NOVARTIS

Chief Medical Office and Patient Safety

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

REDACTED PROTOCOL

Inclisiran (CKJX839A12011)

Title	Monitoring of pregnancy outcomes in women treated with inclisiran: a non-interventional study
Protocol version identifier	v02 – Amendment 2
Date of last version of protocol	28-Sep-2022
EU PAS register number	EUPAS42905
FDA PMR number	4186-3
Active substance	Inclisiran (KJX839)
	ATC code: C10AX16
Medicinal product	Leqvio 284 mg solution for injection in pre-filled syringe
Product reference	EU procedure number: EMEA/H/C/005333
	US FDA procedure number: NDA 214012

Name of marketing authorization holder(s)	Novartis Europharm Limited, Ireland (EU) Novartis Pharmaceutical Corporation (US)
Joint PASS	No
Research question and objectives	The overall objective of this non-interventional study is to collect data on pregnancy outcomes in patients treated with inclisiran during or prior to pregnancy. The primary objective: • To estimate the proportion of major congenital malformations among pregnancies exposed to inclisiran during pregnancy reported to Novartis amongst (i) live births and (ii) live births plus still births plus termination of pregnancy for fetal anomaly (TOPFA).
Country (-ies) of study	Worldwide (countries where the product is marketed)
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List of abbreviations

AE	Adverse Event
ASCVD	Atherosclerotic Cardiovascular Disease
CDC	Center for Disease Control and Prevention
CI	Confidence Interval
CIOMS	Council for International Organisations of Medical Sciences
CRO	Contract Research Organization
DLP	Data Lock Point
EDD	Estimated date of delivery
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food & Drug Administration
FH	Familial Hypercholesterolemia
FU	Follow-up
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
HA	Health Authority
HCP	Healthcare provider
HeFH	Heterozygous Familial Hypercholesterolemia
ICD-10	International Classification of Diseases, version 10
IUGR	Intra-uterine growth restriction
IV	Intravenous
LDL-C	Low-Density Lipoprotein Cholesterol
LMP	Last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	Marketing Authorization Holder
MAP	Manual for Argus Processing
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Study
NOS	Not otherwise specified
NVS	Novartis
PASS	Post-Authorization Safety Study
PCSK9	Proprotein Convertase Subtilisin/Kexin type 9
PGD	Pharmacovigilance Guidance Document
POPs	Patient Oriented Programs
PRAC	Pharmacovigilance and Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
QPPV	Qualified Person for Pharmacovigilance
QS&E	Quantitative Safety & Epidemiology
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGA	Small for Gestational Age

SOPs	Standard Operating Procedures
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TOPFA	Termination of Pregnancy for Fetal Anomaly
WHO	World Health Organisation

1 Responsible parties

Table 1-1 Responsible parties

Role	Person
Main protocol author(s)	[redacted] MSc, MSc ETH [redacted] Novartis Pharma AG [redacted] [redacted] MD [redacted] Novartis Pharma AG [redacted] [redacted] MD [redacted] Novartis Pharma AG [redacted]
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2 Abstract

Title

Monitoring of pregnancy outcomes in women treated with inclisiran: a non-interventional study

Version and date

v02, 28-Sep-2022

Name and affiliation of main author

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Rationale and background

Inclisiran is a double-stranded small interfering ribonucleic acid (siRNA) that inhibits the production of proprotein convertase subtilisin/kexin type 9 (PCSK9). Inclisiran has been evaluated in a clinical development program as an adjunct to diet and maximal tolerated statin treatment for the treatment of adults with primary hyperlipidemia with existing atherosclerotic cardiovascular disease (ASCVD), risk equivalent patients or heterozygous familial hypercholesterolemia (HeFH) who are not able to achieve goals to reduce LDL-C. The current indication of inclisiran in the European Union (EU) includes adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet, in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. The EU marketing authorisation for inclisiran was granted on 09 December 2020. The current inclisiran EU label discourages its use during pregnancy (EU SmPC wording states: *As a precautionary measure, it is preferable to avoid the use of inclisiran during pregnancy*). Therefore a considerable uncertainty exists regarding whether inclisiran may actually be used by pregnant women.

Based on the absence of direct or indirect harmful effects in reproductive toxicity studies, Novartis does not consider pregnancy as a safety concern. However, due to limited human data, Novartis agreed to add “Use in pregnancy and breastfeeding” as a missing information in the Risk Management Plan (RMP). Novartis included this non-interventional study (NIS) as an additional pharmacovigilance activity in the RMP to monitor actual use of inclisiran in pregnancy and to collect pregnancy and infant outcomes. The study utilizes a structured approach for data collection with targeted checklists to obtain follow-up information from exposed pregnancies with improved collection, quality, and processing of information.

This post-authorisation safety study (PASS) is a worldwide, single-arm descriptive non-interventional study that collects prospective and retrospective data in women exposed to inclisiran during pregnancy. It uses 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. Data collected in the FU checklists are in line with data elements to include when designing a pregnancy registry, as recommended by the US Food and Drug Administration. The study enables estimation of pregnancy outcomes within the prospectively 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. This non-interventional study design 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. Novartis therefore considers this NIS to be the most “time-effective” and scientifically and operationally feasible method to obtain data on pregnancy and infant outcomes after maternal exposure to inclisiran.

Research question and objectives

Considering lack of specific preclinical safety findings, the primary objective was defined as follows:

• To estimate the proportion of major congenital malformations among pregnancies exposed to inclisiran during pregnancy prospectively reported to Novartis amongst (i) live births and (ii) live births plus still births plus termination of pregnancy for fetal anomaly (TOPFA).

Secondary objectives:

• To estimate the proportion of major congenital malformations among pregnancies exposed to inclisiran prior to the last menstrual period (LMP) prospectively reported to Novartis amongst (i) live births and (ii) live birth plus still births and TOPFA.

• To compare the frequency of major congenital malformations among pregnancies exposed to inclisiran during pregnancy and prior to LMP with the background frequencies in the general population and primary hyperlipidemia patients obtained from external data sources and/or literature.

• To estimate the proportion in pregnancies exposed to inclisiran prior to LMP and during pregnancy (and compare, if available, with background frequencies in the general population and primary hyperlipidemia patients) of other adverse pregnancy, birth and infant outcomes.

Study design

This is a non-interventional study (NIS) utilizing a structured approach for data collection with targeted checklists to obtain follow-up information from exposed pregnancies with improved collection, quality, and processing of information compared to the traditional PV approach. The study is based on pregnancy case reporting in the Novartis global safety database. The data collection is governed within the routine pharmacovigilance processes, and data for this study are extracted from the global safety database for the aims of this study. The study is thus classified as being secondary use of data. Patient recruitment will be based on spontaneous reporting of pregnancy cases from mothers, HCPs, or other persons. To maximize evidence generation in this observational study, pregnancy cases originating from other sources will also be included, i.e. Novartis clinical trials, post-marketing observational studies, patient-oriented programs (if applicable), and scientific publications.

Setting and study population

All prospective and retrospective pregnancy cases exposed to inclisiran during pregnancy or prior to LMP reported to the Novartis global safety database (Argus) will be eligible for the study. This includes cases from spontaneous post-marketing reporting (including personal communication with healthcare providers), Novartis clinical trials, post-marketing observational studies, patient-oriented programs (if applicable), and scientific publications. The pregnancy cases from spontaneous post-marketing reporting will be collected from healthcare providers (HCPs) and non-HCPs through interview(s) using targeted FU checklists. Data will be collected at enrollment, at the end of 2nd / beginning of 3rd trimester (between 24 and 30 weeks of pregnancy), between expected date of delivery (EDD) and EDD + 30 days, EDD + 3 months and EDD + 12 months.

Pregnancy cases prospectively reported to Novartis via spontaneous post-marketing report sources, post-marketing observational studies, patient-oriented programs (if applicable) and Novartis clinical trials are eligible for inclusion in the analysis and results' summary.

Retrospective pregnancy cases are defined as pregnancy cases with known pregnancy outcome at the time of initial reporting to Novartis, i.e. pregnancy outcome or abnormal findings from a prenatal test are known. Cases originating from scientific publications (e.g. case reports) will also be considered as retrospective. Retrospective pregnancy cases will be analyzed and presented separately from the prospective cases in acknowledgement of the high risk of reporting bias resulting from retrospective reporting. Necessary follow-up information will be collected for such retrospective cases.

Exclusion criteria:

• Cases for whom adequate follow-up information cannot be obtained

• Pregnancies of female partners of male patients taking inclisiran

Variables

Primary outcome: Major congenital malformations among pregnancies exposed to inclisiran during pregnancy

Secondary outcomes: Major congenital malformations among pregnancies exposed to inclisiran prior to LMP; minor congenital malformations; overall congenital malformation (major + minor + unspecified); pregnancy outcomes: live birth, stillbirth, spontaneous abortion, induced termination, ectopic pregnancy, molar pregnancy; adverse birth outcomes: preterm births, low birth weight, neonatal death; other infant outcomes and pregnancy outcomes including e.g. infant death, small for gestational age (SGA), intrauterine growth restriction (IUGR), developmental delays, neonate and infant hospitalizations, adverse drug reactions, breastfeeding status and breastfeeding exposures.

Proportions of all outcomes will be stratified by timing of inclisiran exposure: 1) during pregnancy (operationally defined as the last dose of inclisiran received at or after the date of the LMP); 2) prior to LMP (last dose of inclisiran received prior to the LMP). Very short half-life of inclisiran in plasma does not justify defining a separate peri-LMP exposure period, so it will not be assessed as an exposure category in this NIS. Subgroup analyses by further exposure categories (e.g. last dose received within 6 months prior to LMP, during 1st trimester only etc.) may be undertaken if sufficient sample size is accrued.

In addition, the following characteristics of inclisiran use will be collected: dose, route, indication for use, start and stop dates. Other variables such pregnancy history, history of onset and other characteristics of disease, socio-demographics, gestational age, co-morbidities, maternal concomitant medications, neonate and infant medications, disease severity and duration, and other relevant potential confounders will be collected.

Data sources

Cases reported to the Novartis safety database will include those cases reported from spontaneous post-marketing reports, post-marketing observational studies, (if applicable) patient support programs, Novartis clinical studies, and scientific publications. Reports may be submitted by patients or HCPs, however, only reports from non-HCPs that consent to contacting their HCP to confirm the data reported in the FU checklists would be included in the analyses. Reports include only pregnancy cases with a documented use of inclisiran during pregnancy or prior to LMP.

Study size

The proposed NIS will apply until 10 years from market authorization or 500 prospectively reported live births with known status of malformations, whichever occurs first.

If the prevalence of major malformations of 3% is applied we can expect to observe approximately 15 cases of major malformations among the 500 prospectively reported live births with known status. For the primary study objective, the calculated prevalence of major malformations among live births in this scenario will be 3.0% (95%CI 1.8-4.9%).

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 along with the PSURs, or as stand-alone documents.

Data analysis will focus on the prospective cases because the retrospective cases are subject to different reporting biases. Retrospective pregnancy cases will be analyzed and presented separately from the prospective cases.

Data analysis will include the estimation of proportion and 95%CI of malformations, and specific pregnancy and infant outcomes. The proportion of congenital malformations will be calculated amongst: (1) live births; (2) live births, stillbirths and TOPFA.

To consider a more restrictive definition of "prospective cases" as per FDA guidance, a subgroup analysis will be performed in women without any prenatal test before initial reporting. If sample size allows, additional subgroup analysis may be performed by timing of inclisiran exposure in pregnancy and concomitant pregnancy exposure to statins or other lipid-lowering medications. Further stratified analyses may be undertaken. Details of the planned analyses will be provided in the SAP.

Observed frequencies of pregnancy outcomes in inclisiran-exposed patients will be compared with background frequencies in the general population as well as primary hyperlipidaemia patients not exposed to inclisiran. The background frequencies will be obtained from the literature or appropriate

external data sources (e.g. EUROCAT, Metropolitan Atlanta Congenital Defects Program (MACDP), etc).

Formal comparative analyses estimating measure of effect (e.g. risk ratios) may be undertaken if the reference population is judged to be adequate for such an analysis and an adequate number of prospective pregnancy cases is available for meaningful interpretation (at the latest when 100 cases are reached). Details will be included in the SAP.

The decision regarding the appropriate external data source for a comparative analysis will be made based on the geographical distribution of included cases, and presence of key confounders in the available external data sources (e.g. age and demographic variables, comorbidities, obstetric history etc.) that would allow to minimize possible biases related to the background risk of major malformations and other adverse outcomes in the inclisiran-treated population. Details will be included in the SAP.

Milestones

Planned dates of study milestones:

Start date of data collection; i.e. start date of data extraction: 31 December 2021

Last date of data collection; i.e. date from which the analytical dataset is completely available: 31 January 2031

Interim report 1: 31 March 2022 (integrated in PSUR with DLP 31-December-2021)

Interim report 2: 31 March 2023 (integrated in PSUR with DLP 31-December-2022)

Interim report 3: 31 March 2024*

Interim report 4: 31 March 2025*

Interim report 5: 31 March 2026*

Interim report 6: 31 March 2027*

Interim report 7: 31 March 2028*

Interim report 8: 31 March 2029*

Interim report 9: 31 March 2030*

Interim report 10: 31 March 2031*

Registration in the EU PAS register: 30 September 2021

Final report of study results: 31 July 2031

*The interim reports 3 to 10 will be integrated in PSURs as appropriate. Dates for the reports refer to planned submission dates.

3 Amendments and updates

Amendment 1

Amendment rationale

On 10-Jun-2022, the US Food and Drug Administration (FDA) submitted comments and recommendations on the initial version of this study protocol (v00). Based on the request from FDA, the study changes as reflected in Table 3-1 were included into the amended protocol version (v01) finalized on 29-Jun-2022.

Amendment 2

Amendment rationale

On 29-Jul-2022, the US Food and Drug Administration (FDA) provided one additional comment to the amendment v01. Based on the request from FDA, an additional design change was included into the amended protocol version (v02) as reflected in the table below.

In addition, on 08-Sep-2022, due to data privacy concerns and protecting patient privacy as per the General Data Protection Regulation in the European Union and European Economic Area, Novartis has taken the company position to *not* collect demographic data for the father when an exposed pregnancy is reported. This change required an update to the Inclisiran Pregnancy Baseline Follow-Up Checklist (see Section 12.1) and was also included into the amended protocol version (v02) as reflected in the following table. However, it will not have an impact on the Statistical Analysis Plan or the study analyses.

Table 3-1 Study protocol amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	29 June 2022	1 'Responsible parties'	Update	Update of MAH contact person
2	29 June 2022	2 'Abstract'	Update	Update to reflect the changes in Amendment 1
3	29 June 2022	4 'Milestones'	Update	Alignment of the interim report dates to the planned submission dates of the interim reports: previous version of the table reflected internal finalization dates rather than actual submission dates.
4	29 June 2022	5 'Rationale and background'	Update	Minor changes of wording
5	29 June 2022	6.2 'Secondary objectives'	Amendment	Neonate and infant hospitalizations were added to the secondary study objectives
6	29 June 2022	7.1 'Study design'	Update	Wording was added to clarify the plan for recruiting study participants (i.e. spontaneous reporting)

Number	Date	Section of study protocol	Amendment or update	Reason
7	29 June 2022	7.2 ‘Setting and study population’	Amendment	Wording on sources of pregnancy cases was updated. The inclusion criteria were broadened to consider also cases from Novartis clinical trials and from scientific publications. Wording on exclusion criteria updated to reflect that incomplete cases would still be included in the NIS
8	29 June 2022	7.3 ‘Variables’	Amendment	Added one additional data collection time point planned for the mid of pregnancy (20 weeks)
9	29 June 2022	7.3.2 'Outcomes'	Amendment	Clarification of definitions of key pregnancy and neonate/infant outcomes including references (update of text and tables 7-2, 7-3, and 7-4). Added neonate and infant hospitalizations to the list of other pregnancy and birth outcomes.
10	29 June 2022	7.3.3 ‘Other variables’	Amendment	Neonate and infant medications and other infant characteristics were added to the list of other key variables and confounders.
11	29 June 2022	7.4 ‘Data sources’	Update	Wording on sources of pregnancy cases in the Novartis safety database was updated.
12	29 June 2022	7.4.1 'Intensive follow up scheme'	Amendment	In case the pregnancy baseline follow-up checklist is received already during the first trimester (i.e. until 84 days = 12 completed weeks of gestation), another data collection will occur at mid of second trimester (20 weeks of pregnancy). Clarification that alternative contact information of physicians and health care providers are collected to minimize losses-to-FU.
13	29 June 2022	7.9 ‘Limitations’	Update	Added that alternative contact information of physicians and health care providers will be collected to minimize losses-to-follow-up.

Number	Date	Section of study protocol	Amendment or update	Reason
14	29 June 2022	11 ‘References’	Update	Updated section with new references
15	28 September 2022	1 ‘Responsible parties’	Update	Update of MAH contact person
16	28 September 2022	2 ‘Abstract’	Update	Update to reflect the changes in Amendment 2
17	28 September 2022	7.3 ‘Variables’	Amendment	Amendment to reflect the changes in intensive follow-up scheme: the additional data collection point was expanded to cover the entire study population and will take place between 24 and 30 weeks of pregnancy (rather than week 20, cf. change number 8 in this table)
18	28 September 2022	7.3.3 ‘Other variables’	Amendment	Removed collection of paternal characteristics
19	28 September 2022	7.4.1 'Intensive follow up scheme'	Amendment	The additional data collection point will cover the entire study population and will take place between 24 and 30 weeks of pregnancy (rather than week 20, cf. number 12 in this table). Clarification added that 4 follow-up attempts will not apply to this additional data collection point.
20	28 September 2022	7.4.1 'Intensive follow up scheme'	Update	Further clarification added to Table 7-6 regarding specific data collected at various follow-up timepoints.
21	28 September 2022	12.1 ‘Annex 1 – List of stand-alone documents’	Update	Updated to reflect new versions of Pregnancy Baseline checklist (updated to reflect changes in Amendment 2); and Pregnancy Outcome checklist (only document name corrected, no changes to checklist itself)

4 Milestones

The collection of the pharmacovigilance data began with the first launch of inclisiran worldwide (i.e. 01 February 2021). The first data extraction (=start of data collection for the NIS) will happen at the data lock point for the second inclisiran periodic safety update report (PSUR) at 31 December 2021.

Annual interim reports of the NIS will be submitted on a yearly basis (integrated in PSUR or as stand-alone documents, as appropriate).

A stand-alone final report of the results of the NIS will be submitted to Health Authorities and will be made public in the EU PASS registry according to the PASS regulations.

The underlying data collection process will apply until a sample of 500 prospective pregnancy cases exposed to inclisiran with known pregnancy outcome is available or 10 years from the first inclisiran launch worldwide, whichever occurs first. Thereafter, this study will be complete, the final report issued and the degree of follow-up reduced to conventional pharmacovigilance.

If an earlier interim report allows a conclusion on the reproductive safety in inclisiran-treated patients, and such a conclusion is endorsed by the concerned health authorities, the study would be completed at an earlier date. After the enhanced follow-up process is completed, all subsequent cases will be processed as per conventional pharmacovigilance processes.

The expected dates of study milestones, assuming a duration of 10 years, are presented in the following table.

Table 4-1 Planned dates of study milestones

Milestone	Planned date
Start of data collection	31 December 2021
End of data collection	31 January 2031
Interim report 1 (integrated in PSUR with DLP 31 December 2021)	31 March 2022
Interim report 2 (integrated in PSUR with DLP 31 December 2022)	31 March 2023
Interim report 3[a]	31 March 2024
Interim report 4[a]	31 March 2025
Interim report 5[a]	31 March 2026
Interim report 6[a]	31 March 2027
Interim report 7[a]	31 March 2028
Interim report 8[a]	31 March 2029
Interim report 9[a]	31 March 2030
Interim report 10[a]	31 March 2031
Final report of study results (stand-alone report)	31 July 2031
Registration in the EU PAS register	30 September 2021

[a)] The interim reports 3 to 10 will be integrated in PSURs as appropriate. Dates on above table for the reports refer to planned submission dates.

5 Rationale and background

Inclisiran is a double-stranded small interfering ribonucleic acid (siRNA) that inhibits the production of proprotein convertase subtilisin/kexin type 9 (PCSK9). Reduced intrahepatic PCSK9 decreases low-density lipoprotein cholesterol (LDL-C) receptor recycling and increases expression of the LDL-C receptor on the hepatocyte cell surface, thereby increasing LDL-C uptake and lowering LDL-C levels in the circulation (Dyrbus et al 2020, Fitzgerald et al 2017).

Inclisiran has been evaluated in a clinical development program as an adjunct to diet and maximal tolerated statin treatment for the treatment of adults with primary hyperlipidemia with existing atherosclerotic cardiovascular disease (ASCVD), risk equivalent patients or heterozygous familial hypercholesterolemia (HeFH) who are not able to achieve goals to

reduce LDL-C (Ray et al 2017). The current indication of inclisiran in the European Union (EU) includes adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet, in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated statin dose, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. The EU marketing authorisation for inclisiran was granted on 09 December 2020.

The current inclisiran label discourages its use during pregnancy (EU SmPC wording states: *As a precautionary measure, it is preferable to avoid the use of inclisiran during pregnancy*). Therefore a considerable uncertainty exists regarding whether inclisiran may actually be used by pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. There are limited clinical data from the use of inclisiran in pregnant women.Based on the absence of direct or indirect harmful effects in reproductive toxicity studies, Novartis does not consider pregnancy as a safety concern. However, due to limited human data, Novartis agreed to add “Use in pregnancy and breastfeeding” as a missing information in the Risk Management Plan (RMP).

Novartis included this non-interventional study as an additional pharmacovigilance activity in the RMP to monitor actual use of inclisiran in pregnancy and to collect pregnancy and infant outcomes. The study utilizes a structured approach for data collection with targeted checklists to obtain follow-up information from exposed pregnancies with improved collection, quality, and processing of information (Geissbühler et al 2020).

Pregnancy registries have been a frequently used method to collect safety information on human exposure during pregnancy. However, these registries have limitations, including difficulties in recruiting patients and poor follow-up rates, which negatively affects public health because of delays or failures to obtain meaningful results (Bird et al 2018, Gelperin et al 2016).

A systematic review of pregnancy registries for 34 products authored by United States Food and Drug Administration (FDA) staff found that, for products rarely used during pregnancy, registry enrolment was low. Worldwide, spontaneous reports collected information from a larger number of pregnancies than pregnancy exposure registries: a median registry enrolment was 36 pregnancies compared with a median of 450 spontaneous reports of pregnancy exposure contemporaneously received by manufacturers (Bird et al 2018). A recently published study by Novartis authors showed that using enhanced pharmacovigilance methods, prospectively collected information on pregnancy outcomes can be collected faster and from a larger patient population than using a registry and with a better quality than that of conventional spontaneous reports (Geissbühler et al 2020). One major limitation of the spontaneous report data is that they are collected passively, relying on healthcare providers and patients to submit reports and the information received is often incomplete or of low quality and consistency for analysis. Therefore, the methodological approach of this NIS was designed by Novartis in order to address these limitations.

This is a non-interventional post-authorisation safety study (PASS) using 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. Data collected in the FU checklists are in line with data elements to include when designing a pregnancy registry, as recommended by the US Food and Drug Administration (2019). The study design enables computer-programmed

estimation of pregnancy outcomes within the prospectively 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. Observed frequencies of pregnancy outcomes in inclisiran-exposed patients may then be compared with background frequencies in the general population as well as primary hyperlipidaemia patients not exposed to inclisiran, obtained from the literature or appropriate external data sources.

This non-interventional study design 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 this NIS to be the most “time-effective” and scientifically and operationally feasible method to obtain data on pregnancy and infant outcomes after maternal exposure to inclisiran.

6 Research question and objectives

The overall objective of this NIS is to collect data on pregnancy outcomes in patients treated with inclisiran during pregnancy or prior to pregnancy (including congenital malformations, spontaneous abortions, stillbirths and other adverse birth outcomes) as well as infant outcomes at 3 and 12 months post-delivery, including breastfeeding status and exposures, neonatal and infant deaths and developmental delays.

The findings from this study will be used to evaluate the missing information 'Use in pregnancy and breastfeeding', according to the RMP.

6.1 Primary objective

Considering lack of specific preclinical safety findings, the primary objective was defined as follows:

- To estimate the proportion of major congenital malformations among pregnancies exposed to inclisiran during pregnancy prospectively reported to Novartis amongst (i) live births and (ii) live births plus still births plus termination of pregnancy for fetal anomaly (TOPFA).

6.1.1 Primary outcome

Major congenital malformations among pregnancies exposed to inclisiran during pregnancy

6.2 Secondary objectives

- To estimate the proportion of major congenital malformations among pregnancies exposed to inclisiran prior to the last menstrual period (LMP) prospectively reported to Novartis amongst (i) live births and (ii) live birth plus still births and TOPFA.
- To compare the frequency of major congenital malformations among pregnancies exposed to inclisiran during pregnancy and prior to LMP with the background frequencies in the general population and primary hyperlipidemia patients obtained from external data sources and/or literature.
- To estimate the proportion in pregnancies exposed to inclisiran prior to LMP and during pregnancy (and compare, if available, with background frequencies in the general population and primary hyperlipidemia patients):
  - Minor congenital malformations among (i) total live births, (ii) live birth plus stillbirths and TOPFA
  - Overall congenital malformations (major + minor + unspecified) among (i) total live births, (ii) live birth plus stillbirths and TOPFA
  - Pregnancy outcomes including live birth, stillbirth, spontaneous abortion, induced termination, ectopic pregnancy, molar pregnancy
  - Other adverse birth outcomes including preterm births, low birth weight, neonatal death
  - Other infant outcomes and pregnancy outcomes, including e.g. infant death, neonate and infant hospitalizations, small for gestational age (SGA), intrauterine growth restriction (IUGR), developmental delays, adverse drug reactions, breastfeeding status and breastfeeding exposures

6.2.1 Secondary outcomes

- Major congenital malformations among pregnancies exposed to inclisiran prior to LMP
- Among pregnancies exposed to inclisiran prior to LMP and during pregnancy:
  - Minor congenital malformation
  - Overall congenital malformation (major + minor + unspecified)
  - Pregnancy outcomes: live birth, stillbirth, spontaneous abortion, induced termination, ectopic pregnancy, molar pregnancy
  - Adverse birth outcomes: preterm births, low birth weight, neonatal death
  - Other infant outcomes and pregnancy outcomes including e.g. infant death, neonate and infant hospitalizations, SGA, IUGR, developmental delays, adverse drug reactions, breastfeeding status and breastfeeding exposures

7 Research methods

7.1 Study design

This is a worldwide, single-arm descriptive non-interventional study that collects prospective and retrospective data in women exposed to inclisiran during pregnancy. It uses a structured approach for data collection with targeted checklists to obtain follow-up information from exposed pregnancies with improved collection, quality, and processing of information compared to the traditional PV approach (Geissbühler et al 2020).

The study is based on pregnancy case reporting in the Novartis global safety database (Argus). All "prospective" and "retrospective" pregnancy cases reported to the Novartis global safety database (Table 7-1) via spontaneous reports and other post-marketing sources are included. Data from checklists are entered into the Novartis global safety database per Novartis standard operating procedures (SOPs) governing pharmacovigilance safety procedures and Manual for Argus Processing (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. The data collection is governed within the routine pharmacovigilance processes, and data for this study are extracted from the global safety database for the aims of this study. The study is thus classified as beeing secondary use of data.

Patient recruitment will be based on spontaneous reporting of pregnancy cases from mothers, HCPs, or other persons. To maximize evidence generation in this observational study, pregnancy cases originating from other sources will also be included, i.e. Novartis clinical trials, post-marketing observational studies, patient-oriented programs (if applicable), and scientific publications.

7.2 Setting and study population

All prospective and retrospective pregnancy cases exposed to inclisiran during pregnancy or prior to LMP reported to the Novartis global safety database (Argus) will be eligible for the NIS. This includes cases from spontaneous post-marketing reporting (including personal communication with healthcare providers), Novartis clinical trials, post-marketing observational studies, patient-oriented programs (if applicable), and scientific publications. The pregnancy cases from spontaneous post-marketing reporting may be collected from healthcare providers (HCPs) and non-HCPs; however, if a non-HCP reports a pregnancy case and doesn't consent to contacting their HCP to confirm the data reported in the FU checklists, they are not included

in the analyses (see also exclusion criteria below). The frequency of such cases will be noted in the reports.

7.2.1 Inclusion criteria

Cases reporting maternal exposure to inclisiran during or prior to pregnancy will be included in the study. This includes cases from spontaneous post-marketing reporting (including personal communication with healthcare providers), Novartis clinical trials, post-marketing observational studies, patient-oriented programs (if applicable), and scientific publications. Pregnancy cases prospectively reported to Novartis via spontaneous post-marketing report sources, post-marketing observational studies,patient-oriented programs (if applicable) and Novartis clinical trials are eligible for inclusion in the analysis and results' summary.

Retrospective pregnancy cases are defined as pregnancy cases with known pregnancy outcome at the time of initial reporting to Novartis, i.e. pregnancy outcome or abnormal findings from a prenatal test are known. Cases originating from scientific publications (e.g. case reports) will also be considered as retrospective. Retrospective pregnancy cases will be analyzed and presented separately from the prospective cases in acknowledgement of the high risk of reporting bias resulting from retrospective reporting. Necessary follow-up information will be collected for such retrospective cases.

Table 7-1 provides details on the prospective vs. retrospective case classification in this NIS.

Table 7-1 Prospective and retrospective case definition[a]

Timing and results of prenatal testing	Classification
Pregnancy outcome has not occurred and prenatal tests have not been performed at the time of reporting	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	Prospective
Prenatal test results were available and were known to be abnormal at the time of entry	Retrospective
Outcome of pregnancy known at the time of report	Retrospective

a) Definitions of retrospective and prospective cases as per EMA (2006) guidance

b) 'Entry' is considered the date of initial report received by Novartis for cases included in the NIS

7.2.2 Exclusion criteria

Criteria for exclusion from sending FU checklists to the reporters include:

- Patients that upon initial report refuse to be contacted to obtain FU information, refuse to provide contact details of the HCPs that can confirm the reported data and/or refuse to provide consent to use the reported data for the purposes of this NIS.
- Indirect cases (reported by someone other than the patient or the HCP) for which the patient or HCP cannot be identified based on the information provided.
- Cases lacking reporter contact details (e.g. cases from social media).
- Pregnancies of female partners of male patients taking inclisiran. Such cases will continue to be processed as per MAP.

The study analysis will be restricted to cases confirmed by HCPs only. The number of pregnancy cases that are included in Argus but excluded from all analyses in the NIS will

be noted in the reports.

7.3 Variables

Data will be collected through interview(s) using targeted FU checklists. The targeted FU checklists (current versions listed in Annex 1) include questions about pregnancy history, history of onset and other characteristics of disease, and current medication use. Other variables such as socio-demographics, gestational age, co-morbidities, concomitant medications, disease severity and duration, and other relevant potential confounders will be collected. Data will be collected at enrollment, at the end of 2nd / beginning of 3rd trimester (between 24 and 30 weeks of pregnancy), between expected date of delivery (EDD) and EDD + 30 days, EDD + 3 months and EDD + 12 months (please refer to the following section and Table 7-6). Data collected in the FU checklists are in line with data elements to include when designing a pregnancy registry, as recommended by the US Food and Drug Administration (2019).

7.3.1 Exposure

Proportions of all outcomes will be stratified by timing of inclisiran exposure:

1. Exposure to inclisiran during pregnancy (operationally defined as the last dose of inclisiran received at or after the date of the LMP)
2. Exposure to inclisiran prior to LMP (last dose of inclisiran received prior to the LMP)

Primary outcome (major congenital malformations) will be evaluated in pregnancies exposed to inclisiran during pregnancy. Major congenital malformations in pregnancies exposed to inclisiran prior to pregnancy will be evaluated as part of the secondary objectives.

Very short half-life of inclisiran in plasma does not justify defining a separate peri-LMP exposure period, so it will not be assessed as an exposure category in this NIS. However, long pharmacodynamic effect of inclisiran makes it warranted to include all cases exposed prior to LMP, regardless of the exact timing of exposure. In the unlikely scenario that many cases would be reported with a very long interval between last inclisiran exposure and pregnancy onset, an additional sensitivity analysis stratifying by pre-pregnancy exposure timing (e.g. last dose received within 6 months or within 1 year prior to LMP) may be considered, to be detailed in the Statistical Analysis Plan (SAP).

For the exposure to inclisiran during pregnancy, additional subgroup analysis by trimester of exposure may be performed, if sufficient number of cases is collected (details to be provided in the SAP).

In addition, the following characteristics of inclisiran use will be collected: dose, route, indication for use, start and stop dates.

7.3.2 Outcomes

The pregnancy and infant outcomes listed below are defined according to MAP, or will be recorded in the adverse events section, coded using the Medical dictionary for regulatory activities (MedDRA) terminology. For the latter, standardized Novartis searches will be performed to identify relevant events. Full listing of all the variables collected, related definitions and data transformations is provided in the SAP.

Table 7-2 below lists the operational definitions used for the analyses of the primary or secondary outcomes related to congenital malformations.

Table 7-2 Definitions of the primary outcome and secondary outcomes related to congenital malformations

Study outcome	Definition in MAP	Comments / references
Congenital malformation = Major*	A congenital abnormality that requires medical or surgical treatment, has a serious adverse effect on health and development, or has significant cosmetic impact.	WHO/CDC joint definition: structural changes that have significant medical, social or cosmetic consequences for the affected individual, and typically require medical intervention (WHO 2020). In addition to initial classification as major/minor/NOS, all congenital malformations will undergo adjudication process (see Section 7.4.2) and be classified according to EUROCAT and MACDP criteria (both systems follow the same general approach but provide specific lists of malformation types to be classified as major or minor). Decision on whether congenital malformations meet criteria of major or minor will be made based on the adjudication process
Congenital malformation = 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.	WHO/CDC joint definition: structural changes that pose no significant health problem in the neonatal period and tend to have limited social or cosmetic consequences for the affected individual (WHO 2020) In addition to initial classification as major/minor/NOS, all congenital malformations will undergo adjudication process and be classified according to EUROCAT and MACDP criteria (both systems follow the same general approach but provide specific lists of malformation types to be classified as major or minor)
Congenital malformation = not otherwise specified (NOS)	Reported congenital anomaly without diagnostic information or other structural anomalies not well described.	Decision on whether malformations are to be designated as “unspecified / NOS” to be made based on the adjudication process
Overall congenital malformations	Composite of the following outcomes: Congenital malformations classified as major, minor, or NOS	-

*To be used in the analysis of the primary outcome

EUROCAT – European Surveillance of Congenital Anomalies; MACDP – Metropolitan of Atlanta Congenital Defects Program; NOS – not otherwise specified

Table 7-3 provides definitions for the secondary pregnancy and birth outcomes, as well as references and corresponding ICD-10 codes (if applicable). Of note, the study itself does not use ICD-10 for coding of the study outcomes, the codes are provided only to show which of the outcomes use comparable definitions with the conditions coded by ICD-10.

Of note, outcomes related to congenital malformations are assessed independently of pregnancy and birth outcomes, thus for the descriptive analyses most of the outcomes listed below can be sub-classified based on malformation status (e.g. any live birth, live birth with congenital malformations, live birth without congenital malformations, live birth with fetal outcome unknown). Detailed breakdown of these variables with the corresponding definitions are provided in the study SAP.

TOPFA, the specific variable needed for the analyses of congenital malformations, corresponds to the subcategory of the outcome "induced termination with congenital malformations".

Table 7-3 Definitions of the secondary pregnancy and birth outcomes

Study outcome	Definition in MAP	Comments / references, corresponding ICD-10 code* if applicable
Live birth	The patient gives birth to live neonate regardless of gestational age (combining outcomes in MAP: "premature live birth", "term live birth" and "postmature live birth")	ICD-10 codes: Z37.0, Z37.2, Z37.5
Premature** live birth	Patient gives birth to a live neonate before 37 completed weeks of gestation	ICD-10 codes: P07.2, P07.3 WHO defined preterm* births as births before 37 completed weeks of gestation (WHO 2016)
Stillbirth	The patient gives birth to a stillborn (no signs of life) at or after 22 weeks of gestation is completed	ICD-10 codes: Z37.1, Z37.3, Z37.4, Z37.6, Z37.7 Death before birth, among fetuses that are, by order of priority, of at least 1000 g birthweight, and/or at least 28 weeks gestation, and at least 35 cm long. Because of the increased viability of babies born with lower gestational age in some parts of the world, and due to differences in capacity in measurement, some groups and individuals define stillbirths differently. For example, they may include fetuses of a lower gestational age. <...> all stillbirths at 22 weeks and 28 weeks should be reported for international comparisons (WHO 2021)
Ectopic pregnancy	Implantation of the embryo outside the uterine cavity	ICD-10 code O00: A condition in which a fertilized egg grows outside of the uterus, usually in one of the fallopian tubes.

Study outcome	Definition in MAP	Comments / references, corresponding ICD-10 code* if applicable
Blighted ovum	Absence of an embryo in a normal-appearing gestational sac visible on ultrasound	ICD-10 code O02.0
Molar pregnancy / hydatitiform 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	ICD-10 code O01: A gestational disorder characterized by an abnormal placenta with marked enlargement of the chorionic villi and hyperplasia of the villous trophoblastic cells.
Spontaneous abortion	Composite, includes any of the following reported outcomes: • Blighted ovum (see above) • Hydatitiform mole (see above) • Spontaneous abortion: fetus is spontaneously aborted (prior to 22 weeks gestation); prior fetal status via prenatal testing may or may not be known. • Abortion NOS: used in cases where spontaneous / elective / therapeutic abortion is not specified.	ICD-10 codes O01, O02, O03 "Miscarriage" is defined by WHO as fetal death prior to 22 weeks gestational age (WHO 2016)
Induced termination	Composite, includes any of the following reported outcomes: • Therapeutic abortion: If an abortion procedure occurs due to abnormal fetus, fetal death or risk to the mother • Elective termination: Termination of pregnancy due to choice of mother of an otherwise normal fetus	ICD-10 codes O04, O07
Intrauterine growth restriction (IUGR)	As reported in the adverse events	Events to be retrieved based on MedDRA coding
Maternal complications during pregnancy, including any adverse drug reaction	As reported in the adverse events	Events to be retrieved based on MedDRA coding

* The study does not use ICD-10 for coding of the study outcomes, codes are provided to show which of the outcomes use comparable definitions.

** In this study, the terms "premature" and "preterm" will be used interchangeably.

Finally, Table 7-4 provides definitions for the neonatal and infant outcomes. As described in the SAP, the analyses described below may be modified if unexpected data quality or data retrieval operational issues are identified once the first interim report with the full analysis is generated, and/or if the number of cases with non-missing information is too low for meaningful analysis.

Table 7-4 Definitions of secondary neonatal and infant outcomes

Study outcome	Definition	Comments / references
Neonatal death	Death occurring <28 days after date of birth	Neonatal death: Death after birth and within the first 28 days of life (WHO 2016, WHO 2021)
Infant death	Death occurring ≥28 days after date of birth	-
Neonate hospitalization	Any adverse event reported as serious adverse event with the hospitalization flag; occurring <28 days after date of birth	WHO: the neonatal period refers to the first 28 days of life (WHO 2016)
Infant hospitalization	Any adverse event reported as serious adverse event with the hospitalization flag; occurring ≥28 days after date of birth	-
Low birth weight (LBW)	Weight at birth < 2500g (assigned per MAP)	This variable includes all three WHO subcategories “low birth weight (1500-2499 g)”, “very low birth weight (1000-1499 g)”, and “extremely low birthweight (<1000 g)” (WHO 2016)
Small for gestational age (SGA)	As reported in the infant adverse events	Events to be retrieved based on MedDRA coding
Breastfeeding status	Yes (those reported as currently breastfed or weaned), vs No (never breastfed) vs Unknown	-
Breastfeeding exposure to inclisiran	As reported in the infant adverse events	Events to be retrieved based on MedDRA coding
Developmental delay	As reported in the infant adverse events	Events to be retrieved based on MedDRA coding
Any adverse drug reactions reported	As reported in the infant adverse events	Events to be retrieved based on MedDRA coding

7.3.3 Other variables

Key variables that are collected via FU checklists and may be used for the descriptive analyses of the pregnancy and infant cohort characteristics or further evaluation e.g. for stratified analyses are listed in the following table.

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

Table 7-5 Other key variables and confounders

Variable	Operational Definition
Country	Country of report
Indication	Indication for use of inclisiran
Maternal Age (years)	Maternal age (years), continuous and categorical (specific age categories for analysis to be defined in SAP)
Maternal Race	Maternal (Caucasian, Black, Asian/Pacific Islander, Native American, Other)

Variable	Operational Definition
Maternal Ethnicity	Maternal (Hispanic, Non-Hispanic).
Maternal Height	Maternal height (cm)
Maternal body weight	Maternal body weight at LMP (kg)
Maternal Pre-pregnancy BMI	Maternal pre-pregnancy BMI (<18.5, 18.5-24.9, 25-29.9, >=30).
Number of fetuses	Number of fetuses (1, 2, >=3)
Other medications taken by the mother during pregnancy	Medication name, dose, frequency, administration route, indication, start and stop date, trimester of exposure
Contraception	Yes/no use of contraception, specific method if known, contraception failure Yes/no
Prenatal tests	Test name, date, any abnormal results
Maternal exposures that may affect the outcome of the current pregnancy	Yes/No with free-text comments: Smoking Alcohol use Recreational Drugs Environmental or Occupational Exposure
Maternal conditions that may affect the outcome of the current pregnancy	Yes/No for the following conditions with free-text comments: Hypertension Heart disease Seizure Diabetes Eclampsia Pre-eclampsia Thyroid disorder Infections History of infertility Fertility treatment Autoimmune disease Other
Characteristics and prior treatment of hypercholesterolemia	Duration of hypercholesterolemia, type (heterozygous, homozygous, non-familial, other, unknown) Treatment prior to inclisiran initiation
History of ASCVD	Yes/no or unknown, if Yes specify type
Previous obstetric history	Total number of prior pregnancies, outcome of previous pregnancies
Family history	Fetal malformations or other poor pregnancy outcomes (e.g. congenital anomaly or mental retardation) in the immediate family
Infant date of birth	Date
Infant gender	Male or female
Infant status	Living or deceased, if deceased: date of death, age at death, cause of death
Infant physiological measurements	Age at measurement, weight, length, head circumference
Any congenital malformations identified since birth	Yes/no, if Yes specify type, diagnosis date
Infection or other infant illness or hospitalizations	Yes/no, if Yes specify type, event start and end dates, treatment given
Drug therapies in the neonate and infant	Medication name, start and stop date

Variable	Operational Definition
Infant vaccinations	All vaccinations as recommended yes/no Any reaction after vaccination that needed medical care

7.4 Data sources

Pregnancy cases with a documented use of inclisiran during pregnancy or prior to LMP in the Novartis safety database will include cases reported from spontaneous post-marketing reporting (including personal communication with healthcare providers), Novartis clinical trials, post-marketing observational studies, patient-oriented programs (if applicable), and scientific publications. Reports may be submitted by patients or HCPs, however, only reports from non-HCPs that consent to contacting their HCP to confirm the data reported in the FU checklists would be included in the analyses.

Concomitant or prior medications entered into the database will be coded using the World Health Organisation (WHO) Drug Reference List. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

7.4.1 Intensive follow up scheme

The follow up (FU) is composed of two main activities:

1. Intensive FU activities
   a. Additional FU attempts before a patient is considered "lost to FU": Country Organizations (COs) will routinely make at least 4 FU attempts at each FU time point (except FU 1a) before a patient is considered "lost to FU". Such attempts should, when possible, be made simultaneously with the initial reporter and one or more HCPs (when such information is provided), and by all available means of contact (phone, e-mail, letter, fax, etc.). To minimize losses-to-FU, the targeted FU checklists (see below) collect alternative contact information of physicians and health care providers including obstetricians, midwifes, pediatricians and any other specialists involved in patient care.
   b. (If applicable) for specific Patient Oriented Programs (POPs) with continuous interactions with patients, external service providers (ESPs) will be requested to collect the necessary FU information (when allowable by local regulations). If not feasible for ESPs to implement, the responsibility to ensure FU activities remains with the COs.
   c. Automated check for overdue FUs: Data Science & Analytics group will generate a listing of overdue FUs. This listing will be distributed to the countries, which will then perform the FU using the applicable targeted FU checklist (according to the intensive FU scheme).
   d. Global Medical Safety Function will contact directly COs with long overdue FU (>30 days). When necessary, assigned pharmacovigilance responsible person will liaise with global medical affairs and/or clinical development teams to request their support in obtaining the necessary FU (using the system in place for enhanced FU of events of special interest).
2. Targeted FU checklists: a specific set of targeted FU checklists (listed in Annex 1)

will enable the collection of all necessary information to evaluate safety data on inclisiran exposure prior to LMP and during pregnancy and associated pregnancy, fetal and infant outcomes. Data collected in the FU checklists are in line with data elements to include when designing a pregnancy registry, as recommended by the US Food and Drug Administration (2019). In case of no response, further attempts will be made by COs as per schedule in Table 7-6. 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. Additional FU may be requested in case of congenital anomaly and/or concurrent adverse events. Additional FU will be done according to applicable regular Novartis PV SOP.

Cases are followed up as per the schedule in Table 7-6, using targeted follow-up checklists.

Table 7-6 Follow-up schedule using targeted FU checklists*

FU number	Checklist name	Date of collection	Type of information collected	Attempts cycle (in case of no response)
FU 1	Inclisiran Follow-up Checklist - Pregnancy Baseline	As soon as possible after initial report, or at initial report if possible	Baseline characteristics and demographics of the mother, information on pregnancy exposures, risk factors and prenatal tests (if known)	At least 4 attempts, at a minimum of 1 week and maximum of 1 month apart, unless EDD is reached (in such case merge FUs 1 and 2).
FU 1a	Inclisiran Follow-up Checklist - Pregnancy Outcome	Between LMP + 24 weeks and LMP + 30 weeks	Updated information on the pregnancy exposures, prenatal test results and/or information on the pregnancy outcome if ended prematurely	If no response received, next regular FU attempt to be performed at FU 2
FU 2	Inclisiran Follow-up Checklist – Pregnancy Outcome	Between EDD and EDD + 30 days	Information related to the delivery and neonate details	At least 4 attempts, at a minimum of 1 week and maximum of 1 month apart.
FU 3	Inclisiran Follow-up Checklist – Infant Status	EDD + 3 months	Information related to infant health status and development	At least 4 attempts, at a minimum of 1 week and maximum of 1 month apart.
FU 4	Inclisiran Follow-up Checklist – Infant Status	EDD + 12 months	Information related to infant health status and development	At least 4 attempts, at a minimum of 1 week and maximum of 1 month apart.

* FU schedule and requirements to be included in inclisiran pharmacovigilance guidance document (PGD).
EDD – estimated date of delivery; LMP – last menstrual period

7.4.2 Adjudication process

Each individual case of reported congenital abnormality will undergo an adjudication process. The adjudication panel will consist of three independent external experts such as

teratologists or disease area experts. Two of the three experts will perform the initial independent adjudication of individual case. The third expert will be contacted in case of different opinions by the two adjudicators. Adjudicators will evaluate the data to determine whether the malformation was major or minor using European Surveillance of Congenital Anomalies (EUROCAT) and, in addition, the Metropolitan of Atlanta Congenital Defects Program (MACDP) classification criteria, as well as assign an appropriate ICD-10 code in order to enable comparisons with external data sources and evaluate temporality of the event.

Reports with insufficient information for adjudication will be classified as "congenital anomaly not otherwise specified (NOS)".

7.5 Study size

The NIS will apply until 10 years from market authorization or 500 prospectively reported live births with known status of malformations, whichever occurs first.

In the US, the prevalence of major congenital malformations was reported to be 3% of live births (CDC 2020). The European surveillance of congenital anomalies (EUROCAT) reported a prevalence of 2.6% of live births (EUROCAT 2019). 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).

If the prevalence of major malformations of 3% is applied we can expect to observe approximately 15 cases of major malformations among the 500 prospectively reported live births with known status. For the primary objective, the calculated prevalence of major malformations among live births in this scenario will be 3.0% (95%CI 1.8-4.9%) (Rothman 2012). Of note, the prevalence of malformations observed in this study is likely to be higher as the inclisiran-exposed women are likely to be of higher average age than the general population, and more likely to suffer from predisposing comorbidities or medication exposures. If this is true, a somewhat smaller number of pregnancies may be required to obtain the same study power as calculated below under more conservative assumptions.

The following table Table 7-7 demonstrates the detectable risk ratios of risk increase of major malformations with 80% power and α=0.05 (two-sided test), assuming that the frequency of major malformations in the general population is 3% (i.e. the prevalence of birth defects reported in US (CDC 2020)).

The estimations are provided according to (Armstrong 1987) for sample sizes ranging from 100 to 800 live births with known outcome; and the corresponding enrollment requirements are also presented assuming that approximately 50% of all reported cases result in live births with known outcome (a scenario that may be expected in such a NIS, see (Geissbühler et al, 2020).

Table 7-7 Detectable increase in risk of major malformations (population rate = 3%) for various sample sizes

Number of live births with known outcome	Detectable risk ratio with 80% power, α=0.05	Number of pregnancies required if **50%** result in live birth with known outcome
100	3.3 or greater	200
300	2.2 or greater	600
500	1.9 or greater	1000
800	1.7 or greater	1600

If 500 live births with a known outcome are included, assuming a background prevalence of 3% the NIS will have 89% power (two-sided test, α set at 0.05) to detect a doubling of risk as statistically significant. In other terms, if the true proportion of birth defects is 6%, there is an 89% probability that the observed two-sided 95% confidence interval (CI) will exclude 3% with a sample size of 500 live births with known status of malformations. Targeting a 500 live births study size is therefore considered appropriate.

If after 10 years, either 500 cases have not been obtained, or if a conclusion can still not be drawn with the number of cases available at that point in time, then the impact of the risk would be considered very low and no conclusion would be reached. The NIS will be discontinued after discussion with the health authorities as appropriate. When the NIS is discontinued pregnancy reports will be followed-up via regular Novartis PV as per SOP.

7.6 Data management

This NIS is based on pregnancy case reporting in the Novartis global safety database (Argus). Cases are followed up using targeted follow-up checklists. The current versions of the checklsits are listed in Annex 1. Data collected in the FU checklists are in line with data elements to include when designing a pregnancy registry, as recommended by the US Food and Drug Administration (2019).

Data collected through the targeted checklists will be entered into the Argus global safety database per Novartis 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 Organisation (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 databasing conventions and deviation to MAP for all information required in the FU checklists will be described in the inclisiran Pharmacovigilance guidance document (PGD).

7.7 Data analysis

All analyses will be performed by Novartis. A statistical analysis plan (SAP) detailing the analysis to be conducted for this NIS will be developed prior to the first data lock point. Annual interim reports will be integrated into the periodic safety update report (PSUR), as appropriate. Details of all pregnancy cases will be provided at corresponding inclisiran PSUR Data lock points (DLPs), beginning with the 2nd PSUR to be submitted after the EU Marketing Authorization is granted. Cases pending pregnancy outcome follow-up at the time of data lock will be excluded from the analysis.

The data analysis will focus on the prospective cases as described in Table 7-1 because the retrospective cases are subject to different reporting biases so only prospective cases will allow quantitative analysis to better assess the risk of reproductive toxicity. However, despite potential recall biases, retrospective cases could be informative regarding the patterns of malformations, so the retrospective pregnancy cases will also be analyzed and presented separately from the prospective cases. Case details will be provided for all retrospective cases along with summary statistics. Comparison with background data will not be performed for retrospective cases in view of the high risk of bias from retrospective reporting.

Analyses will include the estimation of proportion (and 95% confidence interval) of malformations (major, minor, and overall), and of specific pregnancy outcomes such as live births, stillbirths, spontaneous abortions and elective terminations. The proportion of congenital malformations will be calculated amongst:

(1) live births
(2) live births, stillbirths and TOPFA

Proportions will be estimated by timing of drug exposure in pregnancy (during pregnancy and prior to LMP, as well as by trimester if sample size allows).

To consider a more restrictive definition of "prospective cases" as per FDA guidance (Food and Drug Administration (2019)), a subgroup analysis will be performed in women without any prenatal test before initial reporting. If sample size allows, additional subgroup analysis may be performed by concomitant pregnancy exposure to statins or other lipid-lowering medications:

(1) No concomitant exposure to statin or other lipid-lowering medications at any time during pregnancy
(2) Exposure to statins during the first trimester
(3) Exposure to other lipid-lowering medications during the first trimester
(4) Exposure to statins or other lipid-lowering medications during second or third trimester

Descriptive analysis will be performed for all prospective pregnancy cases including case disposition (outcome known, pending, and lost to follow-up) and maternal characteristics (i.e., age, ethnicity, region) by providing the number and percentage of pregnancies in each category.

Distributions of continuous variables will be summarized with means +/- standard deviations, medians, interquartile range and absolute range. Categorical variables will be summarized with proportions. Numbers and proportions for pregnancy outcomes will be reported. The 95% confidence intervals for proportions of study outcomes will be constructed based on the exact (Clopper-Pearson) method.

The following information where available will be summarised:

- Country of origin and source of reports
- Exposure characteristics (prior to pregnancy, during pregnancy, specific trimester of exposure: 1st trimester, etc.)
- Concomitant exposure to statins, other lipid-lowering medications and other co-medications
- Type of congenital anomalies
- Adverse birth and pregnancy outcomes (including stillbirth, spontaneous abortion, preterm births, low birth weight, SGA, IUGR, neonatal death)
- Breastfeeding status and exposures during breastfeeding
- Other infant outcomes (e.g. neonatal and infant death, neonate and infant hospitalizations, developmental delays) and maternal complications during pregnancy (including any adverse drug reactions)

Further stratified analyses may be undertaken, e.g. by region. Details of the planned analyses will be provided in the SAP.

Observed frequencies of pregnancy outcomes in inclisiran-exposed patients will be compared with background frequencies in the general population as well as primary hyperlipidaemia patients not exposed to inclisiran. The background frequencies will be obtained from the literature or appropriate external data sources (e.g. EUROCAT, National Center for Health Statistics Natality data, Center for Disease Control and Prevention's (CDC's) Metropolitan Atlanta Congenital Defects Program (MACDP), etc).

Formal comparative analyses estimating measure of effect (e.g. risk ratios) may be undertaken if the reference population is judged to be adequate for such an analysis and an adequate number of prospective pregnancy cases is available for meaningful interpretation (at the latest when 100 cases are reached; to be further elaborated in the SAP).

The decision regarding the appropriate external data source for a comparative analysis will be made based on the geographical distribution of cases included in this NIS, and presence of key confounders in the available external data sources (e.g. age and demographic variables, comorbidities, obstetric history etc.) that would allow to minimize possible biases related to the background risk of major malformations and other adverse outcomes in the inclisiran-treated population. Details will be included in the SAP.

7.8 Quality control

The SOPs for pharmacovigilance will be followed to perform quality control of the data entered to the Argus safety database. The designated case processing team will undergo additional training specific to pregnancy 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.

Data recording and documentation retention will follow standard operating procedures defined for collection and retention of data in the Novartis global safety database – Argus. As a measure of quality control for the classification of malformations, each individual case of reported congenital abnormality will undergo a formalized adjudication process. To ensure a continuously high quality of case adjudication, two experts will independently perform the adjudication of each individual case. A third expert will be involved in case of different opinions by the two adjudicators. Programming and statistical analyses will be performed in accordance with relevant SOPs to ensure quality control. Program code will undergo program verification by a second person (reviewer) and will be archived.

7.9 Limitations of the research methods

The NIS is based on spontaneous reports received by the Novartis global safety database with the potential limitations of under-reporting, selective reporting of adverse outcomes, and loss to follow-up (Geissbühler et al 2020). To reduce the potential for selection bias due to loss to follow-up , contact attempts via multiple contact modalities are systematically and repeatedly performed under the processes of this NIS. In addition, prospective cases (where pregnancy outcome is unknown at the time of reporting) and retrospective cases will be evaluated separately given the risk of selective reporting of adverse outcomes in retrospective reporting. To further improve quality of reported data, only reports where the information in FU checklists could be verified by an HCP will be included in the analysis.

This study does not have an internal comparator group. Comparative analyses will be performed using available appropriate external data sources and/or literature, as mentioned above. A direct comparison between prevalence estimates of congenital malformation and other outcomes of interest obtained through this NIS with external reference general

populations is hampered by potential differences in data collection methods. Therefore, these comparisons should be interpreted with caution. Indeed, Novartis cannot ensure that the inclisiran group and the external comparator group would have comparable demographics or disease severity allowing for a reliable conclusion. To minimize this risk, the planned comparative analyses against external references will be carefully designed taking into account the differences in the data collection and the demographic characteristics of the underlying population with the aim to minimize possible information bias.

In addition, as patient-level data will not be available in the comparator group, the analysis will not be able to fully account for differences in other potential risk factors for adverse pregnancy outcomes between patients in the NIS and those in the comparator group. Therefore, these comparisons will need to be interpreted with caution and may be inadequate alone to suggest causality.

Adverse birth outcomes, infant complications, breastfeeding status and exposures and complications during pregnancy are included in the checklists and are secondary outcomes of interest in this NIS. Information available to Novartis on these outcomes will be included in the interim and final reports as summarized above. However, in view of the large amount of data being requested in the checklists, a possibility remains that not all outcomes may be possible to include in the planned secondary analyses given the potential for missing or incomplete information. To minimize this risk, systematic and repeated contact attempts via different modalities are planned with the aim to obtain most complete follow-up information on the primary and secondary study outcomes. In addition, alternative contact information of physicians and health care providers including obstetricians, midwifes, pediatricians and any other specialists involved in patient care are collected to minimize losses-to-follow-up.

Despite these limitations, the selected NIS design approach allows for worldwide capture of cases providing a larger pool of patients than a “traditional” registry approach. Additionally, 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 considers this study design to be the most “time- effective’ and scientifically and operationally feasible method to obtain data to identify safety signals related to the missing information on the use of inclisiran in pregnancy in primary hyperlipidemia patients.

7.10 Other aspects

Not applicable

8 Protection of human subjects

Confidentiality of records and the personal data of the subjects remain protected in accordance with applicable law of personal data protection.

Regulatory and ethical compliance

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in non-interventional studies are protected (consistent with the principles that have their origin in the Declaration of Helsinki) and that the study data are credible and responsibly reported.

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).

Informed consent procedures

This non-interventional study is classified as a post-authorization safety study (PASS) with secondary use of data (SUD) because the study uses already existing data collected in the context of routine PV monitoring which is extracted from the global safety database. Thus, no additional informed consent is needed. The detailed reasoning for the classification of the study as SUD is as follows:

- This NIS uses data available in the Novartis global safety database (Argus) to assess reproductive toxicity using a structured data collection and analysis process. The purpose of the NIS is the same as that for routine pharmacovigilance (PV) monitoring of pregnancy cases. The intensified monitoring activities of this NIS are embedded within the routine PV activities.
- When a pregnancy following a drug exposure in utero is reported voluntarily to Novartis, follow up is done according to the Guidelines on Good Pharmacovigilance practices (GVP) (European Medicines Agency 2019). This requires follow up on the outcome of the pregnancy and the development of the child after birth. FU checklists in context of this NIS are sent at the same time points as routine PV checklists for other products without a defined NIS based on this data. Therefore, the data collection and processing does not extend beyond routine PV monitoring of pregnancy cases and does not involve any collection of data beyond the scope of routine PV monitoring. However, for the study duration of the NIS, the healthcare provider (HCP) of pregnancy cases will be contacted several additional times at each follow up if the checklists are not returned to minimize missing information.
- As with all adverse event reports, the country organization (CO) has access to the personal data of non-HCP reporters for follow up purposes. This NIS does not involve collection of any personal data which would not be collected during routine PV activities. For routine PV monitoring activities, the CO only transmits de-identified data to the global safety database (Argus). Each CO follows local data privacy laws and any local informed consent process needed for PV data, and hence also for all cases included in this NIS.

9 Management and reporting of adverse events/adverse reactions

Since this NIS 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 publically disclosed according to the applicable regulation and the applicable Novartis SOPs.

Upon study completion and finalization of the study report, the results of this non-interventional study may be either submitted for publication and/or posted in a publicly accessible database of results. Manuscripts will not be submitted for publication prior to submission of the underlying reports to the relevant health authorities. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

11 References

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12 Annexes

12.1 Annex 1 – List of stand-alone documents

Table 12-1 List of stand-alone documents

Number	Document reference number	Date	Title
1	0902b6988cdd3c5e	27 September 2022	Inclisiran Pregnancy Baseline Follow-Up Checklist:, version 2.0
2	0902b6988ce73251	27 September 2022	Inclisiran Pregnancy Outcome Follow-up Checklist, version 2.0
3	0902b69885a9dd46	06 November 2020	Inclisiran Infant Health Status Follow-up Checklist, version 1.0

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:
Monitoring of pregnancy outcomes in women treated with inclisiran: a non-interventional study

EU PAS Register® number: not yet registered
Study reference number (if applicable): N/A

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:

No progress reports planned for the study, up to 10 interim reports

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:

Further measures of association to be specified in the SAP

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 exposure measurement are planned, as exposure information is collected directly from patients and/or HCPs

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, 6.1.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	7.3.2

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
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:				
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:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
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?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Further measures to control confounding, 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?	☐	☐	☒	
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: 28/September/2022

Signature: _____