Non-Interventional Study Protocol

Study Number TV44400-CNS-40159

Real-world safety of Copaxone in Offsprings of Breastfeeding and treated RMS pAtients – COBRA study

Phase 4

Protocol Approval Date: 5th May 2020

Responsible Parties

Sponsor's Safety Physician

Not applicable

Sponsor's Medical Affairs Project Lead

[redacted]

Principal Investigator

[redacted]

For adverse events reporting:

Not applicable

AMENDMENTS AND UPDATES

Not applicable.

Table 1: Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason

SYNOPSIS

<table>
<tr><td>Protocol Title:</td><td>Real-world safety of Copaxone/FOGA in Offsprings of Breastfeeding and treated RMS pAtients – COBRA study</td></tr>
<tr><td>Protocol ID</td><td>TV44400-CNS-40159</td></tr>
<tr><td>Phase</td><td>IV, RWE</td></tr>
<tr><td>Study Objectives</td><td>To assess the outcome of offspring during the initial period of up to 18 months of development who were breastfed by mothers undergoing glatiramer acetate treatment</td></tr>
<tr><td>Study sites</td><td>Katholisches Klinikum Bochum gGmbH
vertreten durch die Geschäftsführung
Neurologische Universitätsklinik Prof. Dr. K. Hellwig
St. Josef Hospital
Klinikdirektor Prof. Dr. med. R. Gold
Gudrunstrasse 56, 44791 Bochum</td></tr>
<tr><td>Study Design</td><td>Non-interventional study designed for retrospective analysis of the clinical German MS and Pregnancy Registry.</td></tr>
<tr><td>Number of Study Patients</td><td>As this study is non-interventional study designed for retrospective analysis of the clinical German MS and Pregnancy Registry, no power assessment was conducted.</td></tr>
<tr><td>Study Population</td><td>Offsprings of mothers with RMS who were breast feeding</td></tr>
<tr><td>Inclusion Criteria</td><td>☐ GA was administered during breastfeeding period – GA Cohort.
☐ No DMT was administered during breastfeeding period – Control Cohort.</td></tr>
<tr><td>Exclusion Criteria</td><td>Treatment with DMT other than GA during breastfeeding period.</td></tr>
<tr><td>Study Procedures/Frequency</td><td>Not applicable</td></tr>
<tr><td>Study Duration</td><td>Up to 18 months period following childbirth</td></tr>
<tr><td>Estimated Study Timelines</td><td><table>
<tr><th>Milestone</th><th>Completion Date</th></tr>
<tr><td>Protocol sign off</td><td>30 Apr 2020</td></tr>
<tr><td>Data analysis phase 1</td><td>15 May 2020</td></tr>
<tr><td>Data analysis phase 2</td><td>15 Jun 2020</td></tr>
<tr><td>Clinical study report</td><td>15 Aug 2020</td></tr>
<tr><td></td><td></td></tr>
</table></td></tr>
<tr><td>Study Endpoints:</td><td>Offspring’s Related Outcome Measures:
☐ Frequency (no. of events) and incidence (no. of children with events) of hospitalizations.
☐ Frequency and incidence of antibiotic treatments.
☐ Growth parameters: weight, length and head circumference.</td></tr>
</table>

	Incidence of Pediatrician reports on children development delay (based on routinely measured parameters: turning, attempt to grasp, sitting, turning towards voices, first words, standing).
Statistical Analysis:	• Statistical analyses of both Feasibility and Confirmatory stages will be descriptive in nature. Therefore, no formal hypotheses testing are planned for the study outcome measures. Statistical Analyses for Feasibility Stage: Summarize demographics and clinical characteristics as well as available risk factors with the end of: • Assessing if will have sufficiently large number of female subjects in both cohorts and overall, and, • Assessing if mother's key risk factors for negative birth outcome, of the two cohorts will allow an unbiased comparison between the study cohorts in the study endpoints. Statistical Analysis for Confirmatory Stage: Assess the outcome of offspring during the initial period of up to 18 months of development who were breastfed by mothers undergoing glatiramer acetate treatment. Statistical Methodology: • Summary statistics of study outcome measures will be displayed by both study cohorts (GA Cohort and Control Cohort) and overall. Potential lack of balance in risk factors between study cohorts will be identified using a by cohort, side-by-side display of descriptive statistics of the risk factors and their 95% confidence intervals. • In the case that the study cohorts will be found to be unbalanced with regard to risk factors, all between cohorts' comparisons will be conducted using baseline adjusted modeling as appropriate. • In the case that Principal Investigator will identify that results of baseline adjusted comparisons are still biased (confounded) due to lack of balance in risk factors, either propensity scores matching, if sample size will allow, or risk factors / propensity score adjusted comparisons will be performed. • Incidence tables of binary outcome measures (e.g. proportion of children hospitalized) will display the No. of participants with events and relative percentages as well as the 95% two-sided confidence intervals.. • Frequency tables of events (e.g. No. of hospitalizations, No. of relapses) will display the annualized number of events as well as its two-sided 95% confidence interval. • Descriptive statistics of continuous outcome measures (e.g. weight, head circumference) at end of follow-up duration will include N, mean, SD, SE, Median, IQR min and max values. Graphical display for these will be provided using Box-Plots.

	• Analyses will be repeated for the subgroups of the GA Cohort as deemed appropriate.

Milestones

Milestone	Planned date
Protocol Sign Off	30 Apr 2020
Data analysis phase 1	15 May 2020
Data analysis phase 2	15 Jun 2020
Clinical study report	15 Aug 2020

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ATC	Anatomical therapeutic chemical classification system
CCI	Charlson Comorbidity Index
DDD	Defined Daily Dose
DESTATIS	Federal Office of Statistics [Statistisches Bundesamt]
DMT	Disease modifying therapy
EBM	Uniform assessment standard [Einheitlicher Bewertungsmaßstab]
FOGA	Follow-on glatiramer acetate
GA	Glatiramer Acetate
ICD-10-GM	International Classification of Diseases, 10th Revision, German Modification
InGef	Institute for Applied Health Research Berlin [Institut für angewandte Gesundheitsforschung Berlin]
max	Sample maximum
min	Sample minimum
MPR	Medication Possession Ratio
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NDC	National Drug Code
SD	Standard deviation
SHI	Statutory Health Insurance
OPS	Key of operations and procedures [Operationen- und Prozedurenschlüssel]
PZN	Pharmaceutical Registration Number [Pharmazentralnummer]
Q1	25th percentile
Q3	75th percentile
RMS	Relapsing Multiple Sclerosis

MILESTONES

Table 2: Milestones

Milestone	Planned date
Protocol Sign Off	30 Apr 2020
Data analysis phase 1	15 May 2020
Data analysis phase 2	15 Jun 2020
Clinical study report	15 Aug 2020

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1. RATIONALE AND BACKGROUND

Copaxone is the most frequently used DMT during pregnancy due to its safety profile. Potentially, for the same reason, it can be beneficial for MS mothers during breastfeeding period. Currently glatiramer acetate is not recommended during breastfeeding. Most of the DMTs are contraindicated during breastfeeding period and at the current time, a decision should be made as whether to re/start GA after the delivery or to breastfeed.

2. INTRODUCTION

Multiple Sclerosis (MS) is a common neurological disease in young adults, affecting approximately 500,000 individuals in Europe [1]. MS is an autoimmune disease characterized by both diffuse and localized inflammation, demyelination of neurons, and nonspecific brain and spinal cord damage [2]. The course of the disease is variable and patients commonly experience a period of clearly defined attacks followed by periods of complete or partial recovery. This type of MS is classified as Relapsing-Remitting MS (RRMS), and it accounts for nearly 85% of all cases [3, 4]. During attacks, patients may experience deficits in any number of systems (motor, sensory, optic, sphincteric, etc.) [5]. Treatment of MS is aimed at halting attacks when they occur. Treatments usually last for years. Nonspecific immunosuppressive agents are the mainstay of therapy [6]. The future of MS research will be aimed at repairing and reversing damage to the myelin sheath; however, the understanding of disease etiology is still limited [7].

As with most autoimmune diseases, MS disproportionately affects females with a threefold increased risk as compared to males. The common age of onset is during the third and fourth decades of life, coincidentally a woman's childbearing years [2, 8]. Due to medical advancements in the past two decades, clinicians have become more supportive of young adults with MS who choose to start a family. Because of the development of disease modifying drugs (DMTs), healthcare professionals have the ability to reduce the accumulation of CNS damage and resulting disability by extending the time between relapses. Women with MS have become more confident in their ability to safely and successfully become pregnant and have a healthy child. The therapeutic management of MS in the pregnant woman has been adequately covered in recent years [9, 10]. However, an in-depth investigation into the safety of DMTs in breastfeeding women and their infants is limited. Given that approximately 72% of women choose to breastfeed and up to 30% of women with MS may relapse within the first 3 months postpartum, the safety of medications used to treat MS while breastfeeding is of paramount concern to mothers and their infants [10, 11].

The effect of breastfeeding under glatiramer acetate on child development and risk of infections is unknown. GA is a large molecule, unlikely to be excreted in the human milk. In rats, there is no significant effect on offspring [12], however there are no clinical data in humans.

Treatment with GA during pregnancy is not associated with changes in mean birth weight and length [13, 14].

3. COMPLIANCE STATEMENT

The current retrospective study is an observational database analysis based on fully anonymized German MS registry and is regarded as a non-interventional phase IV study. As a result, no ethical approval or consent from an ethics committee or review board was required for this study.

Principal Investigator is responsible for performing the study in accordance with this protocol. Agreement of the principal investigator's employer to conduct and administer this study in accordance with the protocol is documented in separate study agreement with the sponsor.

4. STUDY OBJECTIVES

To assess the outcome of offspring during the initial period of up to 18 months of development who were breastfed by mothers undergoing glatiramer acetate treatment

The study objectives can be divided into two parts, where part I is deemed the descriptive phase and will enable part II, which will depend on the patient counts and results of part I.

Objectives of part I:

1. Retrieve clinical German MS and Pregnancy Registry data for the assessment of study feasibility.
2. Feasibility criteria, allowing to proceed to the "confirmatory" stage will be based on two criteria:
    - will have sufficiently large number of female subjects in both cohorts and overall, and
    - mother's key risk factors for negative birth outcome, of the two cohorts will allow an unbiased comparison between the study cohorts in the study endpoints:
        - mother’s age at time of conception,
        - exclusive breastfeeding,
        - duration of exposed breastfeeding
        - preterm birth

Feasibility assessment will derive the following decisions:

- continue with phase 2 Confirmatory stage or
- delay study and obtain more information from the clinical German MS and Pregnancy Registry, and/or,
- obtain more data from Swedish pregnancy registry, or,
- discontinue Study.

3. To describe mothers’ demographics and clinical characteristics including: Age, RMS disease duration, No. of relapses during pregnancy, No. of steroid pulses during pregnancy, pregnancies under GA, GA exposure duration in pregnancy, GA exposure duration during breastfeeding, follow-up duration.
4. Assess study outcome measures with the objective of determining study feasibility

Objectives of part II:

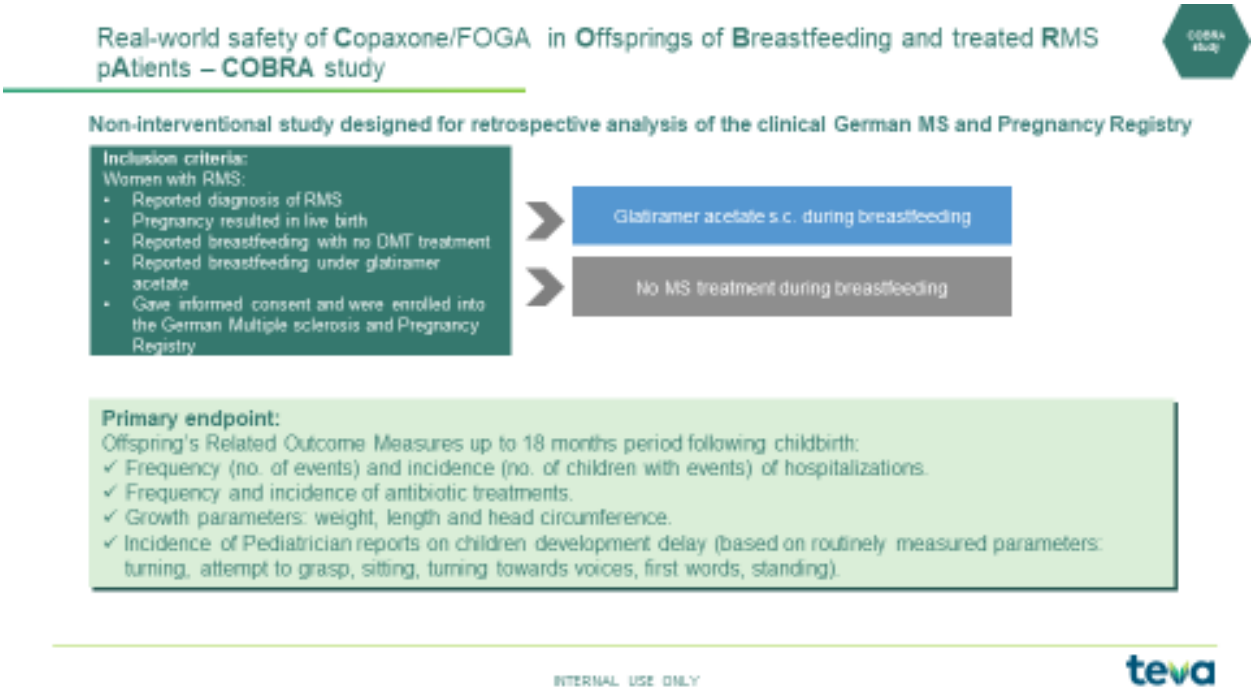
Depending on the patient counts, characteristics as well as the comparability of the identified patient groups, the specific objective of study part II is:

To assess the outcome of offspring during the initial period of up to 18 months of development who were breastfed by mothers undergoing glatiramer acetate treatment.

5. STUDY DESIGN

5.1. Overall Study Design

This is a non-interventional study designed for retrospective analysis of the clinical German MS and Pregnancy Registry.



5.2. Study Population

5.2.1. Patient Population

Part I:

The first part of the study will describe the demographic and clinical characteristics of the distinct RMS patient populations:

- GA was administered during breastfeeding period – GA Cohort.
- No DMT was administered during breastfeeding period – Control Cohort.

Additionally, the two identified main cohorts will further be divided into the following subgroups (sample size permitting):

- Subgroup 1: Patients treated with GA before and during pregnancy as well as during breastfeeding.

- Subgroup 2: Patients treated with GA during pregnancy and breastfeeding but not before pregnancy.
- Subgroup 3: Patients treated with GA before pregnancy and during breastfeeding but not during pregnancy.
- Subgroup 4: Patients included in Subgroup1, Subgroup 2, Subgroup 3- above defined subgroups.
- De-Novo Subgroup 5: Patients treated with GA for the first time during breastfeeding.

All subgroups analyses are subjected to having a sufficient subgroups population size. The second part of the study will compare the two study cohorts in the study endpoints as statistical methodology is outlined in the relevant parts of the protocol as outlined in the study synopsis and in 7.2.

The following groups of interest will be compared:

- GA was administered during breastfeeding period – GA Cohort.
- No DMT was administered during breastfeeding period – Control Cohort

5.2.2. Inclusion Criteria

Patients will be included in the study only if they meet all of the following criteria:

- Women with relapsing forms of multiple sclerosis identified by the following:
    - Reported diagnosis of RMS
    - Pregnancy resulted in live birth
    - Reported breastfeeding with no DMT treatment
    - Reported breastfeeding under glatiramer acetate
    - Gave informed consent and were enrolled into the German Multiple sclerosis and Pregnancy Registry

- Women who have been treated with glatiramer acetate during the breastfeeding period identified by the following:
    - Reported glatiramer acetate treatment during entire pregnancy and breastfeeding period OR
    - Reported glatiramer acetate treatment initiation during pregnancy and continuation during breastfeeding OR

  - Reported glatiramer acetate treatment discontinuation during pregnancy, restart of treatment at some point before delivery and breastfeeding under glatiramer acetate treatment OR
  - Reported glatiramer acetate treatment discontinuation during pregnancy and restart of treatment at some point during breastfeeding OR
  - Reported no glatiramer acetate treatment during pregnancy but (re-)start of treatment at some point during breastfeeding
  - Reported breastfeeding while under glatiramer acetate treatment for at least one day

- Women who haven't been treated with any DMT during the breastfeeding period identified by the following:
  - Reported DMT discontinuation before conception OR
  - Reported DMT discontinuation of glatiramer acetate in the first trimester OR
  - Reported no past DMT treatment
  - Reported diagnosis of RMS
  - Pregnancy resulted in live birth
  - Gave informed consent and were enrolled into the German Multiple sclerosis and Pregnancy Registry

5.2.3. Exclusion Criteria

Patients will be excluded from participating in this study if they meet any of the following criteria:

- Women with other forms of multiple sclerosis who breastfed
- Women treated with other DMTs than glatiramer acetate during breastfeeding period

5.3. Data Elements:

Part I

In part I of the study, the following outcomes related to demographic and clinical characteristics will be assessed for all of the identified main- and subgroups.

The **demographic characteristics** will be determined by:

- Age

- Education
- Body mass index (BMI) at the beginning of pregnancy
- Gestational week at entry into the German Multiple Sclerosis and pregnancy registry

The following **clinical characteristics** will be determined:

- Disease duration at conception
- No. of relapses during pregnancy,
- No. of steroid pulses during pregnancy,
- GA exposure during pregnancy,
- GA exposure duration in pregnancy,
- GA exposure duration during breastfeeding,
- follow-up duration
- no. of relapses in the 2 years preceding conception

The observation period covers January 2011 to January 2020. All women with RMS enrolled into the German Multiple Sclerosis and Pregnancy Registry who reported breastfeeding either under glatiramer acetate or under no DMT are eligible for this study. Women reporting at least one day of breastfeeding while under glatiramer acetate treatment are included into the GA cohort. The control cohort consists of RMS women who were not treated with any DMT during breastfeeding (see inclusion criteria).

Part II

In part II of the study, the following outcomes related to offspring will be compared between the GA cohort and the Control cohort:

- Frequency (no. of events) and incidence (no. of children with events) of hospitalizations.
- Frequency and incidence of antibiotic treatments.
- Growth parameters: weight, length and head circumference.
- Incidence of Pediatrician reports on children development delay (based on routinely measured parameters: turning, attempt to grasp, sitting, turning towards voices, first words, standing).

6. DATA HANDLING, DATA QUALITY CONTROL, AND DATA RECORD KEEPING

6.1. Data Source

This is a retrospective registry data analysis using the national German Multiple Sclerosis and Pregnancy Registry from January 2011 – January 2020 from the St. Josef-Hospital, Ruhr-University Bochum research database.

The national German Multiple Sclerosis and Pregnancy Registry aims to obtain safety information of disease modifying drug exposure during pregnancy and breastfeeding. In addition to safety aspects, disease course during pregnancy and postpartum and the identification of predictors of disease activity are investigated. During the last twelve years more than 2,000 pregnant MS patients were prospectively enrolled in the registry and at least 250 new pregnancies are followed every year.

Data was generated prospectively by standardized questionnaires in telephone interviews in every remaining trimester during pregnancy after study entry, in month 1, 3 and 6 during the postpartum period and yearly around the childes birthday. Women were enrolled in any case during pregnancy. If the enrollment date was during the second or third trimester of pregnancy, data concerning the previous trimester were generated at the first interview after study entry.

The database includes information on the following: contact information, baseline characteristics, potential confounder, socioeconomic status, medical history, family history, pregnancy course, disease activity during pregnancy, pregnancy Outcome, disease activity postpartum, child development.

The national German Multiple Sclerosis and Pregnancy Registry is approved by the local institutional review board of the Ruhr-University Bochum (Reg-Nr.: 18-6474-BR). Study enrolment is voluntary and requires informed consent. In accordance with the approval by the local institutional review board of the Ruhr-University Bochum, consent is given by conclusive conduct during the telephone interview. Prior to a woman´s participation in this study, an informed consent must be given at least orally. However, to access data from healthcare providers, a written consent and a signed agreement to relieve them from their obligations of confidentiality is needed. The Informed Consent and Confidentiality Release Form and the Patient Information Sheet for obtaining the woman´s consent is reviewed and approved by the local institutional review board of the Ruhr-University Bochum. The Registry addresses all data protection regulations in Germany. In addition, the Registry conducts regular audits of the data and its management and has rigorous validation methods to establish that enrolment data are complete, accurate, and reliable.

6.2. Data Collection

6.2.1. Data Collection/Handling

A completely anonymized file comprising all observations and variables required for the planned analyses will be created from information contained exclusively within the source material (the full German Multiple Sclerosis and Pregnancy Registry). It is a requirement that all analyses are conducted on the site of the data provider. Data files from the German Multiple Sclerosis and Pregnancy Registry must stay in-house due to data protection regulations. Results are made available on an aggregated level.

6.2.2. Quality Control/Data Validation

Data is collected via telephone interviews during pregnancy and the postpartum period, conducted by regularly trained MS nurses or research associates with pregnant MS patients, mothers suffering from MS or their treating physicians.
Further data is collected from official documents like hospital discharge reports, clinical records and physician´s letters as well as maternity logs and the medical check-up booklets of the infants.
In case of an adverse event reported by pregnant women/mother (e.g. relapse during pregnancy, adverse pregnancy outcome, congenital abnormalities, serious disease of the child), the treating physician is contacted for verification.
All data entry is reviewed for logical errors and subsequent review of data is done by a study data manager. Key variables are double-checked for accuracy of data entry. Access to the database is controlled by password and different privileges are assigned to the staff. Hard copies of the questionnaires and signed informed consent forms are kept in a locked cabinet.

6.2.3. Archiving of Case Report Forms and Source Documents

At the conclusion of the study the following information will be archived by Teva:

- Protocol and Protocol amendments
- Relevant SOPs
- Clinical Study Report (CSR) and it’s appendices

Study site is required to maintain appropriate files for the agreed upon time frame.

7. STATISTICS

7.1. Sample Size and Power Considerations

As this study is non-interventional study designed for retrospective analysis of the clinical German MS and Pregnancy Registry, no power assessment was conducted.

Sponsor reserves the right to attempt and upsize the study using repeated Registry data retrieval, which requires a new agreement and a new contract and/or use of the Swedish pregnancy registry at a later date then currently planned.

7.2. Data Analysis

Statistical analyses of both Feasibility and Confirmatory stages will be descriptive in nature. Therefore, no formal hypotheses testing are planned for the study outcome measures.

Statistical Analyses for Feasibility Stage: Summarize demographics and clinical characteristics as well as available risk factors with the end of:

- Assessing if will have sufficiently large number of female subjects in both cohorts and overall, and,
- Assessing if mother's key risk factors for negative birth outcome, of the two cohorts will allow an unbiased comparison between the study cohorts in the study endpoints.

Statistical Analysis for Confirmatory Stage: Assess the outcome of offspring during the initial period of up to 18 months of development who were breastfed by mothers undergoing glatiramer acetate treatment.

Statistical Methodology:

- Summary statistics of study outcome measures will be displayed by both study cohorts (GA Cohort and Control Cohort) and overall. Potential lack of balance in risk factors between study cohorts will be identified using a by cohort, side-by-side display of descriptive statistics of the risk factors and their 95% confidence intervals.
- In the case that the study cohorts will be found to be unbalanced with regard to risk factors, all between cohorts' comparisons will be conducted using baseline adjusted modeling as appropriate.
- In the case that Principal Investigator will identify that results of baseline adjusted comparisons are still biased (confounded) due to lack of balance in risk factors, either propensity scores matching, if sample size will allow, or risk factors / propensity score adjusted comparisons will be performed.
- Incidence tables of binary outcome measures (e.g. proportion of children hospitalized) will display the No. of participants with events and relative percentages as well as the 95% two-sided confidence intervals..
- Frequency tables of events (e.g. No. of hospitalizations, No. of relapses) will display the annualized number of events as well as its two-sided 95% confidence interval.
- Descriptive statistics of continuous outcome measures (e.g. weight, head circumference) at end of follow-up duration will include N, mean, SD, SE, Median, IQR min and max values. Graphical display for these will be provided using Box-Plots.
- Analyses will be repeated for the subgroups of the GA Cohort as deemed appropriate.

7.3. Limitations of the research methods

Although measures will be taken to ensure the Registry has robust data collection, certain limitations should be acknowledged. As the participation is voluntary, it is possible that even in prospectively reported cases, potential bias could exist.

It is possible that outcomes among women lost to follow-up could differ from those with documented outcomes, but it is not possible to assess with any certainty what impact the potential biases the losses to follow-up may have on the analysis. Lost to follow-up is minimized in the German Multiple Sclerosis and Pregnancy Registry by close meshed contacts and personal care provided by rarely fluctuating staff. The German Multiple Sclerosis and Pregnancy Registry has an average lost-to-follow-up rate of 3 %, therefore these differences might be negligible.

The number of cases with missing data for each characteristic of the study cohort will be displayed so that it will be clear how many cases were included in each analysis/ display of clinical characteristics.

8. ETHICS

The current retrospective study is an observational database analysis based on fully anonymized German MS registry and is regarded as a non-interventional phase IV study. As a result, no ethical approval or consent from an ethics committee or review board was required for this study.

8.1. Health Authorities and Independent Ethics Committees/Institutional Review Boards

Not applicable.

8.2. Informed Consent

Not applicable.

8.3. Patient Confidentiality

Not applicable.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Since this is a non-interventional study based on secondary use of data, the reporting of suspected adverse reactions as in the form of individual case safety reports (ICSRs) is not required according to the GVP module VI.

9.1. Definitions

9.1.1. Adverse Event

An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product, regardless of whether it has a causal relationship with this treatment.

An adverse event can, therefore, be any unfavourable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study or of any concurrent disease, whether or not considered related to the study drug.

9.1.1.1. Adverse Drug Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

9.1.2. Serious Adverse Event

The physician should assess the seriousness of all adverse events.

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- death
- a life-threatening adverse event (i.e., the patient was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death
- inpatient hospitalisation or prolongation of existing hospitalisation, which means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event. Hospitalisations scheduled for an elective procedure or for treatment of a pre-existing condition that has not worsened during participation in this study will not be considered serious adverse events. Hospitalisation for intravenous steroid treatment of a relapse will not be considered a SAE unless it is a worsening of the condition beyond expected disease progression
- persistent or significant disability or incapacity (refers to a substantial disruption of one’s ability to conduct normal life functions)
- a congenital anomaly/birth defect

- an important medical event that may not result in death, be life-threatening, or require hospitalisation, but may jeopardise the patient and may require medical intervention to prevent one of the outcomes listed in this definition. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

In addition, the below will be considered serious adverse event:

- all possible drug-induced liver injury events with hyperbilirubinemia (defined as aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≥3 times the upper limit of the normal range [ULN], plus either bilirubin ≥2 times the ULN) or Hy's Law events that result in treatment cessation (note: the latter should be reported as a serious adverse event)

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a non-serious adverse event.

9.2. Recording Adverse Events

Not applicable.

9.3. Reporting Requirements for Adverse Events

Not applicable.

10. PRODUCT COMPLAINTS

Not applicable.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The principal investigator is responsible for the preparation of a CSR, in cooperation with the sponsor. The final report is signed by the sponsor and by the principal investigator.

Study results will be considered for publication and will follow the International Committee of Medical Journal Editors (ICMJE 2013) guidelines. In addition, communication in appropriate scientific meetings will be considered.

When reporting results of this study, the appropriate STROBE checklist (STROBE 2007) will be followed.

The primary publication from this study will report the results of the study in accordance with the current "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (www.ICMJE.org). Publication of the results will occur in a timely manner according to applicable regulations. Authorship will be based on meeting all the following 4 criteria:

- substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
- drafting the work or revising it critically for important intellectual content
- final approval of the version to be published
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

The publications committee established by the sponsor will oversee this process. Additional publications may follow.

No patent applications based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorization of the sponsor.

12. REFERENCES

1. M. Pugliatti et al., The epidemiology of multiple sclerosis in Europe. European Journal of Neurology 2006, 13: 700–722

2. Compston A., Coles A. Multiple sclerosis. The Lancet. 2008;372(9648):1502–1517. doi: 10.1016/s0140-6736(08)61620-7

3. Lublin F. D., Reingold S. C. Defining the clinical course of multiple sclerosis: results of an international survey. Neurology. 1996;46(4):907–911. doi: 10.1212/wnl.46.4.907

4. Multiple Sclerosis by the Numbers: Facts, Statistics, and You, Healthline, June 2015,

5. Noseworthy J. H., Lucchinetti C., Rodriguez M., Weinshenker B. G. Multiple sclerosis. The New England Journal of Medicine. 2000;343(13):938–952. doi: 10.1056/nejm200009283431307

6. Olek M. Treatment of progressive multiple sclerosis in adults. June 2015, http://www.uptodate.com/contents/treatment-of-progressive-multiple-sclerosis-in-adults

7. Olek M. Treatment of acute exacerbations of multiple sclerosis in adults. http://www.uptodate.com/contents/treatment-of-acute-exacerbations-of-multiple-sclerosis-in-adults

8. Niedziela N. M., Adamczyk-Sowa M., Pierzchała K. Epidemiology and clinical record of multiple sclerosis in selected countries: a systematic review. International Journal of Neuroscience. 2014;124(5):322–330. doi: 10.3109/00207454.2013.840618

9. Amato M. P., Portaccio E. Fertility, pregnancy and childbirth in patients with multiple sclerosis: impact of disease-modifying drugs. CNS Drugs. 2015;29(3):207–220. doi: 10.1007/s40263-015-0238-y

10. Bove R., Alwan S., Friedman J. M., et al. Management of multiple sclerosis during pregnancy and the reproductive years. Obstetrics & Gynecology. 2014;124(6):1157–1168. doi: 10.1097/aog.0000000000000541

11. Hale T. Medications and Mothers' Milk. Plano, Tex, USA: Hale; 2014

12. Copaxone SmPC 2019

13. Hellwig K et al. Presented at AAN 2019 (4-10 May; Philadelphia, Pennsylvania, USA). Poster P2-096

14. Herbstritt S et al. Mult Scler. 2016;22(6): 810–816