NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	An Active Surveillance Study to Monitor the Real-World Long-term Safety of Somatrogon Among Paediatric Patients in Europe
Protocol number	C0311023
Protocol version identifier	2.0
Date	20 March 2023
EU Post Authorisation Study (PAS) register number	Study to be registered before the start of data collection
Active substance	Somatrogon
Medicinal product	Ngenla
Product reference	EU/1/21/1617/001 for 24 mg/1.2 mL solution for injection in pre-filled pen EU/1/21/1617/002 for 60 mg/1.2 mL solution for injection in pre-filled pen
Procedure number	EMEA/H/C/005633
Marketing Authorisation Holder (MAH)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Joint PASS	No
Research question and objectives	The primary research question for this study is: What is the long-term safety in paediatric patients treated with somatrogon in real-world routine clinical practice? **Primary Objective**: Estimate the incidence rates of neoplasms, and diabetes mellitus

	type 2, the primary safety events of interest in paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care. **Secondary Objectives:** a) Estimate the incidence rates of clinical endpoints related to immunogenicity, medication errors, the secondary safety events of interest, in paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care. b) Evaluate long-term efficacy by measuring insulin-like growth factor-1 (IGF-1) levels, and height in paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care c) Estimate the hazard ratios of neoplasms, and diabetes mellitus type 2, the primary safety events of interest, between paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care. d) Estimate the hazard ratios of the clinical endpoints related to immunogenicity, the secondary safety events of interest, between paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care.

Countries of study	France, Spain, Sweden, and the UK
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Marketing Authorisation Holder

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
CIP	Code Identifiant de Présentation (Presentation ID Code)
CNAM	Caisse Nationale d'Assurance Maladie (French National Health Insurance Fund)
CNIL	National Commission for Data Protection in France
DRG	Diagnosis-related group
EMA	European Medicines Agency
EMR	Electronic Medical Records
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GDPR	General Data Protection Regulation
GH	Growth hormone
GHD	Growth hormone deficiency
GP	General practitioners
GPP	Good Pharmacoepidemiology Practices
hGH	Human growth hormone
HR	Hazard ratio
HV	Height velocity
ICD	International Classification of Diseases

Abbreviation	Definition
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGF-1	Insulin-like growth factor-1
INE	Instituto Nacional de Estadística (Institute of National Statistics)
IRB	Institutional Review Board
LPD	Longitudinal Patient Database
NBHW	National Board of Health and Welfare
NHS	National Health Service
PAS	Post-Authorisation Studies
PASS	Post-Authorisation Safety Study
PIN	Personal Identification Number
PMSI	Programme de médicalisation des systèmes d'information (French National Hospital Discharge Database)
QC	Quality control
QMS	Quality Management System
SAP	Statistical Analysis Plan
SDS	Standard deviation score
SLSP	System level security policy
SNDS	Système National des Données de Santé (French administrative healthcare database)
SOP	Standard operating procedure
TBD	To be determined

Abbreviation	Definition
THIN	The Health Improvement Network
UCD	Unité Commune de Dispensation (Smallest Unit of Dispensation)
UK	United Kingdom

3. RESPONSIBLE PARTIES

Principal Investigators of the Protocol

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Country Coordinating Investigators

Not applicable.

4. ABSTRACT

Full Study Title: An Active Surveillance Study to Monitor the Real-World Long-term Safety of Somatrogon Among Paediatric Patients in Europe

Protocol version: 2.0, 20 March 2023

Main Author: Kofi Asomaning, Pfizer Inc., 500 Arcola Road, Collegeville, PA 19426 USA

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-1). Growth hormone (GH) and IGF-1 are the primary mediators of the promotion of growth in paediatric individuals and play a role in the regulation of body composition and metabolism in paediatric individuals and adults. Growth hormone deficiency (GHD) results in inadequate production of IGF-1, which together with insufficient direct effects of GH subsequently results in abnormal linear growth in children. Paediatric patients affected with GHD have been treated with daily administration of recombinant hGH replacement therapy for many years which is proven to be effective and have a good short-term safety profile;[Pfäffle et al 2013; Lundberg et al 2020] subsequently, hGH has been approved in many countries around the world for other conditions associated with growth failure and/or abnormal body composition. However, the burden of daily administration and its concomitant side effects (eg injection site discomfort and arthralgia) may cause a reduction in compliance and limit the therapeutic utility of existing formulations.

Somatrogon (PF-06836922, also referred to as MOD-4023) is a long-acting once-weekly subcutaneously-administered form of hGH (marketing authorisation granted in the EU in February 2022 and UK in March 2022) developed for the treatment of children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of GH. Yet, there is limited literature to date on the long-term sequelae of prolonged hGH use.[Pfäffle et al 2013; Lundberg et al 2020] The mitogenic properties of mediators in the GH pathway, as well as prior evidence to suggest an association between impairment of glucose metabolism and recombinant hGH use, merit a need to fill a gap on understanding long-term safety outcomes for GHD therapy.

The primary purpose of this study will be to assess the long-term safety of somatrogon, a long-acting hGH, under routine clinical care and is intended to reflect outcomes that occur in real-world clinical practice.

This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is a commitment to the EMA.

Research Question and Objectives:

The primary research question for this study is: What is the long-term safety in paediatric patients treated with somatrogon in real-world routine clinical practice?

Primary Objective:

Estimate the incidence rates of neoplasms, and diabetes mellitus type 2, the primary safety events of interest in paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care.

Secondary Objectives:

a) Estimate the incidence rates of clinical endpoints related to immunogenicity, medication errors, the secondary safety events of interest, in paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care.

b) Evaluate long-term efficacy by measuring IGF-1 levels, and height in paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care.

c) Estimate the hazard ratios of neoplasms, and diabetes mellitus type 2, the primary safety events of interest, between paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care.

d) Estimate the hazard ratios of the clinical endpoints related to immunogenicity, the secondary safety events of interest, between paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care.

The safety events of interest noted above, are based on the current understanding of the important potential risks associated with somatrogon. However, other endpoints may be added as understanding of the safety profile of somatrogon evolves and feasibility of their assessment permits.

Study Design:

This is a population-based cohort study using routinely collected electronic healthcare data in France, Spain, Sweden, and the United Kingdom (UK). The study population will be comprised of paediatric patients (ie, patients from 3 years to below the age of 18) receiving once weekly somatrogon following registration of the product in the European Union (EU) and UK, and an internal comparator population of paediatric patients treated with daily somatropin accrued during the same time period as the somatrogon treated patients.

Population:

The source population for this study will be comprised of paediatric patients contributing data to the 4 electronic healthcare databases. The active surveillance population includes all

paediatric patients receiving at least 1 somatrogon prescription/dispensing during the study accrual period. The study will also include an internal comparator population of paediatric patients receiving at least 1 prescription/dispensing of once daily somatropin during the study accrual period. Additionally, patients in all databases will have 12 months (depending on feasibility that will be assessed before the end of data collection, this may be reduced to 6 months) of continuous medical history available prior to the index date (defined as start of somatrogon or once daily somatropin within the study period of February 2022 to February 2032) to allow for adequate capture of baseline characteristics.

Study follow-up will span a 10-year study period, throughout which patients can accrue and will be evaluated in two stages. First, patients will be accrued within the first 5 years and followed for a minimum of 5 and up to 10 years to evaluate long-term safety events of interest. Second, in sensitivity analyses, all patients that accrue after the 5-year mark, will be analysed both separately and together with the study population.

Variables:

- Exposure:
    - ≥1 somatrogon prescription/dispensing during study accrual period.
    - ≥ 1 prescription/dispensing of once daily somatropin during study accrual period (for the internal comparator group).
- Outcomes: The primary outcomes of interest are neoplasms and diabetes mellitus 2. The secondary outcomes of interest are immunogenicity, medication errors, and long term efficacy characterized by IGF-1 levels and height.
- Key covariates: patient demographics and clinical characteristics, measured risk factors, co-morbidities, concomitant medications at baseline and co-medications during follow-up.

Data Sources: The study will be performed in the following selected data sources:

- France – Système National des Données de Santé (SNDS; an administrative claims database covering approximately 66 million in the population)
- Spain –Longitudinal Patient Database (LPD; a longitudinal patient data based on electronic medical records covering approximately 1 million individuals in the population)
- Sweden – the Total Population Register, Patient Register, the Swedish Prescribed Drug Register, and the National Swedish Growth Hormone Registry. The Swedish register systems are a large source of population-based data (covering approximately 10 million)

- UK – The Health Improvement Network (THIN) database; an electronic primary healthcare records database (covering approximately 20 million)

Study Size:

All somatrogon-treated paediatric patients in all data sources during the study accrual period will be included in the study. Preliminary feasibility assessment of data in the Swedish nationwide and regional registers from 2008 to 2019 indicates that there were approximately 4,000 patients treated with somatropin per year with 1700 patients estimated to be paediatric patients. In the UK THIN database from 1995-2020, there were approximately 3,375 patients treated with somatropin with 20% (650 patients) estimated to be paediatric patients. In Spain, from 2013-2022, there were approximately 700 patients treated with somatropin, from which 642 received a first dose as pediatric patients. Similar information from France was unavailable. Based on incidence rates of the primary safety events of interest in somatropin treated paediatric patients from previous GHD studies, the range of person-years of somatropin exposure needed to observe one event for neoplasms and diabetes is estimated to be 1,124 to 62,500. Comparative analyses for neoplasms will be performed if there are ≥1,305 patients in the somatrogon-treated group, which would allow for an HR of 3.00 or higher to be detected between somatrogon and once daily somatropin-treated groups. Comparative analyses for diabetes mellitus type 2 will be performed if there are ≥2,344 patients in the somatrogon-treated group, which would allow for an HR of 3.00 or higher to be detected between somatrogon and once daily somatropin-treated groups.

Data analysis:

The primary analysis will be descriptive. All eligible patients during the study period will be included, with no upper limit on the sample size. Due to database heterogeneity, analyses will be conducted separately by data source and data will not be pooled.

Baseline demographic and clinical characteristics for each treatment group will be described. For all the safety events of interest and efficacy measurements of interest, descriptive statistics, counts and proportions, crude incidence rates (ie, number of events per person years) and age/sex standardized incidence rates with associated two-sided 95% confidence intervals will be calculated as appropriate.

The summary of event rates will be based on survival analysis of time to first event based on an index date defined for each treatment group with appropriate censoring rules applied for those who do not experience an event by end of follow-up period including those who die, those who are lost to follow-up (eg, via migration out of the country as documented in the data source), or end of study period.

The feasibility of more formal comparative analyses to evaluate safety events of interest and obtain hazard ratios that adequately adjust for potential confounders will be assessed in the interim reports. Since the size of the once daily somatropin-treated comparator group is

expected to be much larger than the somatrogon-treated group, statistical power will be limited by the uptake of somatrogon.

Milestones: Data collection is planned to start on 15 June 2024 and end on 15 June 2032. The first interim report is planned to be submitted within three years of EU approval of somatrogon, taking into account the lag in data availability in respective data sources. Subsequent interim reports are planned for every 2 years thereafter. The final study report planned for submission will take place within 6 months from the end of data collection.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	07 March 2023	Cover page, Section 4 and Section 8	The research question has been revised to: "What is the long-term safety in paediatric patients treated with somatrogon in real-world routine clinical practice?"	EMA requested that the protocol research question be reworded to be in line with the purpose of the study, long-term safety.
1	07 March 2023	Section 4 and 7	The primary purpose has been revised to read: "The purpose of this study will be to assess the long-term safety of somatrogon, a long-acting hGH, under routine clinical care and is intended to reflect outcomes that occur in real-world clinical practice."	EMA requested that the primary purpose in the protocol be reworded to the primary purpose of the study as stated in the somatrogon RMP.
1	07 March 2023	Section 4 and Section 6	The planned dates for start and end of data collection, 4 interim reports, and final study report have been revised.	Milestone dates provided in the original protocol will be revised in collaboration with the EMA, to account for operational aspects of study implementation.

6. MILESTONES

Milestone	Planned date
Registration in the EU PAS register	Prior to start of data collection
Start of data collection[a]	15 June 2024
End of data collection[b]	15 June 2032
Interim report 1	15 December 2024
Interim report 2	15 December 2026
Interim report 3	15 December 2028
Interim report 4	15 December 2030
Final study report	15 December 2032

EU: European Union; PAS: post authorisation study.

a. For studies with secondary data collection, the start of data collection is defined as the planned date for starting data extraction for the purposes of the primary analysis.

b. For studies with secondary data collection, the end of data collection is defined as the planned date on which the analytical dataset will be first completely available; the analytic dataset is the minimum set of data required to perform the statistical analysis for the primary objective(s).

7. 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-1). Growth hormone (GH) and IGF-1 are the primary mediators of the promotion of growth in paediatric individuals and play a role in the regulation of body composition and metabolism in paediatric individuals and adults. Growth hormone deficiency (GHD) results in inadequate production of IGF-1 which together with indirect effects of GH subsequently results in abnormal linear growth in children. Paediatric patients affected with GHD have been treated with daily administration of recombinant hGH replacement therapy, such as somatropin, for many years which is proven to be effective and have a good short-term safety profile;[Pfäffle et al 2013; Lundberg et al 2020] subsequently, hGH has been approved in many countries around the world for other conditions (eg, idiopathic short stature) associated with growth failure and/or abnormal body composition. However, the burden of daily administration and its concomitant side effects (eg, injection site discomfort and arthralgia) may cause a reduction in compliance and limit the therapeutic utility of existing formulations.

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This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is a commitment to the EMA.

8. RESEARCH QUESTION AND OBJECTIVES

The primary research question for this study is: What is the long-term safety in paediatric patients treated with somatrogon in real-world routine clinical practice?

Primary Objective:

Estimate the incidence rates of neoplasms, and diabetes mellitus type 2, the primary safety events of interest in paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care.

Secondary Objectives:

a) Estimate the incidence rates of clinical endpoints related to immunogenicity, medication errors, the secondary safety events of interest, in paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care.

b) Evaluate long-term efficacy by measuring IGF-1 levels, and height in paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care.

c) Estimate the hazard ratios of neoplasms, and diabetes mellitus type 2, the primary safety events of interest between paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care.

d) Estimate the hazard ratios of the clinical endpoints related to immunogenicity, the secondary safety events of interest, between paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care.

The safety events of interest noted above, are based on the current understanding of the important potential risks associated with somatrogon. However, other endpoints may be added as understanding of the safety profile of somatrogon evolves and feasibility of their assessment permits.

9. RESEARCH METHODS

9.1. Study design

This is a population based cohort study using routinely collected electronic healthcare data in France, Spain, Sweden, and the UK, during a study period of February 2022 to February 2032. Table 1 summarizes these data sources and their capabilities of addressing research objectives. The study population will be comprised of paediatric patients (ie, patients from 3 years to below the age of 18) who initiate once weekly somatrogon following registration of the product in the EU and UK, and an internal comparator population of paediatric patients who initiate treatment with daily somatropin accrued during the same time period as the somatrogon treated patients.

Table 1. Summary of study objectives and country-specific databases that have data to address them.

	Système National des Donnees de Sante (SNDS)	**Longitudinal Patient Database (LPD) in Spain**	**Sweden Growth Hormone Registry and national health and demographic registers**	**The Health Improvement Network (THIN)**
Primary objective	yes	yes	yes	yes
Secondary objective 2a	yes*	yes	yes	yes***,†
Secondary objective 2b	no	no	yes	no
Secondary objective 2c	yes	yes	yes	yes
Secondary objective 2d	yes**	yes	yes	yes†

*not for medication errors as weight is not collected in this database.

**for hospitalized outcomes only.

***medication error accuracy contingent on UK shared care between primary care physicians and secondary care providers.

† not for all immunogenicity clinical endpoints.

9.2. Setting

9.2.1. Inclusion criteria

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

- All paediatric (from 3 years to below the age of 18 years) patients receiving at least 1 somatrogon prescription/dispensing or at least 1 prescription/dispensing of daily somatropin during the study accrual period.

- 12 months (depending on feasibility that will be assessed before the end of data collection, this may be reduced to 6 months) of continuous medical history available prior to the index date (defined as start of somatrogon or once daily somatropin within the study period) to allow for adequate capture of baseline characteristics.

9.2.2. Exclusion criteria

There are no exclusion criteria for this study.

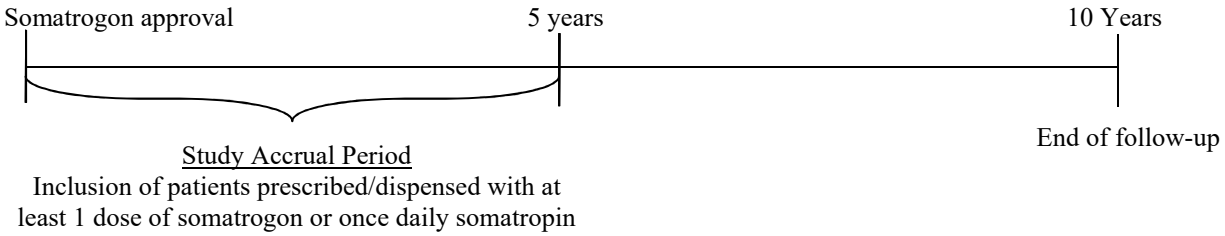
9.2.3. Index Date and Follow-Up

The index date will be the date of the first filled prescription/dispensing of somatrogon or once daily somatropin as recorded in the data sources. The patients will be followed from the index date to whichever of the following that occurs first:

- Primary or secondary safety event of interest (follow-up time will be from the index date to the date of the event, at which the patient will be censored for that particular event of interest. Follow-up will continue for the other safety events of interest)
- Death
- Lost to follow-up (eg, via migration out of the country as documented in the data source(s)), or
- End of the study follow-up

The study will span a 10-year study period, throughout which patients can accrue and will be evaluated in 2 stages. First, patients will be accrued within the first 5 years and followed for a minimum of 5 and up to 10 years to evaluate long-term safety events of interest, Figure 1. Second, in sensitivity analyses, all patients that accrue after the 5-year mark, and therefore, with less than 5 years of follow-up, will be analyzed both separately and together with the study population. (Section 9.7.2.4)

Figure 1. Patients Inclusion and Follow-up



9.3. Variables

Operational definitions of the following variables will be described in the statistical analysis plan (SAP).

Exposure:

- First filled Somatrogon prescription/dispensing following registration of the product in EU and UK.
- For the internal comparator, first filled somatropin prescription during the same study period as somatrogon patients.

As noted above, operational definitions of exposure will be specified in the SAP (eg, if feasible and subject to sample size, by: somatrogon use, those who switch between somatrogon and somatropin, or somatropin use).

Outcomes

The following are the safety events of interest:

Primary-

- neoplasms
- diabetes mellitus type 2

Secondary-

- immunogenicity

  Where feasible, to evaluate immunogenicity within the respective databases, the following clinical endpoints related to immunogenicity will be captured:

  - Bronchospasm
  - Allergic conjunctivitis
  - Allergic dermatitis
  - Atopic dermatitis
  - Eyelid oedema
  - Henoch-Schonlein purpura
  - Hypersensitivity
  - Rash
  - Allergic rhinitis
  - Swelling face
  - Swelling of eyelid
  - Urticaria

- Medication errors

  Where feasible, to evaluate medication errors for somatrogon within the respective databases, utilizing prescription information and weight

measurements, the following endpoints related to medication errors will be captured:

- Underdosing defined as a:
  - 50% decrease in dose for a single administration (or, dispensing that is <0.33 mg/kg body weight)
  - Missing a dose within the course of 2 weeks
- Overdosing defined as:
  - 50% increase in dose for a single administration (or, dispensing that is >0.99 mg/kg body weight)
  - An extra dose administration within 4 days of the last dose

(The recommended dose for somatrogon is 0.66 mg per kilogram of body weight via a single weekly injection, adjusted by the doctor if necessary.)

For somatropin, the recommended dose in mg per kilogram of body weight via a daily injection, will be manufacturer dependent. Analogous to somatrogon, underdosing and overdosing will be defined as a 50% decrease and increase in dose for a single administration, respectively.

- Long-term efficacy

  Where feasible, to evaluate long-term efficacy within the Swedish Growth Hormone Registry database, the following endpoints related to long-term efficacy will be captured:

  - IGF-1 levels
  - Height (height velocity (HV), height standard deviation score (SDS), change in height SDS, and final height).

Covariates:

The study will collect all relevant data including patient demographics and clinical characteristics, measured risk factors, co-morbidities, concomitant medications at baseline and co-medications during follow-up to address the study objectives. These data (as available in data sources) will include, but not be limited to:

- Age
- Sex
- Duration of GHD
- Prior medications, including therapies for GHD
- Concomitant medications used at baseline and during follow-up

- Comorbidities: dyslipidemia, reduced bone mineral density, atherogenic risk, thyroid function impairment, neoplasias, intracranial hypertension, intracranial hemorrhage, intracranial aneurysm, type 2 diabetes

9.4. Data sources

This study plans to utilize administrative healthcare databases in France, electronic secondary data collected in the Spain LPD database, the national population-based electronic healthcare registers in Sweden, and electronic primary healthcare records database in the UK. These secondary data sources are selected based on the availability of the expected required data elements and projected number of patients with somatrogon exposure post-approval within the data source country. The inclusion of their data in all reports will reflect data availability at the time of data base lock for each report. The proposed data sources are briefly described below:

- **France-**The French administrative health care claims database ('Système National des Données de Santé', SNDS) covers approximately 99% of the total 67 million population. In addition to demographic characteristics, SNDS contains outpatient data including drugs dispensation with number of units, laboratory tests performed (tests results are not captured), and registration status in the long-term disease database for chronic conditions identified with ICD-10 codes. In SNDS, somatrogon (and somatropin) will be mainly self-administered by the patient in the outpatient sector (including a first administration supervised by a physician). In the case where treatment is administered and invoiced during a hospitalization, data will be available only if the treatment is registered in the 'list en sus' or 'retrocession list'. The outpatient data are linked to hospitalisation data (national hospital discharge database, PMSI) through a unique personal identification number (Scailteux and Droitcourt, 2019). The PMSI captures information relating to inpatient or ambulatory care admissions to a public or private hospital in France, including discharge diagnoses, procedures and drugs administered during hospitalization and invoiced in addition to the diagnosis-related group (DRG). All diagnoses are coded according to ICD-10. Height and weight measurements are not available in this claims database. The contents of SNDS include but are not limited to:

    - Sociodemographics: age (through date of birth (MMYY)), sex, lowest income level (based upon whether patient is a recipient of basic universal health coverage), and deprivation index.

    - Hospital data: date of admission, ward type, admission following ER visit (yes/no), date of discharge, discharge diagnoses (1 principal, 1 related and up to 50 associated), DRG, procedures, drugs invoiced in addition to the DRG, external consultation at hospital, and costs.

- Outpatient prescription data: number of prescriptions reimbursed, prescriber's specialty, and costs.

- Pharmaceutical information:
  - Outpatient (community pharmacy): brand, generic name, Anatomical Therapeutic Chemical (ATC) code, CIP code ('Code Identifiant de Présentation', for each specific packaging), size, strength.
  - Inpatient (hospital: list 'en sus', retrocession list): brand, generic name, ATC code, UCD code ('Unité Commune de Dispensation', for the smallest unit of dispensation [eg, pill, vial]), dosage form and strength, amount administered.

Lag in data availability for SNDS varies from 1 month (outpatient data) to 12 months (hospital data).

- **Spain**-The LPD database contains anonymized electronic data collected from approximately 3,000 office-based primary and secondary physicians, representing about one million patients (covering approximately 3% of the national population). The patient population is representative of the Spanish population according to geographic coverage, and age and gender distribution, as provided by the Instituto Nacional de Estadística (INE). Healthcare contacts done outside of the national health system are not captured (private sector).

  The electronic medical records (EMR) collect medical information from the practice management software used by the physician during patients' office visits for recording their daily patient interactions in EMRs. The panel of contributing physicians is maintained as a representative sample of the primary care and specialist physician population in Spain. Panel physicians volunteer to make available anonymized, patient-level information from their practices for clinical research purposes.

  The patient identifier is unique through all general practitioner and specialist practices. Data are captured directly from patients' EMRs, with no intervention being made to collect or complete the data. The LPD is therefore, secondary data collected in a non-interventional way, reflecting routine clinical practice. In-hospital treatment administration, including for somatrogon (or somatropin), is not available in the LPD database, only prescription at discharge is collected in these situations.

The unique patient identifier is used across all general and specialist visits, enabling longitudinal follow-up of patients in the Spanish LPD. Data available in the LPD include:

- Demographic characteristics: age and gender only
- Outpatient data: The LPD provide systematic ongoing information from primary and secondary physician office-based visits on patients' consultations, diagnoses and treatments. In LPD, clinical outcomes are only captured in outpatient data. These diagnoses are directly recorded as International Classification of Diseases, Ninth Revision (ICD-9) codes.
- Outpatient prescription data: for prescribed and reimbursed medications there are prescription dates, ATC class codes, substance name, route of administration, strength, daily dose, and duration.
- Pharmaceutical information:
  - Outpatient (pharmacy): pharmacy dispensation is not available.
  - Inpatient: Prescribed treatments at discharge, but not in-hospital administration, is collected.

Data are transmitted online on a monthly basis, and the lag in outpatient data availability for LPD is 1 month.

- **Sweden-**The Swedish register system is a large, relatively complete source of population-based data, including data on the entire Swedish population (10.2 million in 2022). Based on each Swedish resident's unique personal identification number, issued to all Swedish residents alive in 1947 or born/immigrated thereafter, linkage of data from different registers is possible.[Ludvigsson et al 2009] The registers are maintained by governmental bodies (eg, the National Board of Health and Welfare, Statistics Sweden), who may perform data linkages and provide pseudonymized data for research purposes. In Sweden, somatrogon (and somatropin) will be available in the Prescribed Drug Register (PDR), as it will be exclusively introduced in the outpatient setting; if given during hospitalization it will not be in the PDR or National Patient Registry (NPR). The relevant databases that will be used in this study include the NPR, the PDR, the Cancer Register,[Barlow et al 2009] and the Cause of Death Register (CDR; Brooke et al 2017), and the demographic databases at Statistics Sweden. The National Swedish Growth Hormone can also be linked to the National Register data. Data on comorbidities and

hospitalization will be extracted from the Patient Register and the Cancer Registry. The relevant contents of registers include but are not limited to:

- Demographics: age, sex, place of residence, place of birth, citizenship, immigrant status, immigration date, race/ethnicity.
- Diagnoses made in in- and out-patient care, recorded by ICD codes, as well related admission and discharge dates. Incident cancer diagnosis is morphologically confirmed.
- Ambulatory prescription and dispensations: date, prescriber profession, brand name, formulation, package, DDD, dispensed amount, and expenditures. All drugs are classified according to the ATC classification system.[Wettermark et al 2007]
- Growth data: Ethiology for GH treatment, co-morbidity and other hormone treatments, birth length and weight as well as gestational age, years on and start of growth hormone treatment, parental height, growth rate during first treatment year, weight and height at start and at puberty onset, age and final height, IGF-1 and GH maximum from 24-hr growth hormone profiling. [Emilsson et al 2015 for a general overview of treatment registries]

The lag time in diagnosis/prescription fill to the incorporation of data into the national registers is between 1 month and 1 year depending on the register. There is a 15-month lag between clinical data being entered into the system and the data being available for analysis (eg, the Cancer Registry has a delay of 15 months). The implication of this is that complete data for 2022 is available in the registers at the end of 2023. Additionally, there is typically a waiting time of 10-12 months between the time of data order submission and delivery of the data by the register holders.

- **UK**- The Health Improvement Network (THIN) database contains longitudinal, non-identified primary care EMR for approximately 4% of the UK population. This anonymised data collection, which goes back to 1994, is nationally representative of the UK population. This translates to more than 20 million historic patients and 2.3 million active patients. Preparations are underway to add an additional 1 million active patients into the panel over the coming year. Data collected from electronic general practitioners (GP) records include, but are not limited to: symptoms, diagnoses, and referrals (coded using the hierarchical Read code system), drug prescriptions (using ATC codes), lifestyle choices (eg, smoking and alcohol habits), biological measures (height and weight), laboratory tests (and results), and communication from secondary care providers in the form of digitalised letters (ie, free text). Treatment is administered in a “shared care” setting with primary care physicians (GPs) and secondary care providers sharing the patient. Communications between primary

and secondary care is in the form of letters. During this time the GP may read and code the letter into patient records (eg, patient height). Alternatively, the full letter might be appended to administrative read codes (eg, "letter received" corresponds to the read code 9N3D.00). Self-administration of somatrogon/somatropin are not captured in outpatient data (including first administration that is supervised by a physician). If somatrogon/somatropin are initiated while in secondary care (ie, hospitals, based on discharge summaries) and then continued in a primary care setting (ie, is a repeat medication), it will be captured in THIN. Feasibility assessments of this GP database indicate that at least one height measurement is available for approximately 40% of somatropin treated pediatric patients (<18 years at first prescription) and weight measurements for 48% of somatropin treated pediatric patients in this database. Laboratory results, specifically IGF-1, were available for 4% of approximately 2,300 patients (<18 years, with GHD) unique patients as of December 2020. Although two read codes were used (plasma IGF-1 level and serum insulin-like growth factor 1 level), these are poorly recorded in THIN's structured data. The contents of THIN include but are not limited to:

- Sociodemographic characteristics: age, sex, and ethnicity (ethnicity data is opt-in and is less well complete)

- Hospital data: THIN is a primary care database. However, as described above, for patients who are managed in a hospital (ie, secondary care), the specialist relays patient information back to the GP via a letter. In this manner, data on outpatient and hospitalization visits and procedures are captured. The letter conveys a description of what events occurred. The letter can include - but is not limited to – diagnosis, signs/symptoms, drugs prescribed, biological measures such as height and weight, labs tests and lab results. It is also possible that the health care provider reads the letter and codes the information into the patient's record. Referrals to secondary settings and discharge letters back from secondary care to primary care setting are captured in the database and may be coded into the patient health record from the discharge letters or recorded as free text.

- Patient prescription data: prescribed products, the frequency and timing of prescriptions are captured. Repeat prescriptions are also recorded (date and quantity).

There is a 1-month lag between clinical data being entered into the system and the data being available for analysis.

9.5. Study size

All somatrogon-treated paediatric patients in all data sources during the study accrual period will be included in the study. Table 2 shows the estimated incidence rate of the primary safety events of interest in somatropin-treated paediatric patients from previous GHD studies.

Table 2. Incidence Rate of the Primary Safety Events of Interest in Somatropin-treated Paediatric Patients from Previous GHD Studies

Study	Event	Incidence Rate per 1,000 Person-years	Person-years of Exposure Needed to Observe One Event
KIGS[a]	Neoplasms	0.89	1,124
	Cancer	0.18	5,556
	Diabetes mellitus type 2	0.016	62,500
NCGS[b]	Neoplasms	NA	NA
	Cancer	0.19	5,264
	Diabetes mellitus type 2 (includes 8 unclassified diabetes mellitus cases)[c]	0.14	7,143
	Diabetes mellitus type 2 (excludes 8 unclassified diabetes mellitus cases)[c]	0.10	10,000
GeNeSIS[d]	Neoplasms	NA	NA
	Cancer	0.21	4,762
	Diabetes mellitus type 2	0.52	1,923

GHD-Growth hormone deficiency; NA-Not applicable.
a. Pharmacoepidemiological database with data of children treated with recombinant human GH (Kabi International Growth Study Genotropin; Pfizer Inc., New York, NY). Enrolled patients 1987-2012. IGHD: N=39116, Patient years of exposure=126,754. Data on file.

b. Open-label, multicenter, post-marketing surveillance study, the National Cooperative Growth Study (NCGS), to monitor the safety and efficacy of its rhGH products in children with growth disorders (Genentech, Inc). 1985-2006. N=54,996. Patient years of exposure=192,345.

c. Bell J, Parker KL, Swinford RD, Hoffman AR, Maneatis T, Lippe B. Long-term safety of recombinant human growth hormone in children. J Clin Endocrinol Metab. 2010 Jan;95(1):167-77. doi: 10.1210/jc.2009-0178. Epub 2009 Nov 11. PMID: 19906787.

d. GeNeSIS (Genetics and Neuroendocrinology of Short Stature International Study; Eli Lilly, Indianapolis, IN, USA); 19 054 children with no recorded history of cancer. Patient years of exposure ~ 64,784.

Table 3 shows estimated prevalence of paediatric GHD patients in each selected country, and estimated number of somatropin-treated paediatric patients in each database. Preliminary feasibility assessment of data in the Swedish nationwide and regional registers from 2008 to 2019 indicates that there was approximately 4,000 patients treated with somatropin each year, with 1700 patients in 2019 estimated to be paediatric patients. In the UK THIN database from 1995-2020, there were approximately 3,375 patients treated with somatropin

with 20% (650 patients) estimated to be paediatric patients. In Spain, from 2013-2022, there were approximately 700 patients treated with somatropin, of which 642 received a first dose as a paediatric patient. Similar information from France was unavailable.

Table 3. Estimated Prevalence of Paediatric GHD in each Country, and Estimated Count of Somatropin Patients in each Database

Country	Approx. paediatric population size in selected countries (Millions)[a]	Approx. paediatric GHD prevalent cases in selected countries[b]	Database	National coverage (%)	Total approx. number of unique somatropin patients in database	Total approx. number of unique somatropin paediatric patients in database	Period of coverage of database
France	6.71	1,676	SNDS	99	Unavailable	Unavailable	2009-2019
Spain	9.35	2,337	LPD	3.2	700	642	2013-2022
UK	6.66	1,666	THIN	6	3,375	~650	1995-2020
Sweden	2.20	550	National registries	100	~4,000 per year	~1,700	2008-2019

GHD-Growth hormone disease; Approx-Approximate; LPD-Longitudinal Patient Database; SNDS-The French administrative health care database (Système Nationale des Données de Santé); THIN- The Health Improvement Network.

a. Paediatric population (<18 years) approximated to 20% of 2019 population. https://ec.europa.eu/eurostat/documents/2995521/11081093/3-10072020-AP-EN.pdf/d2f799bf-4412-05cc-a357-7b49b93615f1 https://www.populationpyramid.net/europe/2019/

b. Prevalence of childhood GHD in Europe approximated to be 1/4,000. Orso M, Polistena B, Granato S, et al. Pediatric growth hormone treatment in Italy: a systematic review of epidemiology, quality of life, treatment adherence, and economic impact. PLoS One 2022; 17(2): e0264403. https://doi.org/10.1371/journal.pone.0264403.

Sample size calculations were undertaken to estimate the number of patients required to assess each of the primary safety events of interest. All sample size calculations were conducted using PASS software version 20.0.3, with Logrank test.

Sample size calculation to estimate the number of patients required to assess the risk of neoplasms

Sample size calculations were undertaken to estimate the number of patients required to assess the risk of neoplasms. Table 4 presents detectable hazard ratios among somatrogon

treated patients compared with once daily somatropin-treated patients. Assuming a range of 1,305 - 20,000 patients exposed to somatrogon, the minimum hazard ratios (HRs) between treatment groups that could be detected with at least 80% power at the 5% significance level are summarized. Based on the estimates presented in Table 4 , assuming 0% annual rate of switching from somatrogon-treated patients to once daily somatropin-treated patients, and 0% annual rate of switching from once daily somatropin-treated patients to somatrogon treated patients, and a neoplasm incidence rate of 0.9/1000 person-years in once daily somatropin-treated paediatric patients (Table 2), sample sizes of 1,305 and 20,000 somatrogon-treated patients would allow for HRs of 3.00 and 1.41, respectively, to be detected between the somatrogon-treated and once daily somatropin-treated groups. Comparative analyses for neoplasms will be performed if there are ≥1,305 patients in the somatrogon-treated group, which would allow for an HR of 3.00 or higher to be detected between somatrogon and once daily somatropin-treated groups. The occurrence of switching will inevitably require a greater sample size and higher thresholds to inform the conduct of comparative analyses.

Table 4. Minimum Detectable Hazard Ratios Among Somatrogon-treated Patients Compared with Once Daily Somatropin-treated Patients with 80% Power, alpha = 0.05, 10-year Study with 5 Years Uniform Accrual, 5% Loss to Follow Up Per Year in Somatrogon-treated group - Neoplasms

Incidence rate per 1,000 person-years of neoplasms in once daily somatropin treated group	Sample size of patients in once daily somatropin treated group (N1)	Sample size in Somatrogon population (N2)	Hazard Ratio
0.9	1,305	1,305	3.00
0.9	2,000	2,000	2.54
0.9	4,000	4,000	2.01
0.9	5,000	5,000	1.89
0.9	10,000	10,000	1.60
0.9	20,000	20,000	1.41

Table 4 assumptions:

- α=0.05
- Power=0.8
- Different somatrogon-treated patient population sizes: n=1,305, 2,000, 4,000, 5,000, 10,000, 20,000
- 1:1 ratio between somatrogon-treated patient population and comparator group of once daily somatropin-treated patients
- Estimated incidence rate of neoplasms in comparator group of once daily somatropin-treated patients: 0.9 per 1,000 person-years
- 10-year total study duration (5 years patient accrual, and minimum 5 years follow-up for last enrolled patient)

- Constant rate of accrual
- 5% annual loss to follow up among somatrogon-treated patients, and 5% annual loss to follow up among once daily somatropin-treated patients
- Assuming 0% annual rate of switching from somatrogon-treated group to once daily somatropin-treated group, and 0% annual rate of switching from once daily somatropin-treated group to somatrogon-treated group.

Sample size calculation to estimate the number of patients required to assess the risk of diabetes mellitus type 2

Sample size calculations were undertaken to determine the number of patients required to assess the risk of diabetes mellitus type 2. Given the wide variability of results obtained in the estimation of the incidence rate of diabetes mellitus type 2 (Table 2), sample size calculations were repeated assuming incidence rate for diabetes mellitus type 2 of 0.1/1,000 person-years, and 0.01/1,000 person-years. Table 5 presents detectable hazard ratios among somatrogon-treated patients compared with once daily somatropin-treated patients. Assuming a range of 2,000 - 20,000 patients exposed to somatrogon, the minimum HRs between treatment groups that could be detected with at least 80% power at the 5% significance level are summarized. Based on the estimates presented in Table 5, assuming 0% annual rate of switching from somatrogon-treated patients to once daily somatropin-treated patients, and 0% annual rate of switching from once daily somatropin-treated patients to somatrogon treated patients, and incidence rate of 0.5/1,000 person-years in once daily somatropin-treated paediatric patients (Table 2), sample sizes of 2,000 and 20,000 somatrogon-treated patients would allow for HRs of 3.21 and 1.57, respectively, to be detected between the somatrogon-treated and once daily somatropin-treated groups. Comparative analyses for diabetes mellitus type 2 will be performed if there are ≥2,344 patients in the somatrogon treated group, which would allow for an HR of 3.00 or higher to be detected between somatrogon and once daily somatropin-treated groups. The occurrence of switching will inevitably require a greater sample size and higher thresholds to inform the conduct of comparative analyses.

Table 5. Minimum Detectable Hazard Ratios Among Somatrogon-treated Patients Compared with Once Daily Somatropin-treated Patients with 80% Power, alpha = 0.05, 10-year Study with 5 Years Uniform Accrual, 5% Loss to Follow Up Per Year in Somatrogon-treated group – Diabetes Mellitus Type 2

Incidence rate per 1,000 person-years of diabetes mellitus type 2 in once daily somatropin treated group	Sample size of patients in once daily somatropin treated group (N1)	Sample size in Somatrogon population (N2)	Hazard Ratio
0.5	2,000	2,000	3.21
0.5	2,344	2,344	3.00
0.5	4,000	4,000	2.44

Table 5. Minimum Detectable Hazard Ratios Among Somatrogon-treated Patients Compared with Once Daily Somatropin-treated Patients with 80% Power, alpha = 0.05, 10-year Study with 5 Years Uniform Accrual, 5% Loss to Follow Up Per Year in Somatrogon-treated group – Diabetes Mellitus Type 2

Incidence rate per 1,000 person-years of diabetes mellitus type 2 in once daily somatropin treated group	Sample size of patients in once daily somatropin treated group (N1)	Sample size in Somatrogon population (N2)	Hazard Ratio
0.5	5,000	5,000	2.26
0.5	7,368	7,368	2.00
0.5	10,000	10,000	1.84
0.5	15,000	15,000	1.67
0.5	20,000	20,000	1.57
0.1	2,000	2,000	7.59
0.1	4,000	4,000	5.04
0.1	5,000	5,000	4.47
0.1	10,000	10,000	3.21
0.1	11,688	11,688	3.00
0.1	15,000	15,000	2.71
0.1	20,000	20,000	2.44
0.1	36,765	36,765	2.00
0.01	10,000	10,000	12.06
0.01	20,000	20,000	7.58
0.01	25,000	25,000	6.61
0.01	50,000	50,000	4.47
0.01	75,000	75,000	3.65
0.01	100,000	100,000	3.21
0.01	116,811	116,811	3.00
0.01	367,475	367,475	2.00

Table 5 assumptions:

- α=0.05
- Power=0.8
- Different somatrogon-treated patient population sizes: n=2,000, 2,344, 4,000, 5,000, 7,368, 10,000, 11,688, 15,000, 20,000, 25,000, 36,765, 40,000, 50,000, 75,000, 100,000, 116,811, 367,475
- 1:1 ratio between somatrogon-treated patient population and comparator group of once daily somatropin-treated patients
- Estimated incidence rate of diabetes mellitus type 2 in comparator group of once daily somatropin-treated patients: 0.5 per 1,000 person-years, 0.1 per 1,000 person years, 0.01 per 1,000 person-years
- 10-year total study duration (5 years patient accrual, and minimum 5 years follow-up for last enrolled patient)

- Constant rate of accrual
- 5% annual loss to follow up among somatrogon-treated patients, and 5% annual loss to follow up among once daily somatropin-treated patients
- Assuming 0% annual rate of switching from somatrogon-treated group to once daily somatropin-treated group, and 0% annual rate of switching from once daily somatropin-treated group to somatrogon-treated group.

9.6. Data management

All data for this study will be collected through the routine data collection practices of databases in the 4 participating countries. Investigators in each country will either independently generate the data needed for the study by linking the national databases or receive study specific data generated by the owner of the databases (ie, responsible authorities).

Overall, 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. The process for data management may vary by country however, the investigators will check the data for consistency in terms of range of values, units of measurement, and relevance of clinical information. Additionally, frequency tables of variables of interest will be generated to check for plausibility and consistency.

Details regarding utilizing data from the 4 countries and other aspects of data management are below:

France

Based on the data extraction criteria provided by Certara France, the Caisse nationale de l'Assurance Maladie (CNAM) statisticians will search for patients within the SNDS and will develop the relevant targeting algorithm. After validation of this algorithm with Certara France, the CNAM will extract the data required for this study. As this is an extraction from the SNDS claims database, no specific data are collected from patients or doctors.

The extracted data will then be made available to the Certara France project team in a dedicated project area on the SNDS portal (subject to the favourable opinion of the relevant committees). Authorized Certara France users will be able to access data extracted from the portal. Certara France is committed to strictly respecting the benchmark determining the criteria of confidentiality, expertise and independence for research laboratories and design offices provided for by the decree of 17 July 2017.

The data will be kept for the number of years authorized for the conduct of the study and the publication of the results, then they will be permanently deleted.

The data will be received from SNDS in text format according to the selection criteria of the study. SAS® software (SAS Institute Inc., Cary, North Carolina, United States) or R will be used to process the data, including its management and analysis, manage the analytic

datasets, and conduct data analysis. This study will follow the relevant chapters of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and the International Conference on Harmonisation (ICH) guidelines for data management. In addition, the data will be checked for consistency in terms of range of values, units of measurement, and relevance of clinical information (eg, a pregnancy diagnosis for a male patient).

Spain

In Spain, data will be extracted from EMR as text files and stored on secure IQVIA servers in a dedicated data folder accessible only to trained IQVIA personnel involved in the study. Datasets will be extracted for analysis as specified in the Data Management Plan and SAP, following standard IQVIA procedures.

The LPD databases collect medical information from proprietary practice management software used by the physician during patients' office visits for recording their daily patient interactions in EMRs. A panel of physicians using this software volunteers to make available anonymized, patient-level information from their practices for clinical research purposes. Data are entered during usual patient care and submitted to the co-ordinating centers, cleaned and de-identified. This data collection allows retrospective analysis of a patient's written prescriptions and care history within a single panel practice.

The data are hosted on servers located in data centers belonging to IQVIA, which ensures a high level of data security and confidentiality. All European data are collected and processed in full compliance with General Data Protection Regulation (GDPR) and local privacy regulation requirements.

Data analysis and results generation will strictly follow the approved SAP. If for any reason any statistical method needs to be carried out in different way than described in the SAP, amendment to the SAP with required documentation and new approval is essential. Data will be analysed using Statistical Analysis System (SAS) version 9.4 (or upper) or R, or other similar statistical software.

Sweden

In Sweden, national healthcare registers cover almost the entire Swedish population. Identification of health outcomes and treatment groups for this study will use nationwide Swedish healthcare registers, as described in Section 9.4. The team will ensure correctness of the raw data (although not monitor) before data management starts. Records from different registries will be merged by unique personal identifier and pseudonymized before delivery of the datasets to the research team. More specifically, the information to be used from the various registers will be linked by the National Board of Health and Welfare (NBHW). The NBHW is a register holder and responsible for the information in the national health registers. The NBHW will link information from the registers through the personal identification numbers (PINs). The PIN is given to each citizen of Sweden at birth or

immigration. The datasets constructed by NBHW will be delivered to Karolinska Institutet Center of Pharmacoepidemiology, without the PINs. The PIN has been substituted by a serial number, allowing to identify an individual, without revealing her or his identity (pseudonymization). Patient-level data are kept on secure servers, and will not be made available to the Sponsor. Delivery of coded format data in SAS files from the National Board of Health and Welfare and Statistics, Sweden is possible and will be exported, managed, and analysed using SAS or R .

UK

THIN® database is regulated by an Advisory Committee to ensure that it continues to be used in a way that maximises its research value in the best interests of the public whilst protecting the rights of its data subjects.

THIN® database is compliant with GDPR and approved by the National Health Service (NHS) Research Ethics Committee. The database is anonymised at source (not personal data) and patients can opt out at any point of records being collected.

9.7. Data analysis

The primary analysis will be descriptive and all eligible patients during the study period will be included, with no upper limit on the sample size. Due to database heterogeneity, analyses will be conducted separately by data source and data will not be pooled.

Baseline demographic and clinical characteristics for each treatment group will be described. For all the safety events of interest and efficacy measurements of interest, descriptive statistics, counts and proportions, crude incidence rates (ie, number of events per person years) and age/sex standardized incidence rates with associated two-sided 95% confidence intervals will be calculated as appropriate.

The summary of event rates will be based on survival analysis of time to first event based on an index date defined for each treatment group with appropriate censoring rules applied for those who do not experience an event by end of follow-up period including those who die, those who are lost to follow-up (eg, via migration out of the country as documented in the data source), or end of study period. Rates will be expressed as events/1,000 person-years of follow-up.

The primary objective of the study is active surveillance (to estimate the incidence rates of neoplasms, and diabetes mellitus type 2, the primary safety events of interest in paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care). Conducting quantitative, confounding-controlled comparative analyses will depend on having a sufficient sample size. The feasibility of more formal comparative analyses to evaluate safety events of interest that adequately adjust for potential confounders will be assessed in the interim reports, and at study end will be based on statistical power as described below. Since the size of the once daily somatropin-treated comparator group is expected to be a magnitude larger than the somatrogon-treated group,

statistical power will be limited by the uptake of somatrogon (which is difficult to estimate a priori).

As described in Section 9.5 (Study Size), the comparative analyses by data source will only be performed at the time of the final report if the number of patients in the somatrogon treated group would allow for an HR of 3.00 or higher to be detected with 80% power at the 5% significance level, assuming 0% annual switching between somatrogon and once daily somatropin-treated groups. Specifically, comparative analyses by data source for:

- neoplasms will only be performed at time of the final report if there are ≥1,305 patients in the somatrogon-treated group
- Diabetes mellitus type 2 will only be performed at time of the final report if there are ≥2,344 patients in the somatrogon-treated group.

If comparative analyses can be performed, incidence rates of the primary safety events of interest will be compared between somatrogon-treated patients and the comparator group of daily somatropin-treated patients using multivariable Cox regressions adjusting for potential confounders. The adjusted hazard ratio from the Cox model will be presented along with a 95% confidence interval.

Given the low number of patients anticipated to have IGF-1 laboratory results, height, and weight measurements, and the high potential for missing values/measurements for some clinic visits, no comparative analysis for IGF-1, height, and medication errors will be conducted.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed and maintained by the sponsor. 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.

9.7.1. Subgroup Analysis

Patients will be initiating treatment of somatrogon (or somatropin, for the internal comparator group) during the study accrual period, but may have a history of using other recombinant hGH therapy, prior to study entry. As feasible, for the descriptive and comparative analysis (will only be performed at the time of the final report if the number of patients in the somatrogon-treated group would allow for an HR of 3.00 or higher to be detected with 80% power at the 5% significance level, assuming 0% annual switching between somatrogon and once daily somatropin-treated groups), a subgroup analysis among prevalent users of GH therapies and new users of GH therapies will be performed to quantify neoplasms and diabetes mellitus type 2 rates.

9.7.2. Sensitivity Analysis

9.7.2.1. Switching

Given the 10-year span of the study period, treatment switching between recombinant GH therapies may occur among patients after study accrual. Patient subgroups such as somatropin exposed, somatrogon exposed, or switching between somatropin and somatrogon may be observed. While there is prior literature to suggest that switching recombinant GH can occur (eg, due to health plan change) [Rashid et al 2014 Biol Ther] and in a small proportion of patients,[Lundberg et al 2020; Pfäffle et al 2013] no impact on efficacy or safety has been observed in the paediatric population with GHD.[Romer et al 2011; Sävendahl et al 2020]. In the descriptive and comparative analysis (will only be performed at the time of the final report if the number of patients in the somatrogon-treated group would allow for an HR of 3.00 or higher to be detected with 80% power at the 5% significance level, assuming 0% annual switching between somatrogon and once daily somatropin-treated groups) analytic methods in the SAP will address treatment switching by censoring participants at the time of switching, or including treatment as a time-varying covariate (with a lagged time for exposure, as appropriate).[Belleudi et al 2018]

9.7.2.2. Latency period

Diabetes and neoplasm development may be delayed relative to the time of treatment exposure. For this reason, an approach where follow-up time commences 6 months after index date (eg, a 6-month lag time) will be used in both the descriptive and comparative analysis. In doing so, analyses will guard against the inclusion of events which may have previously gone undiagnosed.

9.7.2.3. Competing events

In the presence of competing events, the occurrence of an event of interest is precluded by another event (ie, death). If the frequency of all-cause mortality is substantial over the 10 year study period competing-risk methods to account for the competing event of death may be employed. The standard product limit method of estimating a survivor function for an event of interest may yield biased results as the probability of occurrence is modified by an antecedent competing event. By extending the capabilities of conventional survival analysis to deal with time-to-event data that have multiple causes of failure, the Fine and Gray method can be applied to the comparative analysis, estimating the sub-distribution relative hazards. [Fine and Gray 1999]

9.7.2.4. Patients accrued with <5 years of follow-up

To facilitate the accrual of a larger study population, this study will extend its accrual period beyond 5 years. Such patients will be eligible to contribute to analyses even though they accrue after the 5-year mark from somatrogon approval. Since their follow up will be less than 5 years and there may be decreased opportunity for outcome detection, separate analyses will be conducted for this subset of the study population, prior to combining this subset with the patients entering the cohort during the study accrual period.

9.8. Quality control

Investigators in respective countries are responsible for following their standard institutional procedures to ensure data quality and integrity, including archiving of statistical programs, appropriate documentation of data cleaning and validity for created variables description of available and confirmation of endpoints. Processes by country are:

France

Assessment of availability and completeness of variables, including missing data and implausible ranges, as described in previous sections, will be conducted. The study will be based on the analysis of secondary data, and as such no source data verification is relevant. Certara, the data vendor for SNDS, will implement the study as an accredited partner with CNAM, the SNDS data owner representative. Data extraction delivered by the CNAM will be checked for plausibility and completeness by the Certara statistical team. In addition, CNAM agreed to share SAS codes used for extraction which will be reviewed independently by 2 Certara programmers. The lead statistician will comply with Certara's quality control process for each programming code, which includes a check list to limit coding mistakes. All outputs will then be checked by the lead epidemiologist and study director. All programs will be reviewed by an independent statistician and the primary analysis will be recorded independently. In relation to any data cuts received and data outputs, Certara internal data security policy (SLSP – System Level Security Policy) will apply. Certara will store the data cuts and outputs in a dedicated folder within the file server. The Asset Custodian will ask for user's accesses (for the team in charge of data analysis) and IT team will provide the requested accesses upon validation from the system owner.

Spain

At the study level, all aspects of the study from protocol development to the reporting of the results are conducted within the work-frame of IQVIA Quality Management System (QMS) and in accordance with IQVIA policies and procedures:

According to these policies and procedures, a Quality Control plan for the study will be developed and executed, which will include quality control on study methodology, statistical analysis plan, programming, data management and analysis, study results, conclusions, and study report. Furthermore:

- The study Quality Control plan will establish ownership for the execution of the individual Quality Control steps. The principle of the independence of Quality Control applies.
- The Principal-in-Charge of the study will ensure that individuals responsible for the execution of specific Quality Control steps will have knowledge, capability and experience which are adequate for the task.
- The result of the execution of the individual steps of the Quality Control plan will be documented, and include the required corrective actions, if any.

- The execution of any required corrective action will be documented.
- The executed Quality Control plan will be subjected to a final review and approval for sufficiency and completeness from the Principal-in-Charge of the study

Also, the Principal-in-Charge of the study will verify training compliance of IQVIA employees contributing to the study.

Sweden

Swedish national health registers have been previously demonstrated to have a high degree of completeness with automated transfer, but is not monitored [Ludvigsson et al 2011; Ludvigsson et al 2016], as well as used to assess GH safety.[Tidblad et al 2021] Health and demographic information within Sweden is routinely collected in a series of registers with a relatively high degree of completeness resulting from mandatory registration for all physicians, publicly and privately funded, to deliver data to the Swedish NBHW.[Barlow L et al 2009; Wettermark et al 2007]

Data received from the register holders will be stored, managed and analysed according to the SOPs established by the Centre for Pharmacoepidemiology at Karolinska Institutet, who will obtain all permission necessary to conduct this study. The internal quality control procedures will ensure the necessary compliance with local data protection, storage and arching, patient privacy laws and regulations. At a minimum, the statistical programming and analysis will be reviewed and supervised by a senior statistician and all study documents (eg, protocol, report) will be reviewed by all members of the research team. A senior epidemiologist will supervise the project and review the output before submission to the Sponsor. Clinical expertise is available for appropriate interpretation of the results. All project staff members receive comprehensive orientation training. All analyses will be conducted according to the Guidelines for Good Pharmacoepidemiology Practices (GPP), and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

UK

There are multiple layers of quality control (QC) for the THIN database. This ranges from QC at the practice level and on an individual patient level. At the practice level, if the data collection is corrupted and cannot conform to the schema the data collection is redone. On an individual level, QC steps assess 1) if the registration information is accurate (eg, patient is permanent, has applied to join the GP practice and has not left the practice) and 2) if the record has anomalies (such as negative age, undefined sex, negative follow up time etc.). Patient records with insufficient registration information and/or contain anomalies are rejected. There are over a dozen QC steps; some are specific to THIN but many are comparable to other primary care databases. The QC steps are automatically executed on a weekly basis for the whole of THIN. These steps ensure the data used in the analysis is of high quality.

Preliminary investigations into the variables mentioned using structured data show promising results. The analysis will be led by a senior data scientist with the support of a secondary data scientist to verify the code and results. A data extract will be performed at the start of the study (and subsequent timepoints) and archived on Cegedim servers; the code and outputs for the analysis will be tracked with git. Taken together this will ensure reproducibility over the 10 year study period.

9.9. Limitations of the research methods

The study has a number of strengths:

- Cohort studies utilizing secondary electronic healthcare data sources are the most efficient design for studies of rare disease, long duration, and rare events, more especially, when the primary events under study, ie, malignancy and diabetes, are well captured in these data sources.
- This study will use population-based data sources from France, Spain, Sweden and UK. These large real-world data sources are representative of patient populations in their respective countries and will provide invaluable data to characterise the safety of somatrogon with respect to neoplasms, diabetes mellitus type 2, and immunogenicity.
- Loss to follow-up or attrition of patients over the 10-year duration of the study is of major concern. The loss is expected to be minimal in the databases with total or near total national coverage in France and Sweden. In such databases, any loss to follow up could only be due to emigration which is expected to be minimal in families with children with lifelong diseases such as GHD. In the Spanish LPD, loss to follow up can occur if a patient changes the health insurance provider (albeit this is not common for chronic diseases), or if the patient changes his/her residence resulting in follow-up in a center not included in the LPD database. For paediatric patients in a longitudinal study, this may be frequent. Similarly, in the THIN databases, loss to follow-up can occur when a patient transfers from a physician or clinic within the coverage of the database to one outside

The following are the potential limitations of this study:

- Given the use of data sources from 4 distinct European countries in this study, there will be variability in data capture across the data sources.
- The statistical power of the planned comparative analyses may be limited by market uptake of somatrogon which will impact the size of the somatrogon-treated group, and the exact extent cannot be determined a priori. Relatedly, conducting quantitative, confounding-controlled comparative analyses will depend on having a sufficient sample size. In terms of sufficient a priori confounder control, this study may be limited in part by yet unknown patient characteristics of those who receive the new to market treatment, somatrogon.

- The secondary objective of 'evaluating long-term efficacy by measuring IGF-1 levels, and height in paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care, will only be evaluated in Sweden (using data from the National Swedish Growth Hormone Registry), and if feasible, in a portion of patients in the UK THIN database when IGF-1 laboratory results, pubertal staging, height, and weight measurements are available. Similarly, the secondary objective to 'estimate the incidence rates of medication errors', will be evaluated in Sweden only, and if feasible, in UK THIN and Spain's LPD, but not SNDS. Laboratory data, height, and weight measurements are not available in the French SNDS claims database. Laboratory data values (eg, IGF-1) are not available in the Spanish LPD database.

- The French SNDS, Spain LPD, UK THIN, and Swedish databases and registry, respectively, do not capture administration of medications. SNDS and THIN provide reimbursed prescription data. Spanish IQVIA LPD databases do not capture the dispensation of the medication, only the prescription (dose and frequency). Whereas the Swedish registry provides dispensation data. While dispensation is a good proxy for administration there is still the possibility that a medication was dispensed but not taken.[Velentgas 2013].

- Exact injected dosing will be unknown. In Sweden, SNDS, Spanish LPD, and THIN, dosing will be based on packaging and frequency of reimbursed prescriptions. For Sweden's PDR, exact dosage will not be available but dose will be based on packaging, frequency of prescriptions, amount and strength dispensed.

- For SNDS only, clinical outcomes such as immunogenicity are only captured in hospitalisation data since outpatient diagnosis data are not available in this data source (to note, some diagnoses could be available in the outpatient database as reasons for registration in the long-term disease database; such chronic conditions are identified with ICD-10 codes).

- Given the potential latency for neoplasm development, the study may underestimate its occurrence during the 10-year study period. Moreover, as indication specific data elements are not available in SNDS, THIN, Swedish national data, it is possible that GH treatment was indicated for patients as a direct result of a neoplasm (eg, removal of an intracranial tumor led to GHD, GH treatment is given, but there is a neoplasm recurrence; Boguszewski et al 2021).

- Exposure to more than one recombinant GH treatment during study follow-up may occur. In the comparative analysis, censoring follow-up time after a switch, or parameterizing treatment exposure as a time-varying covariate, serves to in part to account for this. However, these methods assume that patients who switch are prognostically similar to patients who do not switch, which may not necessarily be true.

- Medication errors resulting from the administration or consumption of treatment by the wrong patient, or at the wrong time, or at the wrong dosage strength, will not be captured in this study. Moreover, medication errors as currently defined will not account for titration used to maintain IGF-1 levels. For example, patients may have had a scheduled dose decrease of 15% due to IGF-1 SDS>2 or adverse events. If a patient had a dose prescribed that required a 15% decrease in dose, this would be captured as a medication error when in fact it is not. Lastly, sufficient accuracy of estimating medication error (for Sweden, Spain LPD, and UK THIN) at a single dose or at a weekly level will be limited, because it is a function of data availability and timing of both weight measures and GH treatment. For instance, in the Swedish GH registry the provider has to report missing doses every 6 months; medication errors are captured as an aggregate measure at the 3–6-month level.

- Broad definitions of immunogenicity clinical endpoints, such as hypersensitivity, may overestimate their occurrence and does not account for multiple symptoms stemming from one unifying, underlying condition (eg, hypersensitivity and allergic conjunctivitis, as it relates to atopic dermatitis).

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

This study involves data that exist in anonymised structured format and contain no patient personal information.

10.2. Patient consent

As this study involves anonymised 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.

10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/IECs, from databases. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer. Country specific requirements are listed below:

France: Ethical approval for the use of the SNDS data will be sought from the National Commission for Data Protection (CNIL) in France. All correspondence with the CNIL must be retained. Copies of CNIL approvals must be forwarded to Pfizer.

Spain: All retrospective studies must be approved by a reference EC in Spain.

Sweden: Approval from the National Ethical Authority and from the NBHW will be required.

UK: The UK-THIN database Scientific Research Committee reviews the appropriateness of all research proposals which aim to use THIN data. All retrospective studies based on UK-THIN data are exempt from local IRB/EC board review, but any contact of general practitioners or patients via THIN Research Services will require separate ethical approval.

10.4. 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 the following documents:

- Guide on Methodological Standards in Pharmacoepidemiology issued by ENCePP (ENCePP Guidelines 2021), Module VIII of the EMA's Guideline on good pharmacovigilance practices (GVP) –Post-authorisation safety studies (EMA GVP Module VIII),
- Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE) (Andrews, 2015),

- Guidelines for Good Epidemiological Practice (GEP) issued by the International Epidemiological Association (IEA) (GEP, 2019),

- International Ethical Guidelines for Health-related Research Involving Humans issued by the Council for International Organisations of Medical Sciences (CIOMS) in collaboration with the World Health Organisation (WHO) (CIOMS, 2018), and

- The United States Food and Drug Administration's (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (FDA, GPP, 2005)

11. 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 (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

This study will be registered in the EU PAS Register prior to the start of data collection. The final study results will be disclosed through the EU PAS register. Submission of the interim and final reports is planned per the schedule outlined in Section 6.

A manuscript(s) may be prepared for publication in a peer-reviewed journal upon completion of the study.

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 party responsible 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.

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: An Active Surveillance Study to Monitor the Real-World Long-term Safety of Somatrogon Among Paediatric Patients in Europe.

EU PAS Register® number: Study to be registered before the start of data collection
Study reference number (if applicable): C0311023

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]	☒	☐	☐	Section 6
1.1.2 End of data collection[2]	☒	☐	☐	Section 6
1.1.3 Progress report(s)	☐	☐	☒	n/a
1.1.4 Interim report(s)	☒	☐	☐	Section 6
1.1.5 Registration in the EU PAS Register®	☐	☐	☐	Section 6
1.1.6 Final report of study results.	☒	☐	☐	Section 6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	Section 8
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	Section 7

[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**
2.1.2 The objective(s) of the study?	☒	☐	☐	Section 8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	Section 7
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	X	☐	n/a
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	X	☐	n/a

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)	☒	☐	☐	Section 9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	Section 9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	Section 8, 9.7
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))	☒	☐	☐	Section 8, 9.7
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)	☐	☐	☒	n/a

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	Section 9.2

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	Section 9.2.3
4.2.2 Age and sex	☒	☐	☐	Section 9.2.1
4.2.3 Country of origin	☒	☐	☐	Section 9.1
4.2.4 Disease/indication	☒	☐	☐	Section 9.1
4.2.5 Duration of follow-up	☒	☐	☐	Section 9.2.3
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	Section 9.2

Comments:

Somatropin and somatrogon are indicated for GHD and for this reason the study population will all have this disease

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)	☒	☐	☐	Section 9.2.1, 9.7
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	n/a
5.3 Is exposure categorised according to time windows?	☒	☐	☐	Section 9.7.2
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	Section 9.3

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	Section 9.7.1
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	Section 9.2.1

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?	☒	☐	☐	Section 9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☐	☐	☒	N/A
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)	☐	☐	☒	N/A
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)	☐	☐	☒	N/A

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)	☒	☐	☐	Section 9.7
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	Section 9.7.2

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	Section 9.7.2

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)	☐	☐	☒	n/a

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:				Section 9.4
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	Section 9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	Section 9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	Section 9.4
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)	☒	☐	☐	Section 9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	Section 9.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	Sections 9.4, 9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Section 9.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	Section 9.4
9.3.3 Covariates and other characteristics?	☐	☐	☒	n/a
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	n/a

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	Section 9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	Section 9.5
10.3 Are descriptive analyses included?	☒	☐	☐	Section 9.7
10.4 Are stratified analyses included?	☒	☐	☐	Section 9.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	n/a
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	n/a
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	n/a
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	Section 9.7.2

Comments:

For Section 10, item 10.4, data will be stratified by site due to data source heterogeneity.

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)	☒	☐	☐	Section 9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	Section 9.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	n/a

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?	☒	☐	☐	Section 9.9
12.1.2 Information bias?	☒	☐	☐	Section 9.9
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).	☐	☐	☒	n/a
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)	☒	☐	☐	Study 9.5

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?	☒	☐	☐	Section 10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	n/a

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.3 Have data protection requirements been described?	☒	☐	☐	Sections 10.4, 9.6

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?	☐	☐	☒	n/a

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)?	☒	☐	☐	Section 12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	Section 12

Comments:

Name of the main author of the protocol: Kofi Asomaning

Date: 20/March/2023

Signature:

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

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