure, IGF-I levels were also increased (up to 40%). However, as the dose of somapacitan is individually titrated based on safety and efficacy and IGF-I levels, specific recommendations for dosing are not considered necessary (see below clinical assessment).

Somapacitan AUC<sub>0-168h</sub> was not influenced by a mild hepatic impairment (+9%), while a moderate hepatic impairment increased the AUC<sub>0-168h</sub> by 3.69-fold. Lower levels of IGF-I were observed in subjects with mild and moderate hepatic impairment compared to subjects with normal hepatic function (see section 2.2.4). The cause of this is most likely the known GH-resistance for subjects with hepatic disease. Although higher somapacitan doses are needed to obtain an adequate treatment response as compared to subjects with normal hepatic function, as the dose of somapacitan is individually titrated based on safety and efficacy and IGF-I levels, specific recommendations for dosing are not considered necessary (see below clinical assessment). However, as no data are available in patients with severe hepatic impairment and a more pronounced effect may be expected, caution should be exercised when treating patients with severe hepatic impairment, as recommended in the SmPC (section 4.2).

## ***Pharmacokinetic interaction studies***

Considering the similarity of somapacitan with GH, the drug-drug interaction potential is expected to be similar to other marketed GH products and it is considered acceptable that drug-drug interaction section of the proposed label is brought in line with the clinically important drug interactions of somatropin (see further Pharmacodynamics).

Overall the pharmacokinetics have been sufficiently evaluated.

### **2.4.3. Pharmacodynamics**

#### ***Mechanism of action***

Somapacitan is a recombinant human GH derivative through the binding on the endogenous albumin this GH gets long-acting properties. As for human somatropin, the mechanism of action of somapacitan is either directly via binding to the GH receptor or indirectly via insulin-like growth factor I (IGF-I). The IGF-I standard deviation score (SDS) is defined based on a healthy reference population, who will per definition have around 2.5% of IGF-I measurements above +2 SDS.<sup>12</sup>

#### ***Primary and Secondary pharmacology***

Under physiological conditions, GH is secreted episodically in a pulsatile fashion during a 24-hour period, with the main GH peaks occurring during sleep. The timing and magnitude of GH secretion are impacted by gender, activity, nutritional status, age and visceral adiposity.<sup>13</sup>

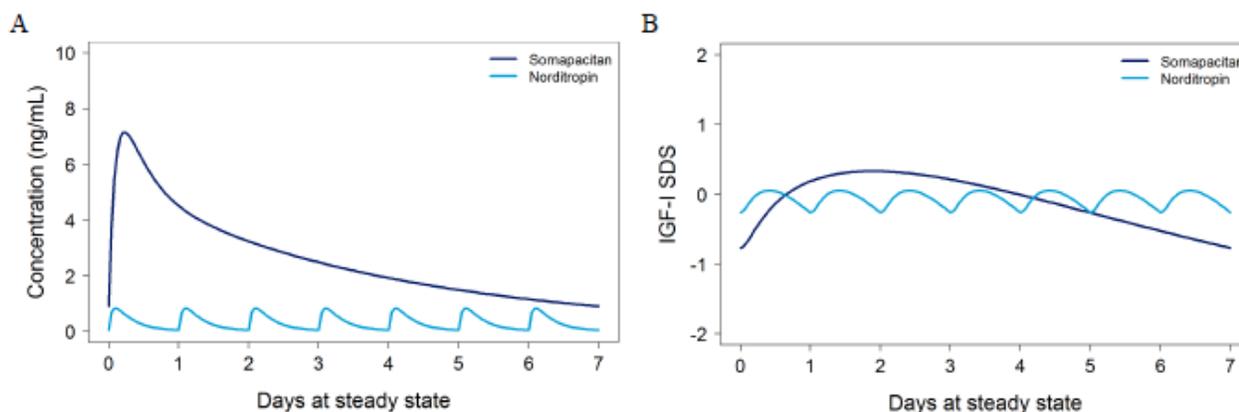
Current daily replacement therapies mimic neither the pulsatility nor the circadian pattern of endogenous GH. The GH profile of standard daily GH replacement therapy (somatropin) varies over 24 hours after dosing (Figure 5A). Once-weekly somapacitan dosing provides an initial peak exposure on day 1 that gradually decreases over the 7 days post-administration. The higher magnitude of exposure for somapacitan should be viewed in the context of the lower receptor binding affinity (3 to 4 times), pharmacokinetic and pharmacodynamics properties of weekly somapacitan as compared to daily somatropin, allowing once-weekly dosing.

Furthermore, somapacitan and somatropin produce different IGF-I profiles (Figure 5B). Once-weekly somapacitan has an IGF-I maximum ( $C_{max}$ ) occurring 32–72 hours after dosing with IGF-I values within the normal range, whereas for daily GH replacement therapy IGF-I levels remain relatively constant at steady state.

---

<sup>12</sup> Bidlingmaier M, Friedrich N, Rebecca T, Emeny JS, Wolthers OD, Roswall J, et al. Reference Intervals for Insulin-like Growth Factor-1 (IGF-I) From Birth to Senescence: Results From a Multicenter Study Using a New Automated Chemiluminescence IGF-I Immunoassay Conforming to Recent International Recommendations. *J Clin Endocrinol Metab.* 2014;99(5):1712-21.

<sup>13</sup> Melmed S. Pathogenesis and Diagnosis of Growth Hormone Deficiency in Adults. *N Engl J Med.* 2019;380(26):2551-62.



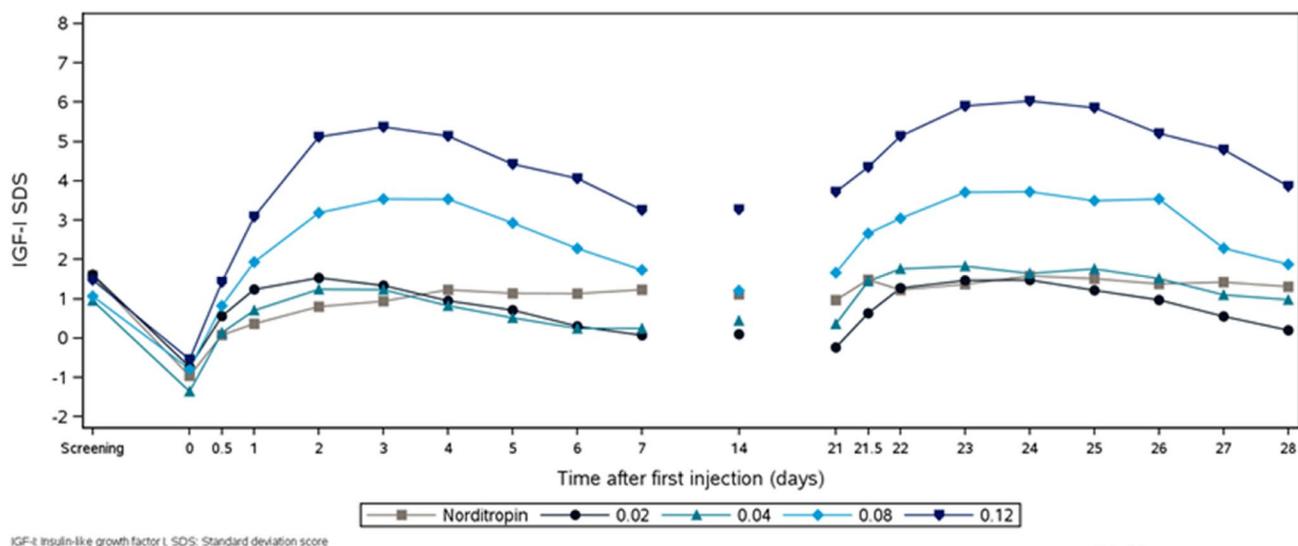
Notes: Lines are geometric means of hGH or somapacitan concentrations (panel A) and means of IGF-I SDS (panel B) of individual predictions in the fixed dose periods after titration as observed in phase 3 for somapacitan (average dose 2.4 mg weekly) and Norditropin (average dose 0.3 mg daily). Data from trials 4054, 4043 and 4244.

**Figure 5 PK (A) and IGF-I (B) profiles during steady-state dosing of somapacitan and somatropin (Norditropin)**

Individual dose titration based on IGF-I SDS levels is important to assure that IGF-I levels are maintained within the upper normal range (0 to +2 SDS), following current clinical practice in AGHD.<sup>14,15</sup> Multiple dosing of somapacitan in patients with AGHD resulted in IGF-I SDS responses above baseline at all investigated dose levels of somapacitan (0.02, 0.04, 0.08, 0.12 mg/kg) (Figure 6). Furthermore, the IGF-I response increased with increasing doses of somapacitan at steady state, with mean AUC<sub>0-168h</sub> of 25842, 28839, 39097 and 77808 ng·h/l, respectively.

<sup>14</sup> 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 Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. *Eur J Endocrinol.* 2007;157(6):695-700.

<sup>15</sup> Molitch ME, Clemmons D, Malozowski S, Merriam GR, Vance ML. Evaluation and Treatment of Adult Growth Hormone Deficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2011;96:1587-609.



**Figure 6 IGF-I SDS levels after different dose levels of somatropin (0.004 mg/kg) and somapacitan (0.02, 0.04, 0.08, 0.12 mg/kg)(study 3947)**

The somapacitan-induced IGF-I SDS levels were sustained during the weekly dosing interval.

In patients with AGHD, the mean maximum IGF-I SDS response appeared within 2–4 days ( $t_{max}$ ) after somapacitan dosing which was delayed compared to the median time of maximal somapacitan exposure of approximately 24 hours (1 day) after dose administration.

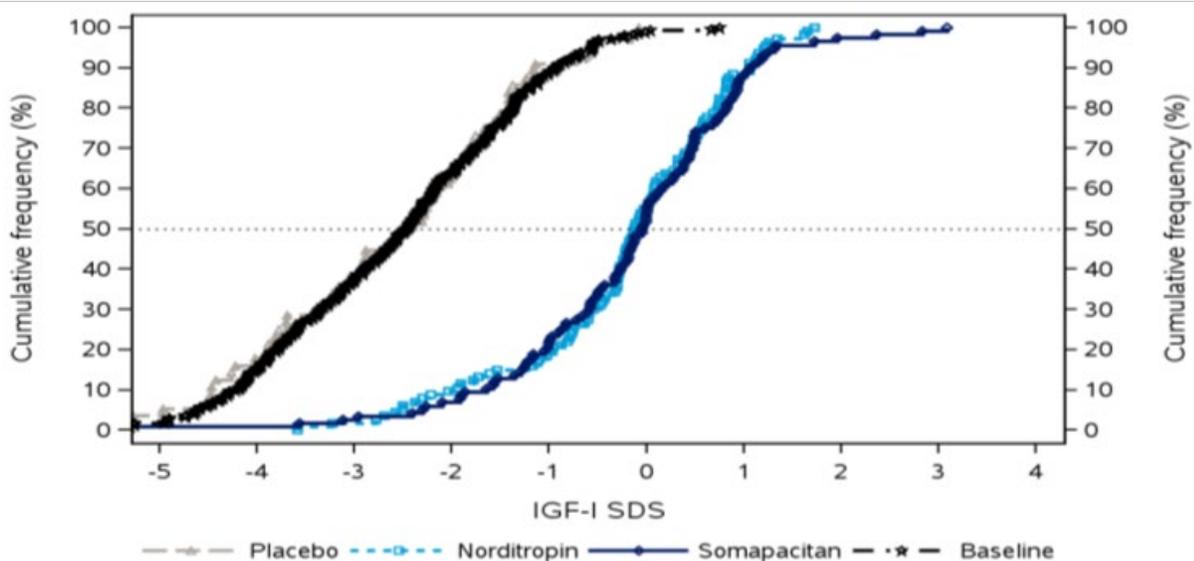
There was no statistically significant difference on  $AUC_{0-168h}$  and  $C_{max}$  between daily somatropin (0.004 mg/kg/day  $\approx$  0.03 mg/kg/week) and once-weekly somapacitan (0.02 and 0.04 mg/kg/week).

Weekly dosing resulted in an undulating steady-state IGF-I response. Steady-state was reached after 1–2 once-weekly doses of somapacitan.

As expected IGFBP3 followed the IGF-I pattern observed after the exposition of somapacitan although the response was somewhat muted.

#### Association between dosing, IGF-I SDS, and clinical effects

Somapacitan like somatropin is dosed to achieve IGF-I SDS levels within the IGF-I SDS target range. In pivotal study 4054, similar IGF-I levels were obtained with somapacitan and somatropin, as supported by the superimposable distribution of IGF-I SDS levels at week 34 (Figure 7). Similar IGF-I SDS ranges will induce similar IGF-I mediated indirect clinical effects of growth hormone via the liver apart from the direct clinical effects of growth hormone replacement treatment on fat masses.



Abbreviations: IGF-I SDS: insulin-like growth factor-I standard deviation score

**Figure 7 IGF-I SDS at week 34 - empirical distribution plot (trial 4054)**

Based on the IGF-I SDS distribution data, it is reasonable to predict that IGF-I mediated effects ('indirect' effects of growth hormone) would be comparable for somapacitan and somatropin.

Somapacitan and somatropin exert direct effects on fat cells. In pivotal study 4054 observed direct effects tended to be lower for somapacitan as compared somatropin treatment. Several factors may explain these differences, such as differences in the AGHD study population which reflects differences in sensitivity to the effects of growth hormone between AGHD patients, insufficient exposure of somapacitan, and a lower affinity to adipose tissue for somapacitan as compared to somatropin due to the albumin binding moiety in somapacitan<sup>16</sup>. In addition, differential effects of somapacitan on different adipose tissues may partly be explained by different expression of the IGF-I receptor and growth hormone receptor in different adipose tissues.

Some observations which indicate differences in the pharmacodynamic effects of somapacitan and somatropin, and differences in the pharmacodynamic effects of somapacitan in particular AGHD subgroups are stated below.

In the same AGHD subgroup, dosing of weekly somapacitan should be about 1.14 times higher than the total dose of somatropin per week to achieve similar IGF-I SDS levels.

Defined IGF-I SDS target ranges were not achieved in 22% of somapacitan-treated study patients in pivotal clinical study 4054, and in 20% of Japanese AGHD study patients in study 4244 who had been treated with growth hormone prior to participation in the respective study (Table 3). In both studies these proportions tended to be higher in particular subgroups, such as women on oral oestrogen treatment, and study patients with childhood-onset growth hormone deficiency (respectively 42% and 34% of the study patients in these subgroups in main phase study 4054).

<sup>16</sup> Kopchick JJ, Berryman DE, Puri V, Lee KY, Jorgensen JOL. The effects of growth hormone on adipose tissue: old observations, new mechanisms. *Nat Rev Endocrinol.* 2020;16(3):135-46.

**Table 3 Proportion of somapacitan-treated patients not reaching IGF-I SDS targets (studies 4054 and 4244)**

|                             | Pre-defined lower IGF-I SDS target | Proportion of patients not reaching lower IGF-I SDS target |                |  |                                   |                              |                          |
|-----------------------------|------------------------------------|--|----------------|--|-----------------------------------|------------------------------|--------------------------|
|                             |                                    | All<br>n (%)   | Males<br>n (%) | Females (not on oral oestrogen)<br>n (%) | Females (oral oestrogen)<br>n (%) | Childhood onset GHD<br>n (%) | Adult onset GHD<br>n (%) |
| <b>Trial 4054 main</b>      | -0.5                               | 26<br>(22%)  | 6<br>(10%)     | 4 (17%)                                  | 16 (42%)                          | 13 (34%)                     | 13<br>(16%)              |
| <b>Trial 4054 extension</b> | -0.5                               | 36<br>(32%)  | 11<br>(20%)    | 6 (25%)                                  | 19 (53%)                          | 16 (43%)                     | 20<br>(26%)              |
| <b>Soma/soma</b>            |                                    | 11<br>(20%)  | 3<br>(12%)     | 3 (14%)                                  | 5 (56%)                           | 4 (22%)                      | 7<br>(19%)               |
| <b>Pbo/soma</b>             |                                    |  |                |  |                                   |                              |                          |
| <b>Trial 4244</b>           | 0                                  | 9<br>(20%)   | 5<br>(21%)     | 3 (17%)                                  | 1 (25%)                           | 5 (56%)                      | 4<br>(11%)               |

**Abbreviations:** n = number of patients completing titration period; pbo = placebo; soma = somapacitan.  
**Note:** Percentage is calculated based on number of patients not reaching target in the group/subgroup divided by the total number of patients in the group/subgroup. Numbers reflect status at end of the titration period, i.e. first measurement of IGF-I in fixed dose maintenance phase.

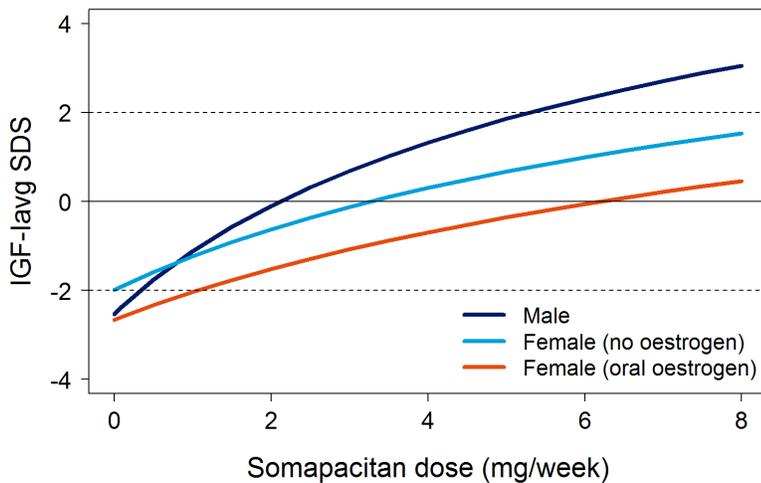
It is well-known that particular subgroups of AGHD patients are less sensitive to growth hormone treatment such as women and women on oral oestrogen therapy compared to men and childhood-onset AGHD patients (e.g. see Figure 8).<sup>17,18,19</sup> As indicated with respect to the post-hoc exposure-response analysis in the pharmacokinetics section, increased somapacitan dosing is likely to induce a higher clinical response. Considering this exposure-response relationship and differences in growth hormone sensitivity between AGHD subgroups, somapacitan dosing should be adapted for particular subgroups.

Observed clinical effects of somapacitan and other study treatments in different subsets of study patients are discussed in the clinical efficacy and clinical safety sections below.

<sup>17</sup> Melmed S. Pathogenesis and Diagnosis of Growth Hormone Deficiency in Adults. *N Engl J Med.* 2019;380(26):2551-62.

<sup>18</sup> van Bunderen CC, Glad C, Johannsson G, Olsson DS. Personalized approach to growth hormone replacement in adults. *Arch Endocrinol Metab.* 2019;63(6):592-600.

<sup>19</sup> 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 Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. *Eur J Endocrinol.* 2007;157(6):695-700.



Notes: Lines are typical patient relationships using the PK model and original PK/PD model. Profiles are for a reference patient, white 85 kg age 40 years, except for the investigated covariate.

**Figure 8 IGF-I<sub>avg</sub> SDS versus somapacitan dose by gender and oral oestrogen use**

#### *Potential safety risks of weekly somapacitan dosing*

Although it is reassuring that no difference in AUC between somapacitan and somatropin can be observed, concerns related to the undulating IGF-I pattern with apparent higher  $C_{max}$  and lower  $C_{through}$  remain. Such weekly IGF-I pattern is not known from physiological nor pharmaceutical conditions, therefore, the consequences for safety and efficacy are not well understood. In the somapacitan clinical development program, the safety profile of somapacitan was consistent with currently approved daily growth hormone replacement therapies. There was no indication that AGHD patients treated with somapacitan compared to those treated with somatropin were at increased risk of cardiovascular events, hyperglycaemia, or neoplasia.

Long-term safety risks of somapacitan beyond a treatment period of 1.5 years are yet unclear. These will be evaluated in a proposed post-authorization safety study (PASS).

#### *Missed doses*

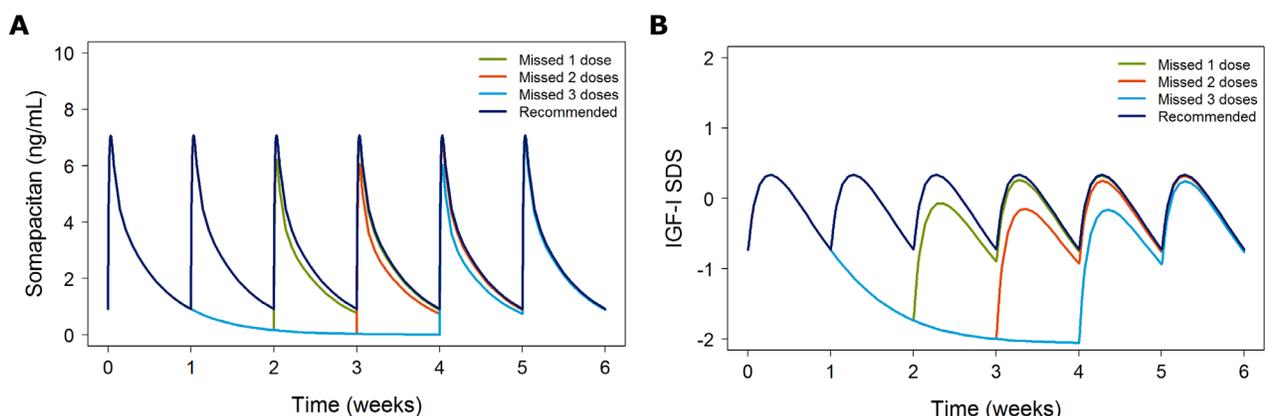
Systemic somapacitan concentrations rise soon after subcutaneous administration. Subsequently, these concentrations decrease progressively to zero in about 2-3 weeks (Figure 9).

After one week after administration of a somapacitan dose, the next somapacitan dose is to be administered. However, AGHD patients may miss one or more somapacitan doses for different reasons in clinical practice.

Simulated somapacitan concentrations and IGF-I SDSs in case of no, one, two, and three missed doses are presented in Figure 9.

If one somapacitan dose is missed, this dose may be administered up to three days after the planned dosing day. A subsequent somapacitan dose may then be administered on the planned dosing day.

If a longer time has passed from the planned dosing day of one missed somapacitan dose, or if two or more somapacitan doses have been missed, somapacitan dosing should be resumed as before the doses were missed.



Notes: Lines are geometric means (A) and means (B) of individual predictions in the fixed dose periods after titration as observed in phase 3.

**Figure 9 Simulated PK (A) and IGF-I (B) profiles following 1, 2, or 3 missed doses of somapacitan compared to regular dosing**

#### 2.4.4. Discussion on clinical pharmacology

There was no statistically significant difference on  $AUC_{0-168h}$  and  $C_{max}$  between daily somatropin (0.004 mg/kg/day  $\approx$  0.03 mg/kg/week) and once-weekly somapacitan (0.02 and 0.04 mg/kg/week).

Somapacitan and somatropin exert direct effects on adipose tissue and indirect effects on other tissues via stimulation of IGF-I expression and release from the liver.<sup>20</sup>

A steady-state IGF-I response was reached after 1–2 once-weekly doses of somapacitan. This weekly undulating pattern is non-physiologic. In normal physiology and after daily somatropin injections, a stable IGF-I level is observed.

The somapacitan induced IGF-I levels displayed a greater peak to trough variation over the one-week dosing interval compared to daily somatropin. Dosing of weekly somapacitan should be about 1.14 times higher than the total dose of somatropin per week to achieve similar IGF-I SDS levels in the same subgroup of AGHD patients.

Similar IGF-I SDS levels may induce similar clinical effects in similar AGHD subgroups. It is, however, well known that several AGHD subgroups such as women on oral oestrogen treatment, and study patients with childhood-onset growth hormone deficiency are less sensitive to growth hormone treatment. Exposure-response data indicate that larger pharmacodynamic effects of somapacitan may be observed if higher somapacitan doses would be provided to AGHD patients. Similar effects of somapacitan and somatropin could be obtained at a higher exposure of somapacitan as compared to somatropin. Hence, somapacitan dosing regimen should be adapted for particular AGHD subgroups.

Clinical safety within the somapacitan clinical development program was comparable for weekly somapacitan and daily somatropin. However, long-term safety risks of somapacitan beyond a treatment period of 1.5 years are yet unclear and remain of concern. These risks will be evaluated in a post-authorization safety study (PASS).

<sup>20</sup> Melmed S. Pathogenesis and Diagnosis of Growth Hormone Deficiency in Adults. *N Engl J Med.* 2019;380(26):2551-62.

If one somapacitan dose is missed, this dose may be administered up to three days after the planned dosing day. A subsequent somapacitan dose may then be administered on the planned dosing day.

If a longer time has passed from the planned dosing day of one missed somapacitan dose, or if two or more somapacitan doses have been missed, somapacitan dosing should be resumed as before the doses were missed. Secondary pharmacodynamics were not reported in the pharmacodynamic studies. However, these parameters (mainly glucose homeostasis) are elaborately discussed in the safety section of this report (see below).

### **2.4.5. Conclusions on clinical pharmacology**

The peak to trough variation of IGF-I in a once weekly dosing interval of somapacitan is of concern since long-term safety risks are unknown. These risks will be evaluated in a PASS.

Dosing of weekly somapacitan should be about 1.14 times higher than the total dose of somatropin per week to achieve similar IGF-I SDS levels in the same subgroup of AGHD patients.

Similar IGF-I SDS levels may induce similar clinical effects in similar AGHD subgroups. Exposure-response data indicate that larger pharmacodynamic effects may be observed, if higher somapacitan doses would be provided to AGHD patients. As some subsets of AGHD patients such as women, women on oral oestrogen therapy, and childhood-onset AGHD patients are less sensitive to growth hormone treatment, the somapacitan dosing regimen should be adjusted for these AGHD subgroups. For AGHD patients in the transition age, higher doses are also needed.

## **2.5. Clinical efficacy**

### **2.5.1. Dose response study(ies)**

Conducted dose-response studies are discussed above.

According to proposed SmPC, somapacitan is dosed and titrated individually for each patient in order to achieve IGF-I levels between -0.5 and +2 standard deviation scores of normal.

### **2.5.2. Main study(ies)**

#### **Study 4054**

##### ***Methods***

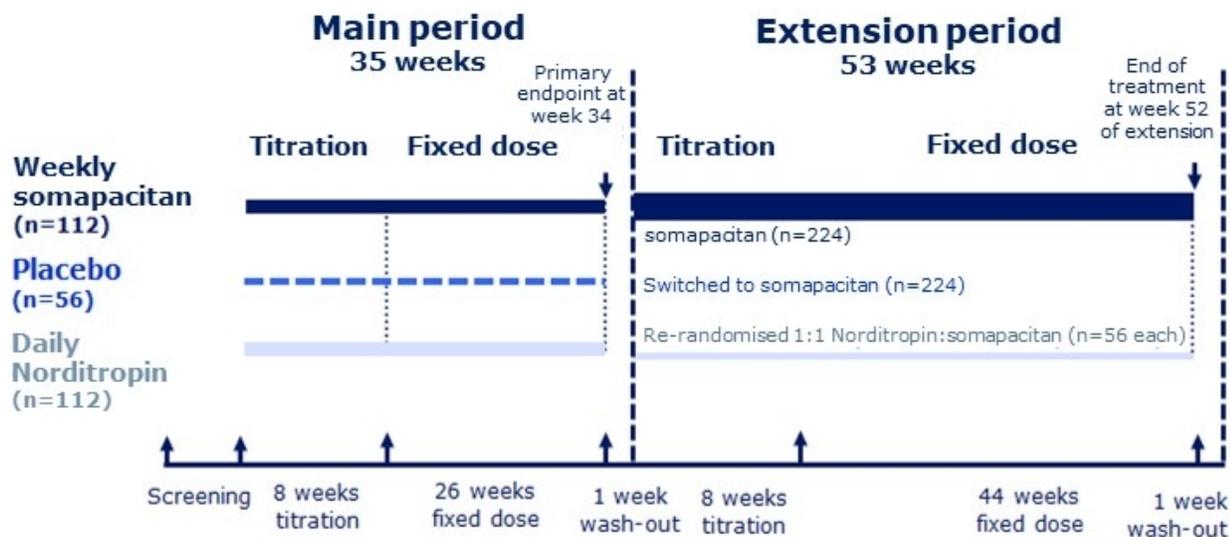
The main study of this application is study 4054. This study was a multicentre, multinational, randomized, parallel-group, placebo-controlled (double-blind) and active-controlled (open-label) study. The study was primarily designed to compare in a double-blind study setting the efficacy and safety of once-weekly dosing of somapacitan with once-weekly dosing of placebo in AGHD patients who were growth hormone treatment-naïve or with no exposure to growth hormone or growth hormone secretagogues for at least 180 days prior to randomization. In a third, open-label study arm, the clinical effects of open-label daily treatment with somatropin product Norditropin were evaluated.

The study design is presented in Figure 10. The study consisted of the following periods:

- 2-week screening period
- 35-week randomized, double-blind main period consisting of:
  - 8-week titration period,
  - 26-week fixed-dose treatment period,
  - 1-week washout period
- 53-week open-label extension period consisting of:
  - 8-week titration period,
  - 44 week fixed-dose treatment period,
  - 1-week washout period.

Hence, the patients were treated for 34 weeks in the main period and 52 weeks in the extension period, thus for a total of 86 weeks.

The washout periods were set to 1 week to confirm antibody response. Last efficacy measurements of the main treatment period were obtained at the end of the 34-week treatment period. The half-life of daily somatropin is 2.6 hours. In the extension treatment period, study patients were re-randomized to active study treatment with the same or longer interval between subsequent doses as in the main treatment period. Clinical evaluations in the extension treatment period were conducted after an 8-week titration period. It is not expected that a one-week washout period will influence the clinical results of the extension treatment period.



**Figure 10** Design of study 4054

## **Study Participants**

The study was conducted at 92 sites in 16 countries worldwide.

Main inclusion criteria

- Male or female of at least 23 years of age and not more than 79 years of age at the time of signing informed consent
- Confirmed diagnosis of AGHD

For all countries except Japan:

- Patients must satisfy one of the following criteria:
  - ITT or glucagon test: a peak growth hormone of  $< 3$  ng/mL ( $3 \mu\text{g/L}$ )
  - GHRH + arginine test according to BMI<sup>a</sup>
  - Three or more pituitary hormone deficiencies and IGF-I SDS  $< -2.0$

For Japan only:

- Adult-onset: if caused by organic disease with multiple pituitary hormones deficiency, patients must satisfy at least one of the following criteria. If isolated growth hormone deficiency patients must satisfy at least 2 of the following criteria
- Childhood-onset: patients with a history of childhood growth hormone deficiency must satisfy at least 2 of the following criteria. If caused by organic disease with multiple pituitary hormones deficiency, patients must satisfy at least one of the following criteria:
  - ITT: a peak growth hormone of  $\leq 1.8$  ng/mL
  - Glucagon test: a peak growth hormone of  $\leq 1.8$  ng/mL
  - GHRP-2 tolerance test: a peak growth hormone of  $\leq 9$  ng/mL
- Growth hormone treatment-naïve or no exposure to growth hormone or growth hormone secretagogues for at least 180 days prior to randomization with any registered or investigational growth hormone or growth hormone secretagogue product
- If applicable, hormone replacement therapies for any other hormone deficiencies, adequate and stable for at least 90 days prior to randomization as judged by the investigator
- IGF-I SDS  $< -0.5$  at screening relative to the mean of the age and sex normal ranges according to the central laboratory measurements
- Patients without diabetes mellitus<sup>b</sup>

GHRH = growth hormone releasing hormone; GHRP-2 = growth hormone releasing peptide-2; IGF-I = insulin-like growth factor; IGF-I SDS = insulin-like growth factor - I standard deviation score; ITT = insulin tolerance test; SD = standard deviation.

<sup>a</sup> BMI  $< 25$  kg/m<sup>2</sup>: a peak growth hormone  $< 11$  ng/mL ( $11 \mu\text{g/L}$ ); BMI 25–30 kg/m<sup>2</sup>: a peak growth hormone  $< 8$  ng/mL ( $8 \mu\text{g/L}$ ); BMI  $> 30$  kg/m<sup>2</sup>: a peak growth hormone  $< 4$  ng/mL ( $4 \mu\text{g/L}$ ).

<sup>b</sup> Exceptions to this criterion include patients diagnosed with diabetes mellitus provided that all of the following criteria are met: diabetes mellitus  $\geq$  6 months prior to screening; stable oral anti-diabetic treatment; no history of use of injectable anti-diabetic agents; HbA1c  $<$  7.0% at screening; no diabetes-related co-morbidities at screening; no proliferative retinopathy or severe non-proliferative diabetic retinopathy. Patients with diabetes mellitus enrolled at Japanese sites were not allowed to participate in the studies as diabetes mellitus is a contraindication for GH treatment in Japan.

#### Main exclusion criteria

- active malignant disease or history of malignancy

Exceptions to this exclusion criterion included:

- Resected in situ carcinoma of the cervix and squamous cell or basal cell carcinoma of the skin with complete local excision, and
- Patients with growth hormone deficiency attributed to the treatment of intracranial malignant tumours of leukaemia provided that a recurrence-free survival period of at least 5 years is documented in the patient's medical records.

It is noted that study patients were diagnosed in line with diagnostic criteria for AGHD in international consensus guidelines<sup>21</sup>. It is also noted that the selection criteria for study participation were different in Japan compared to the rest of the world. The applicant analyzed the primary endpoint separately for Japan and the rest of the world (see below). As this procedure concerns an EU marketing authorization application the results obtained in the Japanese population are not discussed in depth in this report.

Since AGHD patients up to 79 years were included, clinical effects in AGHD patients aged 80 years and above have not been evaluated in study 4054.

## **Treatments**

### Main treatment phase

Somapacitan and placebo were administered subcutaneously once weekly.

Somatropin product Norditropin FlexPro was administered subcutaneously once daily.

### *Starting doses*

The starting doses for both active substances are summarized in Table 4. Starting doses expressed in mg per week of somapacitan and somatropin were similar. Chosen starting doses of somatropin (0.7 -2.1 mg/week) fall within the dose ranges which have been accepted in treatment guidelines<sup>22</sup> and are also in line with the SmPC of the somatropin product Norditropin (0.7- 3.5 mg/week).

The starting doses of somapacitan were tested to be safe in the completed clinical study NN8640-3947 (multiple-dose in AGHD patients, phase 1).

---

<sup>21</sup> Ho KK. 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 Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia.

<sup>22</sup> Cook et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in growth hormone-deficient adults and transition patients - 2009 update. *Endocr Pract.* **2009** Sep-Oct;15 Suppl 2:1-29.

**Table 4 Starting dose for somapacitan/placebo and somatropin study patients**

| Group                                       | Starting dose of somapacitan or placebo (mg/ week) | Starting dose of somatropin (expressed in mg/week) |
|---|--|--|
| Patients between 23 and 60 years of age     | 1.5  | 1.4  |
| Women on oral oestrogen irrespective of age | 2.0  | 2.1  |
| Patients older than 60 years                | 1.0  | 0.7  |

*Dose adjustments in the titration period*

Dose adjustments were allowed during the first 8 weeks titration period (at week 2, 4, 6 and 8). Dose adjustments were based on IGF-I SDS. After last dose adjustment (if any) in the main study at week 8, the individual dose level was fixed.

Blood samples for IGF-I, IGFBP-3 and PK were taken 10-11 days after the previous dose adjustment visit. Hence, dose adjustments were performed about 4 days after the IGF-I titration samples were collected. Besides the IGF-I based dose adjustment during the titration period, dose reduction could be considered during the entire study period at the investigator's discretion for safety concerns. If adverse events with a probable relationship to study treatment were persistent but continuation in the study was acceptable, as judged by the investigator and patient, dose reduction in steps of 25% could be considered.

Dose adjustments were handled according to the below dose-titration algorithms for somapacitan and somatropin (Table 5). It was aimed to achieve IGF-I SDS levels in the physiological range of -0.5 up to +1.75 standard deviation scores (SDS). The size of the dose adjustments during the titration period was derived based on PK/PD analysis of data from previous clinical studies with somapacitan.

**Table 5 Dose titration algorithm for study treatment**

| IGF-I SDS interval           | Somapacitan or placebo<br>Increment/reduction of weekly dose |                             | Somatropin<br>Increment/reduction of weekly dose<br>(i.e. seven times changes per day) |                             |
|------------------------------|--|-----------------------------|--|-----------------------------|
|                              | $\Delta$ IGF-I SDS > 1                                       | $\Delta$ IGF-I SDS $\leq$ 1 | $\Delta$ IGF-I SDS > 1   | $\Delta$ IGF-I SDS $\leq$ 1 |
| IGF-I SDS > 3                | - 1 mg   |                             | - 0.7 mg   |                             |
| 1.75 < IGF-I SDS $\leq$ 3    | - 0.5 mg   |                             | - 0.35 mg  |                             |
| -0.5 < IGF-I SDS $\leq$ 1.75 |  | + 0.5 mg                    |  | + 0.35 mg                   |
| -2 < IGF-I SDS $\leq$ -0.5   | +0.5 mg  | + 0.5 mg                    | + 0.35 mg  | + 0.35 mg                   |

|                     |       |          |          |          |
|---------------------|-------|----------|----------|----------|
| IGF-I SDS $\leq$ -2 | +1 mg | + 1.5 mg | + 0.7 mg | + 1.4 mg |
|---------------------|-------|----------|----------|----------|

$\Delta$ : change in insulin-like growth factor I standard deviation score from screening

For somapacitan, the minimum and maximum weekly doses were set to 0.1 mg and 8 mg, respectively. For daily somatropin, the minimum and the maximum daily doses were set to 0.05 mg and 1.1 mg.

Titration of placebo subjects mirrored the titration of somapacitan subjects to avoid unblinding. The subjects in the placebo group also received instructions on dose adjustment to mimic a pattern of dose adjustment in the subjects receiving somapacitan.

The dose titration schedule in the protocol was to be followed in order to allow titration to an optimal therapeutic dose for all subjects. If a subject had not completed at least 3 dose adjustment evaluations, this was considered a protocol deviation, as fewer than 3 completed dose adjustment evaluations were not expected to be sufficient to achieve therapeutic doses in a majority of subjects.

When the main period ended, the dose titration was repeated for all patients who continued into the extension period following the same dose titration scheme. This ensured that patients on once-weekly somapacitan in the extension period were kept blinded to whether they received placebo or active treatment in the main period.

#### *Method of administration*

Somapacitan and placebo patients injected themselves once-weekly s.c. with a pre-filled pen in the morning.

Somatropin patients injected themselves daily s.c. in the evening with a pre-filled pen (standard treatment practice), except during observed study treatment administration (where injections were done in the morning (at least 12 hours after injection the evening before)). The evening before blood sampling for anti-hGH antibodies the injections should occur at least 12 hours prior to sampling.

Injections were done in the thighs and/or abdomen alternating within these body areas for every injection.

#### Extension treatment phase

All patients who completed the 35-week main study period continued the treatment in the 53-week extension period as below:

- Somapacitan treated patients continued their once-weekly treatment.
- Somatropin treated patients were re-randomized 1:1 to somapacitan or somatropin within the same strata as used for the first randomization.
- Placebo patients were switched to somapacitan treatment.

Dose titration was repeated for all patients during the first 8 weeks of the extension period as described above for the main study period.

For the extension period, the last dose was administered by the patient at home during week 86.

## **Objectives**

### *Primary objective*

To demonstrate the efficacy of once-weekly dosing of somapacitan compared to placebo after 34 weeks of treatment in AGHD patients.

*Secondary objective related to efficacy*

To evaluate the efficacy and safety of somapacitan for up to 86 weeks of treatment in AGHD patients (i.e. during the main and extension periods of the study).

**Outcomes/endpoints**

An overview of pharmacodynamic and efficacy endpoints of study 4054 is presented in Table 6. These endpoints concern well-known evaluations of general disease characteristics and treatment effects in AGHD patients.<sup>23,24,25,26,27</sup>

The primary efficacy endpoint was the change in truncal fat percentage at the end of the main treatment period (week 34) compared to baseline.

The secondary efficacy endpoints included body composition measurements (e.g. fat, lean body mass and bone mineral content).

**Table 6 Pharmacodynamic and efficacy endpoints of study 4054**

| <b>Endpoints</b>                      |  |
|---------------------------------------|--|
| <b>Body composition</b>               | <ul style="list-style-type: none"> <li>• <b>Truncal fat % (primary endpoint)</b></li> <li>• Visceral adipose tissue</li> <li>• Truncal fat mass</li> <li>• Android fat mass</li> <li>• Gynoid fat mass</li> <li>• Total fat mass</li> <li>• Truncal lean body mass</li> <li>• Appendicular skeletal muscle mass</li> <li>• Total lean body mass</li> <li>• Total bone mineral content (at week 87)</li> <li>• Total bone mineral density (at week 87)</li> </ul> |
| <b>Body weight related parameters</b> | <ul style="list-style-type: none"> <li>• Body weight</li> <li>• Waist circumference</li> </ul>   |
| <b>Pharmacodynamics</b>               | <ul style="list-style-type: none"> <li>• IGF-I SDS</li> <li>• IGFBP-3 SDS</li> </ul>   |

<sup>23</sup> Reed et al. Adult growth hormone deficiency- benefits, side effects, and risk of growth hormone replacement. *Frontiers in endocrinology*. June 2013. Volume 4: 1-14.

<sup>24</sup> Sartorio et al. Body composition analysis by dual energy x-ray absorptiometry and anthropometry in adults with childhood-onset growth hormone (GH) deficiency before and after six months of recombinant GH therapy. *J Endocrinol Invest*. 1997 Jul-Aug;20(7):417-23.

<sup>25</sup> Brod et al. Assessing the impact of growth hormone deficiency and treatment in adults: development of a new disease-specific measure. *J Clin Endocrinol Metab*. 2014 Apr;99(4):1204-12.

<sup>26</sup> Frenzl & Ware. Patient-reported functional health and well-being outcomes with drug therapy: a systematic review of randomized trials using the SF-36 health survey. *Med Care*. 2014 May;52(5):439-45.

<sup>27</sup> Bharmal et al. Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. *Health Qual Life Outcomes*. 2009 Apr 27;7:36.

|                                   |   |
|-----------------------------------|---|
| <b>Cardiometabolic parameters</b> | <ul style="list-style-type: none"> <li>• Blood lipids</li> <li>• IL-6</li> <li>• hsCRP</li> </ul> |
| <b>Patient-reported outcomes</b>  | <ul style="list-style-type: none"> <li>• TSQM-9</li> <li>• TRIM-AGHD</li> <li>• SF-36</li> </ul>  |

Abbreviations: IGF-I SDS = insulin-like growth factor - I standard deviation score; IGFBP-3 SDS = insulin-like growth factor binding protein - 3; IL-6 = interleukin 6; hsCRP = high-sensitivity C-reactive protein; SF-36 = Short Form 36; TSQM-9 = Treatment Satisfaction Questionnaire for Medication; TRIM-AGHD = Treatment Related Impact Measure-Adult Growth Hormone Deficiency.

Treatment compliance was assessed by recording of doses (date and time of each dose as well as any missed doses), comparing the prescribed and actual doses, adherence and drug accountability. Treatment compliance was further evaluated based on time stamps from ecaps throughout the extension period of the study.

### **Sample size**

The sample size calculation was based on the assumptions of a true mean difference of 2.5% between somapacitan and placebo and a SD of 4.5% for the primary endpoint, and a 2-sided, 2-sample t-test with a significance level of 5% and a 2:1 randomisation ratio between somapacitan and placebo. A total of 104 subjects in the somapacitan group and 52 subjects in the placebo group completing the main trial should ensure 90% power for detecting a difference between somapacitan and placebo.

As a secondary comparison, the treatment difference at week 34 between somapacitan and Norditropin was estimated and the corresponding 95% CI was calculated. This secondary comparison of somapacitan with Norditropin was used to assist the clinical judgment of the clinical relevance of the estimated treatment difference (ETD) between somapacitan and placebo. In this secondary comparison of the primary endpoint, including 104 subjects in the Norditropin group it was expected with probability 0.87 that half the length of the 95% confidence interval constructed for the difference between somapacitan and Norditropin to be at most 1.3%, resulting in a total of 260 subjects to be included in the trial (without adjustment for withdrawals).

### **Randomisation**

Eligible study patients were randomized in a 2:2:1 ratio to receive either once-weekly somapacitan, a daily somatropin or once-weekly placebo.

A study-specific, web-based randomization system interactive voice/web response system was used for randomization and stratification.

The randomization was stratified according to 2 region levels (Japan and all other countries), sex (male and female) and diabetic status (diagnosed with diabetes mellitus vs. not diagnosed with diabetes mellitus). All study patients completing the main study period continued on active treatment in an open-label design for an additional 53-week extension period.

## ***Blinding (masking)***

The main study was double-blind with respect to somapacitan and placebo; the active control arm was open-label. The extension period was open-label.

To avoid unblinding, placebo doses were adjusted to mimic the dose titration for the somapacitan treatment. The DXA scans were provided to the imaging laboratory for reading in a blinded manner.

The investigators and study sites remained blinded throughout the study and were informed about the patient's treatment allocation and results after the database lock of the extension period.

The central laboratory responsible for measurements of IGF-I and IGFBP-3 (PD) and the special laboratories analysing PK and antibody samples had access to or received a report listing the assigned treatment for each patient.

The extension period was open-labelled but the blinding between somapacitan and placebo was maintained throughout the study.

## ***Statistical methods***

All statistical tests conducted were 2-sided on the 5% level. The region was defined as a factor with 2 levels: Japan and all other countries.

Two analysis sets were defined in the protocol, prior to unblinding/release of the treatment randomization, and in accordance with ICH E9:

**Full analysis set (FAS)** – used for evaluation of efficacy endpoints, includes all randomized subjects that received at least one dose of randomized treatment. Only in exceptional cases could subjects be excluded from the FAS. Subjects were analysed as randomized.

**Safety analysis set** – used for evaluations of safety endpoints and included all randomized subjects that received at least one dose of randomized treatment. Subjects were analysed as treated.

If an endpoint could not be calculated for a patient, this patient was excluded from the analyses of that endpoint.

Analysis of primary endpoint Change from baseline to end of the main treatment period (week 34) in truncal fat percentage

Body composition was measured by DXA and truncal fat percentage was defined as 100 times truncal fat mass (kg) divided by the sum of truncal fat mass (kg) and truncal lean body mass (kg). Truncal fat percentage as a function of time since baseline was expected to be stable if the study patient stayed on the randomized treatment in the main study period.

For each of the complete data sets, the change from baseline to week 34 was analysed using an ANCOVA model with treatment, GHD onset type, sex, region, diabetes mellitus and sex by region by diabetes mellitus interaction as factors and the baseline truncal fat value as a covariate.

The superiority of somapacitan over placebo was considered confirmed if the upper boundary of the 2-sided 95% CI of the treatment difference (somapacitan – placebo) was below 0 (i.e. greater reduction from baseline in truncal fat percentage in the somapacitan treated group than in the placebo-treated group).

The secondary comparison, comparison of somapacitan with somatropin, was used to assist the clinical judgment of the clinical relevance of the estimated treatment difference between somapacitan and placebo.

#### *Other exploratory analysis of the primary endpoint*

Using the same model as were used for the primary analysis of the primary endpoint, an additional exploratory analysis was done by including treatment by sex, treatment by region and treatment by GHD onset type interaction terms, one at a time, to the model. For region, subgroup analysis was also done based on the primary analysis model.

#### *Analysis of supportive secondary endpoints*

Changes from baseline to end of the main treatment period (week 34) were analysed using an ANCOVA, or mixed models repeated measurements (MMRM) model with treatment, GHD onset type, sex, region, diabetes mellitus and sex by region by diabetes mellitus interaction as factors and baseline value as a covariate.

From the statistical model, the treatment differences (for lipids and cardiovascular endpoints, the treatment differences were reported as ratios) at week 34 between somapacitan and placebo and between somapacitan and somatropin were estimated and the corresponding 95% CIs and p-values were calculated for each endpoint. Subjects without post-randomization data for the analysed endpoint were not included in the analysis.

Changes in body composition endpoints and lipids were analysed using the ANCOVA. Data on lipids were log-transformed before analysis.

Changes in IGF-I SDS and IGFBP-3 SDS from baseline were analysed using the MMRM described above. An unstructured covariance matrix was used to describe the variability of the repeated measurements for a subject.

Changes in scores of TRIM-AGHD (total and individual domain scores) and SF-36v2 (physical and health component summary scores and individual domain scores) from baseline were analysed using the MMRM described above. The TSQM-9 scores (effectiveness, convenience and global satisfaction scores) were also analysed using the MMRM, except baseline as a covariate.

The changes in cardiovascular parameters (hsCRP and IL-6) from baseline were analysed using the MMRM. The data for changes in cardiovascular parameters was log-transformed before analysis, both baseline value and values assessed at post-randomization visits.

Changes in body weight from baseline were analysed using the MMRM described above. An unstructured covariance matrix was used to describe the variability of the repeated measurements for a subject.

All other results are presented by descriptive statistics.

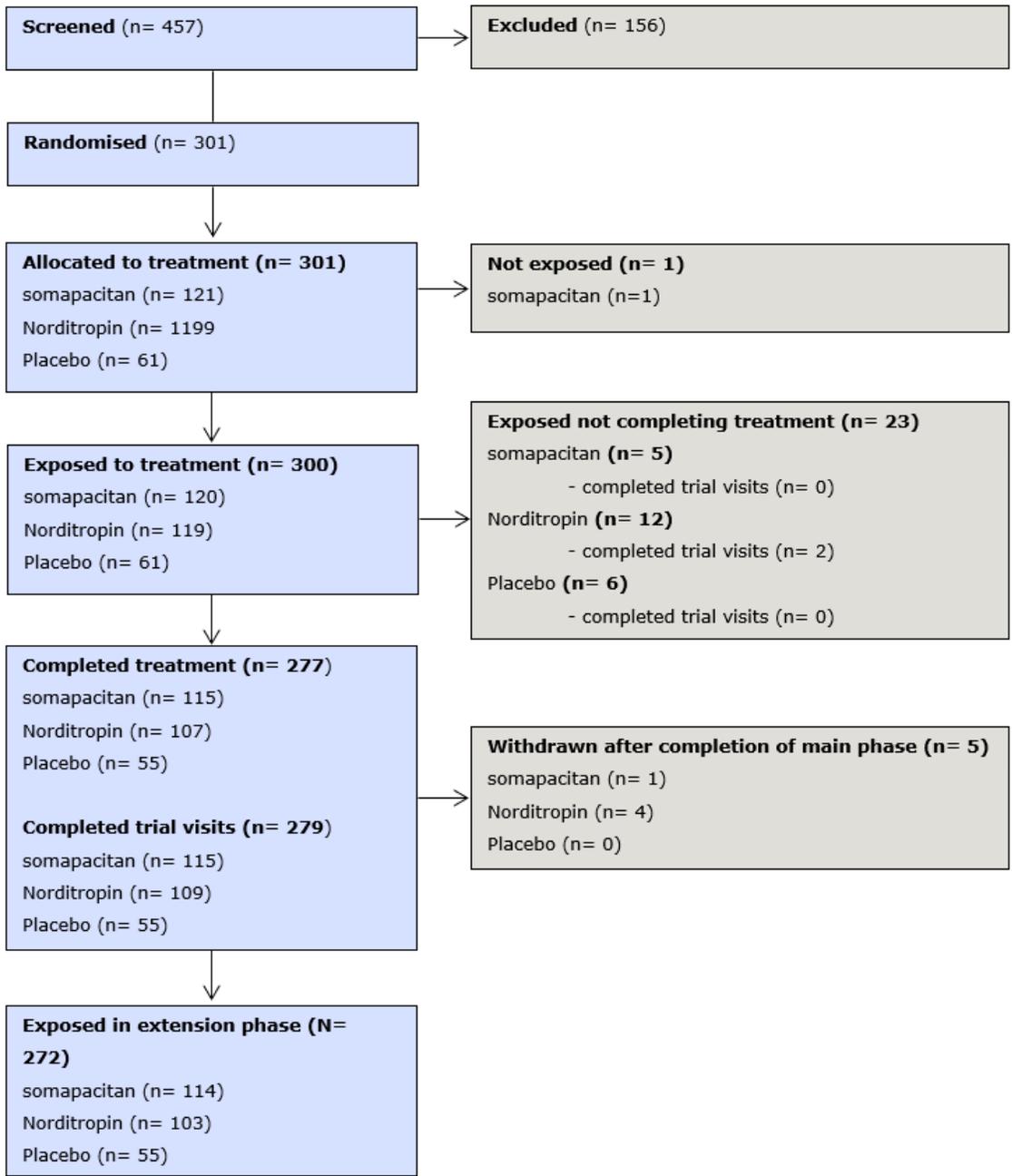
Conducted statistical analyses took into account relevant factors that may affect clinical efficacy results of study results. Such an approach is common for the evaluation of clinical effects which are influenced by multiple factors.

## **Results**

### **Participant flow**

#### Main treatment period

The study participant flow in the main treatment period is presented in Figure 11. 457 AGHD Patients were screened. 156 Patients were excluded, mainly because of not meeting the eligibility criteria (150/156 patients). The main reasons for screening failure were IGF-I SDS levels  $< -0.5$  (48.7%), the inability to confirm the diagnosis of growth hormone deficiency (18.6%), testosterone levels out of the normal range (18.6%), and free T4 levels outside the normal range (9.6%). Six AGHD patients were excluded for other reasons (5: deviation from time window, 1: personal reasons).



Notes:

- Blue boxes indicate patients enrolled in the main trial phase, grey boxes indicate patients not completing the main trial phase.
- Norditropin= somatropin

**Figure 11 Patient disposition main treatment phase of study 4054**

A total of 301 AGHD patients were randomized and 300 patients were exposed. One patient was randomized but did not receive any study drug and was therefore not included in any analyses (no reason was provided). 23 Of 300 (7.7%) exposed study patients did not complete study treatment. The reasons why randomized study patients did not complete the main treatment phase are reported in Table 7.

**Table 7 Reasons for randomized patients not completing the main treatment phase (study 4054)**

|  | Somapacitan | Somatropin | Placebo | Total |
|--|-------------|------------|---------|-------|
| Randomised but not exposed                                       | 1           | 0          | 0       | 1     |
| Discontinued trial product                                       | 0           | 4          | 1       | 5     |
| - Adverse events   | 0           | 4          | 1       | 5     |
| - Discontinued trial product and withdrawn from trial            | 0           | 2          | 1       | 3     |
| - Discontinued trial product but completed all main trial visits | 0           | 2          | 0       | 2     |
| Withdrawn <sup>a</sup>   | 5           | 8          | 5       | 18    |
| - Protocol violation   | 2           | 0          | 0       | 2     |
| - Lost to follow-up  | 0           | 1          | 0       | 1     |
| - Withdrawal by patients   | 3           | 6          | 4       | 13    |
| - Other  | 0           | 1          | 1       | 2     |
| Total  | 6           | 12         | 6       | 24    |

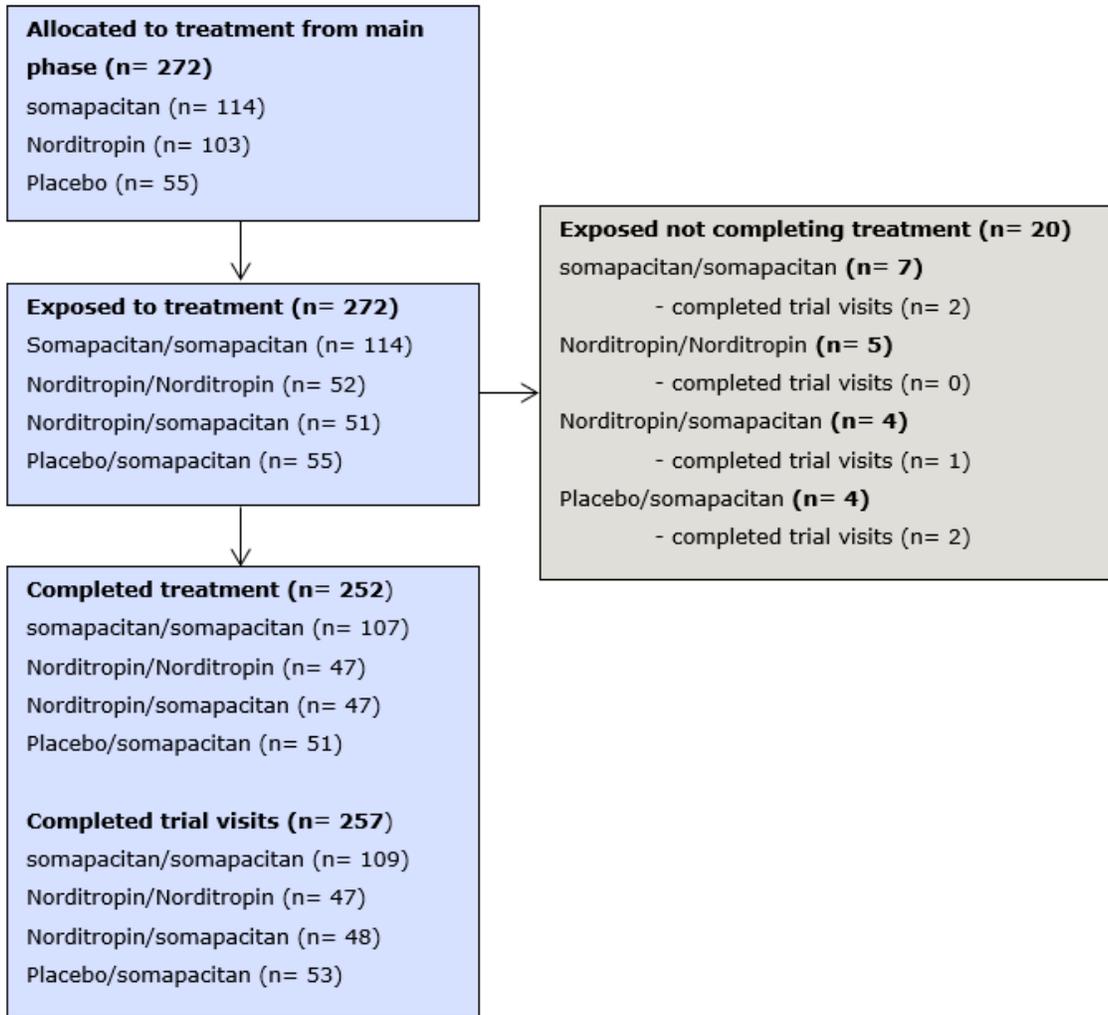
**Notes:** Patients not completing treatment in the main treatment phase are categorised as “Discontinued trial product” or “Withdrawn”. For each of these categories, subcategories specify the reason for premature trial product discontinuation or withdrawal from trial. Patients withdrawn from the trial following premature trial product discontinuation are not included in the Withdrawn category but summarised separately as ‘discontinued trial product and withdrawn from trial’.

A total of 277 (92%) patients completed treatment (34 weeks of treatment). Five (5) patients discontinued study product due to adverse events in the placebo (1 patient) and somatropin (4 patients) groups. These cases are further discussed in the clinical safety section below.

Five of the 277 study patients who completed the main treatment phase were not exposed to study treatment in the extension treatment period. Most of these patients (4/5) had been randomized to somatropin; one patient had been randomized to somapacitan (1/5). From the reported reasons for non-inclusion in the extension treatment phase, none are clearly related to the use of particular study medication in the main study treatment phase.

Extension treatment period

272 Study patients were exposed in the extension treatment period (Figure 12). Of these, 257 study patients completed the study. After the provision of study medication, 9 study patients discontinued study treatment, and 11 study patients withdrew prematurely. In most of these cases (10/20), study patients decided to withdraw study medication because of personal reasons (not specified) (Table 8).



Notes: Blue boxes indicate patients exposed in the extension trial phase, grey boxes indicate patients not completing the extension trial treatment phase. 'somapacitan/somapacitan': patients continuing treatment with somapacitan in the extension phase; 'Norditropin/Norditropin': patients continuing treatment with somatropin product Norditropin in the extension phase, 'Norditropin/Somapacitan': patients re-randomised from somatropin product Norditropin in the main phase to somapacitan in the extension phase; 'Placebo/somapacitan': patients reallocated from placebo to somapacitan treatment in extension phase.

**Figure 12 Patient disposition in extension treatment period**

**Table 8 Reasons for patients not completing the extension treatment phase (study 4054)**

|   | Somapacitan/<br>Somapacitan | Somatropin/<br>Somatropin | Somatropin/<br>Somapacitan | Placebo/<br>Somapacitan | Total     |
|---|-----------------------------|---------------------------|----------------------------|-------------------------|-----------|
| Discontinued trial product                                  | 3                           | 0                         | 4                          | 2                       | 9         |
| - Adverse events  | 1                           | 0                         | 2                          | 1                       | 4         |
| - Withdrawal by patients                                    | 2                           | 0                         | 0                          | 1                       | 3         |
| - Other   | 0                           | 0                         | 2                          | 0                       | 2         |
|   |                             |                           |                            |                         |           |
| - Discontinued trial product and withdrawn from trial       | 1                           | 0                         | 3                          | 0                       | 4         |
| - Discontinued trial product but completed all trial visits | 2                           | 0                         | 1                          | 2                       | 5         |
|   |                             |                           |                            |                         |           |
| Withdrawn   | 4                           | 5                         | 0                          | 2                       | 11        |
| - Lost to follow-up   | 1                           | 1                         | 0                          | 0                       | 2         |
| - Withdrawal by patients                                    | 3                           | 3                         | 0                          | 1                       | 7         |
| - Other   | 0                           | 1                         | 0                          | 1                       | 2         |
|   |                             |                           |                            |                         |           |
| <b>Total</b>  | <b>7</b>                    | <b>5</b>                  | <b>4</b>                   | <b>4</b>                | <b>20</b> |

Notes: Patients not completing treatment in the extension treatment phase are categorised as “Discontinued trial product” or “Withdrawn”. For each of these categories, subcategories specify the reason for premature trial product discontinuation or withdrawal from trial. Patients withdrawn from the trial following premature trial product discontinuation are not included in the Withdrawn category but summarised separately as ‘discontinued trial product and withdrawn from trial’. Treatment arms: ‘somapacitan/somapacitan’: patients continuing treatment with somapacitan in the extension phase; ‘somatropin/somatropin’: patients continuing treatment with somatropin product Norditropin in the extension phase, ‘somatropin/somapacitan’: patients re-randomised from somatropin product Norditropin in the main phase to somapacitan in the extension phase; ‘Placebo/somapacitan’: patients reallocated from placebo to somapacitan treatment in extension phase

### *Treatment adherence*

The majority of patients adhered to the planned treatment. The mean adherence tended to be higher with somapacitan (95.5%) than with somatropin (90.6%) in the main treatment phase (diary data). Adherence in the main treatment phase of study 4054 was  $\geq 97.5$  up to 100% in 78.3% of study patients treated with somapacitan and 73.9% of study patients treated with somatropin.

## Recruitment

Study 4054 was initiated on 31 October 2014. The last visit of the last patient of the main treatment phase was on 1 May 2017.

## Conduct of the study

There were 6 amendments to the protocol.

## Baseline data

Baseline characteristics of study patients are summarized in Table 9.

Of the 300 AGHD patients (48.3% male and 51.7% female) investigated, 91 (30.3%) patients had suffered from GHD since childhood (organic: 36 (12.0%) patients; idiopathic: 55 (18.3%) patients), while 209 (69.7%) patients were first diagnosed as adults.

The mean (SD) age was 45.1 (15.0) years, with the majority of patients in the age group from 23 to 64 years. The mean BMI of 27.4 (6.3) kg/m<sup>2</sup> indicated a somewhat overweight population.

The patients were enrolled at 92 sites in 16 countries. Most patients were enrolled in the US (26.3%), Japan (15.3%), Australia (10.0%), India and Romania (both 9.3%).

Most patients were white (66.7%) or Asian (28.7%).

One patient (age 28 years/BMI 19.7 kg/m<sup>2</sup>, GHD childhood onset) had an extremely low height of 1.07 m at baseline and a body weight of 22.5 kg. The AGHD diagnosis was reconfirmed in this patient.

The mean body weight, BMI, and waist circumference of placebo-treated study patients at baseline tended to be lower than those of somapacitan- and somatropin-treated patients. Upon inclusion of BMI as a covariate in the primary analysis model, the results of the primary analysis remained similar. Hence, any difference in BMI between study arms at baseline did not affect the results of the primary analysis.

**Table 9 Summary of baseline characteristics – full analysis set**

|                                  | <b>Somapacitan</b> | <b>Somatropin</b> | <b>Placebo</b> | <b>Total</b> |
|----------------------------------|--------------------|-------------------|----------------|--------------|
| Number of study patients         | 120                | 119               | 61             | 300          |
| <b>Age (years)</b>               |                    |                   |                |              |
| Range                            | 23 -75             | 23 - 77           | 23 - 76        | 23 - 77      |
| Mean (SD)                        | 44.6 (14.3)        | 45.7 (15.3)       | 45.0 (15.7)    | 45.1 (15.0)  |
| Median                           | 44                 | 46                | 46             | 44.5         |
| <b>Male (%)</b>                  | 48.3%              | 48.7%             | 47.5%          | 48.3%        |
| <b>Ethnicity (%)</b>             |                    |                   |                |              |
| Hispanic or Latino               | 5.0%               | 6.7%              | 6.6%           | 6.0%         |
| Other                            | 95.0%              | 91.6%             | 93.4%          | 93.3%        |
| Unknown                          | 0%                 | 1.7%              | 0%             | 0.7%         |
| <b>Race (%)</b>                  |                    |                   |                |              |
| Asian                            | 28.3%              | 30.3%             | 26.2%          | 28.7%        |
| Black or African American        | 1.7%               | 2.5%              | 3.3%           | 2.3%         |
| Native Hawaiian or other Pacific | 0.8%               | 0%                | 0%             | 0.3%         |

|   |                      |                      |                      |               |
|---|----------------------|----------------------|----------------------|---------------|
| Islander                                    |                      |                      |                      |               |
| White                                       | 68.3%                | 64.7%                | 68.9%                | 67.0%         |
| Hispanic or Latino                          | 0.8%                 | 0.8%                 | 1.6%                 | 1.0%          |
| Unknown                                     | 0%                   | 1.7%                 | 0%                   | 0.7%          |
| <b>Country (%)</b>                          |                      |                      |                      |               |
| Australia                                   | 10.8%                | 8.4%                 | 11.5%                | 10.0%         |
| Germany                                     | 2.5%                 | 2.5%                 | 3.3%                 | 2.7%          |
| India                                       | 9.2%                 | 9.2%                 | 9.8%                 | 9.3%          |
| Japan                                       | 15.0%                | 15.1%                | 16.4%                | 15.3%         |
| Latvia                                      | 0%                   | 0.8%                 | 3.3%                 | 1.0%          |
| Lithuania                                   | 0.8%                 | 2.5%                 | 6.6%                 | 2.7%          |
| Malaysia                                    | 3.3%                 | 2.5%                 | 0%                   | 2.3%          |
| Poland                                      | 6.7%                 | 1.7%                 | 1.6%                 | 3.7%          |
| Romania                                     | 10.0%                | 11.8%                | 3.3%                 | 9.3%          |
| Russian Federation                          | 5.8%                 | 5.0%                 | 8.2%                 | 6.0%          |
| South Africa                                | 3.3%                 | 3.4%                 | 1.6%                 | 3.0%          |
| Sweden                                      | 0%                   | 1.7%                 | 0%                   | 0.7%          |
| Turkey                                      | 3.3%                 | 0.8%                 | 4.9%                 | 2.7%          |
| Ukraine                                     | 2.5%                 | 0.8%                 | 6.6%                 | 2.7%          |
| United Kingdom                              | 0.8%                 | 5.0%                 | 0%                   | 2.3%          |
| United States                               | 25.8%                | 28.6%                | 23.0%                | 26.3%         |
| <b>Height (m)</b>                           |                      |                      |                      |               |
| Range                                       | 1.38 – 1.87          | 1.07 – 1.93          | 1.39 – 1.83          | 1.07 – 1.93   |
| Mean (SD)                                   | 1.65 (0.10)          | 1.64 (0.14)          | 1.63 (0.10)          | 1.64 (0.12)   |
| Median                                      | 1.65                 | 1.64                 | 1.64                 | 1.64          |
| <b>Body weight (kg)</b>                     |                      |                      |                      |               |
| Range                                       | 44.5 – 134.1         | 22.5 – 140.9         | 38.0 – 114.9         | 22.5 – 140.9  |
| Mean (SD)                                   | 76.2 (21.0)          | 76.0 (22.7)          | 69.8 (19.7)          | 74.8 (21.5)   |
| Median                                      | 72.9                 | 74.1                 | 69.0                 | 72.4          |
| <b>BMI (kg/m<sup>2</sup>)(m)</b>            |                      |                      |                      |               |
| Range                                       | 17.6 – 47.2          | 17.0 – 45.0          | 13.3 – 44.3          | 13.3 – 47.2   |
| Mean (SD)                                   | 27.9 (6.3)           | 27.7 (6.2)           | 26.1 (6.4)           | 27.4 (6.3)    |
| Median                                      | 26.9                 | 26.8                 | 25.4                 | 26.7          |
| <b>Waist circumference (cm)</b>             |                      |                      |                      |               |
| Range                                       | 66.9 – 135.5         | 45.8 – 151.1         | 61.0 – 119.0         | 45.8 – 151.1  |
| Mean (SD)                                   | 93.9 (14.7)          | 94.0 (16.1)          | 88.5 (14.2)          | 92.8 (15.3)   |
| Median                                      | 93.1                 | 94.6                 | 87.1                 | 92.8          |
| <b>Growth hormone deficiency onset (%)</b>  |                      |                      |                      |               |
| Adulthood                                   | 68.3%                | 72.3%                | 67.2%                | 69.7%         |
| Childhood - idiopathic                      | 17.5%                | 17.6%                | 21.3%                | 18.3%         |
| Childhood - Organic                         | 14.2%                | 10.1%                | 11.5%                | 12.0%         |
| <b>Diabetes mellitus (%)</b>                | 5.8%                 | 5.0%                 | 4.9%                 | 5.3%          |
| <b>IGF-I SDS at screening, mean (range)</b> | -2.58 (-5.23; -0.50) | -2.53 (-5.56; -0.51) | -2.68 (-5.36; -0.62) | Not available |

Abbreviations: BMI = body mass index, IGF-I SDS= insulin-like growth factor I standard deviation score

A total of 16 (5.3%) patients (somapacitan: 7 (5.8%) patients; somatropin: 6 (5.0%) patients; placebo: 3 (4.9%) patients) were reported as diabetic at baseline. Mean (SD) fasting glucose (somapacitan: 4.94 (0.67) mmol/l; somatropin: 5.03 (0.70) mmol/l; placebo: 4.91 (0.59) mmol/l) and mean (SD) fasting insulin (somapacitan: 79.9 (76.6) pmol/l; somatropin: 73.6 (52.0) pmol/l; placebo: 62.1 (43.0) pmol/l) were within normal ranges at baseline, though with greater baseline insulin levels in the somapacitan and placebo groups. Mean HbA1c was 5.4% across treatment groups.

Mean values for thyroid parameters (free T4, T4 and TSH) were all within normal range at baseline. No clinically relevant findings or differences between treatment groups were observed in vital signs at baseline or in ECG at baseline.

#### *Medical history and concomitant illnesses*

According to the applicant, the medical history and concomitant diseases reflected the study population of AGHD patients.

The most frequent system organ classes reported in medical history were surgical and medical procedures (90 patients, 30.0%) and benign, malignant and unspecified neoplasms (80 patients, 26.7%). The following 4 preferred terms were reported in  $\geq 5\%$  of the patients in medical history: craniopharyngioma (22 patients, 7%); pituitary tumour (16 patients, 5%); pituitary tumour benign (25 patients, 8%); pituitary tumour removal (18 patients, 6%).

The majority of patients reported concomitant illnesses within endocrine disorders (e.g. hypopituitarism, hypothyroidism, hypogonadism) (283 patients, 94%). The concomitant illnesses reported in at least 10% of the patients are listed below (Table 10).

Hypopituitarism and related diseases, and hypertension and dyslipidaemia were frequently reported in this group of AGHD patients. For some patients, GHD was also reported within concomitant illnesses.

**Table 10 Most frequent concomitant illnesses  $\geq 10\%$  of the patients**

|                          | <b>Somapacitan<br/>(n= 120)</b> | <b>Somatropin<br/>(n= 119)</b> | <b>Placebo<br/>(n= 61)</b> | <b>Total<br/>(n= 300)</b> |
|--------------------------|---------------------------------|--------------------------------|----------------------------|---------------------------|
| Adrenal insufficiency    | 13.3%                           | 14.3%                          | 21.3%                      | 15.3%                     |
| Diabetes insipidus       | 22.5%                           | 10.1%                          | 18.0%                      | 16.7%                     |
|                          |                                 |                                |                            |                           |
| Hypogonadism             | 14.2%                           | 13.4%                          | 14.8%                      | 14.0%                     |
| Hypopituitarism          | 52.5%                           | 46.2%                          | 42.6%                      | 48.0%                     |
| Hypothyroidism           | 25.8%                           | 31.1%                          | 29.5%                      | 28.7%                     |
| Secondary hypogonadism   | 14.2%                           | 10.9%                          | 23.0%                      | 14.7%                     |
| Secondary hypothyroidism | 9.2%                            | 10.9%                          | 18.0%                      | 11.7%                     |
| Dyslipidaemia            | 16.7%                           | 13.4%                          | 14.8%                      | 15.0%                     |
| Hyperlipidaemia          | 12.5%                           | 13.4%                          | 8.2%                       | 12.0%                     |
| Vitamin D deficiency     | 19.2%                           | 16.0%                          | 14.8%                      | 17.0%                     |
| Headache                 | 10.8%                           | 11.8%                          | 6.6%                       | 10.3%                     |
| Depression               | 12.5%                           | 10.9%                          | 4.9%                       | 10.3%                     |
| Hypertension             | 13.3%                           | 16.8%                          | 13.1%                      | 14.7%                     |

#### *Treatment exposure*

The treatment exposure and doses in each treatment arms in the main and extension study are summarised in Table 11. It is noted that the study treatment doses of somapacitan (2.33-2.61 mg/week) tended to be higher compared to those treated with somatropin (1.89 mg/week). Since the affinity of somapacitan for the growth hormone receptor is 3-4 times less than that of somatropin due to the attached serum albumin, a higher weekly concentration of somapacitan than somatropin is needed to achieve similar effects in terms of IGF-I production.

**Table 11 Summary of study treatment exposure in main and extension treatment phases of study 4054 expressed in mg per week**

| Exposure in main treatment period          | Placebo/somapacitan | Somapacitan/somapacitan | Somatropin/somatropin | Somatropin/somapacitan | Somatropin /-  |
|--|---------------------|-------------------------|-----------------------|------------------------|----------------|
| N  | 61                  | 120                     | 52                    | 51                     | 16             |
| Mean number of days (SD)*                  | 228 (36.1)          | 232 (36.2)              | 238 (4.8)             | 238 (3.7)              | 144 (98.8)     |
| Mean treatment dose (mg)**                 | 2.18                | 2.52                    | 2.17                  | 2.31                   | 2.94           |
| Mean treatment dose (mg/kg)**              | 0.034               | 0.037                   | 0.028                 | 0.035                  | 0.064          |
|  |                     |                         |                       |                        |                |
| Exposure in extension treatment period     | Somapacitan         | Somapacitan             | Somatropin            | Somapacitan            | Not applicable |
| Mean number of days (SD)*                  | 357 (40.4)          | 355 (52.4)              | 349 (48.8)            | 343 (76.6)             |                |
| Mean treatment dose (mg)**                 | 2.56                | 2.33                    | 1.89                  | 2.61                   |                |
| Mean treatment dose (mg/kg)**              | 0.042               | 0.034                   | 0.028                 | 0.041                  |                |
| Mean number of days (SD) in complete study | 550 (145.3)         | 569 (122.5)             | 588 (49.4)            | 581 (76.6)             | 144 (98.8)     |

SD= standard deviation

\*Exposure days are calculated as time from first date on randomized treatment to last date on randomized treatment for somatropin and plus six days for somapacitan in the given period. Exposure days in complete study is sum of main and extension.

\*\* Stable dose at last titration visit 10 for main and visit 23 for extension. Weight measured at baseline. Study treatment doses are expressed in amounts per week.

## Numbers analysed

In total, 300 AGHD patients were randomized and exposed to study treatment (once-weekly somapacitan: 120 patients; daily somatropin: 119 patients; placebo: 61 patients). All 300 AGHD patients were included in the full analysis set and the safety analysis set, which were identical in the current study.

One patient was randomized to receive somapacitan treatment but did not receive this study treatment and was therefore not included in any analysis sets. The reason for this is unknown.

## Outcomes and estimation

### Main treatment period

#### *Primary endpoint – change in truncal fat percentage from baseline to week 34*

The estimated mean change from baseline to the end of the main treatment period (week 34) in truncal fat percentage was greater for somapacitan than for placebo (Table 12). The difference between somapacitan and placebo in the change in truncal fat percentage was statistically significant. The results obtained after daily somatropin and weekly somapacitan are in favour of the daily treatment regimen.

Secondary statistical analyses, excluding patients without week 34 data for the endpoint (\*\*\*) and patients with less than 3 dose adjustments (\*\*\*\*) and sensitivity analyses were similar to the results from the primary analyses.

**Table 12 Estimated change in truncal fat percentage (%) from baseline to week 34 (Full analysis set)**

| Change from baseline       |                    | Somapacitan (n= 120)* | Somatropin (n= 119)*   | Placebo (n= 61)* | Primary comparison**: difference somapacitan - placebo (95% CI) p-value | Secondary comparison**: difference somapacitan - somatropin (95% CI) p-value |
|----------------------------|--------------------|-----------------------|------------------------|------------------|---|--|
| Truncal fat percentage (%) | Week -3<br>Week 34 | 39.11<br>-1.17        | 38.10<br>-2.39         | 36.90<br>+0.49   | -1.53<br>(-2.68; -0.38)<br>P= 0.009                                     | 1.17<br>(0.23 ; 2.11)<br>p-value not reported                                |
|                            |                    |                       | Secondary analysis***  |                  | -1.65<br>(-2.83; -0.47)<br>P= 0.006                                     | 1.40<br>(0.44; 2.35)<br>p-value not reported                                 |
|                            |                    |                       | Secondary analysis**** |                  | -1.68<br>(-2.87; -0.50)<br>0.006  | 1.36<br>(0.40; 2.32)<br>p-value not reported                                 |

\* Observed changes in mean percentages.

\*\* Primary analysis: changes in truncal fat percentage from baseline to the 34 week's measurements was analysed using an analysis of covariance model with treatment, growth hormone deficiency onset type, sex, region, diabetes mellitus and sex by region by diabetes mellitus interaction as factors and baseline as a covariate.

\*\*\* Changes in truncal fat percentage from baseline to the 34 week's measurements was analysed using an analysis of covariance model with treatment, growth hormone deficiency onset type, sex, region, diabetes mellitus and sex by region by diabetes mellitus interaction as factors and baseline as a covariate. Subjects without week 34 data for the endpoint are excluded from the analysis.

\*\*\*\* Changes in truncal fat percentage from baseline to the 34 week's measurements was analysed using an analysis of covariance model with treatment, growth hormone deficiency onset type, sex, region, diabetes mellitus and sex by region by diabetes mellitus interaction as factors and baseline as a covariate. Subjects without week 34 data for the endpoint and less than 3 dose adjustment evaluations are excluded from the analysis.

### *Secondary outcomes*

#### *Change in body composition assessments – from baseline to week 34*

The estimated mean differences in body composition endpoints from baseline to week 34 and the secondary endpoint analysis of body composition outcomes are presented in Table 13.

In general, fat masses in different parts of the body tended to decrease upon treatment with somapacitan and somatropin, whereas these fat masses tended to increase upon placebo treatment. In addition, increases in truncal lean body mass, appendicular skeletal muscle mass, and total lean body mass tended to be larger for study patients treated with somapacitan and somatropin as compared to placebo treatment.

Comparing somapacitan with daily somatropin treatment reveals overall inferior results for the weekly somapacitan dosing regimen. As this is considered a secondary endpoint in an open-label arm, these observations should be interpreted with caution, especially in the context of the findings of the GCP inspection.

However, in the present study, the body composition (including the truncal fat measures) were acquired with dual energy x-ray absorptiometry which seems to be a relatively objective instrument of measure.

**Table 13 Change from baseline to week 34 in body composition parameters (Full analysis set)**

| Change from baseline                            |                    | Somapacitan (n= 120)* | Somatropin (n= 119)* | Placebo (n= 61)*    | Primary comparison**:<br>difference somapacitan - placebo (95% CI)<br>p-value | Secondary comparison*<br>*: difference somapacitan -somatropin (95% CI)<br>p-value |
|---|--------------------|-----------------------|----------------------|---------------------|---|--|
| Body fat mass (g)                               | Week -3<br>Week 34 | 27559.38<br>-85.47    | 27260.57<br>-855.71  | 24820.88<br>+305.47 | -266<br>(-1197; 664)<br>P= 0.57   | 724<br>(-39; 1487)<br>P= 0.06  |
| Truncal body fat mass (g)                       | Week -3<br>Week 34 | 14777.05<br>-180.98   | 14121.73<br>-619.67  | 12669.57<br>+417.86 | -496<br>(-1049; 57)<br>P= 0.08  | 411<br>(-41; 864)<br>P= 0.07   |
| Visceral adipose tissue (VAT)(cm <sup>2</sup> ) | Week -3<br>Week 34 | 138.31<br>-11.61      | 125.35<br>-9.68      | 105.81<br>+4.00     | -14<br>(-21; -7)<br>P= 0.0001   | -1<br>(-7; 4)<br>P= 0.63   |
| Android body fat mass (g)                       | Week -3<br>Week 34 | 2480.21<br>-81.52     | 2395.42<br>-158.98   | 2089.18<br>+56.32   | -116<br>(-223; -10)<br>P= 0.03  | 74<br>(-12; 161)<br>P= 0.09  |
| Gynoid body fat mass (g)                        | Week -3<br>Week 34 | 4212.24<br>+22.66     | 4209.46<br>-128.59   | 4079.46<br>+8.35    | 15<br>(-144; 175)<br>P= 0.85  | 146<br>(16; 276)<br>P= 0.03  |
|   |                    |                       |                      |                     |   |  |
| Truncal lean body mass (g)                      | Week -3<br>Week 34 | 22297.20<br>+800.27   | 22464.16<br>+832.77  | 20698.51<br>+402.69 | 452<br>(25; 880)<br>P= 0.04   | -38<br>(-388; 311)<br>P= 0.83  |
| Appendicular skeletal muscle mass (ASMM)(g)     | Week -3<br>Week 34 | 20303.95<br>+565.21   | 20353.44<br>+482.76  | 18956.27<br>-76.22  | 679<br>(340; 1019)<br>P= 0.0001   | 96<br>(-182; 374)<br>P= 0.50   |
| Total lean body mass (g)                        | Week -3<br>Week 34 | 45477.71<br>+1395.88  | 45658.60<br>+1359.33 | 42530.26<br>+334.43 | 1144<br>(459; 1829)<br>P= 0.001   | 49<br>(-513; 610)<br>P= 0.87   |

\* Observed changes in mean values.

\*\* Change from baseline to the 34 week's measurements was analysed using an analysis of covariance model with treatment, growth hormone deficiency onset type, sex, region, diabetes mellitus and sex by region by diabetes mellitus interaction as factors and baseline as a covariate.

### IGF-I SDS and IGFBP-3 SDS

IGF-I and IGFBP-3 standard deviation scores (SDS) increased upon treatment with somapacitan or somatropin (Table 14). These scores hardly changed upon placebo study treatment.

The mean IGF-I SDS increased from a baseline value below -2 to a value within the mean of the reference range after 34 weeks of active treatment (somapacitan: -2.54 to -0.17; somatropin: -2.53 to -0.23), whereas IGF-I levels remained similar in placebo-treated study patients (-2.64 to -2.62). A similar pattern was observed in mean IGFBP-3 SDS, though observed increases tended to be smaller than observed for IGF-I SDS.

Observed changes in IGF-I SDS and IGFBP-3 SDS were larger upon somapacitan treatment compared to placebo treatment (difference 2.40 (95% CI 2.09 – 2.72) vs. 1.51 (95% CI 1.22 – 1.81)). Changes in IGF-I and IGFBP-3 SDS were similar for somapacitan and somatropin study treatment.

**Table 14 Secondary endpoint analysis of IGF-I SDS and IGFBP-3 SDS –change from baseline (week 0) to week 34 (Full analysis set)**

|             |         | Somapacitan<br>(n= 120)* | Somatropin<br>(n= 119)* | Placebo<br>(n= 61)* | Primary<br>comparison**:<br>difference<br>somapacitan<br>- placebo<br>(95% CI)<br>p-value | Secondary<br>comparison**:<br>difference<br>somapacitan<br>-<br>somatropin<br>(95% CI)<br>p-value |
|-------------|---------|--------------------------|-------------------------|---------------------|---|---|
| IGF-I SDS   | Week 0  | -2.54                    | -2.53                   | -2.64               | 2.40<br>(2.09; 2.72)<br>P< 0.0001   | 0.02 (-0.23; 0.28)<br>P= 0.85   |
|             | Week 34 | +2.37                    | +2.28                   | +0.05               |   |   |
| IGFBP-3 SDS | Week 0  | -2.08                    | -2.07                   | -2.13               | 1.51<br>(1.22; 1.81)<br>P< 0.0001   | 0.08<br>(-0.16; 0.32)<br>P= 0.50  |
|             | Week 34 | +1.56                    | +1.44                   | +0.12               |   |   |

\*Observed changes in mean values

\*\* Changes from baseline to the 1, 3, 5, 7, 9, 16, 25, 33 and 35 week's measurements was analysed using a mixed-effect model for repeated measurements including treatment, growth hormone deficiency onset type, sex, region, diabetes mellitus and sex by region by diabetes mellitus interaction as factors and baseline as a covariate, all nested within week as a factor.

### PRO questionnaires

SF-36 Overall, SF-36 scores tended to be higher (i.e. indicating improvement) at week 34 compared to baseline. Differences in observed overall scores at week 34 compared to baseline tended to be higher for somapacitan treatment (overall physical score: +2.40 (baseline 44.82), overall mental score: +2.70 (baseline 44.79)) as compared to placebo treatment (overall physical score: +2.01 (baseline 45.40), overall mental score: +1.28 (baseline 41.80)). Respective differences in applied mixed-model for repeated measurements were, however, not statistically significant (overall physical score: 0.53 (95% CI -1.31; 2.37))

$p = 0.57$ ; overall mental score: 2.68 (95% CI -0.07; 5.43),  $p = 0.06$ ). Only observed difference for sub-scales mental health and social functioning were statistically significant.

Observed differences in overall scores at week 34 compared to baseline tended to be lower (i.e. less improvement) for somapacitan treatment as compared to somatropin treatment (overall physical score: +2.87 (baseline 45.58), overall mental score: +4.09 (baseline 44.32)). Similar trends were observed for the subscale scores, except for the sub-scale physical functioning (somapacitan +3.18 (baseline 45.10) vs somatropin +2.46 (baseline 45.94)). Respective differences in applied mixed-model for repeated measurements were however not statistically significant (overall physical score: -1.00 (95% CI -2.5; 0.51)  $p = 0.20$ ; overall mental score: -1.70 (95% CI -3.93; 0.53),  $p = 0.13$ ).

In summary, the improvement in SF-36 overall scores for somapacitan tended to be larger compared to those for placebo treatment, but lower compared to those for somatropin treatment. None of these trends were statistically significant.

#### *TRIM-AGHD*

In all study treatment arms TRIM-AGHD scores tended to decrease, which is indicative of health improvement. Observed decreases in total scores at week 34 tended to be larger for somapacitan (-5.71 (baseline 46.62)) as compared to placebo treatment (-3.65 (baseline 48.42)). Respective difference between somapacitan and placebo in applied mixed-model for repeated measurements was, however, not statistically significant (-2.83 (95% CI -6.72; 1.05),  $p = 0.15$ ). Similar trends were observed for comparisons between the TRIM-AGHD sub-scores of these treatments.

Observed decreases in total scores at week 34 were lower (i.e. indicating less health improvement) for somapacitan (-5.71 (baseline 46.62)) as compared to somatropin treatment (-9.99 (baseline 46.00)) (difference in mixed-model for repeated measurements 4.99 (95% CI 1.84; 8.14),  $p = 0.002$ ). The differences between the TRIM-AGHD subscale scores for somapacitan and somatropin were also statistically significant, except for the cognitive score.

Observed differences in changes in total scores between somapacitan and placebo (-5.71 vs. -3.65) and somapacitan and somatropin (-5.71 vs. -9.99) did not meet the minimal important difference of 10 points. Similar results were observed in the sensitivity analysis, where the analysis of TRIM-AGHD endpoints was repeated in patients who answered the new version of the TRIM-AGHD questionnaire.

#### *TSQM-9*

The TSQM-9 scores (effectiveness, convenience, and global satisfaction scores) after 34 weeks of treatment were used to support the primary objective of evaluating the efficacy of once-weekly dosing of somapacitan (after 34 weeks of treatment) in AGHD patients.

At 34 weeks of treatment, the overall mean satisfaction score was higher for somapacitan (63.1%) than for placebo (54.0%) (estimated treatment difference 8.45; 95% CI 0.66 - 16.24;  $p = 0.03$ ). No statistically significant differences were observed for the mean effectiveness (somapacitan 56.1%, placebo 49.6%; estimated treatment difference 6.60 (95% CI -0.47; 13.67),  $p = 0.07$ ) and mean convenience scores (somapacitan 77.7%, placebo 74.3%; estimated treatment difference 2.86 (95% CI -2.54; 8.27),  $p = 0.30$ ) for these treatments at week 34.

At week 34, the mean effectiveness score was lower for somapacitan (56.1%) than for somatropin (67.1%) (estimated treatment difference -10.74; 95% CI -16.49 up to -4.98;  $p = 0.0003$ ). However, no statistically

significant differences were observed for the mean convenience (somapacitan 77.7%, somatropin 73.9%; estimated treatment difference 4.00 (95% CI -0.40; 8.39),  $p= 0.07$ ) and mean global satisfaction scores (somapacitan 63.1%, somatropin 69.0%; estimated treatment difference -5.45 (95% CI -11.80; 0.89),  $p= 0.09$ ) between these treatments at week 34.

#### *Lipid profile – cholesterol and triglycerides*

Mean total cholesterol levels were in the upper part of the reference range both at baseline and at week 34 for all treatment groups. There were no clinically relevant or statistically significant changes in the lipid profile (total cholesterol, HDL- cholesterol, LDL-cholesterol and triglycerides) from baseline to the end of the main treatment period (week 34) in any of the treatment groups.

#### *Cardiovascular parameters*

There were no clinically relevant changes in cardiovascular parameters (hsCRP and IL-6) from baseline to end of main treatment period (week 34) in any of the treatment groups.

#### Extension treatment period

##### *Change in body composition from baseline to week 87*

The estimated mean differences in all body composition endpoints from baseline to week 87 are presented in Table 15.

The reduction in estimated mean truncal fat percentage at week 87 from baseline was -1.52 % in somapacitan/somapacitan arm and -2.67% in the somatropin/somatropin arm. The estimated treatment difference between the somapacitan/somapacitan and somatropin/ somatropin in change in truncal fat mass percentage was 1.15% ((95% CI: -0.10; 2.40),  $p=0.07$ ).

The gain in estimated total lean body mass at week 87 from baseline was 1739.05 g for the somapacitan/somapacitan treatment regimen and 1305.73 g for the somatropin/ somatropin treatment regimen. The estimated treatment difference between the somapacitan/somapacitan and somatropin/ somatropin in the change in truncal lean mass was 433.32 g ((95% CI -404 up to 1271),  $p=0.31$ ).

Comparable effects were seen for most of the other body composition endpoints.

There were no statistically significant treatment differences in any of the body composition endpoints between the somapacitan/somapacitan and somatropin/ somatropin treatment regimen. Overall, decreases in fat masses tended to be less for the somapacitan/somapacitan treatment regimen compared to the somatropin/ somatropin treatment regimen. By contrast, increases in lean body masses and bone mineral content tended to be higher for study patients in the somapacitan/ somapacitan treatment regimen compared to those in the somatropin/ somatropin treatment regimen.

In study patients treated with somatropin in the main treatment phase who were re-randomized to receive somapacitan in the extension treatment phase, decreases in truncal fat percentage compared to baseline tended to be larger during somatropin treatment (-2.28%) as compared to somapacitan treatment in the extension treatment period (-0.96%). Similar trends were observed with respect to other endpoints pertaining to fat masses.

**Table 15 Change in DXA body composition from baseline to week 87 (Full analysis set)**

| Change from baseline                                  |                               | Placebo/<br>somapacitan<br>(n= 61)* | Somapacitan/<br>somapacitan<br>(n= 120)* | Somatropin/<br>somatropin<br>(n= 52)* | Somatropin/<br>somapacitan<br>(n= 51)* | Treatment<br>difference at<br>week 87<br>somapacitan/<br>somapacitan -<br>somatropin/<br>somatropin<br>MMRM<br>(95% CI)<br>p-value |
|---|-------------------------------|-------------------------------------|--|---------------------------------------|--|--|
| Truncal fat<br>percentage<br>(%)                      | Week -3<br>Week 34<br>Week 87 | 37.00<br>+0.38<br>-2.16             | 39.12<br>-1.18<br>-1.63                  | 38.16<br>-2.53<br>-2.63               | 38.26<br>-2.28<br>-0.96                | 1.15<br>(-0.10 ; 2.40)<br>P= 0.07  |
| Body fat mass<br>(g)                                  | Week -3<br>Week 34<br>Week 87 | 24858.35<br>+ 265.33<br>-540.04     | 27561.12<br>-87.25<br>-118.07            | 27968.22<br>-885.71<br>-923.01        | 26822.56<br>-746.47<br>+874.56         | 979.92<br>(-249; 2209)<br>P= 0.12  |
| Truncal body<br>fat mass (g)                          | Week -3<br>Week 34<br>Week 87 | 12717.40<br>+366.62<br>-311.85      | 14778.15<br>-182.11<br>-196.18           | 14504.95<br>-687.04<br>-685.56        | 14001.34<br>-602.32<br>+364.08         | 606.38<br>(-90; 1303)<br>P=0.09  |
| Visceral<br>adipose tissue<br>(VAT)(cm <sup>2</sup> ) | Week -3<br>Week 34<br>Week 87 | 107.24<br>+4.41<br>-9.34            | 138.44<br>-11.61<br>-6.71                | 132.50<br>-10.33<br>-5.17             | 123.42<br>-9.32<br>-5.97               | 0.22<br>(-10; 10)<br>P= 0.97   |
| Android body<br>fat mass (g)                          | Week -3<br>Week 34<br>Week 87 | 2094.98<br>+56.32<br>-107.16        | 2478.85<br>-81.52<br>-39.76              | 2432.61<br>-152.00<br>-100.76         | 2404.50<br>-141.79<br>+11.52           | 97.04<br>(-41; 235)<br>P= 0.17   |
| Gynoid body<br>fat mass (g)                           | Week -3<br>Week 34<br>Week 87 | 4052.10<br>+8.35<br>-92.00          | 4209.16<br>+22.66<br>+10.23              | 4303.07<br>-109.51<br>-110.97         | 4171.07<br>-117.46<br>+140.02          | 141.53<br>(-68; 351)<br>P= 0.18  |
| Truncal lean<br>body mass (g)                         | Week -3<br>Week 34<br>Week 87 | 20682.63<br>+419.71<br>+1197.30     | 22291.53<br>+806.09<br>+1152.79          | 22772.38<br>+928.63<br>+975.79        | 21965.99<br>+765.19<br>+1015.12        | 269.19<br>(-183; 721)<br>P=0.24  |
| Appendicular<br>skeletal<br>muscle mass<br>(ASMM) (g) | Week -3<br>Week 34<br>Week 87 | 18957.56<br>-77.60<br>+447.96       | 20307.96<br>+561.10<br>+538.45           | 20452.84<br>+476.19<br>+464.75        | 19987.03<br>+658.38<br>+632.18         | 97.02<br>(-362; 556)<br>P= 0.68  |
| Total lean<br>body mass (g)                           | Week -3<br>Week 34<br>Week 87 | 42491.93<br>+375.49<br>+1717.15     | 45476.03<br>+1397.61<br>+1719.87         | 46140.98<br>+1505.83<br>+1464.51      | 44682.82<br>+1444.12<br>+1681.82       | 433.32<br>(-404; 1271)<br>P= 0.31  |
| Bone mineral<br>content (g)                           | Week -3<br>Week 34<br>Week 87 | 2244.4<br>+ 9.37<br>-25.61          | 2300.0<br>+9.99<br>+5.02                 | 2236.5<br>+7.91<br>-10.18             | 2267.0<br>+15.09<br>+32.33             | 16.07<br>(-16.00; 48.15)<br>P= 0.32  |
| Bone mineral<br>density<br>(g/cm <sup>2</sup> )       | Week -3<br>Week 34<br>Week 87 | 1.11<br>+0.01<br>-0.01              | 1.11<br>+/- 0<br>+/- 0                   | 1.10<br>+/- 0<br>+/- 0                | 1.10<br>+/- 0<br>+0.01                 | 0.009<br>(-0.01; 0.02)<br>P= 0.26  |

CI: confidence interval, MMRM: mixed models repeated measurements

\* Observed mean changes.

### *IGF-I SDS and IGFBP-3 SDS*

A marked increase in mean IGF-I SDS was observed from baseline to week 87 for all treatment regimens. Study patients who received placebo treatment in the main treatment period and somapacitan in the extension treatment period also demonstrated an increase in the level of IGF-I SDS, with the mean levels similar to other treatment regimens at the end of the treatment.

Similar trends were observed for IGFBP-3, though observed increases were smaller than observed for IGF-I SDS.

No statistically significant differences in change from baseline to week 87 in IGF-I SDS and IGFBP-3 SDS were observed between the somapacitan/somapacitan and somatropin/ somatropin treatment regimens.

### *PRO questionnaires*

#### *SF-36*

For all SF-36 sub-scores and overall scores, the estimated change from baseline to the end of treatment period (week 87) tended to be smaller -indicating less improvement- for the somapacitan/somapacitan treatment regimen compared to the somatropin/ somatropin treatment regimen. Regarding the overall scores, the difference in estimated changes from baseline to week 87 were statistically significant for the overall mental score (somapacitan/somapacitan 4.09, somatropin/somatropin 6.87; estimated treatment difference -2.77 (95% CI -5.4; -0.1),  $p=0.04$ ), but not for the overall physical score (somapacitan/somapacitan 2.79, somatropin/somatropin 3.81; estimated treatment difference -1.02 (95% CI -3.1; 1.0),  $p=0.33$ ).

#### *TRIM-AGHD*

For the TRIM-AGHD the estimated decreases from baseline to week 87 in all five scores (cognitive score, energy score, physical score, psychological score, total score) were smaller for the somapacitan/somapacitan treatment regimen compared to the somatropin/somatropin treatment regimen. These data indicate that less improvement was observed for the somapacitan/somapacitan treatment regimen as compared to the somatropin/somatropin treatment regimen. The estimated change for the total scores between these treatment regimens was statistically significant in favour of the somatropin/somatropin treatment regimen (somapacitan/somapacitan -8.01, somatropin/somatropin -15.32; estimated treatment difference 7.32 (95% CI 3.3; 11.3),  $p= 0.0003$ ). However, the estimated treatment difference in the total score between these treatment regimens did not meet the minimal important difference of 10 points.

#### *TSQM-9*

At week 87, the convenience subscore of the TSQM-9 questionnaire was higher for the somapacitan/somapacitan treatment regimen (80.0%) compared to the somatropin/somatropin treatment regimen (72.6%). The difference in the TSQM-9 convenience sub score between these treatment regimens was statistically significant in favour of somapacitan (estimated treatment difference: 7.09 (95% CI: 1.7 – 12.4),  $p=0.01$ ). By contrast, observed differences in the effectiveness (65.7 vs. 69.6%) and global satisfaction subscores (68.1 vs. 71.7%) of the TSQM-9 questionnaire at week 87 tended to be smaller for the somapacitan/somapacitan treatment regimen as compared to the somatropin/ somatropin treatment regimen. Estimated treatment differences at week 87 in effectiveness score (-4.62 (95% CI -11.8; 2.6),  $p= 0.21$ ) and global satisfaction score (-4.19 (95% CI -11.8; 3.4),  $p= 0.28$ ) were however not statistically significant between the somapacitan/somapacitan and somatropin/somatropin treatment regimen.

### *Lipid profile – cholesterol and triglycerides*

There were no statistically significant differences in lipid parameters (i.e., total cholesterol, HDL-cholesterol, LDL cholesterol and triglycerides) between the somapacitan/somapacitan and the somatropin/somatropin treatment regimen.

#### *Cardiovascular parameters*

There were no statistically significant treatment differences in cardiovascular parameters between the somapacitan/somapacitan and somatropin/somatropin treatment regimens.

## **Ancillary analyses**

### ***Clinical efficacy according to age, time of GHD onset, and gender***

With respect to study 4054, the efficacy of somapacitan compared to placebo concerning the primary endpoint (change in truncal fat percentage at week 34 compared to baseline) in the main treatment period was evaluated for different intrinsic subgroups including demographic factors (age and gender) and disease factors (GHD onset). Extrinsic factors were not evaluated.

#### *Age*

Reduction in the estimated change from baseline in truncal fat percentage tended to be larger for patients  $\geq 65$  years of age ( $n= 13$ ) than patients  $\leq 64$  years of age ( $n= 107$ ) after 34 weeks of treatment with somapacitan (i.e.  $-2.16$  vs  $-0.98\%$  for patients aged  $\geq 65$  years and  $\leq 64$  years respectively). For both age groups, a reduction in truncal fat percentage was observed with somapacitan compared to placebo (estimated treatment difference:  $\geq 65$  years of age:  $-1.52\%$ ;  $\leq 64$  years of age:  $-1.71\%$ ). In study patients  $\leq 64$  years, this difference was statistically significant (95% CI  $-2.99$ ;  $-0.43$ ).

In study patients under 65 years, the changes in truncal fat percentage at week 34 compared to baseline, were smaller for sompacitan ( $n= 107$ ;  $-0.98$ ) compared to somatropin ( $n= 101$ ;  $-2.16$ ) (estimated treatment difference  $1.19$  (95% CI  $0.14$ ;  $2.23$ )). A similar trend was observed for this endpoint in study patients aged 65 years and above (somapacitan ( $n= 13$ ):  $-2.16$ , versus somatropin ( $n= 18$ ):  $-2.48$ ), but this trend was not statistically significant (estimated treatment difference  $0.32$  (95% CI  $-2.07$ ;  $2.70$ )).

Due to a low number of patients  $\geq 75$  years of age (5 patients in study 4054) no subgroup analysis was conducted in this age category.

#### *GHD onset (childhood or adult-onset)*

In both growth hormone deficiency of childhood ( $-1.07$  vs  $+0.90\%$ ; estimated treatment difference  $-1.97\%$ ) and adult-onset ( $-1.09$  vs  $+0.32\%$ ; estimated treatment difference:  $-1.41\%$ ), decreases in truncal fat percentage tended to be higher in study patients treated with somapacitan compared to those treated with placebo. Observed differences were only statistically significant in study patients with adult-onset growth hormone deficiency (95% CI  $-2.72$ ;  $-0.10$ ).

In the SmPC of somatropin product Norditropin FlexPro different starting doses are recommended for childhood-onset ( $0.2 - 0.5$  mg/day) and adulthood-onset ( $0.1 - 0.3$  mg/day). However, no significant effects of weekly somapacitan were found on PK or PK/PD parameters in study 4054 and other Phase 3 studies. Since somapacitan doses are individually titrated based on individual needs, clinical response, and IGF-I level, the applicant did not propose particular dose recommendations for patients with childhood-onset and adult-onset AGHD.

## *Gender*

A reduction in truncal fat percentage was observed with somapacitan compared to placebo for both male (-1.69 vs. +0.80%; estimated treatment difference: -2.49%) and female (-0.57 vs. +0.35%; estimated treatment difference: -0.92%) AGHD study patients. Estimated treatment difference versus placebo was statistically significant in male AGHD study patients (95% CI -4.19; -0.79), but not in female AGHD study patients (95% CI -2.50; +0.66).

From medical literature, it is known that male patients are more responsive to growth hormone as compared to female patients (Burman et al. 1997; Johannsson et al. 1996). In line with this, in both the SmPCs of somatropin products (e.g. Norditropin Flexpro) and in proposed SmPC concerning somapacitan, (starting) doses for growth hormone are higher for female as compared to male AGHD patients.

## ***Post-hoc simulation study***

In study 4054, there was one 8-week dose titration period in the main treatment phase, and another one in the extension treatment phase. Dose adjustments were allowed every two weeks. This means that a maximum of four dose titration steps was allowed. 47% Of AGHD study patients did not obtain IGF-I levels above 0 at the end of the dose titration period.

A simulation study was conducted to investigate the doses and exposures that would likely be needed to achieve average IGF-I levels > 0 SDS for each AGHD study patient who did not reach IGF-I levels above 0 at the end of the dose titration period in the main treatment phase of study 4054 (i.e. at visit 11).

## Methods

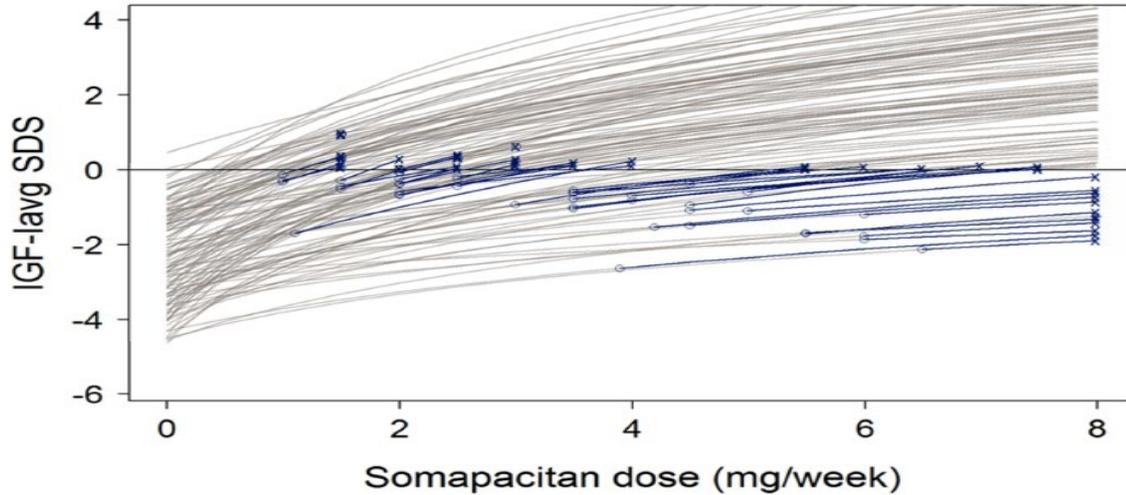
The PK/PD dataset of the somapacitan study population in the main treatment phase of study 4054 was used for the analysis. Study patients were grouped according to whether they reached IGF-I SDS levels above 0, based on a single IGF-I measurement after dose titration. Study patients who did not complete dose titration were excluded from this analysis and the dataset. The dataset consisted of 116 titration completers.

Individual prediction of exposure and IGF-I average SDS following dose increase in the range 0.1 up to a maximum of 8 mg per week were based on the pre-defined analysis of individual dose-exposure-IGF-I response curves by population PK/PD modelling.

In AGHD study patients who already reached IGF-I SDS levels above 0, no new dose-exposure-response prediction was performed. In study patients who did not reach an IGF-I SDS level above 0, somapacitan doses were consecutively increased according to recommended posology until it was predicted that the IGF-I average SDS level reached 0. The predicted dose-exposure-response pair was reported for the lowest somapacitan dose that provided an IGF-I SDS level above 0. In study patients who did not reach an IGF-I average SDS level above 0 and where it was predicted that IGF-I average SDS above 0 could likely not be reached within the dose range of 0.1-8 mg/week, the predicted dose-exposure-response pair at 8 mg/week were reported.

## Results

A graphical representation of the predicted increases in doses and IGF-I average SDS is presented in Figure 13.



Note: Population PK/PD dataset (titration completers). Grey lines denote the individual predicted dose-response for all study patients. Blue points and lines denote data from the subset of "patients not reaching IGF-I SDS above 0" based on the single IGF-I measurement after titration. Circles denote the dose and IGF-Iavg SDS pairs obtained after titration. Note that some patients reached IGF-Iavg SDS above 0 based on all available samples, although the IGF-I measurement taken after titration was below 0 SDS, and vice versa. Crosses indicate predicted dose levels required to reach IGF-Iavg SDS above 0 or predicted IGF-Iavg SDS at 8 mg for those predicted not to reach IGF-Iavg SDS above 0.

**Figure 13 Predicted individual dose-IGF-I response curves for patients not reaching IGF-I SDS above 0 (trial 4054 main)**

According to individual predictions, an IGF-Iavg SDS > 0 can be reached upon continued dose titration in many AGHD study patients in whom an IGF-Iavg SDS level > 0 was not achieved in the main treatment phase of study 4054 (47%). A total of 90% of the population reached, or would likely be able to reach, an IGF-I SDS above 0 within the proposed dose range (up to 8 mg) and based on continued titration towards an IGF-I SDS level of 0 to +2.

The simulation study in patients not reaching IGF-I SDS > 0 in trial 4054 main was also performed in an important AGHD subgroup (Table 16). Since some of the AGHD subgroups are small, caution is needed with respect to the interpretation of obtained results.

**Table 16** Number and proportion of somapacitan-treated patients reaching, or being likely/unlikely to reach IGF-I SDS target of >0 by important subsets (*post-hoc* simulation study based on trial 4054 main)

| Category                      | Group                   | Reached IGF-I SDS>0 | Did not reach IGF-I SDS>0      |                                  | Total      |
|-------------------------------|-------------------------|---------------------|--------------------------------|----------------------------------|------------|
|                               |                         |                     | Likely to reach IGF-Iavg SDS>0 | Unlikely to reach IGF-Iavg SDS>0 |            |
| <b>All</b>                    | N                       | 62 (53%)            | 42 (36%)                       | 12 (10%)                         | 116 (100%) |
| <b>Sex and oral oestrogen</b> | Male                    | 39 (71%)            | 16 (29%)                       | 0                                | 55 (100%)  |
|                               | Female (no oestrogen)   | 11 (46%)            | 12 (50%)                       | 1 (4%)                           | 24 (100%)  |
|                               | Female (oral oestrogen) | 12 (32%)            | 14 (38%)                       | 11 (30%)                         | 37 (100%)  |
| <b>GHD onset</b>              | Childhood onset         | 15 (39%)            | 17 (45%)                       | 6 (16%)                          | 38 (100%)  |
|                               | Adult onset             | 47 (60%)            | 25 (32%)                       | 6 (8%)                           | 78 (100%)  |
| <b>Age</b>                    | 25 years or younger     | 4 (29%)             | 8 (57%)                        | 2 (14%)                          | 14 (100%)  |
|                               | Older than 25 years     | 58 (57%)            | 34 (33%)                       | 10 (10%)                         | 102 (100%) |

Note: Population PK/PD dataset (titration completers). Note that 4 patients in the FAS (N=120) were not titration completers. Patients grouped by whether they reached, could likely reach or were unlikely to reach IGF-I SDS >0 based on individual predictions.

## Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 17** Summary of efficacy for study 4054

|  |   |
|--|---|
| Title:<br>A multicentre, multinational, randomized, parallel-group, placebo-controlled (double-blind) and active-controlled open-label study to compare the efficacy and safety of once-weekly dosing of somapacitan with once-weekly dosing of placebo and daily somatotropin in adults with growth hormone deficiency for 35 weeks, followed by a 53-week open-label extension period. |   |
| Study identifier   | NN8640-4054 (REAL 1)<br>Further abbreviated into 'study 4054' |
| Design   | Multicentre, randomized, parallel study                       |

|  |   |  |   |
|--|---|--|---|
|  | Duration of main phase:   | 35 weeks (34 weeks of study treatment + 1 week washout)                            |   |
|  | Duration of Run-in phase:   | Not applicable   |   |
|  | Duration of Extension phase:  | 53 weeks (52 weeks of study treatment + 1 week washout)                            |   |
| Hypothesis                                     | Superiority somapacitan over placebo treatment<br>Exploratory somapacitan versus somatropin treatment |  |   |
| Treatments groups                              | Somapacitan   |  | One dose subcutaneously once-weekly. Individual dose titration based on IGF-I SDS at week 2, 4, 6, and 8, followed by 26 weeks fixed-dose treatment (total: 34 weeks). N= 120 (Full analysis set) |
|  | Somatropin  |  | One dose subcutaneously once-weekly. Individual dose titration based on IGF-I SDS at week 2, 4, 6, and 8, followed by 26 weeks fixed-dose treatment (total: 34 weeks). N= 119 (Full analysis set) |
|  | Placebo   |  | One dose subcutaneously once-weekly. Individual dose titration based on IGF-I SDS at week 2, 4, 6, and 8, followed by 26 weeks fixed-dose treatment (total: 34 weeks). N= 61 (Full analysis set)  |
| Endpoints and definitions                      | Primary endpoint  | Truncal fat percentage (TFP)   | Mean change from baseline to end of main treatment period (week 34) in truncal fat percentage determined by dual energy x-ray absorptiometry (DXA)  |
|  | Secondary endpoint  | Total fat mass (TFM)   | Mean change from baseline to end of main treatment period (week 34) in total fat mass (g) determined by dual energy x-ray absorptiometry (DXA)  |
|  | Secondary endpoint  | Total lean body mass (TLBM)  | Mean change from baseline to end of main treatment period (week 34) in total lean body mass (g) determined by dual energy x-ray absorptiometry (DXA)  |
|  | Secondary endpoint  | Treatment related impact measure-AGHD (TRIM-AGHD)                                  | Mean change from baseline in treatment satisfaction questionnaire for medication - Global satisfaction subscale   |
|  | Secondary endpoint  | Treatment satisfaction questionnaire to medication-9 (TSQM-9) convenience subscale | Reported convenience to study medication at week 34   |
| Database lock                                  | First patient first visit: 31 October 2014<br>Last patient last visit: 01 May 2017                    |  |   |
| <b>Results and Analysis</b>                    |   |  |   |
| <b>Analysis description</b>                    | <b>Primary Analysis</b>   |  |   |
| Analysis population and time point description | Full analysis set after completion of clinical study  |  |   |

|   |  |   |                         |                            |
|---|--|---|-------------------------|----------------------------|
| Descriptive statistics and estimate variability | Treatment group                          | Somapacitan                             | Somatropin              | Placebo                    |
|   | Number of subjects                       | 120                                     | 119                     | 61                         |
|   | Change in TFP<br>Week -3<br>Week 34      | 39.11<br>-1.17                          | 38.10<br>-2.39          | 36.90<br>+0.49             |
|   | Change in TFM<br>Week -3<br>Week 34      | 27559.38<br>-85.47                      | 27260.57<br>-855.71     | 24820.88<br>+305.47        |
|   | Change in TLBM<br>Week -3<br>Week 34     | 45477.71<br>+1395.88                    | 45658.60<br>+1359.33    | 42530.26<br>+334.43        |
|   | Change in TRIM-AGHD<br>Week 0<br>Week 34 | 46.62<br>-5.71                          | 46.00<br>-9.99          | 48.42<br>-3.65             |
|   | TSQM-9<br>Convenience at week 34         | 77.7%                                   | 73.9%                   | 74.3                       |
| Effect estimate per comparison*                 | TFP                                      | Comparison groups                       | Somapacitan vs. placebo | Somapacitan vs. somatropin |
|   |  | Difference changes compared to baseline | -1.53                   | 1.17                       |
|   |  | 95% CI                                  | -2.68; -0.38            | 0.23; 2.11                 |
|   |  | P-value (2-sided)                       | 0.009                   | < 0.05                     |
|   | TFM                                      | Comparison groups                       | Somapacitan vs. placebo | Somapacitan vs. somatropin |
|   |  | Difference changes compared to baseline | -266                    | 724                        |
|   |  | 95% CI                                  | -1197; 664              | -39; 1487                  |
|   |  | P-value (2-sided)                       | 0.57                    | 0.06                       |
|   | TLBM                                     | Comparison groups                       | Somapacitan vs. placebo | Somapacitan vs. somatropin |
|   |  | Difference changes compared to baseline | 1144                    | 49                         |
|   |  | 95% CI                                  | 459; 1829               | -513; 610                  |
|   |  | P-value (2-sided)                       | 0.001                   | 0.87                       |
|   | TRIM-AGHD                                | Comparison groups                       | Somapacitan vs. placebo | Somapacitan vs. somatropin |
|   |  | Difference changes compared to baseline | -2.83                   | 4.99                       |
|   |  | 95% CI                                  | -6.72; 1.05             | 1.84; 8.14                 |
|   |  | P-value (2-sided)                       | 0.15                    | 0.002                      |
|   | TSQM-9<br>Convenience                    | Comparison groups                       | Somapacitan vs. placebo | Somapacitan vs. somatropin |
|   |  | Difference changes compared to baseline | 2.86                    | 4.00                       |
|   |  | 95% CI                                  | -2.54; 8.27             | -0.40; 8.39                |
|   |  | P-value (2-sided)                       | 0.30                    | 0.07                       |

|       |   |
|-------|---|
| Notes | * Change from baseline to the 34 week's measurements was analysed using an analysis of covariance model with treatment, growth hormone deficiency onset type, sex, region, diabetes mellitus and sex by region by diabetes mellitus interaction as factors and baseline as a covariate. |
|-------|---|

## Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

## Clinical studies in special populations

### Age

According to the selection criteria for study participation in these studies, AGHD patients up to 79 years of age were eligible for study participation. An overview of the subjects aged 65 years and above who have been included in controlled (studies 3947, 4054, 4244, 4043) and non-controlled (studies 3915 and 4237) studies is presented in Table 18. Studies 3915 and 4237 did not include subjects above the age of 64 years (study 3915 subjects aged 20-45 years, study 4237 subjects 45-64 years).

In total, 96 patients/subjects aged 65 years and above were included across the studies. In the controlled studies, the majority of elderly patients/subjects were aged between 65-74 years (77/89= 86.5%) with only a few patients/subjects aged 75 years or above (12/89= 13.5%). In the non-controlled studies, no subjects aged 75 years of age were included.

**Table 18 Summary of elderly subjects by trial type (all studies)**

|                               | Age 65-74<br>N (%) | Age 75-79<br>N (%) | Total<br>N (%) |
|-------------------------------|--------------------|--------------------|----------------|
| <b>Total</b>                  | 89 (92.7)          | 7 (7.3)            | 96 (100.0)     |
| <b>Controlled studies</b>     | 77 (80.2)          | 7 (7.3)            | 84 (87.5)      |
| <b>Non-controlled studies</b> | 12 (12.5)          | --                 | 12 (12.5)      |

Notes: Controlled trials include 3947, 4054, 4244 and 4043. Non-controlled trials include 4297 and 4298

As stated in the ancillary analysis section above, similar trends with respect to the primary endpoint changes in truncal fat percentage at week 34 compared to baseline were observed in somapacitan- and placebo-treated study patients in study 4054 aged up to 64 years of age (n= 158) and those aged 65 years and above (i.e. up to 79 years) (n= 23). Based on this, the applicant expects similar effects of replacement therapy between AGHD patients aged 65-79 years and AGHD patients aged 79 years and above, as no substantial phenotypic differences between these patients are anticipated.

The applicant has not evaluated the clinical effects of somapacitan in paediatric patients. Marketing authorization of somapacitan is currently applied for adults with growth hormone deficiency.

### Renal and hepatic impairment

The applicant has not evaluated the clinical effects of AGHD study patients with renal and/or hepatic impairment. This is not of concern, since somapacitan dosing is titrated individually in each AGHD patient based on IGF-I standard deviation scores.

## ***Supportive study(ies)***

Two supportive studies (study 4244 and 4043) were conducted. The methodology and main results of these studies are summarized below.

### Study 4244 (Japan)

#### *Design and methods*

Study 4244 was a national, multicentre, randomized, open-label, parallel-group, active-controlled study. The study was designed to compare the safety of once-weekly somapacitan with daily somatropin in previously treated Japanese AGHD patients for 52 weeks (20 weeks dose titration, 32 weeks fixed-dose treatment). Study patients were randomized 3:1 to somapacitan or somatropin. Study patients were stratified according to gender.

Adult AGHD patients up to 79 years of age diagnosed and treated with human growth hormone for at least 6 months with an IGF-I levels between -2 and +2 standard deviation scores were eligible for inclusion. Patients with diabetes mellitus were not allowed to participate as diabetes mellitus is a contraindication for GH treatment in Japan.

Starting doses of respectively somapacitan and somatropin were 1.5 and 1.4 mg/week in patients aged 18-60 years, 2.0 and 2.1 mg/week in female patients on oral oestrogen irrespective of age, and 1.0 and 0.7 mg/week in patients over 60 years of age. Study treatment doses could be adjusted every 4th week based on IGF-I standard deviation scores during the first 20 weeks. Sampling for IGF-I to support the dose titration was performed 3 days after the previous dose adjustment visit.

The primary endpoint was the incidence of adverse events, including injection site reactions, from the first administration of study product to the end of the study period (53 weeks, including 1-week follow-up). The secondary efficacy endpoints were change from baseline (randomization) to end of the treatment period (week 52) in adipose tissue compartments and TSQM-9 scores. Other assessments including IGF-I and IGFBP-3 were also evaluated.

#### *Results*

A total of 62 Japanese patients were exposed in the study (53.2% male and 46.8% female patients). The age range was 20–75 years. Mean IGF-I standard deviation scores at baseline were 0.64 and 0.88 for study patients randomized to respectively somapacitan and somatropin treatment. Overall, no clinically relevant differences between the treatment groups were evident at baseline.

Based on the estimated changes from baseline, the expected growth-induced effect on the abdominal adipose tissues compartments visceral adipose tissue (VAT) (somapacitan: -2.25; somatropin: -0.51), subcutaneous adipose tissue (SAT) (somapacitan: -4.96; somatropin: 6.57), and total adipose tissue (TAT) (somapacitan: -6.67; somatropin: 6.17) obtained prior to the study was maintained for up to 52 weeks of treatment for both somapacitan and somatropin. No statistically significant treatment difference in change from baseline between somapacitan and somatropin were found for any of the abdominal adipose tissue endpoints (estimated treatment differences VAT: -1.74 (95% -18.13; 14.66), SAT -11.53 (95% -35.54; 12.48), TAT -12.85 (-47.31; 21.62)). However, in contrast with study 4054, observed trends in effects with respect to aforementioned endpoints were in favour of weekly somapacitan as compared to daily somatropin treatment.

After 52 weeks of study treatment, the mean IGF-I standard deviation scores were similar for somapacitan and somatropin (somapacitan: 0.61; somatropin: 0.52).

Improvement from baseline to week 52 appeared across all three TSQM-9 domains (convenience (somapacitan: 14.01; somatropin: 7.22), effectiveness (somapacitan: 7.99; somatropin: 3.12), global satisfaction (somapacitan: 10.07; somatropin: 3.18)) for both somapacitan and somatropin. For all three domains, unlike in study 4054, larger improvements tended to be observed with somapacitan as compared to somatropin. These differences were not statistically significant (estimated treatment differences convenience: 6.79 (95% CI -1.04; 14.61), effectiveness 4.87 (95% CI -3.46; 13.20), global satisfaction 6.88 (95% CI -1.08; 14.85)).

### Study 4043

#### *Design and methods*

Study 4043 was a multicentre, multinational, randomized, open-label, parallel-group, active-controlled study. The study was designed to compare the safety of once-weekly somapacitan with daily somatropin in previously treated AGHD patients for 26 weeks. The secondary objective was to evaluate the degree of treatment satisfaction of once-weekly dosing of somapacitan during 26 weeks of treatment in AGHD patients previously treated with daily growth hormone.

The study consisted of an 8-week dose titration period, an 18-week fixed-dose treatment period, and a 1-week washout period. Study patients were randomized 2:1 to somapacitan or somatropin.

Adult AGHD patients up to 79 years of age diagnosed and treated with hormone replacement therapy for at least six months were eligible for inclusion. The key exclusion criteria in study 4043 included active malignant disease or a history of malignancy. Patients with diabetes mellitus enrolled at Japanese sites were not allowed to participate in the studies as diabetes mellitus is a contraindication for growth hormone treatment in Japan.

Starting doses of respectively somapacitan and somatropin were 1.5 and 1.4 mg/week in patients aged 18-60 years, 2.0 and 2.1 mg/week in female patients on oral oestrogen irrespective of age, and 1.0 and 0.7 mg/week in patients over 60 years of age. Study treatment doses could be adjusted based on IGF-I SDS. During the first 8 weeks, study treatment doses could be adjusted every 2nd week which allowed for four opportunities for dose adjustment. Sampling for IGF-I to support the dose titration was performed 3 days after the previous dose adjustment visit. Consistent with the confirmatory study 4054, the weekly dose range of somapacitan was 0.1 mg to 8 mg, and the daily dose range for somatropin was 0.05 mg to 1.1 mg in study 4043. In alignment with the Japanese prescribing information, the maximum daily dose of somatropin was 1.0 mg for the Japanese patients included study 4043. The treatment duration was 26 weeks (8 weeks dose titration and 18 weeks fixed-dose period).

The primary endpoint was incidence of adverse events, including injection site reactions from baseline to the end of the treatment period (26 weeks). The secondary efficacy endpoint was change from baseline (randomization) to end of treatment period (week 26) in TSQM-9 scores. Other assessments including IGF-I and IGFBP-3 were also evaluated.

#### *Results*

A total of 92 patients were exposed in the study (54.3% male and 45.7% female patients). A total of 58.7% of the patients were White and 19.6% were Asian. The age range was 19–77 years. Overall, no clinically

relevant differences between the treatment groups were evident at baseline. Though the mean IGF-I SDS at screening was within reference range, some patients in the somapacitan group had IGF-I SDS below -2 indicating that their pre-study GH may not have been optimal (pre-study mean GH dose: 0.5 mg/day). The study included patients from 6 countries (Denmark, Sweden, Germany, France, UK and Japan) with 58.7% of the patients being White and 19.6% being Asian. Race and ethnicity were not reported for 20 patients in France due to local regulations.

The IGF-I profile was maintained throughout the study in both treatment groups. At baseline, the mean IGF-I standard deviation score of somapacitan was 0.28 and that of somatropin was 0.91. The mean IGF-I SDS after 26 weeks treatment was similar for somapacitan and somatropin (somapacitan: 0.22; somatropin: 0.35).

Improvement from baseline to week 26 appeared across all three TSQM-9 domains (convenience (somapacitan: 15.3; somatropin: 3.0), effectiveness (somapacitan: 9.7; somatropin: 3.8), global satisfaction (somapacitan: 5.4; somatropin: -1.2)) for both somapacitan and somatropin. For all three domains, greater improvement tended to be observed with somapacitan as compared to somatropin. Except for a higher convenience for somapacitan (estimated treatment differences: convenience: 8.22 (95% CI 1.51; 14.93)) these differences were not statistically significant (estimated treatment differences effectiveness 3.30 (95% CI -4.14; 10.75), global satisfaction 3.07 (95% CI -4.70; 10.83)). In line with this, in study 4054, only the convenience subscore tended to be higher for somapacitan as compared to somatropin treatment (see above).

### **2.5.3. Discussion on clinical efficacy**

#### ***Design and conduct of clinical studies***

Clinical efficacy of somapacitan was evaluated in three clinical studies. These studies concerned a confirmatory efficacy and safety study in growth hormone treatment naïve AGHD patients (study 4054), and two supportive studies in AGHD patients who were previously treated with growth hormone (studies 4244 and 4043).

**Study design.** Study 4054 consisted of a main treatment phase of 35 weeks, followed by an extension treatment phase of 53 weeks. In the main treatment phase of pivotal study 4054, study patients were randomized to receive double-blind somapacitan or placebo treatment, or open-label somatropin treatment. Somatropin (e.g. EU/1/06/332, EU/1/00/164) is currently indicated for growth hormone supplementation in AGHD patients and is, therefore, an acceptable active comparator for somapacitan treatment. The chosen design is appropriate to compare the clinical effects of somapacitan and placebo treatment. There is, however, an increased risk of bias of study results (e.g. information bias) with respect to open-label somatropin treatment as compared to double-blind somapacitan and placebo treatment. Due to this increased risk of bias, treatment comparisons between somapacitan and somatropin treatment should be interpreted with caution. However, in the present study, the body composition (including the truncal fat measures) were acquired with dual-energy x-ray absorptiometry which seems to be a relatively objective instrument of measure.

It is acknowledged that objective evaluations enhance the interpretability of study results in study 4054. Though there was no evidence of intentional data manipulation, study results of study 4054 should still be interpreted with caution since the findings of the GCP inspection may have affected the quality and integrity

of the study data as detailed above (under GCP inspection). However, no data manipulation was reported and findings were not considered to have a significant impact on final reliability of the reported data and clinical study data may still be interpreted.

The total study treatment period in study 4054 was 87 weeks (main treatment phase plus extension treatment phase). Such a total study treatment period is limited considering that AGHD patients need life-long growth hormone supplementation. Hence, long-term effectiveness and safety of somapacitan treatment – i.e. over multiple years – is yet unknown. This information will be further collected post-approval.

Study patients who received somapacitan treatment in the extension period of study 4054 had been treated with somapacitan, placebo, or somatropin in the earlier main treatment period. The switch from main to extension phase of the study was performed with a week interval without treatment. No washout effects of previous study treatment are expected in the extension period across different study treatments as study treatment will be titrated up to the optimal dose during the first 8 weeks of the extension period. Any remaining washout effects of the main treatment period will have disappeared after this treatment period. Hence, a washout period of one week at the end of the main treatment period is acceptable.

Supportive studies 4244 and 4043 were randomized, open-label active-controlled studies in which the clinical effects of somapacitan and somatropin were compared in AGHD patients who had received prior growth hormone supplementation. Due to the open-label design of these studies, the results of these studies should be interpreted with caution because of an increased risk of bias. Apart from this, due to the lack of a placebo arm in both studies, there may be a lack of assay sensitivity in both clinical studies.

Study treatment was administered subcutaneously in studies 4054, 4244, and 4043. Somapacitan and placebo were administered once per week, whereas somatropin was administered daily. It is appropriate that the starting doses of study treatment in clinical studies 4054, 4244, and 4043 took into account age, gender, and oestrogen status, since it is known that the need of growth hormone supplementation varies for these factors (Johannsson et al. 1997, Hoffman et al. 2004).

It is noted that starting doses of somapacitan/placebo and somatropin expressed in doses per week were comparable if aforementioned factors are taken into account (i.e. adults up to 60 years of age: 1.5 vs. 1.4 mg/week, patients > 60 years of age: 1.0 vs. 0.7 mg/week, women on oral oestrogen: 2.0 vs. 2.1 mg/week). However, upon subsequent dose titration within a particular AGHD subgroup (e.g. men), dosing of weekly somapacitan should be about 1.14 times higher than the total dose of somatropin per week to achieve similar IGF-I SDS levels. This is due to the lower receptor binding affinity and the pharmacokinetics and pharmacodynamics properties of somapacitan as compared to somatropin.

The starting doses and dose titration steps in conducted clinical studies appear to be in line with international recommendations for growth hormone replacement therapy in AGHD patients (Cook et al. 2009).

**Study population.** It is appropriate to conduct a pivotal study in treatment-naïve AGHD patients. Overall, applied diagnostic tests for diagnosing AGHD in study 4054 based on insulin tolerance test (Biller et al. 2002), growth hormone-releasing hormone and arginine test according to BMI (Aimaratti et al. 1998, Ho and Participants 2007, Uean et al. 2009), and three or more pituitary hormone deficiencies and IGF-I SDS (Hartman et al. 2002) are appropriate for diagnosing AGHD (Reed et al. 2013). Included AGHD study patients in pivotal study 4054 appear to be representative for AGHD patients in clinical practice considering applied eligibility criteria.

It is noted that the inclusion criteria in study 4054 for non-Japanese and Japanese AGHD patients are different. In Japan, inclusion criteria in study 4054 were different compared to the rest of the world.

Differences include that in- and exclusion criteria in Japan unlike the rest of the world were dependent on the type of onset of AGHD (childhood or adulthood), and the presence/absence of diabetes mellitus. Apart from this, the diagnostic criteria for insulin tolerance tests, glucagon tests, and pituitary hormone deficiency were different for Japanese and non-Japanese AGHD study patients in study 4054.

Also, in study 4043, selection criteria for study participation were slightly different for Japanese and non-Japanese study patients, since patients with diabetes mellitus were excluded in Japan.

In study 4244, which was only conducted in Japan, there were uniform selection criteria for study participation (although these did not match the inclusion of study 4054).

**Endpoints.** The primary endpoint of study 4054 was the change at week 34 compared to baseline with respect to the truncal fat percentage. This primary endpoint was agreed by the CHMP in a previous scientific advice. Fat-related endpoints were also accepted for two other growth hormone depot preparations (e.g. Nutropin depot and somatropin Biopartners).

Secondary endpoints included endpoints with respect to body composition determined by DXA scanning such as changes compared to baseline in visceral adipose tissue, other fat masses, truncal lean body mass, appendicular skeletal muscle mass, lean body mass, total bone mineral content, and total bone mineral density. Adipose tissue compartments were also evaluated in study 4244, but not in study 4043.

IGF-I SDS, IGFBP-3 SDS, and TSQM-9 were evaluated in all studies.

Body weight, waist circumference, blood lipids, IL-6, hsCRP, TRIM-AGHD, and SF-36 were only evaluated in study 4054.

The aforementioned endpoints are considered appropriate for the evaluation of the clinical effects of growth hormone in AGHD patients.

#### *Statistical analysis*

It is well-known that the clinical effects of growth hormone treatment may be different in different geographical regions, gender, and diabetic status (Reed et al. 2013). Because of this, it is supported that randomization was stratified according to these factors and that these factors were also taken into account as factors in an analysis of covariance.

### ***Efficacy data and additional analyses***

The **patient disposition** in the main and extension treatment phases of study 4054 was clarified by the applicant. Included study patients appear to be representative of AGHD patients in clinical practice. Premature treatment of study discontinuation of AGHD study patients treated with somapacitan did not tend to occur more frequently than among AGHD study patients treated with somatropin or placebo.

AGHD patients up to 79 years of age were included in clinical studies. No clinical studies have been conducted in AGHD patients aged 79 years and above. Observed trends with respect to the primary endpoint change in truncal fat percentage at week 34 compared to baseline for somapacitan and placebo treatment were similar for AGHD patients aged 65 years and above as compared to those up to 64 years. Similar effects of somapacitan are expected in AGHD patients aged 65-79 years and AGHD patients aged 79 years and above, as no substantial phenotypic differences between these patients are anticipated.

Overall, the **baseline characteristics** of the included study patients were comparable. The body weight at baseline of placebo-treated study patients tended to be lower compared to study patients treated with somapacitan and somatropin (mean 69.8 vs 76.0-76.2 kg; median 69 vs 72.9-74.1). In line with this, the BMI (26.1 vs. 27.7-27.9 kg/m<sup>2</sup>) and mean waist circumference (88.5 vs 93.9-94.0 cm) also tended to be lower for placebo-treated study patients as compared to somapacitan- and somatropin-treated study patients (93.9-94.0 cm). Later, it was shown that observed differences with respect to the primary endpoint would remain similar if BMI was used as a covariate in an explorative post-hoc analysis.

Most study patients were included in the United States (26.3%), Japan (15.3%), and Australia (10%). Over 20% of included study patients were included in different countries within the European Union (e.g. Germany, Romania, Poland, United Kingdom). This supports external generalization of the study results of study 4054 to AGHD patients within the European Union.

**Treatment exposure** in patients treated with somapacitan in the main treatment period tended to be somewhat higher compared to patients treated with placebo of somatropin (mean treatment dose 2.52 vs. 2.17-2.31 mg per week). These differences are small. However, in the extension treatment period, mean study treatment doses of somatropin-treated patients tended to be somewhat lower (1.89 mg/week) compared to somapacitan-treated patients in this treatment period (2.33-2.61 mg/week). The affinity of somapacitan for the growth hormone receptor is 3-4 times less than that of somatropin due to the attached serum albumin. This implies that a higher weekly concentration of somapacitan than somatropin is needed to achieve a similar effect in terms of IGF-I production.

The mean adherence in the extension treatment phase tended to be higher for study patients treated with somapacitan in the extension treatment phase compared to those treated with somatropin in respective study phase (somapacitan/somapacitan (i.e. treated with somapacitan in both the main and extension treatment period): 84.6 %; somatropin/somatropin (i.e. treated with somatropin in both the main and extension treatment period): 77.6%) (ecap data).

#### *Primary endpoint – Change from baseline in truncal fat percentage*

Observed decrease in truncal fat percentage at week 34 compared to baseline was higher for somapacitan (-1.17) compared to placebo treatment (+0.49) (estimated difference -1.53 (95% CI -2.68; -0.38),  $p = 0.009$ ). These differences appear to be limited. Moreover, changes in truncal fat percentage at week 34 compared to baseline were smaller for somapacitan (-1.17) as compared to somatropin treatment (-2.39) (estimated difference 1.17 (95% CI 0.23; 2.11),  $p < 0.05$ ). Similar results were obtained in sensitivity analyses in which study patients without week 34 for the primary endpoint were excluded, and upon exclusion of these study patients and study patients with fewer than 3 dose adjustments. Similar trends were observed all over the world. At D120, the clinical relevance of aforementioned clinical effects of somapacitan compared to those of placebo and somatropin respectively was considered unclear. Therefore, a major objection was formulated about this issue.

The applicant identified several factors that could contribute to underestimating the clinical effects of somapacitan on body composition relative to placebo and/or daily growth hormone replacement (somatropin). These include too low IGF-I SDS levels, i.e. under -0.5 SDS in this study. Somapacitan was underdosed in 22% of study patients in the main treatment phase of study 4054. This proportion tended to be higher in particular subgroups in which the study patients are less sensitive to the effects of growth hormone (e.g. women on oral oestrogen treatment (42%), patients with childhood-onset AGHD (34%) (main treatment phase)). The applicant explained that study patients in these subgroups may have been unequally

randomized among the different treatment groups. It is agreed that the aforementioned factors might explain the limited efficacy of somapacitan in study 4054.

#### *Secondary endpoint – change in body composition assessments*

Changes in total body fat mass (g) at week 34 compared to baseline for somapacitan, somatropin, and placebo treatment were -85.47, -855.71, and +305.47. Hence, in line with the primary endpoint, observed differences compared to baseline were smaller for somapacitan as compared to somatropin. Similar results were obtained with respect to most other body composition endpoints.

As an exception, changes in total lean body mass (g) at week 34 compared to baseline were similar for somapacitan (+1395.88), and somatropin (+1359.33) (estimated treatment difference 49 (95% CI -513; 610),  $p = 0.87$ ), though differences tended to be larger for somapacitan as compared to placebo and placebo (+334.43) (estimated treatment difference 1144 (95% CI 459; 1829),  $p = 0.001$ )).

#### *Secondary endpoint – quality of life assessments*

The quality of life assessments (SF-36, TRIM-AGHD, and TSQM-9) did not show any clinically relevant difference between treatment arms (placebo, somapacitan and daily somatropin).

In the extension treatment period body composition endpoints were compared between a somapacitan/somapacitan arm ( $n = 120$ ) and a smaller somatropin/ somatropin arm ( $n = 52$ ). Observed treatment effects with respect to endpoints related to fat mass in the main treatment period were maintained throughout the extension treatment period. Reductions in truncal fat percentage (-2.63 vs. -1.63%), body fat mass (-923.01 vs. -118.07 g), and truncal body fat mass (-685.56 vs. -196.18 g) tended to be larger for patients treated with somatropin in both parts of study 4054. For the quality of life assessments (SF-36, TRIM-AGHD, and TSQM-9) no consistent trends were observed between the somapacitan/somapacitan and somatropin/somatropin treatment regimens.

Due to the small somatropin/somatropin group ( $n = 52$ ), the results should be interpreted with caution.

Though this is acknowledged, changes with respect to lean body mass and bone mineral content endpoints tended to be larger for study patients treated with somapacitan/somapacitan ( $n = 120$ ) as compared to those treated with somatropin/somatropin ( $n = 52$ ) during both the main and extension treatment period.

In study patients treated with somatropin in the main treatment phase who were re-randomized to receive somapacitan in the extension treatment phase ( $N=51$ ), decreases in truncal fat percentage compared to baseline tended to be larger during somatropin treatment (-2.28%) as compared to somapacitan treatment in the extension treatment period (-0.96%).

Changes with respect to visceral adipose tissue correlated with IGF-I changes from baseline. This was observed both for somapacitan and somatropin. However, the clinical effects with respect to other adipose tissue parameters in the main phase of study 4054 for somapacitan were less pronounced than those of somatropin, although the mean IGF-I SDS levels were similar for somapacitan and somatropin. Therefore, there is a loss of chance to achieve significant clinical outcomes for patients treated with somapacitan compared to patients treated with somatropin.

Further, a discrepancy was observed in trends in the overall study population with respect to endpoints pertaining to adipose tissue masses and endpoints pertaining to lean body masses for somapacitan and somatropin treatment. Overall, the clinical effects of somapacitan with respect to adipose tissue masses tended to be smaller compared to those of somatropin, and this was considered a major concern at D150, whereas the clinical effects of both active substances were comparable with respect to lean body masses. An

explanation and additional analyses were requested because of this finding. The applicant provided several explanations for the limited effects of somapacitan on adipose tissue masses observed in study 4054.

First, some AGHD subgroups (e.g. women, women on oral oestrogen, childhood-onset AGHD) are less sensitive to the effects of somapacitan. For patients in the transition age, higher doses are also needed. Second, a considerable proportion of study patients (22%) in the somapacitan group did not reach the predefined IGF-I SDS target in the main study phase. Another factor that might explain the less pronounced clinical effects of somapacitan with respect to fat parameters compared to somatropin, is a lower affinity of somapacitan to adipose tissue. This affinity may be lower for somapacitan as compared to somatropin due to the albumin binding moiety in somapacitan<sup>28</sup>. Differential effects of somapacitan on different adipose tissues could also partly be explained by different expression of the IGF-I receptor and growth hormone receptor. This might explain the differential effects of growth hormone in various tissues.

A potential explanation for the difference of clinical effects of the somapacitan and somatropin on adipose tissue parameters is that various adipose tissue depots may manifest differing exposure-response and absolute exposures of somapacitan or somatropin such that the relative efficacy of the two products differs. Hence, the growth hormone exposure-response in adipose tissues is depot-specific with a lower growth hormone exposure needed to produce clinical effects in visceral adipose tissue as compared to other adipose tissue depots. Moreover, different absolute exposure of somapacitan versus somatropin may be present in different tissues, including adipose tissues. This might also explain that some subsets of patients who need higher doses of somapacitan such as women on oral oestrogen therapy and childhood-onset AGHD patients have a lower response on adipose tissue parameters.

*Post-hoc* analyses in which the clinical effects of weekly somapacitan were compared with those of daily somatropin treatment in different AGHD subgroups indicated that the effects on both lean body masses and adipose masses were comparable for those patients who achieved an IGF-I SDS level between 0 and +2. The results of the *post-hoc* analyses should be interpreted with caution due to inherent statistical/methodological limitations of the nature of a *post-hoc* analysis. Despite this, the dissociation between the effects of somapacitan and somatropin on lean body and adipose masses as observed in study 4054 appears to be driven by AGHD study patients with a less optimal titration (i.e. patients with IGF-I SDS levels below 0) within a fixed 8-week dose titration period. This observation is in line with the assumption that the exposure-response relationship differs for various adipose tissue depots and lean body mass compartments.

Further, the *post-hoc* analyses and also exposure-response evaluations show that IGF-I SDS levels within the IGF-I target range between 0 and +2 can be achieved in the vast majority of AGHD patients upon appropriate somapacitan dose titration. According to conducted *post-hoc* analyses, the duration of the somapacitan dose titration period that is needed to achieve IGF-I levels within the IGF-I target range varies between AGHD patients. This period may be longer than 8 weeks in some patients. Considering the adherence to somapacitan is in general appropriate, but also that the target IGF-I SDS range was not achieved in about 20% of study patients treated with somapacitan, there is more room for improvement of the clinical efficacy by optimization of the dosing regimen of somapacitan than by improvement of its treatment adherence.

Hence, clinical efficacy of somapacitan is expected to increase upon application of a more flexible, optimized somapacitan dosing regimen in individual AGHD patients, which allows somapacitan dose titration beyond 8 weeks until the target IGF-I SDS range of 0 up to +2 or maximal recommended somapacitan dosing (8

---

<sup>28</sup> Kopchick JJ, Berryman DE, Puri V, Lee KY, Jorgensen JOL. The effects of growth hormone on adipose tissue: old observations, new mechanisms. *Nat Rev Endocrinol.* 2020;16(3):135-46.

mg/week) is achieved. This as well as the appropriateness of recommended posology of somapacitan will be evaluated further in different subgroups of AGHD patients in a post-approval safety study (PASS).

### **Additional expert consultation**

Considering major uncertainties with respect to the favourable effects and safety, an *ad hoc* expert group (AHEG) was consulted on 29<sup>th</sup> of October 2020. Efficacy questions and answers are listed below, while safety question is below under Discussion on clinical safety.

#### **Efficacy**

- 1. Please discuss if the efficacy has been sufficiently demonstrated by the currently available data and if new data are needed to substantiate an optimized dosing regimen. Please discuss if it would be sufficient to measure (change in) IGF-1 in patients receiving this optimized dosing regimen - as a surrogate marker for the expected clinical benefit? If so, what would be the clinically relevant target levels of IGF-1?**

There was clear evidence of efficacy in AGHD patients with regard to reduction of percentage of truncal fat; however, body fat mass in grams did not change significantly at week 34 comparing weekly vs placebo. Truncal body fat mass in grams, showed a trend to decrease, not reaching significance ( $p=0.08$ ); additionally there were highly significant reductions of visceral adipose tissue ( $p=0.002$ ), android fat mass ( $p=0.03$ ), and increase in truncal lean body mass (LBM) ( $p=0.04$ ), appendicular skeletal muscle mass ( $p=0.0001$ ), and total LBM ( $p=0.001$ ). At week 87 (extension phase), no significant differences were observed between daily and weekly GH on estimated LBM and truncal fat %, although there was a trend for more improvement after daily GH.

The AHEG experts are of the opinion that dosing regimen in terms of titration duration and administered dose was not optimized for all AGHD patients' subgroups (e.g. women on oral oestrogens). The experts commented that in these subgroups who require higher doses and longer titration time to define the optimal dose, additional data are generated in the post-authorization settings to confirm expectation of greater effects with higher dosing, currently supported by presented modelling and simulation data, and with longer titration period.

Measuring only change in IGF-I concentration, as a pharmacodynamic marker, in AGHD patients receiving this optimized somapacitan once weekly dosing regimen is not considered to be sufficient evidence of expected clinical benefit. In line with the existing AGHD treatment guidelines<sup>29,30</sup>, this should be accompanied with collecting data on changes in body composition and also metabolic improvements, with clinically relevant target levels of IGF-I defined as 0 to +2 SDS, as well as some measure of patients preference using adequate PROM.

- 2. How does the AHEG judge the clinical relevance of the observed effects with somapacitan in terms of change in body composition? Could greater effects be expected with higher doses as argued by the Applicant and, if yes, to what extent, based on the simulated treatment regimen; using continued titration towards an IGF-1 target of 0 to +2 SDS with a maximum dose of 8 mg, as provided by the Applicant?**

The AHEG experts consider that observed effects with once weekly somapacitan in terms of change in body composition vs. placebo are clinically relevant and convincing, and in the same direction as with daily dosed

---

<sup>29</sup> Ho KKY. 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 Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, J. Eur J Endocrinol. 2007;157(6):695–700.

<sup>30</sup> Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R, et al. Hormonal replacement in hypopituitarism in adults: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(11):3888–921.

somatropin in terms of improvements in lean body mass parameters, although some parameters seemed to improve more with daily than with weekly GH. It was observed that some patients were not treated optimally and would need longer uptitration period to reach optimal and higher dose, with maximum acceptable dose of 8 mg, and in those AGHD patients greater effects could be expected upon treatment optimization towards an IGF-I target of 0 to +2 SDS. Initial treatment dose and titration duration should be carefully individualized considering age, gender, previous GH replacement therapy, childhood or adult AGHD onset and other AGHD patient characteristics. Women using oral oestrogen medications are recommended to start treatment with higher doses and would likely need longer period to define optimal dose in clinical practice. Alternatively, a change from oral to transdermal or vaginal estrogens would increase IGF-I values to the expected levels, as stated in the AGHD guidelines.

**3. What is the AHEGs' view on the value for patients of having a weekly injectable somatropin available, also taking the strength and the relevance of the reported health-related quality of life outcomes into account?**

Perceived convenience and the QoL impact on a patient might be different for individual patients. Some may find daily dosing better e.g. fixed daily timings for drug administration easier to remember. While other patients might prefer a weekly dosing medication e.g. less frequent self-injecting administration experienced as less burdensome, for convenience reasons (e.g. with regards to travelling, being less reminded of their illness). Therefore availability of once weekly injectable somatropin is considered to be of value for the majority of AGHD patients.

The generic SF-36 questionnaire showed a trend to improve at week 34 vs. baseline for somapacitan vs placebo, with some significant improvement in 2 subscales in favor of somapacitan. The disease specific questionnaire TRIM-AGHD showed no difference between daily and weekly GH. However, the change from baseline to week 34 was greater with daily than with weekly GH, but the changes observed were small, below what was considered the minimal important difference of 10 points.

Overall satisfaction at week 34 was greater for somapacitan than placebo ( $p=0.03$ ), without differences for effectiveness and convenience scores. Comparing both drugs, effectiveness was lower for weekly than for daily GH, without differences for convenience or global satisfaction.

However, by company's presented data it is not evidenced that once weekly injected somapacitan showed significant value for AGHD patients with regard to improvement of adherence to treatment or convenience vs once daily somatropin, although there was a trend in favor of weekly vs daily GH. At week 87 (extension phase) daily GH showed a minimally greater effect on PROM which did not reach the minimal important difference of 10 points. As far as the convenience subscore of TSQM-9 at week 87 it was significantly better for weekly GH ( $p=0.01$ ), without differences for effectiveness or global satisfaction.

It is suggested by the AHEG that, in order to confirm a compliance claim, treatment compliance of once weekly injected somapacitan versus once daily injected somatropin is clarified in post-marketing settings in the context of AGHD patient characteristics such as age and other, including collected data on quality of life.

**4. Some AGHD patients will not respond to growth hormone treatment. With respect to this, the CHMP has the following questions:**

- a. At what time after treatment initiation can it be concluded that AGHD patients do not respond to (weekly) growth hormone treatment?**

In the view of AHEG, once AGHD patients are adequately titrated to reach the optimal dose, response can be observed in the following subsequent 6 months of replacement treatment with growth hormone administered either as daily somatotropin or as once weekly somapacitan. If clinical response is not observed within this period, only very rare individual AGHD patients would respond with measurable improvement of clinical parameters to a longer period of once weekly somapacitan treatment, in total up to 1 year after treatment start.

**b. Which clinical parameters should be taken into account to decide that an AGHD patient's response to growth hormone treatment is insufficient?**

According to the AHEG experts, sufficiency of clinical response to growth hormone and somapacitan treatment in AGHD patients should be decided based on measurements of IGF-I concentrations as a pharmacodynamic marker of somapacitan effects in AGHD, as well as improvement in clinical parameters of body composition (e.g. decreased body fat mass, increased lean body mass, abdominal circumference measurements) and improvement of other metabolic parameters (such as fasting blood glucose, blood pressure, lipids).

Certain AGHD patients treated with growth hormone could present in clinical practice with reporting only benefit in parameters such as self-perception of body shape or improvement in quality of life symptoms, therefore these should be considered in addition.

**Safety**

**5. What is the view of the AHEG on the overall safety of somapacitan, including the long-term safety, in the target population for which somapacitan is intended to be used, taking into consideration peak and trough IGF-1 levels and the unphysiological IGF-1 profiles obtained upon weekly administration of somapacitan compared with standard daily administration of somatotropin. If additional safety monitoring, besides standard routine pharmacovigilance is considered necessary, which would be the key design characteristics of a post authorization safety study to further investigate the long-term safety of the product?**

The AHEG experts shared the opinion that both somapacitan administered once weekly and daily administered somatotropin obtain unphysiological GH concentration profiles, considering their pharmacokinetic differences compared to peak and trough physiological concentration of endogenously released growth hormone. Although the experts do not expect additional safety concerns including long-term safety with once weekly somapacitan than with daily somatotropin. they are of the view that somapacitan should not be initiated or continued in AGHD patients with any tumors to avoid possibility of any growth of tumor cells, or in patients with any other severe, uncontrolled underlying disease, as stated in the guidelines.

The AHEG experts do find it important that physicians who initiate and monitor growth hormone treatment of AGHD patients need to be trained on PK differences between daily somatotropin and once weekly somapacitan treatment, including the appropriate time to collect blood samples following once weekly somapacitan subcutaneous injection (Day 3 or Day 4 depending on the evidence of pharmacodynamics) to assure appropriate measurement of its pharmacodynamic effects on the IGF-I concentration. The company must provide clear information on this and ensure training of potential prescribers.

As far as additional safety monitoring for somapacitan, it is recommended that the key design characteristics of such post-authorization study should follow AGHD treatment guidelines regarding clinical parameters to evaluate GH treatment effects such as normalization of circulating IGF-I concentration (target of 0 to +2 SDS) and other body composition improvements, as well as metabolic changes. The AHEG experts commented that in these subgroups who require higher doses and longer titration time to define the optimal dose, additional

data are generated in the post-authorization study (see above Question 1) and also, in order to confirm a claim regarding improved treatment adherence, this should be followed and evaluated with validated questionnaire in AGHD patients (see above Question 3).

### ***Assessment of paediatric data on clinical efficacy***

No studies in children were submitted.

#### **2.5.4. Conclusions on the clinical efficacy**

Somapacitan exerts clinical effects on body composition parameters like human growth hormone. However, in conducted pivotal clinical study, the clinical efficacy of weekly somapacitan was less pronounced compared to daily somatropin treatment in the secondary comparison, especially concerning adipose tissue-related body composition parameters. Certain lower effects of somapacitan may be explained - at least in part - by the fact that the IGF-I SDS target range was not achieved in a considerable proportion of AGHD study patients. This applies especially to particular AGHD subgroups who are less sensitive to growth hormone such as female AGHD patients on oral oestrogen. This was acknowledged by the AHEG who considered additional clinical data are required in this subgroup of patients.

Moreover, in the secondary comparison a dissociation between the clinical effects of somapacitan and somatropin on adipose tissue parameters (less pronounced for somapacitan) and lean body mass parameters (comparable for both treatments) was observed. However, *post-hoc* analyses in which the clinical effects of weekly somapacitan were compared with those of daily somatropin treatment in different AGHD subgroups indicated that the clinical effects of these treatments on both lean body masses and adipose masses were comparable for those patients who achieved a IGF-I SDS level between 0 and +2 within or beyond 8 weeks of dose titration. Hence, clinical efficacy of somapacitan is expected to increase upon application of a more flexible, optimized somapacitan dosing regimen in individual AGHD patients, which allows somapacitan dose titration beyond 8 weeks until the target IGF-I SDS range of 0 up to +2 or maximal recommended somapacitan dosing (8 mg/week) is achieved. It is at present unclear whether these results can also be achieved and maintained at an acceptable safety level upon application of such a somapacitan dosing regimen in (different subgroups of) AGHD patients in clinical practice. For this reason, short- and long-term clinical effects of recommended somapacitan dosing regimen in actual AGHD patients, also in those who are less sensitive to the clinical effects of growth hormone such as female AGHD patients on oral oestrogen, will be evaluated further in a PASS.

### **2.6. Clinical safety**

#### ***Patient exposure***

The phase 3 studies (4054, 4043 and 4244) included 333 AGHD patients exposed to once-weekly somapacitan (mean dose: 2.38 mg/week), 166 patients to daily somatropin (mean dose: 0.29 mg/day) and 61 patients to placebo. Total exposure was 363.7 person-years of exposure (PYE) for somapacitan, 152.6 PYE for somatropin, and 38.2 PYE for placebo.

Of the 333 AGHD patients exposed to somapacitan, 319 (95.8%) patients were exposed for more than 6 months, 253 (76.0%) patients for more than 12 months, and 109 (32.7%) patients for more than 18 months. In addition, 143 healthy subjects, 29 subjects with renal impairment, 18 subjects with hepatic impairment, and 34 AGHD patients were exposed to somapacitan in the clinical pharmacology studies. After IGF-I SDS dose titration the mean somapacitan dose was 2.38 mg/week (0.036 mg/kg/week).

A total of 166 AGHD patients were exposed to daily somatropin treatment as an active comparator in the completed clinical studies in AGHD (up to 86 weeks of exposure). The mean somatropin dose was 0.29 mg/day (0.005 mg/kg/day).

A total of 61 AGHD patients were exposed to placebo.

**Table 19 Exposure AGHD (pooled global data)**

|                            | Placebo<br>once-weekly | Somatropin<br>daily | Somapacitan<br>once-weekly |
|----------------------------|------------------------|---------------------|----------------------------|
| Number of exposed subjects | 61                     | 166                 | 333                        |
| Days of exposure*          |                        |                     |                            |
| Mean (SD)                  | 228 (36.1)             | 336 (184.3)         | 399 (165.2)                |
| Median                     | 238                    | 238                 | 364                        |
| Min; Max                   | 28; 252                | 1; 619              | 7; 623                     |
| Treatment dose** (mg)      |                        |                     |                            |
| Mean (SD)                  | 2.20 (0.74)            | 0.29 (0.19)         | 2.38 (1.46)                |
| Median                     | 2.00                   | 0.25                | 2.00                       |
| Min; Max                   | 1.00; 3.50             | 0.05; 1.10          | 0.10; 8.00                 |
| Treatment dose** (mg/kg)   |                        |                     |                            |
| Mean (SD)                  | 0.034 (0.016)          | 0.005 (0.004)       | 0.036 (0.027)              |
| Median                     | 0.032                  | 0.003               | 0.027                      |
| Min; Max                   | 0.014; 0.080           | 0.001; 0.044        | 0.001; 0.171               |
| Total Exposure*** (years)  | 38.2                   | 152.6               | 363.7                      |

SD: Standard deviation;

\* Exposure days are calculated as the time from the first date on randomized treatment to last date on randomized treatment for somatropin and plus six days for somapacitan.

\*\* Stable dose at last titration visit. For subjects in 4054 receiving the same treatment in the main and extension period, only first titration period is included.

\*\*\* Including titration period.

Seventeen percent of patients exposed to somapacitan (58/333) received the maximum dose range (between 4 and 8 mg per week). By contrast, only 7% of patients exposed (12/166) to somatropin received the maximum patients for the last dose range) (between 4.2 and 7.7 mg per week).

## Adverse events

A total of 382 (84.1%) patients reported 2344 adverse events (AEs). A similar percentage of patients reported AEs across treatment groups (somapacitan: 82.6%; somatropin: 78.3%; placebo: 75.4%). The majority of the AEs (96.6 %) were non-serious.

The most commonly reported AEs (not necessarily treatment-related AE) in the somapacitan group were nasopharyngitis (25.2%), headache (12.9%) and arthralgia (6.9%). Further, upper respiratory tract infection, fatigue and arthralgia were frequently reported in the various studies.

The most commonly reported treatment-emergent AEs (TEAEs) were headache (3.0%), arthralgia (2.7%), fatigue (2.7%), and peripheral oedema (2.1%).

During the main treatment phase of study 4054 "back pain" tended to be reported more frequently during somapacitan treatment (9.2%) than during placebo treatment (3.3%) (rate difference 8.7 (95% CI -2.0 up to 19.5%)). "Back pain" is an adverse drug reaction for some somatropin medicinal products (e.g. NutropinAq (EMA/H/C/000315)). It is unknown whether this also applies to somapacitan, but these reactions are more likely related to arthralgia.

Possibly or probably study treatment-related AEs reported in the whole safety analysis set (all studies) are presented in Table 20. No apparent treatment-related trend in frequency, severity, type, or time of onset of AEs was observed. The safety profile of once-weekly somapacitan was similar to that of daily somatropin treatment.

**Table 20 Possibly or probably related adverse events by system organ class and preferred term (reported by > 2% of the patients) - safety analysis set**

|   | placebo   |    | somatropin |     | somapacitan |     |
|---|-----------|----|------------|-----|-------------|-----|
|   | N (%)     | E  | N (%)      | E   | N (%)       | E   |
| Subjects Exposed  | 61        |    | 166        |     | 333         |     |
| All possibly or probably related adverse events             | 12 (19.7) | 19 | 48 (28.9)  | 110 | 85 (25.5)   | 247 |
| <b>General disorders and administration site conditions</b> | 4 (6.6)   | 7  | 24 (14.9)  | 31  | 31 (9.3)    | 52  |
| Fatigue   | 1 (1.6)   | 1  | 7 (4.2)    | 7   | 9 (2.7)     | 11  |
| Oedema peripheral   | 0         | 0  | 6 (3.6)    | 9   | 7 (2.1)     | 17  |
| Injection site bruising                                     | 2 (3.3)   | 3  | 4 (2.4)    | 4   | 1 (0.3)     | 1   |
| <b>Musculoskeletal and connective tissue disorders</b>      | 1 (1.6)   | 1  | 12 (7.2)   | 20  | 20 (6.0)    | 26  |
| Arthralgia  | 1 (1.6)   | 1  | 6 (3.6)    | 6   | 9 (2.7)     | 11  |
| Myalgia   | 0         |    | 3 (1.8)    | 3   | 0           |     |
| <b>Nervous system disorders</b>                             | 4 (6.6)   | 4  | 8 (4.8)    | 16  | 21 (6.3)    | 66  |

|   |         |   |         |    |          |    |
|---|---------|---|---------|----|----------|----|
| Headache                                      | 2 (3.3) | 2 | 0       |    | 5 (3.0)  | 10 |
| <b>Investigations</b>                         | 3 (4.9) | 3 | 7 (4.2) | 13 | 15 (4.5) | 30 |
|   |         |   |         |    |          |    |
| Blood creatine phosphokinase increased        | 0       |   | 0       |    | 4 (1.2)  | 4  |
| <b>Skin and subcutaneous tissue disorders</b> | 3 (4.9) | 4 | 3 (1.8) | 4  | 8 (2.4)  | 12 |
| <b>Gastro-intestinal disorders</b>            | 0       |   | 3 (1.8) | 3  | 7 (2.1)  | 30 |
| <b>Metabolism and nutrition disorders</b>     | 0       |   | 3 (1.8) | 3  | 7 (2.1)  | 8. |

E: Number of adverse events reported

Upon a later review of the safety data on potential adverse drug reactions of somapacitan, the applicant proposed to add several new adverse drug reactions for somapacitan with respect to several system organ classes:

- Endocrine disorders: hypothyroidism (1.8%, common)
- Musculo-skeletal and connective tissue disorders: myalgia (2.1%, common), muscle stiffness (1.2%, common) and joint stiffness (0.6%, uncommon)
- Skin and subcutaneous tissue disorders: rash (1.8%, common), urticaria (1.5%, common) and pruritus (0.9%, uncommon).

### ***Serious adverse event/deaths/other significant events***

#### Deaths

Five (5, 1.3%) patients died during study 4054. All 5 deaths were assessed by the investigator as unlikely to be related to study products (somapacitan: 2 patients; somatropin: 2 patients; placebo: 1 patient). Details on the 5 deaths are provided in Table 21. According to the investigator and applicant, these deaths were unlikely related to GH.

There was no pattern in the types of AEs in the patients who died or time to event.

No deaths were reported in studies 4043 and 4244. No deaths were reported in the clinical pharmacology studies (studies 3915, 3947, 4237, 4297 and 4298).

**Table 21 Deaths by study (AGHD)**

| Phase/<br>Study          | BMI  | Preferred term               | AE onset after<br>exposure | Causality<br>(Main/<br>extension) |
|--------------------------|------|------------------------------|----------------------------|-----------------------------------|
| Phase 3                  |      |                              |                            |                                   |
| Study 4054 AGHD patients |      |                              |                            |                                   |
| somapacitan <sup>a</sup> | 32.4 | Ventricular<br>fibrillation, | Week 51 (Day<br>363)       | Unlikely/                         |

|                          |      |   |                      |                       |
|--------------------------|------|---|----------------------|-----------------------|
|                          |      | Cardiogenic shock,<br>Pneumonia<br>aspiration |                      | Unlikely              |
| somapacitan <sup>b</sup> | 39.9 | Death (Reported<br>term: Unknown<br>cause)    | Week 65 (Day<br>458) | Unlikely/<br>Unlikely |
| somatropin               | 25.8 | Pneumonia                                     | Week 51 (Day<br>360) | Unlikely/<br>Unlikely |
| somatropin               | 28.0 | Influenza                                     | Week 70 (Day<br>493) | Unlikely/<br>Unlikely |
| placebo                  | 29.9 | Adrenocortical<br>insufficiency acute         | Week 23<br>(Day 163) | Unlikely              |
| Study 4043 AGHD patients |      | Not applicable                                |                      |                       |
| Study 4244 AGHD patients |      | Not applicable                                |                      |                       |

Abbreviations: BMI: Body mass index (kg/m<sup>2</sup>) at baseline; AE= adverse event. AE causality to study product given in main/extension respectively, based on judgement of investigators.

a Treated with placebo in the main phase of study 4054;

b Treated with somatropin in the main phase of study 4054.

### Serious adverse events (SAEs)

A total of 47 (10.4%) patients experienced 79 SAEs in the phase 3 clinical studies in AGHD, with 77 of 79 SAEs evaluated by the investigator to be unlikely related to study treatment. Overall, the percentage of patients reporting SAEs was similar for somapacitan (8.7% patients), somatropin (9.6% patients), and placebo (8.2% patients).

The SAEs were observed most frequently within the first year of treatment in the somapacitan group (within the first 3-6 months in the somatropin group).

The majority of the SAEs were recorded as single events in 1 or 2 patients and across different system organ classes (SOCs). During somapacitan treatment, gastroenteritis was reported in 3 patients (0.9%). Vomiting, inguinal hernia, acute adrenocortical insufficiency and fatigue are reported in 2 patients (0.6%) During somatropin treatment nephrolithiasis was reported in 2 patients (1.2%).

Two (2) SAEs in study 4054 were evaluated by the investigator to be possibly or probably related to study product. One patient with high grade papillary urothelial carcinoma diagnosed after about 2.5 years of GH treatment. The other patient reported high haematocrit, haemoglobin and red blood cell count and was also treated with testosterone containing medicinal products. The diagnoses of a malignancy in this limited

population after 2.5 years of treatment adds to the concerns considering the long-term safety. The development of benign and malignant neoplasms will be evaluated in a post-approval safety study (PASS) with respect to somapacitan.

#### *IGF-I and standardised IGF-I (IGF-I SDS)*

As the mean dose administered in the Phase 3 studies was  $0.036 \pm 0.027$  mg/kg/week (mean  $\pm$  SD) it is not to be expected that the mean IGF-I SDS will be above 2. This is also confirmed in the model for IGF-I. However, given the variation a considerable proportion of patients might experience higher levels of IGF-I (>2 SDS). IGF-I levels above the physiological range for a longer duration of time may be a potential safety concern and IGF-I concentrations should therefore be monitored as standard practice. A titration scheme is included in the SmPC (section 4.2) mitigating the risk of sustained IGF-I concentrations above the 2 SDS.

It is not to be expected that a temporary increase of IGF-I will result in any acute safety issue (possible a temporary induction of type 2 diabetes mellitus). Of more concern is the chronic overdosing of growth hormone with the resulting IGF-I levels above 2 SDS. There were no patients with sustained IGF-I SDS above +2. However, the submitted data suggest that under somapacitan treatment more patients have temporarily IGF-I levels above 2 SDS. This is of concern as IGF-I repeatedly above 2 SDS is thought to increase the long-term safety risks of GH treatment.

Among AGHD study patients exposed to somapacitan in study 4054, 3% (4 of 120) and 5% (11 of 220) patients had an IGF-I SDS above +2 at more than one visit during the titration period of the main and extension study phase, respectively. A slightly lower proportion of patients had an IGF-I SDS above +2 in the fixed dose period of the main phase (4%) versus the extension phase (6%) of study 4054.

During the titration periods in study 4054, an IGF-I value below the reference range of -2 SDS at one or more titration visits was reported for 42% of somapacitan-treated AGHD study patients in the main treatment phase and 37% of somapacitan-treated AGHD study patients in the extension treatment phase. There was a reduction in the number of patients with IGF-I SDS values below -2 from the first to last titration visit for both the main (visit 4: 37.5%, visit 10: 15.8%) and extension study phase (visit 17: 30.0%, visit 23: 15.9%).

If one dose is missed, the concentration of somapacitan will decrease, but is expected to be completely restored 2 weeks (i.e. week 3) after the missed dose. The IGF-I levels are also expected to decrease, but regular steady-state profiles are expected to be almost completely restored 2 weeks after the missed dose. In case of a missed dose the IGF-I SDS approaches the -2 SDS diminishing the effect of growth hormone for a considerable time.

### **Laboratory findings**

Apart from some clinical relevant changes reported for one patient only no clinical relevant changes in standard haematology or biochemistry parameters were reported in more than one patient.

No clinically relevant changes from baseline in vital signs (mean systolic and diastolic blood pressure and pulse) were observed following multiple-dose exposure of somapacitan in AGHD patients in any of the phase 3 studies (studies 4054, 4043 and 4244). Similar mean values were observed for somapacitan and somatropin.

## *ECG*

The potential effect of somapacitan on cardiac repolarisation was assessed based on ECGs collected in the Phase 3 study 4054. The ECGs were collected at baseline and close to the expected time of C<sub>max</sub> for somapacitan

Across treatment groups, the majority (>96%) of the patients had ECG readings with QTcF intervals ≤450 msec, and no subjects had QTcF intervals >500 msec.

One subject (in the placebo group) had an ECG reading with a QTcF interval of 481–500 msec. The subject had experienced an increase in the QTcF interval of 26 msec compared to baseline. Concomitant medication (amiodarone, an antiarrhythmic agent known to cause prolongation of action potential duration) might have contributed to the prolonged QTcF interval >480 msec.

Across treatment groups, the majority (≥96%) of the patients had QTcF interval changes ≤30 msec and no subjects had a QTcF increase of >60 msec.

Overall, there were no clinically relevant changes in ECG during study 4054 and no clinically relevant differences in ECG results between somapacitan, somatropin, and placebo.

## ***Safety in special populations***

### *Gender*

Similar trends were observed by gender as in the pooled Phase 3 data. There were no specific safety concerns observed in the AE profile by gender based on the pooled global Phase 3 data. The percentage of women with AEs (88.8%) appeared to be greater than observed in men (76.2%). In line with this, the number of AEs per 100 person years was 464.9 for women versus 280.6 for men. This gender difference was also observed with daily somatropin treatment. Although somapacitan doses were lower in women without oral oestrogen therapy compared to women on oral oestrogen therapy, there was a higher rate of AEs in women not on oral oestrogen therapy compared to those on oral oestrogen therapy.

### *Age*

In AGHD patients aged ≥65 years, there was a higher event rate of AEs across all treatment groups than in patients aged <65 years, especially for somatropin. However, a similar percentage of patients experienced possibly related AEs in the two age groups. This was not the case in the somatropin group, where probably related AEs were more frequent in the patients aged ≥65 years than observed in the patients aged <65 years.

### *Childhood-onset versus adulthood-onset AGHD*

Overall, patients with adulthood-onset of GH reported more AE as compared to patients with childhood-onset of GHD (for both somapacitan as for somatropin). Such a pattern has been observed with respect to other growth hormone medicinal products. There were no specific safety concerns observed in the AE profile by GHD onset based on the pooled global Phase 3 data.

### *BMI*

As requested, the applicant also provided safety data per body mass index (BMI) on the following ranges: normal (<25 kg/m<sup>2</sup>), overweight (25- <30), obese (30 - <40), and very obese (≥40 kg/m<sup>2</sup>). Overall, these results do not show any new safety concern for these subgroups no matter how the data were pooled (pooled global data and by trial, by category of AEs and by SOC, per dose range). It should be noted that overweight

and obese patients were approximately equally represented (respectively 91 and 91 patients of 333 patients exposed to somapacitan) and that AEs (and SAEs) were generally more observed in overweight patients for a dose between 2 and 4 mg. Regarding very obese patients, the low number of patients (13/333 patients) does not allow to conclude that the safety profile is quite similar regardless of the weight category.

### ***Immunological events***

No anti-somapacitan antibodies were detected after treatment with somapacitan in healthy adults or AGHD patients in the 7 completed clinical studies (not assessed in study 4237).

No anti-GH antibodies were detected after treatment with somatropin in AGHD patients in the 4 completed clinical studies, except one patient with a single (transient) positive anti-GH test at week 4 (titration period) and then none thereafter in study 4054 (main phase).

The applicant acknowledged that although antibodies were not observed in the clinical studies, they could reasonably be expected, especially if a lack of efficacy is suspected.

### ***Safety related to drug-drug interactions and other interactions***

The known drug interactions for growth hormone are reported; decreased conversion of cortisone to cortisol increased extrathyroidal conversion of T4 to T3, growth hormone insensitivity in women on oestrogen treatment, and decreased insulin sensitivity. In addition, an interaction between testosterone and somapacitan cannot be ruled out on the basis of reported cases. Proper warnings are included in the SmPC to mitigate the risks related to these pharmacodynamic interactions.

### ***Discontinuation due to adverse events***

In the studies 4054 and 4043, the withdrawal rate for AGHD patients exposed to somapacitan was 4.5–5.8% whereas in the same studies withdrawal rate of 9.7 to 13.5% for somatropin. In total, 7 out of 333 patients exposed to somapacitan discontinued treatment due to AEs, where 6 out of 166 patients on somatropin treatment discontinued treatment due to AEs. Adverse events leading to discontinuation during somapacitan treatment were gastro-enteritis, mild weight increase and oedema, abnormal ECG, nasopharyngitis, common cold with fever, pituitary tumour, thyroid disorder, plasma cell myeloma, fatigue, asthenia and disturbance in attention. Discontinuations due to adverse events during somatropin treatment were diabetes (n=2); gastroenteritis; haemo-concentration (i.e. increased haematocrit, red cell count and haemoglobin concentration); dermatitis atopic, asthenia, somnolence, disturbance in attention, headache, and difficult phlebotomy.

No apparent difference in discontinuation due to AEs (not necessarily TEAES) between somapacitan and somatropin was observed.

### ***Post marketing experience***

Not applicable.

### 2.6.1. Discussion on clinical safety

Three hundred thirty-three (333) patients were exposed to somapacitan in the Phase 3 studies. Additionally, 143 healthy volunteers, 29 subjects with renal insufficiency and 18 patients with hepatic impairment were exposed to somapacitan. Of the patients exposed to somapacitan, 253 (76.0%) patients were treated for more than 12 months. Considering the necessary lifelong treatment with GH, the number of patients that has been treated for more than 12 months is very limited. However, the (short-term) safety of somapacitan might be mirrored to the general safety information of growth hormone. The short-term safety obtained with somapacitan seems comparable to that of other growth hormone-containing products. With respect to the long-term safety (i.e. after 10 or more years of treatment) no conclusions could be drawn based on the limited duration of exposure in conducted studies. The non-physiologic exposure with GH replacement therapy to both growth hormone and IGF-I gave rise to uncertainties considering the long-term safety.

Seventeen percent of patients exposed to somapacitan (58/333) received the maximum dose range (between 4 and 8 mg per week). By contrast, only 7% of patients exposed (12/166) to somatropin received the maximum dose range (between 4.2 and 7.7 mg per week). Although these results should not be directly compared due to high level of inter-individual variability and different arm sizes (166 patients with somatropin, 333 patients with somapacitan), it could question the efficacy of somapacitan at low doses and could consolidate the hypothesis that somapacitan in higher doses results in lower efficacy than somatropin in lower doses.

After IGF-I SDS dose titration the mean somapacitan dose was 2.38 mg/week (0.036 mg/kg/week). The mean daily somatropin dose was 2.03 mg/week (0.035 mg/kg/week, in accordance to the SmPC). On a weight basis comparable amounts of active substance were administered.

The most commonly reported AEs in the somapacitan group were nasopharyngitis (25.2%), headache (12.9%) and arthralgia (6.9%). The AE profile of once-weekly somapacitan was overall similar to that of existing GH products for daily administration (e.g., somatropin) and included the class effects for GH in AGHD (e.g., headache, arthralgia, fatigue, and oedema peripheral). The majority of AEs were reported in less than 5% of the patients, were non-serious, of mild/moderate severity and reported as unlikely to be related to the study treatment.

Five (5, 1.3%) patients died during study 4054. All 5 deaths were assessed by the investigator as unlikely to be related to study treatment: 2 patients (one case treated with placebo/somapacitan died due to ventricular fibrillation, cardiogenic shock and pneumonia aspiration the other case treated with daily somatropin/somapacitan died due to an unknown cause); daily somatropin: 2 patients (one case treated with daily somatropin died influenza the other case treated with daily somatropin/daily somatropin died due to pneumonia); placebo: one patient died due to acute adrenocortical insufficiency). There was no pattern in the types of AEs in the patients who died or time to event.

A total of 47 (10.4%) patients experienced 79 SAEs in the phase 3 clinical studies in AGHD, with 77 of 79 SAEs evaluated by the investigator to be unlikely related to study product. The percentage of patients reporting SAEs was similar for somapacitan (8.7% patients), daily somatropin (9.6% patients) and placebo (8.2% patients). During somapacitan treatment, gastroenteritis was reported in 3 patients (0.9%). Vomiting, inguinal hernia, acute adrenocortical insufficiency and fatigue are reported in 2 patients (0.6%) none of the remaining SAE's were reported in more than one patient. No SAEs were reported following somapacitan single- and/or multiple-dose administrations in healthy subjects or subjects with renal impairment (study 3915; study 4237; study 4298). During daily somatropin treatment nephrolithiasis was reported in 2 patients (1.2%).

Modelling of the IGF-I response indicates that after the initial titration the 95% CI is well within the 2 SDS level for IGF-I. However, given the variation a considerable proportion of patients might experience higher or lower levels of IGF-I (above or below 2 SDS). IGF-I levels above the physiological range for a longer duration of time may be a potential safety concern and IGF-I concentrations should therefore be monitored as standard practice. A titration scheme is included in the SmPC (section 4.2) mitigating the risk of sustained IGF-I concentrations above the 2 SDS.

It is not to be expected that a temporary increase of IGF-I will result in any acute safety issue. Of more concern is the chronic overdosing of growth hormone with the resulting IGF-I levels above +2 SDS. IGF-I SDS levels above +2 were observed in about 5% of AGHD patients at the applied somapacitan dosing regimen in study 4054. Respective proportion could increase upon application of a prolonged somapacitan dose titration period in which higher somapacitan dosing may be recommended to AGHD patients. In the SmPC instructions have been included to minimize the risk of chronic overtreatment with growth hormone.

If one dose is missed, the concentration of somapacitan will decrease, but is expected to be completely restored 2 weeks (i.e. week 3) after the missed dose upon subsequent continued dosing. The IGF-I levels are also expected to decrease, but regular steady-state profiles are expected to be almost completely restored 2 weeks after the missed dose. In case of a missed dose the IGF-I SDS approaches the -2 SDS diminishing the effect of growth hormone for a considerable time. The weekly IGF-I pattern (especially the  $C_{max}$ ,  $C_{through}$  and the un-physiologic weekly fluctuations) were not compared with normal physiology and after administration of daily somatotropin. Further the consequences for the (long-term) safety (and efficacy) are not discussed (preferably including physiological conditions with comparable IGF-I patterns). Considering these uncertainties, long-term safety risks of weekly growth hormone supplementation should be evaluated in a PASS.

The mean fasting blood glucose ranged from 4.9 to 5.2 mmol/l across treatment groups at baseline and after 86 weeks of exposure. The mean HbA<sub>1c</sub> ranged from 5.4 to 5.5 % across treatment groups at baseline and after 86 weeks of exposure. Two (2) daily somatotropin treated patients were diagnosed with diabetes during study 4054. No patient was diagnosed with diabetes mellitus type 2 during somapacitan treatment.

There were no apparent clinically relevant changes in the clinical laboratory haematology or biochemistry parameters, vital signs or ECG assessed in AGHD patients or healthy subjects in any of the treatment groups/studies.

Overall, the short-term safety of somapacitan was considered quite consistent across gender groups and age groups (over and under 65 years of age). Similar trends were observed by age as in the pooled Phase 3 data. There were no specific safety concerns observed in the AE profile by gender or age based on the pooled global Phase 3 data. The percentage of women with AEs appeared to be greater than observed in men.

Patients with adulthood-onset GHD reported more AEs compared to patients with childhood-onset GHD across all treatment groups. However, the percentages of patients with SAEs and probably related events in the somapacitan group were similar for patients with adulthood-onset and childhood-onset GHD.

Somapacitan was well tolerated in subjects with renal and/or hepatic impairment (mild, moderate, severe renal/hepatic impairment and subjects requiring haemodialysis treatment) as well as in subjects with normal renal/hepatic function after 3 once-weekly s.c. somapacitan administrations.

There was no indication of increased risk of anti-somapacitan/anti-GH antibody development for somapacitan compared to daily somatotropin in AGHD patients.

The known drug interactions for growth hormone are reported; decreased conversion of cortisone to cortisol, increased extra-thyroidal conversion of T4 to T3, growth hormone insensitivity in woman on oestrogen treatment and decrease insulin sensitivity. Likewise, testosterone levels may be modified. Warnings are included in the SmPC to mitigate the risks related to these pharmacodynamic interactions.

In the studies 4054 and 4043 the withdrawal rate for AGHD patients exposed to somapacitan was 4.5–5.8% whereas in the same studies withdrawal rate of 9.7 to 13.5% for daily somatropin. In total, 7 out of 333 patients exposed to somapacitan discontinued treatment due to AEs, whereas 6 out of 166 patients on daily somatropin treatment discontinued treatment due to AEs.

No post-marketing safety data are available.

Notwithstanding the limited information a comparable acute safety profile as compared to the currently available GH containing products can be assumed. The very limited information on long-term safety in this less physiological situation i.e. a more stable and less varying GH level and a more undulating IGF-I level on a daily base, was a reason for concern. The concerns focus but are not limited to the (possible) oncogenic potential of growth hormone, the development of diabetes mellitus type 2, and an increase of cardiovascular complications of over exposure. The applicant should acquire a more elaborate safety database post registration in order to obtain information on potential long-term safety risks such as the development of malignancies, and type 2 diabetes mellitus. Long-term clinical effects of an optimized somapacitan dosing regimen resulting in higher somapacitan doses for (particular subgroups of) AGHD patients will therefore be evaluated in a category 3 PASS after marketing authorization (see clinical efficacy section).

### ***Additional expert consultations***

An AHEG was consulted on 29<sup>th</sup> of October 2020 with efficacy and safety questions and answers listed above under Discussion on clinical efficacy.

### ***Assessment of paediatric data on clinical safety***

No information on children is submitted.

## **2.6.2. Conclusions on the clinical safety**

Somapacitan dosed according to the titration scheme as defined in the pivotal study shows the well-known short-term safety profile from growth hormone. No unexpected safety issues are reported. Based on the limited data available, the short-term safety profile reported in the clinical studies of somapacitan is comparable with the safety profile reported for daily somatropin.

The limited information on long-term safety in this unphysiological exposure (both growth hormone and IGF-I levels), as opposed to the daily variations seen in healthy volunteers, remains a concern. Therefore, the applicant should acquire a more elaborate safety database post-registration (PASS) in order to obtain information on the long-term safety in terms of malignancies, and the development of type 2 diabetes mellitus (commitment). Further, as suggested by the experts and supported by the CHMP, the PASS (category 3) should also include measurements considering compliance and medication errors. The assessment of the medication errors is of interest because it might indicate the need for further educational material for health care professionals and patients. The applicant committed in the RMP to observe each

patient in the prospective somapacitan cohort as long as possible, i.e. until study end at 10 years, to achieve similar mean follow-up periods as in the NordiNet IOS and regarding the initiation of the PASS after approval of the detailed study protocol by EMA. The applicant included a commitment into the RMP that the PASS will not be initiated before approval of the detailed study protocol by EMA. With the 'extended titration regimen' as proposed by the applicant resulting in the use of higher doses of somapacitan and a longer titration duration, increased short-term safety issues (frequency and severity) cannot be anticipated especially in women on oral oestrogen therapy. Therefore, both short-term and long-term safety risks of an optimized somapacitan dosing regimen should be evaluated in women on oral oestrogen treatment in a PASS. This position is supported by the experts of the AHEG who require additional clinical data in this subgroup of patients.

## 2.7. Risk Management Plan

### Safety concerns

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

### Pharmacovigilance plan

| Study (study short name and title)<br>Status (planned/on going)   | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|-----------------------|---------------------------|------------|-----------|
| <b>Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit-risk)</b>   |                       |                           |            |           |
| N/A   |                       |                           |            |           |
| <b>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)</b> |                       |                           |            |           |
| N/A   |                       |                           |            |           |

| Study (study short name and title)<br>Status (planned/on going)  | Summary of objectives  | Safety concerns addressed   | Milestones                                     | Due dates  |
|--|--|---|--|--|
| <b>Category 3 – Required additional pharmacovigilance activities</b>   |  |   |  |  |
| <p>A multinational, multicentre, prospective, open label, single-arm, observational, non-interventional post-authorization safety study to investigate long-term safety of somapacitan in adults with growth hormone deficiency (AGHD) under normal clinical practice conditions</p> <p>(NN8640-4515)</p> <p>Planned</p> | <p><b>Primary objective:</b><br/>To assess safety of somapacitan therapy in AGHD under normal clinical practice conditions.</p> <p><b>Secondary objectives:</b><br/>Under normal clinical practice conditions to:</p> <ul style="list-style-type: none"> <li>• characterise the somapacitan titration schemes in subgroups<sup>a</sup></li> <li>• characterise effectiveness in subgroups<sup>a</sup></li> <li>• evaluate effect of somapacitan by patient-reported outcome (PRO) measures.</li> </ul> | <ul style="list-style-type: none"> <li>• Neoplasms</li> <li>• Diabetes mellitus type 2</li> <li>• Medication errors (Incorrect dose administration rate)</li> <li>• Patients with heart failure, NYHA class &gt;2</li> <li>• Patients with severe hepatic impairment</li> <li>• Long-term safety</li> </ul> | <p>Protocol submission</p> <p>Final report</p> | <p>Within 2 months of obtaining marketing authorisation</p> <p>One year after the end of the study</p> |

<sup>a</sup>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.

## Risk minimisation measures

| Safety concerns  | Risk minimisation measures  |
|--|---|
| <b>Important identified risks</b>                      |   |
| None   | N/A   |
| <b>Important potential risks</b>                       |   |
| Neoplasms  | <p><b>Routine risk minimisation measures</b></p> <p><u>Routine risk communication:</u></p> <ul style="list-style-type: none"> <li>SmPC Section 4.3, where a contraindication concerning any evidence of activity of a tumour is included.</li> </ul> <p><u>Risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <ul style="list-style-type: none"> <li>SmPC Section 4.4, where a special warning is included on neoplasms.</li> <li>PL Section 2, where information is included on tumours.</li> </ul> <p><u>Other risk minimisation measures beyond the Product Information:</u></p> <ul style="list-style-type: none"> <li>Medicine's legal status: <ul style="list-style-type: none"> <li>Somapacitan will be a restricted prescription-only medicine, prescribed by specialists.</li> </ul> </li> </ul> <p><b>Additional risk minimisation measures</b></p> <ul style="list-style-type: none"> <li>None proposed</li> </ul>  |
| Diabetes mellitus type 2                               | <p><b>Routine risk minimisation measures</b></p> <p><u>Routine risk communication:</u></p> <ul style="list-style-type: none"> <li>SmPC Section 4.2, where information is included concerning individual dose requirements based on the clinical response and serum IGF-I concentration.</li> </ul> <p><u>Risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <ul style="list-style-type: none"> <li>SmPC Section 4.4, where a special warning is included on glucose metabolism impairment.</li> <li>PL Section 2, where information is included on high blood sugar.</li> </ul> <p><u>Other risk minimisation measures beyond the Product Information:</u></p> <ul style="list-style-type: none"> <li>Medicine's legal status: <ul style="list-style-type: none"> <li>Somapacitan will be a restricted prescription-only medicine, prescribed by specialists.</li> </ul> </li> </ul> <p><b>Additional risk minimisation measures</b></p> <ul style="list-style-type: none"> <li>None proposed</li> </ul> |
| Medication errors (Incorrect dose administration rate) | <p><b>Routine risk minimisation measures</b></p> <p><u>Routine risk communication:</u></p> <ul style="list-style-type: none"> <li>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.</li> <li>SmPC Section 5.1, where information regarding maintenance dose is included.</li> </ul> <p><u>Risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <ul style="list-style-type: none"> <li>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.</li> </ul>  |

| <b>Safety concerns</b>                    | <b>Risk minimisation measures</b>  |
|---|--|
|   | <ul style="list-style-type: none"> <li>PL Section 3, where information is included concerning how and when to use somapacitan.</li> </ul> <p>Other risk minimisation measures beyond the product information:</p> <ul style="list-style-type: none"> <li>Medicine's legal status: <ul style="list-style-type: none"> <li>Somapacitan will be a restricted prescription-only medicine, prescribed by specialists.</li> </ul> </li> </ul> <p><b>Additional risk minimisation measures</b></p> <ul style="list-style-type: none"> <li>None proposed</li> </ul>  |
| Off-label paediatric use                  | <p><b>Routine risk minimisation measures</b></p> <p><u>Routine risk communication:</u></p> <ul style="list-style-type: none"> <li>SmPC Section 4.1, where information is included concerning the therapeutic indication.</li> <li>SmPC Section 4.2, under 'Special population', where information is included on paediatric population below 18 years of age.</li> </ul> <p><u>Risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <ul style="list-style-type: none"> <li>SmPC Section 4.4, where a special warning is included on paediatric population below 18 years of age.</li> <li>PL Section 2, where information is included on paediatric population below 18 years of age.</li> </ul> <p><u>Other risk minimisation measures beyond the Product Information:</u></p> <ul style="list-style-type: none"> <li>Medicine's legal status: <ul style="list-style-type: none"> <li>Somapacitan will be a restricted prescription-only medicine, prescribed by specialists.</li> </ul> </li> </ul> <p><b>Additional risk minimisation measures</b></p> <ul style="list-style-type: none"> <li>None proposed</li> </ul> |
| <b>Missing information</b>                |  |
| Patient with heart failure, NYHA class >2 | <p><b>Routine risk minimisation measures</b></p> <p><u>Routine risk communication:</u></p> <ul style="list-style-type: none"> <li>SmPC Section 4.2, where information is included concerning individual dose requirements based on the clinical response and serum IGF-I concentration.</li> </ul> <p><u>Risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <ul style="list-style-type: none"> <li>None proposed</li> </ul> <p><u>Other risk minimisation measures beyond the Product Information:</u></p> <ul style="list-style-type: none"> <li>Medicine's legal status: <ul style="list-style-type: none"> <li>Somapacitan will be a restricted prescription-only medicine, prescribed by specialists.</li> </ul> </li> </ul> <p><b>Additional risk minimisation measures</b></p> <ul style="list-style-type: none"> <li>None proposed</li> </ul>  |
| Patients with severe hepatic impairment   | <p><b>Routine risk minimisation measures</b></p> <p><u>Routine risk communication:</u></p> <ul style="list-style-type: none"> <li>SmPC Section 4.2, where information is included concerning individual dose requirements based on the clinical response and serum IGF-I concentration.</li> </ul>   |

| <b>Safety concerns</b> | <b>Risk minimisation measures</b>  |
|------------------------|--|
|                        | <ul style="list-style-type: none"> <li>• SmPC Section 4.2, under 'Special population', where information is included on patients with severe hepatic impairment.</li> </ul> <p><u>Risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <ul style="list-style-type: none"> <li>• None proposed</li> </ul> <p><u>Other risk minimisation measures beyond the Product Information:</u></p> <ul style="list-style-type: none"> <li>• Medicine's legal status: <ul style="list-style-type: none"> <li>• Somapacitan will be a restricted prescription-only medicine, prescribed by specialists.</li> </ul> </li> </ul> <p><b>Additional risk minimisation measures</b></p> <ul style="list-style-type: none"> <li>• None proposed</li> </ul> |
| Long-term safety       | <p><b>Routine risk minimisation measures</b></p> <p><u>Routine risk communication:</u></p> <ul style="list-style-type: none"> <li>• None proposed</li> </ul> <p><u>Risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <ul style="list-style-type: none"> <li>• None proposed</li> </ul> <p><u>Other risk minimisation measures beyond the Product Information:</u></p> <ul style="list-style-type: none"> <li>• Medicine's legal status: <ul style="list-style-type: none"> <li>• Somapacitan will be a restricted prescription-only medicine, prescribed by specialists.</li> </ul> </li> </ul> <p><b>Additional risk minimisation measures</b></p> <ul style="list-style-type: none"> <li>• None proposed</li> </ul>                |

## **Conclusion**

The CHMP and PRAC considered that the risk management plan version 0.5 is acceptable.

## **2.8. Pharmacovigilance**

### **Pharmacovigilance system**

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

### **Periodic Safety Update Reports submission requirements**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 28.08.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

## **2.9. New Active Substance**

The applicant declared that somapacitan has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers somapacitan to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

## **2.10. Product information**

### **2.10.1. User consultation**

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

### **2.10.2. Additional monitoring**

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Sogroya (somapacitan) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

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**

### **3.1. Therapeutic Context**

Somapacitan is a long-acting recombinant human GH derivative and indicated for the replacement of endogenous GH in adults with growth hormone deficiency (AGHD).

#### **3.1.1. Disease or condition**

Growth hormone (GH) deficiency is a rare disorder which affects both children and adults. It is characterized by inadequate systemic availability of GH due to inadequate secretion from the anterior pituitary gland or destruction of the gland. The incidence of GH deficiency in adults (AGHD) is about 1.90 for males and 1.42 for females, per 100.000. AGHD may have either childhood or adulthood onset.

As for human somatotropin, the mechanism of action of somapacitan is either directly via binding to the GH receptor or indirectly via insulin-like growth factor I (IGF-I).

GH deficiency is associated with a broad range of signs and symptoms, including central adiposity, decreased muscle mass, decreased bone density, impaired cardiac function, decreased insulin sensitivity, changes in memory, processing speed and attention, lack of well-being, depression, anxiety, social isolation, fatigue, lack of strength, fibromyalgia syndrome, neuromuscular dysfunction, accelerated atherogenesis with increased carotid intima-media thickness, increased low-density lipoprotein, pro-thrombotic state, and decreased sweating and thermoregulation.

The aetiology of GH deficiency can be congenital (resulting from genetic mutations, or from structural defects in the hypothalamic-pituitary areas of the brain), acquired (e.g. as result of traumatic brain injury, infection, radiation therapy, or tumour growth within the hypothalamic-pituitary areas of the brain) or idiopathic. GH deficiency may occur as an isolated hormonal deficiency or in combination with multiple pituitary hormone deficiencies (hypopituitarism).

The most common causes of AGHD are damage to the pituitary gland or hypothalamus caused by a tumour (e.g., pituitary adenoma or craniopharyngioma), surgery or radiotherapy.

The diagnosis of AGHD is established by provocative testing of GH secretion (e.g. insulin tolerance test, combined administration of arginine and GHRH).

### **3.1.2. Available therapies and unmet medical need**

Once the diagnosis of AGHD is established, a replacement regimen with growth hormone should be instituted and titrated taking into account the clinical response and serum IGF-I levels. Several growth hormone products for the treatment of AGHD have been registered within the European Union (e.g. somatropin products Genotropin, Norditropin Flexpro and Norditropin Simplexx). These products typically require daily subcutaneous administration. Dosing of growth hormone products is targeted to achieve normal IGF-I levels (i.e. 0 or at least < 2 standard deviation scores (SDS)).

Clinical studies using biosynthetic GH have confirmed that GH continues to play a role in optimizing health and well-being even after attainment of final adult height and has demonstrated that adults with long-standing GH deficiency derive benefit from GH replacement. In general, women require higher doses of GH to achieve the same IGF-I response. GH secretion normally decreases with age. In addition, GH dose requirements are lower in older patients.

#### *Adverse events*

Common adverse effects of GH treatment include fluid retention (5–18%), hypertension, paresthesias, joint stiffness, peripheral oedema, arthralgia, myalgias, and carpal tunnel syndrome (2%). Adult patients who are older, heavier, or female are more prone to develop these complications. Most of these adverse reactions improve with dose reduction. Insulin resistance and type 2 diabetes can occur or worsen in patients with pre-existing diabetes. Retinopathy, benign intracranial hypertension, and gynecomastia are rare. Although there might have been some concern with respect to the risk of cancer with the use of GH therapy, an increase in the recurrence rates of either intracranial or extracranial tumours has not been demonstrated in AGHD.

#### *Unmet medical need*

Current GH therapy for AGHD is administered as daily s.c. injections and often necessitates many years or life-long treatment. The daily injections are a burden to the patients and may affect treatment adherence and thereby, treatment effectiveness.

Within GH therapy, studies of AGHD patients have shown poor adherence. For example, a survey of 158 AGHD patients who were receiving or had received GH therapy rated only 34% as 'highly' compliant<sup>31</sup>, and a retrospective single-centre cohort study classified compliance as <20% in approximately 9% of 179 AGHD patients.<sup>32</sup> In addition, frequent pain from the injection, bruising and stinging can contribute to the burden associated with daily GH treatment.<sup>33</sup>

A long-acting GH like somapacitan, which is suitable for once-weekly administration could possibly address an important problem with treatment adherence in chronic disease by reducing the number of required injections. In other chronic diseases, research indicates that reduced treatment frequency directly increases treatment adherence.<sup>34,35,36,37</sup>

### 3.1.3. Main clinical studies

The main evidence of efficacy submitted is a single Phase III multicentre, randomized, parallel-group study (study 4054). The study (n= 300) was primarily designed to compare in a 34-week double-blind setting the efficacy and safety of once-weekly dosing of somapacitan with once-weekly dosing of placebo in AGHD patients who were growth hormone treatment-naïve or with no exposure to growth hormone or growth hormone secretagogues for at least 180 days prior to randomization. In a third study arm, the clinical effects of open-label daily treatment with somatropin product Norditropin were evaluated. After completion of this main treatment phase, study patients could enrol into a 53-week open-label extension period in which they were re-randomized to receive somapacitan or somatropin.

The primary endpoint of the study was the change in truncal fat percentage from baseline to week 34 as determined by DXA. Secondary endpoints involved changes from baseline to week 34 with respect to other DXA endpoints, quality of life, and treatment satisfaction. In total, 300 patients were randomized to somapacitan (n= 120), somatropin (n= 119), or placebo (n=61) in the main treatment phase. In the extension treatment phase, 184 study patients were treated with either somapacitan (n= 132) or somatropin (n=52).

In addition, two open-label supportive studies were conducted in AGHD patients who have been treated previously with growth hormone (studies 4244 (n= 62) and 4043 (n= 92)). Participants were randomized to receive weekly somapacitan or daily somatropin. Study 4244 (52 weeks) and study 4043 (26 weeks) consisted of a titration period (study 4244: 20 weeks, study 4043: 8 weeks), followed by a fixed-dose treatment period (study 4244: 32 weeks, study 4043: 18 weeks). Both studies were primarily developed for safety evaluations; secondary efficacy endpoints included changes at the end of compared to baseline concerning adipose tissue compartments (only study 4244) and TSQM-9 scores (both studies).

---

<sup>31</sup> Rosenfeld RG, Bakker B. Compliance and persistence in pediatric and adult patients receiving growth hormone therapy. *Endocr Pract.* 2008;14(2):143-54.

<sup>32</sup> Auer MK, Stieg MR, Hoffmann J, Stalla GK. Is insulin-like growth factor-I a good marker for treatment adherence in growth hormone deficiency in adulthood? *Clin Endocrinol (Oxf).* 2016;84(6):862-9.

<sup>33</sup> Kremidas D, Wisniewski T, Divino VM, Bala K, Olsen M, Germak J, et al. Administration burden associated with recombinant human growth hormone treatment: perspectives of patients and caregivers. *J Pediatr Nurs.* 2013;28(1):55-63.

<sup>34</sup> Claxton A, de Klerk E, Parry M, Robinson JM, Schmidt ME. Patient compliance to a new enteric-coated weekly formulation of fluoxetine during continuation treatment of major depressive disorder. *J Clin Psychiatry.* 2000;61(12):928-32.

<sup>35</sup> Zoellner Y, Balp MM, Marco AG. The role of galenic innovation in improving treatment compliance and persistence: three case studies. *Clinicoecon Outcomes Res.* 2011;3:109-16.

<sup>36</sup> Kishimoto H, Maehara M. Compliance and persistence with daily, weekly, and monthly bisphosphonates for osteoporosis in Japan: analysis of data from the CISA. *Arch Osteoporos.* 2015;10:231.

<sup>37</sup> Johnston SS, Nguyen H, Felber E, Cappell K, Nelson JK, Chu BC, et al. Retrospective study of adherence to glucagon-like peptide-1 receptor agonist therapy in patients with type 2 diabetes mellitus in the United States. *Adv Ther.* 2014;31(11):1119-33.

### **3.2. Favourable effects**

A significant difference for the primary endpoint change at week 34 compared to baseline in truncal fat percentage' was observed for somapacitan compared to placebo treatment. In line with this, changes compared to baseline with respect to body composition parameters, and treatment satisfaction, tended to be larger for somapacitan compared to placebo (see below).

However, the body composition related endpoints are mostly in favour of the daily somatropin treatment compared to weekly somapacitan treatment.

#### *Change in body composition*

The change in truncal fat percentage at week 34 as compared to baseline was larger for somapacitan (-1.17) as compared to placebo treatment (+0.49) (estimated treatment difference -1.53 (95% CI -2.68; -0.38),  $p=0.009$ ). The change in truncal fat percentage at week 34 as compared to baseline was lower for somapacitan (-1.17%) as compared to somatropin treatment -2.39%) (estimated treatment difference 1.17 (95% CI -0.23; 2.11),  $p<0.05$ ). Similar results were obtained in several sensitivity analyses.

Similar trends with respect to the primary endpoint were observed concerning age ( $\leq 64$  years vs. 65 years and above), GHD onset (childhood- vs. adult-onset), and gender.

Changes in total lean body mass (g) at week 34 compared to baseline were larger for somapacitan (+1395.88) compared to placebo (+334.43) (estimated treatment difference 1144 (95% CI 459; 1829),  $p=0.001$ ). Observed changes with respect to this endpoint for somapacitan (+1395.88) and somatropin (+1359.33) were comparable (estimated treatment difference 49 (95% CI -513; 610),  $p=0.87$ ). Other changes in body composition were larger for somapacitan as compared to placebo treatment, except for changes in (truncal and gynoid) body fat mass (g).

In the extension treatment period, the decrease in truncal fat percentage at week 87 as compared to baseline tended to be smaller in study patients treated with somapacitan (-1.63%) than those treated with somatropin (-2.63%) in the whole study period (estimated treatment difference 1.15% (95% CI -0.10; 2.40),  $p=0.07$ ). Similar trends were observed with respect to several particular fat masses (e.g. body fat mass, truncal body fat mass, android and gynoid body fat mass). In patients treated with somatropin in the main treatment phase who were re-randomized to receive somapacitan in the extension treatment phase ( $n=51$ ), decreases in truncal fat percentage compared to baseline tended to be larger during somatropin treatment (-2.28%) as compared to somapacitan treatment in the extension treatment period (-0.96%).

Changes concerning lean body mass and bone mineral content endpoints tended to be larger for study patients treated with somapacitan as compared to those treated with somatropin during both the main and extension treatment period.

#### *Changes in health-related quality of life*

Changes at week 34 compared to baseline for the total score of the TRIM-AGHD questionnaire tended to be smaller for somapacitan (-5.71) as compared to somatropin (-9.99) (estimated treatment difference 4.99 (95% CI 1.84; 8.14),  $p=0.002$ ), though changes compared to baseline for the TRIM-AGHD questionnaire tended to be larger for somapacitan (-5.71) as compared to placebo (-3.65) (estimated treatment difference -2.83 (95% CI -6.72; 1.05),  $p=0.15$ ).

Similar results concerning the TRIM-AGHD questionnaire were obtained in the extension treatment period for patients treated with somapacitan and somatropin during both the main and extension treatment period (estimated treatment difference total score week 87: 7.32 (95% CI 3.3; 11.3),  $p= 0.0003$ ).

#### *Treatment adherence*

The majority of patients adhered to the planned treatment. The mean adherence tended to be higher with somapacitan (95.5%) than with somatropin (90.6%) in the main treatment phase (diary data). Adherence in the main treatment phase of study 4054 was  $\geq 97.5$  up to 100% in 78.3% of study patients treated with somapacitan and 73.9% of study patients treated with somatropin. The proportion of study patients who reported that the study treatment they received was convenient at week 34 tended to be higher among 77.7% of somapacitan-treated and 73.9% of somatropin-treated study patients (estimated treatment difference 4.00 (95% CI -0.44; 8.39),  $p= 0.07$ ).

At week 87 of the extension treatment period, somapacitan-treated study patients (80.0%) reported a higher convenience of study treatment than somatropin-treated study patients (72.6%) (estimated treatment difference 7.09% (95% CI 1.7; 12.4),  $p= 0.01$ ).

#### *Other endpoints*

For other endpoints such as SF-36 summary scores, lipid profile, cardiovascular parameters, body weight and waist circumference differences between somapacitan and placebo overall tended to be larger for somapacitan. However, observed changes overall tended to be smaller for somapacitan compared to somatropin treatment.

### **3.3. Uncertainties and limitations about favourable effects**

In the main treatment phase of study 4054, clinical effects of double-blind somapacitan and placebo treatment and open-label somatropin treatment were evaluated. Serious shortcomings in the ethical conduct of the study were identified at a GCP inspection however data reliability remain sufficient for interpretation in the context of this procedure.

The differences in clinical effects for the primary and secondary endpoints overall tended to be larger for somapacitan compared to placebo in pivotal study 4054. Observed differences from baseline are however small (e.g.  $<2\%$  for decreases in truncal fat percentage,  $<100$  g in body fat mass compared to baseline). The lower efficacy of somapacitan in secondary comparison to somatropin on some fat parameters may be explained by the fact that the IGF-I SDS target range of -0.5 up to +1.75 was not achieved in 22% of study patients in the main treatment phase of study 4054. This proportion was even higher in subgroups of AGHD patients who are less sensitive to growth hormone treatment, such as women on oral oestrogen treatment (42%), and patients with childhood-onset AGHD (34%). AGHD Study patients who are less sensitive to the effects of growth hormone treatment may have been unequally divided among the treatment arms.

Comparisons between somapacitan and somatropin concerned secondary analyses. Although observed clinical effects for somapacitan are smaller than for somatropin respective active treatment comparisons should be interpreted with caution since no definitive conclusions can be made based on these secondary analyses.

The clinical effects of somapacitan with respect to adipose tissue masses overall tended to be smaller compared to those of somatropin, whereas the clinical effects of both active substances on lean body mass parameters were comparable. No consistent improvements were observed upon somapacitan treatment with

respect to the quality of life and well-being as evaluated with SF-36, TRIM-AGHD, and TSQM-9 questionnaires. The observed effects of somapacitan with respect to quality of life and well-being parameters were not consistently more pronounced compared to placebo, and not comparable with those of somatropin using the dosing regimen used in the pivotal clinical study.

The applicant acknowledges that the somapacitan dosing regimen in conducted clinical studies was not appropriate. *Post-hoc* analyses in which the clinical effects of weekly somapacitan were compared with those of daily somatropin treatment in different AGHD subgroups indicated that the effects on both lean body masses and adipose masses were comparable for those patients who achieved an IGF-I SDS level between 0 and +2. According to respective *post-hoc* simulation analyses the proportions of AGHD patients with IGF-I SDS levels above 0 will increase from about 80 to 90%, if somapacitan dose titration beyond 8 weeks would be allowed. Thus, appropriate individual somapacitan dose titration is essential.

Hence, clinical efficacy of somapacitan is expected to increase upon application of a more flexible, optimized somapacitan dosing regimen in individual AGHD patients, which allows somapacitan dose titration beyond 8 weeks until the target IGF-I SDS range of 0 up to +2 or maximal recommended somapacitan dosing (8 mg/week) is achieved. It is at present however unclear whether these results can also be achieved and maintained at an acceptable safety level upon application of such a somapacitan dosing regimen in (different subgroups of) AGHD patients in clinical practice. For this reason, short- and long-term clinical effects of somapacitan and also the appropriateness of recommended somapacitan dosing regimen in actual AGHD patients will be evaluated further in a PASS. In respective PASS, AGHD patients who are less sensitive to the clinical effects of growth hormone such as female AGHD patients on oral oestrogen and patients with childhood onset GHD will be included.

### **3.4. Unfavourable effects**

Three hundred thirty-three (333) patients were exposed to somapacitan in the phase 3 studies besides these 143 healthy volunteers, 29 subjects with renal insufficiency and 18 patients with hepatic impairment were exposed to somapacitan.

The most commonly reported AEs in the somapacitan group were nasopharyngitis (25.2%), headache (12.9%) and arthralgia (6.9%). The most commonly reported TEAE were headache (3.0%), arthralgia (2.7%), fatigue (2.7%) and peripheral oedema (2.1%). The AE profile of once-weekly somapacitan was overall similar to that of existing GH products for daily administration (e.g., somatropin) and included the class effects for GH in AGHD (e.g., headache, arthralgia, fatigue and oedema peripheral). The majority of AEs were reported in less than 5% of the patients, were non-serious, of mild/moderate severity and reported as unlikely to be related to study products.

Five (5, 1.3%) patients died during study 4054. All 5 deaths were assessed by the investigator as unlikely to be related to study products. Two (2) patients were treated with somapacitan, 2 with somatropin, and 1 with placebo.

A total of 47 (10.4%) patients experienced 79 SAEs in phase 3 clinical studies in AGHD, with 77 of 79 SAEs evaluated by the investigator to be unlikely related to study product. The percentage of patients reporting SAEs was similar for somapacitan (8.7% patients), somatropin (9.6% patients) and placebo (8.2% patients).

There were no apparent clinically relevant changes in the clinical laboratory haematology or biochemistry parameters, vital signs or ECG assessed in AGHD patients or healthy subjects in any of the treatment groups/studies.

There was no indication of increased risk of anti-somapacitan/anti-GH antibody development for somapacitan compared to somatropin in AGHD patients.

The known drug interactions for growth hormone are reported; decreased conversion of cortisone to cortisol, increased extra-thyroidal conversion of T4 to T3, growth hormone insensitivity in women on oestrogen treatment and decrease insulin sensitivity.

### 3.5. Uncertainties and limitations about unfavourable effects

The safety database, with 333 patients treated for about 1.5 year with about 76% of patients treated longer than 12 months is limited and does not allow for an assessment of a safety profile on its own assuming that somapacitan is a variant of the known daily growth hormone containing products registered, the safety information from these medicinal products is, to some extent, also helpful for the evaluation of safety risks in somapacitan-treated patients.

The very limited information on the long-term safety of somapacitan in this less physiological situation, i.e. a more stable and less varying GH level and a more undulating IGF-I level is a reason for concern. It is unclear to what extent differences in plasma levels and administration frequency between once-weekly administered somapacitan and daily somatropin affect long-term safety of somapacitan.

Modelling of the IGF-I response indicates that after the initial titration, the 95% CI is well within the 2 SDS level for IGF-I. However, IGF-I SDS levels above 2 were observed in about 5% of AGHD patients at the applied somapacitan dosing regimen in study 4054. On the other hand, nearly 16% of AGHD study patients had an IGF-I SDS < -2 at C<sub>trough</sub> at the end of the titration period in the main and extension treatment phases in study 4054. Thus, using the titration algorithm as used in study 4054 the IGF-I levels are within a range of -2 SDS and +2 SDS for about 80% of the patients.

The safety profile of the proposed extension of the titration regimen of somapacitan in these AGHD patients is unknown. This optimized somapacitan dosing titration regimen which allows dose titration beyond 8 weeks and therefore higher somapacitan doses (up to a maximal dose of 8 mg/week) was only supported by modelling and simulation data. Therefore, the short- and long-term (benefits and) risks of an optimized somapacitan dose titration algorithm which allows dose titration beyond 8 weeks with a maximal dose of 8 mg/week in AGHD patients should be evaluated further. A category 3 PASS will be conducted for this purpose.

### 3.6. Effects Table

Table 22 Effects Table for Sogroya

| Effect                    | Short Description | Unit | Somap (A) | Pla (B) | Somat (C) | Uncertainties/ Strength of evidence <sup>2</sup> | References |
|---------------------------|-------------------|------|-----------|---------|-----------|--|------------|
| <b>Favourable Effects</b> |                   |      |           |         |           |  |            |

| Effect    | Short Description   | Unit | Somap (A) | Pla (B) | Somat (C) | Uncertainties/ Strength of evidence <sup>2</sup>  | References |
|-----------|---|------|-----------|---------|-----------|---|------------|
| TFP       | Change in truncal fat percentage at week 34 compared to baseline                | %    | -1.17     | +0.49   | -2.39     | <b>SoE</b> : A vs B:Δ-1.53 (95%CI:-2.68;-0.38) P= 0.009 ; Treatment effects consistent in different regions<br><b>Unc</b> : Comparisons A vs. C secondary analysis blinded vs. open label treatment, clinical relevance uncertain; A vs C:Δ 1.17 (95%CI: 0.23; 2.11) P< 0.05; discrepancy in effects of A on adipose tissue and lean body parameters. | Study 4054 |
| TFM       | Change in total fat mass (g) at week 34 compared to baseline                    | gram | -85.47    | +305.47 | -855.71   | <b>SoE</b> : <b>Unc</b> : A vs B:Δ -266 (95% CI: -1197; 664) P= 0.57<br>A vs C:Δ 724 (95% CI: -39; 1487) P= 0.06, Clinical relevance uncertain; discrepancy in effects of A on adipose tissue and lean body parameters.   |            |
| TLBM      | Change in total lean body mass (g) at week 34 compared to baseline              | gram | +1395.88  | +334.43 | +1359.33  | SoE : A vs B:Δ1144(95% CI: 459; 1829) P= 0.001 ; A vs C:Δ 49 (95% CI: -513; 610)P= 0.87<br>Clinical relevance uncertain; discrepancy in effects of A on adipose tissue and lean body parameters.  |            |
| TRIM-AGHD | Change in treatment-related impact measure-AGHD at week 34 compared to baseline | NA   | -5.71     | -3.65   | -9.99     | <b>Unc</b> : A vs B:Δ-2.83 (95% CI: -6.72; 1.05) P= 0.15 ; A vs CΔ 4.99 (95% CI: 1.84; 8.14) P= 0.002 ; Clinical relevance uncertain  |            |
| TSQM-9    | Convenience score at week 34  | %    | 77.7      | 74.3    | 73.9      | <b>SoE</b> : A vs C:wk 87 Δ7.09 (95%CI:1.7;12.4) P= 0.01<br><b>Unc</b> : A vs B :Δ2.86 (95% CI: -2.54; 8.27) P= 0.30 ; A vs C :Δ4.00 (95% CI: -0.40; 8.39) P= 0.07  |            |

#### Unfavourable Effects

|               |  |    |  |  |  |   |            |
|---------------|--|----|--|--|--|---|------------|
| GH exposition |  | NA |  |  |  | Somapacitan shows a stable GH level over the duration of treatment however the daily physiological variation of GH is not mirrored<br>Unknown effect on development of DM 2, cardiovascular risks and malignancies as a long term safety issue<br>Placebo: Some variation (more or less comparable with the physiological GH peak in the early morning) is maintained | Study 4054 |
|---------------|--|----|--|--|--|---|------------|

Abbreviations: AGHD: adult growth hormone deficiency, CI: confidence interval, DM: diabetes mellitus, TSQM Treatment satisfaction questionnaire

### **3.7. Benefit-risk assessment and discussion**

#### **3.7.1. Importance of favourable and unfavourable effects**

The clinical features associated with AGHD are – among others - abdominal obesity, decreased lean body mass, reduced muscle strength and exercise capacity and impaired psychological well-being. The increased cardiovascular mortality observed in adult patients with hypopituitarism has been attributed to these metabolic abnormalities. Thus, one of the goals of treatment of AGHD (besides improvement of the quality of life) is to reverse the abnormalities in body composition (increased body fat, decreased lean body mass and bone mass), improve lipid status (decrease in serum cholesterol, increase in HDL-cholesterol), exercise capacity and quality of life.

The main evidence of efficacy submitted is a single phase III multicentre, randomized, parallel-group study evaluating the clinical effects of double-blind somapacitan and placebo treatment and open-label somatropin treatment. Comparisons between somapacitan and somatropin concerned secondary analyses. Respective treatment comparisons should be interpreted with some reservation since study 4054 was primarily developed to compare the clinical effects of somapacitan and placebo treatment.

The observed effect size of somapacitan for the primary endpoint change in truncal fat percentage at week 34 as compared to baseline was larger than that of placebo treatment. Similar trends were observed in several sensitivity analyses for the primary endpoint and for multiple secondary endpoints such as changes in fat masses, lean body mass, quality of life, and treatment satisfaction. The totality of the observed effects compared to placebo is considered clinically relevant.

When compared with daily somatotropin clinical effects of somapacitan with respect to adipose tissue masses (including the primary endpoint change in truncal fat percentage at week 34) tended to be smaller compared to those of somatropin, whereas the clinical effects of both active substances were comparable with respect to lean body masses.

No consistent effects of somapacitan in comparison with those of placebo and somatropin were observed with respect to the quality of life and well-being. The high variability known from the quality of life parameters decrease the sensitivity of such assessment and might explain why a clear and evident beneficial effect is not seen in both the somatropin and the somapacitan groups as compared to placebo.

The IGF-I concentration is currently considered a predictor for the increase in lean body mass where (according to the experts) the growth hormone concentration is predictive for the decrease in adipose tissues. The limited efficacy of somapacitan compared to daily somatropin may be explained by the fact that the IGF-I SDS target range of -0.5 up to +1.75 was not achieved in 22% of study patients in the main treatment phase of study 4054. This proportion was even higher in subgroups of AGHD patients who are less sensitive to growth hormone treatment, such as women on oral oestrogen treatment (42%), and patients with childhood-onset AGHD (34%) (main treatment phase).

Therefore, the observed discrepancy between the effects of somapacitan and somatropin on lean body masses and adipose tissue masses might partly be explained by a suboptimal somapacitan titration in a considerable proportion of AGHD patients resulting in too low IGF-I SDS levels, especially in women on oral oestrogen treatment.

A *post-hoc* exposure-response study and a *post-hoc* simulation study indicate that clinical efficacy (expressed in IGF-I SDS scores) of somapacitan may increase upon application of an extended somapacitan dose

titration in individual AGHD patients in which somapacitan dose titration beyond 8 weeks is allowed to achieve IGF-I SDS levels between 0 and +2 at a somapacitan dosage not exceeding 8 mg per week. These *post-hoc* analyses indicated that a larger proportion of the patients might reach an IGF-I SDS between 0 and +2. The safety results seen after daily somatropin in the pivotal study are in line with reported effects in previous studies with daily growth hormone treatment. Overall, from the limited population evaluated a short-term safety profile emerged which appears not different from the known growth hormone-containing medicinal products (e.g. somatropin product Norditropin).

Although for the long-term safety, no serious safety issues are expected the lack of a long-term follow-up of the unphysiologic growth hormone and IGF-I exposition of somapacitan hampers an adequate assessment. It is unknown to what extent somapacitan affects long-term safety risks such as the development of diabetes mellitus type 2 and malignancies. Therefore this will be further investigated post-authorisation.

Currently available study data and additional evidence from *post-hoc* analyses support the short-term clinical efficacy at an acceptable safety level of a flexible, somapacitan dose titration regimen in AGHD patients. However, it is yet unclear whether similar results can be obtained upon application of such a somapacitan dosing regimen in actual AGHD patients, in particular in AGHD patients who are less sensitive to growth hormone (e.g. women on oral oestrogen, patients with childhood GHD onset). The titration schemes in this subgroup will be further characterised in the planned PASS.

### **3.7.2. Balance of benefits and risks**

Based on the biological effects, somapacitan can be considered a long-acting growth hormone. When compared with placebo somapacitan was shown to decrease truncal fat percentage and improves other body composition endpoints in comparison with placebo. In addition, somapacitan tended to increase treatment satisfaction to a larger extent than placebo treatment. The observed effects of somapacitan are considered clinically relevant as they appear comparable with those of the open-label daily somatropin group. Comparing both drugs, no differences for convenience or global satisfaction was reported.

Study data indicate that somapacitan dosing was too low in a considerable proportion of AGHD patients resulting in too low IGF-I SDS levels, especially in subgroups of AGHD patients who are less sensitive to growth hormone treatment (e.g. women on oral oestrogen treatment, childhood-onset AGHD patients).

Post-hoc analyses indicated that an extended somapacitan dose titration regimen with potential dose titration beyond 8 weeks to achieve IGF-I SDS levels in the range between 0 and +2 might increase the short-term and long-term clinical efficacy of somapacitan in AGHD patients. It is unclear whether this can also be observed in actual AGHD patients as this optimized regimen was not prospectively tested in a clinical study. Further information on the effectiveness (i.e. effects on IGF-I, fat mass and lean body mass) of the modelled titration algorithm in different AGHD subgroups in clinical practice is, therefore, considered needed. Information regarding clinical effects of an adjusted somapacitan dosing regimen should be further collected and evaluated post-authorization in a PASS. Special attention should be given to those who are less sensitive to the clinical effects of somapacitan treatment, such as female AGHD patients on oral oestrogen therapy and patients with childhood-onset GHD.

The short-term safety profile of somapacitan in current dosing regimen appeared to be in line with the known growth hormone-containing medicinal products, though limited safety data are available. Although no serious safety issues are to be expected, the long-term safety risks of unphysiological fluctuations of growth hormone and IGF-I upon weekly somapacitan administrations and potentially increased exposition using an optimized

titration algorithm are unknown and should be further evaluated post-authorization in a PASS. The applicant agreed to perform a PASS evaluating the long-term risks for malignancies and diabetes mellitus type 2. In addition, the effects of the adherence to the weekly somapacitan treatment should be assessed in the PASS. Finally, as patients and physicians are not used to weekly growth hormone treatment, the number of medication errors should be measured in the PASS. This will allow the development of appropriate risk minimisation measures if needed.

At present, the short-term and long-term benefits of somapacitan outweigh its risks for proposed AGHD indication.

Hence, the benefit/risk balance of somapacitan growth hormone replacement treatment for AGHD is positive.

### **3.7.3. Additional considerations on the benefit-risk balance**

Previously the CHMP reviewed another long-acting GH i.e Somatropin Biopartners (EMA/H/C/2196) which received a marketing authorisation in 2013. The applicant agreed on a PASS study to elucidate the long-term risks of the observed exposure with GH and IGF-I. Somatropin Biopartners was never marketed within the EU and was withdrawn in 2017 ("sunset clause"). There is no current data that somapacitan is associated with a higher incidence of injection site reactions. A PASS study is also requested for somapacitan to collect long-term safety data.

The AHEG considered somapacitan as a long-acting growth hormone which exerts clinical effects on both adipose tissue masses as well as lean body masses. According to the AHEG, such effects were observed in conducted clinical studies. The AHEG concluded that observed pharmacological effects of weekly somapacitan were overall comparable to those of daily somatropin. The experts considered that observed effects with once-weekly somapacitan in terms of change in body composition parameters versus placebo are clinically relevant and convincing. The AHEG further discussed the proposed titration algorithm. It was noticed that the somapacitan titration was to be based on the peak level of the somapacitan (3 or 4 days after injection). It was considered important to collect additional information on the long-term safety of the somapacitan.

Clinical data are necessary to further define the algorithm of somapacitan titration and to collect information about the benefits and of the proposed dose titration (in all subgroups of AGHD patients). In this discussion also the effects on the trough levels of somapacitan should be considered.

### **3.8. Conclusions**

The overall B/R of Sogroya (somapacitan) is positive.

## **4. Recommendations**

### ***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 is favourable in the following indication:

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

### ***Conditions or restrictions regarding supply and use***

Medicinal product subject to restricted medical prescription.

### ***Other 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

#### **Risk Management Plan (RMP)**

The 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.

#### ***New Active Substance Status***

Based on the CHMP review of the available data, the CHMP considers that somapacitan is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.