Medicinrådet

Bilag til direkte indplacering af somapacitan i Medicinrådets af evidensgennemgang vedrørende lægemidler til væksthormonmangel

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. somapacitan
2. Ansøgers endelige ansøgning vedr. somapacitan

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Forhandlingsnotat

26.05.2026

MBA/KLE/DBS

Dato for behandling i Medicinrådet	24.06.2026
Leverandør	Novo Nordisk
Lægemiddel	Sogroya (somapacitan)
Ansøgt indikation	Substitution af endogent væksthormon (GH) hos børn i alderen 3 år og derover og unge med vækstforstyrrelse, som skyldes væksthormonmangel (pædiatrisk GHD), og hos voksne med væksthormonmangel (voksen GHD).
Nyt lægemiddel / indikationsudvidelse	Direkte indplacering

Prisinformation

Amgros har forhandlet følgende pris på Sogroya (somapacitan):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (paknings-størrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Sogroya	5 mg (1 stk.)	2991,13	[redacted]	[redacted]
Sogroya	10 mg (1 stk.)	6072,89	[redacted]	[redacted]
Sogroya	15 mg (1 stk.)	6322,08	[redacted]	[redacted]

Prisen er ikke betinget af Medicinrådets anbefaling. Sogroya indplaceres direkte i Medicinrådets eksisterende behandlingsvejledning for anvendelse af væksthormon hos børn og voksne.

Amgros indgår en aftale med leverandøren umiddelbart efter mødet i Medicinrådet.
[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Sogroya er det først langtidsvirkende væksthormon, som har ansøgt Medicinrådet. Der er yderligere to langtidsvirkende lægemidler, som er godkendt i EMA, men som endnu ikke har ansøgt Medicinrådet: Ngenla (somatrogon) fra Pfizer blev godkendt i EMA februar 2022 og Skytrofa (lonapegsomatropin) fra Ascendis blev godkendt i EMA januar 2022.

Sogroya bliver klinisk ligestillet med de øvrige lægemidler under "Anvend" i Medicinrådets behandlingsvejledning inkl. Det kliniske sammenligningsgrundlag for anvendelse af væksthormon hos børn og voksne baseret på en tidligere RADS behandlingsvejledning.

Tabel 2 viser lægemiddeludgifter på udvalgte sammenlignelige lægemidler.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient pr. 28,5 kg

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. 52 uger (SAIP, DKK)
Sogroya	15 mg (1 stk.)	0,16 mg/kg ugentligt*	[redacted]	[redacted]
Omnitrope	15 mg (1 stk.)	0,034 mg/kg dagligt	[redacted]	[redacted]

* En antagelse om en gennemsnitlige vægt på 28,5 kg jævnfør *Opsummering af Medicinrådets evidensgennemgang vedrørende lægemidler til væksthormonmangel*

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Ansøgningen er annulleret	Leverandøren har ikke leveret det relevante materiale	Link til status
England	Anbefalet		Link til anbefaling
Sverige	Ingen informationer		

Opsummering

Leverandøren har givet deres pristilbud i forbindelse med den direkte indplacering i den eksisterende behandlingsvejledning.

[redacted]

Application for the assessment of Sogroya® for children and adults with growth hormone deficiency

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information

Contact information

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Abbreviations

Abbreviation	Definition
AACE	American Association of Clinical Endocrinologists
AE	adverse event
AGHD	adult growth hormone deficiency
ALS	acid-labile subunit
ANCOVA	analysis of covariance
BIM	budget impact model
BMD	bone mineral density
BMI	body mass index
CDC	centers for Disease Control and Prevention
CEA	cost-effectiveness analysis
CI	confidence interval
COVID-19	coronavirus-19 pandemic
CRP	c-reactive protein
CV	cardiovascular
CVD	cardiovascular disease
DXA	dual energy x-ray absorptiometry
ECG	electrocardiogram
EMA	European Medicines Agency
ETD	estimated treatment difference
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FPG	fasting plasma glucose
G-DAT	growth hormone device assessment tool
GH	growth hormone
GHD	growth hormone deficiency
GHD-CIM	Growth Hormone Deficiency – Child Impact Measure
GHR	growth hormone receptor
GHRH	growth hormone releasing hormone
GHRP-2	growth hormone releasing peptide-2
GP	general practitioner
HbA_{1c}	glycosylated haemoglobin

HDL	high-density lipoprotein
hGH	human growth hormone
HIV	human immunodeficiency virus
HOMA	homeostatic model assessment
HR	hazard ratio
HRQoL	health-related quality of life
hsCRP	high sensitivity c-reactive protein
HSDS	height standard deviation score
HV	height velocity
HVSDS	height velocity standard deviation score
ICER	incremental cost-effectiveness ratio
IGF-1	insulin-like growth factor-1
IFGBP-3	insulin growth factor binding protein 3
IL-6	interleukin-6
ITC	indirect treatment comparison
ITT	insulin tolerance test
IV/WRS	interactive voice/web response service
IWRS	interactive web response service
LAGH	long-acting growth hormone
LAR	legally authorise representative
LDL	low-density lipoprotein
LPL	lipoprotein lipase
LY	life-year
MID	minimal important difference
MMRM	mixed model for repeated measurements
MRI	magnetic resonance imaging
N/A	not applicable
NASH	non-alcoholic steatohepatitis
NCGS	National Cooperative Growth Study
NMA	network meta-analysis
NYHA	New York Heart Association
OAD	oral antidiabetic drug
PD	pharmacodynamics
PK	pharmacokinetics
PRO	patient reported outcomes

PSA	probabilistic sensitivity analysis
PYE	patient years
QALY	quality adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
SAE	serious adverse event
SAS	safety analysis set
s.c.	subcutaneous
SD	standard deviation
SDS	standard deviation score
SF-36v2	36-item short form health survey (version 2)
SLR	systematic literature review
SOC	system organ class
TAT	total adipose tissue
TTO	time trade-off
TB-CGHD-O	Treatment Burden Measure–Child Growth Hormone Deficiency–Observer
TB-CGHD-P	Treatment Burden Measure–Child Growth Hormone Deficiency –Parent
TRIM-AGHD	treatment-related impact measure for adult growth hormone deficiency
TSQM	treatment satisfaction questionnaire for medication
UK	United Kingdom
ULN	upper limit of normal
US	United States
VAT	visceral adipose tissue
WHO	World Health Organization
WTP	willingness to pay
YSR	Youth Self Report form
UK	United Kingdom

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Sogroya®

Overview of the medicine	
Generic name	Somapacitan
Therapeutic indication as defined by EMA	Replacement of endogenous growth hormone (GH) in children aged 3 years and above, and adolescents with growth failure due to growth hormone deficiency (paediatric GHD), and in adults with growth hormone deficiency (adult GHD)
Marketing authorization holder in Denmark	Novo Nordisk A/S
ATC code	H01AC07
Combination therapy and/or co-medication	No
Date of EC approval	31/03/2021
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Yes, 24/08/2018
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	No
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Somapacitan is available in the following pack sizes: • 5 mg/1.5 ml (teal): Unit packs containing 1 pre-filled pen. • 10 mg/1.5 ml (yellow): Unit packs containing 1 pre-filled pen. • 15 mg/1.5 ml (rubine red): unit packs containing 1 pre-filled pen. The device for somapacitan is the same device that is used in a wide range of other Novo Nordisk products in e.g. diabetes (e.g. Ozempic®, Wegovy®).

Overview of the medicine	
	Needles are not included. Somapacitan is designed for use with NovoFine Plus or NovoFine 32G needles with a length of 4 mm. If needles longer than 4 mm are used, injection techniques that minimise the risk of intramuscular injection, such as injection into a loosely held skin fold, should be used.

2. Summary table

Summary	
Indication relevant for the assessment	Replacement of endogenous growth hormone (GH) in children aged 3 years and above, and adolescents with growth failure due to growth hormone deficiency (paediatric GHD), and in adults with growth hormone deficiency (adult GHD)
Dosage regiment and administration	The recommended dosing regimen for somapatican is:

Paediatric GHD	**Recommended start dosis**
Treatment naive paediatric patients and paediatric patients switching from other GHD treatments	0.16 mg/kg/week
Adult GHD	**Recommended start dosis**
Naive patients	
Adults (≥18 to <60 years)	1.5 mg/week
Women in oral oestrogen therapy (regardless of age)	2mg/week
Elderly (60 years and above)	1 mg/week
patients switching from other GHD treatments	
Adults (≥18 to <60 years)	2 mg/week
Women in oral oestrogen therapy (regardless of age)	4 mg/week
Elderly (60 years and above)	1.5 mg/week

Summary	
	Administration form Somapacitan is only for subcutaneous use. Somapacitan comes in a prefilled pen which is ready for administration. Needles are not included in the package. Somapacitan should be administrated once-a-week at any time of day. Not necessarily at the same time every time. Somapacitan can be self-administrated or administrated by a caregiver after having received sufficient training by a health care professional and having read the administration guide. Somapacitan is to be injected subcutaneously in the abdomen, thighs, buttocks or upper arms. The injection site should be rotated every week to prevent local lipoatrophy. **Changing the dosing day** The day of weekly injection can be changed as long as the time between two doses is at least 4 days. After selecting a new dosing day, the once weekly dosing should be continued. **Flexibility in dosing time** On occasions when injection at the scheduled dosing day is not possible, once-weekly somapacitan can be administered up to 2 days before or 3 days after the scheduled weekly dosing day as long as the time between two doses is at least 4 days (96 hours). Once-weekly dosing for the next dose could be resumed at the regularly scheduled dosing day. **Storage** Somapacitan should be stored in a refrigerator for up to 6 weeks after first usage, but may be kept temporarily at temperatures up to 30°C for up to a total of 72 hours (3 days).
Choice of comparator	The current standard of care according to the DMC's treatment guideline is somatropin, which comes in different presentations (pens)
Prognosis with current treatment (comparator)	Paediatric GHD Growth hormone deficiency is a rare disease caused by impaired secretion of growth hormone (1). Children with untreated growth hormone deficiency often experience a decrease in height velocity, impaired bone development, and reduced muscle development. In addition, very low blood sugar is seen in newborn children. Growth hormone deficiency in children is associated with reduced quality of life related to the patients' small size, and the disease thereby affects several physical, psychological and social aspects of their lives (2). The current standard treatment for growth hormone deficiency in Denmark is to administer the growth hormone somatropin

by subcutaneous injection daily in the evening just before bedtime. Although the clinical efficacy of this treatment is widely recognized, it is also often associated with poor compliance (missed injections) (3).

Several studies have shown that reduced compliance in the treatment of growth hormone deficiency is associated with significantly reduced growth.

With current standard treatment with somatropin, there is no flexibility in the timing of the injection, as somatropin must be taken once a day just before bedtime. This is a challenge, especially for younger children, who often experience fear and discomfort during the injection, and often leads to a restless and conflict-filled evening routine for many children with growth hormone deficiency and their parents/caregivers (4).

Compliance with daily subcutaneous injections of somatropin before bedtime is reduced for many children, and thus they do not achieve the full effect on height velocity. There is therefore a need for a treatment for patients with growth hormone deficiency that involves fewer injections and flexibility in the timing of injections, thereby reducing discomfort and stress for children and their parents/caregivers every night before bedtime.

Adult GHD

Adult growth hormone deficiency (AGHD) is a rare condition characterised by low levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) (5; 6; 7). It can persist from childhood or be acquired in adulthood from pituitary tumours or their treatment, traumatic brain injuries, or other pituitary disorders (6; 8; 9).

Untreated AGHD is associated with adverse body composition, reflected in increased truncal and visceral fat and decreased lean body mass (6). These alterations contribute to the development of an adverse metabolic profile, which elevates cardiovascular risk and associated mortality (8; 10; 11; 12; 13). Other key clinical features include decreased bone mass and density (8), a higher incidence of fractures (14; 15; 16), and an increased risk of diabetes (17; 18) and non-alcoholic steatohepatitis (NASH) (19; 20).

Similarly to children with GHD, the current standard treatment for adults with growth hormone deficiency in Denmark is to administer the growth hormone somatropin by subcutaneous injection daily in the evening before bedtime.

Adherence to once-daily injections is suboptimal in adults with GHD, with 65% being non-adherent and 35% non-persistent (21). Key contributing factors include injection frequency and associated pain (22; 23), limited ease of use of the device (22; 23), and lack of storage flexibility (23; 24). Moreover, due to a

Summary	
	lack of time and competing priorities, adults are more likely to be non-compliant to therapy (25). As a result, treatment compliance declines over time, ultimately compromising treatment efficacy (26; 27).
Type of evidence for the clinical evaluation	Head-to-head studies

Most important efficacy endpoints (Difference/gain compared to comparator)	REAL 4 – children with GHD
	• Annualized height velocity (HV): Comparable change with an ETD of −0.5 cm/year [95% CI; −1.1, 0.2] for somapacitan vs somatropin
	Change from baseline to 52 weeks in:
	• HV SDS: Comparable change with an ETD of – 0.78 [95% CI; -1.63, 0.08] for somapacitan vs somatropin
	• Height SDS: Comparable change with an ETD of – 0.05 [95% CI; -0.18, 0.08] for somapacitan vs somatropin
	• Bone age: Comparable change with an ETD of – 0.02 [95% CI; -0.06, 0.01] for somapacitan vs somatropin
	• IGF-1 SDS: Comparable change with an ETD of 0.03 [95% CI; -0.30, 0.36] for somapacitan vs somatropin
	• Mean Adherence after 52 weeks:
	  ○ Somapacitan group: mean adherence of 95.8%
	  ○ Somatropin group: mean adherence of 88.3%
	Change from baseline to 52 weeks in QoL:
	• GHD-CIM: Comparable change with an ETD of 1.8 [95% CI; -2.9, 6.6] for somapacitan vs somatropin
	• TB-CGHD-O overall score: Comparable change with an ETD of -2.4 [95% CI; -5.7, 0.9] for somapacitan vs somatropin
	• TB-CGHD-P overall score: somapacitan significantly reduces the treatment burden for caregivers compared with somatropin with an ETD of - 6.0 [95% CI; -10.00, -2.10] for somapacitan vs somatropin
	• G-DAT questionnaire overall score: same proportion of patients found the device ‘easy’ or ‘very easy’ when injecting somapacitan or somatropin (96.3% vs 96.3%)
	REAL 1 – Adults with GHD

Summary	
	Change from baseline to 34 weeks in: • Truncal fat percentage: Comparable change with an adjusted between groups difference of 1.17% [95% CI; 0.23, 2.11] for somapacitan vs somatropin • Total fat mass: Comparable change with an adjusted between groups difference of 0.72kg [95% CI; -0.04, 1.49] for somapacitan vs somatropin • Lean body mass: Comparable change with an adjusted between groups difference of 0.05kg [95% CI; -0.51, 0.61] for somapacitan vs somatropin • Lipids: Comparable change in total cholesterol with an ETD of 1.02 mmol/L [95% CI; 0.98, 1.06] for somapacitan vs somatropin Comparable change in HDL cholesterol with an ETD of 1.03 mmol/L [95% CI; 0.97, 1.09] for somapacitan vs somatropin Comparable change in LDL cholesterol with an ETD of 1.03 mmol/L [95% CI; 0.98, 1.10] for somapacitan vs somatropin Comparable change in triglycerides with an ETD of 0.93 mmol/L [95% CI; 0.85, 1.03] for somapacitan vs somatropin • IGF-1 SDS: Comparable change with an ETD of 0.02 [95% CI; -0.23, 0.28] for somapacitan vs somatropin • QoL: TRIM-AGHD total score with an ETD of 4.99 [95% CI; 1.89, 8.14] for somapacitan vs somatropin SF-36v2 overall physical score with an ETD of -1.00 [95% CI; -2.50, 0.51] for somapacitan vs somatropin SF-36v2 overall mental score with an ETD of -1.70 [95% CI; -3.93, 0.58] for somapacitan vs somatropin TSQM-9 convenience score with an ETD of 4.00 [95% CI; -0.40, 8.39] for somapacitan vs somatropin TSQM-9 effectiveness score with an ETD of -10.74 [95% CI; -16.49, -4.98] for somapacitan vs somatropin
Most important serious adverse events for the intervention and comparator	Somapacitan: • Bladder transitional cell carcinoma Somatropin: • hemoconcentration

Summary	
Impact on health-related quality of life	Reported under efficacy endpoints
Type of economic analysis that is submitted	Cost-minimization
Data sources used to model the clinical effects	N/A
Data sources used to model the health-related quality of life	N/A
Life years gained	N/A
QALYs gained	N/A
Incremental costs	N/A
ICER (DKK/QALY)	N/A
Uncertainty associated with the ICER estimate	N/A
Number of eligible patients in Denmark	Incidence: 180 in year 5 Prevalence: 3,974 in year 5
Budget impact (in year 5)	79.409.960 DKK

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Growth hormone deficiency (GHD) is a rare disease caused by impaired secretion of growth hormone (GH) (1), and is one of the most common endocrine-related causes of short stature (28).

GHD

Children with GHD most commonly present with growth failure, maturation delays (1; 29) and short stature, which can become permanent in adulthood if left untreated (30). Compared with demographically matched controls, children with GHD also have a greater incidence of comorbidities, including cardiovascular disease (CVD), insulin resistance, metabolic conditions (adverse lipid profiles) (31), lower bone mineral density (32), and mental health conditions (33). Furthermore, comorbidities that start during childhood can persist into adulthood (34). Short stature in children with GHD is associated with reductions in QoL compared with healthy peers, affecting numerous physical, social and emotional aspects of daily life (2).

The overall aim of treatment in children with GHD is to normalise height during childhood and adolescence (35), with clinical practice guidelines routinely recommending treatment with GH replacement therapy (35; 36; 37; 38; 39)(3, 5, 15-17). The introduction of GH therapy has resulted in children with GHD achieving their height potential (35; 36; 39; 37; 38) (40; 41; 42), improving their lipid profile and body composition (40; 43), and increasing bone length and density (44; 45; 46; 47). GH therapy has also been shown to improve the QoL of children with GHD (48; 49), including their physical, emotional, and social well-being (50).

Adult GHD (AGHD)

Adult growth hormone deficiency (AGHD) is a rare condition characterised by low levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) (5; 6; 7). It can persist from childhood or be acquired in adulthood from pituitary tumours or their treatment, traumatic brain injuries, or other pituitary disorders (6; 8; 9).

Untreated AGHD is associated with adverse body composition, reflected in increased truncal and visceral fat and decreased lean body mass (6). These alterations contribute to the development of an adverse metabolic profile, which elevates cardiovascular risk and associated mortality (8; 10; 11; 12; 13). Other key clinical features include decreased bone mass and density (8), a higher incidence of fractures (14; 15; 16), and an increased risk of diabetes (17; 18) and non-alcoholic steatohepatitis (NASH) (19; 20).

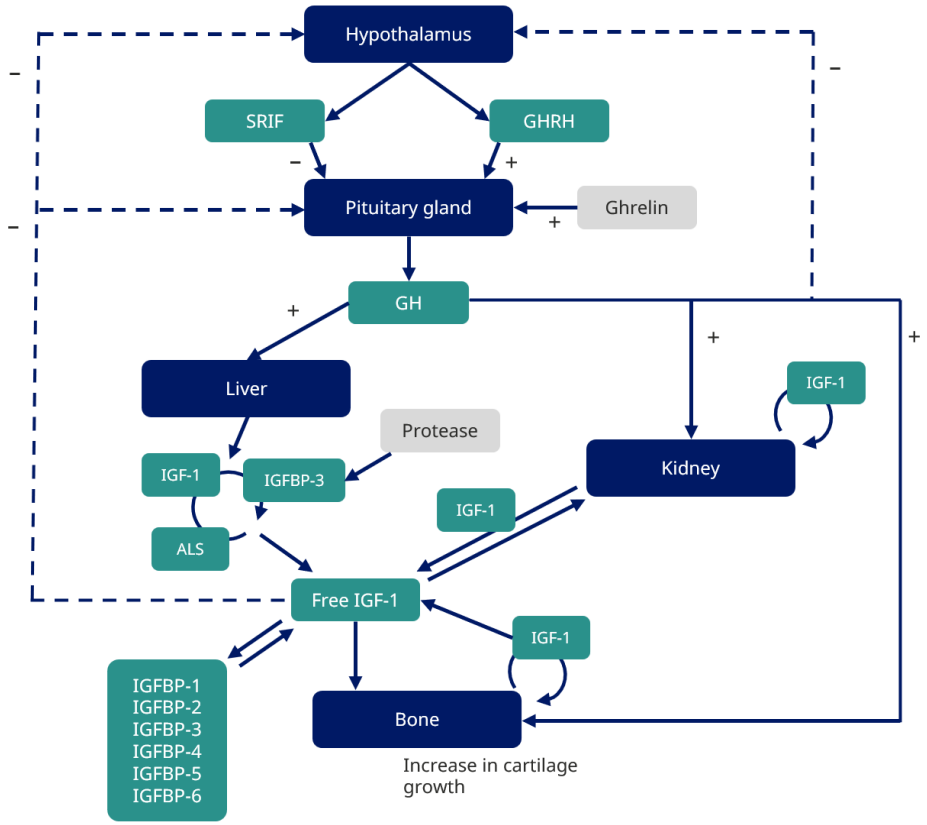
3.1.1 Pathophysiology

GH is the most important hormonal regulator of postnatal longitudinal growth. In children and adolescents, GH is responsible for increasing bone length and density (1; 32; 45), regulating body composition (1), and acts as a counter-regulatory hormone that antagonises the effects of insulin on glucose metabolism (51; 52; 53). GH affects whole-body lipid metabolism and exerts its biological effect through transcriptional regulation and acute changes in the catalytic activity of several enzymes (52). These regulatory processes contribute to the overall growth and maturation of children and adolescents into adults.

GH acts directly on tissue targets or indirectly by induction of transcription factors, primarily IGF-1 (1; 54; 55). The binding of GH to its receptor on cell membranes subsequently activates the Janus kinase-signal transducer and activator of transcription (JAK–STAT) signalling pathway (56). STAT proteins migrate to the nucleus of the cell

inducing the transcription of genes encoding IGF-1, IGF-2, IGF-binding protein 3 (IGF-BP3) and acid-labile subunit (ALS). The interplay between GH and IGF-1 is known as the GH-IGF-1 axis, a complex system involving negative feedback mechanisms.

Figur 1: Overview of the GH-IGF-1 axis



Abbreviations: ALS, acid-labile subunit; GHR, growth hormone receptor; GH, growth hormone; GHRH, growth hormone releasing hormone; IGF-1, insulin growth factor 1; IGFBP, insulin growth factor binding protein; SRIF, somatostatin.
Source: Roelfsema, 2001 (57)

The GH–IGF-1 axis has a leading role in growth and development (56; 58). IGF-1 is part of a complex system involved in regulating cellular division and growth across all cell types (59). IGF-1 binds to two transmembrane tyrosine-kinase-linked receptors, the insulin receptor and the IGF-1 receptor, which then transduce the IGF-1 signal into target cells. As well as controlling growth, GH and IGF-1 have clinically significant effects on carbohydrate, lipid and protein metabolism (29; 60; 58; 61; 62; 63; 30; 59):

- Growth hormone antagonizes insulin's action on peripheral tissues, including adipose tissues, skeletal muscle, and liver. In doing so, GH increases glucose production in the skeletal muscle and liver, and decreases glucose uptake from adipose tissue (64). Conversely, IGF-1 lowers glucose levels and increases insulin sensitivity (61) (62) (65).
- Growth hormone stimulates lipolysis via activation of the lipoprotein lipase (LPL) which hydrolyses triglycerides into free fatty acids, primarily in the visceral

adipose tissue. Conversely, GH and IGF-1 promote skeletal muscle update of free fatty acids (66) (58) (64).

- Insulin-like growth factor-1 mediates the effect of GH on protein metabolism by stimulating protein synthesis in muscle and decreasing proteolysis in the liver (63)

It is important to consider that factors such as nutritional status, concomitant medication (e.g. glucocorticoids, psychotropic drugs, etc.), and psychosocial conditions also influence growth and the GH-IGF axis.

3.2 Patient population

The evidence on the GHD population in Denmark is very scarce and no new evidence has been generated since the Stockholm et al. article (67) which is referenced in the 'RADS, Baggrundsnotat for anvendelse af væksthormon hos børn og voksne, Nov 2013' (68). Hence the following estimations take basis on these figures which are more than 20 years old. [redacted]. The article incidence rate in GHD in DK using national registry data from DK in the years of 1980-1999. The incidence was stated to be 3 and 2 per 100.000 boys and girls with GHD and likewise 3 and 2 per 100.000 men and women with AGHD. The incidence rate used to estimate the incidence in the previous 5 years based on figures from the general population in DK is then 0.00003.

To estimate the prevalence of GHD in DK in the past 5 years the growth rate from the general population in DK from 1st January 2000 to 1st January 2021 has been used in order to project the prevalence stated in the RADS' GHD recommendation from 2013 to 2021 figures (Danmarks Statistik: BEFOLK2). The prevalence rate in the adult population is then estimated to be 0.00045 and 0.00095 in the paediatric population.

Table 1: Incidence and prevalence in the past 5 years

Year	2021	2022	2023	2024	2025
Incidence in Denmark	175	176	178	179	180
Prevalence in Denmark	3,266	3,441	3,617	3,795	3,974
Global prevalence*	N/A	N/A	N/A	N/A	N/A

* For small patient groups, also describe the worldwide prevalence. Sources: Stockholm et al. 2006 (67), RADS, Baggrundsnotat for anvendelse af væksthormon hos børn og voksne, 2013 (68), Danmarks Statistik: BEFOLK2 (69)

The patient population included in this application is children and adults with GHD. The expected number of patients in DK eligible for treatment is presented in Table 2 using similar methodology as in above applying prevalence and incidence rates to figures from the general population as well as population growth rate since 2000 (Danmarks Statistik: BEFOLK2).

Table 2: Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	4,153	4,343	4,544	4,757	4,981

Sources: Stockholm et al. 2006 (67), RADS, Baggrundsnotat for anvendelse af væksthormon hos børn og voksne, 2013 (68), Danmarks Statistik: BEFOLK2 (69)

3.3 Current treatment options

3.3.1.1.1 Paediatric GHD

The primary goal of therapy in children with GHD is the promotion of growth and normalisation of height during childhood and adolescence (35), ensuring children with GHD ultimately reach an adult height which is as close as possible to mean population height (60). Clinical practice guidelines recommend treatment with GH replacement therapy (35) (36) (39) (37) (38). GH therapy accelerates growth (48), improves body composition and increases BMD in children with GHD (44), resulting in improved QoL and reduced economic burden (49). The established standard of care for GHD is daily injections of synthetic GH.

Long-acting formulations with once-weekly administration have demonstrated non-inferiority to daily GH (70), with expert consensus stating that children who are at risk of low adherence may derive particular benefit from them (71).

The established treatment for GHD is somatropin (38), a synthetic form of hGH produced by recombinant DNA technology, which has been available since 1985 (60). Somatropin is administered subcutaneously once daily.

All currently available GH therapies in Denmark require once-daily injections, with burdensome treatment administration and injection pain – factors that have been associated with a negative impact on QoL.

3.3.1.1.2 Poor adherence to daily GH therapy

Despite the recognised benefits of GH therapy in children with GHD, low adherence to once-daily GH therapy is common (29) (72) (4). A large retrospective UK cohort study including children with GHD between ≥3 and <16 years old treated with once-daily

somatropin, demonstrated that non-persistence (a gap of >90 days between prescriptions) is common in real-world practice, and increases with time on therapy; persistence at 12, 36 and 48 months was found to be 72%, 53% and 43%, with a mean number of days between refills of 31.0, 31.9 and 32.3 days (73).

Low adherence is associated with reductions in treatment efficacy, and worsened clinical outcomes compared with children who are compliant with treatment (29) (72) (74) (75) (76). Suboptimal adherence has indeed been associated with inferior growth trajectory; in a retrospective chart study of 201 children started on somatropin, adherent children gained an additional 1.8 cm per year compared with suboptimally adherent children (missing ≥20% of injections), after adjustment for covariates (77). Similarly, in a study of 158 children on daily GH, low adherence (missing >8% of injections) resulted in significantly decreased HV-SDS (1.57 vs. 0.61, p=0.002) (78). The effects of adherence on growth trajectory may also compound as adherence decreases; regression analyses using data from a phase IV observational study found that missing one or two injections per week resulted in a reduction of 0.11 or 0.22 SD in height gain over the first two years of treatment, respectively (79).

The most commonly reported reasons for not adhering to once-daily GH treatment schedules include the burden of treatment administration – such as the frequency of daily injections, issues with reconstitution, injection anxiety and injection-associated pain, and lack of parent/children confidence in administering treatment (68) (29) (72) (4) (80) (81) (82), highlighting the need for a less burdensome form of administration. Administering daily injections to children is often perceived as difficult or worrisome by caregivers (4).

3.3.1.1.3 The burden of current daily GH treatments

As stated in the previous section, multiple factors contribute to the burden of current daily GH treatments which impacts treatment adherence.

Injection pain remains a significant problem. Injection of GH therapy can result in anxiety for many children with GHD, which may be associated with the physical burden of injections causing pain, bleeding and bruising (4) (74) (80). A survey including 34 parents of children with GHD found that 38% worried about causing pain to their child, whilst 47% said that their child exhibited fear of injections (4) (83); in another survey including 69 parents, 37% felt that their child suffered from anxiety relating to injection pain (84).

A recent TTO study, conducted in the UK and Canada, highlighted the burden of injection pain in terms of its impact on HRQoL (83). Two surveys were conducted, in which respondents from a sample of the general population were asked to respond from the perspective of an adult with GHD (Survey 1) and as a parent/caregiver of a child with GHD (Survey 2). In Survey 2, injection pain was considered the most important treatment aspect, associated with a significant disutility of –0.04 ($p<0.001$); this was followed by the desire for a less complex treatment device, which was associated with a significant gain of 0.01 (p=0.006).

3.3.1.1.4 AGHD

While once-daily GH therapy has proven effective in improving body composition, metabolic profile and risk of mortality in adults with AGHD, (6) (8) (19) (85) (86) (87) (88)its demanding daily regimen is often seen as a major disadvantage and patients may experience treatment fatigue (89) (26) (90) (91) (92).

Treatment discontinuation rates in patients with AGHD are high, varying between 13.3–58.9% (93). In a study of 158 adults with GHD, the rate of non-adherence was 65%, with only 34% of patients being classified as highly adherent. Moreover, among patients with AGHD from the National Cooperative Growth Study (NCGS) registry in the US, within 11 months of initiating treatment, the percentage of patients collecting their prescription of GH treatment decreased to 54% (21). Adults, especially those in middle age, are likely to be non-compliant to therapy due to a lack of time and other priorities (25).

Injection pain is recognised to affect treatment compliance (89) (22) (21). A recent time trade-off (TTO) study conducted in the UK and Canada elicited the utilities associated with GH treatments (83). Respondents from the general population (n=1,782 adults and n=1,678 adults with a child <15 years old[1]) were asked to evaluate health states associated with different aspect of GH treatment. Avoiding daily injection pain was associated with the greatest impact on health-related quality of life (HRQoL), with a significant utility gain of 0.030 (95% CI 0.026; 0.035, p<0.001) in adults and 0.044 (95% CI 0.038; 0.051, p<0.001) in adults with a child. Concordantly, in a cross-sectional analysis of adult patients with GHD, 107 were taking GH replacement therapy of which 27.1% (n=29) of patients reported deliberately missing an injection; the most cited reasons for missing injections were being away from home (9.3%, n=10), disliking the daily injection (9.3%, n=10), and pain or discomfort during the injection (4.7%, n=5) (94).

Poor treatment adherence is associated with worsened clinical outcomes. Discontinuation of GH replacement therapy in patients with GHD is associated with an increase in fat mass and a decrease in muscle mass (95). Indeed, in a study of 64 patients who had discontinued treatment for ≥12 months, fat percentage increased by 2.3 percentage-points (p=0.003) (96). Moreover, in an observational, retrospective, Italian study including 43 patients with AGHD, a significant direct correlation between daily GH treatment adherence and IGF-1 z-score was observed over the two-year follow-up (Pearson's r coefficient = 0.61, p<0.05). Patients with high treatment adherence (defined as adherence ≥85%) had improved IGF-1 z-scores compared with the low adherence group (patients with adherence ≤56%) (27). Similar trends have been observed in paediatric and adolescent patients with GHD, with height velocity (HV) positively correlated with treatment adherence (77) (72).

[1] Adults aged ≥18 years evaluated heath states as if they were receiving the GH injections themselves. Adults with a child <15 years evaluated health states as if they were administering injections to a child.

3.3.1.1.5 Unmet need

The currently available GH therapies in Denmark require once-daily injections. Despite the recognised benefits of GH therapy, low adherence to once-daily GH therapy is common both among children and adults with GHD (29) (72) (4) and has been associated with reductions in treatment efficacy, and worsened clinical outcomes (77) (78) (79). The most commonly reported reasons for not adhering to once-daily GH treatment schedules include the frequency of daily injections, issues with reconstitution, injection anxiety and injection-associated pain, lack of time and competing priorities and lack of parent/children confidence in administering treatment (29) (72) (4) (80) (81) (82). Other factors reported to adversely affect adherence to current GH therapies include lack of storage flexibility, devise reusability, lack of choice of device, low device ease of use (e.g., the need for reconstitution), and visible needles (72) (4) (97) (83) (98).

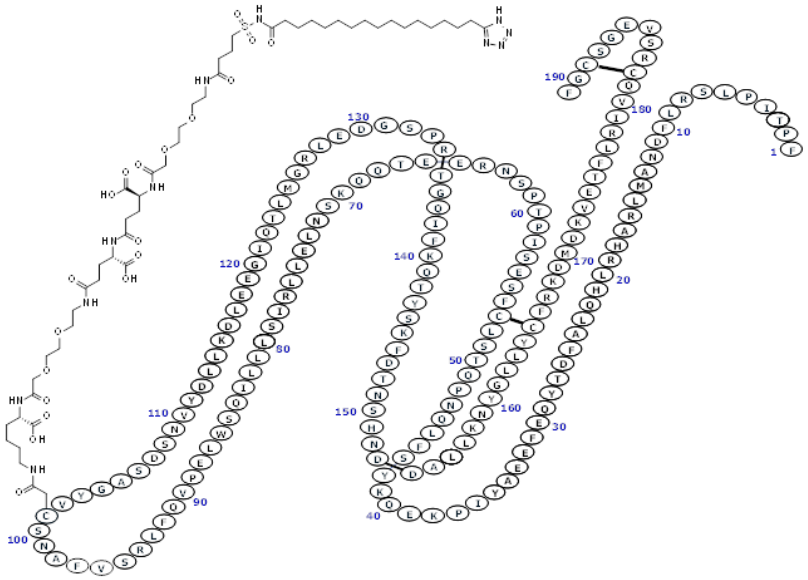
There is therefore an unmet need for an effective once-weekly GH therapy which is ready to use, easy to administer and store, and associated with fewer injections and reduced injection pain. Such a therapy could reduce treatment burden and potentially improving treatment adherence.

3.4 The intervention

Somapacitan is a long-acting, recombinant GH derivative offering a once-weekly treatment option for children with GHD. The somapacitan molecule is 99% identical to somatropin, a naturally occurring GH, in terms of amino acid sequence (99). Somapacitan has a single amino acid substitution in the peptide backbone at position 101 (leucine [L] substituted with cysteine [C]) to which an albumin binding moiety has been attached (100) (101). The albumin-binding moiety consists of an albumin binder and a hydrophilic spacer, that facilitates reversible binding to serum albumin after injection (102) (100) (101) (Figur 2).

The resulting non-covalent reversible binding of the GH molecule to endogenous albumin delays the absorption and elimination of somapacitan, prolonging its in vivo half-life. The receptor potency, pharmacokinetic (PK) and pharmacodynamic (PD) properties of somapacitan make it suitable for once-weekly subcutaneous (s.c.) administration in children with GHD (100) (101).

Figur 2: Somapacitan amino acid chain showing the albumin binding moiety



Source: Novo Nordisk, (103)

The albumin-binding technology used for somapacitan is the same as that used in well-established Novo Nordisk products used in the treatment of diabetes, namely Tresiba® (insulin degludec, a long-acting insulin analogue) and Ozempic® (semaglutide, a long-acting glucagon-like peptide-1 derivative) (100) (104).

The PK properties of somapacitan in children with GHD following a single subcutaneous administration have been investigated at dose levels from 0.02–0.16 mg/kg (105) (106). A population PK/PD modelling has been performed to describe the steady-state PK/PD characteristics of somapacitan in children with GHD (106) (107). In the range of 0.02–0.16 mg/kg, somapacitan exposure increased in a dose-dependent but non-linear manner (105).

The PK properties of somapacitan in adults with GHD following subcutaneous administration have been investigated at dose levels from 0.01–0.32 mg/kg in healthy adults, and in clinically relevant doses up to 0.12 mg/kg in adults with GHD (101) (108). A population PK model was developed to describe the PK characteristics of somapacitan and to evaluate the influence of covariates on the disposition of somapacitan in GHD patients. For the clinically relevant dose range of somapacitan in adults, exposure increase was approximately proportional to dose (101) (108).

The PD effect of somapacitan can be assessed using serum profiles of IGF-1, which is a key marker of GH activity (109). A dose-dependent IGF-1 response is induced following somapacitan administration (106). In the Phase III trial in children with GHD (REAL 4, see section 6.1), mean IGF-I SDS levels increased from baseline levels and were within normal range (−2 to +2) after 52 weeks of treatment. There were no statistically significant differences between once-weekly somapacitan and daily somatropin throughout the trial, and a comparable IGF-1 SDS profile was observed (110).

In the pivotal Phase III trial in adults with GHD (REAL 1, see Section 6.2), mean IGF-1 SDS increased from a baseline value below –2 to a value within the reference range after 34 weeks of treatment. A statistically significant difference in change from baseline to Week 34 in IGF-1 SDS was observed between somapacitan and placebo. There were no statistically significant differences between once-weekly somapacitan and daily somatropin throughout the trial, and a comparable IGF-1 SDS profile was observed (111).

Overview of intervention	
Indication relevant for the assessment	Replacement of endogenous growth hormone (GH) in children aged 3 years and above, and adolescents with growth failure due to growth hormone deficiency (paediatric GHD), and in adults with growth hormone deficiency (adult GHD)
ATMP	N/A
Method of administration	Somapacitan is only for subcutaneous use. Somapacitan comes in a prefilled pen which is ready for administration. Needles are not included in the package.
Dosing	Somapacitan should be administrated once-a-week at any time of day. Not necessarily at the same time every time. Somapacitan can be self-administrated or administrated by a caregiver after having received sufficient training by a health care professional and having read the administration guide. Somapacitan is to be injected subcutaneously in the abdomen, thighs, buttocks or upper arms. The injection site should be rotated every week to prevent local lipoatrophy. **Changing the dosing day** The day of weekly injection can be changed as long as the time between two doses is at least 4 days. After selecting a new dosing day, the once weekly dosing should be continued. **Flexibility in dosing time** On occasions when injection at the scheduled dosing day is not possible, once-weekly somapacitan can be administered up to 2 days before or 3 days after the scheduled weekly dosing day as long as the time between two doses is at least 4 days (96 hours). Once-weekly dosing for the next dose could be resumed at the regularly scheduled dosing day. **Storage** Somapacitan should be stored in a refrigerator for up to 6 weeks after first usage but may be kept temporarily at temperatures up to 30°C for up to a total of 72 hours (3 days). The recommended dosing regimen for somapatican is:

Overview of intervention		
	Paediatric GHD	**Recommended start dosis**
	Treatment naive paediatric patients and paediatric patients switching from other GHD treatments	0.16 mg/kg/week
	Adult GHD	**Recommended start dosis**
	Naive patients	
	Adults (≥18 to <60 years)	1.5 mg/week
	Women in oral oestrogen therapy (regardless of age)	2mg/week
	Elderly (60 years and above)	1 mg/week
	patients switching from other GHD treatments	
	Adults (≥18 to <60 years)	2 mg/week
	Women in oral oestrogen therapy (regardless of age)	4 mg/week
	Elderly (60 years and above)	1.5 mg/week
Dosing in the health economic model (including relative dose intensity)	**Children with GHD:** Based on the REAL 4 clinical trial, a weekly dose of 0.16 mg/kg was used in the cost-minimization analysis, corresponding to a daily dose of 0.023. An average weight of 30 kg was used to calculate an average weekly dose of 4.80 mg per patient. **Adults with GHD:** Based on the REAL 1 clinical trial, an average weekly dose of 2.56 mg was used in the cost-minimization analysis.	
Should the medicine be administered with other medicines?	No	
Treatment duration / criteria for end of treatment	**Children with GHD:** Treatment should be discontinued in patients having achieved final height or near final height, i.e. an annualised height velocity < 2 cm/year and a bone age > 14 years in girls or > 16 years in boys which corresponds to the closure of the epiphyseal growth plates. Once the epiphyses are fused,	

Overview of intervention	
	patients should be clinically re-evaluated for the need for growth hormone treatment. **Adults with GHD:** GHD in adults is a lifelong disease and should be treated accordingly.
Necessary monitoring, both during administration and during the treatment period	**Paediatric GHD** Dose titration: Somapacitan dose may be individualised and adjusted based on growth velocity, adverse reactions, body weight and serum insulin-like growth factor I (IGF-I) concentrations. Average IGF-I standard deviation score (SDS) levels (drawn 4 days after dosing) can guide dose titration. Dose adjustments should be targeted to achieve average IGF-I SDS levels in the normal range, i.e. between -2 and +2 (preferably close to 0 SDS). If the IGF-I (SDS) is > 2, it should be reassessed after a subsequent somapacitan administration. If the value remains > 2, reducing the dose by 0.04 mg/kg/week is recommended. More than one dose reduction may be required in some patients. In patients who have had the dose reduced but are not growing well, the dose may be gradually increased as tolerated up to a maximum dose of 0.16 mg/kg/week. Dose increments should not exceed 0.02 mg/kg per week (102). Treatment evaluation: Evaluation of efficacy and safety should be considered at approximately 6- to 12-month intervals and may be assessed by evaluating auxological parameters, biochemistry (IGF-I, hormones, glucose, and lipid levels) and pubertal status. More frequent evaluations should be considered during puberty. When GHD persists after growth completion, growth hormone treatment should be continued to achieve full somatic adult development including lean body mass and bone mineral accrual (102). The REAL 4 and REAL 3 trials were designed such that the full range of IGF-1 levels could be sampled during somapacitan treatment. Throughout the main and extension periods, peak and trough measurements remained within the target range of -2 to +2 SDS, with mean values close to zero (110) (106). **Adult GHD** Dose titration: The somapacitan dose must be individually adjusted for each patient. It is recommended to increase the dose gradually with 2-4 weeks intervals in steps from 0.5 mg to 1.5 mg based on the patients' clinical response and experience of adverse reactions up to a dose of 8 mg somapacitan per week. Serum insulin like growth factor-I (IGF-I) levels (drawn 3-4 days after

Overview of intervention	
	dosing) can be used as guidance for the dose titration. The IGF-I standard deviation score (SDS) target should aim for the upper normal range not exceeding 2 SDS. IGF-I SDS levels in the target range are usually achieved within 8 weeks of dose titration. Longer dose titration may be necessary in some adult GHD patients (102). Treatment evaluation: Using IGF-I SDS as a biomarker for dose titration, the aim is to reach IGF-I SDS levels within the age-adjusted upper reference range (IGF-I SDS upper reference range: 0 and +2) within 12 months of titration. If this target range cannot be achieved within this period, or the patient does not obtain the desired clinical response, other treatment options should be considered. During somapacitan maintenance treatment, evaluation of efficacy and safety should be considered at approximately 6- to 12-month intervals and may be assessed by evaluating biochemistry (IGF-I-, glucose-, and lipid levels), body composition, and body mass index (102). In the 86 weeks REAL 1 Extension trial treatment with somapacitan lead to comparable mean IGF-1 SDS values to somatropin (111). **Paediatric and adult GHD** Switching from other growth hormone products: Patients switching from a weekly growth hormone to somapacitan are recommended to continue administration at their once weekly dosing day. Patients switching from daily human growth hormone to once-weekly somapacitan should choose the preferred day for the weekly dose and inject the final dose of daily treatment the day before (or at least 8 hours before) injecting the first dose of once-weekly somapacitan (102)**.**
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No
Package size(s)	Somapacitan is available in the following pack sizes: • 5 mg/1.5 ml (teal): Unit packs containing 1 pre-filled pen. • 10 mg/1.5 ml (yellow): Unit packs containing 1 pre-filled pen. • 15 mg/1.5 ml (rubine red): unit packs containing 1 pre-filled pen.

Overview of intervention	
	The device for somapacitan is the same device that is used in a wide range of other Novo Nordisk products in e.g. diabetes (e.g. Ozempic®, Wegovy®). Needles are not included. Somapacitan is designed for use with NovoFine Plus or NovoFine 32G needles with a length of 4 mm. If needles longer than 4 mm are used, injection techniques that minimise the risk of intramuscular injection, such as injection into a loosely held skin fold, should be used.

3.4.1 Description of ATMP

N/A

3.4.2 The intervention in relation to Danish clinical practice

In Denmark there exist 4 different treatments (trade names) all containing somatropin but delivered in different pens. Omnitrope® is the most widely used treatment with a [redacted] market share in terms of volume. Next comes Norditropin® with a [redacted] market share and the remaining [redacted] is shared by Genotropin GoQuick® and Genotropin Miniquick® [redacted]

The clinical content in the 4 pens is similar, but the prices differ, resulting in DMC recommending Omnitrope® as first line treatment and Norditropin® is second line (112).

All of above 4 somatropin treatments are to be administered once-daily just before bedtime with no flexibility in time of dosing in order to obtain the optimal treatment effect (102) (113) (114) (115). Omnitrope®, which the majority of all GHD are treated with in Denmark today cannot be stored at room temparature as both Norditropin® and Genotropin® can, where Omnitrope® has to be kept cool (2-8'c) making it more complicated for patients to travel even shorter distances, vacations, staying overnight at a friend's place, or participating in school camps with overnight stay. In these situations, patients have a higher likelihood of missing doses. Experience from clinical practice shows that such storage restrictions, but also type of device can have a huge impact on compliance necessitating different treatment alternatives (68).

A differentiator in the 4 currently available somatropin treatments in Denmark is the formulation which has an impact on the pain the patients experience when injecting GH. Treatments (pens) with phenol used as preservation instead of benzyl alcohol (which Omnitrope® uses) reduces the injection pain while use of citrate as buffer (pH) instead of histidine increases pain. Of the current available GH treatments in DK, only Norditropin® uses phenol as preservation making it less painful to inject than the other treatments (68).

The once-weekly somapacitan is provided in a ready-to-use, prefilled pen containing premixed liquid somapacitan with no reconstitution required. The pen is portable and can be stored at temperatures of up to 30°C for up to a total of 72 hours (3 days) over 6

weeks' usage. Somapacitan further reduces injection pain due to the histidine buffer, phenol preservative, and uses ultra-thin, ultra-short 32G needles (102) (116) (22). Somapacitan can be administered using smaller volumes meaning that a weekly dose can be administered in a single injection.[2] The pen has a spring-loaded dosing mechanism that requires a lower force on the dosing button than previous GH delivery systems making administration easier for individuals with reduced muscle strength (89). Somapacitan is administered once-weekly and offers an opportunity to considerably reduce the environmental impact of GH therapy compared with once-daily treatments. Switching children with GHD to somapacitan may decrease the number of injections and needles used by 313 over one year.

The reduced treatment frequency and ready-to-use formulation have been shown to result in improved adherence to somapacitan; pooled analysis of two studies comparing somapacitan with somatropin found that participants treated with somapacitan were three times more likely to be optimally adherent (OR: 3.02 [95% CI: 11.2, 8.13]), with an overall adherence rate of 95% in the somapacitan group compared with 88% in the somatropin group (117). Further, an SLR and meta-analysis including 10 studies comparing somapacitan with somatropin found that treatment satisfaction as measured by the TSQM-9, including convenience, was significantly higher in the somapacitan group compared with the somatropin group ($p<0.0001$) (118) (148).

The adherence-related advantages with somapacitan (only once-weekly injections, flexibility in day of dosing, storage flexibility (up to 30°C for up to a total of 72 hours) and reduced injection pain) compared to currently available GHD treatments, are relevant for the DMC and the Expert Committee to consider in the upcoming GHD treatment guideline.

3.5 Choice of comparator(s)

As described in above section, the current standard of care for children and adults with GHD is somatropin, which is available in different types of pens under different trade names, including Norditropin®, which is Novo Nordisk's own somatropin treatment. The Danish Medicines Council's national treatment guidelines, including drug recommendations for the use of growth hormone in children and adults, have listed 4 different pens (trade names) with somatropin for use in children and adults with GHD, and states that the listing of the 4 pens in the recommendation depends on the framework agreements which are contracted through the Amgros' tender and the Danish Medicines Council's assessment of the appropriateness thereof (119).

To date, Amgros has negotiated the lowest price for Omnitrope®, which is also listed as the first choice in the treatment guidelines (119). As stated in the previous section, somapacitan has several advantages compared to the currently available somatropin treatments (Omnitrope®, Norditropin® and Genotropin®: once-weekly dosing, and

[2] Depending on a patient's weight, higher doses requiring two injections may be required. A 30 mg/1.5 mL pen is in development to resolve this.

flexibility in terms of day of dosing effect (102) (113) (114) (115). Somatropin also offers storage flexibility (up to 30°C for up to a total of 72 hours), whereas Norditropin® may be stored outside of refrigerator for a maximum of 3 weeks below 25°C (114). Genotopin® may be stored outside of refrigerator for up to 28 days at a maximum temperature of 25°C (115). The most widely used GH treatment, Omnitrope®, do not offer the option of storage outside of refrigerator (113).

Based on the Danish Medicines Council's national treatment guideline, the relevant comparator for somapacitan in this assessment is somatropin, which is detailed in below table.

Overview of comparator	
Generic name	Somatropin
ATC code	H01AC01
Mechanism of action	Somatropin is human growth hormone produced by recombinant DNA-technology. It is an anabolic peptide of 191 amino acids stabilised by two disulphide bridges with a molecular weight of approximately 22,000 Daltons (114). The major effects of somatropin are stimulation of skeletal and somatic growth and pronounced influence on the body's metabolic processes.
Method of administration	Somatropin should be administered in a daily subcutaneous injection in the evening. The injection site should be varied to prevent lipoatrophy (114).

Overview of comparator	
Dosing	**Paediatric population** 0.025-0.035 mg/kg/day or 0.7-1.0 mg/m2/day When GHD persists after growth completion, growth hormone treatment should be continued to achieve full somatic adult development including lean body mass and bone mineral accrual (114). **Adult population** The dosage must be adjusted to the need of the individual patient. In patients with childhood onset GHD, the recommended dose to restart is 0.2-0.5 mg/day with subsequent dose adjustment on the basis of IGF-1 concentration determination (114). In patients with adult onset GHD, it is recommended to start treatment with a low dose: 0.1-0.3 mg/day. It is recommended to increase the dosage gradually at monthly intervals based on the clinical response and the patient's experience of adverse events. Serum IGF-1 can be used as guidance for the dose titration. Women may require higher doses than men, with men showing an increasing IGF-1 sensitivity over time. This means that there is a risk that women, especially those on oral oestrogen replacement are undertreated while men are overtreated (114). Dose requirements decline with age. Maintenance dosages vary considerably from person to person but seldom exceed 1.0 mg/day.
Dosing in the health economic model (including relative dose intensity)	**Children with GHD:** Based on the REAL 4 clinical trial, a daily dose of 0.034 mg/kg was used in the cost-minimization analysis, corresponding to a weekly dose of 0.238 mg/kg. An average weight of 30 kg was used to calculate an average weekly dose of 7.14 mg per patient. **Adults with GHD:** Based on the REAL 1 clinical trial, an average weekly dose of 2.31 mg was used in the cost-minimization analysis.
Should the medicine be administered with other medicines?	No

Overview of comparator	
Treatment duration/ criteria for end of treatment	**Children with GHD:** Treatment should be discontinued in patients having achieved final height or near final height, i.e. an annualised height velocity < 2 cm/year and a bone age > 14 years in girls or > 16 years in boys which corresponds to the closure of the epiphyseal growth plates. Once the epiphyses are fused, patients should be clinically re-evaluated for the need for growth hormone treatment. **Adults with GHD:** GHD in adults is a lifelong disease and should be treated accordingly.
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	A package with somatropin contains a prefilled multiple dose 1.5 ml pen with solution for injection. Somatropin is available in the following pack sizes: • 5 mg/1.5 ml: Solution for injection in pre-filled pen • 10 mg/1.5 ml: Solution for injection in pre-filled pen • 15 mg/1.5 ml: Solution for injection in pre-filled pen

3.6 Cost-effectiveness of the comparator(s)

As there is no clinically relevant difference between somapacitan and somatropin it is not relevant to perform a cost-effectiveness analysis.

Instead, a simple cost-minimization analysis has been conducted for this assessment. Hence this section is not applicable.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

REAL 4: somapacitan vs somatropin in children with GHD

The primary endpoint was HV at week 52 which is a commonly accepted primary endpoint in confirmatory trials with GH (110). Improvements in HV as well as HSDS have been shown to be associated with long-term benefits in growth for daily GH treatment.

The relevant efficacy outcomes for this assessment are listed in Table 3.

Table 3: Efficacy outcome measures relevant in children with GHD for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Annualized HV (cm/year)	Week 52	Height Velocity (HV) was derived from height measurements recorded at baseline and Week 52. Height velocity =	Standing height (without shoes) was measured by a trained person blinded to treatment allocation. Standing height was measured 3 consecutive times in centimetres or inches and rounded to one decimal.
Mean change from baseline in HV SDS	Week 52	HV SDS was derived using Prader standards as reference data.	
Mean change from baseline in height SDS	Week 52	Height SDS (HSDS) was derived using Centre for Disease Control and Prevention (CDC) standards.	
Mean change from baseline in bone age	Week 52	General Bone Age Limit: Participants were required to have open epiphyses, defined as a bone age of < 14 years for females and < 16 years for males.	X-ray images of left hand and wrist for bone age assessment according to the Greulich and Pyle atlas were taken.
Mean change from baseline in IGF-1 SDS	Week 52	IGF-1 SDS = $\frac{\left(\left(\frac{IGF - I\ value}{Median}\right)^{Skewness}\right) - 1}{Skewness \times Standard\ Deviation}$ Median, skewness and standard deviation were based on reference tables published by Bidlingmaier	Blood samples were drawn for assessment of IGF-1. Samples were drawn prior to trial drug administration, if planned on a sampling day.
Mean adherence in % according to diary (SD)*	Week 52	Adherence to treatment was assessed via subject e-diaries, where doses were recorded in terms of date and time of each dose as well as any missed doses.	Information about the injection of trial product was recorded in the e-Diary device.
Mean change from baseline in GHD-CIM total score	Week 52	A validated disease specific questionnaire which measures the impact of GH treatment on symptoms, physical health and social and emotional wellbeing of children with GHD.	Completed in the e-Diary by the parent/LAR and the questionnaires were

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		Based on the responses, an overall score as well as domain specific scores can be derived. The scores ranges from 0 to 100. A lower score indicates a better health state (120).	preferably completed by the same parent/LAR.
TB-CGHD-O total score, mean	Week 52	A validated disease specific questionnaire which measures the physical burden of GH treatment as well as the burden of GH treatment on emotional wellbeing and interference in daily life activities of children with GHD. Based on the responses, an overall score as well as domain specific scores can be derived. The scores ranges from 0 to 100. A lower score indicates a better health state (121).	Completed in the e-Diary by the parent/LAR and the questionnaires were preferably completed by the same parent/LAR.
TB-CGHD-P total score, mean	Week 52	A validated disease specific questionnaire which measures the burden of GH treatment on the emotional wellbeing of the parent/guardian as well as the interference in daily life activities of the parent/guardian. Based on the responses, an overall score as well as domain specific scores can be derived. The scores ranges from 0 to 100. A lower score indicates a better health state (122).	Completed in the e-Diary by the parent/LAR and the questionnaires were preferably completed by the same parent/LAR.
G-DAT questionnaire Overall, **% 'easy' or 'very easy'**	Week 26	This questionnaire includes 6 questions that were completed by the parent/LAR to gather information on how the parents feel about their child's growth hormone device. The final question was "Overall, how difficult or easy is it to use the device". Answers were scored on a 5-level scale from 'Very difficult' to 'Very easy'.	Completed in the e-Diary by the parent/LAR and the questionnaires were preferably completed by the same parent/LAR.

* Time point for data collection used in analysis. Source: Miller et al. 2022 (110)

REAL 1: somapacitan vs somatropin in naïve AGHD

An individualised dose titration regimen rather than a fixed body weight-based regimen was chosen for this trial (111). Clinical studies suggest that AEs are less frequent in subjects receiving dose-titration as compared to the weight-based dosing (123). As IGF-1 is a biomarker of GH mediated effects, IGF-1 was chosen as a titration target. The dose titration algorithm was selected to reach a mean IGF-1 SDS value during steady state (MVSS) of -0.5 SDS to + 1.75 SDS and is based on PK/PD analysis of data from previous trials with somapacitan. Dose reduction in steps of 25% was selected as lowest anticipated reduction with significant change in GH related AEs (111).

Table 4: Efficacy outcome measures relevant in adults with GHD for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Change from baseline in truncal fat percentage, %	Week 34	Measured by DXA body composition scan	Efficacy was assessed by DXA body composition scan, body weight and waist circumference. Following DXA scan acquisition, each trial site was responsible for transferring each DXA scan to the imaging laboratory for quality review and analysis. DXA analysis data was transferred from the imaging laboratory to Novo Nordisk immediately prior to the DBLs of the main and extension periods. To avoid un-blinding the investigators will receive the results from the analysis after LPLV of the extension period.
% change from baseline in visceral fat, %	Week 34	% measured by DXA body composition scan	
Change from baseline in total fat mass, kg	Week 34	kg measured by DXA body composition scan	
Change from baseline in truncal fat mass, kg	Week 34	kg measured by DXA body composition scan	
Change from baseline in gynoid fat mass, kg	Week 34	kg measured by DXA body composition scan	
Change from baseline in android fat mass, kg	Week 34	kg measured by DXA body composition scan	
Change from baseline in total lean body mass, kg	Week 34	kg measured by DXA body composition scan	
Change from baseline in truncal lean body mass, kg	Week 34	kg measured by DXA body composition scan	
Change from baseline in appendicular skeletal muscle mass, kg	Week 34	kg measured by DXA body composition scan	
Change from baseline in hs-CRP (mg/L)	Week 34	High sensitivity C-reactive protein assesses cardiovascular risk by measuring low levels of CRP indicating inflammation.	Blood samples were drawn for assessment of hs-CRP and IL-6 and analysed by standard procedures at the central laboratory.
Change from baseline in IL-6 (pg/mL)	Week 34	IL-6 is an indicator of chronic inflammatory diseases and is also used to assess cardiovascular risk.	

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Relative change from baseline in HDL cholesterol (mmol/L)	Week 34	High density lipoprotein cholesterol. Higher levels are preferable and an indicator of good health and low risk of cardiovascular disease.	Blood samples were drawn for assessment of the lipid profile and analysed by standard procedures at the central laboratory.
Relative change from baseline in LDL cholesterol (mmol/L)	Week 34	Low density lipoprotein. Lower levels are preferable as higher levels increase risk of cardiovascular disease.	
Relative change from baseline in triglycerides (mmol/L)	Week 34	Higher levels of triglycerides are a risk marker of cardiovascular diseases.	
Relative change from baseline in total cholesterol (mmol/L)	Week 34	Higher levels of total cholesterol increase the risk of cardiovascular disease.	
Change from baseline in IGF-1 SDS	Week 34	Insulin-like Growth Factor-1 Standard Deviation Score: IGF-1 SDS = $\frac{\left(\left(\frac{IGF-I\ value}{Median}\right)^{Skewness}\right)-1}{Skewness \times Standard\ Deviation}$ Median, skewness and standard deviation were based on reference tables published by Bidlingmaier	Blood samples were drawn for assessment of IGF-1. When sampling for IGF-1, patients should be fasting 8 hours before sample collection (water allowed). All samples should be drawn prior to trial drug administration if this was planned on a sampling day. The IGF-I values from visits 3,5,7 and 9 were uploaded to the IV/WRS and used for dose adjustments during the titration period.
Change from baseline in body weight, kg	Week 34	Measured in kg with one decimal.	Body weight was measured in kg with one decimal as one observation (without shoes and overcoat) at screening, randomisation and every 2 to 3 months throughout the trial. It was preferable to measure body weight at the same time of day and preferably using the same scale from visit to visit.
Change from baseline in waist circumference, cm	Week 34	Waist circumference was defined as the minimal abdominal circumferences	Three consecutive measurements of waist circumference should be

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		located midway between the lower rib margin and the iliac crest.	performed and recorded in the eCRF. The waist circumference was measured to the nearest ½ cm using a non-stretchable measuring tape (measuring tapes were provided to the sites).
Change from baseline in TRIM-AGHD total score	Week 34	The Treatment Related Impact Measure-Adult Growth Hormone Deficiency (TRIM-AGHD) is a validated disease specific questionnaire which measures the impact of GH treatment on the functioning and well-being of AGHD patients. The 4 concepts covered by the questionnaire is physical health, energy levels, cognitive ability and psychological health. A lower score indicates a better health state (123).	The PRO questionnaires were completed by the patient and should preferably be completed after all fasting related activities but before any other visit related procedures were conducted. Written instructions on how to complete the questionnaires were provided to the patient.
Change from baseline in SF-36v2 overall physical score	Week 34	The Short Form 36 (SF-36v2) is a validated generic questionnaire that assesses the functional status and well-being of the patient by use of 36 questions.. A higher score indicates a better health state. The SF-36v2 questionnaire is widely used in studies related to AGHD (124).	
Change from baseline in SF-36v2 overall mental score	Week 34		
Change from baseline in TSQM-9 convenience score	Week 34	The Treatment Satisfaction Questionnaire for Medication - 9 items (TSQM-9) is a validated generic questionnaire that measures a patients' satisfaction with medication (125).	

* Time point for data collection used in analysis. Source: Johannsson et al. 2020 (111)

4. Health economic analysis

As there are no clinically relevant differences between the effects and safety observed for somapacitan and somatropin; a simple cost-minimization analysis is proposed as the most suitable analysis to conduct for the assessment of somapacitan. This approach is considered to be conservative, as the once-weekly somapacitan may potentially offer some benefits in terms of better adherence and convenience compared to once-daily somatropin.

Once-daily somatropin is currently the standard of care and due to somapacitan being a once-weekly injection which may be preferred in patients not able to adhere to a once-daily regimen, it is assumed that over time 30% of GH patients, who are currently treated with somatropin, as well as 30% of new GHD patients will start treatment with somapacitan.

4.1 Model structure

GHD in adults is a chronic condition and patients are likely to require treatment over the lifetime.

In GHD in children, treatment may be ended when height velocity is < 1 cm/year or acceptable height is reached (119). This is typically at the age of 15-16 years in girls and at the age of 17-18 years in boys (126).

The simple cost-minimization model is based on the clinical trials, REAL 1 and REAL 4.

The model runs over the same time horizon as the clinical trials and uses the clinical trial populations (completed patients and withdrawn patients) to estimate the costs per patient per year with somapacitan compared to somatropin.

As somapacitan has a similar efficacy and safety profile as somatropin demonstrating no clinically relevant difference in endpoints, extrapolation of efficacy data on a longer time horizon than the trial duration is not considered relevant nor meaningful to conduct.

Discounting was not applied as the analysis is based on same time horizon as the main phase of the clinical trials (up to 52 weeks).

The analysis considers a limited societal perspective where relevant treatment-related costs (drug acquisition costs) have been included. Since drug administration costs and training costs are assumed to be similar for somapacitan and somatropin, these are not included in the analysis.

Costs related to adverse events have not been included in the analysis as they were deemed to have a negligible impact on costs: no significant safety signals have been identified for somapacitan and the safety profile is similar to somatropin. Therefore, the demands on the Danish healthcare system for the management of adverse events related to somapacitan and somatropin are expected to be similar and unlikely to influence results of the health economic analysis.

4.2 Model features

Table 5: Features of the economic model

Model features	Description	Justification
Patient population	Children with GHD (Real 4) Adults with GHD (REAL 1)	In line with the European marketing authorization for Sogroya® (somapacitan)
Perspective	Direct treatment costs	According to DMC guidelines
Time horizon	Children with GHD: 52 weeks Adults with GHD: 52 weeks	To capture all direct treatment costs during the duration of the clinical trials which are relevant for the cost-minimization analysis.
Cycle length	N/A	The model is running for 52 weeks
Half-cycle correction		
Discount rate		
Intervention	Somapacitan	As per the Summary of Product Characteristics for Sogroya®
Comparator(s)	Somatropin	Currently the only marketed GH treatment in Denmark.
Outcomes	Annual drug acquisition costs/patient	Cost-minimization analysis

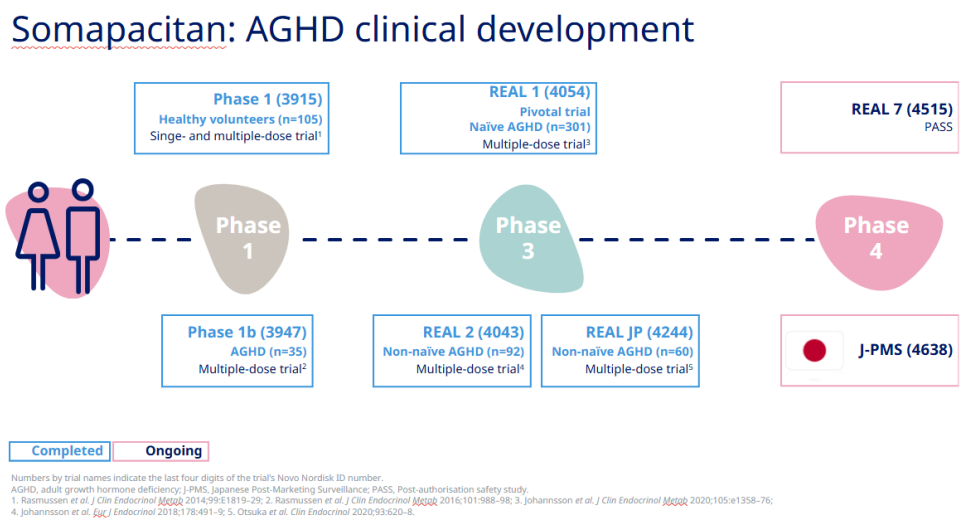
5. Overview of literature

As the clinical assessment and the health economic analysis are exclusively informed by head-to-head studies (REAL 1 and REAL 4) comparing somapacitan with somatropin, which is the most relevant comparator in the Danish Clinical practice, a SLR is not relevant and will be omitted from this application.

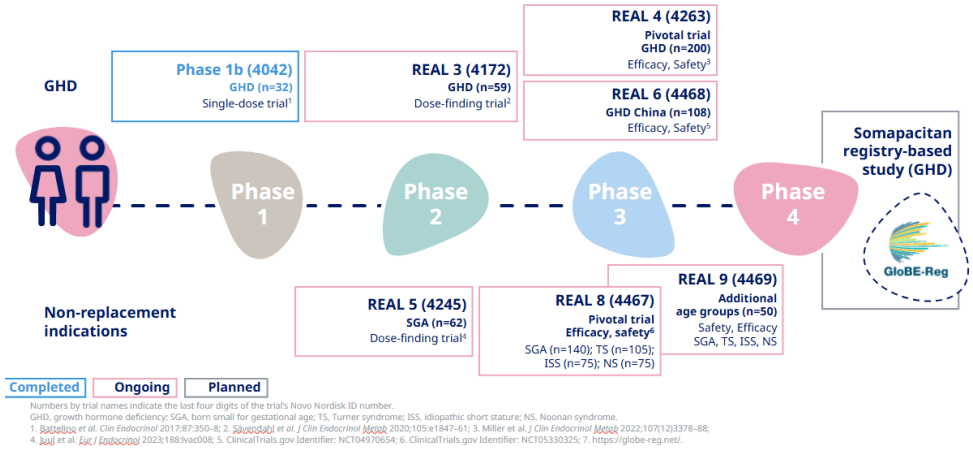
According to the Danish treatment guideline for use of GH in children and adults from July 2023, somatropin is the only marketed GHD treatment in DK. Somatropin is marketed in different brands with various pens (Omnitrope®, Norditropin® Flexpro®, Genotropin® GoQuick® and Genotropin® Miniquick®) which all have the same atc-code and same efficacy and safety profile, with differences mainly seen in terms of different devices, durability, storage conditions at room temperature and preservation ingredients (119).

The clinical trial program for somapacitan consists of head-to-head studies vs somapacitan in both children and adults with GHD as depicted in Figur 3. The clinical assessment and the health economic analysis will be informed by REAL 1 and REAL 4, which are the pivotal trials assessing efficacy and safety of somapacitan vs somatropin in children and adults with GHD.

Figur 3: Somapacitan clinical development program



Somapacitan: GHD clinical development



5.1 Literature used for the clinical assessment

As mentioned in previous section, this application is based on two head-to-head studies with somatropin, which is the relevant comparator to Danish clinical practice, a literature search is not applicable.

Table 6: Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Miller et al. Weekly Somapacitan is Effective and Well Tolerated in Children With GH Deficiency: The Randomized Phase 3 REAL4 Trial. The Journal of Clinical Endocrinology & Metabolism, 2022, 107, 3378–3388. (110) Miller et al. Efficacy, safety, and insulin-like growth factor I of weekly somapacitan in children with growth hormone deficiency: 3-year results from REAL4. Eur J Endocrinol, 2025, Apr 30; 192(5): 651-661. (127)	REAL 4	NCT03811535	Start: 20/05/2019 Completion: 10/11/2021	Somapacitan vs. somatropin for children with GHD
Johannsson et al. Once-weekly Somapacitan is Effective and Well Tolerated in Adults with GH Deficiency: A Randomized Phase 3 Trial. 2020. J Clin Endocrinol Metab, April 2020, 105(4):e1358 – e1376. (111)	REAL 1	NCT02229851	Start: 31/10/2014 Completion: 21/04/2017	Somapacitan vs. somatropin for Adults with GHD

5.2 Literature used for the assessment of health-related quality of life

Not applicable as a CEA/CUA has not been performed for this assessment.

Table 7: Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
N/A	N/A	N/A

5.3 Literature used for inputs for the health economic model

Not applicable as a CEA/CUA has not been performed for this assessment.

Table 8: Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
N/A	N/A	N/A	N/A

6. Efficacy

6.1 Efficacy of somapacitan compared to somatropin for children with GHD

6.1.1 Relevant studies

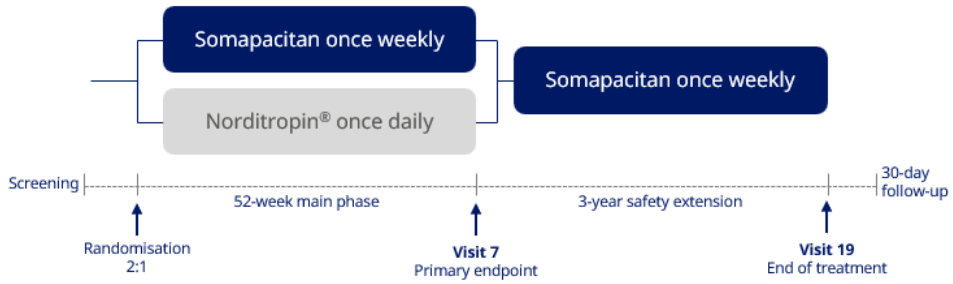
REAL 4

REAL 4 was a Phase III, multicentre, multinational, randomised, open-label trial investigating the efficacy and safety of once-weekly dosing of somapacitan compared with once-daily dosing of somatropin in participants aged ≥2.5 and <11.0 years (boys), and ≥2.5 and <10.0 (girls) with GHD (110).

Children received once-weekly somapacitan or once-daily somatropin for 52 weeks during the main trial period. This was followed by an ongoing 3-year extension period in which all participants was receiving once-weekly somapacitan to evaluate long-term safety. The total trial duration was 4 years, with a minimum follow-up period of 30 days (110).

The trial design is shown in Figur 4.

Figur 4: Summary of REAL 4 trial design



Source: Miller et al. 2022 (110)

This assessment is based on the main phase of REAL 4.

Participants were randomised 2:1 to receive either somapacitan or somatropin during the 52-week main trial period. Randomisation was stratified by region (Japan vs rest of the world), age group (<6 years vs ≥6 years at randomisation), gender (boys vs girls), and GH peak level (<7.0 ng/ml vs ≥7.0 ng/ml) to ensure equal distribution of these characteristics across treatment groups (36). During the subsequent 3-year safety extension trial period, all participants were treated with once-weekly somapacitan. Both trial products were administered as s.c. injections. The trial was open-label; no blinding was conducted.

Somapacitan was provided in a liquid formulation in a FlexTouch® pen-injector device (same device as FlexPro®) and administered at a dosage of 0.16 mg/kg/week throughout the main 52-week trial period and the 3-year extension period (80, 153). Injections were given s.c. and three pen-injector strengths (5, 10, and 15 mg/1.5 mL) were used in the trial based on participant body weight (Table 9) (110).

Table 9: Somapacitan FlexTouch® pen-injector (5, 10, and 15 mg/1.5 mL) selection guide and usage

	5 mg/1.5 mL	10 mg/1.5 mL	15 mg/1.5 mL
Body weight range	5.0–12.5 kg	10.5–25.0 kg	16.0–70.0 kg
Number of participants using pen†	4 (3%)	95 (72%)	33 (25%)

† Based on the pen strength used for the majority of the 52-week trial duration (some participants changed pen-injector during the trial: 4 of 5 participants starting on the 5 mg pen used the 10 mg pen at Week 52; 23 of the 99 participants starting on the 10 mg pen used the 15 mg pen at Week 52).
Source: REAL 4 CSR (128)

Somatropin was provided in a liquid formulation in the FlexPro® pen-injector device at a dosage of 0.034 mg/kg/day for the 52-week main trial period only. For the subsequent 3-year safety extension trial period, all participants were allocated to once-weekly somapacitan. Somatropin was administered s.c.

The primary endpoint was HV at Week 52, measured in cm/year using the following equation:

$$Height\ velocity = \frac{(height\ at\ Week\ 52\ visit - height\ at\ baseline)}{(time\ from\ baseline\ to\ Week\ 52\ visit\ in\ years)}$$

HV was derived from height measurements recorded at baseline and Week 52.

In total, 348 children were screened and 200 children with GHD were randomised and exposed to treatment. Of these, 132 children received somapacitan and 68 received somatropin. All 200 children completed the trial period, and 199 (99.5%) children completed the treatment period. One child discontinued somapacitan treatment prematurely due to a violation of inclusion and/or exclusion criteria. Participant disposition is presented by treatment in Table 10.

Table 10: Summary of participant disposition by treatment; all participants

	Somapacitan N (%)	Somatropin N (%)	Total N (%)
Screened	-	-	348
Randomised	132 (100.0)	68 (100.0)	200 (100.0)
Randomised in error	10 (7.6)	4 (5.9)	14 (7.0)
Exposed†	132 (100.0)	68 (100.0)	200 (100.0)
Discontinued trial product†	1 (0.8)	0 (0.0)	1 (0.5)
Protocol deviation	1 (0.8)	0 (0.0)	1 (0.5)
Withdrawn from trial	0 (0.0)	0 (0.0)	0 (0.0)
Completed trial period	132 (100.0)	68 (100.0)	200 (100.0)
Completed treatment period†	131 (99.2)	68 (100.0)	199 (99.5)
Full analysis set	132 (100.0)	68 (100.0)	200 (100.0)
Per protocol analysis set†‡	122 (92.4)‡	64 (94.0)	186 (93.0)
Safety analysis set†	132 (100.0)	68 (100.0)	200 (100.0)

Treatment period: The period from Visit 2 (Week 0) to Visit 7 (Week 52) without premature discontinuation of randomised treatment. Trial period: The period from Visit 2 (Week 0) to Visit 7 (Week 52).
† Includes participants 'as treated'
‡ In total, 14 children (10 in the somapacitan group and 4 children in the somatropin) group were randomised in violation of inclusion or exclusion criteria and were excluded from the per protocol analysis set
Source: REAL4 CSR (128); Miller et al. 2022 (110)

Two analysis populations were defined: the full analysis set included all randomly assigned participants (used for efficacy outcome analyses) and the safety analysis set included all participants exposed to 1 or more doses of trial product (used for safety outcome analyses). Observation periods included on- treatment (the time from first administration and up until last trial contact or visit 7 or 14 days after last administration, whichever comes first) and in-trial (the time from first administration and up until visit 7 or last trial contact, whichever comes first).

Statistical analysis of REAL 4

HV at week 52 was analyzed using an analysis of covariance model with treatment, sex, age group, region, GH peak group and sex by age group by region interaction term as factors, and baseline height as covariate. The prespecified noninferiority threshold was −1.8 cm/y. Changes in height SDS and HV SDS were analyzed using the same analysis model as was used for analyzing the primary endpoint for the treatment policy estimand with the exception that baseline height SDS and baseline HV SDS were used, respectively, as covariates in the model instead of baseline height. Change in bone age was analyzed using an analysis of covariance model on change in bone age/chronological age assessed at week 52 and the model included treatment, sex, age group, region, GH peak group, and sex by age group by region interaction term as factors and bone age/chronological

age at screening as a covariate. Patient-reported outcomes (exploratory endpoints) were analyzed based on the “on-treatment” observation period using a mixed model for repeated measurements, including the same factors as the primary analysis as well as the baseline assessment for TRIM GHD-CIM.

Adverse events were analysed using descriptive statistics based on the ‘on –treatment’ observation period (primary evaluation) and ‘in-trial’ observation period (secondary evaluation) within the main trial period (52 weeks of treatment).

Safety endpoint changes from baseline to week 52 in glucose metabolism parameters were analyzed using descriptive statistics. In the paediatric population change in glucose metabolism parameters (fasting plasma glucose (FPG), longterm blood glucose (HbA1c) and insulin secretion) are considered as safety outcomes.

All AEs with onset after the first administration of treatment and with start date up until 14 days after last dose or until week 52 (whichever comes first) were included and analyzed using descriptive statistics.

Table 11: Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
REAL 4 NCT03811535 Miller et al. Weekly Somapacitan is Effective and Well Tolerated in Children With GH Deficiency: The Randomized Phase 3 REAL4 Trial. The Journal of Clinical Endocrinology & Metabolism, 2022, 107, 3378–3388. (110)	Phase III, multicentre, multinational, randomised, open-label trial	Main phase: 52 weeks Safety extension phase: 3-years	Prepubertal children with confirmed diagnosis of GHD. Boys aged ≥ 2 years and 26 weeks and < 11.0 years at screening with testis volume <4 mL Girls aged ≥ 2 and 26 weeks and < 10.0 years at screening and with tanner stage 1 for breast development	Once-weekly subcutaneous somapacitan at a dosage of 0.16 mg/kg/week	Once-daily subcutaneous somatropin in the FlexPro® pen-injector device at a dosage of 0.034 mg/kg/day	Primary endpoint: • HV at week 52 measure in cm/year Supportive secondary endpoints: • Change from screening to Week 52 in bone age (years) • Change from baseline to Week 52 in Height SDS (−10 to +10) • Change from baseline to Week 52 in HV SDS (−10 to +10) • Pharmacodynamic changes from baseline to Weeks 52, 104, 156, and 208 in: ○ IGF-1 SDS (−10 to +10) ○ IGFBP-3 SDS (−10 to +10)

6.1.2 Comparability of studies

REAL 4 is a head-to-head study with somapacitan and somatropin, hence this section is not relevant.

6.1.2.1 Comparability of patients across studies

N/A

Table 12: Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	[Study name]		[Study name]		[Study name]	
	[int./ comp.]	[int./ comp.]	[int./ comp.]	[int./ comp.]	[int./ comp.]	[int./ comp.]
Age	N/A	N/A	N/A	N/A	N/A	N/A
Gender	N/A	N/A	N/A	N/A	N/A	N/A
[characteristic]	N/A	N/A	N/A	N/A	N/A	N/A
[characteristic]	N/A	N/A	N/A	N/A	N/A	N/A
[characteristic]	N/A	N/A	N/A	N/A	N/A	N/A

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

Baseline demographics and characteristics are summarised in Table 13. Overall, baseline demographics were similar in the somapacitan and somatropin groups. Baseline height, body weight, GH peak, HV, HVSDS, height SDS and IGF-I SDS were slightly lower in the somatropin group compared with the somapacitan group.

As in the REAL 4 clinical trial we also see an over representation of boys rather than girls with GHD in DK (62% boys) based on a rather old DK registry study (67), which is referenced in the current RADS' GHD recommendation (68). This study further details the median age of onset of GHD in children in DK which is 9.1 years in boys and 8.6 years in girls (67).

Table 13: Summary of demographics and baseline characteristics; FAS

	Somapacitan n=132		Somatropin n=68	
Age group, n (%)				
<6 years	64 (48.5%)		33 (48.5%)	
	Female	*Male*	*Female*	*Male*
Median age	*4.30*	*4.40*	*3.50*	*4.45*
Min; max	*2.8; 5.8*	*2.5; 5.9*	*2.7; 5.7*	*3.4; 5.6*
≥6 years	68 (51.5%)		35 (51.5%)	
	Female	*Male*	*Female*	*Male*
Median age	*8.30*	*8.05*	*7.80*	*8.85*
Min; max	*6.0; 9.6*	*6.1; 10.8*	*6.2; 9.8*	*6.1; 11.0*
Sex				
Male	99 (75.0%)		50 (73.5%)	
Hispanic or Latino	4 (3.0%)		1 (1.5%)	
Not Hispanic or Latino	119 (90.2%)		63 (92.6%)	
Not reported	9 (6.8%)		4 (5.9%)	
Race				
White	78 (59.1%)		36 (52.9%)	
Asian	46 (34.8%)		28 (41.2%)	
Black or African American	0		1 (1.5%)	
Other	1 (0.8%)		0	
Not reported	7 (5.3%)		3 (4.4%)	
GHD cause, n (%)				
Idiopathic	115 (87.1%)		61 (89.7%)	
Organic	17 (12.9%)		7 (10.3%)	
Age, years, mean (SD)	6.38 (2.32)		6.43 (2.42)	
Height, cm, mean (SD)	102.3 (12.5)		100.2 (15.0)	
Body weight, kg, mean (SD)	16.69 (4.60)		16.01 (4.95)	
BMI, kg/m^2, mean (SD)	15.70 (1.59)		15.59 (1.38)	

GH peak, ug/L, mean (SD)	4.93 (2.50)	4.10 (2.77)
Mean HV (cm/year) (SD)	4.3 (1.4)	4.1 (1.4)
Mean HVSDS	−2.35 (1.51)	−2.52 (1.55)
Mean Height (cm) (SD)	102.3 (12.5)	100.2 (15.0)
Mean Height SDS	−2.99 (1.02)	−3.47 (1.52)
Mean IGF-1 SDS	−2.03 (0.97)	−2.33 (1.03)

Abbreviations: BMI, body mass index; FAS, full analysis set; GH, growth hormone; GHD, growth hormone deficiency; HV, height velocity; IGF-1, insulin-like growth factor-1; SD, standard deviation; SDS, standard deviation score.
Source: REAL4 CSR (128); Miller et al. 2022 (110)

Table 14: Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (67)	Value used in health economic model (reference if relevant)
Boys, %	62%	N/A
Age of GHD onset in boys, median	9.1 years	N/A
Age of GHD onset in girls, median	8.6 years	N7A

Source: Stockholm et al. (67)

6.1.4 Efficacy – results per REAL 4: somapacitan vs somatropin in children with GHD

The following efficacy results are presented for the main phase of REAL 4.

There was no significant difference in annualized HV between somapacitan and somatropin after 52 weeks of treatment (ETD −0.5 cm/year [95% CI; −1.1, 0.2]) confirming non-inferiority. Both treatments were equally effective in stimulating HV in treatment-naïve GH-deficient children.

As with the primary endpoint, secondary height-related endpoints HV SDS and height SDS increased from baseline to week 52 for somapacitan and somatropin, with change differences between treatment groups not statistically significant.

Bone age to chronological age ratio advanced similarly in both groups[3], with no changes in skeletal proportions reported. Analysis showed that the change in bone age between

[3] A bone age vs chronological age of less than one indicates immature bone development for age 157. Manzoor Mughal A, Hassan N, Ahmed A. Bone age assessment methods: a critical review. Pak J Med Sci. 2014;30(1):211-5.

somapacitan and somatropin was not statistically significant (ETD −0.02 [95% CI; −0.06, 0.01]) from baseline to 52 weeks of treatment.

Change in mean IGF-I SDS from baseline to week 52 was also similar with no statistically significant differences between treatment groups.

No clinically relevant change in FPG and HbA1c was observed among the children participating in REAL 4 from baseline to week 52. No difference in mean HbA1c or insulin secretion was observed between somapacitan and somatropin at week 52.

The majority of children received the planned treatment with a mean adherence among participants on treatment (i.e., not counting exposure duration in 1 participant after discontinuing treatment) of 95.8% for the somapacitan group and 88.3% for the somatropin group.

The change in TRIM GHD-CIM total score from baseline to week 52 demonstrates high overall similarity in reduced disease burden between treatment groups.

Treatment burden was not collected at baseline as enrolled patients were treatment-naïve at baseline. Thus, treatment burden (TB-CGHD-O and TB-CGHD-P) was assessed between treatments groups at week 52. Results demonstrated that somapacitan treatment burden was significantly lower for caregivers (TB-CGHD-P) compared with the somatropin treatment burden. The Growth Hormone Device Assessment Tool (G-DAT) overall score indicates the same high proportion of respondents (96%) found somapacitan and somatropin in devices of the FlexPro family to be easy or very easy to use.

Table 15: Results from REAL 4 main trial, the head-2-head study comparing somapacitan vs. somatropin in children with GHD

Outcome measures after 52 weeks of treatment	Somapacitan (N=132)	Somatropin (N=68)	Difference
Annualized HV (cm/year)	11.2	11.7	ETD −0.5 cm/year [95% CI; −1.1, 0.2]
Mean change from baseline in HV SDS	8.05	8.82	ETD – 0.78 [95% CI; -1.63, 0.08]
Mean change from baseline in height SDS	1.25	1.30	ETD – 0.05 [95% CI; -0.18, 0.08]
Mean change from baseline in bone age	0.06	0.08	ETD - 0.02 [95% CI; -0.06, 0.01]

Outcome measures after 52 weeks of treatment	Somapacitan (N=132)	Somatropin (N=68)	Difference
Mean change from baseline in IGF-1 SDS	2.36	2.33	ETD 0.03 [95% CI; -0.30, 0.36]
Mean adherence in % according to diary (SD)*	95.8% (10.19)	88.3% (23.57)	
Mean change from baseline in TRIM GHD-CIM total score	-9.6	-9.4	ETD - 0.2 [95% CI; -3.9, 3.4]
TB-CGHD-O total score, mean	10.7	13.1	ETD - 2.4 [95% CI; -5.7, 0.9]
TB-CGHD-P total score, mean	8.7	14.7	ETD – 6.0 [95% CI; -10.0, -2.1]
G-DAT questionnaire Overall, % 'easy' or 'very easy'	96.3%	96.3%	

In-trial; FAS.
*Number of reported dosings from diary in adherence divided by number of planned dosings multiplied by 100.
Abbreviations: FAS, full analysis set; SD, standard deviation; HV, Height Velocity; SDS, SD Score; GHD-CIM, growth hormone deficiency – child impact measure; TB-CGHD-O, treatment burden measure – child growth hormone deficiency – observer; TB-CGHD-P, treatment burden measure – child growth hormone deficiency – parent; G-DAT, growth hormone device assessment tool.
Source: Miller et al. 2022 (110), REAL 4 CSR (128)

6.2 Efficacy of somapacitan compared to somatropin for adults with GHD

6.2.1 Relevant studies

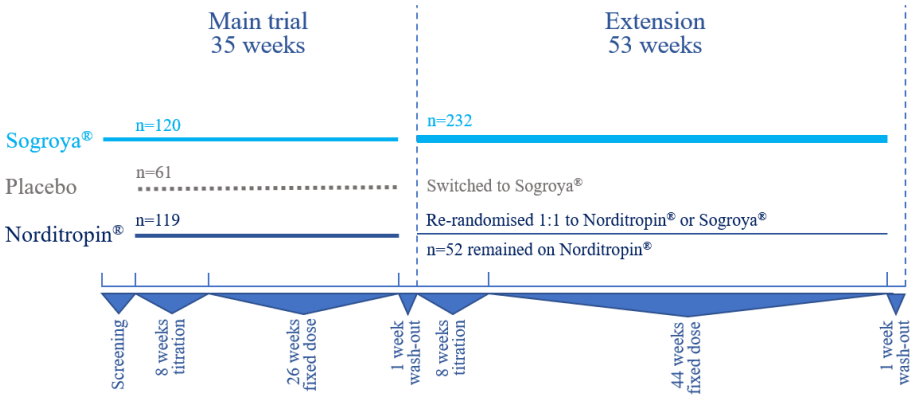
REAL 1

REAL 1 was a multicentre, multinational, randomised, parallel-group, placebo-controlled, partly double-blinded trial comparing the efficacy and safety of once-weekly dosing of somapacitan with once-weekly dosing of placebo and with daily somatropin in people with AGHD over 35 weeks, with an active-controlled, open-label, 53-week extension period (111).

Participants received once-weekly somapacitan, once-daily somatropin, or once-weekly placebo for 35 weeks (8-week titration + 26-week treatment period + 1-week washout). All participants who completed the 35-week main trial period were offered to continue on active treatment for an additional 53-week extension period (8-week titration +

44-week treatment period + 1-week washout). Participants treated with somatropin during the main phase of the trial were re-randomised at a 1:1 ratio to receive either somapacitan or somatropin during the extension period. Participants who received placebo during the main phase of the trial were switched to somapacitan for the extension period (Figur 5).

Figur 5: REAL 1 trial design



Source: Johannsson et al, 2020 (111)

A parallel-group design was chosen as a crossover trial was not possible due to carry-over effects (e.g. on body composition). The titration period allowed for four dose adjustments of somapacitan to achieve an optimal serum IGF-1 concentration, and the 26-week fixed dose treatment period was the expected minimum time needed for body composition changes to develop. The 1-week washout period was to confirm the antibody response. The extension period of the trial allowed for long-term evaluation of the efficacy and safety of somapacitan, with some participants remaining on somatropin treatment to maintain the comparison with active treatment. The maximum total time on treatment for a single participant was 86 weeks.

Individualised dose titration was chosen, since clinical studies have shown that AEs are less frequently experienced with this regimen compared with a fixed dose based on body weight.

Participants were randomised in a 2:2:1 ratio by interactive voice/web response service (IV/WRS) to receive somapacitan, somatropin or placebo. Randomisation was stratified according to region (Japan vs all other countries), sex (male vs female) and diabetic status (diagnosed vs not diagnosed with diabetes mellitus). Participants in the somatropin arm were re-randomised for the extension period in a 1:1 ratio to somapacitan or somatropin within the same strata as used for the first randomisation in the main phase of the trial.

Somapacitan and placebo injection pens were visually identical and these two treatment arms were blinded to each other in the main phase of the trial (both given once weekly). Patients receiving once-daily somatropin were not blinded due to ethical reasons; that is, blinding would have required patients in the once-weekly somapacitan and placebo arms

to receive 6 additional dummy injections per week. The placebo arm was included in the trial in order to demonstrate the consequences of an adult population with GHD not being in growth hormone treatment.

Somapacitan was provided in a liquid formulation in a FlexTouch® pen-injector device (same device as FlexPro®). It was injected subcutaneously in the morning no later than 10:00. The starting doses are shown in Table 16, and were expected to be below the ideal maintenance dose for IGF-1 SDS target for most people with AGHD. These starting doses were applied at the beginning of the main trial period and the extension phase.

Table 16: Starting doses for somapacitan in REAL 1

Patient group	Starting dose of somapacitan	Starting dose converted to daily exposure
Participants aged 23–60 years	1.5 mg/week	0.214 mg/day
Participants aged >60 years	1.0 mg/week	0.143 mg/day
Females on oral oestrogen	2.0 mg/week	0.286 mg/day

Source: Johannsson et al, 2020 (111)

During the first 8 weeks of the main trial period and the extension phase, the dose was titrated every second week from Week 2, allowing four opportunities for dose adjustment. The target IGF-1 SDS was between −0.5 SDS and +1.75 SDS. At Week 8, the individual dose was fixed for the remainder of the corresponding trial period. The dose of somapacitan was adjusted during the titration periods according to the titration algorithm detailed in Table 17.

The minimum weekly dose was 0.1 mg and the maximum weekly dose was 8 mg. Dose reduction in steps of 25% could be made at any time during the study period at the Investigator's discretion for safety concerns.

Table 17: Dose titration algorithm for somapacitan in REAL 1

IGF-1 SDS (1 week and 3 days after last dose adjustment)	Change in weekly dose	
	Δ IGF-1 SDS >1	Δ IGF-1 SDS ≤1
IGF-1 SDS >3	–1 mg	
1.75 < IGF-1 SDS ≤ 3	–0.5 mg	
–0.5 < IGF-1 SDS ≤ 1.75 (target)	–	+0.5 mg
–2 < IGF-1 SDS ≤ –0.5	+0.5 mg	+0.5 mg
IGF-1 SDS ≤ –2	+1 mg	+1.5 mg

Abbreviations: IGF-1, insulin-like growth factor-1; SDS, standard deviation score. Source: Johannsson et al, 2020 (111)

Placebo was provided in the pen device and was injected subcutaneously in the morning no later than 10:00, since this is the intended dosing regimen for somapacitan and to

ensure blinding vs somapacitan. To maintain blinding, placebo doses were adjusted to mimic the dose titration for somapacitan treatment.

Somatropin (10 mg/1.5 mL) was provided in the FlexPro® pen and was injected subcutaneously in the evening, to reflect standard practice. The starting doses for the main trial period and the extension phase are shown in Table 18, and were expected to be below the ideal maintenance dose for IGF-1 SDS target for most people with AGHD.

Table 18: Starting doses for somatropin in REAL 1

Patient group	Starting dose of somatropin
Participants aged 23–60 years	0.2 mg/day
Participants aged >60 years	0.1 mg/day
Females on oral oestrogen	0.3 mg/day

Source: Johannsson et al, 2020 (111)

During the first 8 weeks of the main trial period and the extension phase, the dose was titrated every second week from Week 2, allowing four opportunities for dose adjustment. The target IGF-1 SDS was between −0.5 SDS and +1.75 SDS. At Week 8, the individual dose was fixed for the remainder of the corresponding trial period. The dose of somatropin was adjusted during the titration periods according to the titration algorithm detailed in Table 19. The minimum daily dose was 0.05 mg and the maximum daily dose was 1.1 mg (except for Japan, where it was 1.0 mg). Dose reduction in steps of 25% could be made at any time during the study period at the Investigator's discretion for safety concerns.

Table 19: Dose titration algorithm for somatropin in REAL 1

IGF-1 SDS (1 week and 3 days after last dose adjustment)	Change in daily dose	
	Δ IGF-1 SDS >1	Δ IGF-1 SDS ≤1
IGF-1 SDS >3	–0.1 mg	
1.75 < IGF-1 SDS ≤ 3	–0.05 mg	
–0.5 < IGF-1 SDS ≤ 1.75 (target)	–	+0.05 mg
–2 < IGF-1 SDS ≤ –0.5	+0.05 mg	+0.05 mg
IGF-1 SDS ≤ –2	+0.1 mg	+0.2 mg

Abbreviations: IGF-1, insulin-like growth factor-1; SDS, standard deviation score. Source: Johannsson et al, 2020 (111)

The primary endpoint was the change from baseline to Week 34 in truncal fat percentage. The secondary endpoints were incidence of AEs (including injection site reactions) from baseline (first administration of trial product) to the end of the treatment period (26 weeks) as well as occurrence of anti-somapacitan anti-bodies.

In total, 501 participants were screened, 301 participants were randomised, and 300 participants were exposed to treatment (one participant was randomised but did not

receive any trial drug and was therefore not included in any analyses). A total of 277 participants (92%) completed 34 weeks of treatment. There were 28 participants (9.3%) withdrawn from the main trial period (somapacitan, 7 [5.8%] participants; placebo, 6 [9.8%] participants; somatropin, 15 [12.6%] participants), the majority of which withdrew due to personal reasons. The participant disposition for the main trial period is shown in Table 20.

Table 20: Participant disposition – main trial period

	Somapacitan N (%)	Placebo N (%)	Somatropin N (%)
Randomised	121 (100.0)	61 (100.0)	119 (100.0)
Exposed	120 (99.2)	61 (100.0)	119 (100.0)
FAS	120 (99.2)	61 (100.0)	119 (100.0)
SAS	120 (99.2)	61 (100.0)	119 (100.0)
Completed treatment	115 (95.0)	55 (90.2)	107 (89.9)
Discontinued trial product	0 (0.0)	1 (1.6)	4 (3.4)
Adverse event	0 (0.0)	1 (1.6)	4 (3.4)
Withdrawn	7 (5.8)	6 (9.8)	15 (12.6)
Withdrawal by subject	5 (4.1)	4 (6.6)	12 (10.1)
Protocol violation	2 (1.7)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	1 (0.8)
Other	0 (0.0)	2 (3.3)	2 (1.7)

Abbreviations: FAS, full analysis set; SAS, safety analysis set. Source: Johannsson et al, 2020 (111)

Statistical analysis REAL 1

The following populations were analysed:

- The full analysis set (FAS) included all randomised participants who received at least one dose of randomised treatment, analysed as randomised; the FAS was used for the evaluation of efficacy endpoints
- The safety analysis set (SAS) included all randomised participants who received at least one dose of randomised treatment, analysed as treated; the SAS was used for the evaluation of safety endpoints

Truncal fat percentage as a function of time since baseline was expected to be monotone if the participant remained on the randomised treatment in the main trial period. Based on this assumption, the primary analysis of the primary endpoint was conducted using a multiple imputation technique where the trajectory after a withdrawn subject's last observation was imputed based on data from the placebo arm, thus mimicking an intention-to-treat scenario where withdrawn participants are assumed to

be switched to no treatment (placebo) after withdrawal. Placebo arm data were modelled using analysis of covariance (ANCOVA) with GHD onset type (adult or childhood), sex, region, diabetes mellitus, and sex by region by diabetes mellitus interaction as factors and baseline truncal fat percentage as a covariate. If a truncal fat assessment had been performed after baseline at intermediate time t, this value was combined with the time-normalised model-based estimate, so that the final imputed value for the participant was a sum of the observed value at time t and the model-based estimated change multiplied by (34 weeks – t)/(34 weeks) minus the baseline value. Missing baseline scans were imputed with the average from all participants with baseline data. If VAT, gynoid and android fat mass were missing due to the scanner not being capable of assessing these, affected participants were not included in the analysis. Missing baseline data for secondary efficacy endpoints analysed using mixed model for repeated measures (MMRM) were imputed for participants with post-randomisation data for the analysed endpoint using the mean baseline of all participants. For visits 13 and 14 that took place more than 14 days earlier than planned, assessments for that visit were not included when analysing IGF-1 SDS, IGFBP-3 SDS, TRIM-AGHD, SF-36v2, TSQM-9 scores, CV parameters, and body weight. Missing baseline data for secondary efficacy endpoints analysed using ANCOVA were imputed using the mean baseline of all participants.

The primary endpoint was analysed using an ANCOVA model, with treatment, GHD onset type (adult or childhood), sex, region, diabetes mellitus, and sex by region by diabetes mellitus interaction as factors, and baseline truncal fat percentage as a covariate. Superiority of somapacitan over placebo was considered confirmed if the upper boundary of the two-sided 95% CI of the treatment difference (somapacitan – placebo) was below zero.

Changes from baseline to Week 34 were analysed using an ANCOVA (body composition and lipids) or a MMRM (IGF-1 SDS and body weight) 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.

AEs and all other safety endpoints were analysed using descriptive statistics, and were summarised by treatment, Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC), and MedDRA preferred term. In addition, exact logistic regression analyses on the event of experiencing at least one injection site reaction during the main trial period were performed, with treatment, GHD onset type, sex, region, diabetes mellitus, and sex by region by diabetes mellitus interaction as factors and number of injections taken in the main trial period as offset.

Table 21: Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
REAL 1 NCT02229851 Johannsson et al. Once-weekly Somapacitan is Effective and Well Tolerated in Adults with GH Deficiency: A Randomized Phase 3 Trial. 2020. J Clin Endocrinol Metab, April 2020, 105(4):e1358 – e1376. (111)	Multicentre, multinational, randomised, parallel-group, placebo-controlled, partly double-blind trial	Main phase: 35 weeks Extension phase: 53 weeks	Males or females aged 23-79 years diagnosed with adult-onset GHD or childhood-onset GHD. IGF-1 SDS < -0.5 hGH treatment naïve or no exposure to hGH or GH secretagogues for ≥ 180 days prior to randomization.	Once-weekly subcutaneous somapacitan at a starting dose of 1.5 mg/week in patients aged 23-60 years, 1.0 mg/week in patients aged > 60 years and 2.0 mg/week in females on oral oestrogen.	Once-daily subcutaneous somatropin in the FlexPro® pen-injector device at a starting dose of 0.2 mg/day in patients aged 23-60 years, 0.1 mg/day in patients aged > 60 years and 0.3 mg/day in females on oral oestrogen.	Primary endpoint: • Change from baseline to Week 34 in truncal fat percentage Supportive secondary endpoints: • Change from baseline to Week 34 and Week 87 in: – Truncal fat mass – Truncal lean body mass – Total fat mass – VAT, android fat mass, and gynoid fat mass, if the DXA scanner permits – Lean body mass – IGF-1 SDS and IGFBP-3 SDS – PK assessments of somapacitan and human growth hormone (hGH) in the main phase of the trial (to Week 34) – Treatment Related Impact Measure – AGHD (TRIM-AGHD), SF-36 version 2 (SF36v2), and Treatment Satisfaction Questionnaire for Medication-9

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
						(TSQM-9) patient-reported outcome (PRO) scores[4] – Lipid profile (total cholesterol, HDL-c, LDL-c, and triglycerides) – CV parameters (high sensitivity C-reactive protein [hsCRP] and IL-6) – Body weight – Waist circumference • Change from baseline to Week 87 in BMC and BMD • Adherence, measured based on time stamps from electronic pen caps (ecaps), in the extension period

[4] Changes to TSQM 9 scores were based on the end scores only (Week 34 scores for Main and Week 87 scores for Extension)

6.2.2 Comparability of studies

Not applicable as comparisons are based on head-to-head trials with somapacitan and somatropin.

6.2.2.1 Comparability of patients across studies

N/A

Table 22: Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	[Study name]		[Study name]		[Study name]	
	[int./ comp.]	[int./ comp.]	[int./ comp.]	[int./ comp.]	[int./ comp.]	[int./ comp.]
Age	N/A	N/A	N/A	N/A	N/A	N/A
Gender	N/A	N/A	N/A	N/A	N/A	N/A
[characteristic]	N/A	N/A	N/A	N/A	N/A	N/A
[characteristic]	N/A	N/A	N/A	N/A	N/A	N/A
[characteristic]	N/A	N/A	N/A	N/A	N/A	N/A

6.2.3 Comparability of the study population(s) with Danish patients eligible for treatment

Baseline demographics and characteristics are summarised in Table 23. Overall, baseline demographics were similar in the somapacitan and somatropin groups.

As for children with GHD we also see an over representation of men rather than women with GHD in DK (55% men) (67). However in the REAL 1 clinical trial the gender distribution was almost equally balanced (48% men).

86 in the somapacitan group and 82 in the somatropin group had onset of GHD in adulthood. This is typically a result of an underlying pituitary disease, hypothalamic disease, surgery, radiation therapy, or traumatic brain injury, which is also supported by the description about onset of GHD in adulthood in *the RADS background document about use of GH treatment in children and adults* (68).

Table 23: Baseline characteristics of patients in REAL 1 main phase and extension in adults with GHD for the comparative analysis of efficacy and safety with somapacitan vs somatropin

	Real 1 main phase – Naive AGHD		
	Somapacitan n = 120	Somatropin n = 119	Placebo n = 61
Age (years), mean (SD)	44.6 (14.3)	45.7 (15.3)	45.0 (15.7)
23 - < 65 years, n (%)	107 (89.2)	101 (84.9)	51 (83.6)
≥ 65 years, n (%)	13 (10.8)	18 (15.1)	10 (16.4)
Females on oral oestrogen, n (%)	38 (31.7)	23 (19.3)	10 (16.4)
Female, n (%)	62 (51.7%)	61 (51.3%)	32 (52.5%)
Race, n (%)			
Asian	34 (28.3%)	36 (30.3%)	16 (26.2%)
White	82 (68.3%)	76 (63.9%)	42 (68.9%)
Black or African American	2 (1.7%)	3 (2.5%)	2 (3.3%)
Native Hawaiian or other Pacific Islander	0	0	0
Other/NA	2 (1.7%)	4 (3.4%)	1 (1.6%)
Body weight (kg), mean (SD)	76.2 (21.0)	76.0 (22.7)	69.8 (19.7)
BMI (kg/m^2), mean (SD)	27.9 (6.3)	27.7 (6.2)	26.1 (6.4)
GHD onset, n (%)			
Childhood – idiopathic	21 (17.5%)	21 (17.6%)	13 (21.3%)
Childhood – organic	17 (14.2%)	12 (10.1%)	7 (11.5%)
Adulthood	82 (68.3%)	86 (72.3%)	41 (67.2%)
IGF-I SDS, mean (SD)	N/A	N/A	N/A
GH dose level at screening (mg), mean (SD)	N/A	N/A	N/A

Source: Johannsson et al, 2020 (111); Novo Nordisk CSR REAL 1 (129)

Table 24: Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (67)	Value used in health economic model (reference if relevant)
Male, %	55%	N/A
Age of GHD onset in males, median	51.3 years	N/A
Age of GHD onset in females, median	49.4 years	N/A

Source: Stockholm et al. (67)

6.2.4 Efficacy – results per REAL 1: somapacitan vs somatropin in naïve AGHD

A reduction in truncal fat percentage from baseline to week 34 was observed for both somapacitan and somatropin, however REAL 1 was not powered to test non-inferiority of these two treatments.

The estimated mean change from baseline in DXA endpoints (fat mass endpoints and lean body mass endpoints) from baseline to Week 34 are presented in Table 25. Somapacitan was comparable to somatropin for all measurements apart from gynoid fat mass, which showed a significantly greater loss with somatropin.

A marked increase in mean IGF-1 SDS was observed from baseline to Week 34 following somapacitan (–2.54 to –0.17) and somatropin exposure (–2.53 to –0.23). The difference was similar between somapacitan and somatropin.

There were no clinically relevant changes in total cholesterol, HDL-c, LDL-c, or triglycerides from baseline to Week 34 in any of the treatment groups. There were also no clinically relevant or statistically significant differences between treatment groups. 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 changes in CV parameters (hsCRP and IL-6) from baseline to Week 34 in any of the treatment groups, and there were no statistically significant differences between somapacitan and somatropin.

There were no clinically relevant changes in weight or waist circumference from baseline to Week 34 in any of the treatment groups, and there were no statistically significant differences in estimated waist circumference between somapacitan and somatropin. A statistically significant difference in weight change was found between somapacitan and somatropin, with a greater increase in weight with somapacitan.

The less pronounced effect of somapacitan compared with somatropin observed for the reduction in some of the adipose tissue parameters after 34 weeks of treatment could not be explained by a different response in IGF-I SDS, as mean IGF-I SDS levels and distribution of IGF-I SDS were similar between treatment groups. However, a *post hoc*

analysis was carried out to evaluate separately the effects of somapacitan, somatropin and placebo on female patients on oral estrogen and on the entire trial population, excluding female patients on oral estrogen. The results suggested that the more pronounced effects observed for some of the adipose tissue parameters in the entire trial population may have been influenced by this difference in numbers. Oral estrogen exposes the liver to high levels of estrogen, which has been shown to inhibit the action of GH on its receptor. Women receiving oral estrogen will therefore have a lower IGF-I response to GH, possibly resulting in diminished metabolic effects (e.g., on various fat compartments) (111).

TRIM-AGHD scores decreased (i.e. improved) in all three treatment arms in REAL 1. While some statistically significant differences were found between the somapacitan and somatropin arms, the difference in total score did not meet the MID criteria.

Changes in all SF-36 scores improved from baseline to Week 34 for all treatment arms. The improvements from baseline for all scores were similar for somapacitan and somatropin, except for vitality and general health, which were significantly lower with somapacitan than with somatropin.

The TSQM-9 effectiveness score was statistically significantly lower for somapacitan than for somatropin at Week 34. There were no statistically significant differences observed in convenience and global satisfaction scores between somapacitan and somatropin during the main phase of the trial.

Table 25: Results from REAL 1, the head-2-head study comparing somapacitan vs. somatropin in treatment naïve adults with GHD

Outcome measures after at week 34	Somapacitan (N=120)	Somatropin (N=119)	Treatment difference Somapacitan - somatropin
Change from baseline in truncal fat percentage, % (SD)	-1.16 (2.91)	-2.47 (4.54)	1.17 [95% CI; 0.23, 2.11]
% change from baseline in visceral fat, % (SD)	-9.41 (22.11)	–8.31 (25.46)	- 1.7 [95% CI; -8.0, 4.5]
Change from baseline in total fat mass, kg (SD)	− 0.08 (3.05)	− 0.81 (3.15)	0.72 [95% CI; -0.04, 1.49]
Change from baseline in truncal fat mass, kg (SD)	-0.18 (1.78)	-0.61 (1.89)	0.41 [95% CI; -0.04, 0.86]
Change from baseline in gynoid fat mass, kg (SD)	0.02 (0.51)	− 0.12 (0.47)	+0.15 [95% CI; 0.02; 0.28]

Outcome measures after at week 34	Somapacitan (N=120)	Somatropin (N=119)	Treatment difference Somapacitan - somatropin
Change from baseline in android fat mass, kg (SD)	− 0.08 (0.36)	− 0.15 (0.32)	− 0.12 [95% CI; 0.22; 0.01]
Change from baseline in total lean body mass, kg (SD)	1.38 (2.12)	1.44 (2.29)	0.05 [95% CI; -0.51; 0.61]
Change from baseline in truncal lean body mass, kg (SD)	+0.79 (1.37)	+0.89 (1.35)	-0.04 [95% CI; -0.39, 0.31]
Change from baseline in appendicular skeletal muscle mass, kg (SD)	+0.56 (1.01)	+0.51 (1.25)	0.10 [95% CI; -18, 0.37]
Change from baseline in hs-CRP (mg/L)	0.71	0.56	Treatment ratio: 1.26 [95% CI; 0.98; 1.62]
Change from baseline in IL-6 (pg/mL)	1.06	1.00	Treatment ratio: 1.06 [95% CI; 0.89; 1.26]
Relative change from baseline in HDL cholesterol (mmol/L)	1.04	1.01	Treatment difference ratio: 1.03 [95% CI; 0.97; 1.09]
Relative change from baseline in LDL cholesterol (mmol/L)	0.97	0.94	Treatment difference ratio: 1.03 [95% CI; 0.97; 1.10]
Relative change from baseline in triglycerides (mmol/L)	0.99	1.06	Treatment difference ratio: 0.93 [95% CI; 0.85; 1.03]
Relative change from baseline in total cholesterol (mmol/L)	0.99	0.98	Treatment difference ratio: 1.02 [95% CI; 0.98; 1.06]
Change from baseline in IGF-1 SDS	2.40	2.37	0.02 [95% CI; −0.23; 0.28]
Change from baseline in body weight, kg	1.40	0.27	1.13 [95% CI; 0.13; 2.12]

Outcome measures after at week 34	Somapacitan (N=120)	Somatropin (N=119)	Treatment difference Somapacitan - somatropin
Change from baseline in waist circumference, cm	0.14	-0.49	0.63 [95% CI; –0.56; 1.82]
Change from baseline in TRIM-AGHD total score (SD)	-5.71 (12.69)	-9.99 (1364)	Treatment difference: 4.99 [95% CI; 1.89; 8.14]
Change from baseline in SF-36v2 overall physical score (SD)	2.40 (6.53)	2.87 (6.33)	Treatment difference: -1.00 [95% CI; -2.50; 0.51]
Change from baseline in SF-36v2 overall mental score (SD)	2.07 (8.76)	2.97 (11.33)	Treatment difference: -1.70 [95% CI; -3.93; 0.58]
Change from baseline in TSQM-9 convenience score (SD)	77.84	73.84	Treatment difference: 4.00 [95% CI; -0.40; 8.39]
Change from baseline in TSQM-9 effectiveness score (SD)	57.13	67.86	Treatment difference: -10.74 [95% CI; -16.49; -4.98]

†Assessed only if the DXA scanner permitted.
Abbreviations: CI, confidence interval; FAS, full analysis set; N, number of participants; VAT, visceral adipose tissue.
Source: Johannsson et al, 2020 (111); Novo Nordisk CSR REAL 1 (129)

In the REAL 1 extension phase, the reduction in visceral fat and the increases in total lean body mass and appendicular skeletal muscle mass were maintained in all the active treatment groups at 86 weeks. In the patients continuing on somapacitan in the 52-week extension, the effects after 86 weeks of treatment on the remaining fat mass parameters remained less pronounced with somapacitan compared with somatropin. However, in patients switched from placebo to somapacitan, the effects on body composition were similar to those who received daily GH throughout. Thus, taken together, an overall similar treatment effect of somapacitan and daily GH was observed (111).

7. Comparative analyses of efficacy

Not applicable as both studies in both the paediatric and the adult population are head-to-head studies comparing somapacitan with somatropin.

7.1.1 Differences in definitions of outcomes between studies

N/A

7.1.2 Method of synthesis

N/A

7.1.3 Results from the comparative analysis

N/A

Table 26: Results from the comparative analysis of [intervention] vs. [comparator] for [patient population]

Outcome measure	[Intervention] (N=x)	[Comparator] (N=x)	Result
N/A	N/A	N/A	N/A

7.1.4 Efficacy – results per [outcome measure]

N/A

8. Modelling of efficacy in the health economic analysis

As there are no clinically relevant differences in the effectiveness or safety of somapacitan vs somatropin; a simple cost-minimization analysis has been selected for this application. Hence this section is not applicable.

8.1 Presentation of efficacy data from the clinical documentation used in the model

N/A

8.1.1 Extrapolation of efficacy data

N/A

Table 27: Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
Data input	N/A
Model	N/A
Assumption of proportional hazards between intervention and comparator	N/A
Function with best AIC fit	N/A
Function with best BIC fit	N/A
Function with best visual fit	N/A
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	N/A
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A
Assumptions of waning effect	N/A
Assumptions of cure point	N/A

8.1.1.1 Extrapolation

N/A

8.1.2 Calculation of transition probabilities

N/A

Table 28: Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Disease-free survival	Recurrence	N/A	N/A
	Death	N/A	N/A
Recurrence	Death	N/A	N/A

8.2 Presentation of efficacy data from [additional documentation]

N/A

8.3 Modelling effects of subsequent treatments

N/A

8.4 Other assumptions regarding efficacy in the model

N/A

8.5 Overview of modelled average treatment length and time in model health state

N/A – treatment length in the cost-minimization model is purely based on the treatment length in the clinical trials (up to 52 weeks).

Table 29: Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
N/A	N/A	N/A	N/A

Table 30: Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [months]	Health state 1 [months]	Health state 2 [months]
N/A	N/A	N/A	N/A

9. Safety

9.1 Safety data from the clinical documentation

9.1.1 REAL 4: somapacitan vs somatropin in children with GHD

The REAL 4 safety analysis set (SAS) included all randomised participants that received at least one dose of treatment, analysed as treated; the SAS was used for the evaluation of safety endpoints.

The safety profile of once-weekly somapacitan was similar to the well-known safety profile for somatropin. In total, 135 (67.5%) participants experienced 457 AEs during the 52 weeks of treatment, with 94 (71.2%) participants reporting 310 AEs in the somapacitan group compared with 41 (60.3%) participants reporting 147 AEs in the somatropin group. Similar AE reporting rates were observed for somapacitan (232.3 AEs/100 PYE) and somatropin (212.8 AEs/100 PYE) (110).

The majority (98%) of AEs were mild (82%) or moderate (16%) and considered unlikely to be related to the trial product. No AEs in the somapacitan group led to discontinuation of trial product and no new safety issues or local tolerability issues were identified.

No neutralising antibodies were detected in participants on somapacitan treatment in the 52-week trial period.

Table 31: Overview of safety events in REAL 4 from baseline to 52 weeks

	Somapacitan (N=132) REAL 4 – 52 weeks	Somatropin (N=68) REAL 4 – 52 weeks	Absolute difference
Number of adverse events, n	310	147	163
Number and proportion of patients with ≥1 adverse events, n (%)	94 (71.2%)	41 (60.3%)	10,9%
Number of serious adverse events*, n	8	3	5

	Somapacitan (N=132) REAL 4 – 52 weeks	Somatropin (N=68) REAL 4 – 52 weeks	Absolute difference
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	6 (4.5%)	2 (2.9%)	1.6%
Number of CTCAE grade ≥ 3 events, n	7	1	6
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	4 (3.0%)	1 (1.5%)	1.5%
Number of adverse reactions, n	9	4	5
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	7 (5.3%)	4 (5.9%)	-0.6%
Number and proportion of patients who had a dose reduction, n (%)	1 (0.8%)	2 (2.9%)	-2.1%
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	1 (0.8%)	0	0.8%
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	0	0	0

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition). § CTCAE v. 5.0 must be used if available. Source: Miller et al. 2022 (110), REAL 4 CSR (128)

No serious adverse events with frequency of ≥ 5% were recorded in REAL 4.

Table 32: Serious adverse events (time point)

Adverse events	Intervention (N=x)		Comparator (N=x)	
	Number of patients with adverse events	**Number of adverse events**	**Number of patients with adverse events**	**Number of adverse events**
Adverse event, n (%)	N/A	N/A	N/A	N/A

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or

incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition). Source: REAL 4 CSR (128)

Seven (7) AEs (in 4 children, 3%) were classified as severe by the investigator in the somapacitan group, with no specific pattern of AEs. One (1) AE was classified as severe in the somatropin group. Trial product was temporarily discontinued due to 1 severe AE of headache in each group (the 1 in the somapacitan group was considered SAE). Another child in the somapacitan group had not yet recovered from headache at DBL. Fundoscopy was done with normal results.

Table 33: Summary of most frequent adverse events of grade 3 (severe adverse events)

	Norditropin			somapacitan			Total		
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	68				132				200			
Total patient years at risk	69.1				133.4				202.5			
Events	1	(1.5)	1	1.4	4	(3.0)	7	5.2	5	(2.5)	8	3.9
Nervous system disorders	1	(1.5)	1	1.4	2	(1.5)	2	1.5	3	(1.5)	3	1.5
Headache	1	(1.5)	1	1.4	2	(1.5)	2	1.5	3	(1.5)	3	1.5
General disorders and administration site conditions	0				1	(0.8)	2	1.5	1	(0.5)	2	1.0
Fatigue	0				1	(0.8)	2	1.5	1	(0.5)	2	1.0
Musculoskeletal and connective tissue disorders	0				1	(0.8)	2	1.5	1	(0.5)	2	1.0
Pain in extremity	0				1	(0.8)	2	1.5	1	(0.5)	2	1.0
Respiratory, thoracic and mediastinal disorders	0				1	(0.8)	1	0.7	1	(0.5)	1	0.5
Asthma	0				1	(0.8)	1	0.7	1	(0.5)	1	0.5

N: Number of subjects, E: Number of events, R: Event rate per 100 patient years at risk, %: Percentage
Only adverse events with an onset after the first administration of trial product and up until 14 days after last trial drug administration for withdrawn subjects, and with an onset after the first administration of trial product and up until visit 7 (week 52) or 14 days after last trial drug administration, which ever comes first, for all other subjects, are included.
MedDRA version 24.1.

nn8640/nn8640-4263-main/ctr_20220215_er
25FEB2022:07:55:25 - taesocptsum.sas/taesevaesocptsumontrsas.txt

The REAL 4 clinical study had a 3-year safety extension period which is published in Miller et al. 2025 (131). Longterm safety in children with GHD is also assessed in a 7-year clinical phase 2 trial, REAL 3, which investigates the safety of multiple somapacitan doses and is published in Sävendahl et al. 2020 (106).

Somapacitan is well tolerated and no new significant safety signals have been identified for somapacitan and the safety profile is similar to the well-known somatropin. Therefore, the demands on the Danish healthcare system for the management of adverse events related to somapacitan and somatropin are expected to be similar and unlikely to influence results of the health economic analysis. Hence no safety data is used in the economic model in this assessment.

Table 34: Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	**Frequency used in economic model for comparator**	**Source**	**Justification**
Adverse event, n (%)	N/A	N/A	N/A	N/A

9.1.2 REAL 1: somapacitan vs somatropin in naïve adults with GHD

The REAL 1 safety analysis set (SAS) included all randomised participants that received at least one dose of treatment, analysed as treated; the SAS was used for the evaluation of safety endpoints.

Overall, the safety profile of once-weekly somapacitan was similar to that of daily somatropin treatment. Somapacitan for up to 34 weeks was well tolerated, with no clinically significant safety or local tolerability issues identified

A total of 228 (76.0%) participants experienced 995 AEs during the 34 weeks of treatment, with 87 (72.5%) participants reporting 385 AEs in the somapacitan group, 46 (75.4%) participants reporting 184 AEs in the placebo group, and 95 (79.8%) participants reporting 426 AEs in the somatropin group. The AE rate was similar in the somapacitan (482 AEs per 100 patient years) and placebo (462 AEs per 100 patient years) groups, but higher in the somatropin group (549 AEs per 100 patient years).

The majority of AEs were of mild (70.2%) or moderate (27.1%) severity and were unlikely related to trial product (somapacitan: 76%; placebo: 89%; somatropin®: 82%). At Week 34, the outcome was reported as recovered for the majority of the AEs (somapacitan: 90%; placebo: 88%; somatropin: 85%). There were five participants who discontinued treatment due to AEs in the placebo (1 subject) and somatropin (4 participants) groups, with no treatment discontinuations in the somapacitan group. There were two AEs leading to treatment discontinuation that were assessed as probably related to trial product, diabetes and haemoconcentration in the somatropin group. There were no AEs that led to treatment interruptions in the somapacitan group, but five AEs in three participants in the placebo group and eight AEs in five participants in the somatropin group that led to temporary discontinuation of treatment.

A total of 7 (5.8%) participants experienced 12 SAEs in the somapacitan arm, 5 (8.2%) participants experienced 7 SAEs in the placebo arm, and 11 (9.2%) participants experienced 13 SAEs in the somatropin arm, and the event rate was similar across treatment groups (15, 17.6 and 16.8 events per 100 patient years in the somapacitan, placebo, and somatropin groups, respectively). There was only one SAE that was assessed as probably related to trial product, haemoconcentration in the somatropin group, which was also reported as a suspected unexpected serious adverse reaction (SUSAR); all other SAEs were judged to be unlikely related to trial product. No participants in the somapacitan group interrupted or discontinued trial drug due to SAEs. In the placebo group, one participant interrupted trial drug due to an SAE (ECG T wave abnormal), and in the somatropin group, two participants discontinued treatment due to SAEs (haemoconcentration and atopic dermatitis) and three participants interrupted treatment due to four SAEs (abdominal pain, appendicitis, tibia fracture, and fall). There was one SAE (haemoconcentration in the somatropin group) that led to dose reduction.

There was one death during the trial in the placebo group (acute adrenocortical insufficiency in a 76-year-old subject, possibly due to not taking prednisone during time

of illness despite being advised to). The death was considered unlikely to be related to trial product.

No anti-somapacitan or anti-hGH antibodies were detected in the main part of the trial.

Table 35: Overview of safety events in REAL 1 from baseline to 34 weeks

	Somapacitan (N=120) REAL 1 - 34 weeks	Somatropin (N=119) REAL 1 – 34 weeks	Absolute difference
Number of adverse events, n	385	426	-41
Number and proportion of patients with ≥1 adverse events, n (%)	87 (72.5%)	95 (79.8%)	-7.3%
Number of serious adverse events*, n	12	13	-1
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	7 (5.8%)	11 (9.2%)	-3.4%
Number of CTCAE grade ≥ 3 events, n	11	10	1
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	7 (5.8%)	9 (7.6%)	-1.8%
Number of adverse reactions (injection site reactions), n	12	10	2
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	7 (5.9%)	8 (6.8%)	-0.9%
Number and proportion of patients who had a dose reduction, n (%)	0	1 (0.85%)	-0.85%
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	0	4 (3.4%)	-3.4%
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	0	4 (3.4)	-3.4%

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition). § CTCAE v. 5.0 must be used if available. Source: Johannsson et al, 2020 (111); Novo Nordisk CSR REAL 1 (129)

No serious adverse events with frequency of ≥ 5% were recorded in REAL 1.

Table 36: Serious adverse events (time point)

Adverse events	Intervention (N=x)		Comparator (N=x)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	N/A	N/A	N/A	N/A

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition). Source: Novo Nordisk CSR REAL 1 (129)

The AEs reported as severe were single events observed in single patients, except for 2 events of toothache (somatropin) and headache (somapacitan). A similar fraction of patients reported severe AEs in the somapacitan (5.8%), placebo (6.6%) and somatropin (7.6%) groups. There were no apparent differences in type of severe AEs reported between treatment groups. Notable severe AEs were pancreatitis acute, sepsis, adrenocortical insufficiency acute, haemoconcentration and plasma cell myeloma.

Four (4) severe AEs in 4 patients were judged to be possibly (somapacitan: 2 headaches and 1 intervertebral disc protrusion) or probably (somatropin: 1 haemoconcentration, SAE) related to trial product by the investigator.

Table 37: Summary of most frequent adverse events of grade 3 (severe adverse events)

MedDRA system organ class Preferred term	Placebo N (%)	E	R	Norditropin N (%)	E	R	Somapacitan N (%)	E	R	Total N (%)	E	R
Subjects exposed	61			119			120			300		
Total patient years	39.82			77.54			79.88			197.24		
All severe adverse events	4 (6.6)	6	15.1	9 (7.6)	10	12.9	7 (5.8)	11	13.8	20 (6.7)	27	13.7
Gastrointestinal disorders	2 (3.3)	3	7.5	3 (2.5)	3	3.9	0			5 (1.7)	6	3.0
Toothache	0			2 (1.7)	2	2.6	0			2 (0.7)	2	1.0
Pancreatitis acute	1 (1.6)	1	2.5	0			0			1 (0.3)	1	0.5
Vomiting	1 (1.6)	1	2.5	0			0			1 (0.3)	1	0.5
Diarrhoea	1 (1.6)	1	2.5	0			0			1 (0.3)	1	0.5
Abdominal pain	0			1 (0.8)	1	1.3	0			1 (0.3)	1	0.5
Infections and infestations	1 (1.6)	1	2.5	1 (0.8)	1	1.3	2 (1.7)	4	5.0	4 (1.3)	6	3.0
Gastroenteritis	0			0			1 (0.8)	1	1.3	1 (0.3)	1	0.5
Appendicitis	0			0			1 (0.8)	1	1.3	1 (0.3)	1	0.5
Herpes simplex	0			0			1 (0.8)	1	1.3	1 (0.3)	1	0.5
Sepsis	0			0			1 (0.8)	1	1.3	1 (0.3)	1	0.5
Gastroenteritis viral	1 (1.6)	1	2.5	0			0			1 (0.3)	1	0.5
Clostridium difficile infection	0			1 (0.8)	1	1.3	0			1 (0.3)	1	0.5
Endocrine disorders	1 (1.6)	1	2.5	0			1 (0.8)	1	1.3	2 (0.7)	2	1.0
Adrenocortical insufficiency acute	1 (1.6)	1	2.5	0			1 (0.8)	1	1.3	2 (0.7)	2	1.0
Injury, poisoning and procedural complications	0			1 (0.8)	2	2.6	0			1 (0.3)	2	1.0
Fall	0			1 (0.8)	1	1.3	0			1 (0.3)	1	0.5

Tibia fracture	0			1 (0.8)	1	1.3	0			1 (0.3)	1	0.5
Investigations	0			0			1 (0.8)	2	2.5	1 (0.3)	2	1.0
Blood creatine phosphokinase increased	0			0			1 (0.8)	2	2.5	1 (0.3)	2	1.0
Musculoskeletal and connective tissue disorders	1 (1.6)	1	2.5	0			1 (0.8)	1	1.3	2 (0.7)	2	1.0
Intervertebral disc protrusion	0			0			1 (0.8)	1	1.3	1 (0.3)	1	0.5
Muscle spasms	1 (1.6)	1	2.5	0			0			1 (0.3)	1	0.5
Nervous system disorders	0			0			2 (1.7)	2	2.5	2 (0.7)	2	1.0
Headache	0			0			2 (1.7)	2	2.5	2 (0.7)	2	1.0
Blood and lymphatic system disorders	0			1 (0.8)	1	1.3	0			1 (0.3)	1	0.5
Haemoconcentration	0			1 (0.8)	1	1.3	0			1 (0.3)	1	0.5
General disorders and administration site conditions	0			0			1 (0.8)	1	1.3	1 (0.3)	1	0.5
Pyrexia	0			0			1 (0.8)	1	1.3	1 (0.3)	1	0.5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0			1 (0.8)	1	1.3	0			1 (0.3)	1	0.5
Plasma cell myeloma	0			1 (0.8)	1	1.3	0			1 (0.3)	1	0.5
Respiratory, thoracic and mediastinal disorders	0			1 (0.8)	1	1.3	0			1 (0.3)	1	0.5
Sleep apnoea syndrome	0			1 (0.8)	1	1.3	0			1 (0.3)	1	0.5
Skin and subcutaneous tissue disorders	0			1 (0.8)	1	1.3	0			1 (0.3)	1	0.5
Dermatitis atopic	0			1 (0.8)	1	1.3	0			1 (0.3)	1	0.5

N: Number of subjects having the given event, or an event in the given system organ class at least once,
E: Number of adverse events reported, R: Event rate per 100 patient years,
%: Percentage of exposed subjects having the event
MedDRA version 20.0

Longterm safety in adults with GHD has been demonstrated in the REAL 1 extension study, which has a 53-week safety extension phase, which is published in Johannsson et al. 2020 (111).

Somapacitan is well tolerated and no new significant safety signals have been identified for somapacitan and the safety profile is similar to the well-known somatropin. Therefore, the demands on the Danish healthcare system for the management of adverse events related to somapacitan and somatropin are expected to be similar and unlikely to influence results of the health economic analysis. Hence no safety data is used in the economic model in this assessment.

Table 38: Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	**Frequency used in economic model for comparator**	**Source**	**Justification**
Adverse event, n (%)	N/A	N/A	N/A	N/A

9.2 Safety data from external literature applied in the health economic model

No safety data from external literature was used in the health economic model in this application. Only safety data from the two head-to-head trials (REAL 1 and REAL 4) has been applied.

Table 39: Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

10. Documentation of health-related quality of life (HRQoL)

The HRQoL instruments included in REAL 1 and REAL 4 are listed below.

Table 40: Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
TRIM-AGHD	Brod M, Hojbjerre L, Adalsteinsson JE, Rasmussen MH. Assessing the impact of growthhormone deficiency and treatment in adults: development of a new disease-specific measure. J Clin Endocrinol Metab. 2014;99(4):1204-12.	Efficacy measure in REAL 1
SF-36	Ware JE, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME. User's Manual for the SF-36v2(R) Health Survey. 3rd ed. Lincoln, RI: QualityMetric incorporated. 2011.	Efficacy measure in REAL 1
TSQM-9	Atkinson MJ, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes. 2004;2:12.	Efficacy measure in REAL 1
TRIM GHD-CIM	Brod M, Højby Rasmussen M, Vad K, Alolga S, Bushnell DM, Bedoin J, et al. Psychometric Validation of the Growth Hormone Deficiency-Child Impact Measure (GHDCIM). Pharmacoecon Open. 2021.	Efficacy measure in REAL 4
TB-CGHD-O (observer)	Brod M, Rasmussen MH, Vad K, Alolga S, Bedoin J. SUN-248 Growth Hormone Deficiency (GHD): Assessing Burden of Treatment in Children and	Efficacy measure in REAL 4

Measuring instrument	Source	Utilization
	Adolescents. J Endocr Soc. 2019;3 (suppl 1): SUN-248.	
TB-CGHD-P (parent)	Brod M, Rasmussen MH, Vad K, Alolga S, Bodoin J. Growth Hormone Deficiency (GHD): Assessing Parent Burden for Child Growth Hormone Deficiency Treatment: The Growth Hormone Deficiency - Parent Treatment Burden Measure (GHD-PTB). ESPE Abstracts (2019) 92 P1-371.	Efficacy measure in REAL 4

Only TRIM-AGHD and TRIM GHD-CIM will be presented in the following as they are the most comparable HRQoL instruments across the paediatric and adult population.

No HRQoL instruments are used in the health economic analysis (cost-minimization analysis).

10.1 Presentation of the health-related quality of life

TRIM-AGHD in REAL 1

10.1.1 Study design and measuring instrument

The Treatment Related Impact Measure-Adult Growth Hormone Deficiency (TRIM-AGHD) is a disease specific questionnaire which measures the impact of GH treatment on the functioning and well-being of AGHD patients (124). The 4 concepts covered by the questionnaire is physical health, energy levels, cognitive ability and psychological health. TRIM-AGHD has 27 items and a total score as well as domain specific scores can be derived. A lower score indicates a better health state. The minimal important difference (MID) value for the subscale scores was 11 points and the MID value for the total score was 10 points.

10.1.2 Data collection

TRIM-AGHD was assessed at randomisation (visit 2) and during trial conduct (at visits 13 and 14).

The questionnaire was completed by the patient and should preferably be completed after all fasting related activities but before any other visit related procedures were conducted. Written instructions on how to complete the questionnaire were provided to the patient. After completion, the questionnaire was reviewed by the investigator for potential AEs, including any change in health and concomitant medication. Filled in questionnaires were sent for central data entry into the clinical database.

The introductory text of the TRIM-AGHD questionnaire was updated after the finalisation of protocol version 2 to: 'The following questions are about how your GHD impacts your functioning and well-being. Please tick the response box that most closely represents your CURRENT EXPERIENCE with GHD. If you have other health conditions, please think only about your GHD when answering these questions'. For a few of the first enrolled patients the updated version was not available at their randomisation visit (baseline visit). Consequently, they answered the old questionnaire throughout the trial. In order to investigate whether the difference in the introductory text in the questionnaire had any impact on the results of the analyses, the analysis of the TRIM-AGHD endpoints was repeated restricted to patients who answered the new questionnaire.

Table 41: Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X (FAS)	Number of patients who completed (% of patients expected to complete)
Baseline somapacitan, n	121	1	120	120
Week 25 somapacitan, n	N/A	N/A	N/A	111
Week 34 somapacitan, n	N/A	N/A	N/A	116
Baseline somatropin, n	119	0	119	119
Week 25 somatropin, n	N/A	N/A	N/A	107
Week 34 somatropin, n	N/A	N/A	N/A	113

10.1.3 HRQoL results

The change from baseline to week 34 in 4 of 5 scores was lower for somapacitan than for somatropin and the differences between somapacitan and somatropin were statistically significant Table 42. However, the difference in total score did not meet the minimal important difference (total score of 10). Similar results were observed in the sensitivity

analysis, where the analysis of TRIM-AGHD endpoints was repeated restricted to patients who answered the new questionnaire Table 43. A statistically significant difference between somapacitan and somatropin was observed in 3 of 5 scores. However, the difference in total score did not meet the minimal important difference (total score of 10).

Table 42: HRQoL TRIM-AGHD summary statistics

	Somapacitan		Somatropin		Somapacitan vs. somatropin
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Change from Baseline to week 34 **Congnitive score**	115	-3.92 (17.29)	112	-7.06 (18.47)	3.80 (95% CI: -0.49; 8.09) p-value: 0.0825
Change from Baseline to week 34 **Energy score**	116	-7.81 (24.07)	112	-13.42 (23.73)	7.05 (95% CI: 1.52; 12.7) p-value: 0.0126
Change from Baseline to week 34 **Physical score**	115	-7.39 (19.25)	112	-11.33 (19.23)	5.00 (95% CI: 0.47; 9.53) p-value: 0.0305
Change from Baseline to week 34 **Psychological score**	116	-4.63 (12.01)	112	-8.93 (14.21)	4.51 (95% CI:1.41; 7.62) p-value: 0.0046
Change from Baseline to week 34 **Total score**	115	-5.71 (12.69)	112	-9.99 (13.64)	4.99 (95% CI: 1.84; 8.14) p-value: 0.0020

Figure 1: Box plot of TRIM-AGHD - total score by visit - full analysis set

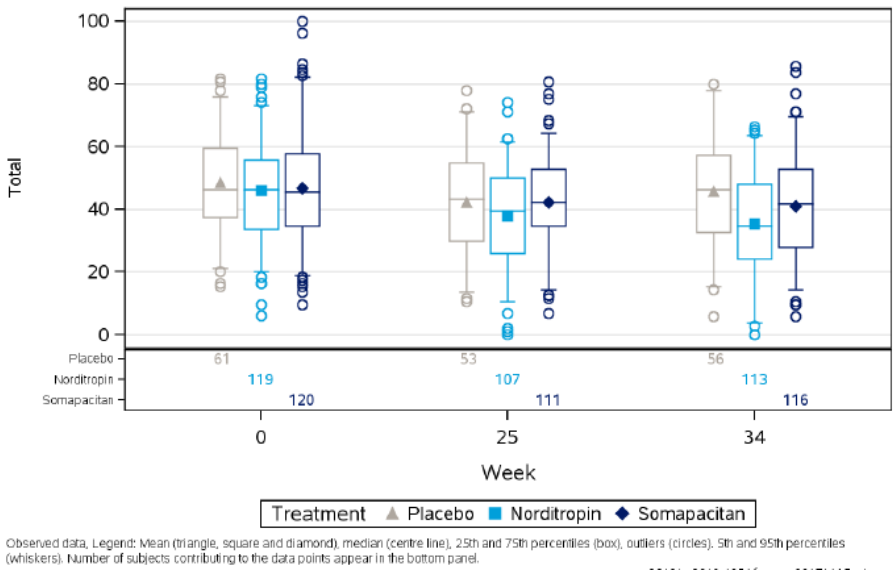


Table 43: HRQoL TRIM-AGHD summary statistics - sensivity analysis excluding subjects answering version 1 of TRIM AGHD

	Somapacitan		Somatropin		Somapacitan vs. somatropin
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Change from Baseline to week 34 **Congnitive score**	107	N/A	102	N/A	3.77 (95% CI: -0.54; 8.07) p-value: 0.0865
Change from Baseline to week 34 **Energy score**	107	N/A	102	N/A	6.27 (95% CI: 0.62; 11.93) p-value: 0.0297
Change from Baseline to week 34 **Physical score**	107	N/A	102	N/A	4.16 (95% CI: -0.48; 8.79) p-value: 0.0787

	Somapacitan		Somatropin		Somapacitan vs. somatropin
Change from Baseline to week 34 **Psychological score**	107	N/A	102	N/A	4.31 (95% CI: 1.23; 7.39) p-value: 0.0046
Change from Baseline to week 34 **Total score**	107	N/A	102	N/A	4.61 (95% CI: 1.45; 7.77) p-value: 0.0020

TRIM GHD-CIM

10.1.4 Study design and measuring instrument

TRIM GHD-CIM is a disease specific questionnaire which measures the impact of GH treatment on symptoms, physical health and social and emotional wellbeing of children with GHD (120). Based on the responses, an overall score as well as domain specific scores can be derived. The scores of TRIM GHD-CIM ranges from 0 to 100. Lower scores indicate better health state, meaning less disease burden or treatment burden.

10.1.5 Data collection

TRIM GHD-CIM was assessed at weeks 0, 26 and 52. The questionnaire was completed by the children's parent or LAR in the e-Diary and were preferably completed by the same parent/LAR.

Table 44: Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline **Somapacitan, n**	132	0	132	98

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 26, TRIM GHD-CIM total score **Somapacitan, n**	N/A	N/A	N/A	103
Week 52, TRIM GHD-CIM total score **Somapacitan, n**	N/A	N/A	N/A	113
Baseline **Somatropin, n**	68	0	68	53
Week 26, TRIM GHD-CIM total score **Somatropin, n**	N/A	N/A	N/A	49
Week 52, TRIM GHD-CIM total score **Somatropin, n**	N/A	N/A	N/A	55

10.1.6 HRQoL results

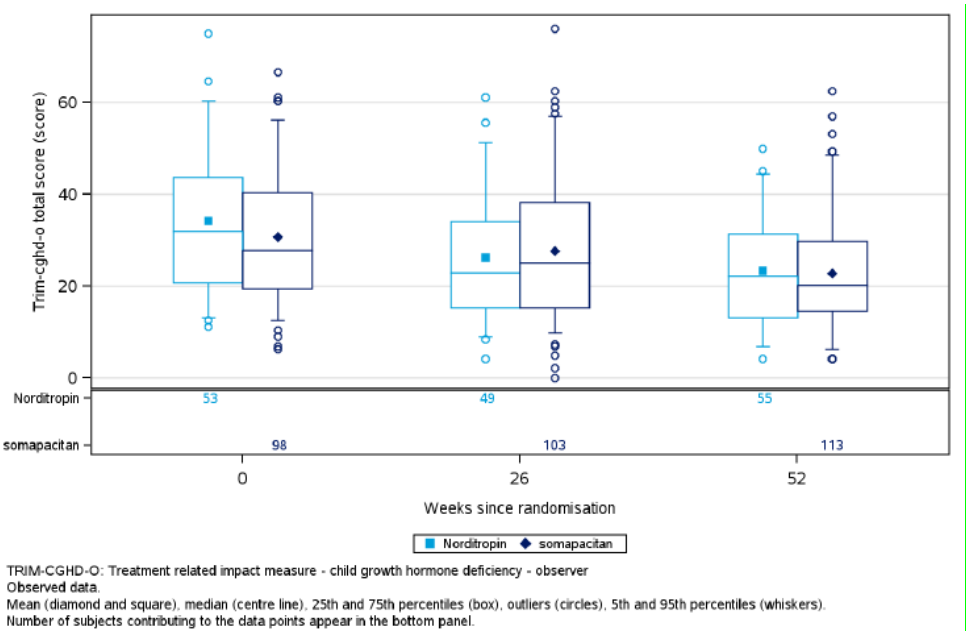
Improvements, assessed as decreased scores relative to baseline, were observed for all domains of TRIM GHD-CIM (physical functioning, emotional well-being, social well-being and total score) for both treatment groups at 52 weeks and to a lesser extent, also after 26 weeks.
After end of the main trial period at 52 weeks, there was a high level of similarity between somapacitan and somatropin for all three dimension scores (physical functioning, emotional wellbeing, social well-being) as well as for the total score.

Table 45: HRQoL TRIM GHD-CIM summary statistics - FAS

	Somapacitan		Somatropin		Somapacitan vs. somatropin
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value

	Somapacitan		Somatropin		Somapacitan vs. somatropin
Change from Baseline to week 52 **Physical functioning**	91	-4.4	46	-4.6	0.2 (95% CI: -3.9; 4.3) p-value: 0.9307
Change from Baseline to week 52 **Emotional well-being**	81	-10.8	44	-8.3	-2.5 (95% CI: -6.6; 1.6) p-value: 0.2329
Change from Baseline to week 52 **Social well-being**	85	-14.9	46	-11.4	-3.5 (95% CI: -10.7; 3.7) p-value: 0.3346
Change from Baseline to week 52 **Total score**	90	-9.6	48	-9.4	-0.2 (95% CI: -3.9; 3.4) p-value: 0.8914

Figure 2: Box plot of TRIM GHD-CIM - total score by visit - full analysis set



TRIM-CGHD-O: Treatment related impact measure - child growth hormone deficiency - observer
Observed data.
Mean (diamond and square), median (centre line), 25th and 75th percentiles (box), outliers (circles), 5th and 95th percentiles (whiskers).
Number of subjects contributing to the data points appear in the bottom panel.

10.2 Health state utility values (HSUVs) used in the health economic model

N/A

10.2.1 HSUV calculation

N/A

10.2.1.1 Mapping

N/A

10.2.2 Disutility calculation

N/A

10.2.3 HSUV results

N/A

Table 46: Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUV A	N/A	N/A	N/A	N/A
HSUV B	N/A	N/A	N/A	N/A

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

N/A

10.3.1 Study design

N/A

10.3.2 Data collection

N/A

10.3.3 HRQoL Results

N/A

10.3.4 HSUV and disutility results

N/A

Table 47: Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV A	N/A	N/A	N/A	N/A
HSUV B	N/A	N/A	N/A	N/A

Table 48: Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUV A				

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Study 1	N/A	N/A	N/A	N/A

11. Resource use and associated costs

11.1 Medicines - intervention and comparator

As listed in Table 49, somapacitan and somatropin (both come in 3 different strengths) have been used in the cost-minimization analysis.

Public list prices in DK have been used (112), but since somatropin comes in several brand names, the price of somatropin used in the cost-minimization analysis is a weighed price according to current market shares for the various somatropin brands [redacted].

The market shares and list prices as of 24th November 2025 are as follows:

Table 49: Market shares and prices used in the health economic model

Somatropin brand name	Market share in DK	PPP in DKK/mg (10mg/1.5 ml)
Omnitrope®	[redacted]	261.57
Norditropin®	[redacted]	267.21
Genotropin®	[redacted]	182.74

For Omnitrope® and Norditropin® the prices of the 10mg/1.5 ml strengths are used in the cost-minimization analysis as this is the most widely used strength. For Genotropin® the price of GoQuick 12 mg has been used as this is the most comparable to Omnitrope® and Norditropin®. Market shares are [redacted]. Source: www.medicinpriser.dk

Based on above, the prices used the cost-minimization model are the following:

- Somapacitan: PPP 620.32 DKK/mg
- Somatropin: PPP 262.12 DKK/mg

For treatment of children with GHD, the dose is weight-based, hence the medicine costs are based on the patient's weight. For this analysis we have assumed an average weight of children (up to 18 years of age) of 30 kg.

According to Danks Pædiatrisk Selskab the average weight of both prepubertal boys and girls at 9 years old is around 30 kg (132). It is crucial that growth hormone treatment is started prepubertal, which is what is reflected in the inclusion/exclusion criteria in REAL 4. Use of an average weight of 30 kg in the cost minimization analysis in children with GHD is based on this.

In the REAL 4 clinical trial the average weight is 16.69 kg in the somapacitan group and 16.01 kg in the somatropin group, which is used in the sensitivity analysis SA1children.

For treatment of adults the dose is fixed and based on the mean dose in REAL 1 (2.56 mg/week for somapacitan and 2.31 mg/week for somatropin), which also take into account the difference in adherence between somapacitan and somatropin. Adherence was 95,5% in the somapacitan groupo and 90,6 for somatropin group (111).

Below is an overview of the medicines used in the model.

Table 50: Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Somapacitan 5 mg/1.5 ml 10 mg/1.5 ml 15 mg/1.5 ml	Children with GHD: 0.16 mg/kg per week (weight-based) = 4.80 mg/week in a 30 kg patient	N/A	Weekly	N/A
	Adults with GHD: 2.56 mg/week (fixed dose)	N/A	Weekly	N/A
Somatropin 5 mg/1.5 ml 10 mg/1.5 ml 15 mg/1.5 ml	Children with GHD: 0.034 mg/kg per day (weight-based) = 7.14 mg/week in a 30 kg patient	N/A	Daily	N/A
	Adults with GHD: 2.31 mg/week (fixed dose)	N/A	Daily	N/A

11.2 Medicines– co-administration

No co-administration medicine is needed for neither somapacitan nor somatropin.

There is no extra costs for needles as it is a requirement in the AMGROS agreement with suppliers to deliver the medicinal product with the needed device for administration of

the medicine, including the number of needles corresponding to the delivered amount of medicine.

11.3 Administration costs

Both somapacitan and somatropin are self-administrated by patients or parents/caregivers. Since drug administration costs and training costs are assumed to be similar for somapacitan and somatropin (same number of trainings in administration GH treatment with nurses), these are not included in the analysis.

Table 51: Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
N/A	N/A	N/A	N/A	N/A

11.4 Disease management costs

Disease management costs are assumed to be similar for somapacitan and somatropin because patients require same management of GHD (same number of GP-visits and specialist visits) regardless of whether they are treated with once-weekly somapacitan or once-weekly somatropin, hence these costs are not included in the health economic model.

There is no difference in preparation of the somapacitan and somatropin as it is delivered in the same device. The device is prepared by the supplier except for attachment of needle, which is done at home prior to injecting the medicine.

Somapacitan is administered in the same way as somatropin, but only once a week instead of once a day.

Regarding monitoring of IGF-I level, treatment with somapacitan does not require further monitoring or hospital visits than somatropin. Monitoring of IGF-I level is standard clinical practice in DK regardless of growth hormone medicine, which is also described in the *Background document for use of GH in children and adults* (68).

Table 52: Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
N/A	N/A	N/A	N/A	N/A

11.5 Costs associated with management of adverse events

The safety of somapacitan was similar to the safety profile of once-daily somatropin. Somapacitan was well tolerated with no new safety issues identified.

The majority of AEs in both children and adults with GHD (98% and 97%) were mild or moderate and all SAEs were resolved and assessed by the investigator to be unlikely related to trial product.

Costs related to adverse events have not been included in the analysis as they were deemed to have a negligible impact on costs: no significant safety signals have been identified for somapacitan and the safety profile is similar to somatropin. Therefore, the demands on the Danish healthcare system for the management of adverse events related to somapacitan and somatropin are expected to be similar and unlikely to influence results of the health economic analysis.

Table 53: Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
N/A	N/A	N/A

11.6 Subsequent treatment costs

Neither patients treated with somapacitan nor patients treated with somatropin require subsequent treatment.

Table 54: Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
N/A	N/A	N/A	N/A	N/A

11.7 Patient costs

As patients require same management of GHD (same administration, monitoring and number of GP-visits and specialist visits) regardless of whether they are treated with once-weekly somapacitan or once-weekly somatropin, the costs incurred by patients and their families are assumed to be similar for the two treatments. Hence these costs are not included in the health economic model.

Table 55: Patient costs used in the model

Activity	Time spent [minutes, hours, days]
N/A	N/A

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Costs for home care nurses, out-patients rehabilitation and palliative care are not related to treatment with somapacitan and somatropin.

12. Results

12.1 Base case overview

Table 56: Base case overview

Feature	Description
Comparator	Once-daily somatropin
Type of model	Cost-minimization analysis
Time horizon	1-year analysis based on the clinical trials REAL 1 and REAL 4 main phases
Measurement and valuation of health effects	No clinical effects or QoL effects are included as this is a cost-minimization analysis
Costs included	Medicine costs
Dosage of medicine	Based on weight
Average time on treatment	Somapacitan: 52 weeks Somatropin: 52 weeks

12.1.1 Base case results

Table 57: Base case results per patient per year for children with GHD

	Somapacitan	Somatropin	Difference
Medicine costs per patient per year	154.831 DKK	97.321 DKK	57.510 DKK
Medicine costs – co-administration	N/A	N/A	N/A
Administration	N/A	N/A	N/A

	Somapacitan	Somatropin	Difference
Disease management costs	N/A	N/A	N/A
Costs associated with management of adverse events (DKK)	N/A	N/A	N/A
Subsequent treatment costs	N/A	N/A	N/A
Patient costs	N/A	N/A	N/A
Palliative care costs	N/A	N/A	N/A
Total costs per patient per year	**154.831 DKK**	**97.321 DKK**	**57.510 DKK**
Life years gained (health state A)	N/A	N/A	N/A
Life years gained (health state B)	N/A	N/A	N/A
Total life years	**N/A**	**N/A**	**N/A**
QALYs (state A)	N/A	N/A	N/A
QALYs (state B)	N/A	N/A	N/A
QALYs (adverse reactions)	N/A	N/A	N/A
Total QALYs	**N/A**	**N/A**	**N/A**
Incremental costs per life year gained			**N/A**
Incremental cost per QALY gained (ICER)			**N/A**

Table 58: Base case results per patient per year for adults with GHD

	Somapacitan	Somatropin	Difference
Medicine costs per patient per year (DKK)	82.576 DKK	31.486 DKK	51.090 DKK
Medicine costs – co-administration	N/A	N/A	N/A

	Somapacitan	Somatropin	Difference
Administration	N/A	N/A	N/A
Disease management costs	N/A	N/A	N/A
Costs associated with management of adverse events	N/A	N/A	N/A
Subsequent treatment costs	N/A	N/A	N/A
Patient costs	N/A	N/A	N/A
Palliative care costs	N/A	N/A	N/A
Total costs per patient per year	**82.576 DKK**	**31.486 DKK**	**51.090 DKK**
Life years gained (health state A)	N/A	N/A	N/A
Life years gained (health state B)	N/A	N/A	N/A
Total life years	**N/A**	**N/A**	**N/A**
QALYs (state A)	N/A	N/A	N/A
QALYs (state B)	N/A	N/A	N/A
QALYs (adverse reactions)	N/A	N/A	N/A
Total QALYs	**N/A**	**N/A**	**N/A**
Incremental costs per life year gained			**N/A**
Incremental cost per QALY gained (ICER)			**N/A**

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

In treatment of children with GHD there are some uncertainties that may impact the cost minimization analysis. These are the average weight and the dose in mg/kg used in the model.

A deterministic sensitivity analysis has therefore been conducted to address these uncertainties.

In the sensitivity analysis *'SA1children'* the average weight of 30 kg has been changed to the mean weight at baseline in children in the REAL 4 clinical trial. This was 16.7 kg (110).

A sensitivity analysis *'SA2children'* using the actual dose of somapacitan and somatropin in the REAL 4 trial has also been conducted. The actual dose of somapacitan was 0.0227mg/kg/day and the actual dose of somatropin was 0.0341mg/kg/day, which reflects the difference in adherence between the two groups (95,8% in the somapacitan group and 88,3 % in the somatropin) (110).

The results of the deterministic sensitivity analyses are presented in Table 59.

In treatment of adults with GHD uncertainty about the dose also exists even though the dose is independent of the patient's weight. In REAL 1 during the first 8 weeks, the dose was titrated every 2nd week from week 2 and adjusted according to the IGF-1 SDS levels, as already explained in section 6.2.1.

The health economic base case analysis is based on the mean dose of somapacitan and somatropin in the REAL 1 trial (111). But due to the individual titration of dose in the first 8 weeks of treatment a series of sensitivity analyses (*'SA1adults', 'SA2adults', 'SA3adults', 'SA4adults'*) has been performed where the dose is varied by +/- 20% for somapacitan and somatropin. The results are presented in Table 59.

Table 59: One-way sensitivity analyses results – children with GHD

Sensitivity analysis	Change	Reason / Rational / Source	Incremental cost (DKK)
SA1children	Patients' weight changed to mean baseline weight (kg) in REAL 4 trial	Actual baseline weight in REAL 4 trial varies from average weight in paediatric population. Average weight per patient in paediatric population: 30 kg Actual mean baseline weight in somapacitan patients: 16.69 kg Actual mean baseline weight in somatropin patients: 16.01 kg	34.201 DKK

Sensitivity analysis	Change	Reason / Rational / Source	Incremental cost (DKK)
SA2children	Dose of treatment changed to actual mean dose in REAL 4 trial	Actual dose in REAL 4 trial varies slightly from recommended dose. Recommended somapacitan dose: 0.1600 mg/kg/week Actual somapacitan mean dose: 0.1590 mg/kg/week Recommended somatropin dose: 0.0340 mg/kg/day Actual somatropin mean dose: 0.0341 mg/kg/day	56.133 DKK

Table 60: One-way sensitivity analyses results – adults with GHD

Sensitivity analysis	Change	Reason / Rational / Source	Incremental cost (DKK)
SA1adults	Somapacitan dose increased by 20%	Treatment dose was titrated individually every 2nd week during the first 8 weeks of treatment according to the patients' IGF-1 SDS levels, which causes uncertainty about the actual treatment dose. Somapacitan dose increased by 20% (from 2.56 mg/week to 3.07 mg/week)	67,606 DKK
SA2adults	Somapacitan dose reduced by 20%	Treatment dose was titrated individually every 2nd week during the first 8 weeks of treatment according to the patients' IGF-1 SDS levels, which causes uncertainty about the actual treatment dose. Somapacitan dose reduced by 20% (from 2.56 mg/week to 2.05 mg/week)	34,575 DKK
SA3adults	Somatropin dose increased by 20%	Treatment dose was titrated individually every 2nd week during the first 8 weeks of treatment according to the patients' IGF-1 SDS levels, which causes	44,793 DKK

Sensitivity analysis	Change	Reason / Rational / Source	Incremental cost (DKK)
		uncertainty about the actual treatment dose. Somatropin dose increased by 20% (from 2.31 mg/week to 2.77 mg/week)	
SA4adults	Somatropin dose reduced by 20%	Treatment dose was titrated individually every 2nd week during the first 8 weeks of treatment according to the patients' IGF-1 SDS levels, which causes uncertainty about the actual treatment dose. Somatropin dose reduced by 20% (from 2.31 mg/week to 1.85 mg/week)	57,388 DKK

12.2.2 Probabilistic sensitivity analyses

Not relevant to perform PSA for the cost-minimization analysis.

13. Budget impact analysis

Number of patients (including assumptions of market share)
As described in section 3.2, the number of patients with GHD in DK is based on same evidence as referenced in the the 'RADS, Baggrundsnotat for anvendelse af væksthormon hos børn og voksne, Nov 2013' (68). It refers to a publication from 2006 presenting incidence rate in GHD in DK using national registry data from DK in the years of 1980-1999.

For this assessment the incidence rate from the Stockholm article has been used to estimate the incidence of children and adults with GHD in DK the next 5 years. The prevalence has been extrapolated to 2026-2030 figures using the growth rate from the general population in DK from 1st January 2000 to 1st January 2025 (Danmarks Statistik: BEFOLK2). The prevalence rate in the adult population is then estimated to be 0.00045 and 0.00095 in the paediatric population.

The population growth rate was 0.062 in adults and 0.040 in children (Danmarks Statistik: BEFOLK2).

Based on the benefit of somapacitan vs somatropin with regards to weekly dosing instead of daily dosing associated with improved adherence, it is expected over a 5 -year

period 30% of GH patients, who are currently treated with somatropin, as well as 30% of new GHD patients will start treatment with somapacitan.

The estimated number of patients treated with somapacitan and somatropin in a situation with a recommendation of somapacitan in the treatment guideline vs a non-recommendation are presented in Table 61 below.

Table 61: Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market shares)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Somapacitan	291	651	909	1189	1494
Somatropin	3,862	3,692	3,635	3,567	3,487
			Non-recommendation		
Somapacitan	0	0	0	0	0
Somatropin	4,153	4,343	4,544	4,757	4,981

Cost inputs

The costs included in the budget impact model is only the medicine costs.

As for the cost-minimization analysis, public PPP list prices for somapacitan and the various brands of somatropin have been used (112). For somatropin a weighted price has been estimated based on the market shares of the 3 brands marketed with somatropin.

Similarly, as for the cost-minimization analysis an average weight of 30 kg per child with GHD has been used resulting in a weekly dose of 4.80 mg for somapacitan and 7.14 for somatropin, whereas for the adult population the dose is fixed to 2.56 mg/week for somapacitan and 2.31 mg/week for somatropin regardless of weight.

Budget impact

The expected budget impact of recommending somapacitan to children and adults with GHD and compliance issues with once-daily GHD treatment in Denmark (assumed to be up to 30% of current somatropin treated patients as well as new GHD patients over a 5-year period) is presented in Table 62.

Table 62: Expected budget impact based in PPP (DKK) of recommending somapacitan for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	DKK 239,671.643	DKK 267,490.859	DKK 290.230.533	DKK 314.647.080	DKK 340.866.887
The medicine under consideration is NOT recommended	DKK 224,181.514	DKK 232.802.472	DKK 241.872.200	DKK 251.415.095	DKK 261.456.926
Budget impact of the recommendation	**DKK 15,490.129**	**DKK 34.688.388**	**DKK 48.358.333**	**DKK 63.231.984**	**DKK 79.409.960**

14. List of experts

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Appendix A. Main characteristics of studies included

Table 63: Main characteristic of REAL 4

Trial name: REAL 4	NCT number: NCT03811535
Objective	The primary objective of REAL 4 was to compare the effect of somapacitan vs somatropin on longitudinal growth in children with GHD
Publications – title, author, journal, year	Weekly Somapacitan is Effective and Well Tolerated in Children With GH Deficiency: The Randomized Phase 3 REAL4 Trial. Miller et al. The Journal of Clinical Endocrinology & Metabolism, 2022, 107, 3378–3388.
Study type and design	Multicentre, multinational, randomised, open-label phase 3 trial. Participants were randomised 2:1 to receive either somapacitan or somatropin during the 52-week main trial period.
Sample size (n)	N = 200 132 patients were randomized to somapacitan, and 68 patients to somatropin.
Main inclusion criteria	• Prepubertal participants: – Boys aged ≥2 years and 26 weeks and <11.0 years at screening with testis volume <4 mL – Girls aged ≥4 years and 26 weeks and <10.0 years at screening with tanner stage 1 for breast development • Confirmed diagnosis of GHD: – Determined by two different GH stimulation tests performed in the last 12 months prior to randomisation, defined as a peak GH level of ≤10.0 ng/ml using the World Health Organization (WHO) International Somatropin 98/574 standard. For Japan: in the last 12 months prior to screening as determined by one GH stimulation test for participants with intracranial organic disease or symptomatic hypoglycaemia and two different GH stimulation tests for other participants defined as peak growth hormone level of ≤6 ng/ml by assay using recombinant GH standard

Trial name: REAL 4	NCT number: NCT03811535
	- If only one GH stimulation test is available before screening, then confirmation of GHD by a second and different GH stimulation test must be done - For participants with at least two additional pituitary hormone deficiencies (other than GHD) only one GH stimulation test is needed • Impaired height defined as at least 2.0 SDs below the mean height for chronological age and gender at screening according to the standards of Centers for Disease Control and Prevention (CDC) • Impaired height velocity, defined as annualised height velocity below the 25th percentile for chronological age and gender according to the standards of Prader calculated over a time span of minimum 6 months and maximum 18 months prior to screening • IGF-I −1.0 SDS at screening, compared with the age- and gender-normalised range measured at the central laboratory • No prior exposure to GH therapy or IGF-1 treatment
Main exclusion criteria	• Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with standing height measurements • Current inflammatory diseases requiring systemic corticosteroid treatment for longer than 2 consecutive weeks in the last 3 months prior to screening • Participants requiring inhaled glucocorticoid therapy at a dose of greater than 400 µg/day of inhaled budesonide or equivalents for longer than 4 consecutive weeks in the last 12 months prior to screening • Diagnosis of attention deficit hyperactivity disorder • Concomitant administration of other treatments that may have an effect on growth, e.g. methylphenidate for treatment of attention deficit hyperactivity disorder
Intervention	Somapacitan, once-weekly (n=132) Dosing: 0.16 mg/kg/week
Comparator(s)	Somatropin, once-daily (n=68) Dosing: 0.034 mg/kg/day
Follow-up time	52 weeks

Trial name: REAL 4		NCT number: NCT03811535
Is the study used in the health economic model?	Yes	
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** • The primary endpoint was height velocity at week 52 • The supportive secondary endpoints were: – Change from screening to Week 52 in bone age (years) Change from baseline to Week 52 in: – Height Standard Deviation Score (HSDS) (−10 to +10) – Height Velocity SDS (−10 to +10) Pharmacodynamic changes from baseline to Weeks 52, 104, 156, and 208 in: – IGF-1 SDS (−10 to +10) – IGFBP-3 SDS (−10 to +10) • The supportive secondary safety endpoints were: – Change in fasting plasma glucose (FPG) (mmol/L) from baseline to week 52 – Change in homeostatic model assessment (HOMA) (%) from baseline to week 52 – Change in glycated haemoglobin (HbA1c) (% point) from baseline to week 52 • Exploratory endpoints – patient reported outcomes – Change from baseline to week 52 in Growth hormone deficiency – child impact measure (GHD-CIM) – Assessment at week 52 of Treatment Burden Measure – Assessment at week 52 of Child-Growth Hormone Deficiency – Observer (TB-CGHD-O) – Assessment at week 52 of Treatment Burden Measure – Child-Growth Hormone Deficiency – Parent (TB-CGHD-P) – Assessment at week 26 of Growth Hormone Device Assessment Tool (G-DAT) **Other endpoints:**	

Trial name: REAL 4		NCT number: NCT03811535
	• Change in fasting plasma glucose (FPG) (mmol/L) from baseline to week 52 • Change in homeostatic model assessment (HOMA) (%) from baseline to week 52 • Change in glycated haemoglobin (HbA1c) (% point) from baseline to week 52	
Method of analysis	The primary endpoint was HV at Week 52, measured in cm/year using the following equation (80): HV was derived from height measurements recorded at baseline and Week 52. The secondary efficacy endpoints were analysed based on the 'in-trial' observation period during the main trial period. Data were analysed as the change from screening (Week 0) to Visit 7 (Week 52) for the following measurements: • Bone age (years) • HSDS (−10 to +10) • HVSDS (−10 to +10) HSDS was derived using Centers for Disease Control and Prevention (CDC) 25 standards and HVSDS was derived using Prader standards as reference data. The time interval used for the derivation of baseline HV was defined as: from date of pre-trial height assessment (a minimum of 6 months and maximum of 18 months prior to screening) to date of randomisation visit. Change in height SDS and HVSDS were analysed using the same analysis model as was used for analysing the primary endpoint for the primary estimand (treatment policy strategy) except for using baseline height SDS and baseline HVSDS, respectively, as a covariate in the model instead of baseline height. The estimate for the treatment difference at Week 52 was reported with corresponding 95% CI and p-value. Change in bone age was analysed using an analysis of covariance (ANCOVA) model on change in bone age/chronological age assessed at Week 52 and the model included treatment, gender, age group, region, GH peak group and gender by age group by region interaction term as factors and bone age/chronological age at screening as a covariate. The treatment difference estimate was reported with corresponding 95% CI and p-value. Participants without post-randomisation data for the analysed endpoint were not included in the analysis.	
Subgroup analyses	N/A	

Trial name: REAL 4		NCT number: NCT03811535
Other relevant information	N/A	

Table 64: Main characteristic of REAL 1

Trial name: REAL 1		NCT number: NCT02229851
Objective	The primary objective of REAL 1 was to demonstrate the clinical efficacy of once-weekly dosing of somapacitan after 34 weeks of treatment in adults with GHD	
Publications – title, author, journal, year	Once-weekly Somapacitan is Effective and Well Tolerated in Adults with GH Deficiency: A Randomized Phase 3 Trial. Johannsson et al. J Clin Endocrinol Metab, April 2020, 105(4):e1358–e1376	
Study type and design	Multicentre, multinational, randomised, parallel-group, placebo-controlled, partly double-blind phase 3 trial. A parallel-group design was chosen as a crossover trial was not possible due to carry-over effects (e.g. on body composition). Participants were randomised in a 2:2:1 ratio by interactive voice/web response service (IV/WRS) to receive somapacitan, somatropin or placebo. Somapacitan and placebo injection pens were visually identical and these two treatment arms were blinded to each other in the main phase of the trial (both given once weekly). Patients receiving once-daily somatropin were not blinded due to ethical reasons.	
Sample size (n)	N = 300 121 patients were randomized patients to somapacitan, 61 patients to placebo and 119 patients to somatropin.	
Main inclusion criteria	• Male or female aged 23–79 years. • Diagnosed with adult-onset GHD (either alone or associated with multiple hormone deficiencies [hypopituitarism] as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or traumatic brain injury) or childhood-onset GHD (as a result of congenital, genetic, acquired or idiopathic causes). Confirmed diagnosis in all countries except Japan by the following criteria: o ITT or glucagon test: peak GH response of <3 ng/mL	

Trial name: REAL 1		NCT number: NCT02229851
	○ GH-releasing hormone + arginine test according to BMI ▪ For BMI <25 kg/m^2, a peak GH <11 ng/mL ▪ For BMI 25–30 kg/m^2, a peak GH <8 ng/mL ▪ For BMI >30 kg/m^2, a peak GH <4 ng/mL ○ Three or more pituitary hormone deficiencies and IGF-1 SDS less than –2.0 Confirmed diagnosis in Japan by the following criteria: ○ Adult or childhood onset with multiple pituitary hormone deficiencies satisfying ≥1 of the following criteria, adult or childhood onset with isolated GHD satisfying ≥2 of the following criteria: ▪ ITT test using recombinant GH standard: peak GH ≤1.8 ng/mL ▪ Glucagon test using recombinant GH standard: peak GH ≤1.8 ng/mL ▪ GHRP-2 tolerance test using recombinant GH standard: peak GH ≤9 ng/mL • IGF-1 SDS less than –0.5 • hGH treatment-naïve or no exposure to hGH or GH secretagogues for ≥180 days prior to randomisation • Stable dose of other hormone replacement therapies for ≥90 days prior to randomisation • Systemic corticosteroids were not allowed other than in replacement doses within 90 days prior to randomisation • Levels within normal limits of testosterone (male participants), free T4, and adrenal function	
Main exclusion criteria	• Females who are pregnant, breastfeeding, or intending to become pregnant, or participants of either sex who are of reproductive age and not using adequate contraceptive measures as required by local regulation or practice. • Diagnosis of diabetes mellitus, unless all of the following criteria are met ○ Diagnosed clinically ≥6 months prior to screening ○ Stable OAD treatment and dose for ≥90 days prior to screening ○ No previous use of injectable diabetes therapy ○ HbA1c <7.0% at screening ○ No diabetes-related co-morbidities as judged by the Investigator ○ No proliferative retinopathy or severe non-proliferative diabetic retinopathy, confirmed by fundus photography performed ≤90 days prior to randomisation	

Trial name: REAL 1	NCT number: NCT02229851
	• Active malignant disease or history of malignancy, except for resection of in situ carcinoma of the cervix uteri, complete eradication of squamous cell or basal cell carcinoma of the skin, or intracranial malignant tumours or leukaemia that have been recurrence-free for ≥5 years • History of pituitary adenoma or other benign intracranial tumour, except for tumours that have been surgically removed ≥365 days prior to randomisation, or stable and clinically non-functioning adenomas that do not meet criterion for surgery and with no growth for ≥3 years, documented by two MRI or CT scans ≤9 months prior to randomisation • Clinically significant hepatic disease (ALT >3x ULN) or chronic renal impairment (creatinine >1.5x ULN) • History of positive results of tests for hepatitis B, hepatitis C, or HIV antibodies • Weight loss of >5% within 180 days prior to randomisation or use of weight loss medications within 12 months of randomisation • Active Cushing's syndrome or heart insufficiency of NYHA class >2 • History of acromegaly • Systemic corticosteroids other than in replacement doses within 90 days before randomisation • Inability to undergo DXA scanning
Intervention	Somapacitan, once-weekly (n=121) Starting dose: • Participants aged 23–60 years: 1.5 mg/week • Participants aged >60 years: 1.0 mg/week • Females on oral oestrogen: 2.0 mg/week During the first 8 weeks of the main trial period and the extension phase, the dose was titrated every second week from Week 2, allowing four opportunities for dose adjustment. The target IGF-1 SDS was between −0.5 SDS and +1.75 SDS. At Week 8, the individual dose was fixed for the remainder of the corresponding trial period. The minimum weekly dose was 0.1 mg and the maximum weekly dose was 8 mg. Dose reduction in steps of 25% could be made at any time during the study period at the Investigator's discretion for safety concerns.

Trial name: REAL 1	NCT number: NCT02229851

IGF-1 SDS (1 week and 3 days after last dose adjustment)	Change in weekly dose	
	Δ IGF-1 SDS >1	Δ IGF-1 SDS ≤1
IGF-1 SDS >3	–1 mg	
1.75 < IGF-1 SDS ≤ 3	–0.5 mg	
–0.5 < IGF-1 SDS ≤ 1.75 (target)	–	+0.5 mg
–2 < IGF-1 SDS ≤ –0.5	+0.5 mg	+0.5 mg
IGF-1 SDS ≤ –2	+1 mg	+1.5 mg

Abbreviations: IGF-1, insulin-like growth factor-1; SDS, standard deviation score.

Comparator(s)

Somatropin, once-daily (n=119)

Starting dose:

- Participants aged 23–60 years: 0.2 mg/day
- Participants aged >60 years: 0.1 mg/day
- Females on oral oestrogen: 0.3 mg/day

During the first 8 weeks of the main trial period and the extension phase, the dose was titrated every second week from Week 2, allowing four opportunities for dose adjustment. The target IGF-1 SDS was between −0.5 SDS and +1.75 SDS. At Week 8, the individual dose was fixed for the remainder of the corresponding trial period. The minimum daily dose was 0.05 mg and the maximum daily dose was 1.1 mg (except for Japan, where it was 1.0 mg). Dose reduction in steps of 25% could be made at any time during the study period at the Investigator's discretion for safety concerns.

IGF-1 SDS (1 week and 3 days after last dose adjustment)	Change in daily dose	
	Δ IGF-1 SDS >1	Δ IGF-1 SDS ≤1
IGF-1 SDS >3	–0.1 mg	
1.75 < IGF-1 SDS ≤ 3	–0.05 mg	
–0.5 < IGF-1 SDS ≤ 1.75 (target)	–	+0.05 mg
–2 < IGF-1 SDS ≤ –0.5	+0.05 mg	+0.05 mg
IGF-1 SDS ≤ –2	+0.1 mg	+0.2 mg

Abbreviations: IGF-1, insulin-like growth factor-1; SDS, standard deviation score.

Follow-up time

34 weeks

Is the study used in the health economic model?

Yes

Primary, secondary and exploratory endpoints

Endpoints included in this application:

The primary endpoint was the change from baseline to Week 34 in truncal fat percentage.

The supportive secondary efficacy endpoints were:

- Change from baseline to Week 34 in:

Trial name: REAL 1	NCT number: NCT02229851

- Truncal fat mass
- Truncal lean body mass
- Total fat mass
- VAT, android fat mass, and gynoid fat mass, if the DXA scanner permits
- Lean body mass
- IGF-1 SDS an d IGFBP-3 SDS
- Treatment Related Impact Measure – AGHD (TRIM-AGHD), SF-36 version 2 (SF36v2), and Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) patient-reported outcome (PRO) scores[5]
- Lipid profile (total cholesterol, HDL-c, LDL-c, and triglycerides)
- CV parameters (high sensitivity C-reactive protein [hsCRP] and IL-6)
- Body weight
- Waist circumference

- Incidence of AEs, including injection site reactions

Other endpoints:

The supportive secondary safety endpoints for the main trial period were:

- Occurrence of anti-somapacitan antibodies
- Incidence of clinical technical complaints
- Changes from baseline in physical examination, electrocardiogram (ECG) results, and vital signs
- Changes from baseline in clinical laboratory test results, including haematology, biochemistry, urine analysis, fasting glucose, fasting insulin, and HbA_{1c} levels
- PK assessments of somapacitan and human growth hormone (hGH) in the main phase of the trial (to Week 34)

Method of analysis

The primary endpoint was analysed using an ANCOVA model, with treatment, GHD onset type (adult or childhood), sex, region, diabetes mellitus, and sex by region by diabetes mellitus interaction as factors, and baseline truncal fat percentage as a covariate.

Changes from baseline to Week 34 were analysed using an ANCOVA (body composition and lipids) or a MMRM (IGF-1 SDS and body weight) 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.

[5] Changes to TSQM 9 scores were based on the end scores only (Week 34 scores for Main and Week 87 scores for Extension)

Trial name: REAL 1		NCT number: NCT02229851
	AEs and all other safety endpoints were analysed using descriptive statistics, and were summarised by treatment, Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC), and MedDRA preferred term. In addition, exact logistic regression analyses on the event of experiencing at least one injection site reaction during the main trial period were performed, with treatment, GHD onset type, sex, region, diabetes mellitus, and sex by region by diabetes mellitus interaction as factors and number of injections taken in the main trial period as offset.	
Subgroup analyses	N/A	
Other relevant information	N/A	

Appendix B. Efficacy results per study

Results per study

Table 65: Results per study – REAL 4

Results of REAL 4 (NCT03811535)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (SD)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Annualized HV (cm/year)	Somapacitan	132	11.2	−0.5 cm/year	−1.1 - 0.2	N/A The non-inferiority margin is -1.8 cm/year	N/A	N/A	N/A	Statistical analyses was done using an analysis of covariance model with treatment, gender, age group, region, GH peak group and gender by age group by region interaction term as factors.	Miller et al. Weekly Somapacitan is Effective and Well Tolerated in Children With GH Deficiency: The Randomized Phase 3 REAL4 Trial. The Journal of Clinical Endocrinology &
	Somatropin	68	11.7								
Mean change from baseline in HV SDS	Somapacitan	132	8.05	– 0.78	-1.63 - 0.08	0.0743	N/A	N/A	N/A		
	Somatropin	68	8.82								
Mean change from	Somapacitan	132	1.25	– 0.05	-0.18 - 0.08	0.4247	N/A	N/A	N/A		
	Somatropin	68	1.30								

Results of REAL 4 (NCT03811535)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (SD)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
baseline in height SDS											Metabolism, 2022, 107, 3378–3388.
Mean change from baseline in bone age	Somapacitan	132	0.06	- 0.02	-0.06 - 0.01	0.1700	N/A	N/A	N/A		
	Somatropin	68	0.08								
Mean change from baseline in IGF-1 SDS	Somapacitan	132	2.36	0.03	-0.30 - 0.36	0.8544	N/A	N/A	N/A	Change form baseline in IGF-I SDS is analysed using a mixed model for repeated measurements, with treatment, gender, age group, region, GH peak group and gender by age group by region interaction terms as factors and baseline IGF-I SDS as a covariate, all nested within week as a factor.	
	Somatropin	68	2.33								
Mean adherence	Somapacitan	132	95.8% (10.19)	N/A	N/A	N/A	N/A	N/A	N/A	Number of reported dosings from diary in adherence	

Results of REAL 4 (NCT03811535)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (SD)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
in % according to diary (SD)*	Somatropin	68	88.3% (23.57)							divided by number of planned dosings multiplied by 100.	
Mean change from baseline in GHD-CIM total score	Somapacitan	132	-9.6	- 0.2	-3.9 - 3.4	0.8914	N/A	N/A	N/A	Change from baseline to Week 52 was analysed using a mixed model for repeated measurements, with treatment, gender, age group, region, GH peak group and gender by age group by region interaction and baseline value as a covariate, all nested within week as a factor.	
	Somatropin	68	-9.4								
TB-CGHD-O total score, mean	Somapacitan	132	10.7	- 2.4	-5.7 - 0.9	0.1552	N/A	N/A	N/A		
	Somatropin	68	13.1								
TB-CGHD-P total score, mean	Somapacitan	132	8.7	– 6.0	-10.0 - -2.1	0.0031	N/A	N/A	N/A		
	Somatropin	68	14.7								
G-DAT questionn	Somapacitan	132	96.3%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Novo Nordisk. Clinical Trial Report. REAL

Results of REAL 4 (NCT03811535)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (SD)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
aire Overall, % 'easy' or 'very easy'	Somatropin	68	96.3%								4 CSR Data on file

Table 66 Results per study – REAL 1

Results of REAL 1 (NCT02229851)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (SD)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change from baseline in truncal fat percentage, %	Somapacitan	120	-1.16 (2.91)	1.17	0.23-2.11	N/A*	N/A	N/A	N/A	Change from baseline was analysed using an analysis of covariance model with treatment, GHD onset type, sex, region, DM and sex by region by DM interaction as	Johannsson et al. Once-weekly Somapacitan is Effective and Well
	Somatropin	119	-2.47 (4.54)								

Results of REAL 1 (NCT02229851)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (SD)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
% change from baseline in visceral fat, %	Somapacitan	120	-9.41 (22.11)	- 1.7	-8.0-4.5	0.581	N/A	N/A	N/A	factors and baseline as a covariate.	Tolerated in Adults with GH Deficiency: A Randomized Phase 3 Trial. J Clin Endocrinol Metab, April 2020, 105(4):e1358 –e1376
	Somatropin	119	–8.31 (25.46)								
Change from baseline in total fat mass, kg	Somapacitan	120	–0.08 (3.05)	0.72	-0.04- 1.49	0.063	NA	NA	NA		
	Somatropin	119	–0.81 (3.15)								
Change from baseline in truncal fat mass, kg	Somapacitan	120	-0.18 (1.78)	0.41	-0.04- 0.86	0.075	NA	NA	NA		
	Somatropin	119	-0.61 (1.89)								
Change from baseline in gynoid fat mass, kg	Somapacitan	120	0.02 (0.51)	0.15	0.02- 0.28	0.028	NA	NA	NA		
	Somatropin	119	–0.12 (0.47)								

Results of REAL 1 (NCT02229851)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (SD)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Change from baseline in android fat mass, kg	Somapacitan	120	–0.08 (0.36)	0.07	–0.01- 0.16	0.092	NA	NA	NA		
	Somatropin	119	–0.15 (0.32)								
Change from baseline in total lean body mass, kg	Somapacitan	120	1.38 (2.12)	0.05	-0.51- 0.61	0.865	N/A	N/A	N/A		
	Somatropin	119	1.44 (2.29)								
Change from baseline in truncal lean body mass, kg	Somapacitan	120	0.79 (1.37)	-0.04	-0.39- 0.31	0.830	N/A	N/A	N/A		
	Somatropin	119	0.89 (1.35)								
Change from baseline in	Somapacitan	120	0.56 (1.01)	0.10	18- 0.37	0.500	N/A	N/A	N/A		

Results of REAL 1 (NCT02229851)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (SD)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
appendicular skeletal muscle mass, kg	Somatropin	119	0.51 (1.25)								
Change from baseline in hs-CRP (mg/L)	Somapacitan	120	0.71	N/A	N/A	N/A	1.26	0.98- 1.62	0.08	Change from baseline were analysed using a mixed-effect model for repeated measurements including treatment, GHD onset type, sex, region, DM and sex by region by DM interaction as factors and baseline as a covariate, all nested within week as a factor. Data are log transformed before analysis	Novo Nordisk. Clinical Trial Report. REAL 1 CSR Data on file
	Somatropin	119	0.56								
Change from baseline in IL-6 (pg/mL	Somapacitan	120	1.06	N/A	N/A	N/A	1.06	0.89- 1.26	0.50		
	Somatropin	119	1.00								
Relative change from baseline in HDL cholesterol (mmol/L)	Somapacitan	120	1.04	N/A	N/A	N/A	1.03	0.97- 1.09	0.33	Change from baseline was analysed using an analysis of covariance model with GHD onset type, sex, region, DM and sex by region by DM interaction as factors and baseline as a covariate. Data	
	Somatropin	119	1.01								

Results of REAL 1 (NCT02229851)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (SD)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Relative change from baseline in LDL cholesterol (mmol/L)	Somapacitan	120	0.97	N/A	N/A	N/A	1.03	0.97- 1.10	0.29	are log transformed before analysis.	
	Somatropin	119	0.94								
Relative change from baseline in triglycerides (mmol/L)	Somapacitan	120	0.99	N/A	N/A	N/A	0.93	0.85- 1.03	0.18		
	Somatropin	119	1.06								
Relative change from baseline in total cholesterol (mmol/L)	Somapacitan	120	0.99	N/A	N/A	N/A	1.02	0.98- 1.06	0.40		
	Somatropin	119	0.98								

Results of REAL 1 (NCT02229851)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (SD)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change from baseline in IGF-1 SDS	Somapacitan	120	2.40	0.02	−0.23- 0.28	0.853	N/A	N/A	N/A	Changes from baseline was analysed using a mixed-effect model for repeated measurements including treatment, GHD onset type, sex, region, DM and sex by region by DM interaction as factors and baseline as a covariate, all nested within week as a factor	
	Somatropin	119	2.37								
Change from baseline in body weight, kg	Somapacitan	120	1.40	1.13	0.13- 2.12	0.027	N/A	N/A	N/A	Change from baseline was analysed using a mixed-effect model for repeated measurements including treatment, GHD onset type, sex, region, DM and sex by region by DM interaction as factors and baseline as a covariate, all nested within week as a factor	
	Somatropin	119	0.27								

Results of REAL 1 (NCT02229851)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (SD)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change from baseline in waist circumference, cm	Somapacitan	120	0.14	0.63	–0.56- 1.82	0.297	N/A	N/A	N/A	Change from baseline was analysed using an analysis of covariance model with treatment, GHD onset type, sex, region, DM and sex by region by DM interaction as factors and baseline as a covariate.	
	Somatropin	119	-0.49								
Change from baseline in TRIM-AGHD total score	Somapacitan	120	-5.71 (12.69)	4.99	1.89- 8.14	0.002	N/A	N/A	N/A	Changes in TRIM-AGHD scores from baseline was analysed using a mixed-effect model for repeated measurements including treatment, GHD onset type, sex, region, DM and sex by region by DM interaction as factors and baseline TRIM-AGHD scores as a covariate, all nested within week as a factor	
	Somatropin	119	-9.99 (13.64)								
Change from baseline in	Somapacitan	120	2.40 (6.53)	-1.00	-2.50- 0.51	0.195	N/A	N/A	N/A	Changes in SF-36 scores from baseline was analysed using a mixed-effect model for	

Results of REAL 1 (NCT02229851)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (SD)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
SF-36v2 overall physical score	Somatropin	119	2.87 (6.33)							repeated measurements including treatment, GHD onset type, sex, region, DM and sex by region by DM interaction as factors and baseline SF-36 scores as a covariate, all nested within week as a factor.	
Change from baseline in SF-36v2 overall mental score	Somapacitan	120	2.07 (8.76)	-1.70	-3.93- 0.58	0.135	N/A	N/A	N/A		
	Somatropin	119	2.97 (11.33)								
Change from baseline in TSQM-9 convenience score	Somapacitan	120	77.84	4.00	-0.40- 8.39	0.074	N/A	N/A	N/A	Change in TSQM scores were analysed using a MMRM with treatment, GHD onset type, sex, region and sex by region interaction term as factors and baseline as a covariate, all nested within week as a factor.	
	Somatropin	119	73.84								
Change from baseline in TSQM-9	Somapacitan	120	57.13	-10.74	-16.49-(-) 4.98	0.000	N/A	N/A	N/A		
	Somatropin	119	67.86								

Results of REAL 1 (NCT02229851)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (SD)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
effectiveness score											

*This was not designed as a confirmatory test and no hierarchical test strategy was constructed; therefore, no p value was calculated.

Appendix C. Comparative analysis of efficacy

Not applicable as both studies in both the paediatric and the adult population are head-to-head studies comparing somapacitan with somatropin.

Table 67 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Appendix D. Extrapolation

As there is no clinically relevant difference in the effectiveness of somapacitan vs somatropin a simple cost-minimization analysis is used for this assessment excluding any clinical efficacy data of somapacitan and somatropin. Hence this section is not applicable.

Extrapolation of [effect measure 1]

D.1.1 Data input

N/A

D.1.2 Model

N/A

D.1.3 Proportional hazards

N/A

D.1.4 Evaluation of statistical fit (AIC and BIC)

N/A

D.1.5 Evaluation of visual fit

N/A

D.1.6 Evaluation of hazard functions

N/A

D.1.7 Validation and discussion of extrapolated curves

N/A

D.1.8 Adjustment of background mortality

N/A

D.1.9 Adjustment for treatment switching/cross-over

N/A

D.1.10 Waning effect

N/A

D.1.11 Cure-point

N/A

Appendix E. Serious adverse events

Serious adverse events in REAL 4:

Treatment	Sex/Age/BMI	SAE Preferred term	Severity/Causality	Action taken to trial product
Somapacitan	M/6.5/17.2	Vomiting	Moderate/Unlikely	Dose not changed
	M/6.5/17.2	Dehydration	Moderate/Unlikely	Dose not changed
	M/3.3/17.3	Asthma	Severe/Unlikely	Trial product interrupted (1 week)
	M/7.9/15.2	Headache	Severe/Unlikely	Trial product interrupted (1 week)
	F/2.8/17.6	Umbilical hernia	Mild/Unlikely	Dose not changed
	M/4.1/16.2	Otitis Media	Mild/Unlikely	Dose not changed
	M/4.1/16.2	Adenoidal hypertrophy	Moderate/Unlikely	Dose not changed. Exacerbation of adenoid hypertrophy
	M/6.9/14.5	Cryptorchism	Moderate/Unlikely	Dose not changed. SAE due to hospitalization to have bilateral orchidopexy
Somatropin	F/3.0/17.1	Gastroenteritis	Moderate/Unlikely	Dose not changed
	F/6.7/16.3	Covid-19	Mild/Unlikely	Trial product interrupted (2 weeks)

Serious adverse events in REAL 1:

Treatment	Sex/Age/BMI	SAE Preferred term	Severity/Causality	Action taken to trial product
Placebo	F/30/34.0	Gastrointestinal disorder/panceatitis acute/Mild acute pancreatitis	Severe/Unlikely	Dose not changed

	M/52/29.2	Investigations/Electrocardiogram T wave abnormal/	Mild/Unlikely	Drug interrupted
	M/56/27.3	Metabolism and nutrition disorders/Hypontraemia	Moderate/Unlikely	Drug interrupted
	F/54/29.4	Gastrointestinal disorder/vomiting	Severe/Unlikely	Dose not changed
	F/54/29.4	Gastrointestinal disorder/diarrhoea	Severe/Unlikely	Dose not changed
	F/54/29.4	Infections and infestations/gastroenteritis viral	Severe/Unlikely	Dose not changed
	F/76/29.9	Endocrine disorders/Adrenocortical insufficiency acute/Adrenal crisis due to patient not taking prednisone during time of illness	Severe/Unlikely	Not applicable
Somatropin	F/46/33.8	Gastrointestinal disorder/abdominal pain	Severe/Unlikely	Drug interrupted
	M/68/23.3	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/Plasma cell myeloma/ Multiple myeloma	Severe/Unlikely	Dose not changed
	F/24/28.8	Endocrine disorders/Secondary adrenocortical insufficiency	Moderate/Unlikely	Dose not changed
	M/77/25.5	Infections and infestations/ Clostridium difficile infection/	Severe/Unlikely	Not applicable
	F/36/23.1	Renal and urinary disorders/Chronic kidney disease	Moderate/Unlikely	Dose not changed
	M/45/34.2	Blood and lymphatic system disorders/Haemoconcentration	Severe/Probable	Drug withdrawn
	M/45/34.2	Investigations/Blood testosterone increased/	Moderate/Unlikely	Dose reduced
	M/49/25.7	Skin and subcutaneous tissue disorders/Dermatitis atopic/	Severe/Unlikely	Drug withdrawn
	F/64/20.4	Infections and infestations/ Appendicitis	Moderate/Unlikely	Drug interrupted
	M/61/32.5	Injury, poisoning and procedural complications/Tibia fracture/	Severe/Unlikely	Drug interrupted

	M/61/32.5	Injury, poisoning and procedural complications/Fall	Severe/Unlikely	Drug interrupted
	M/51/23.5	Renal and urinary disorders/Nephrolithiasis	Moderate/Unlikely	Dose not changed
	F/66/28.3	Injury, poisoning and procedural complications/Drug dispensation error	Mild/Unlikely	Dose not changed
Somapacitan	M/50/26.0	Infections and infestations/ Gastroenteritis	Severe/Unlikely	Dose not changed
	M/50/26.0	Infections and infestations/ Sepsis	Severe/Unlikely	Not applicable
	M/50/26.0	Endocrine disorders/Secondary adrenocortical insufficiency acute	Severe/Unlikely	Not applicable
	M/50/26.0	Infections and infestations/Herpes simplex	Severe/Unlikely	Not applicable
	M/50/26.0	Gastrointestinal disorder /Stomatitis	Moderate/Unlikely	Not applicable
	M/50/26.0	Infections and infestations/Viral upper respiratory tract infections	Moderate/Unlikely	Not applicable
	M/24/26.6	General disorders and administration/site conditions/Pyrexia/Viral fever	Severe/Unlikely	Dose not changed
	M/46/26.5	Infections and infestations/ Gastroenteritis	Moderate/Unlikely	Dose not changed
	F/56/23.5	Gastrointestinal disorders/ Inguinal hernia/	Moderate/Unlikely	Dose not changed
	F/28/19.5	Infections and infestations/ Appendicitis	Severe/Unlikely	Dose not changed
	M/47/34.9	Infections and infestations/ Gastroenteritis	Moderate/Unlikely	Dose not changed
	F/53/19.4	Gastrointestinal disorders/Vomiting	Mild/Unlikely	Not applicable

Appendix F. Health-related quality of life

N/A

Appendix G. Probabilistic sensitivity analyses

Not relevant to perform PSA for the cost-minimization analysis.

Table 68. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Probabilities				
N/A	N/A	N/A	N/A	N/A

Appendix H. Literature searches for the clinical assessment

As the clinical assessment and the health economic analysis are exclusively informed by head-to-head studies (REAL 1 and REAL 4) comparing somapacitan with somatropin, which is the most relevant comparator in the Danish Clinical practice, a SLR is not relevant and will be omitted from this application.

H.1 Efficacy and safety of the intervention and comparator(s)

N/A

Table 69 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A
CENTRAL	N/A	N/A	N/A

Table 70 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
N/A	N/A	N/A	N/A

Table 71 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
N/A	N/A	N/A	N/A	N/A

H.1.1 Search strategies

N/A

Table 72 of search strategy table for [name of database]

No.	Query	Results
#1	N/A	N/A

H.1.2 Systematic selection of studies

N/A

Table 73 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	N/A	N/A	N/A
Intervention	N/A	N/A	N/A
Comparators	N/A	N/A	N/A
Outcomes	N/A	N/A	N/A
Study design/publication type	N/A	N/A	N/A
Language restrictions	N/A	N/A	N/A

Table 74 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1	N/A	N/A	N/A	N/A	N/A	N/A

H.1.3 Excluded fulltext references

N/A

H.1.4 Quality assessment

N/A

H.1.5 Unpublished data

N/A

Appendix I. Literature searches for health-related quality of life

As the clinical assessment and the health economic analysis are exclusively informed by head-to-head studies (REAL 1 and REAL 4) comparing somapacitan with somatropin, which is the most relevant comparator in the Danish Clinical practice, a SLR is not relevant and will be omitted from this application.

I.1 Health-related quality-of-life search

N/A

Table 75 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A

Table 76 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
N/A	N/A	N/A	N/A

Table 77 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
N/A	N/A	N/A	N/A	N/A

I.1.1 Search strategies

N/A

Table 78 Search strategy for [name of database]

No.	Query	Results
#1	N/A	N/A

I.1.2 Quality assessment and generalizability of estimates

N/A

I.1.3 Unpublished data

N/A

Appendix J. Literature searches for input to the health economic model

As the clinical assessment and the health economic analysis are exclusively informed by head-to-head studies (REAL 1 and REAL 4) comparing somapacitan with somatropin, which is the most relevant comparator in the Danish Clinical practice, a SLR is not relevant and will be omitted from this application.

J.1 External literature for input to the health economic model

N/A

J.1.1 Example: Systematic search for […]

N/A

Table 79 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A
CENTRAL	N/A	N/A	N/A

N/A

J.1.2 Example: Targeted literature search for [estimates]

N/A

Table 80 ources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
N/A	N/A	N/A	N/A

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