Observational Pregnancy Safety Study of Women Exposed to Nifurtimox During Pregnancy to Describe the Risk of Pregnancy and Maternal Complications and Other Events of Interest on the Developing Fetus, Neonate, and Infant

Acronym/Title	Observational Pregnancy Safety Study of Women Exposed to Nifurtimox During Pregnancy to Describe the Risk of Pregnancy and Maternal Complications and Other Events of Interest on the Developing Fetus, Neonate, and Infant
Protocol version and date	V.1.0, 24 JAN 2022
IMPACT study number	21944
Study type / Study phase	Observational, post-approval, Phase IV, Post-market surveillance ☒ PASS Joint PASS: ☐ YES ☒ NO
NCT number	Study not yet registered
Active substance	Nifurtimox
Medicinal product	Lampit®
US NDA number	NDA 213464
Study Initiator and Funder	Bayer AG

Research question and objectives	This observational study is designed to describe the risk of pregnancy and maternal complications occurring in women with Chagas' disease who are exposed to nifurtimox at any time from the first day of their last menstrual period through pregnancy (i.e., defined pregnancy exposure window) and the effects on the developing fetus and neonate and infant. The objectives of this pregnancy safety study are to collect and describe: • selected fetal/neonatal/infant outcomes (i.e., major congenital malformations (MCM), small for gestational age, and postnatal growth and development) at birth and up to the first year of life of infants born to women exposed to nifurtimox during the defined pregnancy exposure window. pregnancy outcomes of interest (i.e., live birth, spontaneous abortions, stillbirths, elective abortions, and preterm births) and pregnancy complications in women with Chagas disease exposed to nifurtimox during the defined pregnancy exposure window.
Countries of study	All countries where nifurtimox is approved to be marketed by Bayer
Author	PPD, PPD Safety, Epidemiology, Registries & Risk Management United BioSource (UBC), LLC 920 Harvest Drive, Suite 200 Blue Bell, PA 19422 PPD Pharmacovigilance – Benefit Risk Management Bayer AG Building M084 13353 Berlin, Germany

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG
MAH contact person	PPD Regulatory Affairs Strategy Bayer U.S. LLC 100 Bayer Boulevard Whippany, NJ 07981-0915

The study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

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1. List of Abbreviations

ACOG	American College of Obstetricians and Gynecologists
AE	Adverse Event
AFP	Alpha-Fetoprotein
AR	Adverse Reaction
CDC	Centers for Disease Control and Prevention
CRF	Case Report Form
CRO	Contract Research Organization
CVS	Chorionic Villus Sampling
DMP	Data Management Plan
EC	Ethics Committee
EDD	Estimated Date of Delivery
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
FDA	Food and Drug Administration
GVP	Good Pharmacovigilance Practices
HCG	Human Chorionic Gonadotropin
HCP	Healthcare Provider
ICBDSR	International Clearinghouse for Birth Defects Surveillance Research
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
DMPIRB	Investigational Review Board
IUGR	Intrauterine Growth Retardation
LMP	Last Menstrual Period
MACDP	Metropolitan Atlanta Congenital Defects Program
MCM	Major Congenital Malformation
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Medical Review Plan
NCHS	National Center for Health Statistics
Ob/Gyn	Obstetrician/Gynecologist
PASS	Post Authorisation Safety Study
PFO	Patent Foramen Ovale
PIH	Pregnancy Induced Hypertension
PROM	Premature Rupture of Membranes
SAE	Serious Adverse Event
SCC	Study Coordinating Center
SME	Subject Matter Expert
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UBC	United BioSource Corporation
US	United States
WHO	World Health Organization

2. Responsible Parties

2.1 Study Initiator and Funder

Role: PPD
Name: PPD
E-mail: PPD

Role: PPD
Name: PPD

Role: PPD
Name: PPD

Role: PPD
Name: PPD

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Role: PPD
Name: PPD

Role: PPD
Name: PPD

Contact details of the responsible parties at Bayer AG are available upon request. Signatures of the responsible parties are collected in Annex 3.

2.2 Contractors, Collaborators, Committees

Role: CRO

Name, Company: PPD

United BioSource (UBC), LLC

The CRO will serve as the Study Coordinating Center (SCC). The SCC will provide overall study management, obtain IRB/EC approval of the study in all countries, and complete any other regulatory obligations for study conduct. In the US and in any other co untries where direct contact is possible with the pregnant woman, the SCC will collect data directly from the pregnant woman and her HCPs as well as the infant's HCPs. The SCC will enter all data into the study database and will prepare the interim and final reports. In countries where HCPs will be enrolled and collect all

data regarding the pregnancy and outcome and perform infant follow-up, the SCC will maintain contact with the HCP and receive the collected data for entry into the study database.

PPD will serve as the PPD for the study. PPD will be the PPD, and PPD will oversee the SCC operations. PPD will provide statistical support.

Contact details of the responsible parties at UBC are kept as a stand-alone document (Annex 1). Contact details for the Central Investigator and any site personnel for each country and site participating in the study are listed in a stand-alone document (see Annex 1) which is available upon request.

Information on the Steering Committee Members and the respective Charter are kept as stand-alone documents (see Annex 1). Changes of responsible persons and/or the composition of the committees will be documented by updating the respective lists, but do not require formal protocol amendments.

3. Abstract

Acronym/Title	Observational Pregnancy Safety Study of Women Exposed to Nifurtimox During Pregnancy to Describe the Risk of Pregnancy and Maternal Complications and Other Events of Interest on the Developing Fetus, Neonate, and Infant
Protocol version and date	V 1.0, 24 JAN 2022
IMPACT study number	21944
Study type / Study phase	Observational, post-approval, Phase IV, Post-Market surveillance ☒ PASS Joint PASS: ☐ YES ☒ NO
Author	PPD, PPD Safety, Epidemiology, Registries & Risk Management United BioSource (UBC), LLC 920 Harvest Drive, Suite 200 Blue Bell, PA 19422 USA PPD Pharmacovigilance – Benefit Risk Management Bayer AG Building M084 13353 Berlin, Germany

Rationale and background	In order to better describe the safety profile of nifurtimox when exposure occurs at any time from the first day of the woman's last menstrual period through pregnancy (i.e., the defined pregnancy exposure window), an observational safety study was designed to describe the risk of nifurtimox exposure on pregnancy and on fetal, neonatal, and infant outcomes. The minimal data on human pregnancy exposures to nifurtimox makes such a study an essential component of overall safety surveillance for this product.
Research question and objectives	This study is designed to describe the risk of pregnancy and maternal complications occurring in women with Chagas' disease who are exposed to nifurtimox during the defined pregnancy exposure window and the other events of interest on the developing fetus, neonate and infant. The objectives of this pregnancy safety study are to collect and describe: • selected fetal/neonatal/infant outcomes (i.e., major congenital malformations (MCM), small for gestational age, and postnatal growth and development) at birth and up to the first year of life of infants born to women exposed to nifurtimox during the defined pregnancy exposure window. • pregnancy outcomes of interest (i.e., live birth, spontaneous abortions, stillbirths, elective abortions, and preterm births) and pregnancy complications in women with Chagas Disease exposed to nifurtimox during the defined pregnancy exposure window.
Study design	This is an observational study of pregnancy exposures to nifurtimox. Reports of pregnancy exposures will be collected whether or not the pregnancy outcome is known at the time of enrollment. That is, some exposed pregnancies will be enrolled in the study at the time of known pregnancy outcome (retrospective pregnancy report) and some exposed pregnancies will be enrolled before the outcome is known (prospective pregnancy report). The study population is referred to as 'pregnant women' in this protocol and includes both women who are pregnant at the time of enrollment and those who are no longer pregnant at the time of enrollment but were exposed to nifurtimox at any time from the first day of their last menstrual period through pregnancy. Information on pregnancies that occur in any woman exposed to

	nifurtimox in the defined pregnancy exposure window will be collected by the nifurtimox Study Coordinating Center (SCC) from healthcare providers who are treating pregnant women with Chagas' disease with nifurtimox, and from women who were exposed to nifurtimox during the defined pregnancy exposure window and their secondary contacts (i.e., individuals both within and outside her household who will know her whereabouts should she become lost to follow-up).The study will collect data for approximately 10 years.
Population	Women with Chagas' disease who have been exposed to at least 1 dose of nifurtimox during the defined pregnancy exposure window and fetuses, neonates, and infants through 12 months of age who were exposed to at least one dose of nifurtimox *in utero*.
Variables	The key variables of interest include maternal demographic and clinical information regarding pregnancy and maternal complications; MCMs found during prenatal testing; pregnancy outcome; MCM identified *in utero* or in the neonate or live born infant; delivery information; prior pregnancy and outcome history; maternal comorbidities, maternal environmental exposures (e.g., smoking, alcohol consumption, occupational exposure, illicit drug use); nifurtimox exposure (dose, duration of exposure); and medications taken during pregnancy. When a pregnancy outcome is a live birth, the key variables of interest include MCMs identified *in utero* after birth; serious illnesses requiring hospitalization; medications with indication; and growth and development milestones at birth to 12 months of age (1).
Data sources	Data will be collected from various sources, when and/or if applicable, including telephone interviews conducted by the SCC directly with the pregnant women and her healthcare providers (HCPs), case report forms (CRFs) submitted by HCPs contracted to identify and follow eligible pregnancies, reports sent to the Study Coordinating Center (SCC) from reports received directly by Bayer, and medical records obtained for identified MCMs.
Study size	It is anticipated that approximately 5 pregnancies will be reported per year, or 50 over the data collection period.
Data analysis	Given the anticipated low enrollment rate, formal hypothesis testing for increased MCMs is not tenable. Data analyses will be descriptive in nature as sample sizes will likely not be sufficiently large to conduct formal comparisons to external data sources or to provide precise estimates for calculated incidence

	rates for primary outcomes. Data from the Metropolitan Atlanta Congenital Defects Program (MACDP) (2, 3) incidence rate of major defects (reported at 3% in the US), and data available in South America (reported birth defect incidence ranging from 0.9% - 1.6%, (4-6) will be used to put the estimated incidence in perspective. Data regarding MCM will be presented as proportions (percent of total outcomes) and incidence rates and 95% CI will be presented according to person-year exposure. Data will be presented for the proportion of the total number of pregnancies that result in spontaneous abortion, elective abortion, fetal death/stillbirth, or preterm delivery, and for infants that are small for gestational age. The proportion of pregnancies that result in live births of infants that experience complications, such as delays in growth and development milestones, and hospitalizations during the first year of life for infants at 3, 6, 9, and 12 months, will be calculated.
Milestones	The start-up activities for the pregnancy safety study are expected to begin in Q1 2022. Interim progress reports will be submitted to the FDA annually each January thereafter through January 2032. The completion of the study is anticipated in January 2032. The final study report will be submitted to FDA in Q3 2032.

4. Amendments

NA

5. Milestones

Table 1 presents planned milestones for the study. These milestones are based on a timely review and approval of the study. Administrative changes to milestones due to delays in study preparation and enrollment do not require amendments to the protocol. Revised study timelines and milestones which do not constitute a need for a formal protocol amendment are tracked in a stand-alone document (Annex 1).

The start-up activities for the pregnancy safety study are expected to begin in Q1 2022. Interim progress reports will be submitted to the FDA in January 2023 and annually each January thereafter through January 2032. The completion of the study is anticipated in January 2032. The final study report will be submitted to FDA in Q3 2032.

Table 1: Milestones

Milestone	Planned date
Start -up activities	Q1 2022

End of data collection	January Q1 2032
Interim progress reports	January 2023 and annually each January thereafter through January 2032
Final report of study results	Q3 2032

6. Rationale and Background

Chagas' disease (American Trypanosomiasis) is caused by the protozoan parasite *Trypanosoma cruzi (T. cruzi)* and is a vector-borne disease transmitted to humans by large, reduviid bugs infected with the parasite. For more than 50 years, nifurtimox, a nitroheterocyclic compound, has been used to treat Chagas' disease due to it trypanocidal activity against all parasitic forms. It was the first drug used for Chagas' disease treatment, and there is still only one alternative treatment option (benznidazole) available. Nifurtimox was first introduced in 1965 and the first marketing authorization was granted in Argentina in 1970. It is currently approved and authorized to be marketed by Bayer in Argentina, Bolivia, Chile, El Salvador, Guatemala, Uruguay, the United States, and Honduras.

Nifurtimox is commercially available under the brand name LAMPIT. Nifurtimox has been classified by the World Health Organization (WHO) as a vitally important medicine and is included on the WHO Model List of Essential Medicines for Chagas' disease.

In the US, nifurtimox is indicated in pediatric patients (birth to less than 18 years of age and weighing at least 2.5 kg) for the treatment of Chagas' disease (American Trypanosomiasis), caused by *T. cruzi*. In other countries where nifurtimox is approved to be marketed by Bayer, the indication also includes patients over 18 years of age. Product labeling indicates that nifurtimox is not recommended to be used during pregnancy.

Based on findings from animal studies, nifurtimox can potentially cause fetal harm when administered to a pregnant woman. There are no data on the use of nifurtimox in pregnant women. Based on preclinical studies, nifurtimox passes the placental barrier. When administered orally to pregnant mice, rats, and rabbits during organogenesis, nifurtimox was associated with reduced fetal body weights in rodents, and abortions, fetal death, and reduced number of live fetuses in rabbits. Therefore, the use of nifurtimox is not recommended during pregnancy.

The estimated background risk of MCM and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of MCM and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively (2). Data available in South America indicate the incidence of congenital malformations to range from 0.9% (4) to 1.6% (5, 6), with great variability by geographic region.

Published data from case-control and observational studies on chronic Chagas' disease during pregnancy are inconsistent in their findings. Some studies showed an increased risk of pregnancy loss, prematurity and neonatal mortality in pregnant women who have chronic Chagas' disease while other studies did not demonstrate these findings. Chronic Chagas' disease is usually not immediately life-threatening.

As such, there are no data to assess drug-associated risks of maternal complications or effects on the fetus, neonate or infant. In order to better describe the safety profile of nifurtimox exposures during pregnancy, Bayer has designed an observational pregnancy safety study of women and fetuses exposed to nifurtimox during pregnancy and the effects of prenatal exposure on postnatal development. The study will collect and evaluate the risk of pregnancy and maternal complications, other events of interest on the developing fetus and neonate, and other events of interest on the infant (Section 8.1.1). The lack of data on human pregnancy exposures during the period of nifurtimox exposure in clinical trials makes such a study an essential component of overall surveillance of nifurtimox safety.

The study will begin collecting information on any eligible pregnancies that occur during the study period. Reports will be collected whether or not the pregnancy outcome is known at the time of enrollment. That is, some exposed pregnancies will be enrolled at the time of known pregnancy outcome (retrospective pregnancy report) and some exposed pregnancies will be enrolled before the outcome is known (prospective pregnancy report).

7. Research Questions and Objectives

The study will describe the frequencies of events of interest in fetuses, neonates and infants up to 12 months of age who were exposed to nifurtimox *in utero* and maternal complications of pregnancy in women who were exposed to at least one dose of nifurtimox during the defined pregnancy exposure window.

7.1 Objectives

The objectives of this pregnancy safety study are to collect and describe:

- selected fetal/neonatal/infant outcomes (i.e., major congenital malformations(MCM), small for gestational age, and postnatal growth and development) at birth and through up to the first year of life of infants born to women exposed to nifurtimox during the defined pregnancy exposure window.
- pregnancy outcomes of interest (i.e., live birth, spontaneous abortions, stillbirths, elective abortions, and preterm births) and pregnancy complications in women with Chagas disease exposed to nifurtimox during the defined pregnancy exposure window.

8. Research Methods

8.1 Study Design

This is an observational study of pregnancy exposures to nifurtimox. Reports will be collected whether or not the pregnancy outcome is known at the time of enrollment. That is, some exposed pregnancies will be enrolled in the study at the time of known pregnancy outcome (retrospective pregnancy report) and some exposed pregnancies will be enrolled before the outcome is known (prospective pregnancy report).

The study population is referred to as ‘pregnant women’ in this protocol and also includes both women who are pregnant at the time of enrollment and those who are no longer pregnant at the time

of enrollment but were exposed to nifurtimox at any time from the first day of their last menstrual period through pregnancy (i.e., the defined pregnancy exposure window).

Information on pregnancies that occur in any woman exposed to nifurtimox during the defined pregnancy exposure window will be collected by the nifurtimox Study Coordinating Center (SCC) from healthcare providers who are treating pregnant women with Chagas' disease with nifurtimox, and from women who were exposed to nifurtimox during the defined pregnancy exposure window and their secondary contacts (i.e., individuals both within and outside her household who will know her whereabouts should she become lost to follow-up). The SCC will conduct proactive outreach as indicated in Section 8.2.4 of this protocol to encourage reporting of pregnancy exposures and enrollment into the study.

As the pregnancy safety study is observational, medical treatment for each pregnant woman, neonate and infant should be consistent with routine local clinical practice and will not be mandated or required in any way by the study protocol. No additional diagnostic or monitoring procedures will be applied. The choice of ongoing medical treatment for the duration of the pregnant woman's and neonate's/infant's participation in the study will be made independently by the HCP in the regular course of practice and will not be influenced by her participation in this observational study.

Pregnant women will be followed until their pregnancy outcome is known. Live births will be followed through 12 months of age. Data will also be collected from women whose pregnancy was completed during the study period and prior to her enrollment into the study. The study will enroll pregnant women and collect data for approximately 10 years.

8.1.1 Primary Endpoints

The primary endpoints are:

- Pregnancy outcomes
    - Spontaneous abortion
    - Elective abortion
    - Fetal death/still birth
    - Preterm delivery
    - Live birth.
- MCM identified in the developing fetus, neonate or infant,
- Other events of interest identified in the developing neonate and infant,
    - Hospitalizations
    - Growth and development milestones as described by the Centers for Disease Control and Prevention (1)
    - Neonatal or infant mortality
    - Diagnosis of congenital Chagas' disease
- Maternal complications of pregnancy,
    - Premature rupture of membranes

- Preeclampsia
- Severe pregnancy induced hypertension
- Proteinuria
- Gestational diabetes

- Measures of fetal growth deficiency (small for gestational age)

8.2 Setting

The study will actively pursue and attempt to capture as many nifurtimox exposures during pregnancy as possible that occur during the study period in all countries where nifurtimox is approved to be marketed by Bayer. Women can self-enroll into the study or may be enrolled by their HCP. In countries where the pregnant women are enrolled by HCPs, evidence of assessment of all eligibility criteria by the physician or a delegate, as well as enrollment of a pregnant women in the study, should be documented in her medical records.

8.2.1 Eligibility

8.2.1.1 Inclusion Criteria

Women meeting the following criteria will be eligible:

1. Females exposed to at least 1 dose of nifurtimox at any time during the defined pregnancy exposure window.
2. Written informed consent (for adolescents under the age of majority, written informed assent by the pregnant minor (where applicable) and written informed consent by the parent/legal guardian).

8.2.1.2 Exclusion Criteria

None

8.2.2 Withdrawal

In this observational study, withdrawal from the study is independent of the underlying therapy and will not affect the pregnant woman's medical care. Each woman may withdraw from the study at any time and without giving a reason. If a woman wants to terminate study participation, no further data will be collected. In case a woman would like to withdraw the consent given earlier, she should inform her doctor and the site should document the withdrawal in the Case Report Form as well as in the her medical records. All data collected prior to the date of her withdrawal will be included in the study unless otherwise specified. If the request to withdraw is made to the SCC, the SCC will document this in the study database. Once the woman is withdrawn, the SCC will make no further attempt to contact her or her HCP.

8.2.3 Replacement

Enrollment in the pregnancy safety study is ongoing through ten years. At the end of enrollment, women who drop out will not be replaced (e.g., withdrawal, loss to follow-up).

8.2.4 Recruitment of Pregnant Women

In the US and other countries where direct outreach is possible, proactive outreach will occur to solicit reports of women exposed to nifurtimox during the defined pregnancy exposure window . Direct to prescriber HCP awareness mailings targeting prescriber lists will be done at least annually. Information will be sent requesting that they identify any women who becomes pregnant while exposed to nifurtimox and invite them to participate in the study. The limitations to generalizability of the study population are described in Section 8.9.

The goal for effective outreach is to ensure that all HCPs who have direct pregnant women or infant contact are completely familiar with the study and are able to educate and communicate information about the study to appropriate pregnant women. The study will use effective recruitment strategies (7) that have also proven to be effective in previous pregnancy safety studies.

- Brochures will be provided to pregnant women at the time of enrollment and upon request.
- Awareness resources and recruitment strategies may include:
    - Nifurtimox Pregnancy Surveillance Program web site
    - Link to the study on Bayer's web site in the US
      FDA List of Pregnancy Exposure Registries (www.fda.gov/science-research/womens-health-research/list-pregnancy-exposure-registries)
    - Pregnancy Safety Study brochures included in HCP mailings to nifurtimox prescribers and available on request from the SCC (available in English and Spanish)
    - Outreach to Chagas' disease support groups, patient advocacy groups, and infectious disease specialist networks
    - Toll-free number and study web address printed on the LAMPIT US Full Prescribing Information (to be added after the study is active)
    - Publication of study methods in scientific peer-reviewed journals

8.2.5 Representativeness

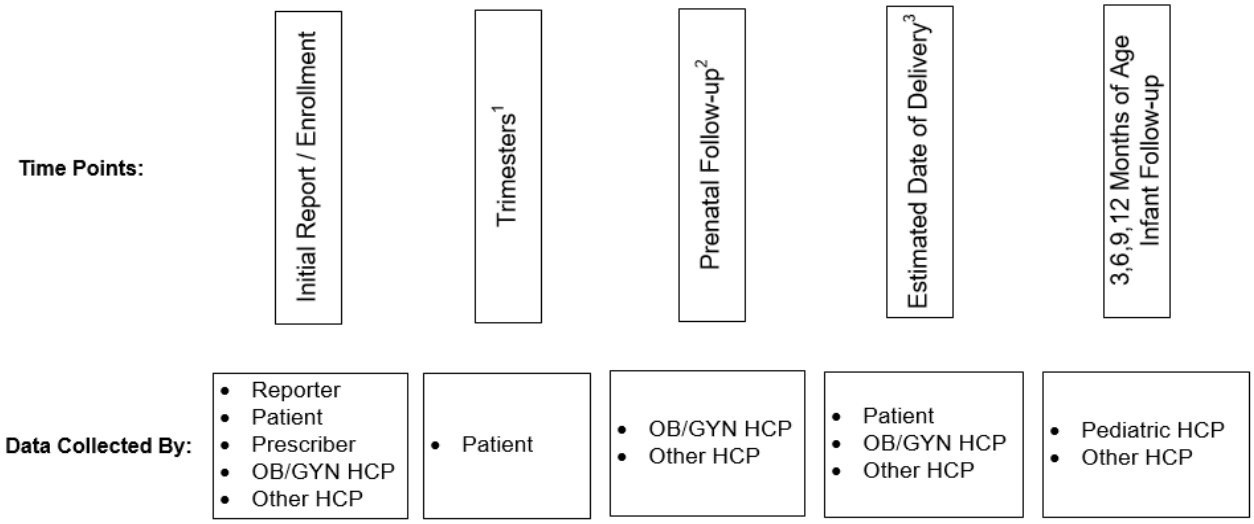
The inclusion criteria for this study are broad in order to represent the general population, i.e., exposure to nifurtimox during the pregnancy exposure window and provision of informed consent. There are no exclusion criteria. All pregnant women who are identified as meeting the eligibility criteria will be invited to enroll in the pregnancy safety study by the SCC or their treating HCP. However, women who agree to enroll in the study may represent particularly high or low risk pregnancies, and those who enroll after the pregnancy outcome is known may be more likely to report adverse outcomes.

8.2.6 Visits

No mandatory visits, tests, or assessments are required for this study. Pregnant women and infants will be treated according to the standard of care.

A Study Contact Schedule (Figure 1) is provided below to indicate the contacts and sources of data per time point.

Figure 1: Pregnancy Safety Study Contact Schedule



Abbreviations: HCP = Healthcare Provider; OB/GYN = Obstetrician/Gynecologist
[1]Trimesters Follow-up: Tri 1 - 14 weeks ± 2 weeks, Tri 2 - 21 weeks ± 2 weeks, Tri 3 - 34 weeks ± 2 weeks
[2]Prenatal Follow-up: 34 weeks ± 2 weeks
[3]Estimated Date of Delivery: 40 weeks ± 2 weeks

8.2.6.1 Initial Report / Enrollment

The following information will be collected at Enrollment from the pregnant women and women whose pregnancies are complete. Information will also be collected from the prescribing HCP on any reported pregnancy, whether or not the pregnancy outcome is known. The SCC will review the information collected and will follow-up with the pregnant woman, where possible, and with the prescriber for supplemental information if needed. Since an exposed pregnancy can be reported at any time, the SCC is trained to collect the appropriate data based on the pregnancy status and outcome. The data to be collected are aligned with the appropriate time points but could be requested as soon as the outcome is reported or collected later based on the actual delivery date.

- Reporter (HCP, pregnant woman, other)
    - Date of report
    - Type of reporter
    - Name of reporter
    - Contact information of pregnant woman (name, address, phone, e-mail)
        - Preferred method of contact (phone, e-mail, text)
        - Secondary contact information
    - Pregnancy status
    - Names of nifurtimox prescriber and other HCPs
        - Name of nifurtimox prescriber and contact information

        - Name of Ob/Gyn or other HCP providing care for the pregnant mother and contact information
        - Name of pediatrician or other HCP providing care for the infant (if determined, depending on timing of enrollment) and contact information
- Consent
    - Date of written consent, and written assent where required
- Eligibility criteria
- Maternal demographics
    - Birth date, race, and ethnic origin
    - Level of education
    - Pre-pregnancy height and weight and Body Mass Index
- Obstetrical history
    - Number of previous pregnancies and outcome of each
    - Complications in previous pregnancies
    - Previous fetal/neonatal abnormalities
- Maternal medical history
    - Chagas' disease history
        - Date of diagnosis
        - Treatments
    - Concomitant Disease
    - Family history of MCM
        - Relevant maternal/paternal family history of pregnancy complications/MCM
- Current pregnancy information
    - Date of first day of last menstrual period (LMP)
    - Estimated date of conception (pregnancy start date) hierarchy is based on the data collected. If all data are available, the estimated data of conception uses #1 to estimate the pregnancy start date:
        1. Date of conception = Estimated gestational age using ultrasound, if collected or, if this information is not available, then
        2. Date of conception = first day of the last menstrual period (LMP) date.
    - Estimated delivery date (EDD)
    - Number of fetuses
    - Pregnancy confirmed by serum HCG
    - Method of pregnancy conception, including in vitro fertilization

- Pregnancy complications
- Prenatal testing
    - Type (amniocentesis, ultrasound, chorionic villus sampling (CVS), glucose tolerance, maternal serum screening, alpha-fetoprotein (AFP), genetic, other)
- Outcome – if reported retrospectively
- Pregnancy report type (prospective, retrospective)

- Medication use during pregnancy
    - Exposure to nifurtimox
        - Overall start date, dose, stop date or ongoing
        - Trimesters of exposure (1, 2, 3)
        - Gestational age at time of exposure in weeks/days (if available)
    - Other concurrent medication use (prescription and non-prescription including pre-natal vitamins)
        - Indication
        - First start date, dose, stop date or ongoing
        - Trimesters of exposure (1, 2, 3)
        - Gestational age at time of exposure in weeks/days (if available)
    - Possible risk factors (social and environmental)
        - Alcohol use
        - Smoking
        - Illicit drug use
        - Any potentially teratogenic exposures (e.g., occupational, environmental)
        - Other
    - Serious and nonserious adverse events (AEs) : maternal and fetal

8.2.6.2 Trimester Follow-up with the Pregnant Woman

In countries where direct data collection is possible, data will be collected at this time point directly from the pregnant woman if the pregnancy is still ongoing. In all other countries, the HCP will determine the status of the pregnancy and collect these data to report to the SCC.

End of 1st Trimester: Follow-up will be collected at 14 weeks ± 2 weeks gestation. If enrollment and baseline data collection fall within this window (i.e., 12-16 weeks gestation), follow-up will not be requested until the 2nd trimester.

Mid 2nd Trimester: Follow-up will be collected at 21 weeks ± 2 weeks gestation.

Mid 3rd Trimester: Follow-up will be collected at 34 weeks ± 2 weeks gestation.

The following information will be collected from the pregnant woman at each trimester:

- Source of information
- Date of contact
- Change in current pregnancy status
- Current gestational age in weeks and days at time of follow-up by ultrasound or LMP date
- Pregnancy status/outcome (i.e., ongoing pregnancy, miscarriage, live birth, spontaneous loss, elective termination, ectopic or molar pregnancy, fetal death, pregnancy complications)
- Gestational age at pregnancy outcome (weeks, days)
- Changes in nifurtimox treatment, if applicable
- Changes in other medications (new, continuing or discontinued)
- Changes in concurrent conditions and risk factors, including any new concurrent conditions
- Changes in maternal contact information
- Changes in maternal HCP and/or pediatrician contact information
- Changes in secondary contact information
- Serious and nonserious AEs: maternal
- Targeted prenatal testing (to be collected from pregnant woman if it is not provided by her HCP)
    - Type (amniocentesis, ultrasound, CVS, glucose tolerance, maternal serum screening, alpha-fetoprotein (AFP), genetic, other) and dates
    - Evidence of a structural defect (specify defect)
    - Gestational age at time of diagnosis

8.2.6.3 Prenatal Follow-up with the HCP

Pregnancy information will be collected at this time point from the obstetric HCP.

Follow-up with the pregnant woman's HCPs will be collected at 34 weeks ± 2 weeks gestation

The following information will be collected from the HCP:

- Source of information
- Date of contact
- Pregnancy status and outcome, including risk factors and changes in medical condition and medications
- Current gestational age in weeks and days at time of follow-up by ultrasound or LMP date
- Targeted prenatal testing
    - Type (amniocentesis, ultrasound, CVS, glucose tolerance, maternal serum screening, alpha-fetoprotein (AFP), genetic, other) and dates
    - Evidence of a structural defect (specify defect)

- Gestational age at time of diagnosis

- Changes in maternal contact information
- Pregnancy-related serious and nonserious AEs: maternal

8.2.6.4 Estimated Date of Delivery Follow-up with the Pregnant Woman and/or HCP

Follow-up will be collected at 40 weeks ± 2 weeks gestation.

The following information will be collected from the pregnant woman (where possible), the OB/GYN HCP, and pediatric HCP as needed, at the time of the EDD Follow-up. This information will also be collected from women whose pregnancy outcome was known at the time of enrollment.

- Source of information
- Date of contact
- Outcome and date of outcome (i.e., live birth, spontaneous abortion, miscarriage, stillbirth, ectopic or molar pregnancy, fetal loss, therapeutic or elective abortion)
    - Factors which may have contributed to the outcome (e.g., nifurtimox, other medications, prenatal maternal infection, or fever-causing illness)
    - If elective termination, specify primary reason (i.e., identified MCM, increased risk of an MCM, non-medical reasons, other)
    - Method of delivery
    - Pregnancy complications
        - Obstetric and delivery complications [preterm delivery, premature rupture of membranes (PROM), preeclampsia/severe pregnancy-induced hypertension (PIH)/proteinuria, gestational diabetes, IUGR, Other]
    - Gestational age at pregnancy outcome (weeks)
    - Number of fetuses/newborns
        - For each:
            - Infant gender
            - Birth weight (kg)
            - Birth length (cm)
            - Head circumference (cm)
            - Apgar scores (1, 5 and 10 minutes)
            - Tests/procedures performed and any associated diagnoses
            - Medications/treatments
            - Infant overall status
            - MCM
                - MCM defect description

- Association with nifurtimox exposure (if HCP reported)
- Other factors which may have contributed

- Pregnancy-related serious and nonserious AEs: maternal and neonate/infant

8.2.6.5 Infant 3, 6, 9, and 12 Months of Age Follow-up

Information at this time point will be collected from the infant's HCP. If additional information is needed, the mother will be contacted in countries where direct contact is possible.

Follow-up will be collected at age 3, 6, 9 and 12 months of age ± 2 weeks. Information will be collected for each infant if there was a multiple birth.

The following information will be collected from the infant's pediatric HCP:

- Source of information
- Date of contact
- Infant vital status (for each infant, if multiple birth)
- Relevant testing/procedures performed and any associated diagnoses
- MCM
    - MCM description(s)
    - Association with nifurtimox exposure (if HCP reported)
    - Other factors which may have contributed
- Any growth and developmental problems identified
    - Validated tool(s) used as part of assessment, if any
    - Result of assessment
    - Action taken (e.g., close monitoring, additional testing)
    - Diagnosis, if any
    - Medications/treatments
    - Association with nifurtimox exposure (if HCP reported)
- Any hospitalizations for serious conditions
- Serious ad nonserious AEs: infant

8.2.7 Loss to Follow-up

To reduce the number of pregnant women or infants who become loss to follow-up, in countries where it is allowed, the pregnant woman will be asked to provide her preferred method of contact (telephone, e-mail, text) and to designate two secondary contacts at the time of enrollment. Secondary contacts are individuals both within and outside the pregnant woman's household who will know her whereabouts should she become lost to follow-up. In countries where contact can only be made with the study site, the SCC will contact the HCP using multiple follow-up methods (i.e., fax, telephone, or e-mail) based on prior success or HCP contact preference to minimize the occurrence of missing data.

If the requested data are not obtained within the appropriate timeframe, at least 4 attempts will be made to contact the pregnant woman and/or the HCP within 3 months of last follow-up contact to obtain information about the outcome of the pregnancy before a case is considered lost to follow-up. If needed, and where allowed, the SCC will contact her secondary contacts.

All data collected prior to considering the pregnant woman lost to follow-up will be used for analysis and reporting purposes to the extent possible.

8.3 Variables

The SCC or the HCP will collect study-relevant data for each pregnant woman (as described in section 8.4) and document it in the Case Report Form (CRF). The CRF is kept as stand-alone document (see Annex 1). Variables will be collected following the Bayer standard.

8.3.1 Exposure Definition

The defined pregnancy exposure window is exposure to at least one dose of nifurtimox at any time from the first day of the woman's last menstrual period through pregnancy outcome.

8.3.2 Outcome Definitions

Pregnancy Outcomes

Pregnancy outcomes will be classified into one of the following mutually exclusive categories and are defined in Table 2 below:

- Spontaneous abortion,
- Elective abortion,
- Fetal death/still birth,
- Molar or ectopic pregnancy,
- Pre-term delivery,
- Live birth.

An attempt will be made to assess all outcomes for the presence of MCM.

Table 2: Definitions for Pregnancy Outcomes

Event	Definition
Spontaneous abortion*	Any loss of a fetus due to natural causes less than 20 weeks gestation as a spontaneous abortion (8, 9). If available, data from gross or pathological examination of the abortus or fetus will be evaluated for structural defects.
Elective/Induced (therapeutic) abortion	Elective or induced (therapeutic) abortion is the termination of pregnancy through medical or surgical procedures (8, 10, 11). If available, data from gross or pathological examination of the abortus or fetus will be evaluated for structural defects.

Event	Definition
Fetal death/Still birth*	Fetal death or stillbirth refers to fetuses born dead at > 20 weeks gestation or weighing > 500 grams. Fetal death occurring > 20 weeks but less than 28 weeks gestation is considered an early fetal loss. Fetal death occurring > 28 weeks is considered a late fetal loss (10, 12). If available, data from gross or pathological examination of the abortus or fetus will be evaluated for structural defects. * The study will make the final classification between fetal death/still birth and spontaneous abortion based on gestational age and weight. If these parameters are not available, the study will accept the classification indicated by the HCP.
Preterm delivery	Births delivered prior to 37 completed weeks of gestation per 100 births. Gestational age is based on the obstetric estimate of gestation (CDC) (13).
Live Birth	A live birth refers to a complete expulsion from its mother of a surviving neonate breathing or showing any evidence of life such as a heartbeat, umbilical cord pulsation, or definite movement of voluntary muscles, whether the umbilical cord has been cut or the placenta is attached (8).
Ectopic or Molar Pregnancy	Any reported ectopic or molar pregnancy will be sub-classified in the respective pregnancy outcome including induced abortion, live birth, or spontaneous pregnancy loss. (14).
Small for Gestational Age	In full-term infants, birth weight at or below 10th percentile for sex and gestational age is commonly considered as SGA (CDC 2008); in preterm infants, Fenton growth charts which provide precise assessment of growth vs. gestational age for both boys and girls (Fenton 2013) will be used for the definition of SGA.
Pre-eclampsia	Pre-eclampsia is high blood pressure and signs of liver or kidney damage that occur in women after the 20th week of pregnancy. (NIH 2021).

8.3.3 Major Congenital Malformations in the Fetus, Neonate, and Infant

Major Congenital Malformations

Congenital anomalies comprise a wide range of abnormalities of body structure or function that are present at birth and are of prenatal origin. For efficiency and practicality, the focus is commonly on major structural anomalies. These are defined as structural changes that have significant medical,

social or cosmetic consequences for the affected individual, and typically require medical intervention.

The Pregnancy Safety Study has adopted the term major congenial malformation (MCM) for an abnormality that may often be referred to as a "congenital abnormality" or a "birth defect" and defines MCM according to the following criteria:

1. any major structural defect diagnosed with signs/symptoms, using the selected major congenital anomalies list extracted from the Birth defects surveillance: a manual, CDC, (Annex 2).
2. on a case-by-case basis, through evaluator review and agreement from external advisors (if required), any structural defect detected in the prenatal evaluation of a pregnancy or in the gross or pathologic examination of an abortus, fetus, or deceased infant will be included, if available, to increase the sensitivity of pregnancy study monitoring.

To maintain as much consistency with the CDC birth defect surveillance system as possible without missing a potential signal, only cases meeting the CDC MACDP criteria will be counted for the primary analyses. Additionally, risk estimates will not include outcomes that are not associated with nifurtimox exposure (e.g., genetic syndromes, prematurity-related outcomes, positional effects). The CDC guidelines disqualify the following as MCM: (1) those findings that are present in infants with outcomes at < 36 weeks gestational age or if gestational age is unavailable, weighing < 2500 grams, and are attributed to prematurity alone, such as patent ductus arteriosus (PDA), patent foreamen ovale (PFO), and inguinal hernias, and (2) infants with only transient or infectious conditions, or biochemical abnormalities, who are classified as being without birth defects unless there is a possibility that the condition reflects an unrecognized MCM. (15)

Structural Defects

Definitions of structural defects are shown in Table 3.

Table 3: Definition of Structural Defects

Major structural defect	a defect which occurs in less than 4% of the population and which has either cosmetic or functional significance to the child (e.g., a cleft lip)
Minor structural defect	a defect which occurs in less than 4% of the population but which has neither cosmetic nor functional significance to the child (e.g., complete 2,3 syndactyly of the toes).

Structural defects will be separated into 1 of 3 groups based on developmental pathogenesis. The major purpose for doing so is to consider biologic plausibility. Defects will be categorized into malformations, deformations, and/or disruptions as defined in Table 4.

Table 4: Categorization of Structural Defects

Malformation	an arrest at a normal stage of embryologic differentiation or development, e.g., a cleft lip.

Deformation	a defect due to deformation of a structure which has previously formed normally. The defect is usually due to mechanical forces such as uterine constraint, e.g., a club foot.
Disruption	a defect due to destruction of a structure which has previously formed normally. Such disruptive defects may be of vascular, infectious, or mechanical origin, e.g., amniotic band disruption.

The following structural defects are excluded as outcome:

Birthmarks: birthmarks will not be included.

Variations of normal: features on the physical examination which occur in greater than 4% of the population and have no cosmetic or functional significance for the child. For example, 2,3 syndactyly of the toes less than one-third of the distance to the tip of the third phalanx, will not be included.

Deformational defects: Those deformational defects that do not require casting or surgery will not be included.

8.3.4 Other Events of Interest in Neonates and Infants through 12 Months of Age

Other events of interest occurring in developing neonates and infants will include:

- Hospitalizations,
- Growth and development milestones,
- Neonatal or infant mortality.
- Congenital Chagas' disease

8.3.5 Maternal Complications

Maternal complications of pregnancy will include:

- Premature rupture of membranes (PROM),
- Preeclampsia
- Severe pregnancy-induced hypertension (PIH)
- Proteinuria,
- Gestational diabetes

Measures of fetal growth deficiency (small for gestational age).

8.3.6 Classification and Evaluation of Outcomes

A Subject Matter Expert (SME), a teratologist or a specialist with similar expertise, will adjudicate all reports of MCM. All documents provided to the SME will be anonymized. The SME will evaluate the anonymized individual reports of MCM to determine if there is an increase in a specific type(s) of MCM. In cases of complex congenital malformations additional specialists will be asked to adjudicate the MCM(s), as needed. Additionally, if there are any cases with MCM identified in

abortions (spontaneous/therapeutic/elective) a thorough analysis of products of conception will be reviewed and adjudicated by the specialist if the information is available.

8.4 Data Sources

Data will be collected from various sources, when and/or if applicable, including telephone interviews conducted by the SCC with the pregnant woman and her HCPs, reports sent to the SCC from reports received directly by Bayer, and medical records obtained for identified MCMs. In countries where HCP sites are enrolled, reports will come from the HCPs and their sites. For reports received after pregnancy outcome, applicable information will be collected from the woman (where allowed) and from her HCP and the infant's HCP (if applicable for a live birth).

All efforts will be made to encourage pregnant women who do not consent to participate in the study to report their pregnancy information to the Bayer pharmacovigilance system.

8.5 Study Size

Given the small target population based on the labeled recommendation that nifurtimox should not be used during pregnancy, enrollment is expected to be limited. It is anticipated that approximately 50 exposed pregnancies will be reported over the 10 year data collection period.

Due to the expected rarity of the exposure in pregnancy, very few observations of MCM are expected. Table 5 provides the binomial probability of observing the MCM, given the background rate is 3%, under various enrollment scenarios. The table indicates that the probability of observing 1 event, is a possibility given a background rate of 3%. However, the probability observing 4 or more MCM (reflecting an increased rate of 8%) is p = 0.063. A sample size of N = 50 will be sufficient to detect MACDP malformations at rates > 8%.

Table 5: Probability of Observing Events Given Various Enrollment Scenarios and Assuming a Background MCM Rate of 3%

Sample Size	Number of MCM	Probability of observing at least the given number of events of major defects presented in each row
N=50	1 or more	0.782
	2 or more	0.445
	3 or more	0.189
	4 or more	0.063
	5 or more	0.017

8.6 Data Management

A Contract Research Organization (CRO) will develop the data collection system (Section 2.2). The CRF will be part of the data capture system which allows documentation of all variables and covariates in a standardized way. Detailed information on data management, including procedures for data collection, retrieval and preparation are given in the Data Management Plan (DMP). The DMP and information on the data collection system are kept as stand-alone documents (Annex 1).

Data will be collected on a paper CRF by the SCC or by the HCP who will submit the CRF to the SCC. The SCC staff will enter the data into the study database using double data entry.

All medication documented in the CRF will be coded using the latest version of the World Health Organization Drug Global dictionary available at time of database lock for coding of prior and concomitant medication.

Any diagnoses/diseases/event terms documented in the CRF will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version:

- Co-morbidities (medical history, concomitant diseases)
- Adverse events

For information on quality control, refer to section 8.8

A DMP will be developed as part of the study materials along with the CRF and coding instructions. The data will be regularly checked for potentially reportable safety-related information that requires transfer to Bayer for regulatory compliance.

8.7 Data Analysis

8.7.1 Statistical Considerations

Statistical analyses will be descriptive. The study is not intended to test pre-defined statistical hypotheses.

When the same data points are provided by the woman and the HCP and are contradictory, the data obtained by the HCP will be used in the analysis.

8.7.1.1 Prospective vs. Retrospective Cases

Bias may occur when some abnormal results or outcome information are known prior to enrollment; therefore, pregnant women are advised to enroll in the study as soon as their pregnancy is known, preferably in the first trimester before the condition of the fetus has been assessed through prenatal testing, including ultrasound, amniocentesis and genetic testing. In order to determine the impact of such a bias (i.e., as a result of recalling exposures and other medical history differently once it is known that a pregnancy is compromised), cases will be characterized as either prospective or retrospective. The criterion for prospective enrollment is that at the time of enrollment, the pregnancy outcome is unknown whether or not the woman has had prenatal testing. The criterion for retrospective enrollment is that at the time of enrollment, the pregnancy outcome is known.

Pregnancy reports will be categorized by prospective and retrospective and a listing of pregnant women by this classification and a listing of any MCM by this classification will be presented.

Similar analyses will be done separately for pregnancies classified as prospective versus those classified as retrospective.

8.7.2 General Methods

In countries where data can be collected directly from pregnant women, data may be provided to the SCC by the pregnant women or their HCPs via telephone interview conducted by the SCC or from paper based CRFs submitted via mail or fax by HCPs. The SCC will enter the data into a validated study database. In other countries, an HCP who identified an eligible pregnancy will be contracted by the SCC to perform follow-up of the pregnancy and the neonate/infant. The HCP will provide the requested data to the SCC for entry into the study database.

An SME, a teratologist or a specialist with similar expertise, will adjudicate all reports of MCM. For all summary analyses, the adjudicated values will be used if they differ from the initially reported values. Both original and adjudicated values will be reported in listings.

Identified MCM will be reviewed individually and in aggregate to identify any possible patterns or trends reported. A separate analysis will include only those MCM that have been medically confirmed.

8.7.3 Analysis Datasets

Depending on the endpoint, the analysis population will be pregnancies, live births, fetuses or neonates and infants. Each analysis will refer to one or more of the populations described in this section.

8.7.3.1 All Pregnant Women Analysis Set

The all pregnancies analysis set includes all enrolled pregnant women who have met the inclusion criteria and provided consent, regardless of whether the pregnant woman was enrolled prospectively or retrospectively. It is possible for a woman to be represented more than once if the woman had more than one pregnancy. Each pregnancy will be considered an independent unit as concomitant risk factors (e.g., age smoking status) may change over time.

8.7.3.2 Live Births (including Neonates and Infants)

This is the set of all live births regardless of whether the mother was enrolled prospectively or respectively.

8.7.3.3 Fetuses

This is the set of all live births, fetal death, and early terminations (spontaneous, elective, or therapeutic) regardless of whether the woman was enrolled prospectively or retrospectively.

8.7.4 Description of Statistical Analyses

8.7.4.1 Enrollment Disposition and Baseline Information

Summaries using descriptive statistics (comprise the number of observations [n], mean, standard deviation [SD], median, minimum, and maximum for continuous variables, and n and percent for categorical variables) using the all pregnant women analysis set will be provided for:

- Disposition

- Demographics
- Baseline characteristics and obstetric and medical history

Due to the limited data only listings will be provided for:

- Nifurtimox exposure by peri-conception, trimester, and any time during pregnancy
- Concomitant medications and supplements by trimester and any time during pregnancy
- Tobacco, alcohol, and other teratogenic exposure during pregnancy by trimester and any time during pregnancy.

All outcomes will be presented for pregnant women whose pregnancy outcome is known at enrollment, pregnant women whose pregnancy outcome is not known at enrollment, and all pregnant women analysis. Denominators for percentages will be number of pregnant women in each category.

8.7.4.2 Pregnancy and Fetal Outcomes

An overall summary of pregnancy outcomes will be presented. Outcomes include the number of women with a pregnancy, number of women with pregnancy complete (includes spontaneous abortion, elective abortion, molar or ectopic pregnancy, fetal death/still birth, and live birth), number of pregnancies ongoing, number of pregnancies with outcome lost to follow-up, number of known fetuses, number of live births and, if observed, numbers of spontaneous abortion, elective terminations, and fetal death/still birth.

Due to the limited amount of data expected, characteristics of spontaneous and elective abortions, and fetal deaths will be presented in listings only.

Rules for combining data across forms:

The data sources for pregnancy outcome include the trimester follow-up form, the estimated date of delivery form and the infant follow-up form (if EDD form is missing). Pregnancy status to be reported will primarily come from the trimester follow-up forms but may be updated by the EDD or infant follow-up forms as follows:

- Pregnant women with a trimester form and a pregnancy status of “ongoing” will have the status updated to the most recent Trimester or EDD.
- If there is an Infant follow-up form, the pregnancy status will switch from “ongoing” to “pregnancy complete”.

8.7.4.3 Live Births

Endpoints characterizing a live birth include: gender, estimated gestational age, size relative to gender, weight, length, head circumference, APGAR at 1 minute, APGAR at 5 minutes, APGAR at 10 minutes, medications/treatments tests/procedures performed and any associated diagnoses.

Live birth characteristics will be summarized using descriptive statistics by number of live births with the exception of maternal complications which will be by enrolled pregnancies.

All outcomes will be presented for live births from pregnant women whose pregnancy outcome is known at the time of enrollment, live births from pregnant women whose pregnancy outcome is not known at enrollment and live births from all pregnant women analysis. Denominators for percentages will be number of live births from pregnant women in each category.

8.7.4.4 Major Congenital Malformations in Fetuses, Neonates, and Infants

The primary outcomes of interest are MCM as classified using the selected major congenital anomalies list (Birth defects surveillance: a manual, CDC, Annex 2). For these outcomes, the incidence will be summarized using all live births as the denominator in computing the rates. A 2-sided 95% confidence interval for these rates will be calculated using exact (Clopper-Pearson) methods. Analysis will be repeated by trimester of first exposure and by the timing of exposure or during pregnancy, with the exposure window of interest for MCM being the first trimester. A sensitivity analysis will be performed including still births and elective terminations where an MCM has been identified as the denominator. A separate analysis will include only those MCM that have been medically confirmed.

MCM will be contrasted with population rates reported by the MACDP. The overall incidence of MACDP major congenital malformations is approximately 3% and has been stable with 2.8 % incidence in 1978 to 3.0% incidence in 2005 (test for trend p = 0.19) (16). This comparison rate may be updated if future publications report rates significantly different than 3% for years when the study is active. Data available in South America indicate the incidence of congenital malformations to range from 0.9% (4) to 1.6% (5), with great variability by geographic region (6, 17, 18).

8.7.4.5 Other Events of Interest in Neonates and Infants

Other events of interest occurring in developing neonates and infants will include hospitalizations, , growth and development milestones, and neonatal or infant mortality.

All outcomes will be presented for live births from pregnant women whose outcome is known at enrollment, live births from pregnant women whose pregnancy outcome is not known at enrollment and live births from all pregnant women analysis. Denominators for percentages will be number of live births from pregnant women in each category.

8.7.4.6 Maternal Complications

Obstetric and delivery complications (premature rupture of membranes (PROM), preeclampsia, severe pregnancy-induced hypertension (PIH), proteinuria, gestational diabetes), other) will be summarized using descriptive statistics with all complications reported on the CRF. The all pregnancies analysis set will be used for this analysis.

Newly diagnosed conditions are defined as not being listed as chronic at baseline. Conditions reported on trimester follow-up or EDD forms will be compared to conditions reported on baseline forms. Any event reported on the baseline form will not be considered as a new condition.

All outcomes will be presented for pregnant women whose pregnancy outcome is known at enrollment, pregnant women whose pregnancy outcome is not known at enrollment and all pregnant women analysis. Denominators for percentages will be number of pregnant women in each category.

8.7.4.7 Serious Adverse Events

SAEs will be presented in frequency tables of the incidence proportions of the SAEs observed. Listings of all SAEs will also be provided for pregnant women and neonates/infants.

8.8 Quality Control

8.8.1 Data Quality

Bayer has ethical, legal, and scientific obligations to conduct this study in accordance with established research principles, standard treatment practices and regulations. Bayer or representatives will visit the SCC to assess the data, quality, and study integrity in a manner consistent with applicable health authority regulations and the procedures adopted by the Bayer.

When a site is enrolled in an area where data collection directly from the pregnant woman is not allowed, the involved site personnel will be sufficiently trained on the background and objectives of the pregnancy safety study and on ethical as well as regulatory obligations. Investigators and site personnel will have the chance to discuss and develop a common understanding of the protocol and the CRF. They will be trained on the importance to ensure that all relevant study data should be retrievable from the pregnant woman's medical records.

A CRO will be selected and assigned for development of the data collection system, quality control, verification of the data collection, data analysis and data transfer to Bayer.

All observations will be recorded in a standardized CRF. After data entry, missing or implausible data will be queried, and the data will be validated. A check for duplicate documented pregnant women will be done.

Detailed information on checks for completeness, accuracy, plausibility, and validity are given in the Data Management Plan (DMP).

Medical Review of the data will be performed according to the Medical Review Plan (MRP). The purpose of the Medical Review is to verify the data from a medical perspective for plausibility, consistency, and completeness and to identify potential issues that could affect the robustness of the collected study data or the progress of the study. Detailed information on the Medical review will be described in the MRP.

National and international data protection laws as well as regulations on observational studies will be followed. Electronic records used for capturing documentation (eCRF) will be validated according to FDA Code of Federal Regulations (CFR) Title 21, Part 11 (19). These regulations describe the criteria to consider electronic records including e-signatures to be reliable and generally equivalent to paper records and handwritten signatures. They mandate access controls to ensure that only authorized individuals can use the system, additionally a computer-generated audit trail has to be in place to record the date and time of any actions to create, modify, or delete electronic records.

DMP, MRP and validation documentation are kept as stand-alone documents

8.8.2 Quality Review

Since most data is expected to come from patients, no source data verification (SDV) is possible.

8.8.3 Storage of Records and Archiving

Bayer will ensure to retain study-related documentation incl. documents, Study data, statistical programs and derived data sets for a period of twenty-five (25) years. For the avoidance of doubt, archiving timelines shall ensure that Study-related documentation is retained for at least 10 years after the marketing authorization in Europe for nifurtimox has ceased to exist.

Participating study sites are required to archive and retain study documents for the period stipulated by local regulations.

8.9 Limitations of the Research Methods

The primary limitation of a study utilizing volunteers is selection bias. Women who agree to enroll in the study may represent particularly high or low risk pregnancies. The generalizability of the study results will be limited due to the low numbers of pregnancies expected and will be only generalizable to women fitting the profile of the sample of women who enroll. Retrospective case reports are thought to be subject to further bias in that adverse outcomes may be more likely to be reported, and there is no known denominator of exposed persons for the respective period. Therefore, rates of outcomes cannot be calculated from these data. The comparison of study data with external MACDP or other external sources is limited in that data from these sources do not necessarily represent the same populations.

Another limitation of the study relates to the evaluation of spontaneous abortion rates. Rates of early spontaneous abortion, i.e., at 7 through 9 weeks post-LMP or less, will not be measured in a study that enrolls women after recognition of pregnancy.

The denominator used for the MCM incidence rate calculation excludes pregnancies with fetal losses (spontaneous abortions, elective, therapeutic or induced abortions, or fetal deaths) for which no MCM have been detected, since in most cases it is unknown what percentage of these pregnancies consist of potentially normal outcomes or MCM. The study will attempt to obtain information on MCM detected at the time of the outcome. However, the malformation status of the aborted fetus may not be known. A sensitivity analysis will be performed including still births and elective terminations where an MCM has been identified as the denominator.

8.10 Other Aspects

Not applicable

9. Protection of Human Subjects

9.1 Ethical Conduct of the Study

This study is an observational study where nifurtimox is prescribed in the customary manner in accordance with the terms of the marketing authorization. There is no assignment of a woman to a particular therapeutic strategy. The treatment decision falls within current practice and the prescription of the medicines is clearly separated from the decision to include the pregnant woman in the study. No additional diagnostic or monitoring process is required for participation or during the study. Epidemiological methods will be used for the analysis of the collected data.

9.2 Regulatory Authority Approvals / Authorizations

In addition, the guidelines on good pharmacovigilance practices (20, 21) and since the study qualifies as a PASS, GVP module VIII will be followed.

The study will be carried out within an approved indication in accordance with guidelines and regulations of EMA (22), FDA (23, 24) and applicable local laws and regulations(25). Recommendations given by other organizations will be followed as well(26).

In addition, the guidelines on good pharmacovigilance practices (GVP module VI , and since the study qualifies as a PASS, GVP module VIII) will be followed (20, 27-29).

9.3 Institutional Review Board (IRB)

In all countries where reference to an IEC/IRB is required, documented approval from appropriate IECs/IRBs will be obtained for all participating centers prior to their participation in the study. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the SCC and to Bayer. The IEC/IRB must supply to Bayer, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to applicable laws and regulations.

9.4 Information and Consent from the Pregnant Women

Before documentation of any data, written informed consent will be obtained from the pregnant woman, in accordance with local practice, law or regulation. Information about the study will be explained to the pregnant woman. Pregnant women will be sent a copy of the ICF that was discussed with them and they may voluntarily choose to sign and return the ICF. The ICF must not be altered without the prior agreement of the relevant IRB and Bayer.

For pregnancies occurring in adolescents under legal age, signed assent by the minor (where applicable) and parental / legal guardian signed informed consent will be obtained. Informed consent forms will be provided for persons who are capable to give their consent. For adults and for minors not capable to give their consent, the legal representative should give the consent.

If a woman or the minor or the legally acceptable representative is unable to read, an impartial witness (independent of Bayer and the investigator) will be present during the entire informed consent discussion. The informed consent form and any other information to be provided to pregnant women is read and explained to the woman or her legally acceptable representative. The pregnant woman or her legally acceptable representative have to orally consent to the her participation in the study and, if capable of doing so, have to personally sign and date the informed consent form. Thereafter the witness will personally sign and date the consent form.

In countries where required by law or regulation, the enrolling HCP must have the IECs/IRB written approval/favorable opinion of the informed consent form and any other information to be provided to the pregnant woman prior to the beginning of the observation.

9.5 Insurance

In this observational study, data on routine treatment of pregnant women and infants in daily practice are documented and analyzed with the help of epidemiological methods. Treatment including diagnosis and monitoring of therapy follows exclusively routine daily practice. Current medical daily practice is observed, and for the pregnant woman and infant no risks beyond regular therapy exist – there is no additional hazard arising from study participation. As no study related risks exist, there is no need to protect the pregnant woman additionally by insurance. The general

regulations of medical law and the professional indemnity insurance of the enrolled HCPs and, respectively, the institutions involved provide sufficient protection for both the pregnant woman and investigator.

No study medication will be provided to participants. Thus, product insurance is covered by the existing product liability.

9.6 Confidentiality

Bayer as well as all investigators ensure adherence to applicable data privacy protection regulation. Data are transferred to Bayer in encoded form only. The entire documentation made available to Bayer does not contain any data which, on its own account or in conjunction with other freely available data, can be used to re-identify natural persons.

All records identifying the pregnant woman and infant will be kept confidential and will not be made publicly available. Names will not be supplied to Bayer. If the pregnant woman's name appears on any document, it must be obliterated before a copy of the document is supplied to Bayer. Study findings stored on a computer will be stored in accordance with local data protection laws.

To comply with government regulatory guidelines and to ensure safety of the pregnant woman and the infant, it may be necessary for Bayer, the local research review board, or regulatory authorities to review files as they relate to this study. Only the pregnant woman's or the infant's unique number on the CRFs will identify her.

Documents that are not for submission to Bayer will be maintained by the SCC in strict confidence, except to the extent necessary to allow monitoring by Bayer, and auditing by Bayer and regulatory authorities. No documents identifying pregnant women by name will leave the SCC, and her identity will remain confidential in all publications related to the study.

The investigator will maintain a list to enable the pregnant woman's records to be identified in case of queries. In case of a report of a serious adverse event (SAE), the responsible pharmacovigilance person may ask for additional clarification. In that case, the company is not allowed to directly contact the pregnant woman. All additional information will be provided by her HCP.

In countries where direct to patient contact is possible, identifying information for the pregnant woman and secondary contacts will be collected in order for the SCC to contact her. These personal identifiers will be stored separately from the clinical study database. In countries where it is not possible for the SCC to contact the pregnant woman, her personal identifying information will be stored at the enrolling HCP site for their use in follow-up.

10. Management and Reporting of Adverse Events / Adverse Reactions

10.1 Definitions

Adverse event (AE): Any untoward medical occurrence in a pregnant woman administered a pharmaceutical product and which does not necessarily have to have a causal relationship (association) with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the product, whether or not related to the product.

Adverse Reaction (AR): an adverse reaction is a noxious and unintended response to a medicinal product. This includes adverse reactions which arise from:

- use of a medicinal product within the terms of the marketing authorization
- use outside the terms of the marketing authorization, including off-label use, overdose, misuse
- abuse and medication errors
- occupational exposure

An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between nifurtimox and an occurrence is suspected.

Serious adverse event/serious adverse reaction: an AE or AR is serious if it:

- results in death,
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization.

  A hospitalization or prolongation of hospitalization will not be regarded as a serious adverse event (SAE) if at least one of the following exceptions is met:

  - the admission results in a hospital stay of less than 12 hours;
  - the admission is pre-planned (i.e. elective or scheduled surgery arranged prior to the start of the study);
  - the admission is not associated with an AE (e.g., social hospitalization for purpose of respite care).

    However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on the clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence;
- results in persistent or significant disability or incapacity
- is a congenital anomaly, birth defect or fetal mental impairment
- is medically significant:
  - Medical and scientific judgment should be exercised in deciding whether an AE/AR may be considered serious (due to an important medical event) because it jeopardizes the health of the pregnant woman or infant or may require intervention to prevent another serious condition (death, a life-threatening condition, hospitalization or persistent or significant disability).

10.2 Collection

All non-serious AEs must be documented on the AE Report Form or in the CRF/EDC system and forwarded to Bayer within 7 calendar days of awareness. All serious AEs (SAE) must be documented and forwarded immediately (within one business day of awareness). For each AE, the

investigator or a delegate must assess and document the seriousness, duration, relationship to product, action taken and outcome of the event.

The documentation of any AE/SAE ends with the completion of the observation period of the pregnant woman or the infant. However, any AE/SAE - regardless of the relationship and the seriousness - occurring up to 7 days after the last dose of nifurtimox within the study period has to be documented and forwarded to Bayer within the given timelines, even if this period goes beyond the end of observation.

As long as the pregnant woman has not received any nifurtimox within the frame of the study, AEs /SAEs do not need to be documented as such in this observational study. However, they are part of her medical history.

For any serious product-related AE occurring after study end, as well as for all non-pregnancy outcomes related AEs/ARs the standard procedures that are in place for spontaneous reporting have to be followed.

10.3 Management and Reporting

Non-serious AEs

The outcome of all reported AEs will be followed up and documented. Where required, investigators might be contacted directly by the responsible study staff to provide further information.

Non-serious ARs

All non-serious ARs occurring under treatment with nifurtimox that qualify for expedited reporting will be submitted to the relevant authorities according to EU PV legislation(20, 30, 31) and according to national regulations by Bayer; however, all investigators must obey local legal requirements.

For non-serious ARs occurring under non-Bayer products the investigator has to account for and comply with the reporting system of the product's Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

Serious AEs

Any SAE or pregnancy entered into the CRF/EDC system will be forwarded immediately by the EDC system (or alternatively the CRO manually within one business day of awareness) to the pharmacovigilance country head (PVCH) being responsible for SAE processing. The outcome of all reported SAEs (resolution, death etc.) will be followed up and documented. Where required, investigators might be contacted directly by the pharmacovigilance country person in charge to provide further information.

Submission to the relevant authorities according to national regulations will be done by Bayer for SAEs related to nifurtimox treatment; however, all investigators must obey local legal requirements.

For any serious drug-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed.

For SAEs that occurred while administering non-Bayer products the investigator has to account for and comply with the reporting system of the product's Marketing Authorization Holder (MAH)

within the frame of local laws and regulations as well as other locally applicable laws and regulations.

Submission of SAEs related to non-Bayer products to the relevant authorities according to national regulations will be done by the MAH of the product.

10.4 Evaluation

Whenever new important safety information is received, e.g. case reports from an HCP, the reports are processed and entered into the Bayer global pharmacovigilance safety database. These reports will be reviewed on a regular basis (for information on collection, management and reporting of case reports, refer to section 10.2 and 10.3). If a potential safety signal is suspected, an investigation of the suspected potential signal will be performed according to internal standard operating procedures, for further evaluation within the context of benefit risk.

11. Plans for Disseminating and Communicating Study Results

This study will be registered at "www.clinicaltrials.gov". Results will be disclosed in a publicly available database within the standard timelines.

Interim progress reports will be provided to the US FDA on an annual basis for the duration of the study. The final study report will be submitted at the conclusion of the study.

11.1 Publications

Bayer may prepare one or more manuscripts for publication including a description of the study methods and one describing the results of this observational study. Any manuscripts will be submitted to a peer-reviewed journal or submitted as abstracts/presentations at medical congresses under the oversight of Bayer. Bayer is committed to adhering to the prevailing standards for "Good Publication Practice". Current guidelines and recommendation will be followed (e.g., GPP3 Guidelines, STROBE), as well as the criteria for authorship established by the International Committee of Medical Journal Editors (ICMJE) (32-34). No individual investigator may publish on the results of this study, or their own enrollees, without prior approval from Bayer.

12. References

1. CDC. Information on Milestones & Schedules for Parents with Infants & Toddlers (Ages 0-3) 2021 [Available from: https://www.cdc.gov/parents/infants/milestones.html.
2. Correa A, Cragan JD, Kucik ME. Executive summary. Birth Defects Research Part A: Clinical and Molecular Teratology. 2007;79(2):66-93.
3. CDC. Metropolitan Atlanta Congenital Defects Program (MACDP) 2019 [Available from: http://www.cdc.gov/ncbddd/birthdefects/macdp.html.
4. Gili JA, Poletta FA, Giménez LG, Pawluk MS, Campaña H, Castilla EE, et al. Descriptive analysis of high birth prevalence rate geographical clusters of congenital anomalies in South America. Birth defects research Part A, Clinical and molecular teratology. 2016;106(4):257-66.
5. Groisman B, Bidondo MP, Duarte S, Tardivo A, Barbero P, Liascovich R. [Descriptive epidemiology of major structural congenital anomalies in Argentina]. Medicina. 2018;78(4):252-7.
6. Bidondo MP, Groisman B, Gili JA, Liascovich R, Barbero P, Pingray V. Study on the prevalence and neonatal lethality in patients with selected congenital anomalies as per the data of the National Registry of Congenital Anomalies of Argentina. Archivos argentinos de pediatria. 2015;113(4):295-302.
7. DeWard SJ, Wilson A, Bausell H, Volz AS, Mooney K. Practical aspects of recruitment and retention in clinical trials of rare genetic diseases: the phenylketonuria (PKU) experience. Journal of genetic counseling. 2014;23(1):20-8.
8. WHO/CDC/ICBDSR. Birth defects surveillance: atlas of selected congenital anomalies. Geneva; 2014.
9. American Congress of Obstetricians and Gynecologists. Repeated miscarriages 2016 [Available from: https://www.acog.org/womens-health/faqs/repeated-miscarriages.
10. American Congress of Obstetricians and Gynecologists. Practice Bulletin No. 143: Medical Management of First-Trimester Abortion. Obstetrics & Gynecology. 2014;123(3).
11. American Congress of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 135: Second-trimester abortion. Obstetrics and gynecology. 2013;121(6):1394-406.
12. American Congress of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 102: management of stillbirth. Obstetrics and gynecology. 2009;113(3):748-61.

13. Martin JA, Hamilton BE, Osterman MJK. Births in the United States, 2017. NCHS data brief. 2018(318):1-8.
14. National Birth Defects Prevention Network. ICD-9 & CDC/BPA Codes for Birth Defects. 2004. p. 772.
15. CDC (2021). The Metropolitan Atlanta Congenital Defects Program (MACDP). 2021.
16. Rynn L, Cragan JD, Correa A. Update on overall prevalence of major birth defects—Atlanta, Georgia, 1978–2005. . MMWR. 2008;57:1-5.
17. Groisman B, Gili J, Giménez L, Poletta F, Bidondo MP, Barbero P, et al. Geographic clusters of congenital anomalies in Argentina. Journal of community genetics. 2017;8(1):1-7.
18. Cosme HW, Lima LS, Barbosa LG. PREVALENCE OF CONGENITAL ANOMALIES AND THEIR ASSOCIATED FACTORS IN NEWBORNS IN THE CITY OF SÃO PAULO FROM 2010 TO 2014. Revista paulista de pediatria : orgao oficial da Sociedade de Pediatria de Sao Paulo. 2017;35(1):33-8.
19. Code of Federal Regulations, 21 CFR 11: Electronic records; electronic signature, (2020).
20. Guideline on good pharmacovigilance practices (GVP) Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2), EMA/873138/2011 Rev 2 (2017).
21. Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations IV: Paediatric population, EMA/572054/2016 (2018).
22. Guideline on the Exposure of Medicinal Products during Pregnancy: Need for Post-Authorisation Data EMEA/CHMP/313666/2005, EMEA/CHMP/313666/2005 (2005).
23. FDA. Good Pharmacovigilance Practices and Pharmacoepidemiology Assessment. In: Services UDoHaH, editor. 2005.
24. FDA. Guidance for Industry. Postapproval Pregnancy Safety Studies. In: Services UDoHaH, editor. 2019.
25. Commission implementing regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC of the European Parliament and of the Council, No 520/2012 (2012).
26. EFPIA. EFPIA HCP Code, Code on the Promotion of Prescription-Only Medicines to and Interactions with Healthcare Professionals 2014 [Available from: https://www.efpia.eu/media/24302/3a_efpia-hcp-code-2014.pdf.

27. Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies (Rev 3), EMA/813938/2011 Rev 3 (2017).
28. Guideline on good pharmacovigilance practices (GVP) Module VIII Addendum I – Requirements and recommendations for the submission of information on non-interventional post-authorisation safety studies (Rev 3), EMA/395730/2012 Rev 3 (2020).
29. Guide on Methodological Standards in Pharmacoepidemiology, EMA/95098/2010 (2020).
30. Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products, No 1235/2010 (2010).
31. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use, 2010/84/EU (2011).
32. ICMJE. Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication 2010 [Available from: http://www.icmje.org/.
33. Battisti WP, Wager E, Baltzer L, Bridges D, Cairns A, Carswell CI, et al. Good Publication Practice for Communicating Company-Sponsored Medical Research: GPP3. Ann Intern Med. 2015;163(6):461-4.
34. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Journal of clinical epidemiology. 2008;61(4):344-9.

Annex 1: List of stand-alone documents

Document Name

- 21944 Investigator list
- 21944 Country & Site list
- 21944 CRF
- 21944 DMP
- 21944 MRP

Annex 2: Classification of Major Congenital Malformations

Neural tube defects
- Anencephaly
- Craniorachischisis
- Iniencephaly
- Encephalocele
- Spina bifida

Other central nervous system defects
- Hydrocephaly
- Microcephaly
- Arhinencephaly/Holoprosencephaly

Selected sense organ defects
- Anophthalmos/Microphthalmos
- Anotia/Microtia
- Choanal atresia

Selected congenital heart defects
- Atrial septal defects
- Atrioventricular canal defect
- Common truncus
- Coarctation of aorta
- Endocardial cushion defects
- Hypoplastic left heart syndrome
- Interrupted aortic arch
- Patent ductus arteriosus
- Pulmonary valve atresia
- Transposition of the great arteries
- Tetralogy of Fallot
- Tricuspid valve atresia
- Ventricular septal defects

Oro-facial clefts
- Cleft palate only
- Cleft lip only
- Cleft lip with /without cleft palate

Selected gastrointestinal defects
- Oesophageal atresia/stenosis, tracheoesophageal fistula
- Small intestine absence/atresia/stenosis
- Large intestinal atresia/stenosis
- Ano-rectal absence/atresia/stenosis
- Hirschsprung disease
- Atresia of bile ducts

Selected urinary tract defects

- Renal agenesis/hypoplasia
- Cystic kidney
- Bladder and cloacal exstrophy
- Lower urinary tract obstruction

Selected genital anomalies
- Cryptorchidism/undescended testes
- Hypospadias
- Epispadias
- Indeterminate sex

Limb deficiency defects
- Reduction defects of upper and lower limbs
- Talipes equinovarus/club foot

Diaphragmatic hernia
Selected abdominal wall defects
- Omphalocele/Exomphalos
- Gastroschisis

Selected chromosomal defects
- Down Syndrome
- Trisomy 13 (Patau)
- Trisomy 18 (Edwards) (Metz et al 2015)
- Turner syndrome

References:

CDC 2021, Birth Defects Surveillance Toolkit. , Correa A, Cragan JD, Kucik JE, et al.

Complete codes will be accessed at : CDC (2021). The Metropolitan Atlanta Congenital Defects Program (MACDP) 6-digit code defect list. Retrieved on 2 November 2021, from https://www.cdc.gov/ncbddd/birthdefects/macdp.html

Annex 3: Signature pages

Signature Page

This protocol is electronically signed in the study management system

Title	Observational Single Arm Pregnancy Safety Study of Women Exposed to Nifurtimox During Pregnancy to Describe the Risk of Pregnancy and Maternal Complications and Other Events of Interest on the Developing Fetus, Neonate, and Infant
Protocol version and date	V.1.0, 24 JAN 2022
IMPACT study number	21944
Study type / Study phase	Observational, post-approval, Phase IV ☒ PASS Joint PASS: ☐ YES ☒ NO
NCT number	Study not yet registered
Medicinal product / Active substance	LAMPIT (Nifurtimox)
Study Initiator and Funder	Bayer AG

The signatories confirm that they agree that the study will be conducted under the conditions described in the protocol.

Signatories

- PPD (PPD)
- PPD (MAH contact person; PPD)
- PPD (PPD)
- PPD (PPD)
- PPD (PPD)
- PPD (PPD)
- PPD PPD)