NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	Real-world experience of children with growth hormone deficiency who switched from daily growth hormone to the Long-Acting Growth Hormone Somatrogon
Protocol number	C0311030
Protocol version identifier	2.0
Date	21 May 2026
EU Post Authorization Study (PAS) register number	EUPAS1000000829
Active substance	Somatropin, Somatrogon
Medicinal product	Genotropin, Ngenla
Product reference	Genotropin Powder and solvent for solution for injection 5.3mg 56/167/89-B /C Powder and solvent for solution for injection 5.0 mg Powder and solvent for solution for injection 12mg 56/167/89-B /C Ngenla: EU/1/21/1617/001 for 24 mg/1.2 mL solution for injection in pre-filled penEU/1/21/1617/002 for 60 mg/1.2 mL solution for injection in pre-filled pen
Procedure number	Genotropin: N/A Ngenla: EMEA/H/C/005633
Marketing Authorization Holder(s)	**Genotropin:** Israel: Pfizer Pharmaceuticals Israel Ltd., 9 Shenkar st. Herzliya Pituach 46725. Czech Republic: Pfizer spol. s r.o., Stroupežnického 3191/17, Smíchov, Praha, 150 00 Czech Republic **Ngenla:** Israel: Pfizer Pharmaceuticals Israel Ltd. Czech Republic: Pfizer Europe MA EEIG
Joint PASS	No

Research question and objectives	The purpose of this study will be to assess and compare the effectiveness, adherence and safety of GH treatment in participants who switched from daily Growth Hormone to weekly somatrogon, a long-acting hGH, according to routine clinical care, and is intended to reflect outcomes that occur in real-world clinical practice. This non-interventional study (NIS) is designated as a Post-Authorization Safety Study (PASS) and is conducted voluntarily by Pfizer. **Research question:** Is the effectiveness of weekly long-acting somatrogon comparable to daily somatropin? Primary Objective: • To evaluate and compare the growth hormone treatment effectiveness in participants who switched from daily growth hormone to weekly somatrogon. Secondary Objectives: • To evaluate and compare the safety profile of weekly somatrogon and daily somatropin in children with GHD • To assess proportion of patients that switched-back to daily somatropin • To assess reasons for Switch-back among patients who switched back from somatrogon to daily GH • To evaluate and compare adherence to growth hormone treatment of participants before and after switching to somatrogon treatment.
Country(ies) of study	Israel and Czech Republic
Author	[redacted]

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	**Genotropin:** Israel: Pfizer Pharmaceuticals Israel Ltd., 9 Shenkar st. Herzliya Pituach 46725. Czech Republic: Pfizer spol. s r.o., Stroupežnického 3191/17, Smíchov, Praha, 150 00 Czech Republic **Ngenla:** Israel: Pfizer Pharmaceuticals Israel Ltd. Czech Republic: Pfizer Europe MA EEIG
MAH contact person	[redacted]

1. TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ATC	Anatomical therapeutical chemical
BA	Bone age
BMI	Body mass index
BMI SDS	Body mass index standard deviation score
CI	Confidence interval
CHO	Chinese hamster ovary
CM	Continuous centimeters
CNS	Central nervous system
CPT	Current procedural terminology
CRF	Case report form
CSV	Comma separated value
CTP	C-terminal peptide
CVQC	Critical variables quality control
DNA	Deoxyribonucleic acid
EC	Ethics committee
EDC	Electronic data capture
EHR	Electronic health record
EMA	European Medicines Agency
EMEA	Europe, the Middle East, and Africa
EMR	Electronic medical records

ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
GEP	Good epidemiological practice
GH	Growth hormone
GHD	Growth hormone deficiency
GPP	Good pharmacoepidemiology practices
Hb	Hemoglobin
HbA1c	Hemoglobin A1c
HCO	Healthcare organization
hCG	Human chorionic gonadotropin
HDL	High-density lipoprotein
hGH	Human growth hormone
HMA-EMA	Heads of Medicines Agencies-European Medicines Agency
HV	Height velocity
HVSDS	Height velocity standard deviation score
ICD-9	International classification of diseases, ninth revision
ICMJE	International Committee of Medical Journal Editors
IEA	International Epidemiological Association
IGF-I	Insulin-like growth factor-1
IGFBP-3	Insulin-like growth factor-1 binding protein 3
IR	Incidence rate
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology

ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KIGS	Kabi/Pfizer International Growth Database
KSM	Kahn-Sagol-Maccabi
LAGH	Long-acting growth hormone
MAH	Marketing authorization holder
MedDRA	Medical dictionary for regulatory activities
MFA	Multi-factor authentification
N/A	Not applicable
NIS	Non-interventional study
PAS	Post-authorization safety
PASS	Post-authorization safety study
PDC	Proportion of days covered
REPAR	REgistry of PAtients treated with gRowth hormone
r-hGH	Recombinant-human growth hormone
RSQC	Random sample quality control
RWD	Real world data
SAE	Serious adverse events
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Standard deviation
SDS	Standard deviation score
SGA	Small for gestational age
SQL	Structured query language
TLF	Tables listings figures

TSH	Thyroid stimulating hormone
US	United States

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
[redacted]	[redacted]	[redacted]	[redacted]
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Israel Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]		[redacted]	[redacted]

3. ABSTRACT

Title: Real-world experience of children with growth hormone deficiency who switched from daily growth hormone to the Long-Acting Growth Hormone somatrogon

Protocol version 2.0, dated 21

May 2026

[redacted]

Azoulay

Affiliation: Pfizer Inc.

Rationale and background:

Human growth hormone (hGH) is a 191-amino-acid pituitary protein that stimulates production and release of insulin-like growth factor-I (IGF-I). Growth hormone (GH) and IGF-I are the primary mediators of the promotion of growth in children and play a role in the regulation of body composition and metabolism in children and adults. Growth hormone deficiency (GHD) results in inadequate circulation of IGF-I which subsequently results in abnormal linear growth in children. Children affected with GHD have been treated with daily administration of recombinant hGH replacement therapy for many years which is proven to be safe and effective.

The burden of daily administration of injections and its concomitant side effects (e.g., injection site discomfort, transient edema and arthralgia) may cause a reduction in compliance and limit the therapeutic utility of existing formulations. Somatrogon (Ngenla) is a long-acting, once-weekly, subcutaneously administered form of human growth hormone developed for use as a long-term treatment in children with growth failure.

Data on LAGH in pediatric GH deficiency is mostly limited to clinical trials, and real-world data is currently lacking. Real world data is needed to answer outstanding questions on efficacy, safety and adherence to weekly somatrogon in children with GHD who were previously treated with daily somatropin therapy.

The purpose of this study will be to assess and compare the effectiveness, adherence and safety of GH treatment in participants who switched from daily Growth Hormone to weekly somatrogon, a long-acting hGH, according to routine clinical care, and is intended to reflect outcomes that occur in real-world clinical practice. This non-interventional study (NIS) is designated as a Post-Authorization Safety Study (PASS) and is conducted voluntarily by Pfizer.

Research question and objectives:

Research question:
Is the effectiveness of weekly long-acting somatrogon comparable to daily somatropin?

Primary Objective:

- To evaluate and compare the growth hormone treatment effectiveness in participants who switched from daily growth hormone to weekly somatrogon.

Secondary Objectives:

- To evaluate and compare the safety profile of weekly somatrogon and daily somatropin in children with GHD
- To assess proportion of patients that switched-back to daily somatropin
- To assess reasons for Switch-back among patients who switched back from somatrogon to daily GH
- To evaluate and compare adherence to growth hormone treatment of participants before and after switching to somatrogon treatment.

Study design:

This is a multi-country, non-interventional retrospective cohort study designed to evaluate the real-world effectiveness, safety and treatment adherence of pediatric patients with GHD who switched from daily growth hormone (somatropin) to somatrogon, a long-acting growth hormone (LAGH), treated according to local routine clinical practice.

Population:
The source population are patients included in the Maccabi HCO database in Israel and the **RE**gistry of **PA**tients treated with g**R**owth hormone (REPAR) in Czech Republic. Male and female patients up to age 17 meeting the eligibility criteria will be enrolled into the study, and they should have a minimum 6 months of data on a daily GH treatment (somatropin) and follow up data of at least 6 months after switch to long-acting somatrogon.

Variables:

Exposure: Treatment with somatrogon and somatropin during the study period.

Outcomes: The outcomes for the primary objective are Height, Height SDS, annual Height velocity, and annual Height velocity SDS. The secondary objective outcomes of interest are weight, weight SDS, difference in weight SDS, Body mass index (BMI), BMI SDS, difference in BMI, difference in BMI SDS, bone age and difference in bone age, injection site reactions, treatment adherence and compliance, proportion of patients that switched back and reason for switch back to daily GH.

Key Co-variates:

Will include data resulting from routine clinical care on variables pertaining to participant demographics, clinical characteristics, birth history, medical history, diagnosis of growth hormone deficiency, therapy including prior and current GH, treatment and concomitant medications, effectiveness outcomes, and adverse events.

Data sources:

The study will obtain the existing data collected in the Maccabi HCO and REPAR databases.

Maccabi Healthcare Services is one of Israel's leading healthcare organizations and it includes Kahn-Sagol-Maccabi (KSM) which is their Research and Innovation Center. KSM was founded in 2016, and they provide researchers with real-world data collected from Israeli patients. This includes diagnosis, safety and efficacy data for pediatric patients with growth hormone deficiency. The database includes around 500 GHD patients on somatrogon and the switch population estimate is 350. The maximum number of patients that can be included in the study is 500.

The REPAR registry is a non-interventional, nationwide, multicenter, retrospective and prospective study collecting data on patients who have been treated with growth hormone. The project was initiated and has been running under the auspices of the Czech Society of Endocrinology. REPAR database includes 6250 patients out of which approximately 150 are being treated with somatrogon. The maximum number of patients from Czech Republic that can be included in the study is 170.

Study size:

The study is descriptive in nature without *a priori* hypothesis testing, therefore, a formal sample size estimate is not required. All eligible participants treated will be included. We expect to include at least 300 patients from the Maccabi HCO database in Israel and around 150 patients from REPAR. The maximum number of patients that can be included at a study level is 670.

Data analysis:

Data on the subset of participants in the Maccabi HCO database and from the REPAR registry in Czech Republic meeting inclusion/exclusion criteria will be obtained and analyzed. The data will be converted to SAS format for analysis and reporting and will be processed by Pfizer to create analytical variables and datasets for all analyses specified in the study protocol. All study data will exist as structured data by the start of the study. Data obtained will not undergo any additional cleaning or error checks, and there will be no imputation of missing data. The data received from Maccabi and REPAR will be analyzed, separately. The study is descriptive in nature without *a priori* hypothesis testing.

The primary analysis is to compare effectiveness of GH treatment in participants who switched from daily growth hormone to weekly somatrogon during the course of routine clinical care. Index date defined as the day of switch from Somatropin to Somatrogon. The primary effectiveness endpoints are annual HV, annual HVSDS, Height SDS. The primary effectiveness outcomes will also be presented by subgroups. The statistical approach focuses

on estimating the true difference in each primary endpoint between their 6 months "After Switch" (Post-index period) and "Before Switch" (pre-index period) measurements using confidence intervals, thereby describing the magnitude and precision of the effect. For secondary endpoints including weight, BMI, bone age, treatment adherence and compliance outcomes, 95% two-sided confidence intervals will be reported for the difference in each endpoint between their post-index and pre-index measurements.

Safety data including medication errors will be presented in tabular and/or listing format and summarized descriptively. For Adverse Events, summary descriptive statistics will be performed on the number and percentage of patients with SAEs/AEs, total person-years of exposure, and IRs (incidence rate). The IR and 95% CIs will be calculated as the number of individual events observed during the exposure time, divided by the total number of patient years at risk for the event, multiplied by 100. Adverse events are reported for the post-index period. Continuous variables will be summarized using descriptive statistics which will include the number of patients with data to be summarized (n), mean, standard deviation (SD), median, first and third quartiles (Q1, Q3), minimum, maximum, and the number of missing observations. Descriptive statistics for categorical/qualitative variables will be presented with number of patients (count) and percentage, and this will be presented in the format 'n (%)'. Detailed methodology for summary and statistical analyses of data collected in this study, and suitable sub-group analyses, if applicable, will be documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained by Pfizer. The SAP may modify the plans outlined in the protocol, however, any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment. Handling of missing data will be described in the SAP. No imputation will be performed. Variables to be used in the analyses will be derived as described in the SAP. SAS®, Version 9.4 or later, will be used for all statistical analyses described.
Data will be presented separately by registry.

Milestones:

Final study protocol: 15 December 2025

Study registration in the HMA-EMA Catalogues of RWD studies: 01 December 2025

Proposed Study Start Date: 17 February 2026

Proposed Study End Date: 01 August 2026

Final study report: 30 October 2026

4. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
2.0	21 May 2026	Administrative	Section 2, Responsible parties	Updated list of investigators for Israel	PACL V2.0, 25 February 2026
2.0	21 May 2026	Substantial	Abstract, Section 5, Milestones	Update start and end of data collection and final CSR date	Update to study milestones
2.0	21 May 2026	Substantial	Section 8.3, Variables	Update operational definition for medical history and comorbidities	Reflect available data
2.0	21 May 2026	Administrative	Abstract, Section 8.4 data sources	Clarification on the maximum number of patients from Maccabi that can be included	PACL V1.0, 15 January 2026
2.0	21 May 2026	Administrative	Abstract, Section 8.4 data sources	Clarification on the maximum number of patients from REPAR that can be included	PACL V2.0, 25 February 2026
2.0	21 May 2026	Administrative	Abstract, Section 8.5, study size	Clarification on the maximum number of patients that can be included at a study level	PACL V2.0, 25 February 2026

5. MILESTONES

Milestone	Actual/Planned date
Final study protocol	15 December 2025
Registration in the HMA-EMA Catalogues of RWD studies	01 December 2025
Start of data collection	17 February 2026
End of data collection	01 August 2026
Final study report	30 October 2026

6. RATIONALE AND BACKGROUND

Human growth hormone (hGH) is a 191-amino-acid pituitary protein that stimulates production and release of insulin-like growth factor-1 (IGF-I). Growth hormone (GH) and IGF-I are the primary mediators of the promotion of growth in children and play a role in the regulation of body composition and metabolism in children and adults. These factors are regulated through complex feedback mechanisms involving hGH, and IGF-I (1,2). Growth hormone deficiency (GHD) results in inadequate circulating IGF-I level and is manifested as abnormal growth (linear growth) in children (3,4). Childhood GHD can be congenital, acquired, or idiopathic. The underlying causes for congenital GHD may include genetic abnormalities and pituitary dysfunction due to abnormal neurodevelopment *in utero.* The etiology for acquired GHD may result from brain tumors in the hypothalamic/pituitary region, traumatic brain injury, infiltrative disease, cranial irradiation, and surgical intervention. Generally, the origin of idiopathic GHD is complex and multifactorial, and thus is not fully understood (5).

Data on the incidence and prevalence of GHD are limited. A population-based (nationwide) study in Denmark reported average incidence rate (IR) of 2.58 males, and 1.7 females per 100,000 for childhood onset of GHD (6). For prevalence, rates were comparable in studies conducted in Belgium and the United States (US). The Belgian study, conducted between 1986 and 2001, estimated the prevalence of childhood GHD to be 1/5600. There was male predominance in all the categories (7). In the US study, the prevalence of GHD in the 1990's was at least 1:3480, with male predominance (8). The incidence has remained fairly constant over the last two decades.

Morbidity in children with GHD primarily relates to short stature and abnormal metabolism. The inability to reach normal height can lead to early onset of severe psychosocial problems, along with accompanying problems such as delayed puberty and deficits in facial, dental and (in males) genital development. Lastly, GHD that persists into adulthood is associated with increased risk of cardiovascular morbidity and mortality (3).

Genotropin, which contains the active ingredient somatropin, is a potent metabolic hormone of importance for the metabolism of lipids, carbohydrates, and proteins and is a recombinant-human growth hormone (r-hGH) replacement therapy that has been used for decades in thousands of patients (primarily children) and has proved to be safe and effective (9,10). Genotropin was compared with placebo in six randomized clinical trials totaling 172 adult

GHD patients. At six months, beneficial changes in body composition were observed in patients receiving Genotropin when compared to placebo. In children with inadequate endogenous GH, somatropin stimulates linear growth and increases the growth rate in order to enable short children to obtain normal height. In adults, as well as in children, somatropin maintains a normal body composition by increasing nitrogen retention and stimulation of skeletal muscle growth and by mobilization of body fat. Somatropin has been approved in many countries around the world for other conditions associated with growth failure and/or abnormal body composition (11).

Treatment response is most often assessed by measurement of height and growth velocity and, in pediatric growth hormone deficiency, hGH treatment is usually continued until adult height, epiphyseal closure, or both have been recorded. Currently available somatropins require daily injections to maintain hGH blood levels. The burden of daily injections administration and its concomitant side effects (e.g., transient edema, injection site discomfort and arthralgia) may cause a reduction in compliance (12) and limit the therapeutic utility of existing formulations.

Somatrogon is a long-acting once-weekly subcutaneously administered form of hGH developed for use as a long-term treatment in children with growth failure due to an inadequate secretion of endogenous GH. Somatrogon is a glycoprotein produced in Chinese Hamster Ovary (CHO) cells by recombinant deoxyribonucleic acid (DNA). It is comprised of the amino acid chain of hGH and one copy of the C-terminal peptide (CTP) from the beta chain of human chorionic gonadotropin (hCG) at the N-terminus and two copies at the C- terminus. As a weekly long-acting hGH, somatrogon maintains the same mode of action as currently prescribed daily hGH treatments (13).

Somatrogon binds to the GH receptor and initiates a signal transduction cascade culminating in changes in growth and metabolism. Consistent with GH signaling, somatrogon binding leads to activation of the STAT5b signaling pathway and increases the serum concentration of IGF-I. IGF-I was found to increase in a dose-dependent manner during treatment with somatrogon partially mediating the clinical effect. As a result, GH and IGF-I stimulate metabolic changes, linear growth, and enhance growth velocity in pediatric patients with GHD.

The sub-optimal adherence with daily hGH is well-established as is the burden of daily injections for both patients and caregivers (14,15). Long-acting hGH may obviate the need for the majority of injections currently required with daily hGH products. As demonstrated in animal models and clinical studies, somatrogon may be injected once per week resulting in similar clinical efficacy as compared to daily injections of hGH. In the Phase III clinical trial, the primary objective of non-inferiority (clinically comparable) for weekly somatrogon compared to daily hGH was met (annualized height velocity (HV) at month 12 for once-weekly somatrogon was 10.10 cm/year vs. 9.78 cm/year for daily hGH). Low incidence of serious adverse events (SAEs) was reported in both the weekly somatrogon and daily hGH groups (2.8% and 1.7%, respectively), and the majority of adverse events (AEs) were of mild to moderate severity. Thus, weekly somatrogon administration was generally well-tolerated in pediatric patients (16).

The purpose of this study will be to assess the effectiveness and safety of switching from daily GH to weekly somatrogon, a long-acting hGH, according to routine clinical care and is intended to reflect outcomes that occur in real-world clinical practice. This non-interventional study (NIS) is designated as a Post-Authorization Safety Study (PASS) and is conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

The purpose of this multi-country, non-interventional, retrospective cohort study among patients treated according to routine clinical practice will be to assess the effectiveness and safety of switching from daily GH to weekly somatrogon, a long-acting hGH in a real-world setting, according to routine clinical care.

Research question:
Is the effectiveness of weekly long-acting somatrogon comparable to daily somatropin?

Primary Objective:

- To evaluate and compare the growth hormone treatment effectiveness in participants who switched from daily growth hormone to weekly somatrogon.

Secondary Objectives:

- To evaluate and compare the safety profile of weekly somatrogon and daily somatropin in children with GHD
- To assess the proportion of patients that switched back to daily somatropin among patients receiving somatrogon
- To assess reasons for switch-back among patients who switched back from somatrogon to daily GH
- To evaluate and compare adherence to growth hormone treatment of participants before and after switching to somatrogon treatment.

8. RESEARCH METHODS

8.1. Study Design

This is a multi-country, non-interventional, retrospective cohort study, utilizing structured data of patients up to 17 years old who switched from daily GH to weekly somatrogon, a long-acting hGH treatment, as prescribed by the treating physician according to routine clinical care in a real-world setting. Effectiveness will be assessed by comparing measures of growth among patients on daily growth hormone to their measures of growth velocity after switching to weekly somatrogon.

The study is designed for generalizability and external validity. Its large sample size will allow the evaluation of key endpoints across various subgroups, while longitudinal data will assess the effectiveness and safety of somatrogon (Ngenla) and somatropin. All assessments are part of normal clinical practice in the countries where this non-interventional study is conducted.

We selected a pre-post cohort study design on retrospective data because the countries' treatment landscape changed due to market conditions which included a shortage of daily GH treatments. The transition of all patients from daily therapy to Pfizer's long-acting GH during a short time frame created a natural experiment where the same underlying population was exposed to Pfizer's long-acting GH at distinct periods and patients were able to serve as their own control. A pre-post design allows us to compare clinical and utilization outcomes before and after the switch within the same population, reducing selection bias and reflecting real-

world practice. Randomization was not feasible because the switch was externally mandated, and alternative observational designs (e.g., parallel cohorts) were not possible since no patients remained on the prior therapy after the transition. This approach leverages the market-driven change to generate real-world evidence on the impact of Pfizer's long-acting GH.

Rationale for inclusion and exclusion criteria: Somatrogon is registered for pediatric use, hence patients under the age of 18 will be included. For effectiveness and safety assessment, a minimal period of 6 months pre-index and post index is sufficient. This period will capture patients who switched back to daily GH in the 6 months after switch (Post index) and will allow assessment of reason for switch-back. There are no exclusion criteria for this study.

We expect a sample size of approximately 450 patients (approximately 300 patients from the Maccabi HCO database in Israel and 150 patients from REPAR (REgistry of PAtients treated with gRowth hormone) database in the Czech Republic that will enable the evaluation of key endpoints within numerous pre-specified strata or subgroups, while the longitudinal nature of the data will allow the evaluation of effectiveness and safety of somatrogon over the course of treatment. To evaluate the effectiveness and safety of switching from daily GH to weekly somatrogon within the study population, patients will be stratified by select a priori subgroups, including but not limited to age group, gender, follow-up time (6-months post switch, as well as all available post-switch time-points), medication dosage, diagnosis of the growth disorder.

The study design will enable the evaluation of key primary and secondary endpoints, including the primary outcomes of interest: height, height SDS, annual HV and annual HV SDS, and secondary outcomes of interest: weight, weight SDS, difference in weight SDS, BMI, BMI SDS, difference in BMI SDS, bone age and difference in bone age, safety, adherence, proportion of patients that switched back and reason for switch back to daily GH.

The information is going to be extracted from the medical record created in daily medical practice from patients included in the Maccabi HCO database in Israel and from the REPAR registry in Czech Republic.

8.2. Setting

The source populations are patients included in the Maccabi HCO database in Israel and the REPAR database in the Czech Republic.

The strengths of this study include: 1) the relatively large size of the cohorts available (approximately 450 children), which enhances the precision of estimates, 2) the homogeneity of the pre- and post-index medications, ensuring comparability of treatment exposure, and 3) the short time interval over which the treatment change occurred, which minimizes the influence of time-related confounders.

Male and female patients up to age 17 years meeting the eligibility criteria will be enrolled into the study and must have a minimum 6 months of data on a daily GH treatment (somatropin). Index date will be defined as the date of switch from Somatropin to Somatrogon. Subjects completing 6 months of somatrogon treatment will have their post-index (post-switch) growth data compared to their pre-index (pre-switch) growth data. For the purposes of this study, baseline is defined as the beginning of the 6 months pre-index period. Those subjects switching back to daily somatropin within the first 6 months of the post-index period will be evaluated for reason for switch-back, dose and length of treatment, and not for effectiveness.

Maccabi is the 2nd largest healthcare organization in Israel, serving 25% of the country's population. The same local practice guidelines for GH treatment for pediatric GHD, including

switch from daily GH to Somatrogon, exist for all four healthcare providers in Israel. REPAR is the national registry in the Czech Republic and contains most GH treated patients in the country. As a consequence, the two databases populations are representative of children who switched from daily somatropin to weekly somatrogon. No sampling will be performed.

The planned period covered by this study is as follows: Registration period from 01 October 2022 to 30 April 2025, and the Investigation period from 01 October 2022 to 31 October 2025 (from the start of the registration period to the completion of the observation period of the last patient) allowing at least 6 months of data collected for the last patient. Participants will be followed up to 180 days ± 30 days. All data available in the two databases within the follow-up period will be collected. For the purpose of the primary analysis, only the measurement closest to the 6 months before and after the index date will be utilized. The data between time points can potentially be used for further analysis per SAP.

Schedule for Data Collection for Primary Analysis

Variable	**Daily GH follow up -6 months ± 30 days (Pre index)**	**Switch Date (Index date)**	**Somatrogon follow up 6 months post switch ± 30 days (Post-index)**
Demographics	X		
Clinical characteristics	X		
Medical history and comorbidities	X		
Relevant family history	X		
Drug Indication	X		
Concomintant medications	X	X	X
hGH exposure			
Somatropin	X	X	
Somatrogon		X	X
Auxological measures	X	X	X
Laboratory measures	X	X	X
Adverse events	X	X	X

All treatment information, including medication dosage, administration date, and reasons for discontinuation, along with any other treatment information or changes that occur throughout participation in the study, will be provided by Maccabi HCO and REPAR.

At the start of the specified study, all data collected during routine clinical care visits from medical records will be provided in a structured format and includes data related to safety, treatment effectiveness, and other research outcomes of interest. As routine clinical practice is at the discretion of the treating physicians which may vary by country, the information collected from routine clinical care could vary to some degree from one physician to another. Collected data will be de-identified, and analyzed by Pfizer, to evaluate safety, treatment effectiveness, and other research outcomes of interest.

8.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Prescription of daily GH and weekly somatrogon for any indication as prescribed by the treating physician
2. Patients with 6 months of data in the pre-index and post index period*
3. Patients up to age 17 years at the beginning of the pre-index period

*All patients with 6 months of data in the pre-index period will be enrolled. Those patients with follow up data of at least 6 months post-index will be evaluated for all primary and secondary endpoints. Patients who switched back to daily GH during the post-index period will be evaluated for safety as well as switch-back endpoints of reason for switching back and adherence.

8.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

8.3. Variables

The study will collect data from routine clinical care on variables pertaining to participants demographics, clinical characteristics, medical history, concomitant medications, previous use of daily growth hormone, safety outcomes, effectiveness outcomes and treatment adherence.

Key variables and their role are given in Table 1. Detailed operational definitions will be included in the statistical analysis plan (SAP).

Table 1. Key Variables and Associated Roles

Variable	Role	Data Source-Maccabi	Data Source-REPAR	Operational Definition
Demographics				
Date of birth [1]	Baseline demographic	V	V	Categorical Month, day, year
Age at assessment[2]	Demographics	V	V	Continuous Calculated from date of birth
Sex at birth	Demographics	V	V	Categorical Male, female, other, unknown
Medical history and comorbidities				
Medical history and comorbidities	Clinical characteristics	V	V	Categorical Non-CNS malignancy, CNS tumor, cerebral palsy, immune / inflammatory disorder, hypothyroidism, hypoglycaemia, hypopituitarism / pituitary disorder, adrenal insufficiency, puberty disorder, metabolic disorder, neurodevelopmental disorder, neurologic disorder, genitourinary functional disorder, ophthalmologic disorder,

				visual impairment / blindness, hearing impairment, allergy / eczema, chronic respiratory disorder, inflammatory bowel disease, celiac disease, musculoskeletal disorder (scoliosis), congenital CNS malformation, congenital craniofacial anomaly, congenital genitourinary anomaly, congenital limb anomaly, and genetic / chromosomal abnormality.
Relevant family history				
Biological father's height	Clinical characteristics	V	V	Continuous centimeters (CM)
Biological mother's height	Clinical characteristics	V	V	Continuous centimeters
Drug Indication				
Drug indication (Diagnosis leading to growth hormone treatment)	Clinical characteristics	V	V	Categorical Primary Indication (only one can be selected): • Growth hormone deficiency • Idiopathic short stature • Prader-Willi syndrome • Small for gestational age (SGA) • Turner syndrome • Other
Date of diagnosis	Clinical characteristics	V	V	Categorical Day, month, year

Concomitant medications				
All concomitant medications (Those utilized during pre-index and post-index periods)	Clinical characteristics/exposure	V	V	Categorical Name of Medication
hGH exposure				
Daily GH (Somatropin)				
Somatropin - Dose prior to switch	Exposure/treatment/ medications	V	V	mg/kg/day
Somatropin Start date	Exposure/treatment/ medications	V	V	Categorical Month, day, year
Somatropin End date	Exposure/treatment/ medications	V	V	Categorical Month, day, year
Somatropin adherence	Exposure/treatment/ medications	V (PDC in 6 months ±30 days of treatment)	V (Missed doses in 6 months of treatment, as reported by physician)	For Maccabi - provided to us as PDC. For REPAR - number of missed doses will be provided, according to physician reporting.
Somatrogon (Long acting Growth hormone)				
Somatrogon Dose	Exposure/treatment/ medications	V	V	mg/kg/week
Somatrogon Start date	Exposure/treatment/ medications	V	V	Categorical Month, day, year
Somatrogon End date	Exposure/treatment/ medications	V	V	Categorical Month, day, year
Somatrogon Adherence	Exposure/treatment/ medications	V (PDC in 6 months ±30 days of treatment)	V (Missed doses in 6 months of treatment, as reported by physician)	Maccabi - provided to us as PDC. REPAR - number of missed doses will be provided, according to physician reporting.
Switch back from Somatrogon to Somatropin				
Reason for switch back to Somatropin	Exposure/treatment/ medications	V	V	Categorical Adverse event (MedRA coding), parental/child

				preference, physician's preference, cost, other
Switch back date	Exposure/treatment/ medications	V	N/A	Categorical Month, day, year
Dose of somatrogon at switch back	Exposure/treatment/ medications	N/A	N/A	mg/kg/week
Dose of Somatropin at switch back	Exposure/treatment/ medications	N/A	N/A	mg/kg/day
Discontinuation of Somatrogon (No switch back to Somatropin)				
Reason for discontinuation	Exposure/treatment/ medications	V	V	Categorical Adverse event (MedRA coding), parental/child preference, physician's preference, cost, other
Somatrogon date of discontinuation	Exposure/treatment/ medications	V	N/A	Categorical Month, day, year
Auxological measures				
Age	Clinical characteristic	V	V	Calculation from Date of Birth Days
Height	Primary effectiveness, outcome	V	V	Continuous cm
Height SDS[3]	Primary effectiveness, outcome	V	N/A	Continuous SD
6 months HV	Primary effectiveness, outcome	V	V	Continuous Cm/year
HV SDS[3]	Primary effectiveness, outcome	V	N/A	Continuous SD
Weight	Baseline clinical characteristic/ secondary outcome	V	V	Continuous kg
Weight SDS[3]	Baseline clinical characteristic/ secondary outcome	V	N/A	Continuous SD
BMI	Baseline clinical characteristic/ secondary outcome	V	V	Continuous Calculation from height and weight kg/m2

BMI SDS[3]	Baseline clinical characteristic/ secondary outcome	V	N/A	Continuous SD
Bone Age	Secondary effectiveness	V	V	Continuous Years
Date BA was performed	Secondary effectiveness	V	V	Categorical Month, day, year
Laboratory measures				
IGF-I	Secondary effectiveness	V	V	Continuous
IGFBP-3	Secondary effectiveness	V		Continuous
Thyroxine-total	Secondary effectiveness	V		Continuous
Thyroxine-free	Secondary effectiveness	V		Continuous
TSH	Secondary effectiveness	V		Continuous
Glucose	Secondary effectiveness	V		Continuous
HbA1c, fraction of Hb	Secondary effectiveness	V		Continuous
Cholesterol	Secondary effectiveness	V		Continuous
HDL cholesterol	Secondary effectiveness	V		Continuous
Triglycerides	Secondary effectiveness	V		Continuous
Alkaline phosphatase	Secondary effectiveness	V		Continuous
Adverse events				
All reported SAEs	Outcome, Primary safety	V	V	Categorical. All SAEs will be reported
Date of assessment	Outcome, Primary safety	V	V	Categorical Day, month, year
All other reported non-serious AEs	Outcome, Secondary safety	V	V	Categorical. All AEs will be reported
Date of assessment	Outcome, Secondary safety	V	V	Categorical Day, month, year

[1] Month and year of birth will be collected when permitted according to local regulations.
[2] Age in months

[3] If available

BMI: body mass index; HV: height velocity; HVSDS: height velocity standard deviation score; hGH: human growth hormone; GH: growth hormone; IGF-I: insulin-like growth factor-I; IGFBP-3: IGF binding protein 3; SAE: serious adverse event; SDS: standard deviation score; AE: adverse event; GHD: growth hormone deficiency; TSH: thyroid stimulating hormone.

8.4. Data Sources

The study will utilize existing EMR data from the Maccabi HCO database in Israel and data from the REPAR registry in Czech Republic to collect the exposures, outcomes and all other variables relevant to the study objectives. These secondary data sources were chosen based on their ability to provide the selected/expected variables, and their inclusion in the study report will allow for an accurate reflection of data available at the time of extraction. All data will be delivered in a structured format, ensuring consistency and facilitating accurate mapping of exposures, outcomes, and other study variables. The proposed data sources are briefly described below:

Maccabi HCO is a public, non-profit health organization operating under Israel's National Health Insurance Law. As a regulated entity overseen by the Ministry of Health, Maccabi strictly complies with all national and international standards related to data protection, medical documentation, and patients' privacy. The organization maintains information security protocols, adheres to regulatory frameworks such as the Israeli Privacy Protection Law and applicable global principles, and ensures that all medical records are securely maintained, accessible only to authorized personnel, and properly documented in accordance with healthcare regulations.

Maccabi HCO includes Kahn-Sagol-Maccabi (KSM) which is their Research and Innovation Center. KSM was founded in 2016, and they provide researchers with real-world EMR data collected from Israeli patients through routine medical practice. For diagnosis, Maccabi HCO utilizes ICD-9 codes, for procedures CPT codes, and for medication ATC codes. Their quality assurance process includes automated consistency checks, data validation processes, and targeted reviews to ensure that the datasets are consistent, coherent and accurately represent the source-recorded data for research use.

Their database includes around 500 GHD patients on somatrogon and the switch population estimate is 350. The maximum number of patients that can be included in the study is 500. For the purpose of this study, the deidentified data will be made available to Pfizer in a cloud-based research room.

The Czech Republic REPAR registry is a non-interventional, nationwide, multicenter, retrospective and prospective study collecting data on patients who have been or are treated with growth hormone and who have provided consent to participate in the registry. The project was initiated and is administered under the auspices of the Czech Society of Endocrinology. REPAR database includes 6250 patients out of which approximately 150 are being treated with somatrogon. The maximum number of patients from Czech Republic that can be included in the study is 170.

REPAR developed an internal EDC system, CLADE-IS. This system was designed for the purpose of collecting large volumes of data in clinical trials and registries and is fully adapted to

the structure and requirements of this registry. Only authorized persons have access to the registry using the assigned username and password.
The data are deidentified, and patient records are kept under identification codes that exclude the possibility of patient identification, adhering to all applicable rules and requirements for the protection of personal data.

CLADE-IS, and associated data collection and transfer mechanisms are designed to fully comply with the following requirements:

- Security: The system is hosted in a secure, access-controlled environment with multi-factor authentication (MFA) and role-based access controls. All data is encrypted using industry-standard protocols.
- Traceability
- Auditability

As part of their data quality assurance process, REPAR developed a validation plan which includes the list of all checks to be applied to the collected data, both during data entry (online data checks) and during the data review and cleaning phase. The registry utilizes MedDRA coding for adverse events, and details about their quality control processes are detailed in section 8.8.

8.5. Study Size

No formal sample size computation was performed as this is a convenience sampling process. All eligible participants who meet inclusion/exclusion criteria will be included in the analyses. We expect to include at least 300 patients from the Maccabi HCO database in Israel and around 150 patients from REPAR registry in Czech Republic. The maximum number of patients that can be included at a study level is 670.

8.6. Data Management

All data utilized in this study were acquired through routine data collection practices by Maccabi HCO and REPAR before the start of the study. Data is extracted by the two vendors based on the approved protocol.

The data will be accessed by Pfizer programmers from the designated data vendors (Maccabi HCO and REPAR), aligned with the protocol milestone dates specified in Section 5. This will be performed once per study, as detailed in the protocol and statistical analysis plan. Maccabi HCO will provide access to the datasets in a remote cloud-base environment and REPAR will deliver them in a structured CSV format via secure channels using CONFORM 4.0.10, and the extraction process will include patients meeting the inclusion/exclusion criteria, along with all specified study variables described in Section 8.3.

Maccabi HCO data will be accessed by Pfizer to produce TLFs, but the raw data will remain in the Maccabi cloud-based system.

The REPAR data will be stored internally on a secured dedicated server. For both datasets, the data will be converted to SAS or R format for analysis and reporting and will be processed by Pfizer to create analytical variables and datasets for all analyses specified in the study protocol.

All study data will exist as structured data by the start of the study. Data analysis and results generation will strictly follow the approved SAP. If for any reason any statistical method needs to be carried out differently than described in the SAP, an amendment to the SAP with required documentation and new approval will be performed. All computations and generation of Tables, Listings and Data for figures will be performed using R 4.0 or higher, or SAS Version 9.4 or higher.

The study will follow the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and the International Council for Harmonisation (ICH) guidelines for data management.

Maccabi HCO database includes EMR data collected through routine medical practice in Israel. Data transfer is not permitted under Maccabi's internal policies, so deidentified data is uploaded to a cloud based virtual research environment specific for the study that only designated researchers and users can access. Maccabi will upload a sample of the population dataset so that the file structure can be reviewed by Pfizer before providing access to the full dataset.

Access to database is tightly controlled under Maccabi's Information Security division and is managed and monitored centrally, with periodic reviews. All EMR data provided for research purposes is structured ensuring that individuals cannot be directly or indirectly identified.

Data is extracted by the Maccabi HCO analysts team according to the IRB approved protocol from their deidentified EHR comprehensive databases and tables while creating a specific dataset for each research per the data requirements agreed. Only approved variables are extracted from the source systems.

For the purpose of this study, Maccabi HCO will merge data from multiple database tables or views into a single file in accordance with their quality and data integrity requirements. Merging is performed using SQL or Python, with all steps documented to ensure traceability and accuracy. Part of the Maccabi HCO quality assurance process, one developer will be responsible for data extraction, and a separate developer will conduct quality assurance checks before Pfizer access is provided. All data extraction scripts and codes are saved in the Maccabi HCO secure servers.

For REPAR, several mechanisms of data integration in CLADE-IS are available:

-Data entered manually: The REPAR registry EDC system, CLADE-IS, is accessible to investigators via a regular Internet browser. The records are stored under unique identification codes that do not allow any re-identification of the patient. Investigators will independently generate the data needed for the registry and will check it for consistency in terms of range of values, units of measurement, and relevance of clinical information. Data is entered via web forms, the structure of which is analogous to paper CRF.

-Data provided electronically by sites and imported into CLADE-IS.

-Data obtained by automatic transfer from sites or laboratories within the integration of CLADE-IS.

All data is collected and securely stored on a central server which is monitored continuously.

For the purpose of this study, the data will be extracted from the REPAR database for preselected patients, as specified in the protocol. The final report will be prepared manually by a REPAR data manager and will be reviewed by a second data manager, which is standard practice for REPAR.

The data will be transferred to Pfizer as previously described in this section.

For both Maccabi and REPAR, the following criteria/parameters will be applied to define the study cohort:

- Any <18 patient with at least 6 months of somatropin use pre-index period, regardless of diagnosis history.
- Additional data from the 6-months post-index period will be collected (will include weekly somatrogon, switch back to somatropin or discontinuation)

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8.7. Data Analysis

The data will be accessed by Pfizer programmers from the designated data vendors (Maccabi HCO and REPAR), aligned with the protocol milestone dates specified in Section 5. Maccabi HCO and REPAR reviewed draft protocol to understand data requirements and ensure data availability. Maccabi HCO will provide access to the datasets in a remote cloud-base environment and REPAR will deliver them in a structured CSV format via secure channels using CONFORM 4.0.10, and the extraction process will include patients meeting the inclusion/exclusion criteria, along with all specified study variables described in Section 8.3.

The REPAR data will be stored internally on a secured dedicated server. Maccabi HCO data will be accessed by Pfizer to produce TLFs, but the raw data will remain in the Maccabi system.

For both datasets, the data will be converted to SAS or R format for analysis and reporting and will be processed by Pfizer to create analytical variables and datasets for all analyses specified in the study protocol. All study data will exist as structured data by the start of the study. Data analysis and results generation will strictly follow the approved SAP. If for any reason any statistical method needs to be carried out differently than described in the SAP, an amendment to the SAP with required documentation and new approval will be performed. All computations and generation of Tables, Listings and Data for figures will be performed using R 4.0 or higher, or SAS Version 9.4 or higher.

The study is descriptive in nature without *a priori* hypothesis testing. Detailed methodology for summary and statistical analyses of data collected in this study, and suitable sub-group analyses, if applicable, will be documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained by Pfizer. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment. Handling of missing data will be described in the SAP. No imputation will be performed. Variables to be used in the analyses will be derived as described in Section 8.3 and in the SAP. R 4.0 or higher or SAS®, Version 9.4 or later will be used for all statistical analyses described.

Data on the participants in the Maccabi HCO database and from the REPAR registry meeting inclusion/exclusion criteria will be analyzed. The data will be converted to SAS format for analysis and reporting and will be processed by Pfizer to create analytical variables and datasets for all analyses specified in the study protocol. All study data will exist as structured data by the start of the study. There will be no imputation of missing data. The data received from Maccabi HCO and REPAR will be analyzed separately.

Planned analyses

Primary and secondary analysis
Primary and secondary endpoints, described in section 9.3, will be analyzed and described descriptively. Continuous variables will be summarized using descriptive statistics which will include the number of patients with data to be summarized (n), mean, standard deviation (SD), median, first and third quartiles (Q1, Q3), minimum, maximum, and the number of missing observations. Descriptive statistics for categorical/qualitative variables will be presented with number of patients (count) and percentage, and this will be presented in the format ‘n (%).

Analysis of Primary Endpoints:

The primary analysis is to compare effectiveness of GH treatment in participants who switched from daily growth hormone to weekly somatrogon during the course of routine clinical care. The primary endpoints are:

- annual HV
- annual HVSDS
- Height and Height SDS

The primary effectiveness outcomes will also be presented by subgroups. The following subgroups will be defined as categorized at baseline.

- Age group (0 to 9, 10 to 17 years)
- Sex (Male, Female)
- Peak growth hormone (GH) levels ≤3 ng/mL, >3 ng/mL to ≤7 ng/mL, >7 ng/mL to 10 ng/mL, > 10 ng/mL
- Diagnosis (Growth hormone deficiency, idiopathic short stature, Prader-Willi Syndrome, Small for gestational age, Turner syndrome, Other)
- Somatrogon dosage ranges (<0.62, 0.62-0.70 and >0.70 mg/kg/week)

The purpose of this analysis is to quantify the effect of the treatment switch on the primary effectiveness endpoints of the study participants. This will be performed using a single-arm, before-and-after switch design, where each participant will serve as their own control. The mean and median difference between the post-index and pre-index endpoints will be calculated, along with 95% CI for the differences. The individual difference in each primary endpoint will be calculated for each participant as the difference between their 6 months post-index and pre-index measurements to

estimate the true population mean difference in each primary endpoint and its corresponding 95% confidence interval (CI) using a paired t-test approach. This method accounts for the correlated, pre-post measurements from the same individuals.

Descriptive statistics: Summary statistics will be presented for pre-treatment and post-treatment height velocity, as well as for the difference from the pre-index period. These will include (n), mean, standard deviation (SD), median, first and third quartiles (Q1, Q3), minimum, maximum, and the number of missing observations.

Analysis of the Secondary Endpoints:

- Weight, Weight SDS, difference in Weight SDS
- BMI, BMI SDS, difference in BMI SDS, where difference in BMI SDS is calculated separately for 6 months post-index and pre-index periods.
- Bone age, difference in Bone age between pre-index and post-index 6 months periods
- Bone maturation, calculated as bone age (BA) divided by chronological age (CA) for each 6 months period. The difference in bone maturation between the periods will be calculated.

The endpoints will be analyzed and reported in a similar fashion as for the primary efficacy endpoints.

- Treatment adherence and compliance outcomes

For each patient the individual difference in PDC will be calculated over the two defined observation periods: 6 months pre-index and post-index. The individual difference will be calculated by subtracting the pre-index' PDC from the 'post-index' PDC, where PDC will be calculated as: (Number of days covered /Number of days in observation period) *100.

Adherence and compliance endpoints include:

- The mean difference in PDC percentage from daily GH 6 months period to weekly somatrogon 6 months period.
- The proportion of patients achieving a PDC threshold of ≥*80%* during the daily GH 6 months period and weekly somatrogon 6 months period.
- The proportion of patients who transitioned from non-adherent (daily GH 6 months period PDC < 80%) to adherent weekly somatrogon 6 months period.

The mean difference in PDC percentage with its 95% confidence interval from daily GH 6 months to weekly somatrogon will be analyzed with a paired t-test approach. A 95% confidence interval for the true difference in proportions of PDC ≥80% between the daily GH and weekly somatrogon 6 periods will be constructed with Mantel-Haenszel type of confidence limits for matched-pairs data. The 95% Clopper-Pearson confidence interval will be applied to evaluate the proportion of patients who

transitioned from non-adherent daily GH to adherent weekly somatrogon. The number and percentage of patients who discontinued somatrogon and reason for switch-back to daily GH will be reported.

Treatment adherence data will be analyzed for the overall sample and by age groups (0-9,10-17).

Safety data including medication errors will be presented in tabular and/or listing format and summarized descriptively, where appropriate. For Adverse Events, summary descriptive statistics will be performed on the number and percentage of patients with SAEs/AEs, total person-years of exposure, and IRs. The IR and 95% CIs will be calculated as the number of individual events observed during the exposure time, divided by the total number of patient years at risk for the event, multiplied by 100. Adverse events are reported for the post-index period,

Safety analyses will be based on the full analysis set which includes all subjects who received at least one dose of somatrogon.

8.8. Quality Control

Maccabi HCO and REPAR are responsible for following their standard institutional procedures to ensure data quality and integrity but also for developing appropriate documentation of data cleaning and validity.

Maccabi maintains processes that govern all aspects of data handling, including extraction, transfer, quality assurance, and secure access control, to ensure compliance with privacy regulations and internal policies.

Their quality assurance process includes structured checks for data completeness, consistency, and schema validation, conducted by qualified analysts. Data checks and validation are carried out by a senior epidemiologist and the Chief Data Officer. A clinical-data expert contributes to clinical feature engineering and provides additional data validation.

For REPAR, the data quality control process involves identifying discrepancies between the original source data (CRFs, external data, queries) and the data stored in the clinical database at the time the quality control is performed. The number of discrepancies must be below a predefined acceptable error threshold.

Types of control to be performed on the data:

- Random Sample Quality Control (RSQC): This type of control is performed on all data from the selected sample of subjects.
- Critical Variables Quality Control (CVQC): This type of control is performed only on a few selected (critical) variables but across all subjects in the database. Critical variables are chosen by the data manager and data analyst as key project data. The list of critical variables is included in the Data Validation Plan.

A validation plan includes a list of all checks to be applied to the collected data, both during the data collection phase (online data checks) and during the data review and cleaning phase.

For external data imports, data obtained from an electronic source are transformed directly into the study data model using predefined scripts or custom tools that ensure format conversion, variable mapping, and data validity. After successful transformation and quality control, the data are loaded directly into the study database in accordance with applicable data management rules and with an audit trail. In another scenario, the import utilizes the import mechanism of the CLADE-IS EDC system, which allows data to be imported through system-generated import tables that match the study structure. In this procedure, the source data are transformed into import tables, and the EDC system performs validation based on the import template, including checks of mandatory fields, data types, and logical relationships between variables.

Data-review includes the following activities:

- Continuous data review by an authorized person that might give immediate feedback to the physicians
- Continuous review of the system queries
- The regularly sent/displayed reports
- Translation and medical coding
- SAE reconciliation and AE/SAE review
- Manual controls

Internally at Pfizer, analyses are programmed according to the specifications in the protocol, and the statistical analysis plan and documented in a programming plan that can be part of the SAP or a standalone document. Final deliverables are reviewed and verified by a second, independent programmer who may also perform double programming. All quality checks are documented in the programming plan.

8.9. Limitations of the Research Methods

This is a non-interventional observational study, therefore, there are several potential limitations which are well-described in the literature for comparable studies, such as Kabi/Pfizer International Growth Database (KIGS) (13,14). As a retrospective cohort study, without randomization, there is a potential risk for variable quality and completeness of data. In addition, confounding and biases cannot be excluded, and determination of causation is limited. Follow-up bias is a potential limitation as well, especially if patients with AEs are less likely to return to the treating physician or center for follow-up.

Regarding the secondary endpoints on safety and adverse events, there is a potential risk of underestimating the safety outcomes due to underreporting, misreporting or missing data from the database. The clinician entering data in the database is responsible for evaluation of seriousness and causality of the safety and adverse events and due to the secondary collection of this data further investigation is limited.
Additional potential limitations specific to our study include:

- Data collection will reflect routine clinical practice rather than mandatory assessments at specified time points thereby increasing heterogeneity of the data. For this reason, visit windows (defined in the SAP) will be applied to the statistical analysis.

- There are two data sources for this study, which collect routine data from the respective countries (Israel and the Czech Republic) which may reflect a different routine clinical practices. This may lead to heterogeneity of the data and result in information bias.

- Short follow up period (Up to 6 months±30 days).

- Information bias may also occur related to risk of loss to follow up

8.10. Other Aspects

Not applicable

9. PROTECTION OF HUMAN PARTICIPANTS

9.1. Patient Information

This study involves data that exists in deidentified/anonymized structured format and contains no patient personal information.

9.2. Patient Consent

As this study involves deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

9.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/ECs. All correspondence with the IRB/EC must be retained. Copies of IRB/EC approvals must be forwarded to Pfizer.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

One or more abstracts may be developed and submitted to relevant scientific conference(s) and one or more manuscripts may be developed and submitted to relevant peer-reviewed medical journals. Authorship will follow the guidelines proposed by the International Committee of Medical Journal Editors (ICMJE; www.icmje.org). All authors should meet the criteria for authorship, and all people who meet the criteria should be authors. Any potential

conflicts of interest will be disclosed. The final clinical study report will be submitted to EMA according to Article 46 of the Paediatric Regulation (EC) No. 1901/2006.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the investigator party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

12. REFERENCES

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13. LIST OF TABLES

14. LIST OF FIGURES

Not applicable.

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: Real-world experience of children with growth hormone deficiency who switched from daily growth hormone to the Long-Acting Growth Hormone Somatrogon

EU PAS Register® number: EUPAS1000000829
Study reference number (if applicable):Not applicable

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5
1.1.2 End of data collection[2]	☒	☐	☐	5
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	5
1.1.6 Final report of study results.	☒	☐	☐	5

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 2: Research question	Yes	No	N/A	Section Number
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	8.7

Comments:

Section 3: Study design		Yes	No	N/A	Section Number
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10

Comments:

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	8.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	8.2
	4.2.2 Age and sex	☒	☐	☐	8.2
	4.2.3 Country of origin	☒	☐	☐	8.2
	4.2.4 Disease/indication	☒	☐	☐	8.2
	4.2.5 Duration of follow-up	☒	☐	☐	8.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2

Comments:

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.2
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.7
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.7
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	8.7
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☒	☐	☐	8.3

Comments:

Section 7: Bias		Yes	No	N/A	Section Number
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	8.2
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	8.9
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.9

Comments:

Section 8: Effect measure modification		Yes	No	N/A	Section Number
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	8.7

Comments:

Section 9: Data sources		Yes	No	N/A	Section Number
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.3, 8.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.3, 8.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	8.3, 8.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.3, 8.4
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.3, 8.4
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.3, 8.4
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.4
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.4
	9.3.3 Covariates and other characteristics?	☒	☐	☐	8.4
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan		Yes	No	N/A	Section Number
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	8.7
10.3	Are descriptive analyses included?	☒	☐	☐	8.7

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.4 Are stratified analyses included?	☒	☐	☐	8.1, 8.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	8.2, 8.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	8.7, SAP
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.4, 8.6, 8.8
11.2 Are methods of quality assurance described?	☒	☐	☐	8.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	8.9
12.1.2 Information bias?	☒	☐	☐	8.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	8.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☒	

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.3

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.2

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

[redacted]

ANNEX 3. ADDITIONAL INFORMATION

Not applicable

Document Approval Record

Document Name:	C0311030_SWITCH NIS Protocol_V2.0_21 May2026
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Signed By:	Date(GMT)	Signing Capacity
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[redacted]	[redacted]	[redacted]