PEARLY

Progestogens in EARLY pregnancy

STUDY PROTOCOL

Protocol No.:	DYDR5007	**Protocol Date:**	11 OCT 2021
Study Title:	Maternal and Newborn Safety profile of Progestogens in EARLY pregnancy (PEARLY)		
Protocol Version	2.0		
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Sponsor:	Abbott Products Operations AG		
Global Clinical Director / Global Medical Affairs Director :	Jan Ingemar Olofsson MD, PhD		

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Protocol Signature Page

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Sponsor Representative: _____ 25 Nov 2021
Date

BY SIGNING BELOW, I, THE INVESTIGATOR, AGREE TO CONDUCT THE RESEARCH STUDY AS DESCRIBED IN THIS PROTOCOL.

Principal Investigator (through CRO): _____ 25/11/2021
Date

Clare Barnett
Center for Epidemiology and Health Research
ZEG Berlin
Berlin, Germany

Name of Sponsor:	**Name of Finished Product:**	**Name of Active Ingredient(s):**
Abbott Products Operations AG	Duphaston	Dydrogesterone

Title of Study:

Maternal and Newborn Safety profile of Progestogens in EARLY pregnancy (PEARLY)

Marketing authorization holder

For Russia and China
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Study Site(s) (Planned):
China
Turkey
Russia

Table of contents

List of abbreviations

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
AT	As Treated
AS	Active Surveillance
ATC	Anatomical Therapeutic Chemical
ART	Assisted Reproductive Technology
CATI	Computer-Assisted Telephone Interviews
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CFR	Code of Federal Regulations
CRO	Contract Research Organization
CRF	Case Report Form
DME	Designated Medical Events
DMP	Data Management Plan
DVP	Data Validation Plan
DYD	Dydrogesterone
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDD	Estimated Date of Delivery
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ePRO	Electronic Patient Reported Outcome
EU	European Union
FDA	Food and Drug Administration
FPI	First Patient In
FU	Follow-Up
GEP	Good Epidemiological Practice
GVP	Good Pharmacovigilance Practice
GPP	Good Pharmacoepidemiology Practices
HATC	Herbal Anatomical Therapeutic Chemical
HCP	Health Care Practitioner
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee

IRB	Institutional Review Board
IVF	In-Vitro Fertilization
LTFU	Lost To Follow-Up
LPS	Luteal Phase Support
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MM	Major Malformation
NC-FET	Natural Cycle Frozen Embryo Transfer
NIS	Non-Interventional Study
OPRI	Other Pharmacovigilance Relevant Information
OTC	Over-The-Counter
OR	Odds Ratio
PEARLY	Maternal and Newborn Safety profile of Progestogens in EARLY pregnancy
PII	Personal Identifiable Information
PT	Preferred Term
QRP	Quality Review Plan
RECORD	Reporting of studies Conducted using Observational Routinely collected health Data
REOS	Regular End Of Study
SADR	Serious Adverse Drug Reaction
SAP	Statistical Analysis Plan
SES	Socio-Economic Status
SMAC	Scientific and Medical Advisory Council
SMP	Safety Management Plan
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedures
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
US	United States of America
WHO	World Health Organization
ZEG	Berlin Center for Epidemiology and Health Research (Acronym for “Zentrum fuer Epidemiologie und Gesundheitsforschung Berlin”)

1. Abstract

Title
Maternal and Newborn Safety profile of **P**rogestogen use in **EARLY** Pregnancy (PEARLY).

Rationale and background
Progestogens are commonly prescribed to women for the indication of luteal phase support (LPS) during in vitro fertilization (IVF)/ assisted reproductive technology (ART) treatment, when presenting with early pregnancy bleeding or recurrent pregnancy loss. After more than 60 years on the market the available clinical and pharmacovigilance safety data suggest that dydrogesterone has a favorable benefit-risk profile in the approved indications. However, recent implications and isolated claims by individuals within the scientific community have raised some questions related to the safety of dydrogesterone. Establishing a scientifically sound pregnancy and newborn safety registry will enable high quality safety data on dydrogesterone to be collected.

Research question and objectives
The primary objective is to assess the rate of major malformations in fetuses and newborns by indication and by exposure to progestogens *in the first trimester of pregnancy* with focus on dydrogesterone versus non-dydrogesterone treatments. This study aims to accurately characterize and describe users of progestogens in early pregnancy including past gynecological and obstetric history, indication for progestogen use, type of progestogen use and detail of the course of pregnancy, birth outcome and newborn health. A comparison of live birth rates and rate of malformations in fetuses and newborns will be based on the indication area (recurrent pregnancy loss*, bleeding in early pregnancy** or IVF/ART) and the treatment (dydrogesterone, other progestogens, and other treatments***).

Study design
This multinational, prospective, active surveillance, registry study following two cohorts will include study participants who are pregnant and seeking any type of medical*** treatment, including dydrogesterone and other progestogens, for either (A) recurrent pregnancy loss* and/or bleeding in early pregnancy**or (B) as IVF/ART support. Pregnant women not taking progestogen and are advised an alternative non-medical treatment, in the context of bleeding in early pregnancy, recurrent pregnancy loss, or undergoing natural cycle frozen embryo transfer (NC-FET) can also be included in this study. Eligible study participants will be recruited via an international network of prescribing Health Care Practitioners (HCPs) in China, Turkey, and Russia with the aim to collect data related to maternal safety and newborn safety in women prescribed progestogens during early pregnancy. Study participants will be followed from early pregnancy until 6 – 12 weeks after giving birth. All malformations will be captured via direct contacts with the study participants. Study participants will be sent online questionnaires via the electronic Patient Reported Outcomes (ePRO) solution provided by MediData. Major malformations reported by the study participants will be validated by ZEG Berlin via relevant source documents and if necessary, via contacting the treating HCPs. The total study duration is planned for approximately 4 years including recruitment and follow-up.

Population
Pregnant women aged 18 to 35 who are treated with progestogens, including dydrogesterone, or other treatment for (A) recurrent pregnancy loss* and/or bleeding in early pregnancy** or as (B) IVF/ART support can be included in the study. Study participants are only recruited after the decision on treatment is made. Additionally, study participants will be recruited in different geographical areas in China, Turkey and Russia where dydrogesterone is marketed.

*habitual miscarriage / ** threatened miscarriage
*** Other treatments contain medical i.e., non-drug treatment plan (e.g. yoga, meditation, bed rest), pharmaceutical i.e., prescribed non-dydrogesterone based drug therapy including over-the-counter (OTC) and medicinal i.e., non-pharmaceutical including herbal, traditional medicines etc.

Variables
The primary variable of interest is the rate of major malformations in fetus and newborns. Data are collected on treatment, treatment indication, risk factors and potential confounding factors for malformations.

Data sources
Study data, information on risk factors and potential confounding factors, and information on malformations will be obtained from the study participants directly via ePRO. In case a potential major malformation is reported by the study participant, the reported event will be confirmed via review of medical documentation provided by the study participant or alternatively, obtained via the treating HCP.

Study size
Approximately 11,000 study participants (5,500 early pregnancy bleeding/recurrent pregnancy loss and 5,500 IVF/ART) will by recruited via a network of recruiting HCPs prescribing dydrogesterone or other treatment. Approximately 5,500 study participants per subcohort are statistically sufficient (assumptions: power = 90%, one-sided $\alpha = 0.025$, 20% drop-out rate, incidence proportion of 200 major malformations per 10,000 births) to exclude a 2.0-fold risk (Odds Ratio (OR)). The study is powered to test the non-inferiority of dydrogesterone treatment.

Data analysis
The primary analysis will focus on an “as treated” (AT) population analysis set whereby the outcomes of interest are assigned to the treatment exposure during the first trimester of pregnancy. The risk of major malformations will be assessed by unconditional logistic regression for each indication. Potential confounding or risk factors will be considered either in a pre-analysis step regarding cohort balancing using methods such as propensity scores, or by subsequent inclusion into the logistic model as cofactors for adjustment of the treatment effect. Crude and adjusted ORs and 95% confidence intervals (CI) will be estimated. The null hypothesis to be tested is: $(OR_{MM}) \geq 2.0$ (i.e., the malformation odds ratio for dydrogesterone vs. non-dydrogesterone is higher or equal to 2.0). The alternative hypothesis is defined as $OR_{MM} < 2.0$.

1 Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
V01-00	16-JUL-2021	NA	First version	
V02-00	11-OCT-2021	• Section 3: Rationale and background • Section 5.2.2.1 Inclusion criteria • Section 5.7.3 Interim analyses	Amendments as per recommendation by the Global Ethics Committee	

2 Milestones

Milestone	Planned date
Global Ethics Approval	September 2021
Registration in the EU PAS register	October 2021
Start of data collection (First Patient In)	December 2021
End of data collection (Last Patient Last Follow-Up)	April 2024
Study interim/progress report 1	March 2022
Study interim/progress report 2	December 2022
Study interim/progress report 3	September 2023
Data base lock	August 2024
Final report of study results	November 2024

3 Rationale and background

Progestogens are commonly prescribed to women for the indication of luteal phase support (LPS) during IVF (in vitro fertilization)/ART (assisted reproductive technology) treatment, when presenting with early pregnancy bleeding or recurrent pregnancy loss. While miscarriage is a frequent complication of early pregnancy (estimated to occur in 10–20% of pregnancies), recurrent miscarriage is less common, with prevalence estimates varying between 0.8% recurrent miscarriage is less common, with prevalence estimates varying between 0.8% and 3% [1]. Recommendations for treatment options for miscarriage differ between guidelines, largely a result of the guidelines being continually updated in line with the latest clinical evidence. In practice,

the onus is on the prescribing physician to ensure their practices are based on the most recently available data and local recommendations. After 60 years of availability on the market, the available clinical and post-marketing safety data have indicated that dydrogesterone has a favorable benefit-risk profile in the approved indications. However, recent implications and isolated claims by individuals within the scientific community [2–5] have raised some questions related to the safety of dydrogesterone, including a retrospective cohort study suggested an increased risk of major cardiac malformations in newborns exposed to dydrogesterone [3]. The study was methodologically flawed and has since been retracted by the publishing journal.

This registry study aims to establish a scientifically sound pregnancy and newborn safety data set to document any putative teratogenic risks upon exposure to progestogens. A large sample size registry with detailed characterization of participants' background, treatment and pregnancy outcome will provide generalizability and precision in addition to possible future regulatory requests from health authorities.

4 Research question and objectives

Congenital malformations are structural abnormalities of prenatal origin and can be classified into three groups based on their cause: genetic, environmental or multifactorial (e.g., twinning) [6]. Most congenital malformations (i.e., structural birth defects) result from abnormal development during embryogenesis [7]. The present study is being designed to assess maternal and newborn safety after progestogen exposure in early pregnancy. It aims to accurately characterize the demographic profile of users of progestogens in early pregnancy including past gynecological and obstetric history, indication for progestogen use (specific focus will be given to documenting use during IVF/ART and as treatment for bleeding in early pregnancy or recurrent pregnancy loss), type of progestogen and detail of the course of pregnancy, birth outcome and newborn health. A comparison of live birth rates and rate of malformations in fetus and newborn will be based on indication area and by treatment (dydrogesterone, other progestogens, or other treatment). In keeping with regulatory requirements, reportable adverse drug reactions will be relayed to the relevant marketing authorization holders (MAHs).

4.1 Primary Objectives:

- Assess the rate of major malformations in fetus and newborns by indication and by exposure to progestogens *during the first trimester of pregnancy*, with an emphasis on dydrogesterone versus non-dydrogesterone treatments.

4.2 Secondary Objectives:

- Describe the rate of other malformations by progestogen type and indication of use,
- To describe demographic, reproductive, and maternal health data, as well as available information on prenatal diagnostics and pregnancy outcome for the mother and the newborn.

4.3 Explorative Objectives:

- Characterize the hormonal and non-hormonal utilization patterns of dydrogesterone and non-dydrogesterone treatment in study participants and describe captured background risk scenarios which may serve as causal factors for major fetal and newborn malformations, not only limited to start and stop dates for all products taken during pregnancy, but also including duration, and indication,
- Describe the rate of (spontaneous) miscarriage,
- Describe the rate of induced abortions which may be attributed to maternal health or malformations in the fetus.

5 Research methods

5.1 Study design

The PEARLY study is a prospective, observational, multi-center, multi-country, active surveillance registry study.

Different populations (based on different indications) will be included in the study with different subsequent analyses and separate data collection/follow-up for each of the cohorts of interest (see *Figure 1*). The different indication areas of interest include:

Cohort A: bleeding in early pregnancy/recurrent pregnancy loss

Cohort B: IVF/ART

A comparison of live birth rates and rate of major malformations in fetus and newborns will be based on indication area and by treatment (dydrogesterone, other progestogens, or other treatment).

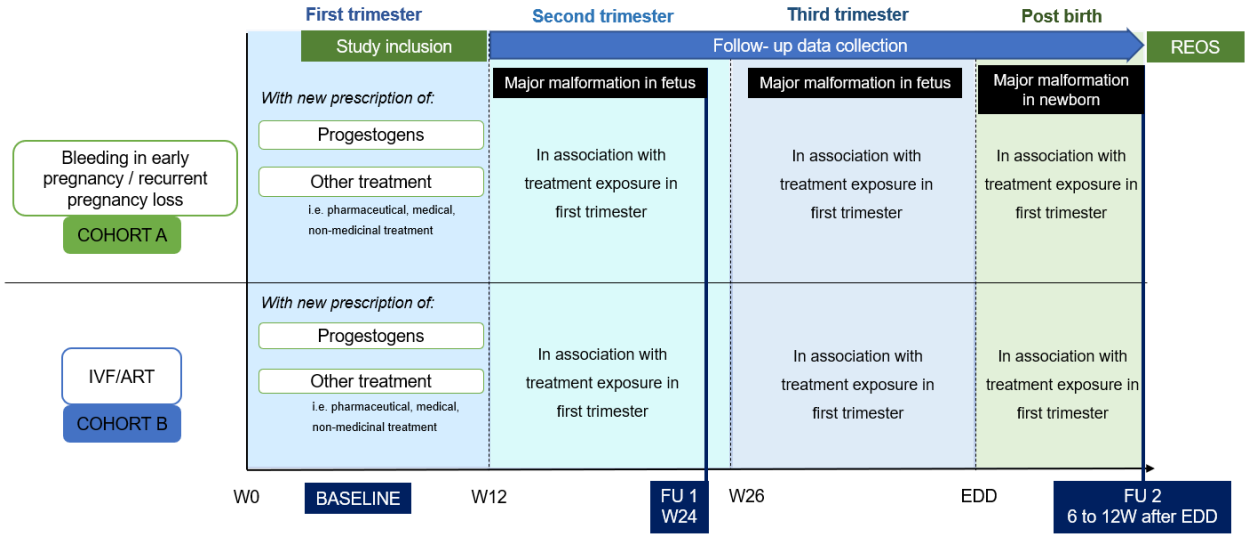
Primary analyses focus on the rate of major malformations with exposure in the first trimester of pregnancy to:

(1) Dydrogesterone versus non-dydrogesterone treatment

For the primary analysis, study participants taking any dydrogesterone preparation during the first trimester of pregnancy (at any time regardless of dosage and duration) as mono-treatment will be considered in the dydrogesterone group. Study participants taking at least one non-dydrogesterone preparation during the first trimester of pregnancy (at any time regardless of dosage and duration) as mono-treatment (i.e. no combination with dydrogesterone or another non-dydrogesterone) will be considered in the non-dydrogesterone group.

Further subgroups regarding specific dosage and duration will be considered in subgroup analyses.

Figure 1: Study Design



DYD: dydrogesterone, EDD: Estimated Date of Delivery, FU: follow-up, W: week, REOS: Regular End Of Study

5.2 Setting

The study will be conducted by the Berlin Center for Epidemiology and Health Research (ZEG Berlin), with the oversight of Abbott AG. The study will be divided into 2 phases: a baseline survey, which includes an initial consultation at baseline with recruiting Health Care Practitioners (HCPs) and completion of a baseline questionnaire by the study participant, and a follow-up phase, which includes two follow-up contacts directly with the study participant at approximately 24 weeks of gestation and 6 to 12 weeks after the initial Estimated Date of Delivery (EDD).

The study will take approximately four years and includes the recruitment and follow-up of approximately 11,000 study participants.

The study will be conducted in Russia, Turkey and China and focuses on recruiting study participants from different geographical regions, healthcare systems and cultural practices. This allows generalizability of the study results to further regions where dydrogesterone is marketed.

During study conduct, ZEG Berlin will establish two project teams – the central ZEG Berlin study team and the local Field Organizations team. The central study team is responsible for ensuring that the study adheres to the protocol and relevant rules and regulations governing non-interventional studies (NIS). The local Field Organizations team is responsible for study administration in local geographic areas, including liaising with recruiting HCPs, study participants, translation of study questionnaires, medical information, and documentation.

5.2.1 Selection of the Study Population

Study participants will be enrolled by recruiting HCPs. The recruiting HCPs are not necessarily involved in the subsequent follow-up (FU) of study participants. The recruiting HCP's role is to explain the nature of the study, its purpose and associated procedures, and the expected duration of follow-up for each study participant prior to their entry into the study.

Potential study participants will be identified by recruiting HCPs following initiation of progestogen or other treatment within the first trimester of pregnancy. Study participants will be recruited based on the inclusion and exclusion criteria as defined in section 5.2.2. Study population. As this is an observational registry study, the decision to prescribe dydrogesterone or other treatment is solely at the discretion of the HCP and the study participant. Study participants will continue to be managed throughout the study according to their HCP's prescribed treatment and will not be allocated to a study intervention.

Study participants will have the opportunity to ask questions and will be informed about their right to withdraw from the study at any time without disadvantage and without having to provide reasons for their decision. This information will be provided during the consenting process. Participation to the study is only possible if the informed consent and data privacy form is signed by the study participant. Once enrolled, a study participant may discontinue (and restart) treatment or may switch to another treatment as advised by the HCP at any time. However, study participants will continue to be followed whether or not they remain on the prescribed treatment, provided that they do not withdraw their consent.

Data will be collected directly from the study participants through electronic patient-reported outcome (ePRO) questionnaires. This means that study participants will be followed by ZEG Berlin independent of the HCP and follow-up is not necessarily linked to a clinical office visit. ZEG Berlin will obtain permission from the study participant to contact *any* treating or diagnosing HCP for clarification of a reported medical events (e.g. major malformations) during the study's observation time.

5.2.2 Study population

Subjects receiving treatment with any progestogen, including dydrogesterone, or other treatment in the first trimester of pregnancy following; (A) a diagnosis of early bleeding in pregnancy or recurrent pregnancy loss, or (B) following IVF/ART embryo transfer will be eligible to be enrolled. The inclusion and exclusion criteria are defined in section 5.2.2.1. and section 5.2.2.2.

Subjects can be screened for the study only after an informed decision for dydrogesterone or alternative treatment has been made by the subject and the recruiting HCP. Indication and contraindications according to the local market authorization/ summary of product characteristics (SmPC) should be carefully considered by the HCP.

5.2.2.1 Inclusion Criteria

- Pregnant women who wish to sustain their pregnancy
- Women who have tested positive (blood or urine) for pregnancy in the first trimester, seeking medical treatment
- Aged 18 – 35 years

AND

- Early bleeding in pregnancy with evidence of an intrauterine pregnancy / unexplained recurrent pregnancy loss (with ≥ 2 previous pregnancy losses) with evidence of an intrauterine pregnancy with visible gestational sac

OR

- Having undergone IVF/ ART embryo transfer and taking progestogen for luteal phase support (LPS), with evidence of an intrauterine pregnancy with visible gestational sac

OR

- Without taking a progestogen and advised an alternative treatment, in context of bleeding in early pregnancy, recurrent pregnancy loss, or undergoing natural cycle frozen embryo transfer (NC-FET)

AND

- Signed informed consent, allowing consent to contact all treating, or diagnosing HCP
- Able and willing to read and comprehend written instructions; comprehend and complete the questionnaires required by the protocol.

5.2.2.2 Exclusion criteria

- Serious disease or disease requiring teratogenic treatment (e.g., Lupus Erythematosus, Multiple Sclerosis, cancer)
- Multifetal pregnancy
- More than four (4) previous IVF embryo transfers
- Previous exposure to dydrogesterone in index pregnancy
- Documented substance abuse
- Treatment with hormones known to cause malformations.Participation in an observational study that might, in the recruiting HCP's opinion, influence the assessment for the current study
- Participation in a randomized clinical trial in the last 3 months
- Previous enrollment in the PEARLY study

5.2.2.3 Withdrawal / drop-out / lost to follow-up (LTFU)

Study participants can refuse to further participate, or may withdraw from the study, at any time and without giving a reason. As this is an observational study, withdrawal from the study is independent of the underlying therapy and will not affect medical care.

If a study participant wishes to terminate study participation, no further data will be collected. Data which were collected prior to withdrawal may be used in the data analysis for the purpose of this study. In case a study participant would like to withdraw the consent given earlier, the withdrawal should be documented in the electronic Case Report Form (eCRF) in the EDC solution by MediData. Study participants who withdraw from the study prior to regular study end will be included in drop-out numbers.

Study participants who experience a spontaneous abortion or pregnancy termination during study conduct will not receive further follow-up (FU) questionnaires. These study participants are considered to have reached regular end of study (REOS) after completion of the follow-up questionnaire in which the spontaneous abortion or pregnancy termination was reported.
A study participant becomes lost to-follow-up (LTFU) when the study questionnaire(s) are no longer completed and re-contact attempts remain unsuccessful. To limit LTFU, ZEG Berlin will implement a well-established active-surveillance (AS) methodology. Automatic reminders (e.g., e-mail) to complete study questionnaires will be issued via the ePRO solution by MediData. In case of ongoing non-response, further manual contact attempts (e.g., telephone) will be initiated by the local field organizations team.

Participants will not be replaced after drop-out or LTFU.

5.2.3 Validation of Self-Reported Events

A self-administered questionnaire used by study participants at short intervals is a sensitive tool which captures almost all serious clinical outcomes [8]. From a methodological point of view, it captures a much higher proportion of these outcomes than methods relying only on the prescribing HCP who may not be involved in the diagnosis and treatment of these outcomes. However, there is a significant difference between the rates of patient-reported and medically confirmed events after validation as laypersons often misclassify adverse events, therefore, assessment of the self-reported events is of utmost importance.

In this study, self-reported events considered as a defined primary outcome, i.e., major malformations defined in section 5.3.1 will be validated with the goal to identify if the reported event was medically confirmed.

The follow-up questionnaires (ePRO) will be programmed with specific constraints allowing for additional questions to be displayed if a potential major malformation is reported by a study participant. Questionnaires with a potential major malformation are automatically flagged and transferred to the medical event validation team at ZEG Berlin. The medical event validation team will work within the EDC solution to validate all events considered as a primary study outcome. During the validation process it may be necessary to re-contact the study participant or diagnosing and/or treating HCP for validation of the information initially received from the study participant to, a) clarify information and b) obtain additional information for medical confirmation of the event. All additional data gathered during this procedure is entered into the eCRF EDC solution by ZEG Berlin. Further details will be described in the Data Management Working Procedures.

ZEG Berlin will oversee the outcome validation process by asking the local field organization to contact the study participant and/or HCP to gather more necessary information. The field organization then will contact the study participant and/or HCP in the local language. The field organization will provide the medical documentation and an English translation to ZEG Berlin for further processing.

Under routine medical conditions, diagnosis of a disease/condition is not always confirmed by a diagnostic method with high specificity. Therefore, the primary study outcomes will be classified by ZEG Berlin's medical event validation team according to a predefined algorithm which will be further specified in the working procedures. The data is captured by ZEG Berlin's medical event validation team in the eCRF section for event validation.

- **Definite Event:**
  Diagnosis confirmed by diagnostic measures with high specificity or written proof available e.g., medical record.
- **Probable Event:**
  Absence of confirmation by a diagnostic measure with high specificity for the diagnosis, but clinical diagnosis confirmed (verbally or in writing) by an HCP or supported by diagnostic tests with low specificity.
- **Possible Event:**
  Condition considered as primary outcome was reported by the study participant only and no confirmation could be obtained to proof or disprove the event or no diagnostic measures were performed that could have clarified the diagnosis.
- **Event not confirmed:**
  Diagnosis reported by the study participant is excluded by diagnostic procedures.
  A different medical condition is diagnosed by the attending HCP.

5.3 Definition of outcome parameters

5.3.1 Definition major malformations

Malformations of primary interest are:

Congenital malformation	
Central nervous system	**Respiratory system**
Agenesis of the corpus callosum Arhinencephaly / Holoprosencephaly Hydranencephaly Hydrocephaly Macrocephaly Meningoencephalocele Microcephaly Neural tube defect (anencephaly, spina bifida, craniorachischisis) Porencephaly Syringomyelia	Branchial cleft cyst Congenital cystic malformation Larynx hemangioma Pulmonary hypoplasia
Head and neck	**Digestive system**
Oral Cleft palate without cleft lip Cleft lip with or without cleft palate Eye Anophthalmos Ankyloblepharon Dacryostenosis Ectropion / Entropion Epibulbar dermoid Exophthalmos congenital Glaucoma Nystagmus Persistent Hyperplastic Primary Vitreous Other Anotia/microtia Choanal atresia Congenital hearing loss/disorder	Annular Pancreas Anorectal atresia / stenosis Bile duct atresia Diaphragmatic hernia Esophageal diverticulum Imperforate anus Hepatomegaly Hirschprungs disease Intestinal Malrotation Microcolon Meconium ileus/plug Obstruction by fibrous band Oesophageal atresia / stenosis Persistent omphalomesenteric duct Pyloric stenosis Pylorospasm

Dysmorphic facies Facial palsy/asymmetric crying facies Hemifacial microsomia Macroglossia Potter facies Torticollis	Rectovaginal fistula Small intestine atresia / stenosis Splenomegaly Tracheo-oesophageal fistula
Cardiovascular system	**Skin**
All congenital cardiovascular malformations are of interest, *excluding:* *Heart murmur* *Systolic murmur* *Haemangioma* The following three events will be evaluated at the interim analysis, and if these are still of primary interest further evaluations will be undertaken: Persistent Atrial septum defect Persistent Patent foramen ovale Persistent Patent ductus arteriosis	Abnormal skin findings, *excluding*: *Hyperpigmented/ hypopigmented macules* *Scars / lesions* *Skin tags* Ichthyosis
Urinary system	**Reproductive system**
Bladder/urethral diverticulum Congenital cystic kidney disease Enlarged kidney Hydroureter/hydronephrosis Hypospadias Other congenital bladder anomaly Patent/persistent urachus Prolapsed bladder Prune belly Renal agenesis Renal (hypo)dysplasia Renal stones Vesicoureteral reflux	Clitoromegaly Cryptorchism Ovarian cysts Epispadias Hermaphroditism Small penis Torsion of testis Pseudohermaphroditism Other congenital genitourinary abnormality
Musculoskeletal system	**Genetic / chromosome**
Abnormal palmar/plantar creases Arthrogryposis Bowed long bones / missing bones Congenital foot malformation Congenital hand malformation Craniosynostosis Genu valgum/genu varum Hip dislocation/Hip dysplasia Joints in abnormal positions Kinematic imbalances due to suboccipital strain (KISS) Limb reduction defects Pectus abnormalities Polydactyly Scoliosis without vertebral anomalies Sprengel deformity Syndactyly Various head shape abnormalities (Ex: plagiocephaly) without craniosynostosisa	Down syndrome Genetic syndromes + microdeletions Klinefelter syndrome Trisomy 13 Trisomy 18 Turner's syndrome **Other** Amniotic bands Aplasia Ascites/Anasarca/Hydrops Cysts of various organs Cystic lymphangioma Gastroschisis Hemihyperplasia/ hemihypertrophy Inguinal hernia Lymphangiectasias Multiple congenital abnormalities Omphalocele Situs inversus

These listed malformations will be identified during follow-up, i.e., major malformation in the fetus, and after delivery, i.e., major malformation diagnosed in newborns (i.e., pre- and postnatally diagnosed malformations).

5.3.2 Variables

5.3.2.1 Variables to determine the primary objective

- Rate of major malformations (as defined in section 5.3.1.) in fetus and newborn

- Prescribed treatment in first trimester for each indication
- Indication of use
- Risk factors and potential confounders as per section 5.3.2.4.

5.3.2.2 Variables to determine the secondary objective

- Rate of other malformations in fetus and newborn
- Progestogen intake in first trimester for each indication
- Indication of use
- Baseline information
    - Age
    - BMI
    - Race
    - Region of residence
    - Socioeconomic status (SES)
    - Other (cf. section 5.3.2.4.)
- Pregnancy outcome
- Newborn health e.g. NICU admission, prematurity, weight/height newborn at delivery
- Maternal health during pregnancy e.g., obstetric disease, lifestyle (smoking and alcohol), infection, pregnancy-related complication

5.3.2.3 Other variables

Further variables, including known risk and potential confounding factors, for malformations will be collected at baseline and during follow-up. Examples include family and personal history of malformations, vitamin and folic acid intake, infections, previous pregnancy history, environmental exposure, obstetric disease, and medical treatment, IVF/ART insertion technique (if applicable) etc. A detailed overview of all variables is shown in section 5.3.2.4.

5.3.2.4 Variables collected per timepoint

Variables	**Baseline**	**FU1** *At week 24*	**FU2** *6-12 weeks after EDD*
Filled by	Participant (ePRO)	Participant (ePRO)	Participant (ePRO)
Study eligibility status (based on inclusion and exclusion criteria)	Assessed by recruiting physician & via participant screening form in EDC system by study participant	NA	NA
Informed Consent	x	NA	NA
Select indication for study inclusion (cohort A or B)	x		
Demographic and social characteristics			
Body weight (in Kg) before current pregnancy	x		
Current body weight		x	x

Variables	Baseline	FU1 *At week 24*	FU2 *6-12 weeks after EDD*
Filled by	Participant (ePRO)	Participant (ePRO)	Participant (ePRO)
Height (in cm)	x		
Birth year	x		
Race	x		
Region of residence (rural, urban)	x		
Education	x		
Monthly household income	x		
Pregnancy/Reproductive History			
Week since last menstrual period	x	x (only for IVF/ART group not being pregnant at study start)	
Time to pregnancy since pregnancy wish	x	x (only for IVF/ART group not being pregnant at study start)	
Previous Pregnancy/-ies and outcome	x		
Including previous malformations	x		
Treatment			
Study treatment for indication	x	x	
Treatment start	x		
Treatment duration	x		
Fertility treatment for current pregnancy	x		
Medical History			
Existing obstetric disease & treatment	x		
Pregnancy-related/new obstetric disease & treatment		x	x
Infections during pregnancy	x	x	x
COVID-19 vaccination	x	x	x
Environmental Exposure			
Vitamin intake	x	x	
Folic acid intake	x	x	
Environmental exposure	x	x	x
Family History			
Family history malformations	x		
Personal history malformations	x		
Consanguinity	x		
Lifetyle			

Variables	Baseline	FU1 *At week 24*	FU2 *6-12 weeks after EDD*
Filled by	Participant (ePRO)	Participant (ePRO)	Participant (ePRO)
Smoking	x	x	x
Alcohol consumption	x	x	x
Study outcome parameters			
Current pregnancy status		x	x
Outcome pregnancy		x	x
Reason for end of pregnancy (if applicable)		x	x
Date of pregnancy end (if applicable)		x	x
Malformations identified in fetus/newborn		x	x
Date of diagnosed malformation (if applicable)		x	x
Diagnostic test identifying the malformation (if applicable)		x	x
Date of delivery			x
Weight newborn at birth			x
Height newborn at birth			x
Sex of the fetus/newborn		x	x

5.4 Data sources

Eligible study participants will be asked to complete study registration by giving their consent to study participation, and providing their contact details required for follow-up. Following their consent, study participants will be asked to complete a questionnaire at baseline visit using the ePRO solution by MediData [9]. The baseline questionnaire will cover basic demographic and gynecological history and a detailed review of obstetric history and risk factors for major malformations. In addition, study participants will be sent two follow-up questionnaires coinciding to the following timepoints – approximately at 24 weeks of gestation and 6 to 12 weeks after the initial EDD. All questionnaires will be completed by the study participant directly via the ePRO questionnaire in Medidata. Direct follow-up (i.e., active surveillance) with study participants enables the collection of comprehensive information on outcomes of interest, regardless of whether they were diagnosed and treated by the HCP.

Follow-up data to be collected from the study participants (ePRO) will describe the clinical status of the pregnancy, potential malformations and change in risk factors as described in section 5.3.2.4 Variables collected per timepoint.

During the informed consent process, study participants are asked to provide the name and address of the diagnosing/treating HCP who is involved in their obstetric care. In case a primary outcome of interest, i.e., a major malformation is reported by the study participant, the reported event will be confirmed via review of medical documentation. Medical documentation can be provided by either the study participant, or by the diagnosing/treating HCP. ZEG Berlin will contact the relevant HCP and inform him/her about the study objectives and will share the subject's informed consent to access the medical information. Follow up by ZEG

Berlin will include obtaining hospital records and/or discharge summaries either via the study participant or diagnosing/treating HCP.

5.5 Study size

Two independent cohorts will be considered in the analysis: (A) study participants with bleeding in early pregnancy and/or recurrent pregnancy loss and (B) study participants receiving IVF / ART. Sample size calculations for both cohorts are similar as based on an incidence proportion of major malformation at birth of 200 per 10,000 births for both indications [10–14]. It is expected that dydrogesterone is associated with a risk of major malformation that is not higher than the risk associated with non-use of dydrogesterone. The study is powered to test the non-inferiority of dydrogesterone treatment.

Assuming a drop-out rate of 20% and a rate of major malformation in fetal newborn of 0.02, sample size calculations show that approximately 5,500 study participants per cohort are statistically sufficient (power = 90%, one-sided α = 0.025) to exclude a 2.0-fold risk (Odds Ratio) in the dydrogesterone cohort. The test statistic used is the one-sided Score test [15].

Table 1 and Table 2 show proposed sample sizes for sub-group specific allocation rates.

Cohort A: bleeding in early pregnancy / recurrent pregnancy loss

Table 1: Group allocation: 30% (dydrogesterone) versus 70% (reference)

Endpoint	Incidence proportion		Non-inferiority OR	Effective sample size		20%-Drop-out inflated sample size	
	Reference	DYD		Reference N_1	DYD N_2	Reference N_1	DYD N_2
Major malformation	0.02	0.02	2.0	3,136	1,343	3,920	1,679

Cohort B: IVF/ART

Table 2: Group allocation: 50% (dydrogesterone) versus 50% (reference)

Endpoint	Incidence proportion		Non-inferiority OR	Effective sample size		20%-Drop-out inflated sample size	
	Reference	DYD		Reference N_1	DYD N_2	Reference N_1	DYD N_2
Major malformation	0.02	0.02	2.0	2,059	2,059	2,574	2,574

The total number of study participants will be 11,000 across all geographical study sites China, Turkey and Russia.

Sample size has been calculated using the Statistical Software PASS 2021 Power Analysis & Sample Size [16].

5.6 Data management

5.6.1 Databases

During the study, two different types of data will be collected: (I) administrative data, which includes contact details of HCPs and study participants, and (II) study data, which includes all questionnaire data including baseline data and all subsequent follow-up forms. All study data will be collected and managed through the EDC system, MediData Rave [17] and ePRO [9]. For data security and privacy reasons, administrative data are stored separately from the study data (e.g., firewall). Access to administrative data will be restricted and only be accessible for the teams who require contact with the study participants and/or diagnosing/treating HCPs.

Where local regulations permit, the consent and informed consent form (ICF) signing process will occur electronically via the MediData eConsent application. All outcome variables and potential covariates will be entered in standardized eCRFs. After data entry, missing or implausible data will be queried, and the data will be validated by ZEG Berlin's study data management team.

Study data will be entered directly into the ePRO questionnaire by the study participants via MediData. The quality control of entered data will be supported by edit checks which include range, coding, missing and date checks as well as cross-reference (consistency) checks between variables.

5.6.2 Database Freeze/Lock

For each interim analysis and for the final analysis the database is frozen at a predefined time point. The data will be 'cleaned' within 4 weeks of the database freeze. For the final freeze (approximately 4 months after the last follow-up questionnaires have been sent to the study participants), no additional incoming data is entered in the database and queries and inconsistencies will be cleaned. After the cleaning process, the database will be locked according to the standard operating procedures and no data entry and changes can be performed – this database will represent the final data source for all final analyses.

5.7 Data analysis

5.7.1 Descriptive analysis

The primary aim of the study is to obtain useful incidence estimates with adequate precision, per country and per cohort of interest. Sample size considerations are based on the primary outcome of malformation rates in newborns measured as frequency of any major malformation (i.e., 200/10,000 births).

The data will be compared between study participants per indication, i.e., (A) prescribed dydrogesterone or alternative treatment following a diagnosis of early bleeding in pregnancy or recurrent pregnancy loss, and (B) prescribed dydrogesterone or alternative treatment following IVF/ART embryo transfer.

All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e., mean, standard deviation, minimum, median, quartiles and maximum). Clinical endpoints will be analyzed with respect to time-on-drug and treatment indication unless sample size is sufficient to allow subclassification of data. Influence of potential confounding factors will be investigated and accounted for in multiple regression.

5.7.2 Primary analysis

The primary analysis cohorts are defined as pregnant women using (I) dydrogesterone during the first trimester versus (II) other treatment and/or treatment combinations and/or no treatment during the first trimester as defined in section 5.1. Further analyses on subcohorts of (II) will be considered as secondary or sensitivity analyses. The safety conclusions regarding risk of major malformation will be based on the “as treated” (AT) population analysis set whereby outcomes of interest are assigned to the treatment used during the first trimester of pregnancy.

The overall incidence of major malformation will be calculated with respect to all pregnancies observed in the respective cohort and compared per indication area.

The null hypothesis is defined as odds ratio (OR) for major malformation H0: (OR_{MM}) ≥ 2 obtained from a comparison of the primary analysis cohorts. The alternative hypothesis is defined as HA: OR_{MM} < 2, respectively.

The risk of major malformation as compared between treatment cohorts will be assessed by unconditional logistic regression. Potential factors of influence, potential confounding factors or risk factors, will be considered either in a pre-analysis step regarding cohort balancing using methods based on propensity scores, e.g., inverse probability of treatment weighting (IPTW) or by subsequent inclusion into the logistic model as cofactors for adjustment of the treatment effect. Crude and adjusted OR and 95% confidence intervals (CI) will be estimated.

All statistical details including derived variables content of tables and proposed format will be detailed in the SAP.

5.7.3 Interim analysis

There are 3 interim analyses planned during the study conduct. It is planned to have the interim/progress reports developed on an annual basis by ZEG Berlin, with the oversight of Abbott. The content of the interim/progress reports should follow a logical sequence and should include all the available data that are judged relevant for the progress of the study, for example, number of subjects who have entered the study, number of exposed subjects or number of subjects presenting the outcome of interest, problems encountered and deviations from the expected study plan.

The interim reports generated from interim analysis will inform the advisory board, regulatory authorities, the funders, and the investigator team about preliminary results, and whether incidence assumptions regarding exposure as basis for the sample size calculation are realistic. Details on the interim analysis will be explicitly described in the SAP. The interim analyses planned for this study are of a descriptive nature and will not allow for adaptation of the study design. However, if a potential (safety) issue is identified during the study, in depth review will be made in collaboration with the SMAC, with the oversight of Abbott and thereafter, any actionable items will be undertaken.

5.7.4 Missing values

Missing values occur during the conduct of an observational study and may represent a potential source of bias. Missing data will be presented in the respective table categories in the descriptive analysis. To perform multivariable statistical models, missing values will be either accepted or imputed using methods such as last observation carried forward or imputation models based on multivariable regression as further described in the SAP.

5.8 Quality control

Prior to first patient-in (FPI), all field organizations and recruiting HCPs will be sufficiently trained on the background and objectives of the study, as well as ethical and regulatory obligations. Recruiting HCPs will have the chance to discuss and develop a common understanding of the study protocol and the study questionnaires. Recruitment will be continuously monitored, and adjustments may be made to the number and type of recruiting HCPs to ensure an adequate number of study participants are recruited in each geographical area and per treatment group.

ZEG Berlin is responsible for a systematic review of the quality standards implemented in the study via regular on-site or remote audits and site visits at the local field organizations, as well as for proposing suitable measures to the principal investigator to improve quality standards.

ZEG Berlin's internal standard operating procedures (SOPs) manual describes standardized procedures to ensure high quality and compliance with all applicable guidelines for NIS. The SOPs are reviewed on a regular basis and updated where necessary to ensure that all processes are in line with legal compliance and integrity of data. In addition, ZEG Berlin works according to study-specific working procedures.

ZEG Berlin is responsible for the EDC system development, quality control, verification of the data collection, statistical analysis and data transfer to Abbott. All processes that are relevant for legal compliance of the study or the integrity of the data are subject to quality control measures. This includes 1) development of study protocol, questionnaires, databases, and data entry screens, 2) data entry specifications, 3) plausibility checks, 4) validation of clinical primary outcomes, 5) adverse outcome reporting, 6) data analysis, 7) report writing, 8) publication of results, 9) archiving of study materials.

Detailed information on checks for completeness, accuracy, plausibility, and validity will be specified in the Data Management Plan (DMP) and the Data Validation Plan (DVP). Standard measures for handling of missing and implausible data and permissible clarifications will be defined.

Medical review of the data will be performed as described in the Safety Management Plan (SMP). The purpose of the medical review is to verify the data from a medical perspective for plausibility, consistency, and completeness, to identify potential issues that could affect the robustness of the collected study data or the progress of the study and to allow correct PV-reporting. Detailed information on the medical review will be described in the SMP.

National and international data protection laws as well as regulations on non-interventional / registry studies will be followed. The EDC system used for capturing the study participant's data will be validated according to 21 Code of Federal Regulations (CFR) Part 11 (FDA, 2012). 21CFR Part 11 regulations 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.

In a subset of study participants source data verification will be conducted. The purpose is to review the documented data for completeness and plausibility, adherence to the study protocol and verification with source documents.

The study will be overseen by an independent Scientific and Medical Advisory Council (SMAC) of internationally acknowledged experts in the field (cf. Section 5.10.4). ZEG Berlin and its research team will be accountable to the SMAC for all scientific matters, with the oversight of Abbott.

5.9 Limitations of the research methods

The general limitations of observational research and the particularities of the non-interventional/registry approach remain valid. In non-experimental studies the possibility of bias and residual confounding can never

be entirely eliminated, and the ability to infer causation is correspondingly limited. As modern epidemiology has evolved, improved insight into potential sources of bias and confounding, as well as refinements of statistical and epidemiologic methodology, help the epidemiologist to estimate the impact of potential bias and residual confounding.

The design of this study pays particular attention to the following typical biases:

- Confounding bias: subject characteristics (i.e., demographics, socioeconomic factors) that influence the outcome might have unbalanced distributions across treatment groups. Potential differences in outcome could be caused by these differences. Several statistical approaches (i.e., multivariable regressions and propensity score analysis) are planned to balance the distribution of characteristics between treatment groups, reducing the chance of confounding bias, and therefore allowing plausible estimates of the association of dydrogesterone use and major malformations.
- Channeling bias: non-random assignment of subjects to treatment can lead to imbalances in risk-factors between the groups being compared and thus bias the estimates of the treatment effect. Various statistical techniques such as propensity score analyses will be considered.
- External validity: if multiple countries are involved, country specific healthcare settings may play a role with regard to the selection of study participants. With the approach used in the PEARLY study, representativeness will be improved by including the participation of obstetric practitioners, as well as clinics and family planning centers, etc., leading to a representative mix of the typical institutions prescribing dydrogesterone.
- Lost to follow-up bias: by using an AS approach, using a multifactorial contact approach directly with study participants, a very low rate of LTFU is expected. In theory, a higher percentage of SAEs could occur in study participants who are LTFU, because significant events (e.g., major malformation) could be the reason for the loss in contact to the study team. An advantage of the AS study design is that the study team has direct contact with participants. Contact will not be lost if the study participants change their HCP, for example.
- Selection bias: the HCP will approach all eligible subjects asking for participating in the study. It is conceivable that study participants who agree to participate in an observational study on maternal and newborn safety may be systematically different from study participants declining participation. However, it is assumed that these differences will not differ between cohorts, and our ability to compare across exposure groups of interest remains valid.
- Information/misclassification bias will probably have no substantial impact on the results as precise information on the exposure and the outcomes of interest will be collected. In addition, reliable information on duration of dydrogesterone on non-dydrogesterone treatment will be collected.

5.10 Other aspects

5.10.1 Archiving and storage of records

ZEG Berlin will ensure that all relevant documents of this observational study including the ICFs, eCRF printouts and other documents will be stored according to all applicable regulations after the end or discontinuation of the study for at least 10 years. Any data to generate results will be stored within the programming system for at least 10 years. In case national regulations have other requirements regarding storage of data, storage will adhere to local jurisdiction. Abbott will be informed about destruction of study documents and need to approve prior to permanent deletion.

5.10.2 Regulatory authority approvals/authorizations

The study will be carried out within an approved indication in accordance with:

- 'Good Epidemiological Practice (GEP) – Proper Conduct in Epidemiologic Research' issued by the European Epidemiology Federation in 2007
- 'Guidelines for Good Pharmacoepidemiology Practices (GPP)' issued by the International Society for Pharmacoepidemiology in 2007
- 'Guideline on Good Pharmacovigilance practices (GVP), Module VIII issued by the European Medicines Agency in 2013
- ENCePP code of conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies, 2010
- The ethical principles that have their origin in the Declaration of Helsinki.
- All applicable guidelines and regulations of European Medicine Agency (EMA), FDA and applicable local law(s) and regulation(s) (e.g. Regulation (EU) No 520/2012 (EU, "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," Official Journal of the European Union, 20 Jun 2012. 2012)) and national and European Regulations for Registry and Observational Studies.

This study is not within the scope of the European Clinical Trial Directive (2001/20/EC). Accordingly, clinical trial applications to individual national authorities will not be filed. Regional regulatory approvals will be obtained as required by national regulations for NIS and registry studies.

5.10.3 Independent ethics committee (IEC) or institutional review board (IRB)

Documented approval from appropriate IECs/IRBs will be obtained for all participating centers prior to study start. When necessary, an extension, amendment or renewal of the IEC/IRB approval will be obtained.

5.10.4 SMAC

The study will be overseen by an independent committee of experts, the SMAC, who will be responsible for regular review and evaluation of collected data during study conduct as well as for the review of the study protocol, statistical analysis plan, interim results, study report, and publications. ZEG Berlin and its research team will be accountable to the SMAC in all scientific matters, with the oversight of Abbott. ZEG Berlin will present all relevant data to the SMAC in a timely fashion. The members of the SMAC are international experts in relevant scientific fields (e.g., Pediatrics, Reproductive Medicine, Obstetrics and Gynecology and Epidemiology). The members will receive remuneration of expenses and an honorarium to compensate for loss of potential earnings during their work for the SMAC. The members will not be involved in or paid for the operational conduct of the study. Members of the SMAC are listed in **Annex 3.1**.

6 Protection of human subjects

Before collection of any data, a signed ICF and data privacy form is obtained by the participant. ICFs must comply with individual study country law and regulations, including approval from local IEC/IRB.

Participants will sign ICFs at study enrollment after being informed about the study. The eligible participants will be informed about the purpose of the study, the character of the study, timing and content of follow-up contacts, and collection of contact information. Consent will include permission to contact participants and their treating HCP, if required. Participants will be asked to provide personal contact information (e.g., telephone number, home and e-mail address). Participants retain the right to withdraw their consent at any time during the study and without consequences. The ICF will include comprehensive information on processing of personal data according to GDPR.

To comply with rules and regulations regarding the privacy of study participant data, a firewall will be established between the ZEG Berlin central study team and local field organizations team. Members of each team are physically situated in different locations and personal identifiable information (PII) of study participants and HCPs is only seen and handled by the field organizations team situated in each country. Data will be stored on a password protected, secured server and only accessible to authorized users (e.g., field organizations team).

7 Management and reporting of adverse events/adverse reactions

All baseline and follow-up questionnaires will be completed by the study participant using the ePRO questionnaire. The ePRO questionnaires are sent directly to study participants and do not necessarily follow a defined clinical visit or investigation. This means that information reported by the study participants may have occurred days, weeks, or months prior to the follow-up information being received by ZEG Berlin.

The EDC solution will be programmed to automatically flag questionnaires with a potential AE. These questionnaires will be forwarded to ZEG Berlin's medical event validation team and processed according to the working procedures and the SMP.

All reported and flagged AEs will be assessed by the medical event validation team for seriousness and drug relationship and reported in alignment with relevant pharmacovigilance regulations.

When there is no indication of a possible causal relationship to a drug available from the HCP, the medical event validation team at ZEG Berlin will determine the likelihood of a causal relationship to the above defined medical product subject to the study for each adverse event in accordance with a predefined algorithm (cf. **Annex 3.2**) and general medical judgement.

The seriousness of an event will be judged on the basis of the accepted SAE/SADR definition given in ICH-E2A (see GVP Annex IV) by the medical event validation team. The version of the list of Designated Medical Events (DMEs) included as **Annex 4** is used to determine further serious cases, whenever none of the ICH-E2A seriousness-criteria are met.

This is an observational registry study where the primary outcome of interest is the assessment of major malformations in the fetus and newborn. The collection of non-serious adverse drug reaction (ADR) data is not foreseen. Dydrogesterone has been available on the market for pregnancy related indications for the last 60 years; dydrogesterone is indicated for early bleeding in pregnancy, recurrent pregnancy loss and IVF/ART support . The adverse event profile of the drug is well established, and the collection of these data will not add to the scientific literature available. Therefore, the other pharmacovigilance relevant information (OPRI) and the following non-serious ADRs will not be collected in this study:

- Nausea
- Abdominal pain
- Vomiting
- Diarrhea
- Dry mouth
- Indigestion
- Rash
- Itching
- Hives/ Urticaria
- Cough
- Breast swelling

- Depression (unless serious)
- Mood swings
- Trouble falling asleep
- Headache/Migraine
- Dizziness
- Somnolence
- Drowsiness
- Oedema
- Weight gain

All other non-serious ADRs reported will be provided in pseudonymised, tabulated form in the interim study reports, including non-serious ADRs under drugs that are not marketed by Abbott.

Serious adverse drug reactions (SADRs) will be reported via CIOMS-I form to the responsible MAH. In case an event is found to be serious only after the event assessment, a CIOMS-I report will be sent consecutively.

All malformations in fetus/newborns that will be validated and terminations of pregnancy with exposure to a medical drug will be reported to Abbott via CIOMS-I form regardless of their potential relationship to that medical drug and regardless of whether Abbott is the MAH of the drug that the study participant and the fetus were exposed to. The CIOMS-I form will include all available relevant information about the case.

The Safety Management Plan (SMP) shall set forth rules and procedures concerning pharmacovigilance reporting and shall supersede any and all prior pharmacovigilance and safety agreements.

ZEG Berlin will not monitor whether the marketing authorization holders meet their reporting obligations to the Health Authorities according to (inter)national rules.

8 Plans for disseminating and communicating study results

The study protocol and other relevant study materials will be submitted to the appropriate Ethical Committees (incl. the ethics committee of the Medical Association in Berlin, Germany and Data Privacy Officers in Germany). The study will be registered in the public study registry of the U.S. National Institutes of Health's (see http://clinicaltrials.gov) and the 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study database (see http://www.encepp.eu/encepp_studies/index.html). ZEG Berlin is planning to receive the ENCePP quality seal for this study.

Furthermore, it is planned to use the analysis dataset for scientific communication (e.g. peer-reviewed publication, conferences). Any publications concerning this study shall abide by the guidelines of the International Committee of Medical Journal Editors (ICMJE). All publications, presentations or other disclosure will be discussed with Abbott prior for submission.

A final study report will be developed by ZEG Berlin with the oversight of Abbott at the end of the study and presented to the SMAC. The final study report and all appendices will be compliant with STROBE statement (Strengthening the Reporting of Observational studies in Epidemiology) and RECORD statement (Reporting of studies Conducted using Observational Routinely collected health Data). The final approved study report will be submitted to registry databases ENCePP and clinicaltrials.gov.

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Annex 1. List of stand-alone documents

None

Annex 2. ENCePP checklist for study protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Maternal and Newborn Safety profile of Progestogens in EARLY pregnancy (PEARLY)

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

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

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

ENCePP Checklist for Study Protocols (Revision 4)
EMA/929209/2011
Page 1 of 6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	3
2.1.2 The objective(s) of the study?	☒	☐	☐	4
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	5.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	5.7.2
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	5.5

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	5.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	5.1
3.3 Does the protocol specify measures of occurrence? (e.g. rate, risk, prevalence)	☒	☐	☐	4
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH))	☒	☐	☐	5.7.2
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	7

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	5.2.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	5.2
4.2.2 Age and sex	☒	☐	☐	5.2.2.1
4.2.3 Country of origin	☒	☐	☐	5.2
4.2.4 Disease/indication	☒	☐	☐	5.2.2.1

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.2.5 Duration of follow-up	☒	☐	☐	5.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	5.2.1

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	5.2.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	5.9
5.3 Is exposure categorised according to time windows?	☒	☐	☐	5.7
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	5.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	--
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	5.7.2

Comments:

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	4
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	5.3.1 5.4
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	5.9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	--

Comments:

ENCePP Checklist for Study Protocols (Revision 4)
EMA/929209/2011

Page 3 of 6

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	5.3.2
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	5.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	5.9

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	5.7.2

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	5.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	5.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	5.3.2
9.2 Does the protocol describe the information available from the data source(s) on:				5.3.2
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☐	5.3.2
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☐	5.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	5.3.2
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	--
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	--
9.3.3 Covariates and other characteristics?	☐	☒	☐	--
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	--

Comments:

Coding will be described in the Data Management Plan

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	5.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	5.5
10.3 Are descriptive analyses included?	☒	☐	☐	5.7.1
10.4 Are stratified analyses included?	☒	☐	☐	5.7.2
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	5.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	5.9
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	5.7.4
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	5.7.2

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	5.10.1
11.2 Are methods of quality assurance described?	☒	☐	☐	5.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	5.10.4

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	5.9
12.1.2 Information bias?	☒	☐	☐	5.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	5.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☒	☐	--

Comments:

ENCePP Checklist for Study Protocols (Revision 4)
EMA/929209/2011

Page 5 of 6

Section 13: Ethical issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	5.10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	--
13.3 Have data protection requirements been described?	☒	☐	☐	6

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	1

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	8
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	8

Comments:

Name of the main author of the protocol: Clare Barnett

Date: 15-JULY-2021

Signature: 

ENCePP Checklist for Study Protocols (Revision 4)
EMA/929209/2011

Page 6 of 6

Annex 3. Additional information

Annex 3.1. Members of Scientific Medical and Advisory Council

Professor David Grimes (US, Chair) - *Specialty in Obstetrics, Gynaecology and preventative medicine*

Professor Sara Öberg (Sweden) - *Specialty in Epidemiology*

Professor Michael J. Rieder (Canada) – *Specialty in Paediatrics*

Professor Ying Cheong (UK) – *Specialty in IVF*

Dr. Roy Farquharson (UK) – *Specialty in Miscarriage*

Annex 3.2. Drug relationship [18].

Categories (Code)	Definition
no (1)	The time course between administration of the study drug and occurrence or worsening of the adverse event rules out a causal relationship and/or another cause is confirmed and no indication of involvement of the study drug in the occurrence/worsening of the adverse event exists.
unlikely (2)	The time course between administration of the study drug and occurrence or worsening of the adverse event makes a causal relationship unlikely and/or the known effects of the study drug or of the substance class provide no indication of involvement in occurrence/worsening of the adverse event and another cause adequately explaining the adverse event is known and/or regarding the occurrence/worsening of the adverse event a plausible causal chain may be deduced from the known effects of the study drug or the substance class, but another cause is much more probable and/or another cause is confirmed and involvement of the study drug in the occurrence/worsening of the adverse event is unlikely.
possible (3)	Regarding the occurrence/worsening of the adverse event, a plausible causal chain may be deduced from the pharmacological properties of the study drug or the substance class, but another cause just as likely to be involved is also known or although the pharmacological properties of the study drug or the substance class provide no indication of involvement in the occurrence/worsening of the adverse event, no other cause gives adequate explanation
probable (4)	The pharmacological properties of the study drug or of the substance class and/or the course of the adverse event after dechallenge and, if applicable, after rechallenge and/or specific tests (e.g. positive allergy test, antibodies against study drug/metabolites) suggest involvement of the study drug in the occurrence/worsening of the adverse event, although another cause cannot be ruled out.

definite (5)	The pharmacological properties of the study drug or of the substance class and the course of the adverse event after dechallenge and, if applicable, after rechallenge and specific tests (e.g. positive allergy test, antibodies against study drug/metabolites) indicate involvement of the study drug in the occurrence/worsening of the adverse event and no indication of other causes exists.

Annex 4. Designated Medical Event (DME) list

As a help to prioritise the review of reports of suspected Adverse Drug Reactions (ADRs) in the framework of the day-to-day pharmacovigilance activities the European Medicines Agency has developed the Designated Medical Event (DME) list. This is used by the European Medicines Agency, as well as EEA Member States, to identify reports of suspected ADRs that deserve special attention, irrespective of statistical criteria used to prioritise safety reviews. Therefore, the DME list serves as a safety net to ensure that signals are not missed.

The list includes MedDRA Preferred Terms that identify serious medical concepts often causally associated with drugs across multiple pharmacological/therapeutic classes. It may not address product specific issues, and conditions with high prevalence in the general population are excluded.

The content of the DME list is not definitive and may change as further experience with its use is gathered.

The DME list is published for transparency purposes only.

PT name
Acute hepatic failure
Acute kidney injury
Agranulocytosis
Anaphylactic reaction
Anaphylactic shock
Anaphylactoid reaction
Anaphylactoid shock
Angioedema
Aplasia pure red cell
Aplastic anaemia
Autoimmune haemolytic anaemia
Autoimmune hepatitis
Autoimmune pancreatitis
Azotaemia
Blindness
Bone marrow failure
Deafness
Deafness neurosensory
Deafness permanent
Deafness transitory
Dermatitis exfoliative
Dermatitis exfoliative generalised
Drug reaction with eosinophilia and systemic symptoms
Drug-induced liver injury
Erythema multiforme
Febrile neutropenia
Granulocytopenia
Haemolysis
Haemolytic anaemia
Hepatic failure

Hepatic infarction
Hepatic necrosis
Hepatitis fulminant
Immune thrombocytopenic purpura
Intestinal perforation
Ischaemic pancreatitis
Neutropenic colitis
Neutropenic infection
Neutropenic sepsis
Oedematous pancreatitis
Optic ischaemic neuropathy
Pancreatitis
Pancreatitis acute
Pancytopenia
Product contamination microbial
Progressive multifocal leukoencephalopathy
Pulmonary arterial hypertension
Pulmonary fibrosis
Pulmonary hypertension
Renal failure
Reye's syndrome
Rhabdomyolysis
Stevens-Johnson syndrome
Sudden cardiac death
Sudden hearing loss
Sudden visual loss
Thrombotic thrombocytopenic purpura
Torsade de pointes
Toxic epidermal necrolysis
Toxic optic neuropathy
Transmission of an infectious agent via product
Ventricular fibrillation

The DME list can be found under the following link:

https://www.ema.europa.eu/documents/other/designated-medical-event-dme-list_en.xls