

## Observational Study Protocol

<b>Study Protocol Number</b>	EMR700568-012
<b>Title</b>	Prospective observational long-term safety registry of Multiple Sclerosis patients who have participated in cladribine clinical trials (PREMIERE).
<b>EudraCT Number</b>	2009-017978-21
<b>Sponsor</b>	<p>In USA <b>EMD Serono, Inc.</b> An affiliate of Merck KGaA, Darmstadt, Germany One Technology Place, Rockland, MA02370 Phone: +1 781 982 9000 Fax: +1 781 681 2902</p> <p>In Rest of The World <b>Merck Serono SA – Geneva</b> An affiliate of Merck KGaA, Darmstadt, Germany 29 quai des Bergues 1201 Geneva / Switzerland</p>
<b>Medical Responsible</b>	<p>PPD [REDACTED]</p> <p>EMD Serono Research &amp; Development Institute, Inc. A subsidiary of Merck KGaA, Darmstadt, Germany 45A Middlesex Turnpike Billerica MA 01821, USA Phone: PPD [REDACTED] E-mail: PPD [REDACTED]</p>
<b>Sponsor's Legal Representative (EU)</b>	Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany
<b>Study Protocol Version</b>	20 July 2016 /Version 4.0 including amendment No. 2

**Replaces Study Protocol Version** Version 3.0; 23 July 2012

**Current Protocol Amendment** Amendment No. 2 (Global), 20 July 2016



This document is the property of Merck KGaA, Darmstadt, Germany, or one of its subsidiaries. It is intended for restricted use only and may not – in full or part – be passed on, reproduced, published or used without express permission of Merck KGaA, Darmstadt, Germany, or its affiliate. Copyright © 2016 by Merck KGaA, Darmstadt, Germany, or its subsidiary. All rights reserved

**SIGNATURE PAGE**

**Protocol Lead responsible for designing the study:**

I approve the design of the study.

---

*Signature*

---

*Date of Signature*

PPD  
[Redacted Signature]

EMD Serono Research & Development Institute,  
Inc.

A subsidiary of Merck KGaA, Darmstadt, Germany  
45A Middlesex Turnpike  
Billerica MA 01821, USA

Phone: PPD [Redacted]  
E-mail: PPD [Redacted]

**PRINCIPAL REGISTRY PHYSICIAN SIGNATURE**

**Study Title:** Prospective observational long-term safety registry of Multiple Sclerosis patients who have participated in cladribine clinical trials (PREMIERE).

**Protocol Version/Date:** Version 4.0 including amendment 2 / 20 July 2016

**Center Number:** *Principal Registry Physician's site number in the registry*

**Principal Registry Physician:** *Principal Registry Physician's full name, title and academic degree (e.g., Associate Professor, M.D., M.Sc., Prof. Dr. med., etc.)*

I, the undersigned, am responsible for the conduct of the registry at this site and affirm that

- I understand and will conduct the registry according to the protocol, any approved protocol amendments, Good Pharmacoepidemiology Practices (GPP) [1], Good Clinical Practice [2] and all applicable Regulatory Authority requirements and national laws.
- I will not deviate from the protocol without prior written permission from the Sponsor and prior review and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to prevent immediate danger to a subject.

---

*Signature*

*Date of Signature*

*Insert Name, academic qualifications*

*Insert Position (job title)*

*Insert Address of Institution*

*Insert Phone, fax, e-mail*

Each Principal Registry Physician (PRP) will sign a copy of this page. The original signed signature sheets will be filed in the Registry Master File.

**Further Sponsor Responsible Persons**

PPD [REDACTED]

EMD Serono Research & Development Institute, Inc.  
A subsidiary of Merck KGaA, Darmstadt, Germany  
45A Middlesex Turnpike  
Billerica, MA 01821, USA  
Phone: PPD [REDACTED]  
Email: PPD [REDACTED]

PPD [REDACTED]

EMD Serono Research & Development Institute, Inc.  
A subsidiary of Merck KGaA, Darmstadt, Germany  
One Technology Place  
Rockland, MA02370, USA  
Phone: PPD [REDACTED]  
E-mail address: PPD [REDACTED]

## Table of contents

Table of contents .....	6
Table of Figures .....	8
List of Abbreviations .....	9
1            Synopsis .....	11
2            Sponsor, registry physicians and Study Administrative Structure .....	14
3            Background Information .....	15
4            Study Objectives .....	17
5            Study design .....	18
5.1          Study Population .....	18
5.2          Study Enrollment .....	18
5.2.1        Physician Enrollment .....	18
5.2.2        Subject Enrollment .....	19
5.3          Inclusion Criteria .....	19
5.4          Exclusion Criteria .....	19
5.5          Study Region/Location .....	20
5.6          Study Cohort .....	20
5.7          Follow-up and Study Duration .....	20
5.7.1        Study Termination .....	21
5.7.2        Lost to Follow-up .....	21
6            Study Endpoints .....	21
6.1          Primary Endpoints .....	21
6.2          Secondary Endpoint .....	22
6.3          Definitions related to study Endpoints .....	22
7            Assessment of Medication Exposure .....	24
7.1          Prior Exposure to Cladribine .....	24
8            Data sources and Study Procedures .....	24
8.1          Data Sources .....	25
8.2          Schedule of Interviews and Subject Questionnaires .....	26
8.3          Baseline Subject Demographic and Other Characteristics .....	26
8.3.1        Registry Baseline Data Elements .....	27
8.3.1.1      Information from registry enrollment interview .....	27

8.3.1.2	Information from medical health records review .....	27
8.3.1.3	Data elements from the clinical trial database .....	27
8.3.1.4	Interviews at pregnancy baseline and offspring baseline .....	28
8.4	Follow-Up Interviews .....	29
8.5	Reporting of Adverse events .....	30
8.5.1	Definitions .....	31
8.5.1.1	Adverse Events .....	31
8.5.1.2	Adverse Drug Reaction.....	31
8.5.1.3	Serious Adverse Events .....	31
8.5.1.4	Serious Adverse Drug Reaction.....	32
8.5.1.5	Definition of the Adverse Event Reporting Period.....	33
8.5.2	Recording of Adverse Events in the CRF (Methods of Recording and Assessing Adverse Events) .....	33
8.5.3	Procedure for Reporting Serious Adverse Events .....	34
8.5.3.1	Pregnancy and In Utero Drug Exposure .....	34
8.5.4	Safety Reporting to Regulatory Authorities, Investigators and Independent Ethics Committees/Institutional Review Boards .....	35
9	Data Analysis and Statistics.....	36
9.1	Registry size.....	36
9.2	Data analysis .....	36
9.2.1	General Considerations.....	36
9.2.2	Treatment/Analysis Period .....	37
9.3	Study Reporting and Analysis .....	37
9.3.1	Missing Data.....	38
10	Ethical, Scientific and Regulatory Aspects .....	38
10.1	Good Practice and Scientific Advice (Responsibilities of the PRP) ..	38
10.1.1	Guiding Principles .....	38
10.1.2	Opinion of External Experts and Scientific Boards.....	38
10.2	Subject information and informed consent.....	38
10.3	Subject Identification and Privacy.....	39
10.4	Independent Ethics Committee or Institutional Review Board .....	39
10.5	Regulatory Authorities.....	40
11	Registry Management.....	40

11.1	Manual of operations .....	40
11.2	Case report form handling .....	40
11.3	Source documents .....	41
11.4	Site Filing and Archiving.....	41
11.5	Monitoring, Quality Assurance, and Inspection by authorities .....	41
11.6	Changes to the Protocol .....	41
11.7	Registry Report and Publication Policy.....	42
11.7.1	Final Report .....	42
11.7.2	Publication .....	42
12	References.....	42
13	Appendices .....	44
Appendix I	Schedule of Interviews .....	44
Appendix II	Schedule of interviews for pregnancies and offspring .....	45
Appendix III	Major structural birth defects or genetic syndromes .....	46

## Table of Figures

Figure 1	Registry Overview Diagram .....	21
----------	---------------------------------	----



## List of Abbreviations

AE	Adverse event
ADR	Adverse Drug Reaction
CRO	Clinical research organization
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
e-CRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDS	Global Drug Safety
GPP	Good Pharmacoepidemiology Practices
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LLN	Lower limit of normal
LMP	Last menstrual period
MOP	Manual of operations
MS	Multiple Sclerosis
P1	Original cladribine clinical trial physician
P2	Usual health care provider
PRP	Principal registry physician
RRMS	Relapsing-remitting MS

SADR Serious Adverse Drug Reaction  
SAE Serious Adverse Event  
SAP Statistical Analysis Plan  
SUSAR Suspected Unexpected Serious Adverse Reaction

# 1 Synopsis

<b>Study title</b>	Prospective observational long-term safety registry of Multiple Sclerosis patients who have participated in cladribine clinical trials (PREMIERE).
<b>Study number</b>	EMR700568-012
<b>Sponsor</b>	Merck Serono SA - Geneva
<b>Design</b>	Non-Experimental registry
<b>Study under IND</b>	<input checked="" type="checkbox"/> yes <input type="checkbox"/> no
<b>FDA “covered trial”</b>	<input type="checkbox"/> yes <input checked="" type="checkbox"/> no
<b>Study center(s)/country(ies)</b>	<p>The registry will include sites that participated in the Sponsor oral cladribine clinical trials in Multiple Sclerosis (MS), conducted in several countries worldwide including North and South America, Europe, Africa, and Asian-Pacific regions.</p> <p>It is estimated that, approximately 234 sites will participate in the registry (up to 42 in the US).</p>
<b>Planned registry period (first enrollment-last subject out)</b>	<p>Enrollment of subjects in the registry will start after subjects have completed or discontinued participation in selected Sponsor oral cladribine clinical trials in MS.</p> <p>However, for analysis purposes, data from the clinical trials will also be included. For each subject there are two periods of follow-up: the clinical trial will provide follow-up for the first period and the registry will provide follow-up for the second period.</p> <p>The duration of follow-up in the registry will extend up to the end of the registry, which is planned for 2018, or 8 years after the subject’s first enrolment into a cladribine clinical trial, whichever occurs first.</p>
<b>Study objectives</b>	The main purpose of the registry is to collect long-term safety data on oral cladribine in subjects with MS and to estimate the frequency of serious adverse drug reactions (SADR) over a period of time, extending beyond cladribine exposure, in a population of subjects who have been exposed to oral cladribine. Subjects participating in selected

	<p>Sponsor cladribine clinical trials in MS or in corresponding cladribine extension studies will be eligible for enrollment.</p> <p>The focus will be on SADR (which include malignancies and serious infections), AEs in the ‘Blood and Lymphatic System Disorders’ and ‘Neoplasms Benign, Malignant, and Unspecified’ System Organ Classes (SOCs), pregnancies among exposed women and pregnancy outcomes, including congenital anomalies or other important health conditions in the offspring. Resolution of persistent lymphopenia will also be assessed among subjects with persistent lymphopenia.</p>
<p><b>Study design and plan</b></p>	<p>This is a subject registry study with a non-experimental cohort design that will provide long-term follow-up of subjects who participated in Sponsor oral cladribine clinical trials in MS.</p> <p>Subjects will be enrolled through the clinical trial investigator or through the usual health care provider of the subject (clinical trial physician or otherwise) according to the health care system or to current medical practices in each of the participating countries.</p> <p>Overall, the registry is prospective. However, lag interval information regarding exposure and events that occur between trial end and registry enrollment will be collected retrospectively.</p> <p>Prospective collection of AEs in the ‘Blood and Lymphatic System Disorders’ and ‘Neoplasms Benign, Malignant, and Unspecified’ System Organ Classes (SOCs) and MS-related SAEs will be started upon local approval of protocol amendment 1 (version 2.0) dated 23 July 2012.</p>
<p><b>Planned number of registry subjects</b></p>	<p>The registry target population includes all subjects who participated in Sponsor oral cladribine phase I to III clinical trials in MS associated with a protocol approved prior to the time of submission of the marketing application and completed (last patient, last visit) after November 2008. This corresponds to five clinical trials (protocols number 25643, 26593, 27820, 27967 and 28821) and 2175 subjects.</p>
<p><b>Schedule of visits and interviews</b></p>	<p>Upon receipt of the signed written informed consent, subjects can be enrolled in the registry. The principal registry physician (PRP), or trained personnel from the site will perform the registry enrollment interview.</p>

	<p>During the first 2 years after enrollment into the registry, each enrolled subject will be interviewed every 3 months at the time of routine visits or will be contacted by telephone. Thereafter, the contacts will occur yearly until the end of follow-up.</p> <p>The duration of follow-up for offspring of female subjects born during registry participation or during the lag interval period will be for one year after delivery or until the end of registry, whichever occurs first.</p>
<p><b>Inclusion and exclusion criteria</b></p>	<p><b><u>Inclusion Criteria</u></b></p> <p>All subjects enrolled in studies 25643, 26593, 27820, 27967 and 28821 will be eligible for enrollment in the registry once their participation in the clinical trial has ended. The following inclusion criteria must be fulfilled:</p> <ul style="list-style-type: none"> <li>• Prior enrollment into selected clinical trials, regardless of randomization to either IMP or placebo, once participation in the clinical trial or in the clinical trial extension has ended</li> <li>• Written informed consent is given</li> </ul> <p><b><u>Exclusion Criteria</u></b></p> <p>The following reasons will exclude subjects from registry participation:</p> <ul style="list-style-type: none"> <li>• Subjects who cannot be reached by phone,</li> <li>• Subjects who are unable to answer the registry questionnaires and who do not have a next of kin or caregiver available to answer the registry questionnaires,</li> <li>• Subjects who – either during the lag interval or subsequently – enter an interventional study.</li> </ul>
<p><b>Primary endpoints</b></p>	<ul style="list-style-type: none"> <li>• Cumulative incidence of SADR, including malignancies and serious infections</li> <li>• Time to resolution of lymphopenia, among registry participants with persistent lymphopenia</li> <li>• Cumulative incidence of AE in the ‘Blood and Lymphatic System Disorders’ and ‘Neoplasms Benign, Malignant, and Unspecified’ System Organ Classes (SOCs).</li> </ul>

<p><b>Secondary endpoint</b></p>	<ul style="list-style-type: none"> <li>• Pregnancy outcomes, including congenital malformations, spontaneous abortion, elective abortion, stillbirth, ectopic pregnancy, molar pregnancy, and other important health conditions in the offspring.</li> </ul>
<p><b>Statistical methods (includes number of subjects)</b></p>	<p>The registry target population consists of 2175 subjects.</p> <p>There are no plans for any statistical inference. This study will adhere to the <i>Guidelines for Good Pharmacoepidemiology Practices (GPP)</i> [1] and to their recommendations regarding the use of statistical inferences and significance testing. Accordingly, data evaluations and interpretations will be based on point estimates and 95% confidence intervals for evaluation of the statistical precision around the point estimate.</p>
<p><b>Good Practice and Guidelines (ethical and scientific practice)</b></p>	<p>This study will be conducted under the <i>Guidelines for Good Pharmacoepidemiology Practices</i> [1], the <i>ICH Guideline for Good Clinical Practice</i> [2] the international <i>1991 International Guidelines for Ethical Review of Epidemiological Studies</i> [3], AHRQ’s guide: <i>Registries for Evaluating Patient Outcomes: A User’s Guide</i> [4], and the <i>International Ethical Guidelines for Biomedical Research Involving Human Subjects</i> [5]. Adherence to these guidelines will ensure the quality and integrity of pharmacoepidemiologic research, and will serve to provide adequate documentation of research methods and results.</p>

## 2 Sponsor, registry physicians and Study Administrative Structure

Details of the administrative structure and associated procedures will be defined in a separate Manual of Operations (MOP).

Merck Serono SA - Geneva, and EMD Serono Inc, will sponsor the study and the study implementation will be performed by the sponsor-designated clinical research organization (CRO), PPD (hereunder referred to as “The CRO”).

The study is planned to be performed in countries in North and South America, Europe, Africa, and Asian-Pacific regions. It is estimated that, approximately 234 sites will participate in the registry (up to 42 in the US).

A coordinating registry physician will be identified among the principal registry physicians (PRPs) participating in the registry. The coordinating registry physician will act as the representative for all PRPs for decisions and discussions regarding this study, and will provide expert medical input and advice related to the study design and execution.

Merck Serono Global Drug Safety will be responsible for safety reporting and evaluation.

### 3 Background Information

Cladribine (2-chloro-2'-deoxyadenosine [2-CdA]) is a synthetic anti-neoplastic drug that belongs to the subgroup of agents called purine analogues. Parenteral cladribine is approved in many countries for the treatment of patients with hairy cell leukemia and in some countries for the treatment of chronic lymphocytic leukemia.

An oral formulation of cladribine was tested by the Sponsor in patients with early, relapsing-remitting and relapsing-progressive, multiple sclerosis (MS). MS is a chronic, inflammatory, demyelinating disease of the central nervous system and is one of the most common causes of neurological disability in young adults. At its onset, MS can be clinically categorized as either relapsing-remitting MS (RRMS), observed in 85% of MS subjects, or primary progressive MS. Relapses or "attacks" typically present with neurological symptoms and signs developing over hours to days, persisting for several days or weeks, and then gradually dissipating [6]. The outcome in subjects with relapsing-remitting MS is variable; untreated, approximately 50% of all MS subjects require the use of a walking aid within 10 years after clinical onset, although the consequences on prognosis of newer treatment regimens are not yet clear. Increased attack frequency and poor recovery from attacks in the first years of clinical disease predict a more rapid deterioration [7].

Toxicological evaluations of cladribine given parenterally and orally in appropriate animal models have not yielded significant findings other than those predicted by the pharmacologic mechanisms of this compound. Single-dose and multiple-dose toxicity studies suggested a wide margin of safety for the acute toxicity of cladribine relative to the proposed clinical use of the drug and demonstrated reversibility of these effects over time. No neurological effects were observed in these studies. Reproductive toxicity studies with parenteral administration of cladribine showed no effects on female fertility or peri-postnatal development of offspring ("Female fertility study of cladribine administered subcutaneously to female mice" [Study 96307] and "Effects of intravenous administration of cladribine on pre-and postnatal development, including maternal function in mice" [Study 300315]). The observed embryo-lethal and teratogenic effects are consistent with the pharmacologic mechanisms of cladribine. Male fertility also remained unaffected, yet reduced testicular weights and increased numbers of nonmotile sperm suggest testicular effects ("Fertility study of cladribine administered subcutaneously to male mice" [Study 96003]). Based on the results of a mouse carcinogenicity study using intermittent dosing, cladribine is not considered to pose a significant carcinogenic risk in humans ("Two year subcutaneous carcinogenicity study of cladribine in mice using an intermittent dosing schedule" [Study 95011]). However, because of its demonstrated genotoxicity, the carcinogenic potential of cladribine cannot be excluded.

Data from clinical trials show that cladribine causes sustained lymphopenia, which could increase the risk of infections. Currently, the long-term effects of cladribine on hematopoiesis are unknown. Other delayed health effects including the occurrence of malignancies can also be postulated, and safety should be monitored for a period extending beyond pharmacological exposure. Additionally, based on preclinical studies, reproductive and developmental toxicity of cladribine in humans cannot be ruled out.

*The efficacy and safety of cladribine tablets for the treatment of RRMS were investigated in a Merck Serono / EMD Serono-sponsored, Phase III, randomized, double-blind, 3-arm, placebo-controlled, multicenter study of 1326 subjects with RRMS (Study 25643, CLARITY). This trial provides the primary evidence of the efficacy and safety of oral cladribine in RRMS.*

*Data from clinical trials show that cladribine results in sustained and dose-related lymphopenia. In the CLARITY trial, the first 2 courses of oral cladribine resulted in decreases in mean absolute lymphocyte counts at Week 16 of 40% in the 3.5 mg/kg and 62% in the 5.25 mg/kg group. A partial recovery was observed by Week 48. Both cladribine dose groups were retreated with 2 courses of cladribine at Weeks 48 and 52. The nadir at Week 55 was comparable to that at Week 16 level in both treatment groups. The long-term effects of cladribine on hematopoiesis are unknown.*

*With regard to the risk of infections related to lymphopenia, in completed clinical trials, the risk ratio for herpetic infection was 1.98 (95%CI: 1.14-3.45). The risk ratio for infectious adverse events (AEs) and serious adverse events (SAEs) were 1.13 (95%CI: 1.01-1.26) and 1.56 (95%CI: 0.82-2.94), respectively.*

*Other delayed health effects including the possibility of an increased risk of malignancies are of interest and safety should therefore be monitored for a period extending beyond pharmacological exposure. The relative risk for any malignancy in placebo-controlled phases of completed clinical trials, was RR=2.31 (95%CI: 0.27 – 19.80). Although this point estimate suggests a two-fold increase in the risk of cancer among cladribine-exposed patients; the estimate is unstable as indicated by the wide 95% CI that contains 1. Malignancies were of various types and no lymphohematopoietic malignancies were observed.*

*In the CLARITY trial, pregnant and breastfeeding women were specifically excluded and all female study participants were required to use adequate contraception throughout the duration of their participation in the trial. Male participants were also required to use contraception so that their partners did not become pregnant. Despite these protocol requirements, 24 pregnancies were reported in 23 of the 898 female subjects who participated in the CLARITY trial. Of these 24 pregnancies, 6 occurred among subjects who received treatment with placebo, 7 occurred among subjects randomized to the 3.5-mg/kg dose, and 11 occurred among subjects who randomized to the 5.25-mg/kg dose of cladribine. Information on the timing of pregnancies in relation to cladribine exposure in CLARITY indicated that of the 24 pregnancies, 6 pregnancies occurred while the subject was receiving treatment (i.e., within a 28-day treatment course), 17 pregnancies occurred while the subject was not receiving treatment, and 1 pregnancy occurred 6 months after the subject had completed the study.*

*Of the 24 pregnancies, 5 resulted in full-term normal live births (2 pregnancies in the 5.25 mg/kg cladribine dose group and 3 pregnancies in the placebo group). Both of the subjects in the cladribine 5.25 mg/kg group who delivered full-term normal babies had received 6 courses of cladribine tablets; conception had occurred approximately 2 weeks and 6 months, respectively, after the subjects had received their sixth course of therapy. Thirteen of the 24 pregnancies were terminated by elective abortions, 1 by therapeutic abortion due to choriocarcinoma, 4 pregnancies ended in miscarriage (3 in the cladribine treatment groups), and 1 pregnancy was ectopic. Although the Sponsor requested information on the terminations of these pregnancies, no postmortem examinations had been conducted.*



Limited information regarding the long-term safety of cladribine greater than 4 years is currently available. During clinical development, the cladribine Data Safety Monitoring Board (DSMB) recommended monitoring the long-term occurrence of malignancies and deaths, and pregnancy outcomes, in subjects exposed to cladribine.

*In June 2011, Merck Serono announced its decision to no longer pursue the global approval process of cladribine tablets for the treatment of relapsing-remitting multiple sclerosis and to withdraw the product from the market in the countries where it was authorized and available (Australia and Russia).*

*The original objectives of the PREMIERE registry study were to produce long-term safety data in order to better characterize the potential safety risks of cladribine, to build an evidence-based risk minimization strategy, and to monitor long-term safety events in a clinical trial population. The ultimate goal was to minimize risk in a larger population of MS patients exposed to cladribine tablets in the post-marketing setting. As cladribine tablets will no longer be available to MS patients in the post-marketing setting, and no large population of patients will be exposed, the original objectives of this study are no longer applicable. However, the Sponsor recognizes its duty of care to appropriately follow patients who have been exposed to cladribine tablets in the clinical trial setting.*

## 4 Study Objectives

The main purpose of this registry is to collect long-term safety data on oral cladribine in subjects with multiple sclerosis (MS) and to estimate the frequency of serious adverse drug reactions (SADR – see definition in section 8.5.1.4) over a period of time extending beyond oral cladribine exposure, in a population of subjects who have been exposed to oral cladribine. Subjects participating in selected Sponsor cladribine clinical trials in MS or in corresponding cladribine extension studies will be eligible for enrollment.

The focus will be on SADR (which include malignancies and serious infections), AE in the ‘Blood and Lymphatic System Disorders’ and ‘Neoplasms Benign, Malignant, and Unspecified’ System Organ Classes (SOCs), pregnancies among exposed women and pregnancy outcomes (including one year of follow-up of offspring). Resolution of persistent lymphopenia will also be assessed among subjects with persistent lymphopenia (see definition in section 6.3).

### Primary Objectives

- To quantify and characterize the risk (cumulative incidence) of SADR, including malignancies and serious infections
- To assess time to resolution of lymphopenia among registry participants with persistent lymphopenia
- To quantify and characterize the risk (cumulative incidence) of AE in the ‘Blood and Lymphatic System Disorders’ and ‘Neoplasms Benign, Malignant, and Unspecified’ System Organ Classes (SOCs)

## Secondary Objective

- To assess pregnancy outcomes, including congenital malformations or other important health conditions in the offspring born to women exposed to oral cladribine

## 5 Study design

This is a subject registry study with a non-experimental cohort design. The study will provide long-term follow-up of subjects who participated in Sponsor oral cladribine clinical trials in MS. Subjects will be enrolled through the clinical trial investigator or through the usual health care provider of the subject (cladribine clinical trial physician or otherwise) according to the health care system or to current medical practices in each of the participating countries.

Overall, the registry is prospective. However, lag interval information regarding exposure and events that occur between trial end and registry enrollment will be collected retrospectively.

Prospective collection of AEs in the ‘Blood and Lymphatic System Disorders’ and ‘Neoplasms Benign, Malignant, and Unspecified’ System Organ Classes (SOCs) and MS-related SAEs will be started upon local approval of protocol amendment 1 (version 2.0), dated 23 July 2012.

### 5.1 Study Population

The registry target population includes all subjects who participated in Sponsor oral cladribine Phase I to III clinical trials in MS associated with a protocol approved prior to the time of submission of the marketing application and completed (last patient, last visit) after November 2008. This corresponds to five clinical trials (protocols number 25643, 26593, 27820, 27967 and 28821) and 2175 subjects.

### 5.2 Study Enrollment

The CRO contracted by the Sponsor, will be responsible for the operational aspects of the registry, e.g., obtaining institutional review board (IRB) or independent ethics committee (IEC) approvals and managing enrollment of physicians, and subjects and data collection.

#### 5.2.1 Physician Enrollment

There are two options regarding who may become the “principal registry physician” (PRP), that is, the physician who routinely cares for the health of the subject outside of the clinical trial setting (e.g., neurologist, primary care physician):

- The physician of the original cladribine clinical trial (P1)
- Another physician, the usual health care provider (P2)

For each subject, only one PRP will be the main clinical contact during follow-up and also responsible for validating all information on the defined study events. Subjects will be asked to update their physician contact information (including the usual care physician) at each follow-up interview.

If the original cladribine clinical trial physician (P1) is not available for the follow-up of subjects for any reason, the CRO should obtain contact details from P1 for the usual health care provider (P2) to facilitate the use of P2 as the PRP for the subject in the registry.

## 5.2.2 Subject Enrollment

As soon as subjects end their participation in the oral cladribine clinical trial in MS (i.e., complete the clinical trial or its extension, or drop out from the clinical trial) they are eligible to be enrolled in the registry. To maximize enrollment of subjects into the registry, it is expected that the P1 will facilitate enrollment by informing the subjects about the registry.

The timing of subject enrollment into the registry relative to the time of clinical trial completion may vary. Therefore, the categories of timing of registry enrollment and availability of a PRP include the following:

- For subjects whose clinical trial participation ended after the date of registry initiation, the P1 will provide the subject with a registry overview, obtain informed consent, and enroll the subject in the registry.
- For subjects who completed their clinical trial participation or who withdrew from the clinical trial prior to the initiation of the registry, the CRO will contact the P1. The P1 will facilitate contact with the subject, inform the subject about the registry, and obtain informed consent from the subject. In cases where the P1 will not be available for the follow-up of subjects, the CRO will request P1 support in the identification of the P2 via the subject. P1 will ask the subject permission to provide P2's contact data to the CRO. P2 will then be informed about the registry and asked to support the steps needed to enroll the subject in the registry.

## 5.3 Inclusion Criteria

All subjects in the target population described in section 5.1 will be eligible for enrollment in the registry once their participation in the clinical trial has ended. The following inclusion criteria must be fulfilled:

- Prior enrollment into selected clinical trials, regardless of randomization to either IMP or placebo, once participation in the clinical trial or in the clinical trial extension has ended
- Written informed consent is given

## 5.4 Exclusion Criteria

The following reasons will exclude subjects from registry participation:

- Subjects who cannot be reached by phone;
- Subjects who are unable to answer the registry questionnaires and who do not have a next of kin or caregiver available to answer the registry questionnaires;
- Subjects who – either during the lag interval or subsequently – enter an interventional study.

## 5.5 Study Region/Location

The registry will include the sites that participated in the Sponsor's oral cladribine clinical trials in MS, which include countries in North and South America, Europe, Africa, and Asian-Pacific regions.

Language, cultural and regulatory aspects of the potentially large number of participating countries will be taken into account during the planning phase of the registry.

## 5.6 Study Cohort

The cohort of cladribine-treated subjects will consist of all subjects who have consented to participate and who were treated with cladribine during the clinical trial period of the identified clinical trials or cladribine extension studies in MS.

There will be no control/comparison group. Subjects who were on placebo during a clinical trial but who switched to cladribine in the extension study will contribute person-time to the cohort of cladribine-treated subjects from the moment they initiate cladribine. Person-time prior to cladribine initiation in subjects originally randomized to placebo, will not be used in the calculation of study endpoints incidences.

## 5.7 Follow-up and Study Duration

### *Study duration*

Enrollment of subjects in the registry will start after subjects completed or discontinued participation in an oral cladribine clinical trial in MS. The end of the registry is planned for 2018, which corresponds to 8 years after the last subject was included in the targeted clinical trials (see section 5.1).

### *Follow-up of MS subjects*

*The duration of follow-up for all subjects will extend up to the end of the registry, which is planned for 2018, or 8 years after enrollment into the first cladribine clinical trial (first visit), whichever occurs first.*

*Subjects with ongoing SAEs, including lymphopenia (i.e. who have not reached a lymphocyte count CTCAE Grade 0 or 1) at the end of PREMIERE, will be followed-up by the Global Drug Safety department until resolution (see definition of the reporting period in section 8.5.1.5).*

### *Follow-up of offspring*

The duration of follow-up for offspring of female subjects born during registry participation or during the lag interval period will be one year after delivery or until the registry end date, whichever occurs first.

*Subjects with ongoing pregnancies or offspring born during registry participation or during the lag interval period who are not at least 1 year old at the end of the registry will be followed-up by*

the Global Drug Safety department until pregnancy outcome is known and offspring is 1 year old, respectively (see definition of the reporting period in section 8.5.1.5).

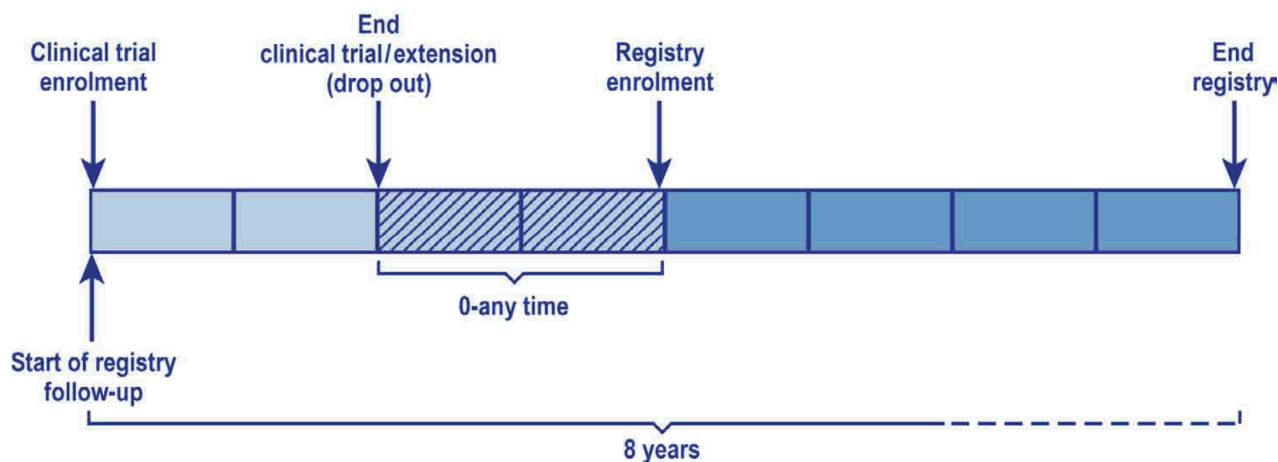
### 5.7.1 Study Termination

Termination of a subject from the registry will occur if the subject decides not to continue his/her participation in the registry or if the subject becomes unable to continue participating. Subjects will be informed that they have the right to withdraw from the registry at any time, without prejudice, and that they are not obliged to state their reasons. If a subject declares his or her wish to discontinue from the registry, the PRP will attempt to establish whether the underlying reason is related to an adverse event (AE) or other study endpoint. The PRP will complete a Subject Discontinuation form and enter the discontinuation information into the electronic case report form of the discontinued subject.

### 5.7.2 Lost to Follow-up

Before considering a subject “lost to follow-up,” the PRP or trained site personnel will make every attempt to contact the subject and maintain him/her in the registry and to ensure that an outcome of interest has not been the underlying reason for the non-response of the subject. If no response is obtained, the CRO will enquire directly with other known health care providers and/or with next of kin/caregivers named by the subject via PRP to check whether the reason for failure to respond is health-related, to determine the vital status of the subject, and, in the case of deceased subjects, to ascertain the cause of death.

Figure 1 Registry Overview Diagram



## 6 Study Endpoints

### 6.1 Primary Endpoints

- Cumulative incidence of SADR, including malignancies and serious infections
- Time to resolution of lymphopenia, among registry participants with persistent lymphopenia

- Cumulative incidence of all AEs in the “Blood and Lymphatic System Disorders” System Organ Class (SOC) and in the “Neoplasms Benign, Malignant, and Unspecified” SOC

## 6.2 Secondary Endpoint

- Pregnancy outcomes, including congenital malformations, spontaneous abortion, elective abortion, stillbirth, ectopic pregnancy, molar pregnancy, and other important health conditions in the offspring

## 6.3 Definitions related to study Endpoints

### Resolution of Persistent Lymphopenia

Subjects who complete or drop out of a cladribine clinical trial with a Grade 3 or Grade 4 lymphopenia as defined by the Common Terminology Criteria for Adverse Events (CTCAE) [8] will be defined as having ‘persistent lymphopenia’ and will be monitored until lymphopenia resolves. Resolution is the achievement of a CTCAE Grade 1 or Grade 0 lymphocyte count.

According to the CTCAE version 4.03 [8], lymphopenia grades are defined as follows:

- Grade 1: < lower limit of normal (LLN) to 800/mm<sup>3</sup> or < LLN to 0.8 × 10<sup>9</sup>/L
- Grade 2: < 800–500/mm<sup>3</sup> or < 0.8–0.5 × 10<sup>9</sup>/L
- Grade 3: < 500–200/mm<sup>3</sup> or < 0.5–0.2 × 10<sup>9</sup>/L
- Grade 4: < 200/mm<sup>3</sup> or < 0.2 × 10<sup>9</sup>/L

### Pregnancy and Pregnancy Outcomes

Pregnancies occurring among female subjects exposed to cladribine will be identified by a subject-reported positive pregnancy test and at least a 2-week delay in menses, or a subject-reported pregnancy diagnosed by a physician.

Pregnancy outcomes will be characterized by using the following definitions (in italics) according to the European Medicines Agency guideline [9].

#### *Live births*

*Complete expulsion or extraction from its mother of a product of conception irrespective of the duration of the pregnancy, which after such separation, breathes or shows any evidence of life.*

Normal

Abnormal:

Pre-term, term, post-term birth

*Pre-term birth: less than 37 completed weeks (less than 259 days) of gestation.*

*Term birth: from 37 to less than 42 completed weeks (259 to 293 days).*

*Post-term birth: 42 completed weeks or more (294 days or more)*

Small for gestational age infants/ intrauterine growth retardation

*Intrauterine growth retardation (small for gestational age): the observed weight of a live born infant or size of a fetus is lower than expected on the basis of gestational age.*

*Gestational age or length: the duration of gestation is measured from the first day of the last normal menstrual period. Gestational age is expressed in completed days or completed weeks (e.g., events occurring 280 to 286 days after the onset of the last menstrual period are considered to have occurred at 40 weeks of gestation).*

Drug withdrawal syndrome in the neonate

Malformations

Morbidity

### ***Fetal death***

*Death prior to complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy; the death is indicated by the fact that after such separation the fetus does not show any evidence of life. Early fetal death (before 22 completed weeks of gestation) comprises ectopic pregnancy and miscarriage.*

#### Ectopic

*Extrauterine pregnancy, early fetal death most often in the Fallopian tube.*

#### Miscarriage

*Spontaneous abortion, molar pregnancy.*

#### Stillbirth

*Late fetal death (after 22 completed weeks of gestation).*

#### Termination of pregnancy

*Induced abortion, elective abortion. Artificial interruption of pregnancy.*

In cases of induced or spontaneous abortions and intra-uterine death, it should be mentioned whether the embryo/fetus had apparent congenital malformations.

### **Major structural birth defects or genetic syndromes**

Descriptions of major congenital anomalies and congenital syndromes of offspring will be collected.

A simplified version of the British Pediatric Association code list will be used for the definition of this endpoint. See Section 13 [Appendix III](#).

### **Developmental disabilities and important health conditions**

Data on routine developmental milestones achievement and important health conditions as reported by a physician will be collected in offspring for the duration of follow-up (see Section 5.7).

## **7 Assessment of Medication Exposure**

After enrollment of subjects in the registry, in accordance with the non-experimental nature of this study, no treatment will be assigned to participants by registry protocol. Physicians will prescribe medications according to their own clinical criteria and practices. Information regarding use of marketed immunosuppressant medications will be collected during the registry.

Subjects will no longer be eligible to participate in PREMIERE if they enroll in an interventional clinical trial, as it may not be possible to know medication exposure.

### **7.1 Prior Exposure to Cladribine**

Data on the subject's prior exposure to cladribine from the clinical trial period will be copied from the clinical trial database and will include the following variables:

- Date of cladribine start;
- Cumulative cladribine exposure (mg per kg of body weight)
- Dose and schedule;
- Date(s) of temporary and/or permanent treatment discontinuation(s).

## **8 Data sources and Study Procedures**

Subjects will be provided information on the registry and will be requested to sign informed consent before any data is collected.

For subjects who refuse to enroll in the registry, attempts will be made to collect selected data, including reason for refusal, and to request informed consent for the use of their baseline data collected during their participation in the clinical trial.

When a subject has signed the informed consent, a unique subject identification number will be assigned. This number will consist of ten characters for the registry protocol number, three digits for a site number and four digits for a sequentially assigned subject number (i.e., 0001, 0002, 0003, etc.).



**Example:** the fifth subject enrolled at site 001 in protocol 0700568012

0700568012	001	0005
Protocol No.	Site No.	Subject No.

Should the subject withdraw from the study, his or her unique subject identification number will not be reallocated.

## 8.1 Data Sources

Data will be obtained from several sources, namely:

The subject questionnaires administered by the PRP or trained site personnel

- Medical record information collected by the PRP at his or her own institution providing information on subject health events and exposure to other immunosuppressants
- The clinical trial database, providing data previously collected during the oral cladribine clinical trials in MS and their extension

The specifics of these data sources are described in the following paragraphs.

### Subject Interviews

After registry enrollment, data will be collected by the PRP or trained site personnel (see Section 13 [Appendix I](#), schedule of Interviews) either during the routine clinical visit or by telephone contact. Structured questionnaires administered to the subject or in cases when the subject is unable, to the next of kin, or caregiver.

There will be a limited number of subjects who withdrew or completed the clinical trial before the registry was established and who have no follow-up data recorded in their medical record (or the medical record is not accessible). Information from this time interval between clinical trial end and registry enrollment, referred to as the “lagged data period,” will be collected directly from the subject. As much as possible medical confirmation will be sought through the PRP.

### Medical Records

For subjects who withdrew or completed the clinical trial before the registry was established (but who are still followed at the site), health records will be retrospectively reviewed to ascertain SADRs, pregnancies, and lymphocyte counts, as well as exposure to immunosuppressants occurring during the lagged data period.

### Clinical Trial Database

Data collected from the clinical trial period will include demographic characteristics, exposure to cladribine and lymphocyte counts at the end of the trial. This data will be linked with the clinical trial data after enrollment of the subject in the registry.

## 8.2 Schedule of Interviews and Subject Questionnaires

### Timing and Frequency of Interviews

On Day 1 of registry enrollment, the interviewer (PRP or trained site personnel) will verify that the informed consent has been signed and will proceed to administer the registry enrollment questionnaire.

During the first 2 years after enrollment into the registry the PRP or trained site personnel will interview the subject every 3 months. Thereafter, the contacts will be every year until the end of follow-up (see Section 13 [Appendix I](#), schedule of Interviews).

A window of  $\pm 2$  weeks around the date of the scheduled visit during the first two years and of  $\pm 4$  weeks thereafter, is acceptable. The structured questionnaire will be administered during routine clinical visits or by phone. The PRP or trained site personnel will enter the questionnaire responses collected in the electronic case report form. The completed questionnaires are source documents and will be filed with the registry participant's medical records on site, per Section 11.4 of the protocol.

At each scheduled contact, information on SAEs, AEs related to 'Blood and Lymphatic System Disorders' and 'Neoplasms Benign, Malignant, and Unspecified' SOCs, lymphocyte counts, and immunosuppressant medications will be collected through a structured questionnaire administered by phone or during a routine visit by the PRP or trained site personnel. A detailed schedule of interviews is provided in the Section 13 [Appendix I](#), schedule of Interviews.

**Pregnancies:** When a pregnancy is identified in a female subject, a specific pregnancy baseline questionnaire will be administered (see Section 8.3). During the pregnancy, the schedule of phone interviews will be adapted so that at least one such interviews takes place between months 4 through 7 after the last menstrual period (LMP), and another at month 10. After the end of the pregnancy, the schedule of interviews will shift to the regular periodicity.

**Offspring of female subjects:** *Data will be collected from the PRP after birth, ideally in parallel to the interview of the mother at month 10 post-LMP, at age 6 months, and at age 1 year. No interviews on the offspring will be performed in the frame of the registry after the date of the registry end. Offspring who are not at least 1 year old at the end of the registry will be followed-up by the Global Drug Safety department (see definition of the reporting period in section 8.5.1.5).*

A schedule of interviews for pregnancies and offspring is provided in Section 13 [Appendix II](#), Schedule of Interviews for Pregnancies and Offspring.

To manage missed interviews or shifts in scheduled interviews of subjects, the registry will maintain the schedule as originally planned.

## 8.3 Baseline Subject Demographic and Other Characteristics

The registry enrollment of a subject will be based on subject interview and, for some subjects, will require information from subject health records. Another component of the enrollment process will consist of inclusion of data collected during the clinical trial period, which will be copied from the

clinical trial database to the registry database after completion of the subject enrollment into the registry.

### **8.3.1 Registry Baseline Data Elements**

Registry baseline data elements include the following data:

#### **8.3.1.1 Information from registry enrollment interview**

At the registry enrollment interview, the following data will be collected from all subjects unless prohibited by country regulations:

- Identification/contact information of subject, next of kin/caregiver, and current treating physician(s).

In subjects who have a lagged interval period and whose medical record is not accessible, a specific questionnaire will address the following:

- Treatment exposure to immunosuppressant medications, including type of treatment and date started;
- Occurrence of SAEs including time and outcome;
- Occurrence of AEs in the ‘Blood and Lymphatic System Disorders’ and ‘Neoplasms Benign, Malignant, and Unspecified’ SOCs including time and outcome
- In subjects tagged as “lymphopenic subjects” ascertainment of performance of a blood test during the lagged data period, and categorization of lymphocyte counts as normal, abnormal or unknown, if available.

#### **8.3.1.2 Information from medical health records review**

For subjects with lagged data period, Sponsor will review data from medical records and the PRP will enter the following data into the registry participant electronic case report form:

- Treatment exposure to immunosuppressant medications, including type of treatment, and date started;
- Occurrence of SAEs including time and outcome;
- Occurrence of a pregnancy in participant woman, including date of LMP, and outcome;
- In subjects tagged as “lymphopenic subjects” ascertainment of performance of a blood test during the lagged data period, and categorization of lymphocyte counts as normal, Grade 1 through Grade 4 or unknown, if available.

#### **8.3.1.3 Data elements from the clinical trial database**

The focus will be on data collected during the subject’s participation in the clinical trial or its extension period as specified following:

- Demographic data, including date of birth, gender, and race;

- Treatment exposure data for cladribine, including time (date started and date stopped), dose, and duration;
- Evidence of CTCAE Grade 3 or Grade 4 lymphopenia at the completion or dropout of the clinical trial, and lymphocyte count. These subjects will be tagged as “lymphopenic subjects” until resolution of their lymphopenia (see definition of resolution in Section 6.3).

### 8.3.1.4 Interviews at pregnancy baseline and offspring baseline

**Pregnancies:** For women who become pregnant during registry participation, a specific pregnancy baseline questionnaire will be added to collect pregnancy-related information.

The information that will be collected during pregnancy follows the specifications provided in the EMA guideline on the exposure to medicinal products during pregnancy [9].

#### Maternal Information

- Contact information for the gynecologist-obstetrician or physician who follows the pregnancy
- Occupation, highest education level attained
- Maternal weight
- **Obstetrical history:** number of previous pregnancies and outcome (live birth, miscarriage, elective termination with specification of gestational length and context, late fetal death, ectopic pregnancy, molar pregnancy), previous maternal pregnancy complications, previous fetal/neonatal abnormalities and type, history of subfertility.
- **Maternal and medical history:** risk factors for adverse pregnancy outcomes including environmental or occupational exposures, e.g., hypertension, diabetes, seizure disorder, asthma, allergic disease, heart disease, depression or other psychiatric disorders, sexually transmitted diseases, hepatitis, AIDS (specify viral load, CD4 count), other.
- **Current pregnancy:** date of last menstrual period (LMP); pregnancy gestational age at the time of baseline interview (specify if based on ultrasound or LMP); estimated date of delivery; number of fetuses; treatment for infertility (specify); exposure to products subject to medical prescription, over-the-counter products, pregnancy supplements such as folic acid, multivitamins (name, dosage, and route; date of first use; date of end of treatment; duration) and indication; recreational drug use, e.g., tobacco, alcohol, illicit drugs (specify amount and if stopped during pregnancy); results of serology tests, e.g., rubella, toxoplasmosis; complications during pregnancy and date (including adverse drug reactions); disease course during pregnancy and any complications; antenatal checkups (specify dates and results), e.g., fetal ultrasound, serum markers (AFP, others), chorionic villi biopsy (CVS), amniocentesis.
- **Family history:** history of congenital abnormality, psychomotor retardation in the family (specify paternal/maternal and relationship), consanguinity between parents (specify degree).

**Pregnancy offspring:** For children born of female subject, a specific baseline interview will be conducted to capture information about congenital malformation and general health and development status. Contact data for the pediatrician or physician following the child will be obtained.

### Baseline Neonatal Information

- Outcome of pregnancy
- Date of birth of the child
- Gestational age at birth
- Gender
- Results of neonatal physical examination including weight at birth, length, head circumference at birth
- Malformations/anomalies diagnosed at birth
- Conditions at birth (including Apgar scores at 1 and 5 minutes, need for resuscitation, admission to ICU)
- Dysmaturity
- Neonatal illness, hospitalization, drug therapies

## 8.4 Follow-Up Interviews

For MS subjects, the information to be ascertained in the follow-up interviews fall into five main categories:

- Updates in contact information
- Occurrence of SAEs (including time of event and outcome)
- Occurrence of AEs in the ‘Blood and Lymphatic System Disorders’ and ‘Neoplasms Benign, Malignant, and Unspecified’ SOCs (including time of event and outcome)
- Capture of any lymphocyte count assessments performed since last visit
- Prescription of immunosuppressant medications including type and start date

It is expected that subjects in PREMIERE will attend their routine MS care visits. The PRP is expected to request blood count and differential if lymphopenia has not resolved (i.e., lymphocyte count is equal or greater than  $0.8 \times 10^9/L$ ). All lymphocyte count results will be captured by the PRP regardless of monitoring frequency. Participating PRP will be instructed to have blood count and differential performed at least yearly until resolution of lymphopenia (i.e., a Grade 1 or Grade 0 lymphopenia), or end of the study period.

### Pregnancy

The follow-up interview during pregnancy will collect information regarding the progress of the pregnancy, exposure to potential risk factors, and the expected date of delivery. Information will also be collected on potential adverse pregnancy outcomes during that period: spontaneous abortion, elected abortion, stillbirth, ectopic pregnancy, and molar pregnancy. The follow-up interview at month 10 or at the end of pregnancy will provide information about the outcome — spontaneous abortion, elected abortion, stillbirth, live birth, or premature; overdue, presence of congenital anomalies, ectopic pregnancy, molar pregnancy, and the date of birth of the baby. Note

that the option of an elective abortion may be an issue in some countries, and may yield invalid answers.

### **Delivery Information**

- Mode of delivery
- Labor/delivery complications (fetal distress/amniotic fluid abnormal)
- Abnormal placenta

### **Fetal Information**

To be collected in case of elective termination, spontaneous abortion, and late fetal death.

- Reason for termination
- Gestational age at termination
- Results of physical examination (gender, external anomalies) and pathology

### **Offspring**

Follow-up information on the child includes any physician-diagnosed abnormal developmental milestones; structural malformations not detected in the neonate, and other important health conditions. A contact with the paediatrician will be attempted to validate information.

## **8.5 Reporting of Adverse events**

After registry enrollment, as for all study information, the primary source of data is the subject. AE/SAE data will be obtained at scheduled or unscheduled interviews based on information spontaneously provided by the subject and/or thorough questioning of the subject. To elicit pregnancy and AEs/SAEs, questioning at each interview should begin with simple non-leading questions.

To identify AEs/SAEs, or a pregnancy, a section of the standard phone interview will ask the subject about all clinically relevant health events (see Section 8.2). Information on offspring of female subjects should be requested for one year after delivery.

If a subject is hospitalized in relation to an SAE or a pregnancy is reported, the trained site should, in a timely manner, make every effort to follow-up with the treating physician or relevant concerned health care provider to obtain all information necessary for the accurate reporting of the event.

In the cases where the subject reports a SAE that is not being treated by the PRP, the registry informed consent will have requested the subject's authorization to contact the treating physician and/or other relevant concerned health care provider for full SAE interview.

## **8.5.1                      Definitions**

### **8.5.1.1                  Adverse Events**

An AE is defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or disease that emerges or worsens relative to study baseline.

When reporting an abnormal laboratory finding, a clinical diagnosis should be recorded rather than the abnormal value itself, if this is available. For example, record “anemia” rather than “decreased red blood cell count” or “hemoglobin = 10.5 g/dL”.

AEs may include the following types of occurrences:

- Medical experiences, such as injury, surgery, accidents, or illnesses, and significant abnormalities in clinical laboratory values, psychological testing, or physical examination findings.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

### **8.5.1.2                  Adverse Drug Reaction**

An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the restoration, correction, or modification or physiological functions. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

### **8.5.1.3                  Serious Adverse Events**

Any SAE requires expedited reporting to the Sponsor’s (GDS) Global Drug Safety Department.

A serious adverse event (SAE) is defined as any adverse event occurring at any dose that results in any of the following outcomes, which are seriousness criteria:

- Results in death. In case of a fatality, the cause of death is considered as the SAE, and the death is its outcome
- Is life-threatening. The term “life-threatening” in this definition refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is otherwise considered as medically important.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of drug dependency or drug abuse.

The treating physician or other relevant concerned health care provider will be asked to assess the relationship of the SAEs to cladribine using the following definitions:

- **Probable:** A causal relationship is clinically/biologically highly plausible, and there is a correlation between the onset of the SAE and administration of cladribine, and between withdrawal of cladribine and resolution of the SAE.
- **Possible:** A causal relationship is clinically/biologically plausible and there is a correlation between the onset of the SAE and administration of cladribine.
- **Unlikely:** A causal relationship is improbable, and another documented cause of the SAE is most plausible.
- **Unrelated:** A causal relationship can be definitively excluded, and another documented cause of the SAE is most plausible.

In this protocol, any adverse pregnancy outcome (e.g., spontaneous abortion, fetal death in utero, ectopic pregnancy, chronic fetal distress, stillbirth, neonatal death, or prematurity-related complication more than is typical for prematurity) should be considered serious. Serious adverse events occurring to offspring of a female subject should also be reported and evaluated as SAEs.

#### **SAEs of particular interest**

Any malignant neoplasia, including non-melanoma skin cancer as well as all serious infections should be considered as a medically significant adverse event and reported to the Sponsor using an SAE Report Form with all related information.

#### **Events Not to Be Considered as AEs / SAEs**

Medical conditions present at the enrollment registry visit that do not worsen in severity or frequency during follow-up in the registry or that do not occur or worsen in severity or frequency during the lag interval period are defined as Baseline Medical Conditions, and are NOT to be considered adverse events.

#### **8.5.1.4 Serious Adverse Drug Reaction**

A serious adverse drug reaction (SADR) is an adverse drug reaction that fulfils at least one seriousness criterion as defined in section 8.5.1.3.



### 8.5.1.5 Definition of the Adverse Event Reporting Period

SAEs are documented from the day informed consent is signed until the subject's last interview (end of study). Beyond that date, ongoing SAEs, including persistent Grade 3 or Grade 4 lymphopenia, and pregnancies will be followed up until event resolution/stabilization or pregnancy outcome is known by the Global Drug Safety Department. Offspring of female subject born during registry participation who are less than 1 year old at the end of the registry will be followed up until 1 year of age by the Global Drug Safety Department.

If PRP/reporter becomes aware of a SAE, which occurred during the lag interval period, but was not reported within a prior cladribine trial, s/he should report this event to the Global Drug Safety department.

If a subject is documented as lost-to follow-up, ongoing SAEs will not be followed up.

### 8.5.2 Recording of Adverse Events in the CRF (Methods of Recording and Assessing Adverse Events)

Complete, accurate, and consistent data on all SAEs experienced for the duration of the reporting period and on all AEs in the 'Blood and Lymphatic System Disorders' and 'Neoplasms Benign, Malignant, and Unspecified' SOCs will be reported on an ongoing basis in the appropriate section of the Case Report Form (CRF). In addition, all SAEs will be documented and reported using an SAE Form.

It is important that each report include a description of the event, its duration (onset and resolution dates/times), its relationship with cladribine, any other potential causal factors, any treatment given or other action taken, and its outcome.

The AE/SAE recording should comply with the following guidelines. Whenever possible, recognized medical terms should be used to describe AEs rather than colloquialisms (for example, "influenza" rather than "flu"), and abbreviations should be avoided.

- AEs/SAEs should be described using a specific clinical diagnosis, if this is available, rather than a list of component signs or symptoms (for example, "congestive heart failure" rather than "dyspnea, rales, and cyanosis").
- Signs and symptoms that are not linked (as "co-manifestations") to an identified disease or syndrome, or for which an overall diagnosis is not available, should be reported as individual events.
- Provisional diagnoses (e.g., "suspected myocardial infarction") are acceptable but should be followed up to a definite diagnosis if one becomes available.

Complete and appropriate data on all SAEs and on all AEs in the 'Blood and Lymphatic System Disorders' and 'Neoplasms Benign, Malignant, and Unspecified' SOCs experienced for the duration of the study will be reported on an ongoing basis in the corresponding pages of the CRF. It is important that each report includes a description of the event, its duration (onset and resolution dates or whether it is ongoing), its relationship to cladribine, any other potential causal factors, any concomitant treatment given or other action taken, and its outcome as of the end of the study.

### 8.5.3                      Procedure for Reporting Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the PRP must immediately (i.e., within a maximum 24 HOURS after becoming aware of the event) inform Sponsor, by fax or by e-mail.

Reporting procedures and timelines are the same for any new information – i.e. follow-up information – on a previously reported SAE.

All written reports should be transmitted using the GDS Alert Report Form, which must be completed by the PRP/Reporter following specific completion instructions.

Relevant pages from the CRF may be provided in parallel (e.g., medical history, concomitant drugs). In all cases, the information provided in the GDS Alert Report Form must be consistent with the data on the event that are recorded in the corresponding sections of the CRF.

The PRP/Reporter must respond to any request for follow-up information (e.g., additional information, outcome and final evaluation, specific records where needed) or to any question the Sponsor may have on the SAE within the same timelines as described for initial reports. This is necessary to permit a prompt assessment of the event by the Sponsor and (as applicable) to allow the Company to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made by the Global Drug Safety of Merck Serono. The Global Drug Safety department may contact the PRP directly to obtain clarification or to discuss a particularly critical event.

The interviewer must notify the Sponsor within 24 hours of his/her awareness of a new SAE or of new follow-up information on a previously reported SAE.

To do so, the interviewer and/or the treating physician must complete a Sponsor GDS Alert Report following specific instructions (GDS Alert Report Form Completion Instructions), using preferably the electronic template, and send it directly to the Global Drug Safety department by electronic mail or facsimile, using the dedicated e-mail address and facsimile numbers specified below:

- PPD [redacted]
- PPD [redacted]

#### 8.5.3.1                      Pregnancy and In Utero Drug Exposure

All pregnancies with an estimated conception date during the period defined in Section 8.5.1.5 must be recorded by convention in the AE page/section of the CRF. The PRP/reporter must notify the Sponsor in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting in Section 8.5.3.

Investigators must actively follow up, document and report on the outcome of all of these pregnancies, even if the subjects are withdrawn from the registry. Offspring of female subjects will be followed-up for one year after delivery or until the registry end, whichever occurs first.

The Investigator must notify the Sponsor of the outcomes using the Pregnancy Report Form, and in case of abnormal outcome, the GDS Alert Report Form when the subject sustains an event and the GDS Parent-Child/Fetus Adverse Event Report Form when the child/fetus sustains an event).

Any abnormal outcome must be reported in an expedited manner as described in Section 8.5.3, while normal outcomes must be reported within 45 days from delivery.

#### **8.5.4                      Safety Reporting to Regulatory Authorities, Investigators and Independent Ethics Committees/Institutional Review Boards**

The Sponsor will send appropriate safety notifications to regulatory authorities in accordance with applicable laws and regulations.

The PRP must comply with any applicable site-specific requirements related to the reporting of SAEs (and in particular deaths) involving his/her subjects to the Ethics Committee/Institutional Review Board (EC/IRB) that approved the study.

In accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, the Sponsor will inform the PRP of “findings that could adversely affect the safety of subjects, impact the conduct of the registry or alter the EC’s/IRB’s approval/favorable opinion to continue the registry.” In particular and in line with respective regulations, the Sponsor will inform the PRP of adverse events that are both serious and unexpected and are considered to be related to cladribine (“suspected unexpected serious adverse reactions” or SUSARs). The PRP should place copies of these Safety reports in the Registry Site File at the site. National regulations with regard to Safety report notifications to Investigators will be taken into account.

The reference safety document against which the assessment of expectedness is made is the Investigator’s Brochure.

In this registry, any unexpected SAEs with an investigator’s causal relationship of “unknown/not assessable” will not be considered by default as “possibly” related and will not be a SUSAR, unless the Sponsor upgrades it.

When specifically required by regulations and guidelines, the Sponsor will provide appropriate Safety reports directly to the concerned lead Independent Ethics Committee (IEC)/IRB and will maintain records of these notifications. When direct reporting by the Sponsor is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety reports provided by the Sponsor and of filing copies of all related correspondence in the Investigator Site File.

For trials covered by the European Directive 2001/20/EC, the Sponsor’s responsibilities regarding the reporting of SAEs/SUSARs will be carried out in accordance with that Directive and with the related detailed guidances.

Reporting of SAEs to regulatory authorities will be in accordance with national regulations and international guidelines<sup>1</sup> for reporting of SAEs occurring during clinical trials.

## 9 Data Analysis and Statistics

There are no plans for any statistical inference. This study will adhere to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)* [1]. Accordingly, data evaluations and interpretations will be based on point estimates and 95% confidence intervals for evaluation of the statistical precision around the point estimate.

Statistical analysis of all data will occur at the end of the registry, and will be performed by the CRO, using SAS<sup>®</sup> statistical software (PPD).

The MedDRA dictionary will be used for coding all primary and secondary endpoints and all reportable SAEs.

### 9.1 Registry size

The purpose of this registry is to comprehensively capture SADR, AEs in the ‘Blood and Lymphatic System Disorders’ and ‘Neoplasms Benign, Malignant, and Unspecified’ SOCs, pregnancy outcomes, and resolution of persistent lymphopenia in subjects exposed to cladribine tablets during the clinical trials. As a result, the cohort size will not be determined using sample size estimating methodology. The registry target population consists of 2175 subjects.

### 9.2 Data analysis

#### 9.2.1 General Considerations

The analysis set will consist of all subjects enrolled in the registry at the time of the analysis.

For safety analyses, subjects will be analyzed according to their actual exposure to oral cladribine.

Life table analysis is the traditional method for evaluating the mortality/morbidity of a fixed population that is followed for a period of time, and the frequency of the events are evaluated at predefined time intervals. Commonly, if effects exist, they are most likely not constant over time, and the life table methodology elucidates the time dependence of the events in relation to the onset of an exposure. The most important aspect of the life table method is the incorporation in the survival analysis of the duration of the time taken to reach the outcome event [10, 11, 12].

Therefore, the main analysis will be to estimate cumulative incidence rates using life-table methodology.

---

<sup>1</sup> Reporting requirements for cases derived from observational (noninterventional) post-authorisation safety studies sponsored by the pharmaceutical industry are laid down in *Volume 9A of the Rules governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use*. However, it is unclear how Volume 9A guidance applies in a preapproval situation. Volume 10 only applies to clinical trials.

## 9.2.2                      Treatment/Analysis Period

The most relevant analysis period will be the cumulative analysis period, which starts from the date of first dose of clinical trial medication to the end of the registry follow-up. In addition, three treatment periods are identified: a) the initial treatment period, from the date of first dose of clinical trial medication to end of the clinical trial participation; b) the extension treatment period (when subjects elects to enroll in a cladribine extension trial) from the date of first dose of cladribine to the end of extension trial participation, c) and the registry study period (where subjects do not receive any experimentally assigned treatment) from the date of enrollment into the registry to the end of registry participation.

The primary analysis will correspond to the cumulative analysis period, which starts from the date of first dose of clinical trial medication to the end of registry follow-up.

### **Baseline Assessments**

Demographic characteristics (e.g., age, sex) at baseline of the registry will be described using descriptive statistics for continuous variables or proportions for categorical variables at entry into the registry. Summaries will be provided by region/country.

### **Safety Analysis**

#### ***Primary Endpoints***

*The cumulative incidence of SADRs and of AEs in the ‘Blood and Lymphatic System Disorders’ and ‘Neoplasms Benign, Malignant, and Unspecified’ SOCs will be summarized, and time to resolution of persistent lymphopenia will be estimated using the life table methodology. The first occurrence of each endpoint occurring during the cumulative analysis period will be considered in the analysis. Cumulative incidence analyses will be presented by MedDRA System Organ Class, High Level Group Term, High Level Term, and Preferred Term.*

#### ***Secondary Endpoints***

The proportion of women and the frequency of the pregnancy outcomes including congenital disorders and important health conditions in the offspring (defined in Section 6.3), will be descriptively summarized. These outcomes will also be described individually for each subject who experiences an outcome.

## 9.3                              Study Reporting and Analysis

### **Study Progress and Safety Reports**

Periodic Progress Reports will be prepared and submitted to Health Authorities as required.

Safety data from this registry will be included in periodic reports submitted to Health Authorities according to applicable regulations.

### 9.3.1 Missing Data

Several attempts will be made to contact subjects and to limit missing data. However, there will be no imputation for missing data. For time-to-event analysis, subjects who do not respond after repeated attempts to contact them will be censored. Details will be included in the Statistical Analysis Plan (SAP).

## 10 Ethical, Scientific and Regulatory Aspects

### 10.1 Good Practice and Scientific Advice (Responsibilities of the PRP)

#### 10.1.1 Guiding Principles

To help ensure the quality and integrity of pharmacoepidemiologic research, and to provide adequate documentation of research methods and results, this study will be conducted under the *Guidelines for Good Pharmacoepidemiology Practices* [1], the *ICH Guidelines for Good Clinical Practice* [2] where applicable, the international *1991 International Guidelines for Ethical Review of Epidemiological Studies* [3], AHRQ's guide: *Registries for Evaluating Patient Outcomes: A User's Guide* [4], and the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* [5].

Outside the preapproval context, the study will comply with the definition of the non-interventional (non-experimental) study provided in Article 2(c) of Directive 2001/20/EC and its refinement provided in Chapter 1.7 Section 1 of Volume 9A of *The Rules Governing Medicinal Products in the European Union* [13]: "In this context, it is considered important to clarify that interviews, questionnaires, and blood samples may be considered as normal clinical practice."

#### 10.1.2 Opinion of External Experts and Scientific Boards

The cladribine DSMB provided guidance to the Sponsor during the development of the registry protocol. External experts from PPD also collaborated in the development of the Registry protocol.

The cladribine DSMB has been kept updated on the status of the registry since its initiation in 2009 and has been informed of all serious adverse events reported for subjects involved in the registry. As the cladribine development program has been terminated, the DSMB is no longer required. The DSMB will, however, continue to be informed of the progress of the registry until their final meeting late in 2012.

### 10.2 Subject information and informed consent

Before a subject can participate in the registry, he or she must give written informed consent. The informed consent process will be in accordance with ICH GCP, the Declaration of Helsinki and local regulatory requirements. At registry enrollment, all subjects will be informed of the registry objectives and overall requirements. Informed consent for enrollment into the registry, access to

data from the clinical trial, and from treating physician or hospital will be obtained by the PRP before any registry-related activities to collect data from or about that subject are carried out.

Adequate information on risks of the study which, in this case, are limited to potential break of confidentiality of some personal identifier and health information, must therefore be given to the subject by the PRP before informed consent is obtained (a person designated by the PRP may give the information, if permitted by local regulations).

Subjects with legal incapacity or limited legal capacity will usually not participate in the registry (see Section 5.4)

Depending on the national regulations, the form may include consent for direct contact with the subject and retrieval of information or supportive documentation from health care providers and/or administrative sources other than the PRP. Also, subjects who refuse to enroll in the registry will be asked to sign consent for use of their clinical trial data to compare registry non-participants with registry participants in terms of demographics, cancer risk factors, and severity of MS.

### **10.3 Subject Identification and Privacy**

A registry study number (a unique, 17-character standard ID number) will be assigned to each subject to allow linkage with the clinical trial identification number and its database. The previous clinical trial study number will also be captured. To keep the subject's identify confidential, the registry will use the study registry number of the subject throughout the study.

Each subject's data collected in the registry will be stored under the registry individual subject number. The CRO will store personal contact information securely and separately from all other data collected in the registry, so that subjects can be contacted regularly for interviews. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data.

Subjects will be informed accordingly, and will be asked to give their consent on data-handling procedures in accordance with national regulations.

#### **Subject and Data Confidentiality:**

Every effort will be made to protect participant confidentiality according to the local and international data privacy and medical record confidentiality guidance [14].

### **10.4 Independent Ethics Committee or Institutional Review Board**

Prior to commencement of the registry at a given site, the registry protocol will be submitted together with its associated documents (e.g., Informed Consent Form, registry CRF) to the responsible Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) for its favorable opinion/approval. The written favorable opinion/approval of the IEC/IRB will be filed in the Investigator Site File and a copy will be filed in the registry master file at the CRO location.

The registry must not start at any site before the Sponsor has obtained written confirmation of a favorable opinion/approval from the concerned IEC/IRB. The IEC/IRB will be asked to provide

documentation of the date of the meeting at which the favorable opinion/approval was given, and of the members and voting members present at the meeting. Written evidence of favorable opinion/approval that clearly identifies the registry, the protocol version and the Subject Information and Consent Form version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to the protocol will also be submitted to the concerned IEC/IRB, before implementation in case of substantial changes in a manner consistent with national regulations (see Section 11.6). Relevant safety information will be submitted to the relevant IECs/IRBs during the course of the registry in accordance with national regulations and requirements.

## **10.5                      Regulatory Authorities**

The protocol and any applicable documentation (e.g., Informed Consent Form) will be submitted or notified to the appropriate regulatory authorities in accordance with the regulations of the countries involved in the registry.

## **11                              Registry Management**

### **11.1                          Manual of operations**

Each participating site will receive the Manual of Operations (MOP), which describes all processes that the PRP or representative must understand.

### **11.2                          Case report form handling**

Data will be collected utilizing a web-based electronic data capture (EDC) system.

The PRP or the trained study site personnel will enter the data required by the registry directly into the web-based system at the time of subject enrollment and during follow-up of individual outcomes. Instructions for proper completion of the electronic case report forms (e-CRFs) and on how to use the EDC system will be provided to the site. An access code with login password will be provided to the registry physician following training. Any additional persons authorized to enter data into the e-CRFs will be provided with a personal access code following training. The PRP is responsible for ensuring that all section of the e-CRF are complete and correct and those entries can be verified against source data.

If a PRP becomes involved in follow-up with other clinicians, the associated documentation provided by other clinicians will be maintained in the subject's registry file at the site.

Data will undergo an automated data quality review process, which checks for completeness and accuracy. In case of data deficiencies, electronic queries will be generated and sent to the site for correction.

The PRP and trained site personnel will obtain subject-reported data through standardized structured subject questionnaires administered.



### **11.3                      Source documents**

The PRP should maintain source documents for each subject enrolled in the registry. Investigator evaluations recorded directly into the e-CRF and subject questionnaires will be considered as source data. Any documentation provided by other clinicians, who may be seeing the subject during the registry, will be considered as source notes and maintained at site.

### **11.4                      Site Filing and Archiving**

The Investigator will be provided with an Investigator Site File upon initiation of the registry. This file will contain all documents necessary for the conduct of the registry and will be updated and completed throughout the registry. It must be available for review by the Monitor, must be ready for inspection by Health Authorities during and after the registry, and must be safely archived for at least 15 years after the end of the registry. The documents to be archived include the Subject Identification List and the signed subject Informed Consent Forms. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor.

All original subject files (medical records and completed registry participant Questionnaires) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

### **11.5                      Monitoring, Quality Assurance, and Inspection by authorities**

The PRP and study staff will be trained on the study procedure prior to registry start. Monitoring will be performed either by site visit or remotely to check the completeness of subject questionnaires and the accuracy of entries on the e-CRFs. Details of monitoring plan will be found in the Manual of Operations. The protocol, each step of the data capture procedures, the handling of data, as well as the eventual registry report; will be subject to independent Clinical Quality Assurance Audits. The CRO, the Sponsor and the Health Authorities may conduct site audits at any time during or after registry operations to ensure the validity and integrity of the data.

### **11.6                      Changes to the Protocol**

Changes to the protocol will be documented in written Protocol Amendments. Major (substantial, significant) amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (non substantial) protocol amendments, including administrative changes, will be filed by Sponsor or the CRO and at each PRP clinic. They will be submitted to the relevant IEC/IRB or to Health Authorities where requested by pertinent regulations.

Any amendment that could have an impact on the subject's agreement to participate in the registry, e.g., changing the number of interviews, requires the subject's informed consent prior to implementation.

## 11.7                      Registry Report and Publication Policy

### 11.7.1                  Final Report

After completion of the registry, a final study report will be written by the CRO in consultation with Sponsor, the Coordinating Registry Physician selected principal registry physicians and selected group of experts.

### 11.7.2                  Publication

Findings of the trial that have public health impact will be communicated to regulatory agencies and the public according to regulatory and scientific guidance. Publications will follow the International Committee of Medical Journal Editors guidelines. [15]

Each participating PRP will inform the Sponsor in advance about any plans to publish or present data from the registry.

Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.) will require pre submission review by the Sponsor.

## 12                        References

1. International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP), revision 2. April 2007. Available at [http://www.pharmacoepi.org/resources/guidelines\\_08027.cfm](http://www.pharmacoepi.org/resources/guidelines_08027.cfm). Accessed 20 December 2011.
2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Note for guidance on good clinical practice (CPMP/ICH/135/95). 2002. <http://www.emea.europa.eu/pdfs/human/ich/013595en.pdf>. Accessed 20 December 2011.
3. Council for International Organizations of Medical Sciences (CIOMS). 1991 International guidelines for ethical review of epidemiological studies. 1991. Available at: [http://www.cioms.ch/publications/guidelines/1991\\_texts\\_of\\_guidelines.htm](http://www.cioms.ch/publications/guidelines/1991_texts_of_guidelines.htm) Accessed 20 December 2011.
4. Gliklich RE, Dreyer NA (editors). Registries for Evaluating Patient Outcomes: A User's Guide. Prepared by Outcome DEcide Center (Outcome Sciences, Inc., dba Outcome) under Contract No. HHS290200500351TO1. AHRQ Publication No. 07-EHC001-1. Rockville, MD: Agency for Healthcare Research and Quality; April 2007.
5. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for biomedical research involving human subjects. 2002. Available at: [http://www.cioms.ch/publications/layout\\_guide2002.pdf](http://www.cioms.ch/publications/layout_guide2002.pdf) Accessed 20 December 2011.
6. Confavreaux C, Vukusic S. Natural history of multiple sclerosis: a unifying concept. *Brain* 2006; 129: 606-16.
7. Kremenchutzky M, Rice GPA, Baskerville J, Wingerchuk DM, Ebers GC. The natural history of multiple sclerosis: a geographically based study 9: observations on the progressive phase of the disease. *Brain* 2006; 129: 584-98.

8. National Cancer Institute, Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v4.03 (CTCAE). 14 June 2010. Available at <http://evs.nci.nih.gov/ftp1/CTCAE/About.html> (see CTCAE\_4.03\_2010-06-14\_QuickReference\_5x7.pdf). Accessed 20 December 2011.
9. European Medicines Agency (EMA), Committee for Medicinal Products for Human Use. Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data [EMA/CHMP/313666/2005]. 14 November 2005. Available at <http://www.ema.europa.eu/pdfs/human/phvwp/31366605en.pdf> . Accessed 20 December 2011.
10. Cutler SJ, Ederer F. Maximum utilization of the life table method in analyzing survival. *J Chronic Dis* 1958 Dec; 8(6): 699-712.
11. Chiang CL. Introduction to stochastic processes in biostatistics. Wiley, New York, 1968.
12. Kahn HA, Sempos CT (editors). Follow-up studies: life tables. In: *Statistical methods in epidemiology*; 168-205. Oxford University Press, New York, 1989.
13. European Commission. The rules governing medicinal products in the European Union. Volume 9A - Pharmacovigilance for Medicinal Products for Human Use. September 2008. Available at: [http://ec.europa.eu/health/documents/eudralex/vol-9/index\\_en.htm](http://ec.europa.eu/health/documents/eudralex/vol-9/index_en.htm). Accessed 20 December 2011.
14. International Society for Pharmacoepidemiology (ISPE). Data privacy, medical record confidentiality, and research in the interest of public health. 1997. Available at: <http://www.pharmacoepi.org/resources/privacy.cfm>. Accessed 20 December 2011.
15. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication. Updated April 2010. Available at: <http://www.icmje.org/>. Accessed 20 December 2011.

### 13 Appendices

#### Appendix I Schedule of Interviews

Registry Period	Day 1	Year 1				Year 2				Year 3 Mo 36	Year 4 Mo 48	Year 5 Mo 60	Year 6 Mo 72	Year 7 Mo 84	Year 8 or 2018 Mo 96 <i>(Whichever comes first)</i>
	Registry baseline	Mo 3	Mo 6	Mo 9	Mo 12	Mo 15	Mo 18	Mo 21	Mo 24						
Informed consent	X														
Inclusion/exclusion criteria	X														
Baseline questionnaire	X														
Identification of lymphopenia	X														
Follow-up questionnaire		X	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Registry Completion / Early Termination</b>															
Lag Questionnaire (Only if applicable)	X														

IC = informed consent;

<sup>a</sup> A window of ± 2 weeks around the date of the scheduled visit during the first two years and of ± 4 weeks thereafter in follow-up scheduled interviews is allowed.

## Appendix II Schedule of interviews for pregnancies and offspring

Pregnancy Period	Pregnancy Reported	4 - 7 Months after LMP <sup>a</sup>	10 Months after LMP <sup>a</sup>	Offspring Age	
				6 mo <sup>a</sup>	1 yr <sup>a</sup>
Pregnancy baseline questionnaire	X				
Pregnancy follow-up questionnaire		X	X		
Baseline neonatal questionnaire			X		
Offspring follow-up questionnaire				X	X

LMP = last menstrual period.

<sup>a</sup> Ideally will coincide with scheduled follow-up interview.

## Appendix III Major structural birth defects or genetic syndromes

### APPENDIX 1: ANTIRETROVIRAL PREGNANCY REGISTRY ORGAN SYSTEM CLASSIFICATION

Continued

#### Contents by organ system

CNS (CNS)  
 Face and Neck (FACE)  
 Cleft Lip and/or Palate (LIP-PAL)  
 Conotruncal Heart Defects (CV-CONO)  
 Obstructive Heart Defects—Right Sided (CV-RT)  
 Obstructive Heart Defects—Left Sided (CV-LT)  
 Heart—Other Defects (CV-O-HRT)  
 Other Circulatory System (CV-O)  
 Respiratory System (RES)  
 Upper Gastrointestinal System (GI-U)  
 Lower Gastrointestinal System (GI-L)  
 Female Genitalia (G-FEMALE)  
 Male Genitalia (G-MALE)  
 Renal and Urinary System (RENAL)  
 Limb Reduction/Addition Defects (LIMB)  
 Other Musculoskeletal Defects (MS-O)  
 Skin and Skin Derivatives (SKIN)  
 Chromosome Anomaly (CHROM)  
 Other Organs and Organ Systems (OTHER)  
 Specified Syndromes/Sequences/Associations (SYND)

CNS (CNS)  
 Anencephaly/acrania  
 Craniorachischisis  
 Iniencephaly  
 Myelomeningocele with hydrocephalus/Arnold–Chiari malformation  
 Meningocele with hydrocephalus  
 Myelomeningocele without hydrocephalus  
 Meningocele without hydrocephalus  
 Lipomeningocele  
 Spina Bifida NOS  
 Encephalocele  
 Holoprosencephaly  
 Other reduction defects of brain  
 Aqueductal stenosis  
 Dandy–Walker malformation  
 Hydranencephaly  
 Other specified Hydrocephalus  
 Hydrocephalus NOS  
 Hydrocephalus secondary to IVH\*  
 Structural defect of central nervous system—other specified  
 Excludes arachnoid cysts  
 Structural defect of central nervous system NOS  
 Structural defect of peripheral nervous system—other specified  
 Structural defect of peripheral nervous system NOS  
 Structural defect of nervous system NOS

Face and Neck (FACE)  
 Anophthalmia/microphthalmia  
 Congenital Glaucoma  
 Congenital cataract/lens anomaly  
 Anterior segment anomaly including iris colobomata  
 Posterior segment anomaly  
 Orbital and periorbital anomaly (eyelids, lacrimal system, orbit)  
 Fused eyelids excluded < 25 weeks\*  
 Stenosis/obstruction of lacrimal duct\*  
 Other specified anomaly of eye  
 Blue sclerae excluded < 36 weeks\*

Epicanthal folds\*  
 Slant to eyes\*  
 Brushfield spots\*  
 Esotropia\*  
 Exotropia\*  
 Nystagmus\*  
 Unspecified anomaly of eye  
 Anotia/Microtia  
 Other specified anomaly of external ear  
 Absence/stricture of external auditory canal  
 Anomaly of middle ear/ossicles  
 Anomaly of inner ear  
 Preauricular skin tag/preauricular pit\*  
 Accessory auricle\*  
 Other ear tag\*  
 Other specified anomaly of ear  
 Bat ear, pointed, elfin, lop, cauliflower\*  
 Absent/decreased cartilage excluded < 36 weeks\*  
 Lowset ears\*  
 Posteriorly rotated ears\*  
 Darwin tubercle\*  
 Unspecified anomaly of ear  
 Incl Congenital Deafness NOS  
 Absent/hypoplastic nose  
 Tubular nose/proboscis/single nostril  
 Choanal atresia  
 Other specified anomaly of nose  
 Flat bridge of nose\*  
 Deviation of nasal septum\*  
 Bent nose\*  
 Unspecified anomaly of nose  
 Microstomia  
 Macrostomia/lateral facial cleft  
 Lip pits  
 Other specified anomaly of lip (other than cleft)  
 Macrocheilia\*  
 Microcheilia\*  
 Natal teeth\*  
 Other specified anomaly of palate (other than cleft)  
 High-arched palate\*  
 Unspecified anomaly of mouth/lip  
 Aplasia/hypoplasia of tongue/microglossia  
 Enlarged tongue/macroglossia  
 Other specified anomaly of tongue  
 Tongue tie/ankyloglossia\*  
 Unspecified anomaly of tongue  
 Short neck\*  
 Webbed neck/Cystic hygroma  
 Webbed neck\*  
 Absent/hypoplastic sternocleidomastoid muscle/torticollis  
 Branchial cleft remnant, cyst, fistula  
 Thyroglossal duct remnant, cyst, fistula  
 Pharyngeal pouch anomaly  
 Other specified anomaly of neck  
 Unspecified anomaly of neck  
 Micrognathia/retrognathia  
 Other abnormalities in jaw size/shape  
 Hypertelorism  
 Hypotelorism  
 Facial asymmetry

Facial palsy	Anomaly of myocardium
Dysmorphic facies	Cardiomegaly*
Other specified anomaly of face	Anomaly of coronary artery/sinus
Includes facial clefting other than cleft lip or palate	Anomaly in cardiac rhythm
Unspecified anomaly of face	Premature atrial contractions*
<b>Cleft Lip and/or Palate (LIP-PAL)</b>	Other specified anomaly of heart
Cleft lip of any type without palate involvement	Unspecified heart anomaly
Cleft lip of any type with palate involvement	<b>Other Circulatory System (CV-O)</b>
Cleft palate alone	Patent Ductus Arteriosus (PDA)
Unspecified cleft	PFO excluded < 36 weeks or on prostaglandins, conditional ≥ 36 weeks < 6 weeks, always code ≥ 36 weeks and ≥ 6 weeks or ≥ 36 weeks with medical/surgical intervention*
<b>Conotruncal Heart Defects (CV-CONO)</b>	Single Umbilical Artery*
Double Outlet Right Ventricle	Aorto-pulmonary collateral
Interrupted Aortic Arch	Other anomaly of great arteries or veins
Pulmonary valve atresia with VSD	Aortic aneurysm
Right-sided aortic arch/double aortic arch/vascular ring	Other specified anomaly of aorta
Tetralogy of Fallot (TOF)	Unspecified anomaly of aorta
Transposition of Great Vessels (TGV)	Pulmonary artery aneurysm
Truncus arteriosus	Other anomaly of pulmonary artery
Other specified conotruncal heart anomaly	Anomalous pulmonary venous return (total or partial)
Unspecified conotruncal heart anomaly	Persistent left superior vena cava
<b>Obstructive Heart Defects—Right Sided (CV-RT)</b>	Stenosis of vena cava
Pulmonary valve atresia/stenosis/hypoplasia with IVS	Anomaly of portal venous system
Mild, minimal, trivial, etc. insufficiency or regurgitation*	Other specified anomaly of great veins
Subvalvular pulmonary stenosis	Unspecified anomaly of great veins
Main pulmonary artery stenosis	Renal artery stenosis
Supravalvular pulmonic stenosis	Peripheral arterio-venous malformation
Peripheral pulmonary artery stenosis	Anomaly of cerebral vasculature (including AV malformation)
Tricuspid valve atresia/stenosis/hypoplasia	Hemangioma must be ≥ 4 cm diameter, multiple or cavernous*
Mild, minimal, trivial, etc. insufficiency or regurgitation*	Lymphangioma
Ebstein anomaly	Other disorders of lymphatics*
Hypoplastic right ventricle	Hydrops fetalis
Other specified right sided heart anomaly	Other specified anomaly of peripheral vascular system
Unspecified right sided heart anomaly	Unspecified anomaly of peripheral vascular system
<b>Obstructive Heart Defects—Left Sided (CV-LT)</b>	Other specified anomaly of lymphatic system
Aortic valve atresia/stenosis/hypoplasia	Unspecified anomaly of lymphatic system
Mild, minimal, trivial, etc. insufficiency or regurgitation*	<b>Respiratory System (RES)</b>
Subvalvular aortic stenosis	Anomaly of larynx
Coarctation of aorta	Anomaly of trachea
Hypoplasia of aorta	Excludes subglottic stenosis secondary to endotracheal intubation
Supravalvular aortic stenosis	Excludes vascular ring compression
Mitral valve atresia/stenosis/hypoplasia	Anomaly of bronchus
Mild, minimal, trivial, etc. insufficiency or regurgitation*	Anomaly of pleura
Hypoplastic Left Heart Syndrome (HLHS)	Agnesis of lung
Hypoplastic left ventricle	Hypoplasia of lung
Other specified right sided heart anomaly	Conditional exclusion < 36 weeks*
Unspecified right sided heart anomaly	Sequestration of lung
<b>Heart—Other Defects (CV-O-HRT)</b>	Cystic adenomatoid malformation of lung
Endocardial Cushion Defects/AV canal VSD	Other cystic dysplasia of lung
Excludes AVC type, code as AV canal	Abnormal lobulation of lung
Ostium primum ASD	Other specified anomaly of lung
Single ventricle	Unspecified anomaly of lung
PFO/secundum ASD	Other specified anomaly of respiratory system
PFO excluded < 36 weeks, conditional ≥ 36 weeks < 6 weeks, always code ≥ 36 weeks ≥ 6 weeks*	Unspecified anomaly of respiratory system
ASD NOS	<b>Upper Gastrointestinal System (GI-U)</b>
Other septal defect	Esophageal atresia without Tracheoesophageal fistula
Positional defects of heart	Esophageal atresia with Tracheoesophageal fistula
Anomaly of pericardium	

Tracheoesophageal fistula without esophageal atresia	Other specified anomaly of fallopian tubes
Stenosis/structure/web of esophagus	Absence/agenesis of uterus
Other specified anomaly of esophagus	Duplication of uterus
Unspecified anomaly of esophagus	Other specified anomaly of uterus
Aplasia/hypoplasia of stomach	Absence/agenesis of uterine cervix or upper vagina
Congenital hiatal hernia	Other specified anomaly of internal female genitalia
Pyloric stenosis	Unspecified anomaly of internal female genitalia
Pylorospasm*	Absence/agenesis of lower vagina
Displacement of stomach	Absence/agenesis/imperforation of vulva/hymen
Other specified anomaly of stomach	Imperforate hymen*
Unspecified anomaly of stomach	Other specified anomaly of cervix, vagina, or external female genitalia
Other specified anomaly of upper gastrointestinal system	Fusion of vulva*
Unspecified anomaly of upper gastrointestinal system	Hypoplastic labia majora excluded < 36 weeks*
<b>Lower Gastrointestinal System (GI-L)</b>	Clitoromegaly*
Stenosis/absence/atresia of duodenum	Embryonal cyst of vagina*
Stenosis/absence/atresia of jejunum	Vaginal/hymenal tags*
Stenosis/absence/atresia of ileum	Unspecified anomaly of external female genitalia
Stenosis/absence/atresia of small intestine NOS	Fistula between female genital tract and GI tract
Stenosis/absence/atresia of large intestine/colon	Fistula between female genital tract and urinary tract
Stenosis/absence/atresia of rectum with fistula	Ambiguous genitalia in genetic female
Stenosis/absence/atresia of rectum without fistula	<b>Male Genitalia (G-MALE)</b>
Stenosis/absence/atresia of anus with fistula	Absence/agenesis of testicle
Stenosis/absence/atresia of anus without fistula	Hypoplasia of testicle
Other specified stenosis/absence/atresia of lower gastrointestinal system	Ectopic testicle
Unspecified stenosis/absence/atresia of lower gastrointestinal system	Undescended testicle
Hirschsprung disease/aganglionosis of intestine	Excluded < 36 weeks
Malrotation of intestine	≥ 36 weeks
Duplication of intestine	Always code if ≥ 1 year of age or with medical/surgical intervention
Intestinal web	Absence/agenesis of scrotum
Microcolon	Hypoplasia of scrotum
Ectopic anus	Hypoplasia secondary to cryptorchidism*
Persistent cloaca	Hydrocele*
Other specified anomaly of small or large intestine	Other specified anomaly of testis or scrotum
Rectal fissure*	Testicular torsion*
Meconium plug*	Unspecified anomaly of testis or scrotum
Meconium peritonitis*	Anomaly of vas deferens or prostate
Unspecified anomaly of small or large intestine	Epispadias
Aplasia/hypoplasia of liver	Primary hypospadias
Dysplasia of liver	Secondary hypospadias
Agenesis/hypoplasia of gall bladder	Tertiary hypospadias
Extrahepatic biliary atresia	Hypospadias NOS
Other specified anomaly of liver, gall bladder, or bile ducts	Primary hypospadias with chordee
Hepatomegaly*	Secondary hypospadias with chordee
Unspecified anomaly of liver, gallbladder, or bile ducts	Tertiary hypospadias with chordee
Agenesis/hypoplasia of pancreas	Chordee with Hypospadias NOS
Accessory/ectopic pancreas	Absence/aplasia of penis
Annular pancreas	Micropenis
Other and unspecified anomaly of pancreas	Other specified anomaly of penis
Excludes Diabetes Mellitus	Excludes redundant foreskin
Other specified anomaly of lower gastrointestinal system	Includes chordee without hypospadias
Unspecified anomaly of lower gastrointestinal system	Unspecified anomaly of penis
<b>Female Genitalia (G-FEMALE)</b>	Other specified anomaly of male genitalia
Absence/agenesis of ovary	Unspecified anomaly of male genitalia
Hypoplasia of ovary	Ambiguous genitalia in genetic male
Cysts of ovary	<b>Renal and Urinary System (RENAL)</b>
Other specified anomaly of ovary	Absence/agenesis/hypoplasia of kidney—bilateral
Absence/agenesis of fallopian tubes	Absence/agenesis/hypoplasia of kidney—unilateral
	Unspecified absence/agenesis/hypoplasia of kidney



Polycystic kidney disease  
Multicystic dysplastic kidney  
Other specified cystic disease of kidney  
Unspecified cystic disease of kidney  
Congenital hydronephrosis  
Atresia/stricture/stenosis of ureter  
Hydroureter  
Other specified obstructive defect of kidney  
Unspecified obstructive defect of kidney  
Extra/accessory kidney  
Duplicated kidney  
Lobulated/fused/horseshoe kidney  
Ectopic kidney  
Enlarged/hyperplastic/giant kidney  
Other specified anomaly of kidney  
Unspecified anomaly of kidney  
Absence/aplasia of ureter  
Accessory/ectopic ureter  
Other and unspecified anomaly of ureter  
Vesicoureteral reflux  
Exstrophy of bladder  
Anomaly of urachus  
Patent urachus\*  
Absence/aplasia of bladder or urethra  
Ectopic bladder  
Diverticulum of bladder  
Duplicated urethra  
Ectopic urethra (not hypospadias)  
Fistula between urinary and GI tract  
Posterior urethral valves  
Other atresia/stenosis of bladder neck or urethra  
Other specified anomaly of bladder or urethra  
Unspecified anomaly of bladder or urethra  
**Limb Reduction/Addition Defects (LIMB)**  
Absence of complete upper limb  
Absence of upper arm and forearm (hand present)  
Absence of upper arm  
Absence of forearm  
Absence of hand/fingers  
Preaxial reduction defect—arm/hand  
Postaxial reduction defect—arm/hand  
Ectrodactyly hand  
Transverse reduction defect of upper limb NOS  
Longitudinal reduction defect of upper limb NOS  
Other specified reduction defect of the arm  
Unspecified reduction defect of the arm  
Absence of complete lower limb  
Absence of thigh and calf (foot present)  
Absence of thigh  
Absence of calf  
Absence of foot/toes  
Preaxial reduction defect—leg/foot  
Postaxial reduction defect—leg/foot  
Ectrodactyly foot  
Transverse reduction defect of lower limb NOS  
Longitudinal reduction defect of lower limb NOS  
Other specified reduction defect of the leg  
Unspecified reduction defect of the leg  
Specified or unspecified reduction defect of unspecified limb  
Absent digits NOS

Polydactyly—postaxial hand  
Skin tags in blacks\*  
Polydactyly—preaxial hand  
Polydactyly—postaxial foot  
Skin tags in blacks\*  
Polydactyly—preaxial foot  
Polydactyly NOS—hand  
Polydactyly NOS—foot  
Other and unspecified polydactyly  
Other limb addition anomaly  
**Other Musculoskeletal Defects (MS-O)**  
Microcephaly  
Macrocephaly (without hydrocephalus)  
Abnormal shape of head—no craniosynostosis  
Dolichocephaly excluded < 36 weeks\*  
Scaphocephaly excluded < 36 weeks\*  
Sagittal craniosynostosis  
Coronal craniosynostosis  
Metopic craniosynostosis  
Lambdoidal craniosynostosis  
Other and unspecified craniosynostosis  
Acrocephalosyndactyly of any type  
Oculoauriculovertebral spectrum/Hemifacial microsomia  
Other specified craniofacial malformation syndrome  
Other specified anomaly of skull and/or face bone  
Large/small fontanelle\*  
Flat occiput\*  
Prominent occiput\*  
Unspecified anomaly of skull and/or face bones  
Pectus carinatum  
Pectus excavatum  
Absent sternum  
Other and unspecified anomaly of sternum  
Anomaly of chest wall  
Absent ribs  
Extra ribs (including cervical)  
Cervical rib\*  
Fused or bifid ribs  
Other and unspecified anomaly of ribs  
Spina bifida occulta/sacral dimple  
Scoliosis/kyphoscoliosis without vertebral anomaly  
Anomaly of cervical vertebra  
Anomaly of thoracic vertebra  
Anomaly of lumbar vertebra  
Anomaly of sacrum/coccyx  
Other and unspecified vertebral anomaly  
Syndactyly—fingers  
Syndactyly—toes  
Webbing of second and third toes\*  
Unspecified syndactyly  
Anomaly of fingers  
Clinodactyly of fifth finger\*  
Long fingers\*  
Anomaly of hand, including palmar creases  
Club hand  
Anomaly of wrist  
Anomaly of forearm  
Anomaly of elbow, including dislocation  
Anomaly of upper arm/humerus  
Anomaly of shoulder, including clavicle

Erb palsy  
 Hypoplasia of arm  
 Poland Anomaly/Absent chest muscle  
 Other specified anomaly of upper extremity  
 Unspecified anomaly of upper extremity  
 Anomaly of toes  
 Overlapping toes\*  
 Anomaly of foot (excluding club foot)  
 Rocker-bottom foot\*  
 Anomaly of ankle  
 Anomaly of calf  
 Excluded: Tibial torsion with clubfoot  
 Anomaly of knee/patella, including dislocation  
 Anomaly of thigh/femur  
 Anomaly of hip, excluding hip dysplasia  
 Hip dysplasia/dislocation  
 Hypoplasia of leg  
 Other specified anomaly of lower extremity (excluding club foot)  
 Unspecified anomaly of lower extremity  
 Varus (inward) anomaly of foot  
 Metatarsus varus/adductus\*  
 Valgus (outward) anomaly of foot  
 Other and unspecified club foot  
 Other specified anomaly of unspecified limb  
 Unspecified anomaly of unspecified limb  
 Arthrogyposis  
 Chondrodystrophy/'Dwarfism'  
 Osteodystrophy  
 Other specified skeletal dysplasia  
 Unspecified skeletal dysplasia  
 Diaphragmatic hernia  
 Other anomaly of diaphragm  
 Umbilical Hernia\*  
 Inguinal Hernia  
 Never code < 36 weeks ≥ 36 weeks, always code in female, conditional in male  
 Omphalocele  
 Gastroschisis  
 Absence of abdominal musculature/Prune Belly  
 Other specified anomaly of anterior abdominal wall  
 Includes Limb-Body Wall complex  
 Unspecified anomaly of anterior abdominal wall  
 Other and unspecified anomaly of muscle  
 Other and unspecified anomaly of tendon  
 Other and unspecified anomaly of bone  
 Other and unspecified anomaly of cartilage  
 Other and unspecified anomaly of connective tissue  
 Other and unspecified anomaly of musculoskeletal system  
 Sacral/pilonidal dimple\*  
 Erb palsy\*  
**Skin and Skin Derivatives (SKIN)**  
 Absence of skin  
 Ichthyosis  
 Epidermolysis Bullosa  
 Ectodermal dysplasia  
 Hyperpigmentation  
 Excluded: Mongolian spots  
 Port wine stain\*

Nevus flammeus\*  
 Cafe-au-lait spots\*  
 Hypopigmentation  
 Skin tags (not face/neck)  
 Birthmark NOS\*  
 Cutis aplasia (scalp)  
 Benign tumor of skin  
 Sebaceous cyst  
 Hairy nevus  
 Other specified anomaly of skin  
 Transvers plamar creases\*  
 Anal tags\*  
 Skin cysts\*  
 Persistent lanugo\*  
 Unspecified anomaly of skin  
 Anomaly of hair  
 Anomaly of nails  
 Anomaly of breast  
 Excluded: Inverted nipples  
 Small nipple\*  
 Accessory/ectopic/supernumerary nipple\*  
 Widely spaced nipples\*  
 Other specified anomaly of skin derivative  
 Unspecified anomaly of skin derivative  
**Chromosome Anomaly (CHROM)**  
 Specific list would include any abnormal chromosome complement and will be clearly defined in affected individuals. For example:  
 Trisomy 13  
 Trisomy 21  
 Turner Syndrome NOS  
 Unspecified mosaicism  
 Unspecified translocation  
 Unspecified additional chromosome(s)  
 Unspecified deletion of chromosome  
 Unspecified duplication of chromosome  
 Unspecified chromosome anomaly  
**Other Organs and Organ Systems (OTHER)**  
 Conjoined twins  
 Amniotic band/Amnion rupture sequence\*  
 Absence/hypoplasia of spleen  
 Accessory spleen  
 Ectopic spleen  
 Other and unspecified anomaly of spleen  
 Hyperplasia of spleen/splenomegaly\*  
 Absence/hypoplasia of adrenal gland  
 Accessory adrenal gland  
 Ectopic adrenal gland  
 Other and unspecified anomaly of adrenal gland  
 Anomaly of pituitary gland  
 Anomaly of thyroid gland  
 Hypothyroidism\*  
 Anomaly of parathyroid gland  
 Hypoparathyroidism\*  
 Anomaly of thymus  
 Thymic hypertrophy\*  
 Other and unspecified anomaly of endocrine gland  
 Hypoglycemia\*  
 Heterotaxy syndrome  
 Ambiguous genitalia in infant of unknown gender  
 Hermaphroditism

---

Male pseudohermaphroditism  
Female pseudohermaphroditism  
Other and unspecified anomaly of sex assignment  
Congenital anomaly NOS  
Anomaly of placenta  
Anomaly of umbilical cord (other than single umbilical artery)  
Umbilical cord atrophy\*  
Lipoma  
Teratoma  
Ascites/Hydrops\*

**Specified Syndromes/Sequences/Associations (SYND)**

This list would be exhaustive and could include anything that is a recognized, named syndrome. Occurrence of any one syndrome will probably be rare.

Congenital Adrenal Hyperplasia  
Fetal Alcohol Syndrome  
Neuroblastoma  
Potter Sequence  
Roberts Syndrome  
Twin-Twin Transfusion  
Water Association  
Velocardiofacial Syndrome—possible  
Zellweger Syndrome  
Congenital syphilis\*  
Benign neoplasms\*  
Phenylketonuria and other inborn errors of metabolism  
not usually associated with birth defects\*

---

\*These items are only included under certain circumstances. Unless otherwise specified for the item, the item is only included if there is another ascertainable defect.

Items marked as 'excluded' are never considered defects.