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Chief Medical Office and Patient Safety

Non-Interventional Study Protocol (PASS) with secondary use of data

Evaluation of pregnancy and infant outcomes in Mayzent patients using PRegnancy outcomes Intensive Monitoring (PRIM) data – The Mayzent-PRIM study

BAF312A2411
REDACTED PROTOCOL

Title	Evaluation of pregnancy and infant outcomes in Mayzent patients using PRegnancy outcomes Intensive Monitoring (PRIM) data – The Mayzent-PRIM study
Protocol version identifier	V1.0
Date of last version of protocol	8 March 2022
EU PAS register number	Study not registered
Active substance	Siponimod
Medicinal product	Mayzent (siponimod) 0.25 mg, 1 mg and 2 mg
Product reference	EMEA/H/C/004712
Procedure number	Not applicable

Name of marketing authorization holder(s)	Novartis Europharm Limited
Joint PASS	No
Research question and objectives	The primary objective: To estimate the proportion of major congenital malformations associated with exposure to siponimod immediately before (up to 10 days before LMP) and during pregnancy among (i) live births and (ii) live births, stillbirths, and termination of pregnancy for fetal anomaly (TOPFA)
Country (-ies) of study	Global
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List of abbreviations

AE	Adverse Event
CDC	Center for Disease Control and Prevention
CI	Confidence Interval
CRO	Contract Research Organization
DLP	Data Lock Point
EDD	Estimated date of delivery
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUROCAT	European Surveillance of Congenital Anomalies
FDA	Food & Drug Administration
FU	Follow-up
HCP	Healthcare professional
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
HA	Health Authority
HCP	Healthcare provider
ICF	Informed consent form
ICSR	Individual case safety report
IgG1κ	Immunoglobulin G1 kappa
IUGR	Intra-uterine growth restriction
LLQ	Lower limit of quantification
LMP	Last menstrual period
LTFU	Lost to follow-up
mAb	Monoclonal antibody
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	Marketing Authorization Holder
MAP	Manual for Argus Processing
MedDRA	Medical Dictionary for Regulatory Activities
MS	Multiple sclerosis
NIS	Non-Interventional Study
NOS	Not otherwise specified
NVS	Novartis
PASS	Post-Authorization Safety Study
PGD	Pharmacovigilance Guidance Document
PK	Pharmacokinetics
POPs	Patient Oriented Programs
PRAC	Pharmacovigilance and Risk Assessment Committee
PRIM	PRegnancy outcomes Intensive Monitoring
PSUR	Periodic Safety Update Report

PT	Preferred Term
PV	Pharmacovigilance
QPPV	Qualified Person for Pharmacovigilance
QS&E	Quantitative Safety & Epidemiology
RMP	Risk Management Plan
RMS	Relapsing multiple sclerosis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOPs	Standard Operating Procedures
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SUD	Secondary use of data
TFU	Targeted follow-up
TFUC	Targeted follow-up checklist
TOPFA	Termination of Pregnancy for Fetal Anomaly
WHO	World Health Organization

1 Responsible parties

Table 1-1 Responsible parties

Role	Person
Main protocol author(s)	[redacted] Novartis Pharmaceuticals Corporation. [redacted] [redacted] Novartis Pharma AG [redacted]
Study Lead	[redacted] Novartis Pharmaceuticals Corporation. [redacted]
Medical Safety Responsible	[redacted] Novartis Pharmaceuticals Corporation [redacted]
Principal investigator (PI)	Not applicable
MAH contact person	[redacted] Novartis Pharma AG [redacted]

2 Abstract

Title

Evaluation of pregnancy and infant outcomes in Mayzent patients using PRegnancy outcomes Intensive Monitoring (PRIM) data – The Mayzent-PRIM study

Version and date

Final v1.0, 8 March 2022

Name and affiliation of main author

[redacted]
Novartis Pharmaceuticals Corporation.
[redacted]

Rationale and background

Siponimod has been found to have a teratogenic and embryotoxic effect in animal studies (i.e. in rats). Furthermore, the receptor family modulated by siponimod (sphingosine 1 - phosphate receptor) is known to be involved in vascular formation during embryogenesis.

Data on siponimod exposure during pregnancy in the clinical program is very limited. Before initiation of siponimod treatment, women of childbearing potential are counselled regarding the potential for serious risk to the fetus and the need for effective contraception during treatment with siponimod. Since it takes approximately 10 days to eliminate siponimod from the body after stopping treatment, the potential risk to the fetus may persist if maternal exposure occurs peri-last menstrual period (LMP) or during pregnancy and therefore an evaluation of the drug exposure immediately before and during pregnancy is warranted.

This study is a non-interventional post-authorization safety study (PASS) making secondary use of PRIM data collected from spontaneous reports and clinical studies using a set of targeted checklists, structured follow-up, rigorous process of data entry and data quality control, and programmed aggregate analysis (Geissbühler et al 2020).

Research question and objectives

Considering siponimod's pharmacokinetic effect and defining "exposure to siponimod during pregnancy" as exposure to siponimod immediately before (i.e. up to 10 days before last menstrual period (LMP)) and during pregnancy, the study will assess the following objectives;

Primary objective:

- To estimate the proportion of **major congenital malformations** associated with exposure to siponimod immediately before (up to 10 days before LMP) and during pregnancy among (i) live births and (ii) live births, stillbirths, and termination of pregnancy for fetal anomaly (TOPFA).

Secondary objectives:

- To estimate the proportion of minor congenital malformations associated with exposure to siponimod immediately before (up to 10 days before LMP) and during pregnancy among live births and live births, stillbirths and TOPFA.
- To estimate the proportion of pregnancy outcomes (live births, stillbirths, spontaneous abortions, elective terminations) associated with exposure to siponimod immediately before (up to 10 days before LMP) and during pregnancy.
- To estimate the proportion of overall congenital malformations associated with exposure to siponimod immediately before (up to 10 days before LMP) and during pregnancy.
- To estimate the proportion of major congenital malformations by system organ class (SOC).
- To estimate the proportion of physical and cognitive development delays at 12 months of age among infants with maternal exposure to siponimod during pregnancy.
- To estimate the proportion of serious infections at 12 months of age among infants with maternal exposure to siponimod during pregnancy.

Study design

The Mayzent PRIM study is a secondary use of data, non-interventional study (NIS) based on Novartis' pharmacovigilance (PV) system leveraging data collected via PRIM using a set of targeted checklists with structured follow-up on pregnancies spontaneously reported to the Novartis global safety database (Argus).

Setting and study population

All prospective and retrospective pregnancy cases reported to the Novartis global safety database mentioning exposure to siponimod in multiple sclerosis (MS) patients will be considered for this study except cases reported as part of the siponimod pregnancy registry study (BAF312A2403).

The primary analysis cohort of interest will be the prospectively-reported pregnancies associated with maternal exposure during pregnancy or up to 10 days before LMP.

Retrospective pregnancy cases are defined as pregnancy cases with known pregnancy outcome [i.e. pregnancy outcome (live birth, stillbirth, spontaneous abortion, induced termination)] or known abnormal findings obtained from a prenatal test at the time of initial reporting to Novartis. Considering the high risk of bias resulting from retrospective reports, retrospective pregnancy cases will be processed, analyzed and presented separately from prospective cases. All necessary follow-up information will be presented for those retrospective cases.

Pregnancies with siponimod exposure prior to 10 days before LMP or exposure via father will be considered as siponimod unexposed cases but will processed and presented in a manner similar to the retrospective cases.

Variables

The key variables for the study are as follows:

- Primary outcome:
  - Major congenital malformations
- Secondary outcomes:
  - minor congenital malformation
  - live births, stillbirths, spontaneous abortions, elective terminations
  - major congenital malformations by system organ class (SOC)
  - physical and cognitive development delays at 12 months of age among infants
  - serious infections at 12 months of age among infants

In addition, the following variables, collected for the mother, may be presented or used in the analysis of the primary and or secondary objectives: race/ethnicity, age at LMP, co-medications and co-morbidities.

Data sources

This study utilizes pharmacovigilance data collected in the Novartis global safety database (Argus). All cases reported in Argus including those cases reported from clinical trials, spontaneous post-marketing reports, post-marketing observational studies, and patient oriented programs will be in scope. Reports include only pregnancy cases with a documented use of siponimod for MS during pregnancy or up to 10 days prior to LMP.

Study size

The study is descriptive in nature and will apply until a maximum of 10 years from market authorization or until 500 prospectively reported live births are assessed, whichever occurs first.

A sample size of 500 live births achieves 89% power to detect a prevalence increase of 3% using a two-sided binomial test for one sample proportion (significance level $\alpha = 0.05$) assuming a background prevalence for major malformation of 3% as reported in the US (CDC 2018).

Data analysis

A statistical analysis plan (SAP) detailing the analysis to be conducted will be developed prior to the first data lock point. Annual interim reports will be provided as described in the Milestones section below.

The primary Mayzent-PRIM analysis cohort will constitute of the prospectively reported pregnancies associated with maternal exposure during pregnancy or up to 10 days before LMP. Since retrospective cases may be subject to reporting biases but still be informative, these will be analyzed and reported separately.

Note that comparison with external background data will only be performed for the primary cohort, due to the high risk of bias for retrospective reports.

Data analysis will include the estimation of proportion and 95% confidence intervals (CI) of malformations and specific pregnancy and infant outcomes. The proportion of congenital malformations will be calculated amongst (i) live births, and (ii) live births, stillbirths, and TOPFA.

If sample size allows, additional subgroup analysis may be performed by timing of siponimod exposure in pregnancy. Further stratified analyses may be undertaken.

Milestones

Planned dates of study milestones:

Start date of data extraction: 25 March 2022

Date from which the analytical dataset is completely available: 25 March 2031

Interim report 1: June 2022

Interim report 2: June 2023

Interim report 3: June 2024

Interim report 4: June 2025

Interim report 5: June 2026

Interim report 6: June 2027

Interim report 7: June 2028

Interim report 8: June 2029

Interim report 9: June 2030

Final report of study results: June 2031

3 Amendments and updates

Date	Reason for update	Introduced changes	Section and title impacted (Current)
20-Aug-2020	PRIM concept sheet V02 HA request	Concept sheet V01 dated 04 March 2020 updated to align with HA request (PRAC assessment report dated 26 Jun 2020): The following additional secondary objectives were included: To estimate the proportions of - major congenital malformations by system organ class, - physical and cognitive development delays at 12 months of age among infants with maternal exposure to siponimod during pregnancy and - serious infections at 12 months of age among infants with maternal exposure to siponimod during pregnancy.	In concept sheet
02-Feb-2021	PRIM concept sheet V03 HA request	Concept sheet update to align with HA request (PRAC assessment report dated 14 Dec 2020): -clarification that no informed consent is required -clarification on inclusion/exclusion criteria -list of variables included -clarification in intensive monitoring scheme -details on data management -details on statistical analysis -update in limitations	In concept sheet
25-Mar-2021	V04 (final CS) HA request	Concept sheet update to align with HA request (PRAC assessment report dated 19 Mar 2021): -removal of criteria for performing analysis -addition of summary for infant AE	In concept sheet
08-Mar-2022	Protocol V1.0 Full protocol developed to allow for ENCEPP registration of the study.	Study protocol developed in alignment with previously agreed Concept Sheet (V04 dated 25 Mar 2021, endorsed by EMA on 20 May 2021) with additional clarifications included.	

4 Milestones

Annual interim reports of the Mayzent-PRIM study will be submitted on a yearly basis as a separate submission parallel to PSURs. A final report of the results of the PRIM will be submitted to Health Authorities and will be made public in the EU PAS Register according to the EU legislation and regulations.

The expected dates of study milestones, assuming a maximum duration of 10 years, are presented in Table 4-1.

Table 4-1 Planned dates of study milestones

Milestone	Planned date
Start of first data extraction	25 March 2022
End of final data extraction	25 March 2031
Interim report 1	June 2022
Interim report 2	June 2023
Interim report 3	June 2024
Interim report 4	June 2025
Interim report 5	June 2026
Interim report 6	June 2027
Interim report 7	June 2028
Interim report 8	June 2029
Interim report 9	June 2030
Final report of study results	June 2031

5 Rationale and background

Mayzent (siponimod) has been found to have a teratogenic and embryotoxic effect in animal studies (i.e. in rats). Furthermore, the receptor family modulated by siponimod (sphingosine 1 - phosphate receptor) is known to be involved in vascular formation during embryogenesis.

Data on siponimod exposure during pregnancy in the clinical program is very limited. Before initiation of siponimod treatment, women of childbearing potential are counselled regarding the potential for serious risk to the fetus and the need for effective contraception during treatment with siponimod. Since it takes approximately 10 days to eliminate siponimod from the body after stopping treatment, the potential risk to the fetus may persist if maternal exposure occurs peri-last menstrual period (LMP) or during pregnancy and therefore an evaluation of the drug exposure immediately before and during pregnancy is warranted.

Due to limited human data, Novartis added “Safety in pregnancy and lactation” as a missing information in the Risk Management Plan (RMP). Novartis initiated PRegnancy outcomes Intensive Monitoring (PRIM) pharmacovigilance activity to monitor the use of siponimod in pregnancy and to collect data on pregnancy and infant outcomes.

This Mayzent-PRIM study will utilize the data collected via the PRIM process to evaluate the effects of siponimod exposure during pregnancy on pregnancy and infant outcomes.

6 Research question and objectives

The overall objective of the Mayzent-PRIM study is to evaluate data on a) pregnancy and infant outcomes related to siponimod exposure in MS patients immediately before (up to 10 days before last menstrual period (LMP)) and during pregnancy; and b) infant outcomes at birth and 12 months post-delivery. The study utilizes data collected on pregnancies reported to the Novartis global safety database and followed up via the PRIM process (Geissbühler et al 2020).

The below objectives will be assessed focusing primarily on prospectively reported pregnancies associated with maternal exposure. 'Exposure to siponimod during pregnancy' will be defined using siponimod pharmacokinetic effect and taken as exposure to siponimod immediately before (i.e. up to 10 days before last menstrual period (LMP)) and during pregnancy.

The findings from this study will be used to evaluate the potential risk of reproductive toxicity, according to the Risk Management Plan (RMP).

6.1 Primary objective

- To estimate the proportion of major congenital malformations associated with exposure to siponimod immediately before (up to 10 days before LMP) and during pregnancy among (i) live births and (ii) live births, stillbirths, and termination of pregnancy for fetal anomaly (TOPFA).

6.1.1 Primary outcome

- Major congenital malformation

6.2 Secondary objectives

- To estimate the proportion of minor congenital malformations associated with exposure to siponimod immediately before (up to 10 days before LMP) and during pregnancy among live births and live births, stillbirths and TOPFA.
- To estimate the proportion of pregnancy outcomes (live births, stillbirths, spontaneous abortions, elective terminations) associated with exposure to siponimod immediately before (up to 10 days before LMP) and during pregnancy.
- To estimate the proportion of overall congenital malformations associated with exposure to siponimod immediately before (up to 10 days before LMP) and during pregnancy.
- To estimate the proportion of major congenital malformations by system organ class (SOC).
- To estimate the proportion of physical and cognitive development delays at 12 months of age among infants with maternal exposure to siponimod during pregnancy.
- To estimate the proportion of serious infections at 12 months of age among infants with maternal exposure to siponimod during pregnancy.

6.2.1 Secondary outcomes

- minor congenital malformation
- live births, stillbirths, spontaneous abortions, elective terminations
- major congenital malformations by system organ class (SOC)
- physical and cognitive development delays at 12 months of age among infants

- serious infections at 12 months of age among infants

7 Research methods

7.1 Study design

The Mayzent-PRIM study is a secondary use of data, non-interventional study (NIS) based on Novartis' pharmacovigilance (PV) system leveraging data collected via PRIM on pregnancies spontaneously reported to the Novartis global safety database.

PRIM is an enhanced pharmacovigilance data collection and processing system via a set of targeted checklists, structured follow-up, rigorous process of data entry and data quality control, and programmed aggregate analysis. This enables computer-programmed estimation of pregnancy outcomes within the collected pregnancy cases, such as the proportion of infants/fetuses with major congenital malformation, pregnancy and birth outcomes as well as infant outcomes through the first 12 months of life. Since it is based on the PV system, PRIM has been shown to be able to collect worldwide information more quickly and form larger samples for analysis than a registry and with better quality than that of conventional spontaneous reporting (Geissbühler et al 2020). The uniform regulatory pharmacovigilance framework to collect data and the use of existing pharmacovigilance systems removes several operational barriers and hence cuts the time needed to accrue the required number of patients. Novartis therefore considers PRIM to be the most "time-effective" and scientifically and operationally feasible method to obtain data on pregnancy and infant outcomes.

All "prospective" and "retrospective" pregnancy cases (defined in Table 7-2) exposed to siponimod and reported to the Novartis global safety database via clinical trials, spontaneous post-marketing reports, post-marketing observational studies, and patient oriented programs are considered for this study.

The enhanced FU process will apply until a maximum of 10 years from market authorization or until 500 live births are processed under this program, whichever occurs first. If after 10 years, no adequate precision is achieved, this program will be terminated and the degree of FU reduced to conventional pharmacovigilance FU. In the case an earlier interim report would allow a conclusion on the potential risk of reproductive toxicity in siponimod-treated patients, and such conclusion is endorsed by concerned health authorities (HAs), the program would be stopped earlier. After enhanced FU process stops, all subsequent new cases will be processed as per MAP and applicable SOP.

Note that since this is a secondary use of pharmacovigilance data study, no informed consent is required.

7.1.1 PRegnancy outcome Intensive Monitoring (PRIM)

PRIM is a non-interventional data collection process based on pharmacovigilance and does not impose a treatment, diagnostic/ therapeutic procedure, or a clinical visit schedule.

Whenever possible (based on the consent of the reporter to provide further information and availability of contact details), cases will be followed and processed following the PRIM principle.

Physicians and patients will be informed of the need to report all cases of pregnancy to Novartis, with or without adverse outcome, in the educational material to healthcare provider (HCP) and patients.

7.1.1.1 Inclusion criteria

Pregnancy cases prospectively reported to Novartis (i.e. reported before pregnancy outcome has occurred) via spontaneous post-marketing report sources, post-marketing observational studies and patient-oriented programs, and reports from the Novartis clinical trials program are eligible for inclusion in PRIM analysis and results' summary. Retrospective cases, although followed up in a similar manner to the prospective cases, will be analyzed and reported separately due to the associated reporting bias. Data collected using the targeted FU checklist are entered into the Novartis global safety database (Argus) per Novartis standard operating procedures (SOPs) governing pharmacovigilance safety procedures.

Table 7-2 provides details on the prospective vs. retrospective cases classification for PRIM.

7.1.1.2 Exclusion criteria

Criteria for exclusion from PRIM

- Patients that upon initial report refuse to be contacted to obtain FU information.
- Indirect cases (reported by someone other than the patient or the HCP) for which the reporter refuses to provide FU information and the patient or HCP cannot be identified based on the information provided.
- Cases lacking details on patient or reporter contact information.
- This program is not applicable for pregnancies of female partners of male patients taking siponimod. Such cases will continue to be processed as per manual of Argus processing (MAP). Siponimod does not cause effects on sperm morphology or male fertility in animals; it also does not elicit any known genotoxic effect, and the potential exposure of a female partner via seminal fluid of a male patient has been estimated to be several folds lower than the doses at which teratogenicity has been observed in animal studies (the women of childbearing potential (WOCBP) exposed to siponimod (0.012 ng/ml) via seminal fluid of a treated male partner, the safety margins for fetal toxicities (as identified in the rabbit EFD and the rat PPND studies) are 583-fold, respectively 2083-fold).
- Pregnancies of female patients who discontinued siponimod prior to the 10 days washout timeframe (>10 days between end of treatment and LMP).

7.1.1.3 Follow-up schedule and targeted follow-up checklists

A specific set of targeted FU checklists will enable the collection of all necessary information to evaluate safety data on siponimod exposure and associated pregnancy, fetal and infant outcomes. Development, approval and distribution of these targeted FU checklists will follow the applicable SOP.

Targeted FU Checklists collect the minimum information necessary, which include the core data points required for analysis.

Cases are followed up as per the schedule in Table 7-1, using targeted FU checklists.

Table 7-1 Follow-up schedule using targeted FU checklists*

FU number	Checklist name	Date of collection	Type of information collected	Additional attempts in case of no response at initial contact
FU 1	Multiple sclerosis pregnancy initial Checklist	As soon as possible after initial report, or at initial report if possible	Baseline characteristics and demographics of the mother	At least 3 attempts, at maximum of 1 month apart
FU 2	Multiple sclerosis Pregnancy outcome FU checklist	Between EDD and EDD+30 days	Information related to the delivery and neonate details	At least 3 attempts, at a maximum of 1 month apart
FU 3	Multiple sclerosis and Infant Health Status FU checklist	EDD + 3 months	Information related to infant health status and development	At least 3 attempts, at maximum of 1 month apart
FU 4	Multiple sclerosis and Infant Health status FU checklist	EDD + 12 months	Information related to infant health status and development	At least 3 attempts, at maximum of 1 month apart

* FU schedule and requirements as per Mayzent product guidance document (PGD) V1.2 effective 13-Aug-2021.
EDD – estimated date of delivery

7.1.2 Adjudication process

Each individual case safety report (ICSR) with reported potential congenital anomaly, i.e. each individual case reporting pregnancy outcome as live birth with a congenital malformation or other outcome (spontaneous abortion, elective termination or stillbirth) for which there is evidence of a birth defect, the patient data are forwarded to independent (external) adjudicators. These cases will be identified from the Novartis global safety database as cases with an AE with seriousness classification “congenital anomaly” and with fetal outcome coded as “congenital anomaly major”, “congenital anomaly minor” or “congenital anomaly NOS (structural)”. An independent expert adjudication panel will be created to evaluate the available data to determine whether a reported malformation should be categorized as major, minor or not otherwise specified (NOS) according to the European Surveillance of Congenital Anomalies (EUROCAT) definitions and Metropolitan of Atlanta Congenital Defects Program (MACDP) classification criteria.

The adjudication panel will consist of three external members, experts in the fields of reproductive toxicology and teratology. Two experts will be responsible for adjudication of individual cases and the third expert will provide the final adjudication in case of difference of

opinion by the two experts. The adjudication panel will be selected from a list of available experts in the field of teratology and reproductive toxicology and with no affiliation to Novartis.

The outcome per EUROCAT classification will be considered as the main classification entered in the Novartis global safety database accordingly. The MACDP classification will be kept in the notes. Reports with insufficient information for adjudication will be classified as "congenital anomaly not otherwise specified (NOS)".

The full adjudication process, role and responsibilities and data handling will be described in a separate adjudication charter.

7.2 Setting and study population

The primary analysis cohort of interest will be the prospectively-reported pregnancies associated with maternal exposure during pregnancy or up to 10 days before LMP.

Retrospective pregnancy cases are defined as pregnancy cases with known pregnancy outcome [i.e. pregnancy outcome (live birth, stillbirth, spontaneous abortion, induced termination)] or known abnormal findings obtained from a prenatal test at the time of initial reporting to Novartis. Considering the high risk of bias resulting from retrospective reports, retrospective pregnancy cases will be processed, analyzed and presented separately from prospective cases. All necessary follow-up information will be presented for those retrospective cases.

Pregnancies with siponimod exposure prior to 10 days before LMP or exposure via father will be considered as siponimod unexposed cases but will processed and presented in a similar way to the retrospective cases.

Table 7-2 provides details on the prospective vs. retrospective case classification for Mayzent-PRIM.

Table 7-2 Mayzent-PRIM prospective and retrospective case classification[a]

Timing and results of prenatal testing	Mayzent PRIM case classification
Pregnancy outcome has not occurred, and prenatal tests have not been performed at the time of reporting or entry[b]	Prospective
Prenatal testing was performed at the time of entry[b], results have not been received by provider/patient/Novartis	Prospective
Prenatal test results were available, and were known to be normal or results were not specified at the time of entry[b]	Prospective
Prenatal test results were available and were known to be abnormal at the time of entry[b]	Retrospective
Outcome of pregnancy known at the time of entry[b]	Retrospective

a) Definitions of retrospective and prospective cases as per EMA guidance
b) 'Entry' is considered the date of initial report received by Novartis for this case

7.2.1 Inclusion criteria – Mayzent-PRIM study analysis

All pregnancy cases with exposure to siponimod for MS and reported to Novartis global safety database via clinical trials, spontaneous post-marketing report sources, post-marketing observational studies, and patient-oriented programs are eligible for inclusion in the Mayzent-PRIM study.

7.2.2 Exclusion criteria – Mayzent-PRIM study analysis

Pregnancy cases identified via pregnancy registry study (BAF312A2403) and cases reported to Novartis for non-MS indications will be excluded from Mayzent-PRIM study.

7.3 Variables

Key exposure, outcome and potential confounding variables are defined in Section 7.3.1, Section 7.3.2 and Section 7.3.3 respectively.

Information provided in the initial report along with data collected using target follow up (FU) checklists will be considered. The target FU checklists will mainly focus on maternal information and include questions about pregnancy history, history of onset and other characteristics of disease, and current medication use. The FU checklists also captured data on other variables such as demographics, gestational age, co-morbidities, concomitant medications, disease severity and duration, and other relevant potential confounders. Exposure data will be collected at enrollment, between expected date of delivery (EDD) and EDD + 30 days, EDD + 3 months and EDD + 12 months.

7.3.1 Exposure

Trimesters will be defined, based on the dose administrated, as follows:

- "Peri-LMP": LMP- 10 days to LMP,
- "1st trimester": LMP to LMP+84 days,
- "2nd trimester": LMP+85 days to LMP+182 days,
- "3rd trimester": LMP+183 days and beyond.

Cases will be classified by timing of siponimod exposure i.e. as "Overall" vs. "Peri-LMP only" vs. "At least 1st trimester" vs. "Only after 1st trimester".

7.3.2 Outcomes

Table 7-3 lists the variables collected via the Pregnancy Outcome FU checklists. These will be mapped, to the extent possible, to the Pregnancy and fetal/infant outcomes defined according to the Manual of Argus Processing (MAP) as described in Table 7-4 and Table 7-5. Note that some variables are kept as part of the narrative i.e. entered only as free text.

Table 7-3 Pregnancy outcome follow-up checklist variables

Variable	Data captured
Medication taken by the mother	Name, dose, route of administration, start/stop, trimester of exposure
Prenatal test	Name, date, abnormal (Yes/No/Not available), result (free text)
Pregnancy outcome	
Live birth	Date of birth, Gestation weeks at birth Timing: full-term vs. premature vs. post mature Normal (yes/no) Neonate demographics (at birth): Gender, weight (kg/lb and percentile),

Variable	Data captured
	Length (cm/in and percentile), Head circumference (cm/in and percentile) Small for gestational age*** (Yes/No) Apgar Score 1min, 5min and 10 min Infant status (alive/deceased) Date of death Cause of death
Termination	Date, Gestation weeks Type: spontaneous abortion/miscarriage vs. induced termination (therapeutic reason vs. elective termination) Medical problem: Blighted ovum, molar pregnancy, ectopic pregnancy, Other (free text)
Stillbirth	Date, Gestation weeks Autopsy (Yes/No/Unknown), free text
Anomalies in the baby or fetus	Anomaly notes (yes/no/unknow) Description (free text) Anomaly of known origin (No/Yes specify) If least one major anomaly (Yes/ No only minor/ None /Unknown)
Complication during or after delivery	None vs. Intrauterine death vs. Other specify

*** Yes, if the birth weight is <10th percentile for the GA (Battaglia and Lubchenco 1967)

Low birth weight will be derived based on the weight at birth. If the weight is <2500g (i.e. 5 pound and 8 ounces) this will be considered low (Cutland C et.al., 2017).

Pregnancy and fetal/infant outcomes that are defined according to Manual of Argus Processing (MAP) are listed in Table 7-4 and Table 7-5. These will be used in the tabulations and analyses of primary or secondary outcomes.

Table 7-4 Definition of key pregnancy outcomes

Outcome	Definition
Full-term live birth	The patient gives birth to live neonate between 37 and 42 completed weeks of gestation.
Premature live birth **	The patient gives birth to a live neonate before 37 completed weeks of gestation.
Post-mature live birth	The patient gives birth to a live neonate after 42 completed weeks of gestation
Elective termination **	Termination of pregnancy due to choice of mother of an otherwise normal fetus.
Therapeutic termination	If an abortion procedure occurs due to abnormal fetus, fetal death or risk to the mother.
Spontaneous abortion **	The fetus is spontaneously aborted (prior to 22 weeks gestation); prior fetal status via prenatal testing may or may not be known.
Stillbirth **	The patient gives birth to a still born (no signs of life) at or after 22 weeks of gestation is completed
Abortion not otherwise specified (NOS)	Used in cases where spontaneous / elective / therapeutic abortion is not specified.

Outcome	Definition
Outcome pending	The outcome of the pregnancy is not known (outcome/due date is pending, or queries are outstanding)
Lost to F/U	No further information is received regarding pregnancy outcome even after pursuing appropriate number of follow-ups for a case

** To be used in the analysis of the secondary outcomes

Source: Manual for Argus Processing - MAP chapter 13 Pregnancy cases, version 10.2, effective 15Jul2021

Table 7-5 Definition of key fetal/infant outcomes

Fetal outcome Argus terminology	Definition
Normal baby/normal infant	Live birth where there is no mention of fetal abnormalities or perinatal complications (regardless of gestational age at birth).
Congenital anomaly major*	A congenital abnormality that requires medical or surgical treatment, has a serious adverse effect on health and development, or has significant cosmetic impact. (Based on the EUROCAT definitions)
Congenital anomaly minor**	A congenital abnormality that does not require medical or surgical treatment, does not seriously affect health and development, and does not have significant cosmetic impact. (Based on the EUROCAT definitions)
Congenital/other (structural) abnormality, NOS	Reported congenital anomaly without diagnostic information or other structural anomalies not well described.
Perinatal complication (nonstructural)	Non-structural perinatal complication of fetus: from 22 weeks of gestation (154 days) to 7 days after birth.
Post-perinatal complication (nonstructural)	Non-structural post-perinatal complications of fetus: following 7 days after birth.
Abnormality, other (nonstructural)	Non-structural abnormalities not related to delivery, other non-structural anomalies not well described or anomalies reported as normal variant
Fetal death / intrauterine death	Fetal death confirmed by pre-natal tests, followed by a spontaneous abortion or requiring a therapeutic abortion, or stillbirth.
Blighted ovum	Absence of an embryo in a normal-appearing gestational sac visible on ultrasound.
Ectopic pregnancy	Implantation of the embryo outside the uterine cavity
Hydatidiform mole	Gestational trophoblastic disease where a non-viable fertilized egg or embryo implants in the utero and grows into a mass (instead of a fetus).
Infant status unknown	Information regarding the infant is not known
Outcome pending	The outcome of the fetus/infant is not known (queries are pending or due date is in the future)
Lost to follow up	No further information is received regarding pregnancy outcome even after pursuing appropriate number of follow-ups for a case or there is no consent to contact reporter.

*To be used in the analysis of the primary outcome

** To be used in the analysis of the secondary outcomes

Source: Manual for Argus processing - MAP chapter 13 Pregnancy cases, version 10.2, effective 15Jul2021

Table 7-6 lists variables collected via the Infant health status follow-up during first year of life FU checklists that will be used in the evaluation of secondary outcomes if sufficient data is reported.

Table 7-6 Other variables to be used as secondary outcomes – Infant health status follow-up during first year of life

Variable	Data captured
Infant status	Living or deceased, if deceased: date of death, age at death, cause of death
Infant demographics	Gender, age at measurement, weight, length, head circumference
Infant health status	Any malformations identified since birth, Did malformations reported at or since birth resolve by themselves, Infection requiring hospitalization**
Breastfeeding	Current breastfeeding status yes/no/weaned;
Developmental delay	Yes/No, if yes, age at diagnosis, physical, mental/cognitive with free-text comments
Vaccination reaction	Yes/No with free text

** To be used in the analysis of the secondary outcomes

7.3.3 Other Variables

Other variables that are collected via FU checklists and may be used for tabulations of key patient characteristics or further evaluation e.g. stratified analyses are listed in Table 7-7.

Any adverse event occurring in the mother during pregnancy related to the pregnancy or in the infant will be collected and captured, per standard PV process, in the event tab in Argus.

Full list of variables to be used in the analyses including any required transformations and calculations will be detailed in the SAP.

Table 7-7 Other variables and confounders

Variable	Data captured
Country	Country of report
Maternal Age (years)	Maternal age (years), continuous and categorical (specific age categories for analysis to be defined in SAP)
Maternal Race/Ethnicity	Maternal (Caucasian, Black, Asian, Hispanic, Other)
Maternal Height	Maternal height (cm or in)
Maternal body weight	Maternal body weight at LMP (kg or lb)
Paternal characteristics	Age, Race/Ethnicity, Height, Weight, collected as the maternal characteristics detailed above
Number of fetuses	Number of fetuses (1, 2, >=3)
Other medications taken by the mother during pregnancy	Medication name, dose/times a day, administration route, indication, start and stop date, trimester of exposure
Contraception	Yes/no/unknown use of contraception, specific method if known, contraception failure Yes/no/unknown
Prenatal tests	Test name, date, any abnormal results Yes/No/Not available, free text for test result

Variable	Data captured
Maternal risk factors/conditions that may affect the outcome of the current pregnancy (Yes/No)	Smoking Alcohol Hypertension Seizure Eclampsia Pre-eclampsia History of infertility
Maternal risk factors/conditions that may affect the outcome of the current pregnancy (Yes/No and free text)	Recreational Drugs Heart disease Diabetes Thyroid disorder Infections Environmental or occupational exposure Fertility treatment Autoimmune disease Other, specify
Duration of MS disease	Duration of MS disease
Patient mobile	Yes/no
EDSS	EDSS
Relapse just before/during pregnancy	Yes/No/Unknown; if yes date; treatment given as free-text
Current course of MS	Primary progressive; Relapsing remitting; Secondary progressive; Other with free text

7.4 Data sources

Cases reported to the Novartis global safety database will include those cases reported from clinical trials, spontaneous post marketing reports, post marketing observational studies and patient oriented programs. Data on the cases received by Novartis Safety will be captured and processed using the follow-up schedule and questionnaires as described in Section 7.1.

Specific data entry conventions are applied, as described in the MAP and PGD, to allow retrieval of exposure, outcome and confounders:

- For exposure, trimesters of administration are entered as tick box by the case processor based on the dose administration information provided in the case.
- Information relative to congenital malformation and pregnancy outcome (Spontaneous abortions, stillbirths, elective terminations) are entered in Argus as birth type and pregnancy outcome as described in Table 7-4 and Table 7-5 based on the case reported verbatim and adjudication (as applicable).
- Low birth weight will be derived from the weight at birth
- Small for gestational age (SGA), serious infections will be identified used MedDRA grouping among events reported in baby.
- Confounders and risk factors will be identified mainly based on the medical history/current medical conditions and adverse events based on MedDRA term groupings.

Cases included in the pregnancy registry study (BAF312A2403), will be excluded from the Mayzent-PRIM analysis cohorts.

All reports whether submitted by patients or healthcare professionals (HCPs) will be considered.

Even though the primary analysis cohort of interest includes only the prospectively reported pregnancies associated with maternal exposure during pregnancy or up to 10 days before LMP; all cases outside this cohort will still be processed in the similar manner.

7.4.1 Data linkage in Novartis global safety database

As per the MAP, individual cases of mother and fetus/infant or father and fetus/infant are linked with each other in Argus and can be identified for data extraction.

7.5 Study size/power calculation

In the US, the prevalence of birth defects was reported to be 3% of live births (CDC 2018). The European surveillance of congenital anomalies (EUROCAT) reported a prevalence rate of 2.3% of live births (EUROCAT 2016). Worldwide about 6% of all newborn infants have serious birth defects of genetic or partially genetic origin and the annual prevalence of congenital malformations was 3.6% of births (Christianson et al 2006).

Table 7-8 provides the power to detect various proportion differences depending on the background prevalence and the number of live births (i.e. sample size).

For example, if 500 live births are included, assuming a background prevalence of 3% (i.e. the prevalence of birth defects reported in US (CDC 2018), this program will have 89% power (two-sided test, α set at 0.05) to detect an 3% increase in risk over the background prevalence (i.e. an observed proportion of 6%). In other terms, if the true birth defects proportion is 6%, with a sample size of 500 live births, in 89% of the cases the observed two-sided 95% confidence interval (CI) will exclude 3%. Targeting a 500 live births sample size is therefore considered appropriate.

As discussed in Section 7.1, this program will apply until a maximum of 10 years from market authorization or 500 live births, whichever occurs first. If after 10 years, no adequate precision is achieved, this program will be terminated since the impact of the risk would be very low and no conclusion would be reached. When the PRIM program is terminated, pregnancy reports will be followed-up via regular Novartis PV as per SOP.

Table 7-8 Power to detect a difference in proportion by sample size and background rate

		Power to detect a difference of*				
Number of cases	**Background prevalence**					
N=	**%**	**0.5%**	**1%**	**2%**	**3%**	**6%**
300	**1%**	0.10	0.26	0.68	**0.91**	**>0.99**
	2%	0.08	0.20	0.54	**0.82**	**>0.99**
	3%	0.07	0.15	0.43	0.72	**0.99**
	6%	0.06	0.11	0.29	0.53	**0.96**
400	**1%**	0.15	0.41	**0.85**	**0.98**	**1.00**
	2%	0.08	0.23	0.64	**0.90**	**>0.99**
	3%	0.08	0.18	0.53	**0.83**	**>0.99**

		Power to detect a difference of*				
Number of cases	**Background prevalence**					
N=	**%**	**0.5%**	**1%**	**2%**	**3%**	**6%**
	6%	0.05	0.11	0.32	0.59	**0.98**
500	**1%**	0.14	0.42	**0.89**	**0.99**	**1.00**
	2%	0.08	0.25	0.71	**0.94**	**1.00**
	3%	0.08	0.21	0.61	**0.89**	**>0.99**
	6%	0.06	0.13	0.39	0.70	**>0.99**

* Derived using two-sided binomial test at α=0.05 (PASS v11)

7.6 Data management

This Mayzent-PRIM study is based on pregnancy cases reported in the Novartis global safety database (Argus). Cases are followed-up using targeted FU checklists. When a new case is created in Argus, it is assigned a unique Argus ID which allows information across data sets to be linked.

Data collected through the targeted checklists will be entered into the Novartis global safety database per Novartis standard operating procedures (SOPs) governing pharmacovigilance safety procedures and MAP. As per the MAP, individual cases of mother and fetus/infant are linked with each other in Argus and can be identified for data extraction. Concomitant or prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Specific database conventions and deviation to MAP for all information required in the PRIM FU checklists will be described in the product specific PGD.

7.7 Data analysis

Novartis will perform all analyses using SAS version 9.4 (or above). A statistical analysis plan (SAP) detailing the analysis to be conducted for Mayzent-PRIM will be developed prior to the first data lock point.

The primary Mayzent-PRIM analysis cohort will constitute of the prospective cases as described in Table 7-2. Since retrospective cases may be subject to reporting biases but still be informative, these will be analyzed and reported separately. Note that comparison with external background data will only be performed for the primary cohort, due to the high risk of bias for retrospective reports.

Note that comparison with external background data will only be performed for the primary cohort, due to the high risk of bias for retrospective reports. Missing data will not be imputed.

Continuous variables will be summarized presenting number of non-missing values, mean, standard deviation, median and range; for categorical variables numbers and proportions will be reported among non-missing. When presented, the 95% confidence intervals for proportions will be constructed based on the exact (Clopper-Pearson) method.

Annual interim data will be provided as per Section 4.

7.7.1 Analysis of primary and secondary endpoints

Analysis of the Mayzent-PRIM data will include estimation of proportion (and 95% confidence interval) of malformations (major [primary endpoint], minor, and overall), and of specific pregnancy outcomes such as, live births, spontaneous abortions, stillbirths and elective terminations. The proportion of congenital malformations will be calculated using two denominators: (1) live births; and (2) live births, stillbirths and TOPFA (termination of pregnancy for fetal anomaly).

Proportion will be estimated overall and by pre-specified timing of drug exposure in pregnancy (as defined in Section 7.3.1).

In addition, major congenital malformations will also be summarized by SOC based on latest available MedDRA classification.

The proportion of physical and cognitive development delays and serious infections at 12 months of age among infants with maternal exposure to siponimod during pregnancy will be provided.

In addition, adverse events reported in infant cases will be summarized including proportions of low birth weight, intrauterine growth retardation and any reported foetotoxic effect.

7.7.2 Case description

The cohort attrition will be presented providing the overall vs. prospective vs. retrospective number of pregnancy cases and fetuses retrieved at the time of the analysis cut-off date via maternal and paternal exposure.

In addition, the following information will be summarized

- Case disposition status (outcome known, pending, and lost to follow-up),
- Maternal characteristics (age (continuous), country/region),
- Reporter type (Health Care Professional (HCP), non-HCP).

7.7.3 Comparison to external data source

Findings from the Mayzent-PRIM study will be compared using unadjusted method to background frequencies observed in the general population i.e. proportion and 95% CI obtained in Mayzent-PRIM study will be presented side by side to the references (e.g. EUROCAT and Center for Disease Control and Prevention's (CDC's) Metropolitan Atlanta Congenital Defects Program (MACDP)).

7.8 Quality control

7.8.1 Data quality management

The standard operational procedures for pharmacovigilance will be followed to perform quality control of the data entered to the Novartis global safety database. Additional training for case processors specific to PRIM data collection and entry and additional checks will be implemented on the core data elements to ensure data quality and support for programmatic data summarization.

7.8.2 Data recording and document retention

Data recording and documentation retention will follow standard operating procedures defined for collection and retention of data in the Novartis global safety database.

Reporting activities will follow the SOPs related to programming in the global Novartis programming system.

7.9 Limitations of the research methods

The limitations of PRIM are in line with those of any voluntary post marketing reporting systems:

- Prospectively reported pregnancies are actively followed up multiple times through the pregnancy and post EDD, however, certain data on certain endpoints could still be missing due to loss to follow up, incomplete or insufficient information.
- The pregnancies collected via PRIM may be biased in an unknown direction i.e. they may not be representative of the pregnancies exposed to siponimod since only patients made aware of PRIM via the educational material may be more likely to report and not all patients may get this educational material.
- Since data collection is limited to siponimod patients, no internal comparator is available.
- Direct comparison between estimates of congenital malformation obtained through PRIM with external reference general populations is hampered by potential differences in data collection methods or underlying population characteristics. The results can nevertheless be put in context with a range of estimates from the general population coming from different data sources with a focus on those which use similar data collection methods as PRIM (Geissbuhler et al 2020).
- Specific Patient Oriented Programs could drive inclusion of siponimod patients for example with specific baseline characteristics such as low socio-economic strata, that could influence pregnancy outcomes. The data from these patients could bias the results of the PRIM analysis in either direction
- Last but not least the main limitation is the inability to establish causality and the possible existence of unknown confounding factors.

7.10 Other aspects

A steering committee which will include an external expert panel responsible for evaluation of aggregate data and review and approval of the data generated by the program will be formed at the initiation of this program. The external panel will include epidemiologists, neurologists, perinatologists, pediatricians and/or neonatologists.

8 Protection of human subjects

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2016), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke, et al 2007), and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct' (European Medicines Agency 2016).

Further, this study is a secondary use of pharmacovigilance data that is collected as per good pharmacovigilance practices (GVP) guidelines and local data privacy laws and de-identified to remove all personal data.

9 Management and reporting of adverse events/adverse reactions

Since this study utilizes spontaneously reported data that is entered into the Novartis safety database, no additional safety data collection procedures are required.

10 Plans of disseminating and communicating study results

The study protocol and the results will be publicly disclosed according to the applicable regulation and the applicable Novartis SOPs.

Upon study completion and finalization of the study report, the results of this NIS may be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

Interim and final reports will be prepared by Novartis Medical Safety department and submitted to the EMA as per the RMP commitment. Such reports will use the Non-interventional Study Report template, simplified as necessary according to the data accumulated.

11 References (available upon request)

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Battaglia F, Lubchenco L. A practical classification of newborn infants by weight and gestational age. J Pediatr, 71(2):159-163.

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Center for Disease Control and Prevention (2020). Center for Disease Control and Prevention, Data on birth defects. Available at https://www.cdc.gov/ncbddd/birthdefects/data.html. Accessed on 13 July, 2020.

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Cutland C, Lackritz E, Mallett-Moore T, et.al. (2017). Low birth weight: Case definition and guideline for data collection, analysis, and presentation of maternal immunization safety data. Vaccine; 35(48Part A): 6492-6500

EUROCAT (2019)] Prevalence tables for congenital anomalies. Available at http://www.eurocat-network.eu/newprevalencetables. Accessed on 13 July, 2020.

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Geissbühler Y, Rezaallah B and Moore A (2020). An alternative to product-specific pregnancy registries? PRIM; PRegnancy Intensive Monitoring. Reprod Toxicol.; 94:13-21.

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International Society for Pharmacoepidemiology (2016). Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf; 25:2-10.

Rothman K (2012). Episheet - spreadsheets for analyzing epidemiologic data [Online]. Available at http://krothman.hostbyet2.com/Episheet.xls. Accessed on 7 July, 2020.

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12 Annexes

12.1 Annex 1 – List of stand-alone documents

None

12.2 Annex 2 – ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Evaluation of pregnancy and infant outcomes in Mayzent patients using PRegnancy outcomes Intensive Monitoring (PRIM) data – The Mayzent-PRIM study

EU PAS Register® number: not yet registered
Study reference number (if applicable): BAF312A2411

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]	☒	☐	☐	4
1.1.2 End of data collection[2]	☒	☐	☐	4
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	4
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	4

[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 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.6 Final report of study results.	☒	☐	☐	4

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	6
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)	☒	☐	☐	5
2.1.2 The objective(s) of the study?	☒	☐	☐	6
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	6
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	7.7

Comments:

No hypotheses to be tested in the study, primary objective is a descriptive analysis

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)	☒	☐	☐	7.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	7.1,7.2
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	7.7
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))	☒	☐	☐	7.7
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)	☒	☐	☐	9

Comments:

There will not be any measures of association due to the descriptive nature of this study.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	7.4
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	4, 7.5
4.2.2 Age and sex	☒	☐	☐	7.2
4.2.3 Country of origin	☒	☐	☐	7.2
4.2.4 Disease/indication	☒	☐	☐	7.2,7.3
4.2.5 Duration of follow-up	☒	☐	☐	7.4
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	7.2

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)	☒	☐	☐	7.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	7.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	7.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	7.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	7.7

Comments:

No additional measures to ensure validity of measurement are planned.

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?	☒	☐	☐	6.1.1, 6.2.1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	7.3.2
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)	☒	☐	☐	7.4.2
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)	☐	☐	☒	

Comments:

No HTA-relevant outcomes

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	7.7
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	7.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	7.9

Comments:

To be elaborated further in the SAP

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)	☒	☐	☐	7.7

Comments:

Further subgroup analyses to be specified in the SAP

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: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	7.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	7.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	7.4
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)	☒	☐	☐	7.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	7.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	7.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	7.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	7.4, 7.4.2
9.3.3 Covariates and other characteristics?	☒	☐	☐	7.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

The full questionnaires for the data collection are also referenced in the Annex and available as stand-alone documents

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	7.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	7.5
10.3 Are descriptive analyses included?	☒	☐	☐	7.7
10.4 Are stratified analyses included?	☒	☐	☐	7.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

No control for confounding as this is a descriptive analysis. Further measures such as stratified analyses etc. to be elaborated further in the SAP

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)	☒	☐	☐	7.6
11.2 Are methods of quality assurance described?	☒	☐	☐	7.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	7.4.2

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?	☒	☐	☐	7.9
12.1.2 Information bias?	☒	☐	☐	7.9
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).	☒	☐	☐	7.9
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)	☒	☐	☐	7.5

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?	☒	☐	☐	8
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.3 Have data protection requirements been described?	☒	☐	☐	8

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?	☒	☐	☐	3

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)?	☒	☐	☐	7.7, 10
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	10

Comments:

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

Date: 1/February/2022

Signature: _____

12.3 Annex 3 – Additional information

Not applicable