PASS PROTOCOL

TITLE:	Non-interventional safety study to investigate pregnancy outcomes in female patients exposed to SC Peginterferon beta-1a and IM Interferon beta-1a reported in a German patient support program
PROTOCOL VERSION IDENTIFIER:	DE-PEG-11650
DATE OF LAST VERSION OF PROTOCOL:	Not Applicable.
EU PAS REGISTER NUMBER:	Study not yet registered
ACTIVE SUBSTANCE:	Interferon beta-1a, Peginterferon beta-1a (Interferon beta-1a: ATC pharmacotherapeutic group L03AB Interferons; Peginterferon beta-1a: ATC-Code: L03AB13 Interferons)
MEDICINAL PRODUCT:	Subcutaneous (SC) and intramuscular (IM) interferon beta therapies: SC Peginterferon beta-1a & IM Interferon beta-1a
PRODUCT REFERENCE:	EU/1/97/033/003 – 004 (IM Interferon beta-1a = Avonex®) EU/1/14/934/001 - 006 (SC Peginterferon beta-1a = Plegridy®)
PROCEDURE NUMBER:	Not applicable
MARKETING AUTHORISATION HOLDER:	Biogen Netherlands B.V. Prins Mauritslaan 13 1171 LP Badhoevedorp The Netherlands
JOINT PASS:	No
RESEARCH QUESTION AND OBJECTIVES:	This non-interventional, voluntary, post-authorization safety study (PASS) is conducted to investigate real-world pregnancy data in adult multiple sclerosis female patients (Clinically Isolated Syndrome (CIS) or Relapsing Remitting MS (RRMS)) receiving either a SC Peginterferon beta-1a therapy or an IM Interferon beta-1a therapy and to analyze data on their children's development up to 48 months of age. This analysis is designed to supplement postmarketing safety data collected from existing Interferon beta Pregnancy Registries. German pregnancy reports are available from MS patients enrolled in a Patient Support Program (PSP) treated with SC Peginterferon beta-1a or IM Interferon beta-1a. Additionally, a standardized questionnaire is used to systematically collect pregnancy outcome data including developmental milestones of the born child and available data on the course of therapy in MS patients who reported "live birth" outcomes.
COUNTRIES OF THE STUDY:	Germany
AUTHOR:	Dr. [redacted]

MARKETING AUTHORISATION HOLDER

MARKETING AUTHORISATION HOLDER (MAH):	Biogen Netherlands B.V. Prins Mauritslaan 13 1171 LP Badhoevedorp The Netherlands
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SIGNATURE PAGE

Protocol DE-PEG-11650 was approved by:

_____ _____

[redacted], MD Date (*DD MMM YYYY*)

EU QPPV & [redacted]

Biogen

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Not applicable

2. LIST OF ABBREVIATIONS

AE	adverse event
AMG	Arzneimittelgesetz (German Drug Law)
ATC	*Anatomical Therapeutic Chemical* (Classification System)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices in Germany)
B.V.	Besloten Vennootschap (Dutch: Limited Company)
CIS	clincally isolated syndrome
CRF	case report form
CRO	contract research organization
DMT	disease modifying therapy
EC	ethics committee
e.g.	for example
ePDF	electronic portable document format
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FLS	flu-like symptoms
GCP	Good Clinical Practice
GVP	Good Pharmacovigilance Practice
ICF	informed consent form
ICH	International Council for Harmonisation
i.e.	that is
IM	intramuscular
IEC	independent ethics committee
Ltd.	limited
MAH	marketing authorization holder
MedDRA	medical dictionary for regulatory activities
MS	multiple sclerosis
MSSC	multiple sclerosis service-center
N.A.	not applicable
NSAE	Non serious adverse event
PAS	post-authorization study
PASS	post-authorization safety study
Patient ID	unique patient identification number
PRAC	Pharmacovigilance Risk Assessment Committee
QC	quality control
QPPV	qualified person for pharmacovigilance
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous

SmPC	summary of product characteristics
SOP	standard operating procedure
WHO	World Health Organization

3. RESPONSIBLE PARTIES

A list of all key sites (e.g., CRO, Multiple Sclerosis Service-Center), with their contact information, is available upon request (see Section 14).

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Biogen may transfer any or all of its study-related responsibilities to a contract research organization (CRO) and other third parties; however, Biogen retains overall accountability for these activities.

4. ABSTRACT

Protocol Title:	Non-interventional safety study to investigate pregnancy outcomes in female patients exposed to SC Peginterferon beta-1a and IM Interferon beta-1a reported in a German patient support program
Version Number:	Version 1.0
Date of Protocol:	30 September 2020
Name and Affiliation of Main Author:	Dr [redacted] Biogen GmbH, Germany
Rationale and Background:	More than 20 years of experience is available on the use of interferon beta treatment to treat multiple sclerosis [Hegen 2015, O'Connor 2014], and their safety and efficacy in MS therapy have been established, even with long-term use. Interferon beta-1a once weekly was approved by the European Medicines Agency (EMA) in 1997 and has a well know safety and tolerability profile, with a long-term experience of more than 23 years. Peginterferon beta-1a, was approved by the EMA in July 2014 and has been available in Germany since September 2014. Two large prospective cohort studies provide evidence for safety data of women in a child-bearing age with MS under interferon beta exposure [Hellwig 2019; Burkhill 2019]. Based on this data, a label change became applicable for the class of interferon beta therapies in September 2019, allowing the use of interferon beta therapies during pregnancy (if clinically needed) and breast-feeding. Real-world pregnancy data reported by German patients is limited. In addition, long-term investigations on child development are lacking. This study is conducted to examine German pregnancy and outcome reports including available data on the child development in women with MS treated with SC Peginterferon beta-1a or IM Interferon beta-1a enrolled in the Patient Support Program (PSP) of Biogen's German MS Service-Center (MSSC). Data has been collected in a validated database from patients seeking unsolicited medical information in the MS Service-Center as well as from participants of the patient support program. In addition to the retrospective analysis of the available pregnancy reports and pregnancy outcome reports, MS patients with reported "live birth" outcomes will be contacted to collect further information on developmental milestones of the born child,

	breast feeding practices, exposure to MS therapies and disease activity.
Research Question and Objectives:	This study's main research question is to assess the course of pregnancy and infant outcomes in pregnant women with MS from Biogen's German MS Service-Center Database. Primary Objective: The primary objective(s) of the study is to evaluate the impact of exposure to SC Peginterferon beta-1a or IM Interferon beta-1a before and during pregnancy on pregnancy outcome in female patients who had registered in the German PSP and of whom a pregnancy report and pregnancy outcome report is available. Secondary Objectives: The secondary objectives of this study are applicable for a subpopulation of the above-mentioned population, i.e. for patients of whom data on a standardized questionnaire collected during a telephone interview is available. The secondary endpoints are as follows: • Average birth weight, average birth length, and head circumference of the newborn • To evaluate the impact of exposure to SC Peginterferon beta-1a or IM Interferon beta-1a before and during pregnancy on child development up to 48 months of age • To assess the SC Peginterferon beta-1a or IM Interferon beta-1a treatment behavior for pregnant women or women becoming pregnant in daily real life • To assess the other MS treatment behavior during/after pregnancy • To assess the use of certain concomitant medications (i.e. non-disease-modifying therapies) taken during pregnancy • To evaluate the effect of SC Peginterferon beta-1a or IM Interferon beta-1a exposure before, during, and after pregnancy on MS disease activity • To assess the effect of breastfeeding under SC Peginterferon beta-1a or IM Interferon beta-1a therapy on the MS disease activity • To assess the benefit of exclusive breastfeeding versus complementary feeding on the MS disease activity in women breastfeeding under SC Peginterferon beta-1a or IM Interferon beta-1a therapy

Study Design:	This non-interventional, voluntary PASS is designed as a single-center open-label survey. Spontaneously reported safety data are available for pregnant MS patients treated with SC interferon beta therapy or an IM interferon beta therapy in the German PSP of the MSSC. In addition, a prospective data collection is performed by completing a standardized paper questionnaire while interviewing MS patients who reported a "live birth" and for which a signed ICF is available.
Population:	All female patients treated with SC Peginterferon beta-1a therapy or IM Interferon beta-1a therapy who fulfill the inclusion criteria are eligible to participate in the study. **Inclusion Criteria** 1. Female patients of at least 18 years at time of informed consent 2. Diagnosed RRMS or CIS (CIS indication only applicable for interferon beta-1a) 3. Exposure to either SC Peginterferon beta-1a therapy or IM Interferon beta-1a therapy before or during pregnancy 4. Registered in the PSP of the MSSC and agreed in writing to the privacy policy of the registration form 5. Reported pregnancy data (pregnancy report and pregnancy outcome report) available at MSSC. Note: only pregnancy data (i.e. obtained until 15 October 2020) will be considered. For the prospective part of the study: 6. Ability to understand the purpose of the study and provide signed and dated study-specific informed consent form (ICF) 7. Pregnancy outcome in the retrospectively collected data was a live birth
Variables:	• Demographic data • SC Peginterferon beta-1a or IM Interferon beta-1a use, including treatment duration, prior to, during and after pregnancy • Concomitant medication prior to and during pregnancy • Pregnancy outcome, including gestation week and description of abnormalities of the fetus, reason for termination, diagnostics, etc. • Complications during pregnancy • Type of delivery, complications during delivery or reasons for an intervention • Placenta normal/abnormal

	• Data on newborn (sex, weight, height, head circumference, Apgar scores) • Weight, height and head circumference of child measured under statuary programs of the standardized German pediatric check-up booklet • Abnormalities diagnosed during pediatric check-ups under statutory programs as reported in the standardized German pediatric check-up booklet • Pregnancy and family anamnesis • Vitamin K prophylaxis • Body weight, height, head circumference of the child as documented for check-ups 2-8 • Lactation (exclusive breastfeeding and breastfeeding with supplemental feedings) • Other MS therapies during or after pregnancy and start relative to birth • MS relapses in the year before pregnancy • MS relapses during pregnancy • MS relapses after pregnancy/birth • EDSS before, during and after pregnancy
Data Sources:	<u>Retrospective Data Capture:</u> MSSC database, i.e. the entered pregnancy report (to be completed as soon as pregnancy becomes known) and pregnancy outcomes report (to be completed after completion of pregnancy). <u>Prospective Data Capture</u> Standardized ePDF questionnaire completed during telephone interview
Study Size:	Since this is an exploratory study and no formal hypothesis-testing will be carried out, there is no formal sample size calculation. The sample size of the prospective study part depends on how many patients are eligible to participate in this observation and will agree to provide data for the questionnaire. Based on the current data entered in the MSSC data base, about 310 patient questionnaires are expected to be completed during the telephone interview. It is expected that about 400 patients will be included in the retrospective study part.
Data Analysis:	This study is an observational study with focus on existing pregnancy reporting forms (retrospective part) and a patient's

	questionnaire which is completed at a single point of time (prospective part). It will not be distinguished between the two treatments, i.e. the data will be pooled for analysis. All documented data are analyzed by descriptive statistics, i.e. absolute frequencies and percentages for categorical variables and mean, standard deviation and percentiles for continuous variables. No formal statistical hypothesis will be formulated, and no statistical tests will be carried out. In case of missing or unknown data, no data imputation will be performed.
Milestones:	Start of data collection (prospective part of the study): December 2020 End of data collection: 31 March 2021 Registration in EU PAS Register: October 2020 Final report of study results: 30 June 2021

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Table 1: Milestones for Protocol DE-PEG-11650

Milestone	Planned Date
Start of data collection (prospective part of the study)	December 2020
End of data collection	31 March 2021
Study progress report	Not applicable
Interim report(s) of study results	Not applicable
Registration in EU PAS Register	October 2020
Final report of study results	30 June 2021

7. RATIONALE AND BACKGROUND

Multiple sclerosis (MS) is the most common autoimmune disease of the central nervous system, mainly affecting women of reproductive age [Hauser and Oksenberg, 2006], with pregnancy and birth outcomes being major concerns for many women with MS. The PRIMS study (Pregnancy in Multiple Sclerosis multicenter European study) showed that, overall, pregnancy did not affect the long-term clinical course of MS [Vukusic 2004]. PRIMS provided evidence that relapse rates go down during pregnancy in MS women, and then restart after giving birth. The study also showed that disability progression is similar between pregnant MS women and the general MS population, suggesting that the overall impact of pregnancy on MS course seems to be neutral [Houtchens et al., 2018; Vukusic 2004].

There is a lack of safety information on drug's use in pregnancy as clinical trials rarely include pregnant women. As a consequence, most information regarding the safety/risk profile of drugs during pregnancy is collected after the drug has been approved and used by pregnant women intentionally or unintentionally.

More than 20 years of experience is available on the use of interferon beta treatment to treat multiple sclerosis [Hegen 2015, O'Connor 2014], and their safety and efficacy in MS therapy have been established, even with long-term use.

Interferon beta-1a once weekly was approved by the European Medicines Agency (EMA) in 1997 and has a well know safety and tolerability profile, with a long-term experience of more than 23 years. The products risk-benefit ratio has remained positive in the long-term treatment.

Peginterferon beta-1a, pegylated interferon beta-1a, was developed as a modern pegylated version of the native protein interferon beta-1a with improved pharmacological properties to provide an interferon with increased interferon efficacy, higher interferon exposure, decreased renal clearance and longer elimination half-life to facilitate adherence by reducing frequency of application. It was approved by the EMA in July 2014 and has been available in Germany since September 2014. Peginterferon beta-1a is injected every 2 weeks. Peginterferon beta-1a hence constitutes an additional option for injectable disease-modifying therapy of RRMS with an established risk-benefit ratio [Calabresi 2014; Arnold 2014; Kieseier 2015; Arnold 2017; Calabresi 2017; Arnold 2018; Newsome 2018], established injectable efficacy [Calabresi 2014; Arnold 2014; Kieseier 2015; Arnold 2017; Calabresi 2017; Arnold 2018; Newsome 2018] and statistically significant lowest total cumulative flu-like symptoms (FLS) duration under the interferons [Hendin 2018]. This might be especially useful in the sensitive period of pregnancy and lactation.

7.1. Profile of Previous Experience

7.1.1. Nonclinical Experience with Interferon Beta

In animal studies an exposition with interferon beta in extremely high doses was correlated with an increased risk of abortion, which has not been verified in humans.

7.1.2. Clinical Experience with Interferon Beta

Available data on the safety of interferons during pregnancy and breastfeeding was limited, as interventional clinical trials generally exclude pregnant patients.

Two large prospective cohort studies provide evidence for safety data of women in a child-bearing age with MS under interferon beta exposure:

- A European Interferon beta Pregnancy Registry, a prospective observational collection of information on women with MS exposed to interferon beta during pregnancy, was established to address the lack of evidence. Using spontaneous and solicited reports, the registry collected data from 26 countries of the European Economic Area. Cumulative data from 2447 pregnancies with 948 reported outcomes were collected from April 2009 to June 2017 in the European Interferon beta Pregnancy Registry.

  An analysis from the registry showed that the prevalence of spontaneous abortions (10.7% vs up to 21%) and live births with congenital anomalies (1.8% vs 2.1 - 4.1%) were comparable with the numbers reported in the general population [Hellwig 2020].

- A population-based cohort study was conducted leveraging healthcare register data from two Nordic countries (Finland and Sweden). In this Nordic register cohort study, the prevalence of infant outcomes after birth have been analyzed (3054 pregnancy events with known pregnancy outcomes) including interferon beta exposed women (n= 814) compared to interferon beta unexposed women (n= 1831).

  Results from the Nordic registers showed no evidence that interferon beta exposure before conception and/or during pregnancy adversely affected pregnancy or infant outcomes in comparison with non-disease modifying therapies (DMT) exposed women. This register also showed no evidence that interferon beta exposure before and during pregnancy affected infant birth weight and head circumference. The proportion of infants who were small for their gestational age (SGA) or large (LGA), as determined by weight, were comparable between the Interferon beta exposed and unexposed cohorts [interferon beta exposed vs unexposed: 2.1% vs 2.0% and 0.8% vs 0.8% respectively]. The mean (+/- SD) infant birth weights were similar between the interferon beta exposed and unexposed cohorts (interferon beta exposed vs unexposed: 3416.7 ± 606.4 g vs 3389.6 ± 587.6 g) (8). The prevalence of very low birth weight (< 1500 g) was 1.2% in the Interferon beta exposed cohort vs 1.1% in the unexposed cohort. The prevalence of low birth weight (1500 – 2499 g) was 3.9% in the Interferon beta exposed cohort vs 4.8% in the unexposed cohort. The mean (+/- SD) infant head circumferences were similar between the live births of interferon beta exposed and unexposed cohorts (interferon beta exposed vs unexposed: 35.0 cm ± 1.4 cm vs 35.0 cm ± 1.5 cm) (8). Less than 2% of infants had low head circumference in both cohorts (interferon beta exposed vs unexposed: 1.9% vs 1.1%. Limitations included lack of available data for all infants, a well-balanced sample distribution in terms of interferon beta exposure before pregnancy (86%) and/or during the first trimester (31%), and a formal analysis for comparing the

outcome measures. The study showed no evidence that interferon beta exposure before and during pregnancy affects the birth weight or head circumference of the newly born infants [Hellwig 2018; Hellwig 2019; Burkill 2019].

Limited data characterizing the transfer of interferons into human milk following their administration in patients with MS who are breastfeeding are available. A study in breastfeeding mothers treated with IM Interferon beta-1a showed that the transfer of interferon beta-1a into human milk is negligible at the doses commonly administered intramuscularly in patients with MS and none of the mothers noticed any adverse effects in their breastfed infants (Hale 2001). The Multiple Sclerosis Centre of Excellence on Reproduction and Child Health considers interferon beta to be "moderately safe" to use during breastfeeding (Bove 2014) and a French consensus group of neurologists concluded that interferon beta can be used during breastfeeding. (Bodiguel 2014).
In another study (Hellwig 2011), interferon toxicity during breastfeeding was assessed as unlikely due to the high molecular weight of the interferon molecule as alveolar epithelial cells form an impenetrable barrier for substances with a molecular weight > 1,000 Daltons (Interferon beta: 22,500D). Second, if ingested orally, interferon beta is likely to be metabolized. The available clinical results from lactating women on the transfer of interferon beta-1a into breast milk, together with the chemical / physiological characteristics of interferon beta, suggests that levels of interferon beta-1a excreted in human milk are negligible.

Based on the available data, the following label change became applicable for the class of interferon beta therapies (inclusive SC Peginterferon beta-1a and IM Interferon beta-1a) in September 2019:

- If clinically needed, the use of interferon beta therapies may be considered during pregnancy.
- Interferon beta therapies can be used during breast-feeding.

7.2. Study Rationale

Real-world pregnancy data specific for the German population is limited. In addition, long-term investigations on child development are lacking.

This study is conducted to examine German pregnancy and outcome reports including available data on the child development in women with MS treated with SC Peginterferon beta-1a or IM Interferon beta-1a enrolled in the Patient Support Program (PSP) of Biogen’s German MS Service-Center (MSSC). Data has been collected in a validated database from patients seeking unsolicited medical information in the MS Service-Center as well as from participants of the patient support program.

In addition to the retrospective analysis of the available reports, MS patients with reported “live birth” outcomes will be contacted to inquire about:

- Developmental milestones of the born child as reported in the standardized German pediatric check-up booklet “Kinderuntersuchungsheft” as defined in the Children’s Policy “Kinderrichtlinien” (Kinderrichtlinien 2020) by the German

Federal Joint Committee “Gemeinsamer Bundesausschuss”, the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany.
- Breast feeding practices
- MS disease activity prior to and during pregnancy as well as postpartum

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Research Question

This study’s main research question is to assess the course of pregnancy and infant outcomes in pregnant women with MS from Biogen’s German MS Service-Center Database.

Another aim is to learn more about if/when in real life SC Peginterferon beta-1a or IM Interferon beta-1a therapy is stopped for women who become pregnant in the real life setting and if/when the interferon-beta therapy is continued postpartum.

Furthermore, it will be assessed if there is a difference in the MS disease progression depending on the interferon beta exposure and breast-feeding practices.

Data of women exposed to SC Peginterferon beta-1a and IM Interferon beta-1a prior to the pregnancy, during the pregnancy and postpartum will be evaluated for course of pregnancy and pregnancy outcome.

8.2. Primary Objective

The primary objective(s) of the study is to evaluate the impact of exposure to SC Peginterferon beta-1a or IM Interferon beta-1a before and during pregnancy on pregnancy outcome in female patients who had registered in the German PSP and of whom a pregnancy report and pregnancy outcome report is available.

8.3. Secondary Objectives

The secondary objectives of this study are applicable for a subpopulation of the above-mentioned population, i.e. for patients of whom data on a standardized questionnaire collected during a telephone interview is available. The secondary endpoints are as follows:

- To evaluate the impact of exposure to SC Peginterferon beta-1a or IM Interferon beta-1a before and during pregnancy on **child development** up to 48 months of age
- To assess the SC Peginterferon beta-1a or IM Interferon beta-1a **treatment behavior** for pregnant women or women becoming pregnant in daily real life
- To assess the other MS **treatment behavior** during/after pregnancy

- To assess the use of certain concomitant medications (i.e. non-disease-modifying therapies) taken during pregnancy
- To evaluate the effect of SC Peginterferon beta-1a or IM Interferon beta-1a exposure before, during, and after pregnancy on MS **disease activity**
- To assess the effect of breastfeeding under SC Peginterferon beta-1a or IM Interferon beta-1a therapy on the MS disease activity
- To assess the benefit of exclusive breastfeeding versus complementary feeding on the MS disease activity in women breastfeeding under SC Peginterferon beta-1a or IM Interferon beta-1a therapy

9. RESEARCH METHODS

9.1. Study Design

This non-interventional, voluntary PASS is designed as a single-center open-label survey.

Spontaneously reported safety data are available for pregnant MS patients treated with SC interferon beta therapy or an IM interferon beta therapy in the German PSP of the MSSC.

In addition, a prospective data collection is performed by completing a standardized questionnaire while interviewing MS patients who reported a “live birth” and for which a signed ICF is available.

9.1.1. Primary Endpoints

- Number and proportion of
  - live births without congenital anomalies,
  - live births with congenital anomalies,
  - ectopic pregnancies,
  - spontaneous abortions,
  - elective abortions,
  - preterm births,
  - stillbirths

A spontaneous abortion is defined as fetal death before 22 weeks of gestation. A still birth is defined as fetal death at > 22 weeks gestation. A preterm birth is a birth before 37 completed weeks of gestation.

9.1.2. Secondary Endpoints

- Average weight, average length, and average head circumference of the children from birth to 48 months
- Number and proportion of abnormalities diagnosed during pediatric check-ups under statutory programs in Germany and reported in the standardized German pediatric check-up booklet “Kinderuntersuchungsheft” (data on check-ups 1-8 will be collected covering the first 46 - 48 months of life). Refer to Annex 3 for recommended timepoints and details on the examinations.
- Number and proportion of women discontinuing SC Peginterferon beta-1a or IM Interferon beta-1a therapy during pregnancy and time to discontinuation in relation to beginning of pregnancy

- Number and proportion of women starting SC Peginterferon beta-1a or IM Interferon beta-1a therapy during pregnancy and time to start in relation to beginning of pregnancy
- Number and proportion of women restarting SC Peginterferon beta-1a or IM Interferon beta-1a therapy after birth and time to restart in relation to birth
- Number and proportion of women starting another MS therapy during/after pregnancy and time to start in relation to birth
- Number and proportion of women using other therapies during pregnancy (categorized by Paracetamol, other therapies for the alleviation of FLS), folic acid, medication for depression, corticosteroids, adrenocorticotrophic hormone, other therapies)
- Number and proportion of MS relapses in women with SC Peginterferon beta-1a or IM Interferon beta-1a therapy before, during and after pregnancy
- Change of EDSS during and after pregnancy to EDSS before pregnancy
- Lactation: number of women breastfeeding under SC Peginterferon beta-1a or IM Interferon beta-1a therapy and duration of SC Peginterferon beta-1a or IM Interferon beta-1a exposed breastfeeding
- Time to first MS relapse after introduction of the first supplemental feedings in women with SC Peginterferon beta-1a or IM Interferon beta-1a therapy during lactation

9.2. Setting

All female patients treated with SC Peginterferon beta-1a therapy or IM Interferon beta-1a therapy who fulfill the inclusion criteria are eligible to participate in the study.

Patients registering in the PSP of the MSSC have to sign a privacy policy allowing the use of collected data for scientific purposes. This written consent covers the extract of data concerning the pregnancy reporting (retrospective part of the study).

All participants taking part in the prospective part of the study will be provided with a study specific patient information form and are informed by the MSSC of all pertinent aspects of the study. Written informed consent will be obtained from the participant (or legal representative) before the telephone interview takes part.

9.2.1. Selection Criteria

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

Inclusion Criteria

1. Female patients of at least 18 years at time of informed consent
2. Diagnosed RRMS or CIS (CIS indication only applicable for interferon beta-1a)

3. Exposure to either SC Peginterferon beta-1a therapy or an IM Interferon beta-1a therapy before or during pregnancy
4. Registered in the PSP of the MSSC and agreed in writing to the privacy policy of the registration form
5. Reported pregnancy data (pregnancy report and pregnancy outcome report) available at MSSC. Note: only pregnancy data (i.e. obtained until 15 October 2021) will be considered.

For the prospective part of the study:

6. Ability to understand the purpose of the study and provide signed and dated study-specific informed consent form (ICF)
7. Pregnancy outcome in the retrospectively collected data was a live birth

9.2.2. Study Location

The study is planned to be performed in Germany enrolling MS patients registered in the PSP of the MSSC.

9.2.3. Overall Study Duration and Follow-Up

9.2.3.1. Enrollment

The study period will start with the identification and enrollment of patients meeting the eligibility criteria. Recruitment is planned for 3 months. The end of study is defined as end of overall data collection when the database for analysis is completely available.

The Sponsor may terminate or prolong this study at any time, after informing the participating parties.

Data of the retrospective study part will be extracted from the German MS Service-Center database on the basis of the PSP registration form, i.e. the signed privacy policy. No separate patient information and consent procedure is planned for this part.

The study participation in the prospective study part starts with signature of the ICF and ends with the completion of the patient questionnaire. As the provision of the ICF by the MSSC and the return of the signed ICF by the patient is done by mail, both actions are expected to take 1-2 weeks. The telephone interview will take place only after having obtained the signed ICF. Depending on the availability of the patient for the telephone interview, another week has to be calculated resulting in an average study duration of about 2-3 weeks per patient in the prospective study part.

Patients in the prospective study part are informed that they have the right to withdraw from the study at any time, without prejudice to their medical care, and that they are not obliged to state their reasons. Any withdrawal must be fully documented in the MSSC data base. Withdrawn patients are not followed-up.

Unique identification numbers will be assigned to all pregnancy reports of participants enrolled in the study to track them throughout the study. In case of multiple pregnancies, separate identification numbers will be assigned for the pregnancies. Any identification

numbers that are assigned will not be reused even if a participant withdraws from the study prematurely.

An individual study participant may be included only once in the study – however, data of multiple pregnancies will be collected separately.

Participants who prematurely withdraw from the study for any reason will not be eligible to re-enroll.

9.2.3.2. Withdrawal of Participants from the Study

Participants in the prospective study part may withdraw consent to be in the study at any time. If withdrawal occurs before the telephone interview, the MSSC will collect no further information. Consent withdrawal of the prospective part of the study will be documented in the MSSC database.

9.2.3.3. Lost to Follow-Up

If a participant could not be contacted by the MSSC following the provision of the signed ICF, the MSSC may consider a participant lost to follow up after 5 failed documented telephone contacts and one failed email contact attempt. In this case, the questionnaire will not be filled in. If the MSSC ascertains a participant has died, the death should be recorded and reported within postmarketing channels as described in Section 11.3.1.1.

9.3. Variables

Information collected for analysis is outlined in Section 16.

9.4. Data Sources

9.4.1. Retrospective Data Capture

Main data source for the retrospective data capture is the MSSC database, i.e. the entered pregnancy report (to be completed as soon as pregnancy becomes known) and pregnancy outcomes report (to be completed after completion of pregnancy).

The following data is extracted from the MSSC database:

- Demographic data (age, height, weight)
- SC Peginterferon beta-1a or IM Interferon beta-1a use, including treatment duration, prior to, during and after pregnancy
- Concomitant medication prior to and during pregnancy
- Pregnancy outcome (live birth without defect, live birth with defects, ectopic pregnancy, spontaneous abortion, elective termination of pregnancy, preterm birth, stillbirth), including gestation week and description of abnormalities of the fetus, reason for termination, diagnostics, etc.
- Complications during pregnancy

- Type of delivery (vaginal delivery: spontaneous, induced, instrumentally supported; Caesarean section: elective, medically indicated), complications during delivery or reasons for an intervention
- Placenta normal/abnormal
- Data on newborn (sex, weight, height, head circumference, Apgar 1 minute, Apgar 5 minutes, Apgar 10 minutes)

9.4.2. Prospective Data Capture

If the pregnancy report or the pregnancy outcome report is incomplete, i.e. the data above was not collected, the open questions will be addressed during a telephone interview performed by the MSSC and the new information will be entered into the MSCC database. No further assessments other than completion of the questionnaire are applicable for patients participating in the prospective study part. The patient questionnaire is completed at a single point of time during the telephone interview performed by the MSSC.

The patient questionnaire covers the following questions:

- Abnormalities diagnosed during pediatric check-ups under statutory programs as reported in the standardized German pediatric check-up booklet "Kinderuntersuchungsheft)" (data on check-ups 1-8 will be collected covering the first 46-48 months of life)
- Pregnancy and family anamnesis
- Vitamin K prophylaxis
- Body weight, height, head circumference of the child as documented for check-ups 2-8.
- Lactation:
  - Exclusive breastfeeding and duration (1st week, 1 month, 2 months, 3 months, 5 months, 6 months, 7-9 months, 10-12 months, > 12 months) of breastfeeding
  - Supplemental feedings (starting month after birth)
- Other MS therapies (non-interferon beta-1a DMTs) during or after pregnancy and start relative to birth (during pregnancy, < 1 week after birth, after 1 week, after 2 weeks, after 3 weeks, after 4 weeks, after 6 weeks, after 2 months, after 3 months, after 4 months, after 5 months, after 6 months, after 7 months, after 8 months, after 9 months, after 10 months, after 1 months, after 12 months or later))
- Frequency of MS relapses in the year before pregnancy
- Time (1st trimester, 2nd trimester, 3rd trimester) and frequency of MS relapses during pregnancy

- Time (< 1st month, 1st – 2nd month, 3rd - 4th month, 5th - 6th month, 7th - 8th month, 9th - 10th month, 11th - 12th month, 13th - 14th month, 15th - 16th month, 17th - 18th month, > 18th months) and frequency of MS relapses after pregnancy/birth
- EDSS before, during and after pregnancy

The information collected by the MSSC will be stored in a secure database.

9.5. Study Size

Since this is an exploratory study and no formal hypothesis-testing will be carried out, there is no formal sample size calculation. The sample size of this study depends on how many patients are eligible to participate in this observation and will agree to provide data for the questionnaire.

As of mid-July 2020, there were n = 202 pregnancy and pregnancy outcome reports for 184 female patients under SC Peginterferon beta-1a and n = 245 pregnancy and pregnancy outcome reports for 199 female patients treated with IM Interferon beta-1a in the MSSC database. The outcome of 368 pregnancies was a live birth, hence qualify for the prospective study part. About 290 patient questionnaires are expected to be completed during the telephone interview (80% return rate estimated). This number might increase until 15th October 2020 - the cut-off point for data collection.

9.6. Data Management

MS Service-Center database:

The Biogen MS Service-Center provides medical information to German MS patients on request. Furthermore, it offers enrollment to a patient support program for SC Peginterferon beta-1a and IM Interferon beta-1a patients including injection handling training and individual adherence coaching form a personal coach upon medical need. Services have been provided since October 2014 from Audimedes GmbH, certified according to ISO 9001:2015 criteria. Compliance with these criteria is audited annually by an external certified audit organization. Database includes data of about 45,000 patients with MS.

From 2014 until December 2019 3, 615 patients under IM Interferon beta-1a treatment and 7,529 patients under SC Peginterferon beta-1a treatment have been enrolled to the patient support program. In the database, demographics and therapeutic history including adverse events, product complaints and pregnancy reports are captured in real time. All personnel dealing with the patient information and database undergo regular training to ensure quality of information, communication skills and quality of data in the database. All data is pseudonymized and pooled for this analysis.

Study database:

Data collection for the retrospective study part will be performed by extracting the relevant data from the existing MSSC database and importing it into an electronic PDF (ePDF) by a CRO. During the telephone interview, missing data will be completed directly in the ePDF, if appropriate. After the CRO has received all completed ePDFs, all

data will be exported and used for analysis by the CRO as well as for updating the MSSC database (Audimedes GmbH).

All relevant data for the prospective study part is documented on standardized patient questionnaires provided as ePDF. The MSSC personnel documents the results of the telephone interview directly in the ePDF and after completion, the ePDF is transferred to the CRO to export and analyze the data together with the retrospective data.

Personal data of patients are gathered, stored and processed exclusively in a pseudonymous form according to national data protection laws.

9.7. Data Analysis

This study is an observational study with focus on existing pregnancy reporting forms (retrospective part) and a patient's questionnaire which is completed at a single point of time (prospective part).

It will not be distinguished between the two treatments, i.e. the data will be pooled for analysis.

All documented data are analyzed by descriptive statistics, that is, no formal statistical hypothesis will be formulated, and no statistical tests will be carried out.

Categorical variables will be summarized descriptively by absolute frequencies and percentages. The denominator for all percentages will be the total number of pregnancies within the respective group, unless otherwise indicated. Percentages will be presented to one decimal place and will not be displayed for zero frequencies. A row denoted "Missing" will be included in all tabulations to clearly indicate the completeness of the collected data, i.e. missing data is included in the denominator of the percentages.

Continuous variables will be tabulated by descriptive statistics, i.e. the total number of pregnancies (n), number of pregnancies with missing values (Nmiss), mean, standard deviation, median, quartiles, minimum and maximum.

If sensible, free text entries will be transferred into appropriate encoding schemes to be analyzed in frequency tables. If appropriate, change of values during/after pregnancy to values before pregnancy will be calculated and analyzed using descriptive statistics or shift tables.

In case of missing or unknown data, no data imputation will be performed. For a complete presentation all obtained data will be listed.

A statistical analysis plan will be drafted and finalized before the end of the overall data collection to describe all analyses in more detail.

9.7.1. Analysis Population

9.7.1.1. Primary Endpoint Analysis

The analysis set for the primary objective will be defined by the group of patients that are registered in the PSP, agreed to the privacy policy of the registration form, and were

eligible to participate in this observation (see 9.2.1**Fehler! Verweisquelle konnte nicht gefunden werden.**).

9.7.1.2. Secondary Endpoint Analysis

The analysis set for the secondary objectives will be defined by the group of patients that gave written informed consent, had a live birth outcome, provided data for the patient questionnaire and were eligible to participate in this observation (see 9.2.1**Fehler! Verweisquelle konnte nicht gefunden werden.**).

9.7.2. Subgroup Analysis

Subgroup analyses will be performed with respect to patient's interferon beta-1a treatment history before during and after pregnancy. The primary endpoint will be evaluated in following subgroups:

- SC Peginterferon beta-1a or IM Interferon beta-1a was taken continuously before and during pregnancy
- SC Peginterferon beta-1a or IM Interferon beta-1a therapy was paused/stopped during pregnancy
- SC Peginterferon beta-1a or IM Interferon beta-1a therapy was started during pregnancy

The secondary endpoints will be evaluated in following subgroups:

- SC Peginterferon beta-1a or IM Interferon beta-1a was taken continuously before, during and after the pregnancy
- SC Peginterferon beta-1a or IM Interferon beta-1a therapy was started during pregnancy
- SC Peginterferon beta-1a or IM Interferon beta-1a therapy was paused during pregnancy and restarted promptly (within 1 week) after "life birth"
- SC Peginterferon beta-1a or IM Interferon beta-1a therapy was stopped during pregnancy and restarted more than a week after "life birth"
- SC Peginterferon beta-1a or IM Interferon beta-1a therapy was stopped during pregnancy and not restarted after "life birth"

9.7.3. Further evaluation

- Age, weight and height of the patients plus pregnancy and family anamnesis will be tabulated as well as gestation week, type of birth, placenta characteristics and Vitamin K prophylaxis.
- Complications during pregnancy and at birth will be listed.

9.7.4. Interim Analyses

No interim analysis is planned for this study.

9.8. Quality Control

The study will be conducted and reported in accordance with the "Guideline on good pharmacovigilance practices (GVP) Module VIII - Post-authorisation safety studies".

Data management and quality assurance for the study are in accordance with the German document „Gemeinsame Bekanntmachung des Bundesinstituts für Arzneimittel und Medizinprodukte (BfArM) und des Paul-Ehrlich-Instituts (PEI) zur Anzeige von Anwendungsbeobachtungen nach §67 Absatz 6 Arzneimittelgesetz und zur Anzeige von nichtinterventionellen Unbedenklichkeitsprüfungen nach §63f und g Arzneimittelgesetz" in the final version of December 20th, 2019.

Retrospective data are automatically checked for plausibility, completeness and mandatory information by programmed edit checks during the data entry by the MSSC in their database. Pregnancy data is further checked for consistency and plausibility by a trained medical documentation officer before being sent to Biogen Pharmacovigilance department. By using the ePDF for the patient questionnaire, data are entered by the MSCC in a standardized way and simple checks are implemented. The prospective and retrospective data of lactation and Interferon therapy will be manually cross-checked for consistency by MSCC.

MSSC checks also the patient questionnaires (ePDF) manually for potential adverse and other safety events and reports the events to the Sponsors Pharmacovigilance as per section 11.3.

For quality control purposes, random samples of all MSSC contacts are checked for compliance with Good Documentation Practice and missed adverse events on a daily basis. Pharmacovigilance relevant information is further checked for consistency and integrity by a trained medical documentation officer and is submitted directly to Biogen or to appointed third parties for pharmacovigilance services.

Due to the non-interventional character of the study, missing values and/or implausibility may persist and will be accepted.

9.8.1. Site Initiation

The MSSC must not enroll any participants in this study prior to completion of a study initiation in which the involved MSSC personnel is trained. This initiation training will include a detailed review of:

- The protocol
- Informed consent and patient information
- Patient Questionnaires and their handling
- Completion of the ePDF

Training of Adverse Event Reporting is performed independently of the study, on a half-yearly basis as refresher on reporting pregnancies, product complaints and adverse events.

9.8.2. Quality Assurance

Quality control procedures will be implemented at each stage of data handling to ensure that all data are reliable and have been processed correctly. The MSSC is responsible for demonstrating timely oversight of all trial data.

During and/or after completion of the study, quality assurance officers named by Biogen or the regulatory authorities may wish to perform onsite audits or inspections. The MSSC will be expected to cooperate with any audit or inspection and to provide assistance and documentation (including source data) as requested.

9.8.3. Monitoring of the Study

Biogen may conduct onsite visits at the MSSC for the purpose of monitoring various aspects of the study. The MSSC must agree to marketing authorization holder (MAH)-authorized personnel having direct access to the participant (or associated) files for the purpose of verifying entries made in the ePDFs, and assist with their activities, if requested. Adequate time and space for monitoring visits should be made available by the MSSC site staff.

9.8.4. Retention of Study Data

The MSSC will hand-over all data generated within this non-interventional study to Biogen GmbH at the end of the trial.

Biogen will archive the study data for a time period determined in the company SOP PRCD-94210 “Global Records Retention and Disposition Schedules”.

9.9. Limitations of the Research Methods

The study will be non-comparative. The lack of an internal reference therapy is a weakness of this study and should be kept in mind when interpreting the data.
In non-interventional studies, the amount of data cleaning is limited. Therefore, missing values and/or implausible values are to be expected. The SAP will provide a detailed description on how to handle those values. In general, no substitution of missing values is planned.

9.10. Other Aspects

Not applicable.

9.10.1. Study Funding

Biogen is the MAH of the study and is funding and conducting the study.

9.10.2. Publications

As there are no investigators participating in the study, Biogen is the sole owner of the study data.

10. PROTECTION OF HUMAN PARTICIPANTS

Biogen and Biogen's MSSC must comply with this protocol and applicable International Council for Harmonisation (ICH), Good Clinical Practice (GCP), and Good Pharmacovigilance Practice (GVP) guidelines, and conduct the study according to local regulations.

The MSSC may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH, GCP, and GVP guidelines. The MSSC should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated. The MSSC is responsible for supervising those individuals and for implementing procedures to ensure the integrity of the tasks performed and any data generated.

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki

10.1. Ethics Committee

The approval of the protocol, ICF, patient questionnaire, and other required study documents must be obtained prior to starting the study. The CRO will submit documents on behalf of Biogen to the competent ethics committee of the scientific expert for assessment. If the MSSC makes any changes to the ICF, Biogen must approve the changes before the ICF is submitted to the ethics committee by the CRO. A copy of the approved ICF must be provided to Biogen. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and Biogen.

Biogen must receive a letter documenting ethics committee approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

10.2. Participant Information and Consent

Prior to any data collection under this protocol, it has to be ensured that a written agreement to the privacy policy of the PSP registration form is available.

Informed consent with the approved ICF must be obtained before progressing with the telephone interviews for the prospective study part. Patients will be contacted by phone and asked about their interest in study participation by the MSSC. The background of the proposed study, the data collected, and the voluntary nature of study participation will be explained to the participant (or the participant's legally authorized representative).

In case of positive feedback, participants will be provided with 2 copies of the ICF by mail and asked to take sufficient time to consider whether to partake in the study. In case of open questions, the MSSC can be contacted at any time.

Participants will be asked to send back one signed and dated original in case a patient agrees to the study participation and has no further questions. The second ICF will remain with the participant.

Confirmation of informed consent must be documented in the participant's MSSC data base prior to any prospective data collection under this protocol.

Each ICF should contain an authorization allowing the MSSC and Biogen to use and disclose protected health information (i.e., participant-identifiable health information) in compliance with local law.

The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

10.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect participant safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

In the event of a protocol modification, the ICF may require similar modifications (see Sections 10.1 and 10.2).

10.4. Participant Data Protection

Prior to any data collection under this protocol, participants must also provide all authorizations required by local law.

During the study, participants' age and gender will be collected. These data will be used in the analysis of the safety profile of the study treatment.

The participant will not be identified by name in the ePDFs, study-related forms, study reports, and related publications, and these reports will be used for research purposes only. Biogen, its partners and designee(s), ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the participant's personal medical data confidential.

10.5. Internal Safety Review

Applicable personnel at Biogen will review all SAEs on a regular basis.

10.6. Compensation for Injury

Not applicable for non-interventional studies.

10.7. Conflict of Interest

Not applicable.

11. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

11.1. Definitions

11.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

11.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- results in death
- places the participant at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- results in a congenital anomaly/birth defect
- is a medically important event

An AE is considered serious due to medical importance by Biogen or designee in case the event is listed on the Biogen internal guideline DEV-JA-1904 “Medically Significant List”. The effective version at the time of reporting is used for the assessment.

11.2. Safety Classifications

11.2.1. Assessment of Events

Biogen or designee will assess all events to determine the following:

- If the event meets the criteria for an SAE as defined in Section 0.
- The relationship of the event to study treatment as per Biogen’s standard data handling process for reports originating from studies

Severity is not collected in this study as the safety data is collected by interviewing mothers by phone by using predetermined standardized questions.

11.2.2. Expectedness of Events

Expectedness of all AEs will be determined by Biogen according to the approved local label.

11.3. Monitoring and Recording Events

11.3.1. Non-Serious and Serious Adverse Events

Any pregnancies and any AEs related to the pregnancies that are analysed as part of this study have been collected and reported to Biogen in the frame of routine pharmacovigilance activities in the past. Non-serious (NSAEs) and serious (SAE) events related to study endpoints about child development and maternal MS relapses (Refer to Section 9.1 for details) will be collected prospectively from the participants in a phone interview by the MSSC and recorded as part of this study. The interview follows a predetermined structure with standardized questions. In addition, the interview may generate updates to the previously provided pregnancy data. This data will be recorded and submitted within the study.

Any other safety events (i.e. AE, pregnancies, medication errors etc.) reported spontaneously by the participants by phone will not be documented as an event within this study but will be documented and reported as spontaneous events according to standard local postmarketing channels.**Deaths**

Death is an outcome of an event. The event that resulted in death should be recorded and reported as an SAE. Biogen or designee will make every effort to obtain death certificates and autopsy reports from the reporter. The term death is reported as an SAE only if the cause of death is not known and cannot be determined.

11.3.2. Reporting Events

Reporting Information for SAEs and NSAEs Collected Prospectively
To report initial or follow-up information on an NSAE or SAE or pregnancy within the study, the MSSC personnel e-mail in addition to the completed questionnaire a completed AE Form and/or pregnancy form (as appropriate) to Biogen drugsafety-germany@biogen.com

11.4. Procedures for Handling Special Situations

11.4.1. Overdose

An overdose is any dose of IM Interferon beta-1a or SC Peginterferon beta-1a given to a patient or taken by a patient that exceeds the dose described in the local label. Overdoses are not considered AEs; however, all overdoses will be recorded and reported by Biogen or designee according to standard local postmarketing channels.

11.4.2. Reporting Pregnancy

In case the participant reports a new pregnancy during the phone interview, the pregnancy data is collected and reported according to standard local post marketing channels.

11.5. Biogen Responsibilities

Biogen or designee's responsibilities include the following:

- Review all AEs to determine seriousness and fulfillment of collection criteria defined in Section 11.2.
- Monitor and record all SAEs and NSAEs as defined in Section 11.1, regardless of the relationship to IM Interferon beta-1a or SC Peginterferon beta-1a
- Determine the relationship of each SAE and NSAEs to IM Interferon beta-1a or SC Peginterferon beta-1a as per Biogen standard procedure
- Record all spontaneously reported AE or pregnancies according to spontaneous reporting process
- Pursue AE follow-up information as per Biogen standard procedure
- Determine the expectedness of all AEs
- Notify all appropriate regulatory authorities as required by local law, within required time frames.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Due to the shortness of the data collection period (i.e. 3,5 months) no interim study report will be submitted.

A final study report will be sent to regulators within 12 months of the end of data collection.

12.1. Ethics Committee Notification of Study Completion or Termination

Not applicable.

12.2. Registration of Study and Disclosure of Study Results

Biogen will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations, this includes also the electronic register of studies of The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

All relevant notifications of the study to authorities and institutions in accordance with any applicable local requirements will be performed.

13. REFERENCES

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14. ANNEX 1: LIST OF STAND-ALONE DOCUMENTS

Table 2: List of Stand-Alone Documents for Protocol DE-PEG-11650

No.	Document Reference Number	Date of Document	Title or Content of Document
1	Not applicable	07 October 2020	List of responsible study parties

15. ANNEX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS (REVISION 4)

Study title: Non-interventional safety study to investigate pregnancy outcomes in female patients exposed to SC Peginterferon beta-1a and IM Interferon beta-1a reported in a German patient support program

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

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Due to the shortness of the data collection period, no progress reports are planned.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.2
2.1.2 The objective(s) of the study?	☒	☐	☐	8.1-8.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

PAS Study.

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)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☒	
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))	☐	☒	☐	
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)	☒	☐	☐	11

Comments:

All documented data are analyzed by descriptive statistics, that is, no formal statistical hypothesis will be formulated, and no statistical tests will be carried out.

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

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)	☐	☐	☒	
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?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Only retrospective data on drug exposure is collected in this study. It will not be distinguished between the two treatments, i.e. the data will be pooled for analysis.

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?	☒	☐	☐	9.1.1 9.1.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.1.1 9.1.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
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:

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

Comments:

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

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4.
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4.
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4.
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4.
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4.
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4.
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.7
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	CRF
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.7
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Exposure of study drug does not need any coding, other medication and free text entries will be categorized in analysis programs and outcomes of children are already categorized in the standardized German pediatric check-up booklet.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.5, 9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☐	☒	☐	
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?	☒	☐	☐	9.7
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

PAS study with one pooled treatment

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

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?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	
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)	☒	☐	☐	9.2.3.1

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?	☒	☐	☐	10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10.1
13.3 Have data protection requirements been described?	☒	☐	☐	10.4

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?	☒	☐	☐	10.3

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)?	☒	☐	☐	12.2

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

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

Date: dd/Month/year

Signature :

16. ANNEX 3: ADDITIONAL INFORMATION

Flowchart

	MSSC database	Patient *questionnaire*
Prior to enrollment (i.e. generating data extract for pregnancy reporting data from MSSC database and obtaining written informed consent for prospective study part)		
Selecting eligible participants by checking Inclusion/Exclusion Criteria	X	X
Ensuring that written agreement on the privacy policy of the PSP registration form is available	X	---
Identification of missing data in MSSC database	X	---
Contacting eligible participants by phone, explaining background of the proposed study, the data collected, and the voluntary nature of study participation, obtaining oral consent for proceeding with the prospective study part	---	X
Provision of Patient Information and collection of written Informed Consent	---	X
After enrollment		
Date of Informed Consent	---	X
Patient's demographics: age, weight, height	X	---
Pregnancy outcome, type of delivery, complications	X	---
Pregnancy anamnesis	---	X
Data on the newborn child	X	X
Family anamnesis of child	---	X
Data on child development (as reported in the standardized German pediatric check-up booklet "Kinderuntersuchungsheft")	---	X
Breastfeeding practices	---	X
Interferon beta treatment history before, during and after pregnancy	X	---
Other MS medications during and after pregnancy	---	X
Concomitant medication during and after pregnancy	X	---
MS disease activity	---	X
Premature Study Termination (only applicable for prospective study part)	X	---

Health checks for children in Germany as reported in the standardized German pediatric check-up booklet "Kinderuntersuchungsheft"

Examination type	Age	Scope of examination
U1	After birth	Skin colour, breathing, muscle tone, reflexes, heartbeat, Vitamin K prophylaxis
Advanced newborn screening	1–3 days old	Blood test to check for metabolic disorders
Newborn hearing screening	1–3 days old	Exclusion of hearing impairments from a hearing loss of 35 dB
Cystic fibrosis screening	1–3 days old	Generally a blood sample taken during advanced newborn screening
Pulse oximetry screening	2 days old, by U2 at the latest	Measurement of the blood oxygen levels using a light sensor on the baby's foot. Low oxygen levels can be a sign of congenital heart defects. Vitamin K prophylaxis
U2	3–10 days old	Body measurements, abnormalities in the skin, chest, stomach and genitals, skeleton, sensory organs, motor skills, reflexes, formation of the hip joint, check for metabolic or hormonal imbalances, Vitamin K prophylaxis
U3	4–5 weeks old	Physical examination similar to U2, age-appropriate development, nutritional state, weight, ocular response, hearing, reflexes, motor skills development, vaccination advice, Vitamin K prophylaxis
U4	3–4 months old	Motion, coordination, response to visual and acoustic stimuli, vaccination advice, Vitamin K prophylaxis
U5	6–7 months old	Head posture, motor skills and coordination (gripping ability), hearing and eyesight, interest in surroundings, vaccination advice, Vitamin K prophylaxis
U6	10–12 months old	Motor skills and coordination, hearing and eyesight, response to strangers, vaccination advice, Vitamin K prophylaxis
U7	21–24 months old	Motion behaviour, language development, comprehension, vaccination advice, Vitamin K prophylaxis
U7a	34–36 months old (shortly before 3rd birthday)	Detection of allergies, socialisation problems, behavioural disorders, overweight, language development, dental, oral and maxillofacial anomalies, vaccination advice, Vitamin K prophylaxis
U8	46–48 months old (shortly before 4th birthday)	Organ check, thorough eye examination and hearing test, dexterity test, language development, independence and interpersonal skills, vaccination advice, Vitamin K prophylaxis

17. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "Non-interventional safety study to investigate pregnancy outcomes in female patients exposed to SC Peginterferon beta-1a and IM Interferon beta-1a reported in a German patient support program", and confirm that to the best of my knowledge it meets scientific standards and accurately describes the conduct of the study.

_____ _____

Prof. Dr. med. [redacted] Date

Prof. Dr. med. [redacted]

[redacted]

Germany