Clinical Study Protocol

EU PAS Number: EUPAS103800

Title: Maternal and Infant Characteristics and Outcomes Following Exposure to HyQvia During Pregnancy: A Case Series Study Based on US Claims Data

Study Number: TAK-771-4004

Document Version and Date: Version 1.0; 23-February-2023

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

HYQVIA RETROSPECTIVE CASE SERIES STUDY PROTOCOL

Study title: Maternal and infant characteristics and outcomes following exposure to HyQvia during pregnancy: a case series study based on US claims data

Study number: TAK-771-4004

Version number: V1.0 (23 FEB 2023)

Ethics statement: This study will be conducted in compliance with the protocol, the Declaration of Helsinki, International Society for Pharmacoepidemiology Guidelines for Good Epidemiology Practices, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Guidelines for Methodological Standards in Pharmacoepidemiology, Good Pharmacovigilance Practices, and all applicable regulatory requirements.

Signature page

Study title: Maternal and infant characteristics and outcomes following exposure to HyQvia during pregnancy: a case series study based on US claims data.

Study number: TAK-771-4004

Version number: V1.0 (23 FEB 2023)

MAH (Marketing Authorization Holder):

Role	[redacted] Safety Pharmacoepidemiology/ Global Evidence and Outcome	**Printed Name**	[redacted]
Signature		**Date (DD-MMM-YYYY)**	

EU and UK QPPV:

Role	European Union (EU) Qualified Person responsible for PV (QPPV) and UK (United Kingdom) QPPV	**Printed Name**	Dr. [redacted], Global Patient Safety Evaluation Takeda Belgium NV Leonardo da Vincilaan 7, 1930 Zaventem, Belgium
Signature		**Date (DD-MMM-YYYY)**	

Investigator:

[redacted], MS PhD
[redacted], US
([redacted])

[redacted], MD DrPH
[redacted], US
([redacted])

By signing below, the investigator acknowledges that he/she has read and understands this protocol, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, good pharmacovigilance practices, and all applicable regulatory requirements. If applicable, he/she will comply with the requirements for obtaining informed consent from all study patients prior to initiating any protocol-specific procedures and for obtaining written initial and ongoing ethics committee(s) protocol review and approval.

Role	Investigator	**Printed Name**	[redacted]
Signature		**Date (DD-MMM-YYYY)**	

Role	[redacted]	**Printed Name**	[redacted]
Signature		**Date (DD-MMM-YYYY)**	

Study information

Title	Maternal and infant characteristics and outcomes following exposure to HyQvia during pregnancy: a case series study based on US claims data
Protocol number	TAK-771-4004
Protocol version identifier	1.0
Date of last version of protocol	23 FEB 2023
EU PAS register number	TBD
Active substance	Immune globulin infusion 10% (Human) with recombinant human hyaluronidase
Medicinal product	HyQvia
Product reference	Not Applicable
Procedure number	Not Applicable
Joint PASS	No
Research question and objectives	What is the safety profile of HyQvia used during pregnancy in a case series of commercially insured pregnant women in the US?
Country(-ies) of study	United States
Author	[redacted] (Global Evidence and Outcome/Safety Pharmacoepidemiology. Takeda Pharmaceuticals, Inc.) [redacted] [redacted]
Marketing authorization holder(s)	Baxalta US Inc.*, 300 Shire Way, Lexington, MA 02421 AND Baxalta Innovations GmbH*, Industriestrasse 67, A-1221 Vienna * Baxalta is now part of Shire/Takeda
MAH Contact Person	[redacted], MS, RAC [redacted] 650 East Kendall Street Cambridge, MA 02142 USA

	Phone: [redacted] Fax: [redacted] Email: [redacted]

TABLE OF CONTENTS

1.0 LIST OF ABBREVIATIONS

Abbreviations	Definition
AE	Adverse Event
ADR	Adverse Drug Reaction
CPT	Current Procedure Terminology
IRB	Institutional Review Board
FDA	United States Food and Drug Administration
LMP	Last Menstrual Period
MAH	Marketing Authorization Holder
NICU	Neonatal Intensive Care Unit
PI	Primary Immunodeficiency
PQC	Product Quality Complaint
SAB	Spontaneous Abortion
SAE	Serious Adverse Event
SGA	Small for Gestational Age
SSR	Special Situation Report

2.0 RESPONSIBLE PARTIES

Investigators:

[redacted], MS PhD, [redacted]

[redacted], MD DrPH, [redacted]

3.0 ABSTRACT

Title

Maternal and infant characteristics and outcomes following exposure to HyQvia during pregnancy: a case series study based on US claims data.

Rationale and background

There is currently limited information on the safety of HyQvia in pregnancy. Given the small number of exposed pregnancies, a controlled cohort study powered to identify modest increases in risk of obstetric and neonatal outcomes is unrealistic. Large healthcare utilization databases can be used for initial safety surveillance to promptly identify serious risks and generate hypotheses.

Research question and objectives

The question is whether exposure to HyQvia during pregnancy increases the risk of major adverse obstetric or neonatal outcomes.

The objective is to describe the frequency of adverse pregnancy outcomes in a series of patients exposed to HyQvia during pregnancy.

Study design

Retrospective case series of HyQvia-exposed pregnancies using data collected from an administrative claims database.

Population

Commercially insured US pregnant women exposed to HyQvia during pregnancy and included in the MarketScan Research Database during the period 2014-2020.

Variables

Exposure is defined based on filled prescriptions or administration (infusion) of HyQvia from 90 days before the last menstrual period (LMP) to the end of pregnancy based on pharmacy dispensing records or clinical procedures. Outcomes of interest include (but are not limited to) major congenital malformations in the infant, spontaneous abortion and stillbirth, preterm birth, small for gestational age, and admission to neonatal intensive care unit (NICU). Other non- pre-specified major adverse maternal and fetal outcomes will be abstracted too. Outcomes will be defined based on the presence of inpatient or outpatient diagnoses and procedures, as well as outpatient pharmacy claims, in the mother or the newborn. Covariates of interest that will be abstracted include medical indication for HyQvia (primary

immunodeficiency), maternal demographic characteristics, comorbid medical conditions, obstetric characteristics/conditions, other maternal medications, and healthcare access and utilization.

Data sources

The MarketScan Research Database is a large population-based administrative claims database of privately insured individuals in the US, anonymized for research purposes.

Study size

The study will monitor all HyQvia-exposed pregnancies in the accumulated data. We estimate to identify around 5 to 10 exposed pregnancies.

Data analyses

This is a descriptive surveillance study. The clinical experience of anonymized exposed pregnancies (cases) will be described based on their complete claims profile. Diagnoses and procedures for mother and newborn coded during clinical encounters as well as pharmacy dispensations will be used to reconstruct the longitudinal medical history of the patient from the first dispensation identified between 90 days before the LMP and the end of pregnancy to the end of follow-up (up to 90 days after end of pregnancy).

Milestones

The end of the data collection for secondary data use, defined as the date from which the analytical data set is available for the analysis, is planned for April 15th 2023. The final report would be completed and submitted by June 30th, 2023.

4.0 AMENDMENTS AND UPDATES

Not applicable

5.0 MILESTONES

Milestone	Planned date	Actual date	Comments
Protocol finalization	28FEB2023	TBD	
Registration in the EU PAS Register and ClinicalTrials.gov	14MAR2023	TBD	
Start of data collection	15MAR2023	TBD	
End of data collection	15APR2023	TBD	
Analysis completion	1MAY2023	TBD	
Final report of study results	30JUN2023	TBD	

6.0 RATIONALE AND BACKGROUND

HyQvia [immune globulin infusion 10% (Human) with recombinant human hyaluronidase] is indicated for the treatment of Primary Immunodeficiency (PI) in adults. PI diseases are a group of rare, genetic disorders resulting from dysfunctions within the immune system, and affect approximately 500,000 people in the United States (US).[1] The prevalence of PI in the US is slightly higher in men (56.3%) than in women (43.7%).[2]

Results from clinical studies have demonstrated that HyQvia can effectively reduce the rate of serious bacterial infections among patients with PI, while allowing for less-frequent infusions and fewer administration sites as compared with conventional subcutaneous immune globulin products.[3] However, data on the safety of HyQvia use in pregnancy are limited. A recent international pregnancy registry study (161301, EUPAS5798/NCT02556775) reported long-term safety outcomes of facilitated subcutaneous immunoglobulin (fSCIG) use before or during pregnancy in 9 mothers with PI (n=7 in the fSCIG arm, and n=2 in alternative treatment arm). Of the 7 mothers exposed to fSCIG, only 5 completed the study. The study showed that no treatment-related adverse events had been observed in the mothers or in their infants.[4] The small sample size, lack of complete information on patient characteristics, medical history, and pregnancy and infant outcomes, renders the existing registry data inadequate to characterize the risk-benefit profile of HyQvia exposure during pregnancy.

Health care utilization databases have become a standard source of real-world evidence for post-marketing surveillance because they include prospectively collected information for large populations and allow for the evaluation of multiple outcomes. The large size of these databases often generates enough statistical power to examine rare outcomes and important subgroups. However, when the number of exposed pregnancies in the population is expected to be small, even nationwide large databases will be insufficient to support an adequately powered controlled cohort study. Yet, some information is better than no-information. With the appropriate careful interpretation, the experience from a small number of exposed pregnancies identified within the healthcare utilization data can provide some boundaries around risks. Unusual patterns and extremely large effects would emerge (e.g., thalidomide), or be deemed improbable.

The specific data source (MarketScan) was selected based on a feasibility evaluation conducted to identify the most appropriate sources for this study. We considered very large health care utilization databases in the US with availability of mother-infant linked data, population-based sample, a large number of pregnancies and demonstrated ability to generate valid evidence on the safety of drugs during pregnancy. The MarketScan Research Database represents claims information from one of the largest commercially insured populations in the US; it contains the largest number of pregnancies among the three commercial databases considered. The other two commercial claims databases considered were the HealthCore Integrated Research Database and Optum Dynamic Assessment of Pregnancies and Infants data. However, these two databases do not offer additional benefits, and the epidemiologists at the Harvard Program on Perinatal Pharmacoepidemiology that will collaborate in the design and interpretation of the current study have extensive experience conducting pregnancy safety studies in MarketScan.[5] Another potential candidate was the nationwide Medicaid data, which represents a diverse vulnerable population of women enrolled in Medicaid.[6] However, the use of new drugs is expected to be delayed in Medicaid, and there is approximately a four-year gap between data recording and availability of the database for research (e.g., data from 2018 was released during 2022). Meanwhile, under CMS privacy rules, patients with data in Medicaid cannot be included in a descriptive case-series analysis and therefore Medicaid data cannot be included in the present study.

The proposed case series is designed to supplement a US Food and Drug Administration (FDA) post-marketing requirement for additional information about the safety profile of HyQvia use during pregnancy (**STN:** BL 125402, approved September 12, 2014). Patients and prescribers need information since some patients with PI may need to remain on the drug while pregnant; and others may inadvertently conceive while on HyQvia.

7.0 RESEARCH QUESTION AND OBJECTIVES

This is a surveillance study to characterize the safety profile of HyQvia when used during pregnancy. The research question of interest is whether exposure to HyQvia during pregnancy increases the risk of major adverse obstetric or neonatal outcomes. The objective is to describe the frequency of adverse pregnancy outcomes in a series of patients exposed to HyQvia during pregnancy. The narratives will report factually, without judgment about causality.

Objective:

- Describe maternal characteristics, patterns of HyQvia utilization and pregnancy outcomes in HyQvia-exposed pregnancies identified within a US healthcare claims database of commercially insured individuals. Outcomes of interest include major congenital malformations in the infant, spontaneous abortion and stillbirth, preterm birth, small for gestational age, and admission to neonatal intensive care unit (NICU). However, the narrative case series approach will abstract information for any clinical diagnosis including non-pre-specified ones.

8.0 RESEARCH METHODS

8.1 STUDY DESIGN

This is a retrospective noninterventional uncontrolled case series of all pregnancies exposed to HyQvia identified in the MarketScan Research Database (MarketScan). MarketScan is a nationwide commercial health insurance claims database that is large enough to allow creation of a nationally representative data sample of US residents with employer-provided health insurance. The observation period will be from January 1, 2014, to December 31, 2020.

We will identify pregnancies resulting in pregnancy losses or livebirths. All live-birth deliveries, spontaneous abortions, terminations and stillbirths will be identified using inpatient and outpatient fetal loss or delivery-related diagnostic and procedure codes from healthcare utilization claims. Completed pregnancies with a livebirth will be linked to liveborn infants when feasible. We have developed a linkage algorithm based on insurance case number (which identifies family units), and date of delivery which has been used to accurately link mother-infant data files.[5,6] Several steps of data cleaning are implemented to ensure accurate linkage and to avoid duplication of pregnancies. The efficiency of linkage of delivery admissions to infants is around 75%. When describing the exposed pregnancies, we will indicate the pregnancy outcome and, for livebirths, whether a newborn was linked in the data.

Typically, strict eligibility criteria are applied to ensure complete capture of exposure, outcomes, and covariates recorded in the claims for the mother and infant. Specifically, to ensure complete claims information, we typically impose requirements for health insurance coverage. Generally, women are required to have insurance coverage with full prescriptions benefits at least during the period from 3 months before the LMP through one month after end of pregnancy. Infants are required to have insurance coverage for at least three months after birth unless they died sooner.

Requirement of the maternal enrollment period prior to LMP allows for identification of medication exposures for which the prescription was filled prior to the LMP but whose supply extended into pregnancy, or long-acting medications that were administered before the LMP (e.g., infusion). It will also provide accurate ascertainment of comorbid conditions that pre-date pregnancy. The requirement for continuous enrollment throughout pregnancy will allow for complete follow-up and complete ascertainment of medication exposures and claims. Requiring enrollment of infants for at least 90 days following birth will allow ascertainment of nearly all major congenital birth defects.

However, since we do not want to exclude any exposed pregnancies, the case series will include all pregnancies with evidence of exposure to HyQvia. When providing the narrative of a given case, we will specify if the mother was enrolled at least 90 days before the LMP and if the mother and infant had complete follow-up or were lost to follow-up due to discontinuation of insurance benefits.

Establishing exposure during the etiologically relevant windows requires information on the dates of LMP and delivery so that the approximate date of conception, gestational age and embryogenesis periods can be determined. Because neither gestational length nor LMP date are available in healthcare utilization data, the LMP will be assigned using validated algorithms based on ICD codes (e.g., International Classification of Diseases Version [ICD]-10 Z3A codes, preterm codes).

8.2 SETTING

The source population will consist of pregnancies identified within MarketScan data from 2014 onwards including the most recent available data at the time of study completion (currently 2020).

8.2.1 Study population

Within the source population we will identify the cohort of commercially insured US pregnant women with administration or dispensation of HyQvia from 90 days before LMP to the end of pregnancy and their infants (for those pregnancies ending in live births that can be linked). We consider the 90 days before pregnancy to evaluate potential carry over effects and prioritize sensitivity when detecting exposures. However, the narratives will specify the timing of administration or dispensation relative to the LMP date.

8.2.2 Inclusion criteria

- Pregnant human females ages 16-44
- Exposed to HyQvia in the etiologic window defined as 90 days prior to the LMP until the end of pregnancy.

8.2.3 Exclusion criteria

- NA

8.3 VARIABLES

8.3.1 EXPOSURE

Maternal HyQvia exposure is derived from pharmacy dispensing records and procedure codes for administration, with exposure status on any given day based on the dispensing or procedure date. Typically, we pre-specify etiologically relevant windows of exposure, which vary according to the outcome of interest. For example, since 1st trimester exposure is the etiologically relevant exposure window for congenital malformations, the exposure definition is based on the date of the prescription dispensing and/or procedure code combined with gestational timing (ie, LMP to LMP+90 days). However, in the current case series study the narratives will provide the timing of exposure and the outcomes without attribution of causality.

8.3.2 OUTCOME

Outcomes are defined on the basis of inpatient and/or outpatient diagnoses and procedures. Pre-defined outcomes of interest include major congenital malformations, pregnancy loss (spontaneous abortion, stillbirth) and among live birth outcomes, preterm birth, small for gestational age (SGA), and

admission to NICU (see Annex 1 for the code lists). However, the narratives will capture any coded major clinical diagnosis (e.g., preeclampsia, post-partum hemorrhage, infections, thrombosis) or procedure (e.g., Cesarean section).

Spontaneous abortion is defined as pregnancy loss before 20 weeks of gestation. Stillbirth is defined as a fetal death after 20 weeks of gestation. These outcomes will be identified using previously validated algorithms.[7] A major malformation is defined as a structural abnormality with surgical, medical, or cosmetic importance. Infants will be followed in the database from LMP to 90 days after delivery. Major malformations will be identified from ICD codes in the infant encounter claims (e.g., hospital discharge for the infant, subsequent infant hospitalization) and the mother's claims for codes indicating a birth defect around the child's date of birth (e.g., in obstetric claims). Claims from both the infant and maternal record will be used because claims pertaining to the care of the infant are sometimes applied to the maternal claims in the first few weeks of life. Two codes are generally required to define the presence of malformations to exclude cases in which a single mention may be recorded to justify a diagnostic test to rule out a condition.[8,9] The narratives will not be restricted to outcomes identified using validated outcome definitions, but will instead specify the number of claims for malformation diagnoses.

Pre-term birth is defined as delivery before 37 weeks of gestation. Pre-term births in this study are identified by the presence of inpatient or outpatient codes for preterm birth in the mother or infant record between delivery and delivery + 30 days using a validated algorithm.[10-12] Low birth weight can be the result of prematurity or fetal growth retardation or restriction. Infants with fetal growth retardation are born small for their gestational age (SGA, birth weight < 10th percentile). We will identify SGA based on infant or maternal records within 30 days of delivery. NICU admissions will be identified by CPT codes in maternal and infant claims within 30 days of delivery.

Infant outcomes will only be available for pregnancies with linked offspring. Therefore, the narratives will specify the linkage status for livebirths. For major malformations, information regarding the pathology results from a pregnancy loss or the indication for termination is rarely recorded. Therefore, we expect to have information on malformations only for linked livebirths.

8.3.3 BASELINE VARIABLES

Additionally, this case series will describe patient and clinical characteristics at baseline, including timing of HyQvia dispensations/administration, maternal demographic characteristics (maternal age), comorbid medical conditions (e.g., pregestational diabetes), obstetric characteristics/conditions (e.g., multiples, infertility treatment), other maternal medications (e.g., antibiotics), healthcare utilization (e.g., number of distinct diagnoses, number of outpatient visits), and infant characteristics (e.g., gestational age at birth, sex). These baseline characteristics are derived from eligibility files (e.g., maternal age), inpatient and outpatient diagnostic and procedural codes, and outpatient pharmacy dispensing records. Characteristics of particular interest because they may affect the risk of adverse pregnancy outcomes and/or be related to HyQvia exposure include:

- HyQvia indication. Primary immunodeficiency (PI) and other codes related to immunodeficiency.
- Proxies for immunodeficiency severity (e.g., number of bacterial infections, antibiotic prescriptions, other immunomodulators or immune globulins)
- Chronic comorbidities: cardiovascular risk factors (e.g., pregestational diabetes, hypertension), asthma, depression.
- Concurrent medications: estrogens, antidepressants, 5-HT3 receptor antagonists (ondansetron), antidiabetics, analgesics, antihypertensives, vaccines.

- Maternal use of suspected teratogenic medications (e.g., specific anticonvulsants)
- Maternal demographics/characteristics: age, obesity, smoking, alcohol, illicit drugs (as documented using ICD diagnostic codes)
- Obstetric characteristics: multiple gestation

No identifiers will be reported to protect confidentiality. MarketScan does not provide information on address or zip code, nor race/ethnicity, nor date of birth. To further prevent any potential identifiability, we will not provide the exact dates of pregnancy or exposures to HyQvia. Instead, we will report one date relative to the other (e.g., infusion occurred 15 days after the estimated LMP).

8.4 DATA SOURCES

The MarketScan database covers >180 million commercially insured US residents nationally. The MarketScan Commercial Claims and Encounters (CCAE) database is a large convenience sample of individuals with employer sponsored private insurance (for employees and/or their spouses or dependents). A major strength of MarketScan data source is the ability to track individuals longitudinally while they are employed through the same employer, even if they switch health insurance plans. This database links paid claims and encounter data to detailed patient information across sites and types of providers, and over time. It contains individual-level demographic and enrollment information, as well as all physician services and hospitalizations and their accompanying diagnoses and procedures. The data is anonymized for research purposes.

The insurance enrollment file contains information on age, sex, US census region, health insurance payer type, and enrollment status. An individual's claims of all types are linkable by an encrypted patient identification number and a unique family identification number that links family members on the same insurance plan.

The medical service claims in the MarketScan database have detailed information for inpatient and outpatient healthcare encounters, including date and place of service, provider type, and plan- and patient-paid amounts. International Classification of Diseases (ICD) coding is used for diagnoses and facility procedures. Diagnostic coding was performed using the Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) until 2015. This coding system utilizes six-character alphanumeric codes to describe diagnoses. Starting October 1, 2015 coding was updated to ICD-10. Current Procedural Terminology© (CPT) codes are used for physician claims and describe medical procedures and physicians' services. Healthcare Common Procedure Coding System (HCPCS) codes are used for procedures, durable medical equipment provided to patients, and drugs administered by physicians.

Pharmacy claims include detailed information on medications dispensed to patients on an outpatient basis, including the NDC, strength, quantity, route of administration (injectable, oral), dispensing date, and plan- and patient-paid amounts. The pharmacy file provides a history of drug dispensing, it records claims for each filled prescription and refill including the date of dispensing, the drug dispensed, and the quantity dispensed (i.e., the days the supply of drug is anticipated to last, number of prescriptions).

Use of the MarketScan Database offers many strengths for pharmacoepidemiologic research, including the very large population-based cohort, reliable assessment of drug exposure, and availability of information on a wide range of potential confounders. To ensure complete information, the analytic cohorts are restricted to subjects with full health care and prescription medications coverage throughout the follow-up periods. This database has previously been used successfully for perinatal epidemiologic research by us and other groups.

8.5 STUDY SIZE

In this case series, all pregnancies in the MarketScan database who meet the inclusion criteria and have complete information regarding the pregnancy outcome will be described. For pregnancies resulting in a live birth, where possible, the mother and infant will be linked using a linkage algorithm. From the feasibility evaluation, 7 pregnancies with exposure to HyQvia anytime during pregnancy were identified. To take into account potential carry-over effects from exposure to HyQvia prior to the LMP, pregnant women exposed to the HyQvia within 90 days prior to the calculated LMP will also be included. The timing of dispensation(s) with respect to LMP will be specified in the narratives.

8.6 DATA MANAGEMENT

No data collection will be needed since the study will use existing healthcare utilization data from the MarketScan Research database.

SAS software will be used for the creation of the analytic file and the case narratives.

8.7 DATA ANALYSIS

A descriptive analysis of the complete claims' profiles will be performed by reporting maternal and infant characteristics and outcomes following prenatal exposure to HyQvia. We will write separate narratives for each individual patient. The description will characterize the sociodemographic characteristics (age), medical history (comorbidities and concomitant medications), the timing of HyQvia dispensations or administration, recorded indication, obstetric characteristics (e.g., infertility treatments, multiples), clinical diagnoses during pregnancy (e.g., infections), obstetric outcomes (e.g., preeclampsia), infant characteristics (sex) and the presence of the pre-specify and other adverse pregnancy outcomes.

A summary report will quantify the frequency of the pre-specified outcomes (e.g., out of xx pregnancies exposed, yy ended in livebirths).

Given the small numbers, no absolute risks (with 95% confidence intervals) will be calculated. Since there is no reference group, no measures of association (e.g., relative risks) will be estimated. No causal inference will be attempted.

8.8 QUALITY CONTROL

The creation of the cohort of pregnancies ending in live and non-live birth outcomes is based on previously developed and validated algorithms.[5] Several steps are implemented to ensure accurate linkage and avoid duplication of pregnancies. The LMP is estimated using validated algorithms. The extraction and summary of information will consider the insurance enrollment status and prescription benefits throughout the period of observation for both the mother and the infant.

8.9 LIMITATIONS OF THE RESEARCH METHODS

The study limitations are consistent with other studies using large healthcare utilization databases, or nationwide registries, and center around the potential for misclassification and selection bias. For instance, exposure is ascertained based on filled prescriptions or administration codes. Non-compliance with the prescription filled would result in false positives and reduce the positive predictive value of the exposure variable. However, since HyQvia is an infusion which is typically either self-administered or administered by the healthcare provider, misclassification of exposure is expected to be minimal. Similarly, ascertainment of outcomes from coded claims can lead to misclassification.

However, the primary limitation is the small sample size. Any apparent association or lack of association (identified by informal comparison with the expected risks based on the literature) can be explained by chance, confounding or other biases. The limited numbers will not allow any proper confounding adjustment (e.g., through standardization to the US pregnant population, or identification of an internal comparison group) or sensitivity analysis. Therefore, the intention is to characterize the exposed pregnancies without attempting any causal inference.

9.0 PROTECTION OF HUMAN SUBJECTS

This is a surveillance study using only publicly available anonymized data. The MarketScan commercial health insurance database is de-identified and HIPPA compliant. The proposed project is not “human research” (it is public health surveillance) and it involves the secondary analysis of previously collected data, therefore there is no recruitment and no informed consent procedure. The electronic claims records are anonymous; the identities of patients are not known. The researchers will not have any access to named or identifiable patient information.

10.0 MANAGEMENT AND REPORTING OF ADVERSE EVENTS

This is a non-interventional study based on secondary use of data collected for other purposes, which consists of fully de-identified data. Therefore, individual case safety reports will not be required.

10.1 DEFINITIONS

10.1.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE
- A laboratory test result that requires the subject/patient to receive specific corrective therapy
- A laboratory abnormality that leads to discontinuation of therapy
- A laboratory abnormality that the healthcare provider considers to be clinically significant

10.1.2 Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded.
- In the view of the Healthcare provider, places the subject/patient at

immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- An SAE may also be any other medically important event that, in the opinion of the Healthcare provider, may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization).

10.1.3 Adverse Drug Reactions

An adverse drug reaction (ADR) is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

10.1.4 Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, strength, purity, effectiveness, or performance of a product or device and combination product after it is released for distribution.

10.1.5 Special Situation Reports

A Special Situation Report (SSR) includes any of the following events:

- Pregnancy: Any case in which a pregnancy patient is exposed to a Takeda Product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Takeda Product. Exposure is considered either through maternal exposure or via semen following paternal exposure.
- Breastfeeding: Infant exposure from breast milk
- Overdose: All information of any accidental or intentional overdose
- Drug abuse, misuse or medication error: All information on medicinal product abuse, misuse or medication error (potential or actual)
- Suspected transmission of an infectious agent: Suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.
- Lack of efficacy of Takeda Product

- Accidental/Occupational exposure
- Use outside the terms of the marketing authorization, also known as “off-label”
- Use of falsified medicinal product
- Use of counterfeit medicinal product
- Drug-drug interactions and drug-food interactions
- Inadvertent or accidental exposure with or without an AE
- Unintended benefit

An SSR should be reported even if there is no associated AE.

10.2 COLLECTION OF ADVERSE EVENTS, SPECIAL SITUATION REPORTS AND PRODUCT QUALITY ISSUES

Collection and notifying of Adverse Events, Special Situation Reports and Product Quality Complains to Takeda Pharmacovigilance

- SAEs, AEs, ADRs, SSRs and PQCs in the healthcare record or other applicable source data that are part of the study objectives or endpoints

  Events/complaints which are part of the study objectives or endpoints will be systematically identified and collected from healthcare records or other applicable source records and summarized as part of any interim analysis and in the final study report. Such events do not need to be notified as individual reports to Takeda Pharmacovigilance.

- SAEs, AEs, SSRs and PQCs in the healthcare records or other applicable source data that are not part of the study objectives and endpoints

  Events/complaints which are not part of the study objectives and endpoints will not be abstracted or collected from healthcare records or other applicable source records.

- SAEs, AEs, ADRs, SSRs and PQCs spontaneously reported to the investigator(s) or research team

  If during the conduct of the study the investigator(s) or a member of the research team is spontaneously informed by a healthcare professional or patient of an SAE, AE, ADR, SSR or PQC where the event/complaints pertains to a Takeda product (or unbranded generic), such information should be forwarded to the relevant Takeda Pharmacovigilance department **within 1 working day for fatal or life-threatening SAEs, within 4 calendar days for other SAEs, and within 7 calendar days for all other events**. This includes events spontaneously notified to the investigator(s) or research team which are study endpoints and also events spontaneously notified which are not study

endpoints. As such reports are spontaneously notified, causality of any adverse events should be assumed unless there is evidence to the contrary.

The relevant Pharmacovigilance contact information for reporting of safety information is shown below.

US SAEs, AEs, ADRs, and SSRs shall be sent to the following contact:

Email: GPSE@takeda.com

PQCs shall be sent to the following contact:

Phone: 1-877-345-8804

Email: TakedaPQCIntake@druginfo.com

11.0 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The proposed case series is designed to supplement a US Food and Drug Administration (FDA) post-marketing requirement for additional information about the safety profile of HyQvia use during pregnancy. The final study report will therefore be submitted to the US FDA. The report will be anonymized, and no identifiers will be reported to protect confidentiality. No information will be provided on address, race/ethnicity, date of birth or other specific calendar dates. The specific narratives for individual patients provided in the report will not be disseminated publicly. Only the summary would be potentially communicated beyond the regulatory agencies. To further prevent any potential identifiability, the summary will not mention the name of the commercial claims database.

12.0 REFERENCES

1. The National Institute of Allergy and Infectious Diseases. Primary immune deficiency diseases (PIDDs) [Internet]. 2022 [cited 2022 Nov 1]. Available from: https://www.niaid.nih.gov/diseases-conditions/primary-immune-deficiency-diseases-pidds.
2. Quinn J, Modell V, Orange JS, Modell F. Growth in diagnosis and treatment of primary immunodeficiency within the global Jeffrey Modell Centers Network. Allergy Asthma Clin Immunol 2022;18(1):19. DOI: 10.1186/s13223-022-00662-6.
3. Wasserman RL. Recombinant human hyaluronidase-facilitated subcutaneous immunoglobulin infusion in primary immunodeficiency diseases. Immunotherapy 2017;9(12):1035-1050. DOI: 10.2217/imt-2017-0092.
4. Borte M, Raffac S, Hrubisko M, et al. Long-term safety of facilitated subcutaneous immunoglobulin treatment in pregnant women with primary immunodeficiency diseases: results from a registry study. Immunotherapy 2022;14(8):609-616. DOI: 10.2217/imt-2021-0336.
5. MacDonald SC, Cohen JM, Panchaud A, McElrath TF, Huybrechts KF, Hernandez-Diaz S. Identifying pregnancies in insurance claims data: Methods and application to retinoid teratogenic surveillance. Pharmacoepidemiol Drug Saf 2019;28(9):1211-1221. DOI: 10.1002/pds.4794.

6. Palmsten K, Huybrechts KF, Mogun H, et al. Harnessing the Medicaid Analytic eXtract (MAX) to Evaluate Medications in Pregnancy: Design Considerations. PLoS One 2013;8(6):e67405. DOI: 10.1371/journal.pone.0067405.
7. Zhu Y, Bateman BT, Hernandez-Diaz S, et al. Validation of claims-based algorithms to identify non-live birth outcomes. Pharmacoepidemiol Drug Saf 2022. DOI: 10.1002/pds.5574.
8. He M, Huybrechts KF, Dejene SZ, et al. Validation of algorithms to identify adverse perinatal outcomes in the Medicaid Analytic Extract database. Pharmacoepidemiol Drug Saf 2020;29(4):419-426. DOI: 10.1002/pds.4967.
9. Palmsten K, Huybrechts KF, Kowal MK, Mogun H, Hernandez-Diaz S. Validity of maternal and infant outcomes within nationwide Medicaid data. Pharmacoepidemiol Drug Saf 2014;23(6):646-55. DOI: 10.1002/pds.3627.
10. Margulis AV, Palmsten K, Andrade SE, et al. Beginning and duration of pregnancy in automated health care databases: review of estimation methods and validation results. Pharmacoepidemiol Drug Saf 2015;24(4):335-42. DOI: 10.1002/pds.3743.
11. Margulis AV, Setoguchi S, Mittleman MA, Glynn RJ, Dormuth CR, Hernandez-Diaz S. Algorithms to estimate the beginning of pregnancy in administrative databases. Pharmacoepidemiol Drug Saf 2013;22(1):16-24. DOI: 10.1002/pds.3284.
12. Toh S, Mitchell AA, Werler MM, Hernandez-Diaz S. Sensitivity and specificity of computerized algorithms to classify gestational periods in the absence of information on date of conception. Am J Epidemiol 2008;167(6):633-40. DOI: 10.1093/aje/kwm367.
13. ISPE. International Society for Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practices (GPP). Revision 3. June 2015. https://www.pharmacoepi.org/resources/policies/guidelines-08027/.
14. EMA. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). 22 November 2017. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf.

ANNEX 1 LIST OF CODES FOR OUTCOME IDENTIFICATION

Table A.1: Congenital Malformation Groups.

GROUP	Malformation Subgroup	ICD-9 Dx	ICD-10 Dx
Cardiovascular Anomalies	Conotruncal Defects	745.0x, 745.1x, 745.2x	Q20.0-Q20.3, Q20.5, Q20.8, Q21.3
	Single Ventricle	745.3x	Q20.4
	Ventricular Septal Defect	745.4x	Q21.0
	ASD	745.5x AND no preterm	Q21.1 AND no preterm
	AV Septal Defect	745.6x	Q21.2
	Right sided defects	746.00, 746.01, 746.09, 746.1x, 746.2x, 746.83, 747.3x AND no preterm, 746.02 AND no preterm	Q22, Q22.0, Q22.1 AND no preterm, Q22.3-Q22.9, Q24.3, Q25.5 AND no preterm, Q25.6 AND no preterm, Q25.7x AND no preterm
	Left sided defects	747.1x, 747.2x, 746.3x, 746.5x, 746.7x, 746.81, 746.82	Q23, Q23.0, Q23.2, Q23.4, Q23.8, Q23.9, Q24.2, Q24.4, Q25.1x-Q25.4x
	PDA	747.0x and no preterm	Q25.0 AND no preterm
	PPHN	(416.0x or 747.83) and no preterm	(I27.0, P29.3x) AND no preterm
	Great cardiac veins	747.4 747.41 747.42	Q26.0-Q26.4
	Other cardiac	745.7x,745.8x, 746.8, 746.84-746.89	Q20.6, Q21.4, Q21.8, Q24.0, Q24.1, Q24.5, Q24.6, Q24.8, Q25.8
	Cardiac NOS	745, 745.9, 746, 746.9x (except 746.99), 747	Q20, Q20.9, Q21, Q21.9, Q24, Q24.9, Q25, Q25.9
Oral cleft		749.xx	Q35.x-Q37.x
Central Nervous System		740.xx-742.xx	Q00.x-Q07.x
Eye Anomalies		743.xx (except 743.6x, 743.8x)	Q10, Q10.4, Q10.7, Q11.x-Q15.x (except Q13.5)
Ear Anomalies		744.0x, 744.23, 744.3x	Q16.x-Q17.x (except Q17.0, Q17.3, Q17.5)
Other vascular (non-cardiac)		747.40, 747.49, 747.6x-747.9x (except 747.83)	Q26.5-Q26.9, Q27.x-Q28.x (except Q27.0, Q27.4)
Respiratory malformations		748.xx (except 748.1x, 748.3x)	Q30.0, Q30.1, Q31.0, Q32.x (except Q32.0), Q33.x (except Q33.1), Q34.x
Gastrointestinal		750.xx-751.xx (except 750.0x, 750.1x, 751.0x)	Q38.x-Q45.x (except Q38.1, Q38.2, Q38.3, Q43.0)
Genital (male and female)	Overall	752.xx (except 752.42, 752.52) (in addition, except 752.5x if preterm), 756.71	Q50.xx-Q52.xx (except Q52.3, Q52.5), Q53.0x, Q53.1xx AND no preterm, Q53.2xx AND no preterm, Q53.9 AND no preterm,

GROUP	Malformation Subgroup	ICD-9 Dx	ICD-10 Dx
			Q54.xx-Q56.xx (except Q55.22), Q64.0, Q79.4
	Hypospadias	752.61	Q54.x (except Q54.4)
	Cryptorchidism	752.5x (except 752.52) (in addition, except 752.5x if preterm)	Q53.xxx AND no preterm
Urinary		753.xx (except 753.7x), 756.71	Q60.xx-Q64.xx (except Q64.0, Q64.4), Q79.4
Musculoskeletal		754.1x, 754.2x, 756.xx (except 756.2x, 756.7x)	Q68.0, Q75.x-Q78.x (except Q76.5), Q79.0, Q79.1, Q79.6, Q79.8, Q79.9
Limb defects (includes hip)		755.xx (except 755.65, 755.63), 754.4x-754.8x (except 754.81, 754.82)	Q65.81, Q65.82, Q66.xx, Q68.1-Q68.8, Q69.x-Q74.x
Abdominal Wall		756.7x	Q79.2- Q79.5x
Other		757.0x, 757.1x, 759.xx (except 759.5x, 759.81-759.83)	Q80.8, Q80.9, Q86.x, Q89.xx
Chromosomal abnormalities		758xx, 75981, 75982, 75983	Q871, Q8711 Q8719 Q8740, Q87410, Q87418, Q8742, Q8743, Q900, Q901, Q902, Q909, Q910, Q911, Q912, Q913, Q914, Q915, Q916, Q917, Q920, Q921, Q922, Q925, Q9261, Q9262, Q927, Q928, Q929, Q930, Q931, Q932, Q933, Q934, Q935, Q937, Q9381, Q9388, Q9389, Q939, Q950, Q951, Q952, Q953, Q955, Q958, Q959, Q960, Q961, Q962, Q963, Q964, Q968, Q969, Q970, Q971, Q972, Q973, Q978, Q979, Q980, Q981, Q983, Q984, Q985, Q986, Q987, Q988, Q989, Q990, Q991, Q992, Q998, Q999

Table A2. Codes for pre-specified pregnancy and perinatal outcomes.

Outcome	ICD-9, ICD-10, and CPT codes
Spontaneous Abortion	ICD-9: 632 634.xx 637.xx CPT: 01965 59812 59820 59821 59830 ICD-10: O02 O021 O030 O031 O032 O033 O0330 O0331 O0332 O0333 O0334 O0335 O0336 O0337 O0338 O0339 O034 O035 O036 O037 O038 O0380 O0381 O0382 O0383 O0384 O0385 O0386 O0387 O0388 O0389 O039 O3102X3 O3102X4 O3102X5 O3102X9
Stillbirth	ICD-9: 656.40 656.41 656.43 V27.1 V27.4 V27.7

Outcome	ICD-9, ICD-10, and CPT codes
	CPT: 88016 ICD-10: O364 O364XX0 O364XX1 O364XX2 O364XX3 O364XX4 O364XX5 O364XX9 Z371 Z374 Z377
Preterm birth	ICD-9: 644.21, 765.0x-765.1x, 765.21-765.28 ICD-10: P0721, P0722, P0723, P0724, P0725, P0726, P0731, P0732, P0733, P0734, P0735, P0736, P0737, P0738, P0739, P072, P0720, O42012, P0501, P0502, P0503, P0504, P0505, P0506, P0511, P0512, P0513, P0514, P0515, P0516, P0701, P0702, P0703, P0714, P0715, P0716, P073, P0730 , O601, O4201, O42019, O42013
NICU admission	CPT Codes: 4168F, 4169F, 99291, 99292, 99295, 99296, 99297, 99468, 99469, 99471, 99472, 99477, 99478, 99479, 99480
Small for gestational age	ICD-9: 656.5x, 764.0x, 764.1x, 764.9x ICD-10: O365110 O365111 O365112 O365113 O365114 O365115 O365119 O365120 O365121 O365122 O365123 O365124 O365125 O365129 O365130 O365131 O365132 O365133 O365134 O365135 O365139 O365190 O365191 O365192 O365193 O365194 O365195 O365199 O365910 O365911 O365912 O365913 O365914 O365915 O365919 O365920 O365921 O365922 O365923 O365924 O365925 O365929 O365930 O365931 O365932 O365933 O365934 O365935 O365939 O365990 O365991 O365992 O365993 O365994 O365995 O365999 P0500 P0501 P0502 P0503 P0504 P0505 P0506 P0507 P0508 P0509 P0510 P0511 P0512 P0513 P0514 P0515 P0516 P0517 P0518 P0519 P059

ICD = International Statistical Classification of Diseases
CPT = Current Procedural Terminology

ANNEX 2 ENCEPP CHECKLIST

Doc.Ref. EMA/540136/2009
Adopted by the ENCePP Steering Group on 15/10/2018

ENCePP Checklist for Study Protocols (Revision 4)

Study title: Maternal and infant characteristics and outcomes following exposure to HyQvia during pregnancy: a case series study based on US claims data

EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	X	☐	☐	5.0
1.1.2 End of data collection[2]	X	☐	☐	5.0
1.1.3 Progress report(s)	☐	☐	X	
1.1.4 Interim report(s)	☐	☐	X	
1.1.5 Registration in the EU PAS Register®	X	☐	☐	5.0
1.1.6 Final report of study results.	X	☐	☐	5.0

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	X	☐	☐	6.0
2.1.2 The objective(s) of the study?	X	☐	☐	7.0
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	X	☐	☐	7.0
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	X	
2.1.5 If applicable, that there is no *a priori* hypothesis?	X	☐	☐	7.0

[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.

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)	X	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	X	☐	☐	8.2
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	X	
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))	☐	☐	X	
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)	☐	☐	X	10.0

Comments:

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

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	X	☐	☐	8.3.1

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	X	☐	☐	8.3.1; 8.9
5.3	Is exposure categorised according to time windows?	X	☐	☐	8.3.1
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	X	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	X	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	X	

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?	X	☐	☐	8.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	X	☐	☐	8.3.2
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)	X	☐	☐	8.3.2
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)	☐	☐	X	

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)	☐	☐	X	
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	X	
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	X	☐	☐	8.9

Comments:

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

Comments:

Section 9: Data sources		Yes	No	N/A	Section Number
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescr bing, claims data, self-report, face-to-face interview)	X	☐	☐	8.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	X	☐	☐	8.4
	9.1.3 Covariates and other characteristics?	X	☐	☐	8.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	X	☐	☐	8.4
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	X	☐	☐	8.4
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	X	☐	☐	8.4
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	X	☐	☐	8.3.1; 8.4
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	X	☐	☐	8.3.2; 8.4
	9.3.3 Covariates and other characteristics?	X	☐	☐	8.3.3; 8.4
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	X	

Comments:

Section 10: Analysis plan		Yes	No	N/A	Section Number
10.1	Are the statistical methods and the reason for their choice described?	☐	☐	X	8.7
10.2	Is study size and/or statistical precision estimated?	X	☐	☐	8.5
10.3	Are descriptive analyses included?	X	☐	☐	8.7

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

Comments:

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

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?	☐	☐	X	
12.1.2 Information bias?	X	☐	☐	8.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	X	☐	☐	8.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	X	☐	☐	8.5; 8.7; 8.9

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?	X	☐	☐	9.0

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	X	
13.3 Have data protection requirements been described?	X	☐	☐	9.0

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?	X	☐	☐	4.0

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)?	X	☐	☐	11.0
15.2 Are plans described for disseminating study results externally, including publication?	☐	☐	X	

Comments:

Name of the main author of the protocol: [redacted]

Date: 23 FEB 2023

Signature: _____