Non-interventional
Post-authorisation Safety Study (PASS) Protocol

Title	A pregnancy exposure registry study to assess clinical follow-up and outcomes of pregnancies exposed to ulipristal acetate 30 mg.
Protocol version identifier	4.0
Date of last version of protocol	30.05.2023
EU PAS register number	EUPAS33796
Active substance	Ulipristal acetate Emergency Contraceptives (G03AD02)
Medicinal Product	A list of medicinal products relevant for this PASS is included in Annex 6.
Procedure numbers	AT/H/0862/001/DC AT/H/0863/001/DC AT/H/1373/001/DC EL/H/0295/001/DC ES/H/0873/001/DC NL/H/4221/001/DC NL/H/4223/001/DC NL/H/4224/001/DC NL/H/4226/001/DC NL/H/4227/001/DC NL/H/4228/001/DC NL/H/4229/001/DC NL/H/4446/001/DC NL/H/5170/001/MR 102648094 (STADA Switzerland) 102667640 (Sandoz Switzerland) 7007511 (duplicate STADA Germany) RVG 126381 (MA number for the Netherlands)
Marketing authorisation holders/ Marketing authorisation applicants	The joint initiative involves several companies via a consortium: Aristo Pharma GmbH Aspen Healthcare Malta Limited BIOGARAN ELPEN Pharmaceutical Co. Inc Exeltis Pharmaceuticals Holding, S.L. Farmitalia s.r.l. HELM AG Hexal AG Mylan Ireland Limited STADA Arzneimittel AG Zentiva Group, a.s.
Joint PASS	Yes

Research question and objectives	The MAHs wish to better investigate and assess specific risks discussed in the Risk Management Plan of the product, concerning failing anticonception and unwanted pregnancy outcomes. The primary objective of this pregnancy registry is to collect all data about pregnancy and pregnancy outcome in women exposed to ulipristal acetate 30 mg for any reason e.g. unrecognized pregnancy before intake or product failure. The secondary objective is to monitor the important potential risks "Effects on pregnancy maintenance/off-label use", "Risk of incomplete abortion and heavy bleeding", "Effects on foetus and newborns" and "Risk of ectopic pregnancy".
Countries of study	Austria, Czech Republic, Finland, France, Germany, Greece, Ireland, Italy, Liechtenstein, Malta, Netherlands, Norway, Poland, Portugal, Romania, Spain, Switzerland, United Kingdom
Author	[redacted]

Marketing authorisation holders

A list of the Marketing authorization holders (MAHs)/Marketing authorization applicants (MAAs) involved in this study is included in Annex 4.

1 Table of Contents

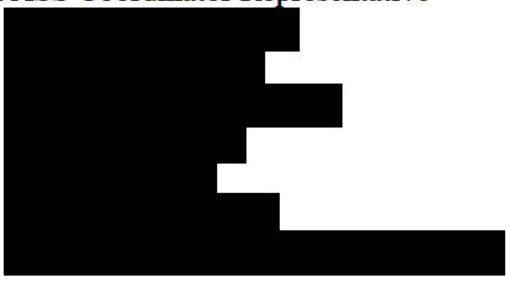
2 List of Abbreviations

D&C	Dilation and Curettage
EC	Ethics Committee
EEA	European Economic Area
EU PAS Register	European Union electronic Register of Post-Authorisation Studies
EURD	European Union Reference Dates
GDPR	General Data Protection Regulation
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professional
LGA	Large for gestational age
MAA	Marketing Authorisation Applicant
MAH	Marketing Authorisation Holder
NCA	National Competent Authority
PASS	Post Authorisation Safety Study
PIL	Patient Information Leaflet
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
SmPC	Summary of Product Characteristics
tbd	To be determined
UK	United Kingdom
URL	Uniform Resource Locator

3 Responsible Parties

For the purpose of this study, a Consortium was formed, consisting of the MAHs/MAAs listed in Annex 4. All MAHs/MAAs involved in the ulipristal consortium are sponsors of this study. The contact person of each MAH/MAA is also included in Annex 4. The Consortium has outsourced tasks relating to this study, such as writing of the protocol, set-up and maintenance of the registry, the study analysis, the writing of the study reports etc. to DADA Consultancy B.V. (PASS Coordinator). The PASS Coordinator Representatives, as listed below, are also the main contact persons for this PASS. A separate Consortium and Service Agreement outlines the responsibilities of each involved party. Information on the management of Adverse Events originating from the registry is included in section 11 of this protocol.

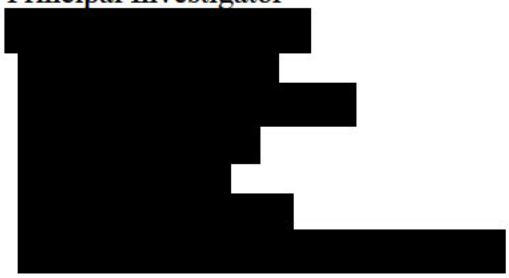
PASS Coordinator Representative



Date and signature

PASS Coordinator email address:

Principal Investigator



Date and signature

4 Abstract

Title	A pregnancy exposure registry study to assess clinical follow-up and outcomes of pregnancies exposed to ulipristal acetate 30 mg. Protocol version 4.0 Date of protocol: 30.05.2023 Author: DADA Consultancy B.V.
Background and Rationale	Ulipristal acetate (thereafter referred to as ulipristal) is a synthetic selective progesterone receptor modulator with antagonistic and partial agonistic effects on the progesterone receptor. It is used for preoperative treatment of uterine leiomyomas (5 mg/day) and for emergency contraception (30 mg orally within the first 120 hours) [**Ozturk-Akgul** (2017)]. By binding to the progesterone receptor, ulipristal stops the surge in luteinising hormone which occurs before ovulation. Ulipristal will therefore either inhibit or delay ovulation [**Aust Prescr** (2016)]. Data on exposure to ulipristal for emergency contraception during pregnancy is limited. Successful pregnancies following ulipristal treatment (5 or 10 mg daily) for symptomatic uterine leiomyomas have been reported [Luyckx et al (2014), Murad (2016), Monleón et al (2014) in **Ozturk-Akgul** (2017)]. In these cases though, subjects became pregnant after at least 3 months of ulipristal treatment termination. **Levy et al** (2014) and **Ozturk-Akgul** (2017) presented cases of pregnancies exposed to emergency contraception ulipristal. This data though, is not sufficient to address the important potential risks "effects on pregnancy maintenance/off-label use", "Risk of incomplete abortion and heavy bleeding", "Effects on foetus and new-borns", "Risk of ectopic pregnancy". Therefore, the Marketing Authorisation Holders (MAHs) of generic Ulipristal acetate 30 mg attempted to join the existing registry of the originator product. This was not possible due to denial of the originator's marketing authorisation holder. Therefore, the generic MAHs will set up and maintain a separate web-based registry and conduct a registry study, as described in this protocol. The MAHs confirm that only one joint registry study will be conducted for all generic products for which this protocol is relevant.
Research question & objectives	The MAHs wish to better investigate and assess specific risks discussed in the Risk Management Plan of the product, concerning failing anticonception and unwanted pregnancy outcomes. The primary objective of this pregnancy registry is to collect all data about pregnancy and pregnancy outcome in women exposed to ulipristal acetate 30 mg for any reason, e.g. unrecognized pregnancy before intake or product failure.

	The secondary objective is to monitor the important potential risks "Effects on pregnancy maintenance/off-label use", "Risk of incomplete abortion and heavy bleeding", "Effects on foetus and newborns" and "Risk of ectopic pregnancy".
Study Design	Post-marketing, non-interventional, web-based joint pregnancy registry. Retrospective collection of pregnancy data and pregnancy outcomes.
Target population and Key Selection Criteria	Pregnant women of any age in all European countries where the product will be launched are concerned, as far as they were exposed to Ulipristal 30 mg: • during the menstrual cycle in which the pregnancy started or • at any time during pregnancy
Variables collected	**<u>Variables collected from participating women</u>** • Subject identifier • Pregnancy information • Ulipristal exposure • Drugs other than Ulipristal received during pregnancy • Illness during pregnancy or chronic illness • Pregnancy outcome **<u>Variables collected from participating HCP</u>** • Patient ID • Pregnancy information • Ulipristal exposure • Elective abortion • Live birth • Congenital anomaly • Neonatal death • Maternal history • Drugs other than ulipristal received during pregnancy • Additional intake of ulipristal during pregnancy • Recreational drug use • Medical condition(s) during pregnancy • Results of serology tests • Prenatal tests • Foetal loss • Foetal loss complications
Data sources	Voluntary reporting of pregnancy exposure to ulipristal acetate 30 mg and pregnancy outcomes, by the women who have taken ulipristal acetate 30 mg or by their healthcare professional (HCPs). In the EEA countries (except Liechtenstein) and the UK, both the SmPC and the PIL of ulipristal acetate 30 mg will include information on this registry study and how to access it, so that consumers and HCPs become aware of its existence. Reporting of pregnancy exposures on ulipristal acetate 30 mg to the pregnancy registry is voluntary.

<table>
<tr><td></td><td>The landing page of the registry for EEA-countries (except Liechtenstein) and the UK (https://www.ulipristal-pregnancy-registry.com) contains information on how to fill-in the data and the purpose of the registry. Data entry is done by the women themselves and/or their HCPs.
In Switzerland and Liechtenstein HCPs are informed about the existence of this registry in the SmPC and requested to report pregnancies directly to the MAH, who will send the request to DADA. DADA will then provide the registry link to the HCPs. In addition, the landing page of the registry for EEA-countries and the UK requests HCPs from Switzerland and Liechtenstein to contact DADA to receive the link to the reporting environment for Swiss and Liechtenstein cases. The Swiss PIL does not contain any information on the registry; hence, women are not asked to provide information on their pregnancies.</td></tr>
<tr><td>Study size</td><td>The pregnancy registry will continue to include subjects for as long as the registry of the innovator product includes subjects.</td></tr>
<tr><td>Data analysis</td><td>Descriptive statistics will be the primary approach for summarizing data from the pregnancy exposure registry. Data will be presented for all subjects enrolled and included in the registry.</td></tr>
<tr><td>Milestones</td><td>
<table>
<tr><th>Milestone</th><th>Planned date</th></tr>
<tr><td>Set up of registry database finalised</td><td>Before product launch (May 2020)</td></tr>
<tr><td>Start of data collection</td><td>Immediately after registry database finalisation and in synchrony with product launch</td></tr>
<tr><td>End of data collection</td><td>The registry will be open for as long as the registry of the originator product includes subjects</td></tr>
<tr><td>Study progress reports</td><td>Yearly; the first report will cover a one-year period post the enrolment of the first patient in the registry.</td></tr>
<tr><td>Interim study reports</td><td>Yearly, along with the study progress report</td></tr>
<tr><td>Registration in EU PAS register</td><td>24 February 2020</td></tr>
<tr><td>Final report of study results</td><td>Six months after the end of data collection</td></tr>
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5 Amendments and updates

Neither the MAHs nor the PASS Coordinator will modify the protocol without prior written agreement of the other party. Changes in any part of the protocol must be documented in the Study Protocol Amendment and approved by the MAHs QPPVs. All amendments that would increase the risk to the subject or may alter the results of the study, must be re-submitted to the Ethics Committee(s) and to regulatory authorities.
If the changes in Study Protocol involve only logistical or administrative aspects [e.g. telephone number(s)], written approvals are necessary from all MAHs, but the changes are not submitted to the Ethics Committee(s) and regulatory authorities.

The list of medicinal products and countries of study as appear under PASS information on the cover page of this protocol, as well as the list of the Consortium members, as appear in Annex 4 may often be updated throughout the duration of this study. These changes will be considered of administrative nature. However, in case the registry goes live in a country not mentioned in the list of countries of this protocol (page 2), the amended protocol will be submitted to the applicable NCAs and ECs, as needed.

Version	Changes
Version 0.1	Not applicable, first version
Version 0.2	Protocol amended according to the comments by the Reference Member State (NL) during the assessment of concerned procedures. Milestones, objectives, inclusion criteria, FU procedure were amended as requested.
Version 0.3	Protocol amended according to the comments by the Reference Member State (NL) during the assessment of concerned procedures. The most recent change in the EURD list was captured (yearly PSURs are not applicable for generic products).
Version 1.0	Protocol amended to include/update information after a database vendor was selected. Format changes also occurred (dividing wording in newly-created sections) and a section on “Management and reporting of adverse events/adverse reactions” was added. The questionnaires were slightly amended. Protocol transferred to EMA PASS protocol template.
Version 2.0	Protocol amended to include the updated list of MAHs/MAAs that comprise the consortium and the updated lists of procedure numbers, countries of study and medicinal products relevant for this PASS. This amendment was of administrative nature.
Version 3.0	Addition of Switzerland, Czech Republic, and United Kingdom. Error in secondary objective corrected. Addition of Biogaran. Changes in MAHs and their contact persons. Minor linguistic changes. Update in list of procedures included in this PASS, and update of the accompanying list of products. Change in registered name of the database provider.
Version 4.0	Addition of Malta and Liechtenstein. Change in MAH QPPV and change in MAH contact address. Update in list of procedures included in this PASS, and update of the accompanying list of products. Procedure for HCP sign-up in Switzerland/ Liechtenstein clarified and information for physicians in Switzerland and Liechtenstein (Annex 5 C) updated.

6 Milestones

Milestone	Planned date
Set up of registry database finalised	Before product launch (May 2020)
Start of data collection	Immediately after registry database finalisation and in synchrony with product launch
End of data collection	The registry will be open for as long as the registry of the originator product includes subjects
Study progress reports	Yearly; the first report will cover a one-year period post the enrolment of the first patient in the registry.
Interim study reports	Yearly, along with the study progress report
Registration in EU PAS register	24 February 2020
Final report of study results	Six months after the end of data collection

7 Rationale and Background

Ulipristal acetate (thereafter referred to as ulipristal) is a synthetic selective progesterone receptor modulator with antagonistic and partial agonistic effects on the progesterone receptor It is used for preoperative treatment of uterine leiomyomas (5 mg/day) and for emergency contraception (30 mg orally within the first 120 hours) [**Ozturk-Akgul** (2017)]. By binding to the progesterone receptor, ulipristal stops the surge in luteinising hormone which occurs before ovulation. Ulipristal will therefore either inhibit or delay ovulation [**Aust Prescr** (2016)].

Data on exposure to ulipristal for emergency contraception during pregnancy is limited. Successful pregnancies following ulipristal treatment (5 or 10 mg daily) for symptomatic uterine leiomyomas have been reported [Luyckx et al (2014), Murad (2016), Monleón et al (2014) in **Ozturk-Akgul** (2017)]. In these cases though, patients became pregnant after at least 3 months of ulipristal treatment termination.

Levy et al (2014) presented safety data for ulipristal for emergency contraception (30 mg) collected via the originator's post marketing surveillance activities since 2009. These data originated from spontaneous reports from HCPs, either directly or through the existing web-based pregnancy registry, literature and reports received by regulatory authorities.

Internal sales data estimated that over 1,400,000 individual women have been exposed to ulipristal for emergency contraception worldwide. Between 1st October 2009 and 14th May 2013, 553 women from 23 countries reported 1049 suspected adverse drug reactions (ADRs). Pregnancy was one of the most reported adverse reactions (282 cases). The timing of drug exposure was not known in 45% of cases. A total of 81 cases with known outcome were exposed before conception, while only 9 were reported as being inadvertently exposed when pregnancy had already started, among which only 2 pregnancies went to term [**Levy et al** (2014)].

All 20 delivered babies were declared to be healthy by the reporter. Among the elective terminations, one case of trisomy 21 foetus in a 42-year-old woman was reported; as she was already 6+ weeks of amenorrhea when she took the drug, this genetic anomaly was considered unlikely to be related to exposure. One case of foetal cardiac defect discovered at 12 weeks of pregnancy was terminated at 13 weeks and the relationship to the drug was assessed as uncertain by the reporter. Four ectopic pregnancies were reported during the post-marketing surveillance, the time of exposure for 2 of these is unknown and no risk factors for ectopic pregnancy have been reported [**Levy et al** (2014)].

Combining pregnancies from post-marketing reports (282) with those from the developmental studies of ulipristal, result in a total of 376 exposed pregnancies reported. Of these, 232 (62%) had a known outcome, 83 (88%) from clinical trials and 149 (53%) from post marketing reports. These pregnancies resulted in 28 live births (29 newborns), 8 from clinical trials and 20 from post-marketing reports; 34 first-trimester spontaneous miscarriages (17 each from clinical trials and post-marketing reports) and 151 induced abortions (58 from clinical trials and 93 from post-marketing data). One newborn was diagnosed with optic nerve atrophy which, on evaluation by an independent Data Safety Monitoring Board, was not attributed to ulipristal exposure in utero; no other anomalies have been reported [**Levy et al** (2014)].

No complications during the course of a pregnancy or delivery were reported. The observed rate of miscarriages (13.8%) compared favourably to the 20% rate reported in the general

population. There was also no indication of an increased rate of ectopic pregnancy following ulipristal 30 mg exposure (1.1%) when compared with the rate observed in the general population [**Levy et al** (2014)].

Ozturk-Akgul (2017) described five cases of unintended pregnancies following the use of ulipristal for emergency contraception. Pregnancy outcomes in women who seeked teratology consultation after exposure to ulipristal (30 mg) between January 2013 and December 2016, were analysed. Five pregnant women were exposed to ulipristal, one of whom decided to terminate the pregnancy for personal reasons. Two of them experienced premature rupture of membranes and the babies were born large for gestational age (LGA). The other two women experienced gestational diabetes, and one of them also delivered an LGA baby. The blood glucose levels of the mothers were normal after delivery and at six weeks postpartum. No birth defects and no growth or developmental abnormalities for the infants were reported during 6 months follow-up.

Data regarding inadvertent ulipristal (30 mg) exposure in early pregnancy or exposure resulting from lack of efficacy, that were discussed above, are not sufficient to address the important potential risks “Effects on pregnancy maintenance/off-label use”, “Risk of incomplete abortion and heavy bleeding”, “Effects on foetus and newborns” and “Risk of ectopic pregnancy”. The involved MAHs sought to join the existing registry of the originator product. This was not possible due to denial of the originator’s product marketing authorisation holder. Therefore, the MAHs will set up a separate web-based registry as described in this protocol. The MAHs confirm that only one joint registry study will be conducted for all generic products for which this protocol is relevant.

8 Research question and objectives

Based on the information above, the concerned MAHs wish to better investigate and assess specific risks discussed in the Risk Management Plan of the product concerning failing anticonception and unwanted pregnancy outcomes.

The primary objective of this pregnancy registry is to collect all data about pregnancy and pregnancy outcome in women exposed to ulipristal acetate 30 mg for any reason, e.g. unrecognized pregnancy before intake or product failure.

The secondary objective is to monitor the important potential risks “Effects on pregnancy maintenance/off-label use”, “Risk of incomplete abortion and heavy bleeding”, “Effects on foetus and newborns” and “Risk of ectopic pregnancy”.

9 Research methods

Drugs that are registered in Switzerland are also authorized for sales in Liechtenstein and can automatically be sold in Liechtenstein. Therefore, for products marketed in Liechtenstein based on a marketing authorisation in Switzerland, the study design in Switzerland applies (see section 9.1.2). If in the protocol explanations are given on the process in Switzerland, Liechtenstein cases are always included even if Liechtenstein is not always explicitly mentioned.

9.1 Study design

9.1.1 Study design in EEA countries (except Liechtenstein) and the UK

This will be a joint PASS based on the data collected via the joint web-based pregnancy registry (primary data collection). On the landing page of the registry website (https://www.ulipristal-pregnancy-registry.com), there will be two environments to choose from; one for women and one for HCPs.

The reporting environment (Annex 5.A) for women will include information on the registry and a statement that the data is collected confidentially (only with subject identifiers, as outlined in section 9.3), as well as information on the study purpose and a link to the registry data privacy notice which explains how their personal data will be handled. After filling in pregnancy and ulipristal exposure information, women will be asked to provide the contact details of their HCP and further follow-up will be attempted with the HCP, who will be asked to participate in the registry and complete the digital questionnaire. This will be done via email, sent via the database after the woman has completed the questionnaire.

Women will be encouraged to enter their data as early as possible after the pregnancy has been diagnosed. To make sure that adequate information on each pregnancy course and pregnancy outcome is collected, follow-up with each woman will be attempted as follows:

- 10 weeks after the initial report
- At the expected delivery date
- If no answer is received, two additional follow up requests will be sent with a one-month interval.

This follow-up will be conducted via email sent through the database. In the email, a link will be provided, via which the woman will be able to complete the questionnaire with any new information.

The reporting environment for HCP will also include information on the study and handling of data and will additionally provide HCPs with two options:

- register a new patient in the registry (this can be a woman who has entered information on her own or a woman whose data does not yet exist on the database), or
- further report the pregnancy outcome of a patient already registered by the same HCP.

The latter choice is to facilitate the possibility for HCPs to interrupt data entry and enter pregnancy results at a later date, when new information become available. HCPs will in such case provide some personal details (name of HCP and email address) so that the new information can be linked to the already existing one. However, HCPs will also be encouraged to fill in the complete form in one session, should they have this information available. The information on the registry for the HCPs is included in Annex 5.B.

To make sure that adequate information on each pregnancy course and pregnancy outcome is collected and that complete data is collected also from HCPs who will not voluntarily return to report follow-up information, follow-up with HCPs will be attempted as follows:

- 10 weeks after the initial report
- At the expected delivery date
- If no answer is received, two additional follow up requests will be sent with a one-month interval.

This follow-up will be conducted via email through the database. In the email, a link will be provided, via which the HCP will be able to complete the questionnaire with any new information.

9.1.2 Study design in Switzerland and Liechtenstein

The general study design is identical in Switzerland and Liechtenstein to the design in the EEA countries and the UK. The difference is in how HCPs are made aware of the registry and that women are not asked to provide information on their pregnancies; in alignment with the originator's PIL in Switzerland, the Swiss PIL does not contain any information on the registry. Cases from Switzerland and Liechtenstein are captured in a separate reporting environment of the registry, which can be accessed via a separate link.

The SmPC of the Swiss product contains a request to HCPs to report pregnancies directly to the MAH in Switzerland. When the MAH receives a notification from an HCP, it forwards the notification to DADA, who will then respond to the HCP via email, thereby providing the data protection information specific for Switzerland and Liechtenstein, information on the study and the link to the reporting environment for HCPs in Switzerland and Liechtenstein.
In addition, the landing page of the registry for EEA-countries and the UK advises HCPs from Switzerland and Liechtenstein to contact DADA to receive the link to the reporting environment for Swiss and Liechtenstein cases. Should a Swiss or Liechtenstein HCP contact DADA directly via [redacted] for access to the registry, DADA will similarly send out an email containing the data protection information specific for Switzerland and Liechtenstein, information on the study and the link to the reporting environment for HCPs in Switzerland and Liechtenstein. In parallel, DADA will also alert the applicable MAH.

Once an HCP has entered the reporting environment, the process is exactly the same as described in section 9.1.1

9.2 Setting

9.2.1 Study Duration

The registry will be open for as long as the registry of the originator product includes subjects.

9.2.2 Study Population

Inclusion Criteria
Pregnant women of any age in all European countries where the product will be launched are concerned, as far as they were exposed to Ulipristal 30 mg:

- during the menstrual cycle in which the pregnancy started or
- at any time during pregnancy.

Number of Subjects
This pregnancy exposure registry will continue to include subjects for as long as the registry of the innovator product includes subjects.

Exclusion criteria

Women that have not consumed ulipristal 30 mg during pregnancy will be excluded from analysis of the study.

Subjects discontinuation and withdrawal
Each woman/HCP has the right not to accept the registry data privacy notice on the landing page of the registry. If they don't click "I took note of the registry data protection notice", they would not be allowed to proceed with answering the registry questions.
There is a possibility to stop answering questions in the registry questionnaire at any time while entering the data in the database.
Participants will be free to withdraw from the registry at any time with future effect.

9.2.3 Study processes

Study medication
In a non-interventional way, women exposed to ulipristal 30 mg during pregnancy, or HCPs whose patients were exposed to ulipristal 30 mg during pregnancy are asked to participate in this pregnancy exposure registry. In Switzerland and Liechtenstein only HCPs are asked to participate.

Study procedures
Both the SmPC and the PIL (except for Swiss products) include information on this registry, so that consumers and HCPs become aware of its existence and how to access it. Swiss and Liechtenstein HCPs are informed about the existence of this registry in the SmPC and requested to report pregnancies directly to the MAH, who will send the request to DADA. DADA will then provide the registry link to the HCPs. In addition, the landing page of the registry for EEA-countries and the UK advises HCPs from Switzerland and Liechtenstein to contact DADA to receive the link to the reporting environment for Swiss and Liechtenstein cases. DADA will then provide the registry link to the HCPs and alert the applicable MAH.
The Swiss PIL does not contain any information on the registry.
Reporting of pregnancy exposures to Ulipristal 30 mg to the pregnancy registry is voluntary.
In case participation to the registry is low, appropriate actions will be proposed within the study progress report.

9.3 Variables

9.3.1 Exposure

Exposure in this study is defined as exposure to ulipristal 30 mg at any time-point during pregnancy or during the menstrual cycle in which the pregnancy started.

9.3.2 Study outcomes

The aim of this pregnancy registry is to collect all data about pregnancy outcome in women exposed to ulipristal 30 mg for any reason e.g. unrecognized pregnancy before intake or product failure.

Information on specific safety concerns will be gathered through this pregnancy exposure registry. These safety concerns are the important potential risks: "Effects on pregnancy

maintenance/off-label use", "Risk of incomplete abortion and heavy bleeding", "Effects on foetus and newborns" and "Risk of ectopic pregnancy".

9.3.3 Other study variables

Variables collected from participating women (only in EEA countries and the UK)

- Subject identifier
  - Date of birth
  - First name initial
  - First three letters of last name
  - Email address
  - Weight
  - Height
- Pregnancy information
  - Date of diagnosis
  - Method of diagnosis
  - Date of last menstrual period
  - Expected delivery date
- Ulipristal exposure
  - Date of ulipristal intake
  - Total dose administered
  - Time from unprotected intercourse to ulipristal intake
  - Pregnancy stage at ulipristal exposure
  - Use of ulipristal on several dates?
  - Brand name of ulipristal
  - Country where ulipristal was bought
- Drugs other than Ulipristal received during pregnancy
  - Medication name
  - Indication
  - Daily dose
  - Route of administration
  - Period of exposure during pregnancy
- Illness during pregnancy or chronic illness
  - Medical condition
  - Start date
  - Stop date
  - Ongoing at the time of outcome?
- Pregnancy outcome
  - Is the pregnancy still ongoing?
    - If yes: expected delivery time?
    - If no: the following information will be requested
  - Elective abortion
    - Date of procedure
  - Live birth
    Healthy child(ren)
    - Pregnancy term in weeks
    - Number of children born
    - Sex of children born
    - Weight of children born

Congenital anomaly
- Concomitant medications
- Intake of alcohol
- Intake of recreational drugs

Neonatal death
- Concomitant medications
- Intake of alcohol
- Intake of recreational drugs

  - Induced therapeutic abortion / Foetal death (>20 weeks of pregnancy) / Ectopic pregnancy
    - Concomitant medications
    - Intake of alcohol
    - Intake of recreational drugs
  - Spontaneous abortion
    - Medical follow-up needed?
    - Curettage or D&C needed?
    - Previous miscarriages?
    - Concomitant medications
    - Intake of alcohol
    - Intake of recreational drugs
- Contact details of HCP

Variables collected from participating HCPs
- HCP contact details
- Patient ID
  - Date of birth
  - First name initial
  - First three letters of last name
  - Email address
- Pregnancy information
  - Date of diagnosis
  - Date of last menstrual period
  - Expected delivery date
- Ulipristal exposure
  - Date of ulipristal intake
  - Total dose administered
  - Time from unprotected intercourse to ulipristal intake
  - Pregnancy stage at ulipristal exposure
  - Pregnancy status before ulipristal intake
  - Brand name of ulipristal
  - Country where ulipristal was bought
- Elective abortion
  - Date of procedure
- Live birth
  - Healthy child(ren)
    - Pregnancy term in weeks
    - Number of children born
    - Sex of children born
    - Weight of children born

- Congenital anomaly
  - Pregnancy term in weeks
  - Number of children born
  - Delivery method
  - List of congenital anomalies
  - Relationship to ulipristal intake & other possible causes
  - Apgar scores (1 min, 5 min)
- Neonatal death
  - Pregnancy term in weeks
  - Number of children born
  - Delivery method
  - Age of neonate at death
  - Cause of death
  - Relationship to ulipristal intake
  - Autopsy performed
  - Apgar scores (1 min, 5 min)
- Maternal history
  - History of pregnancy
  - History of spontaneous abortion (miscarriage)
  - History of foetal death
  - History of elective abortion
  - History of therapeutic abortion
  - History of birth defect
  - Maternal family history of congenital anomaly
  - Other significant family history
- Drugs other than ulipristal received during pregnancy
  - Medication name
  - Indication
  - Daily dose
  - Route of administration
  - Period of exposure during pregnancy
- Additional intake of ulipristal during pregnancy
  - Period of exposure during pregnancy
- Recreational drug use
  - Estimated weekly dose
  - Route of administration
  - Period of exposure during pregnancy
- Medical condition(s) during pregnancy
  - Medical condition
  - Start date
  - Stop date (if applicable)
- Results of serology tests
  - Rubella test
  - Toxoplasmosis test
- Prenatal tests
  - Type of test
  - Test date
  - Evidence of structural defect
- Foetal loss

  - Placenta pathology examination
  - Pregnancy term in weeks at time of foetal loss
  - Number of foetus(es)
  - Relationship to ulipristal intake
  - Factors that may have had an impact on foetal loss
  - In case of ectopic pregnancy
    - Salpingitis or known tubal anomaly
    - Previous ectopic pregnancy
    - Previous tubal surgery
- Foetal loss complications
  - Vaginal bleeding
  - Blood transfusion
  - Curettage
  - Infection
- Other complications

The first letter of the first name and the first three letters of the last name of participating women as well as the birth date are needed in order to prevent duplication of reports, when HCPs and women report the same pregnancy data. These identifiers will not be forwarded to the MAHs, but will only be kept in the database.
Email addresses are needed in order to enable specific functionalities in the registry database; Women will receive automated emails via the database on specified timepoints that will allow them to continue data entry, as described in section 9.1.

When a woman fills in the contact details of her HCP, the latter will be contacted by email and requested to participate in the registry and answer the digital questionnaire. When a HCP fills in information of a woman that does not yet exist on the database, he will be asked to provide his contact details. HCPs will receive automated emails via the database on specified timepoints that will allow them to continue data entry, as described in section 9.1.

9.4 Data sources

Both the SmPC and the PIL (except for Swiss products) include information on this registry, so that women and HCPs become aware of its existence and how to access it. Reporting of pregnancy exposures to ulipristal 30 mg is voluntary. Women and HCP will be encouraged to report pregnancies as early as possible after pregnancy has been diagnosed. Swiss and Liechtenstein HCPs are informed about the existence of this registry in the SmPC and requested to report pregnancies directly to the MAH, who will send the request to DADA. DADA will then provide the registry link to the HCPs. In addition, the landing page of the registry for EEA-countries and the UK advises HCPs from Switzerland and Liechtenstein to contact DADA to receive the link to the reporting environment for Swiss and Liechtenstein cases. DADA will then provide the registry link to the HCPs and alert the applicable MAH.
The Swiss PIL does not contain any information on the registry.

Data collection is done via an online questionnaire. The landing page of the registry for EEA countries and the UK will contain information on how to fill-in the data and the purpose of the registry. Data entry is done by the women themselves and/or their HCPs. The link provided to Swiss and Liechtenstein HCPs does not lead to the landing site, but directly to the data

collection environment. The email with the link to the Swiss and Liechtenstein reporting environment also contains the information otherwise included on the landing page.

The proposed questionnaires are included in Annex 3 of this protocol. The information included may be slightly altered while setting up the registry (as a result of the user acceptance test), but without changing the content of the questions. Functional ergonomics such as linked questions will be included in the digital questionnaires and are not depicted in Annex 3.

9.5 Study size

The registry will be open for as long as the registry of the originator product includes subjects.

9.6 Data management

In EEA countries (except Liechtenstein) and the UK, data will be collected from women and HCPs through a self-reported, internet-based questionnaire accessed through https://www.ulipristal-pregnancy-registry.com. This URL will be included in the product information. Swiss and Liechtenstein HCPs are informed about the existence of this registry in the SmPC and requested to report pregnancies directly to the MAH, who will send the request to DADA. DADA will then provide the registry link to the HCPs. In addition, the landing page of the registry for EEA-countries and the UK advises HCPs from Switzerland and Liechtenstein to contact DADA to receive the link to the reporting environment for Swiss and Liechtenstein cases. DADA will then provide the registry link to the HCPs and alert the applicable MAH.
The Swiss PIL does not contain any information on the registry.
The questions to be included in this digital questionnaire are included in Annex 3.
For the collection of data, an Electronic Data Capture system will be used: SMART-TRIAL, developed by SMART-TRIAL ApS. The oversight of the registry functioning will be ensured by the PASS Coordinator through ad hoc alerts (receipt of alert when a new pregnancy report or follow-up is added to the database) and subsequent review. The data capture tool is under 24/7 surveillance by SMART-TRIAL, so that if a server becomes unavailable, the SMART-TRIAL personnel is immediately notified such that a resolution can be found as quickly as possible. The database will be checked weekly and compared to emails received to detect whether automatic alerts are received in good order. Quality of reports is checked upon receipt of the automated alerts (when a pregnancy report or follow-up is added to the database), as well as with quarterly spot checks and review of audit trails. An effort to align identified inconsistencies will be made by following up with the reporter, as described in section 9.1
Since this will be a joint PASS, each MAH/MAA will receive data on their own products as captured in the registry database, that will be included in the applicable MAHs safety databases and submitted to EudraVigilance and/or other stakeholders, when applicable. When data entered in the database cannot be linked to a single product, all MAHs/MAAs of the Consortium marketing ulipristal acetate 30 mg in the country of origin will receive this information. The PASS coordinator will create the interim study reports, the study progress reports and the final report of study results based on the data available on SMART-TRIAL and making sure there are no inconsistencies between these reports and the events as coded by each MAH. Translation of free text fields to English will be performed, either for each case individually by each MAH/MAA when they receive a pregnancy case, or periodically by the PASS coordinator, while writing the above-mentioned reports.

All statistical analysis will be performed utilizing SAS Analytics Pro, SAS Institute©. Software used for data collection and statistical analysis are 21 CFR part 11 compliant.

9.6.1 Record retention

All data in relation to the registry database software (SMART-TRIAL) is stored on secured Microsoft Azure hardware located in the EU, i.e. Dublin, Ireland. Due to security measures, and conformity regulations with international and country-specific standards, Microsoft does not disclose the details of physical addresses of its data centres to any of its customers, including SMART-TRIAL ApS (registry database software provider). Therefore, SMART-TRIAL ApS cannot, and will not, require Microsoft to disclose the physical location in more detail. However, SMART-TRIAL and Microsoft ensure that all data is stored and backed up within this same geographical location.

Data downloaded from the database will be stored on the MAH/MAA's and PASS Coordinator's servers and will be handled and retained according to internal procedures. MAHs may process this data also in non-EU countries.

9.7 Data analysis

Descriptive statistics will be the primary approach for summarizing data from the pregnancy exposure registry. Data will be presented for all subjects enrolled in the registry.
Subjects' age, number of ulipristal doses, time from unprotected intercourse to administration of ulipristal (in case of ulipristal failure) or weeks of gestational age at exposure (in case of inadvertent exposure to ulipristal during pregnancy) will be summarised using descriptive statistics for continuous variables, while concomitant medications, type of delivery, pregnancy outcome, adverse events during pregnancy, embryo-foetal outcome, infant status, and cytogenetic abnormalities will be summarised with descriptive statistics appropriate for categorical data.
No stratified analysis is foreseen or has been planned for this study.
The most recent MedDRA version at the time of analysis (or at the time of processing, for data already coded before periodic analysis) will be used for the presentation of any reported pregnancy outcome information.

9.7.1 Missing data and Loss to Follow-up

Women and HCPs will be approached to obtain complete information, as described in section 9.1. If nevertheless, a woman/HCP chooses to not answer all of the questions within the registry questionnaire, the data provided will be included in the overall analysis only regarding the completed fields. Descriptive statistics will therefore reflect responses per question.

9.7.2 Annual analysis

An interim study report will be submitted annually. The first interim analysis will cover a one-year period post the enrolment of the first patient in the study. No stopping rules have been formulated and the MAHs/MAAs reserve the right to discontinue the study for any reason, e.g. withdrawal of all ulipristal acetate 30 mg marketing authorisations or insufficient enrolment. The study will only be stopped in consultation with the applicable authorities and committees.

9.8 Quality Control

Since the participating women and HCPs will complete the questionnaires on their own, quality control of responses is not applicable. However, while configuring the database and the digital questionnaires, special attention will be given when creating the response options, so that the possibility of errors/mistakes during data entry is minimised.

Access to the registry database for data processing purposes by approved personnel will be regulated by the PASS coordinator. The PASS Coordinator will be responsible for defining which permissions individual users have within the database, enabling or disabling specific rights for users that may need access to the data. This will allow the PASS coordinator to specify in detail what information/actions each user will have access to.

A full audit log (audit trail) will be recorded and stored for every action regarding this registry in SMART-TRIAL, i.e. viewing, creating, updating, deleting. The PASS coordinator, or those allowed access to the audit log, will be able to both review these actions, specific attribute changes and export the complete log.

User acceptance testing (UAT) of consumers and HCPs will be supervised by the PASS coordinator and performed by an external vendor with extensive experience in the field. The UAT will be performed in the English version. According to the results, the questionnaires may be slightly updated, only with regards to how questions are stated and not changing the content of the questions. Thereafter, a translation in all applicable languages, by a certified translator will follow. The results of the user acceptance test will be documented in a validation report.

A separate Data Management Plan will be created, that will describe all data management processes and quality controls in place.

9.9 Limitations of the research methods

This registry aims to collect data from pregnant women who were exposed to ulipristal 30 mg at any time-point during pregnancy or during the menstrual cycle in which the pregnancy started, and from HCPs of such women. In EEA countries (except Liechtenstein) and the UK, both the SmPC and the PIL include information on this registry, so that consumers and HCPs become aware of its existence and how to access it. Swiss and Liechtenstein HCPs are informed about the existence of this registry in the SmPC and requested to report pregnancies directly to the MAH, who will send the request to DADA. DADA will then provide the registry link to the HCPs. In addition, the landing page of the registry for EEA-countries and the UK advises HCPs from Switzerland and Liechtenstein to contact DADA to receive the link to the reporting environment for Swiss/Liechtenstein cases. DADA will then provide the registry link to the HCPs and alert the applicable MAH.
The Swiss PIL does not contain any information on the registry. Therefore, it is possible that enrolment to this study is low, due to non-awareness of its existence by the target population. Additionally, reporting of pregnancy exposures to ulipristal is voluntary, which may also be a factor leading to low enrolment.

As mentioned already, data will be added into the registry directly by the women and/or HCPs. An additional limitation is the potential for incomplete or inconsistent data, as provided by women and/or HCPs in spite of the implemented follow-up process described in 9.1.

In EEA countries (except Liechtenstein) and the UK it is also possible that data provided by a woman and her HCP contradict each other. Follow-up with the HCP will be attempted in order to clarify these discrepancies, using a request for clarification process of the Electronic Data Capture system. In any case, information as given by the HCP will overrule the information as provided by a woman.

Last, when a woman enters data in the database, she may not provide her HCP's contact details. In such a case, medical confirmation of the case will not be possible (only applicable in EEA countries and the UK).

10 Protection of human subjects

Data processing is necessary to the extent described in this protocol for MAH`s compliance with the legal obligation of pharmacovigilance activities, as the registry was imposed by European Health Authorities based on Article 9(4)(cb) of Regulation No 1235/2010 and Article 21a(b) of Directive 2010/84/EU. The marketing authorization applications of ulipristal in Switzerland were based on Article 13 of the Swiss Therapeutic Products Act (TPA), and are automatically valid in Liechtenstein. Accordingly, the same requirements apply in Switzerland and Liechtenstein as in the EEA countries and the UK. Therefore, in the EEA countries, the UK, Switzerland and Liechtenstein, informed consent is not required in this registry.
Before women / HCPs in the EEA countries and the UK can enter data into the questionnaires they need to confirm that they have taken note of the registry data privacy notice and only then will they participate in the registry.
In the email sent to Swiss and Liechtenstein HCPs they are informed that by signing up via the link provided in the email, they confirm that they have read and accept the privacy notice attached to the email and that they have obtained permission from their patient to provide her information.

Personal information will be collected as outlined in section 9.3. The PASS Coordinator needs these details in order to identify duplicates in SMART-TRIAL, when HCPs report pregnancy cases and be able to connect women- and HCP- reported pregnancies.

The MAHs/MAAs, the PASS Coordinator and the database vendor are compliant with the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation; GDPR) as well as the Swiss Federal Act on Data Protection and the Data Protection Act of 2018 as valid for UK.

As the study is non-interventional, the women are treated as they would be if they were not participating in the registry. This will be an online registry. Participants are informed on the purpose of the registry and requested to take note of the registry data privacy notice as described in Annex 5.
The first letter of the first name, first three letters of last name and date of birth are needed in order to prevent duplication of reports, when HCPs and women report the same pregnancy, email addresses are needed to enable functionalities in the registry study database; women and HCPs will receive automated emails containing a link that will allow them to continue filling in their data on defined timepoints, as described in section 9.1.

In EEA countries (except Liechtenstein) and the UK HCPs will be contacted and requested to participate in the registry, when a woman fills in her HCP's contact details in the digital questionnaire.

To comply with GDPR 679/2016 (General Data Protection Regulation; GDPR) as well as the Swiss Federal Act on Data Protection and the UK Data Protection Act of 2018, in the versions of the (interim) study reports submitted to the different authorities/ethical committees, cases originating in another region (EEA countries, UK or Switzerland and Liechtenstein) will be blacked out.

10.1 Regulation statement

The study will be conducted in accordance with Good Pharmacovigilance Practices, Good Pharmacoepidemiology Practices, applicable local regulatory requirements and in compliance with the Declaration of Helsinki.

10.2 Recruitment

The landing site of the registry for EEA countries (except Liechtenstein) and the UK as well as the email to Swiss and Liechtenstein HCPs will present information on the registry, including (this is not an exhaustive list):

- Description of the registry and its intended purposes
- Information on confidentiality and a link to the registry data privacy notice
- Amount of time that the subject's data will be kept on the database

In EEA countries (except Liechtenstein) and the UK, the woman/HCP will be asked to take note of the registry data privacy notice. Only then will the woman/HCP be able to continue and participate in this registry. Swiss/Liechtenstein HCPs will be informed in the email that by following the link to the Swiss/Liechtenstein reporting environment in the email they agree to the privacy notice attached to the email and that they have obtained permission from their patient to provide her information. Participants will be free to withdraw from the registry at any time with future effect.

10.3 Burdens to the subject

The burden to the participating women/HCPs is no more than it would be without inclusion in the registry, as this is a non-interventional study.
Each woman (only in EEA countries and the UK) is expected to spend approximately 10-15 minutes on filling out the digital questionnaire. Additionally, women may be contacted as needed for follow-up, as described in section 9.1.
Each HCP is expected to spend approximately 10-30 minutes on filling out the digital questionnaire. Additionally, HCPs may be contacted as needed for follow-up, as described in section 9.1.

11 Management and reporting of adverse events/adverse reactions

Raw data, as entered by a woman/HCP will be forwarded to the applicable MAH whose product is connected to the concerned information, according to the timelines outlined in a

separate agreement between the Consortium and the PASS Coordinator. Each MAH will process, document and report to Eudravigilance any ICSRs identified in this study in accordance with the provisions of GVP Module VI, EU Directive 2001/83/EC and their internal processes. Reporting of Swiss and Liechtenstein cases will be done by the relevant MAH in Switzerland in accordance with Swiss legislation. Reporting of UK cases will be done by the relevant MAH in UK in accordance with UK legislation. Procedures for the collection, management and reporting of suspected adverse reactions/adverse events are in place and described in the respective Pharmacovigilance procedures and in the Pharmacovigilance System Master file (PSMF) of each MAH.

If a woman/HCP enters information in the registry but does not provide a brand name, concerned raw data will be forwarded to all the MAHs marketing ulipristal acetate 30 mg in the country of report origin and will be processed in their safety databases. To prevent the submission of duplicate reports to Competent Authorities, one MAH will be assigned per country and will be responsible for case reporting to the Competent Authority of the region of case occurrence (Eudravigilance, MHRA or SwissMedic), when required. The responsibility for cross-reporting of cases to Competent Authorities of other regions lies with each individual MAH.

In addition, any adverse events/ adverse reactions on ulipristal acetate 30 mg received by DADA via other means (e.g. email) will also be forwarded to the applicable MAH(s) as specified above.

Causality assessment
In case of a congenital anomaly, foetal loss or neonatal death reported by an HCP, their causality assessment will be requested in the questionnaire.
When such cases are reported by women who do not provide the details of their HCP(s), the HCP causality assessment will not be available and causality will only be assessed by the applicable MAH/MAA, according to their internal procedures.

New safety information
Any new information which might influence the risk-benefit balance of the medicinal product will be communicated to the concerned competent authorities and ECs of the Member States in which the medicinal product has been authorised.

12 Plans for Disseminating and Communicating Study Results

In accordance with the 2010 EU pharmacovigilance legislation (Articles 10 or 10a of Regulation (EC) No 726/2004; Articles 21a or 22a of Directive 2001/83/EC), information about this PASS will be entered into the publicly available EU-PAS register (currently the ENCePP e-register of studies - http://www.encepp.eu/encepp/studiesDatabase.jsp) by the PASS-Coordinator in the name of the consortium. The study protocol will be entered into the register before the start of data collection. Updates to the study protocol in case of substantial amendments, progress reports where applicable, and the final study report will also be entered in the register.
The statistical results will be discussed with and approved by the consortium.

Any publications in the public domain will occur in accordance with the consortium agreement.

The interim/progress report(s) and the final study report will be in a form according to GVP Module VIII “Post-authorisation safety studies”. It will cover all aspects of the study and will include the interpretation of all relevant data and any conclusions from them. The Registry Study Report will be prepared, whether or not the study will be fully completed and will be written in English.

13 References

Aust Prescr (2016)
Ulipristal acetate for emergency contraception
Aust Prescr 2016;39:228–9

Levy DP, Jager M, Kapp N, Abitbol JL (2014)
Ulipristal acetate for emergency contraception: postmarketing experience after use by more than 1 million women.
Contraception. 2014 May;89(5):431-3.

Ozturk Z, **Akgul** E (2017)
Pregnancy Outcomes Following Ulipristal Acetate Emergency Contraception Failure: A Report of Five Cases.
Fetal Pediatr Pathol. 2017 Jun;36(3):213-219.

Annex 1. List of stand-alone documents

None.

Annex 2. ENCePP checklist for study protocols

Study title: A pregnancy exposure registry study to assess clinical follow-up and outcomes of pregnancies exposed to ulipristal acetate 30 mg.

EU PAS Register® number: EUPAS33796
Study reference number (if applicable): Not applicable

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	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)	☒	☐	☐	7,8
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

2.1.4, 2.1.5: There is no hypothesis or *a priori* hypothesis in this study

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9

[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.

Section 3: Study design	Yes	No	N/A	Section Number
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

3.3, 3.4: Not applicable for this study. Exposure and outcomes are only monitored and voluntarily reported by women/HCPs.

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	7
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9
4.2.2 Age and sex	☒	☐	☐	9
4.2.3 Country of origin	☒	☐	☐	9
4.2.4 Disease/indication	☒	☐	☐	9
4.2.5 Duration of follow-up	☒	☐	☐	9
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9

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)	☒	☐	☐	9
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

5.2 - 5.6: The study concerns a web-based registry set-up for voluntary primary data collection from women exposed to ulipristal 30mg or their health care providers. Exposure is self-determined by these reporters and therefore section 5.2 to 5.6 do not apply.

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?	☐	☐	☒	
6.2 Does the protocol describe how the outcomes are defined and measured?	☐	☐	☒	
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

The primary objective of this pregnancy registry study is to collect all data about pregnancy and pregnancy outcome in women exposed to ulipristal acetate 30mg for any reason, e.g. unrecognized pregnancy before intake or product failure. The secondary study objective is to monitor the important identified risks "Effects on pregnancy maintenance/off-label use", "Risk of incomplete abortion and heavy bleeding", "Effects on foetus and newborns" and "Risk of ectopic pregnancy". However, all this data is to be voluntarily reported, and therefore section 6.1 to 6.4 do not apply.

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

Comments:

Participation to the registry is voluntary and aimed only at women exposed to ulipristal acetate 30mg. Bias cannot be ruled out, as explained in section 9 of the protocol.

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

Comments:

Not applicable for this study.

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9
9.1.3 Covariates and other characteristics?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
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
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)	☒	☐	☐	10

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	9
10.4 Are stratified analyses included?	☐	☒	☐	

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

10.2: The registry will be open for as long as the registry of the originator product includes subjects.

10.4:No stratified analysis is foreseen or has been planned for this study.

10.8: Sensitivity analyses are considered not applicable for this study.

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9
11.2 Are methods of quality assurance described?	☒	☐	☐	9
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9

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?	☒	☐	☐	9
12.1.2 Information bias?	☒	☐	☐	9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

13.2: The protocol is to be submitted for ethical review

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

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

Date: 26/February/2020

Signature: [redacted]

Annex 3 Mock-up Questionnaires

A. Women-specific Questionnaire (only in EEA countries and the UK)

THANK YOU FOR FILLING IN THIS QUESTIONNAIRE

PATIENT ID

Please enter the first letter of your first name		Date of birth (DD/MM/YY)	
Please enter the first three letters of your last name		E-mail address	

HEIGHT (CM) **WEIGHT (KG)**

PREGNANCY INFORMATION

When did you find out you were pregnant? Date: (DD/MM/YY)	
How did you find out you were pregnant? (*tick the appropriate box*)	☐ Ultrasound ☐ Home pregnancy test ☐ Blood test
What was the first day of your last menstrual period? (DD/MM/YY)	
What is/was the expected delivery date? (DD/MM/YY)	

Ulipristal EXPOSURE

On what date did you take Ulipristal?	
What was the total dose you took (30 mg per tablet)?	
How many hours passed between the unprotected sex and when you took Ulipristal?	
What was the brand name of the ulipristal 30 mg that you took?	
In which country did you buy ulipristal 30 mg?	
Were you pregnant when you took Ulipristal?	☐ No ☐ Yes, 1st trimester (inadvertent exposure) ☐ Yes, 2nd trimester (inadvertent exposure) ☐ Yes, 3rd trimester (inadvertent exposure)
Did you use Ulipristal several times?	If yes, specify the date(s):

WHICH MEDICINES OTHER THAN ULIPRISTAL DID YOU TAKE DURING YOUR PREGNANCY?

MEDICINE NAME*	TO TREAT WHICH CONDITION?	DAILY DOSE	HOW DID YOU TAKE IT?	PERIOD OF EXPOSURE DURING PREGNANCY				
				1ST TRIM **	2ND TRIM	3RD TRIM	THROUGHOUT PREGNANCY	UNKNOWN
				☐	☐	☐	☐	☐
				☐	☐	☐	☐	☐
				☐	☐	☐	☐	☐

*including hormonal contraceptive, folic acid
** TRIM means trimester, a period of 3 months of pregnancy

DID YOU HAVE ANY ILLNESSES DURING YOUR PREGNANCY, OR SUFFER FROM ANY CHRONIC DISEASE (e.g. diabetes, hypertension, …)

ILLNESS, DISEASE	START DATE	END DATE	STILL SUFFERING FROM IT?

PREGNANCY OUTCOME

Are you still pregnant? Yes
No

- If yes, what is the expected delivery date? .....
- If no, please provide the following information (as far as you know)

Pregnancy outcome	**Data collected**	**Additional information possibly collected**
☐ I decided to have an abortion	Date of abortion	*No further information is requested.*
☐ The pregnancy continued and I gave birth	☐ Healthy child(ren) Pregnancy term (weeks) In case you had more than 1 baby, please indicate the number of babies born: For each baby, please specify: Sex ☐ F ☐ M Birth weight (kg) Sex ☐ F ☐ M Birth weight (kg) Sex ☐ F ☐ M Birth weight (kg)	*No further information is requested.*
	☐ The baby was born with defects	*Please specify details….* *Please indicate if you used any other medicines in the table "Which medicines other than Ulipristal did you use during pregnancy?"*

<table>
<tr><td rowspan="2"></td><td></td><td>Please specify if you used any alcohol, and if yes, at which stage of pregnancy?
Please specify if you used recreational drugs and if yes, at which stage of pregnancy</td></tr>
<tr><td>☐ The baby died after it was born</td><td>Please specify details….
Please indicate if you used any other medicine in the table “Which medicines other than Ulipristal did you use during pregnancy?”
Please specify if you used any alcohol, and if yes, at which stage of pregnancy?
Please specify if you used any recreational drugs, and if yes, at which stage of pregnancy</td></tr>
<tr><td colspan="2">☐ Abortion for medical reasons (in case of anomaly discovered during a prenatal diagnosis)</td><td rowspan="4">Please specify date: …..
Please indicate if you used any other medicines in the table “Which medicines other than Ulipristal did you use during pregnancy?”
Please specify if you used any alcohol, and if yes, at which stage of pregnancy?
Please specify if you used any recreational drugs, and if yes, at which stage of pregnancy</td></tr>
<tr><td colspan="2">☐ Spontaneous abortion (miscarriage) (< 20 weeks of pregnancy)
Did you need a medical follow up? Yes / no
Did it require a curettage or D&C? Yes / no
Did you experience any miscarriage before? Yes / no</td></tr>
<tr><td colspan="2">☐ Foetal death (> 20 weeks of pregnancy)</td></tr>
<tr><td colspan="2">☐ Ectopic pregnancy(outside the womb)</td></tr>
</table>

Please provide the contact details of your physician/gynecologist:

HEALTH CARE PROVIDER INFORMATION

Last name:	First name:
Medical Specialty:	Clinic/hospital:
Address:	
Country:	
Phone:	Fax:
E-mail:	

B. Healthcare Professional-specific Questionnaire

HEALTH CARE PROVIDER INFORMATION

Last name:	First name:
Medical Specialty:	Affiliation:
Address:	
Country:	
Phone:	Fax:
E-mail:	

PATIENT ID

First letter of the first name	
First three letters of the last name	

Date of birth (DD/MM/YY)	

PREGNANCY INFORMATION

Date of diagnosis	
Date of last menstrual period	
Expected delivery date	

Ulipristal EXPOSURE

Date of ulipristal intake	
Total dose administered (30 mg per tablet)	
Time from intercourse to ulipristal intake (hours)	
Brand name of used ulipristal 30 mg	
Country where ulipristal 30 mg was bought	
Pregnancy stage at ulipristal exposure	☐ Before pregnancy (treatment failure) ☐ 1st trimester (inadvertent exposure) ☐ 2nd trimester (inadvertent exposure) ☐ 3rd trimester (inadvertent exposure)
Pregnancy status before Ulipristal intake	☐ Not pregnant ☐ Pregnant

Pregnancy outcome	**Data collected**	**Additional information possibly collected**
☐ Elective abortion (no medical reason – patient's elective choice)	Date of procedure //	

☐ Live birth	☐ Healthy child(ren) Pregnancy term (weeks) Number of children born For each child, please specify: Sex ☐ F ☐ M Birth weight (kg) Sex ☐ F ☐ M Birth weight (kg) Sex ☐ F ☐ M Birth weight (kg)	
	☐ Congenital anomaly	*See 'Congenital anomaly'*
	☐ Neonatal death	*See 'Neonatal death'*
☐ Maternal death		*The HCP is then contacted rapidly for further information.*
☐ Induced therapeutic abortion (in case of anomaly discovered during a prenatal diagnosis)		*See 'Foetal loss'*
☐ Spontaneous abortion (< 20 weeks of pregnancy)		
☐ Premature foetal death (20-27 weeks of pregnancy)		
☐ Late foetal death (> 28 weeks of pregnancy)		
☐ Ectopic pregnancy		

Congenital anomaly

Pregnancy term (in weeks)

Number of children born

Delivery method ☐ Vaginal ☐ Caesarean

CHILD	LIST OF CONGENITAL ANOMALIES
1	
2	
3	

CHILD	RELATIONSHIP TO Ulipristal INTAKE*	POSSIBLE CAUSES 1=MATERNAL AGE 2=UNKNOWN 3=OTHER, SPECIFY
1		
2		
3		

* possible relationship / no possible relationship / unknown

Apgar scores

CHILD	APGAR	
	1 MIN	5 MIN

1		
2		
3		

Other comments:

MATERNAL HISTORY

History of pregnancy	☐ no		
	☐ yes, how many?	If yes, number of live infants	

History of spontaneous abortion (miscarriage)	☐ no	History of foetal death?	☐ no
	☐ yes, how many?		☐ yes, how many?
History of elective abortion?	☐ no	History of therapeutic abortion?	☐ no
	☐ yes, how many?		☐ yes, how many?

History of birth defect?	☐ no	
	☐ yes, how many?	
	If yes, please specify the defect	

Description of any maternal family history of congenital anomaly

Description of any other significant family history

DRUG(S) OTHER THAN Ulipristal RECEIVED DURING PREGNANCY

MEDICATION NAME*	INDICATION	DAILY DOSE	ROUTE OF ADMINISTRATION	PERIOD OF EXPOSURE DURING PREGNANCY				
				1ST TRIM	2ND TRIM	3RD TRIM	THROUGHOUT PREGNANCY	UNKNOWN
				☐	☐	☐	☐	☐
				☐	☐	☐	☐	☐
				☐	☐	☐	☐	☐

*including hormonal contraceptive and folic acid

WAS THERE ANY ADDITIONAL INTAKE OF ULIPRISTAL DURING PREGNANCY?
☐☐Yes
☐ No

Please choose the applicable period of exposure of Ulipristal during pregnancy

	DURING WHICH TRIMESTER?	IS THE DATE KNOWN?	**IF KNOWN, PLEASE SPECIFY THE DATE:**
1ST INTAKE	☐ 1ST TRIMESTER	☐ Yes ☐ No	..:..:….
2ND INTAKE	☐ 2ND TRIMESTER	☐ Yes ☐ No	..:..:….
3RD INTAKE	☐ 3RD TRIMESTER	☐ Yes ☐ No	..:..:….

RECREATIONAL DRUG USE

RECREATIONAL DRUG USE	YES	NO	ESTIMATED WEEKLY DOSE	ROUTE OF ADMINISTRATION	PERIOD OF EXPOSURE DURING PREGNANCY				
					1ST TRIM	2ND TRIM	3RD TRIM	THROUGHOUT PREGNANCY	UNKNOWN
TOBACCO	☐	☐			☐	☐	☐	☐	☐
ALCOHOL	☐	☐			☐	☐	☐	☐	☐
ILLICIT DRUGS	☐	☐			☐	☐	☐	☐	☐

ILLNESS DURING PREGNANCY OR CHRONIC ILLNESS

MEDICAL CONDITION*	START DATE	STOP DATE	ONGOING AT THE TIME OF OUTCOME

* *eg* diabetes, hypertension or any other medical condition

RESULTS OF SEROLOGY TESTS

Initial serologic tests

RUBELLA TEST PERFORMED?	☐ NO		
	☐ YES	DATE	
		RESULT	☐ POSITIVE
			☐ NEGATIVE

	☐ NO

TOXOPLASMOSIS TEST PERFORMED?	☐ YES	DATE	
		RESULT	☐ POSITIVE
			☐ NEGATIVE, please complete the table below

If initial toxoplasmosis negative, test(s) during pregnancy

DATE	RESULTS	
	☐ POSITIVE	☐ NEGATIVE
	☐ POSITIVE	☐ NEGATIVE

PRENATAL TESTS

☐ NOT DONE ☐ UNKNOWN
☐ DONE, please complete below

TYPE OF TEST*	TEST DATE	IF EVIDENCE OF A STRUCTURAL DEFECT FROM ONE OR MORE OF THESE PRENATAL TESTS 1=NO 2=UNKNOWN 3=DEFECT, SPECIFY

* 1. Ultrasound / 2. AFP/serum markers / 3. Amniocentesis – specify the reason / 4. Cordocentesis – specify the reason / 5. Other – specify type and reason

Neonatal death

Pregnancy term (in weeks)

Number of children born

Delivery method ☐ Vaginal ☐ Caesarean

CHILD	AGE OF NEONATE AT DEATH	CAUSE OF DEATH	RELATIONSHIP TO Ulipristal INTAKE*	AUTOPSY PERFORMED (YES/NO)
1				
2				
3				

* possible relationship / no possible relationship / unknown

Apgar scores

CHILD	APGAR	
	1 MIN	5 MIN
1		
2		
3		

- Was a placenta pathology examination performed: Yes
  No

- If yes, please specify the results:

Other comments:

MATERNAL HISTORY

History of pregnancy	☐ no		
	☐ yes, how many?	If yes, number of live infants	

History of spontaneous abortion (miscarriage)	☐ no	History of foetal death?	☐ no
	☐ yes, how many?		☐ yes, how many?
History of elective abortion?	☐ no	History of therapeutic abortion?	☐ no
	☐ yes, how many?		☐ yes, how many?

History of birth defect?	☐ no	
	☐ yes, how many?	
	If yes, please specify the defect	

Description of any maternal family history of neonatal death

Description of any other significant family history

DRUG(S) OTHER THAN Ulipristal RECEIVED DURING PREGNANCY

MEDICATION NAME*	INDICATION	DAILY DOSE	ROUTE OF ADMINISTRATION	PERIOD OF EXPOSURE DURING PREGNANCY				
				1ST TRIM.	2ND TRIM	3RD TRIM	THROUGHOUT PREGNANCY	UNKNOWN
				☐	☐	☐	☐	☐
				☐	☐	☐	☐	☐
				☐	☐	☐	☐	☐

*including hormonal contraceptive and folic acid

IF ADDITIONAL INTAKE OF Ulipristal DURING PREGNANCY

	PERIOD OF EXPOSURE DURING PREGNANCY			
1ST TRIM.	2ND TRIM	3RD TRIM	PLEASE ADD THE DATE	UNKNOWN
☐	☐	☐		☐

☐	☐	☐		☐
☐	☐	☐		☐

RECREATIONAL DRUG USE

RECREATIONAL DRUG USE	YES	NO	ESTIMATED WEEKLY DOSE	ROUTE OF ADMINISTRATION	PERIOD OF EXPOSURE DURING PREGNANCY				
					1ST TRIM.	2ND TRIM	3RD TRIM	THROUGHOUT PREGNANCY	UNKNOWN
TOBACCO	☐	☐			☐	☐	☐	☐	☐
ALCOHOL	☐	☐			☐	☐	☐	☐	☐
ILLICIT DRUGS	☐	☐			☐	☐	☐	☐	☐

ILLNESS DURING PREGNANCY OR CHRONIC ILLNESS

MEDICAL CONDITION*	START DATE	STOP DATE	ONGOING AT THE TIME OF OUTCOME

* *eg* diabetes, hypertension or any other medical condition

RESULTS OF SEROLOGY TESTS

Initial serologic tests

RUBELLA TEST PERFORMED?	☐ NO		
	☐ YES	DATE	
		RESULT	☐ POSITIVE
			☐ NEGATIVE

TOXOPLASMOSIS TEST PERFORMED?	☐ NO		
	☐ YES	DATE	
		RESULT	☐ POSITIVE
			☐ NEGATIVE, please complete the table below

If initial toxoplasmosis negative, test(s) during pregnancy

DATE	RESULTS	
	☐ POSITIVE	☐ NEGATIVE
	☐ POSITIVE	☐ NEGATIVE

PRENATAL TESTS

☐ NOT DONE ☐ UNKNOWN
☐ DONE, please complete below

TYPE OF TEST*	TEST DATE	IF EVIDENCE OF A STRUCTURAL DEFECT FROM ONE OR MORE OF THESE PRENATAL TESTS 1=NO 2=UNKNOWN 3=DEFECT, SPECIFY

* 1. Ultrasound / 2. AFP/serum markers / 3. Amniocentesis – specify the reason / 4. Cordocentesis – specify the reason / 5. Other – specify type and reason

Foetal loss

- Was a placenta pathology examination performed: Yes
  No

If yes, please specify the results:

Pregnancy term (in weeks) at time of foetal loss

Number of foetus(es)

RELATIONSHIP TO Ulipristal INTAKE*

* possible relationship / no possible relationship / unknown

Factors that may have had an impact on foetal loss

1	
2	
3	
4	
5	

In case of ectopic pregnancy, please specify below:

☐ Salpingitis or known tubal anomaly

☐ Previous ectopic pregnancy

☐ Previous tubal surgery

Other comments:

FOETAL LOSS COMPLICATIONS

Any vaginal bleeding?

☐ No

☐ Yes, please specify: ☐ Spotting
☐ Regular
☐ Heavy

Duration of bleedings:

Were the bleedings clinically excessive? ☐ No
☐ Yes

Specify if a blood transfusion was performed : NO
YES

Need for a curettage?

☐ No

☐ Yes: Please specify the gestational age:

The curettage was performed: ☐ following the usual protocol

☐ because you were worried about excessive bleeding

Any infection?

☐ No

☐ Yes, please specify: ☐ Location of infection:
☐ Infectious agent:
☐ Treatment given:

Was the infection a complication of pregnancy loss? ☐ No ☐ Yes

Any other complication

☐ No ☐ Yes, please describe:

MATERNAL HISTORY

History of pregnancy	☐ no		
	☐ yes, how many?	If yes, number of live infants	

History of spontaneous abortion (miscarriage)	☐ no	History of foetal death?	☐ no
	☐ yes, how many?		☐ yes, how many?
History of elective abortion?	☐ no	History of therapeutic abortion?	☐ no
	☐ yes, how many?		☐ yes, how many?

History of birth defect?	☐ no	
	☐ yes, how many?	
	If yes, please specify the defect	

Description of any maternal family history of foetal loss

Description of any other significant family history

DRUG(S) OTHER THAN Ulipristal RECEIVED DURING PREGNANCY

MEDICATION NAME*	INDICATION	DAILY DOSE	ROUTE OF ADMINISTRATION	PERIOD OF EXPOSURE DURING PREGNANCY				
				1ST TRIM.	2ND TRIM	3RD TRIM	THROUGHOUT PREGNANCY	UNKNOWN
				☐	☐	☐	☐	☐
				☐	☐	☐	☐	☐
				☐	☐	☐	☐	☐

*including hormonal contraceptive and folic acid

IF ADDITIONAL INTAKE OF Ulipristal DURING PREGNANCY

	PERIOD OF EXPOSURE DURING PREGNANCY			
1ST TRIM.	2ND TRIM	3RD TRIM	PLEASE ADD THE DATE	UNKNOWN
☐	☐	☐		☐
☐	☐	☐		☐
☐	☐	☐		☐

RECREATIONAL DRUG USE

RECREATIONAL DRUG USE	YES	NO	ESTIMATED WEEKLY DOSE	ROUTE OF ADMINISTRATION	PERIOD OF EXPOSURE DURING PREGNANCY				
					1ST TRIM.	2ND TRIM	3RD TRIM	THROUGHOUT PREGNANCY	UNKNOWN
TOBACCO	☐	☐			☐	☐	☐	☐	☐
ALCOHOL	☐	☐			☐	☐	☐	☐	☐
ILLICIT DRUGS	☐	☐			☐	☐	☐	☐	☐

ILLNESS DURING PREGNANCY OR CHRONIC ILLNESS

MEDICAL CONDITION*	START DATE	STOP DATE	ONGOING AT THE TIME OF OUTCOME

* *eg* diabetes, hypertension or any other medical condition

RESULTS OF SEROLOGY TESTS

Initial serologic tests

RUBELLA TEST PERFORMED?	☐ NO		
	☐ YES	DATE	
		RESULT	☐ POSITIVE
			☐ NEGATIVE

TOXOPLASMOSIS TEST PERFORMED?	☐ NO		
	☐ YES	DATE	
		RESULT	☐ POSITIVE
			☐ NEGATIVE, please complete the table below

If initial toxoplasmosis negative, test(s) during pregnancy

DATE	RESULTS	
	☐ POSITIVE	☐ NEGATIVE
	☐ POSITIVE	☐ NEGATIVE

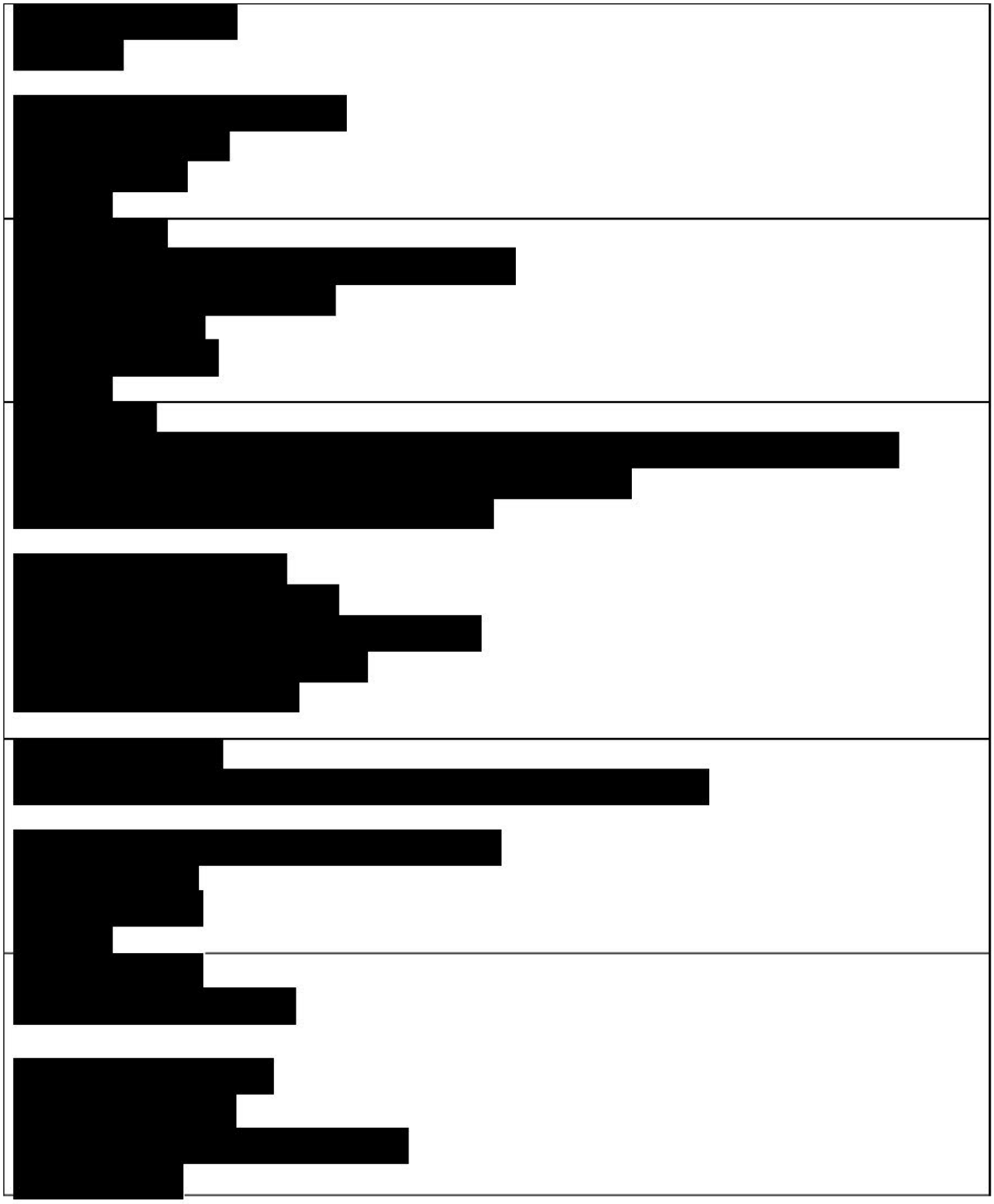
PRENATAL TESTS

☐ NOT DONE ☐ UNKNOWN
☐ DONE, please complete below

TYPE OF TEST*	TEST DATE	IF EVIDENCE OF A STRUCTURAL DEFECT FROM ONE OR MORE OF THESE PRENATAL TESTS 1=NO 2=UNKNOWN 3=DEFECT, SPECIFY

* 1. Ultrasound / 2. AFP/serum markers / 3. Amniocentesis – specify the reason / 4. Cordocentesis – specify the reason / 5. Other – specify type and reason

Annex 4. List of Consortium members and their contact persons



Annex 5. Information to Participants

A. Information for women entering data themselves (only in EEA countries and the UK) (reporting environment):

Thank you for your interest in participating in this registry. Before you continue, it is important for you to understand why this registry was set-up and what participation means for you.

Who is responsible for the creation of this registry?
This joint pregnancy registry is set-up on request of the European Health Authorities by the following pharmaceutical companies as joint data controllers

- Aristo Pharma GmbH
- Aspen Healthcare Malta Limited
- BIOGARAN
- ELPEN Pharmaceutical Co. Inc
- Exeltis Pharmaceuticals Holding, S.L.
- Farmitalia s.r.l
- HELM AG
- Mylan
- Hexal AG
- STADA Arzneimittel AG
- Zentiva Group, a.s.

The registry is managed on behalf of these companies by DADA Consultancy B.V. (registry coordinator), located in the Netherlands, who can be reached at [redacted] for questions related to this registry. For any other request (i.e. medical inquiry, quality complaint, adverse drug reactions) the company from which you purchased your product needs to be contacted.

What is a pregnancy registry and what is the purpose of this registry?
A pregnancy registry is an important program aimed at collecting medical information on women exposed to a pharmaceutical product during their pregnancy. The information collected from the pregnancy registry will allow to gain more information on exposure to ulipristal 30 mg during pregnancy. In the long term, other pregnant women could therefore benefit from your participation and the data collected via this registry. Your information shall only be used for these scientific research purposes.

Disclaimer
Participation in this research is voluntary. If you don't wish to take part, you don't have to.

It is important to know that your identity will remain strictly confidential. Personal data limited to your initials, your email address and date of birth are collected to allow the electronic system to link data reported on the same pregnancy. Your personal data will be encrypted by the system in such a way that your identity will not be known to any of the pharmaceutical companies.

Your email address will also be requested and will be used only within the electronic system, through which you will receive automated emails that will allow you to complete additional information on the course and outcome of your pregnancy in the online questionnaire.

If you have also agreed to provide your physician's contact details, he or she will be contacted via the electronic system. By providing the contact details of your physician, you are authorizing us to contact your physician and you authorize your physician to provide further information on your pregnancy and its outcome.

The registry coordinator (DADA Consultancy B.V.) manages the electronic system and will have access to your personal and medical information. However, the information will only be used for the correct handling and linking of data in the electronic system and will remain strictly confidential.

Information on how your data is being processed and protected can be found in the registry data privacy notice: [link to privacy notice]

If you bought Ulipristal 30 mg in Switzerland or Liechtenstein and intend to report your pregnancy after taking Ulipristal 30 mg tablets, please do not submit your data directly to the registry, but ask your doctor to contact [redacted]

☐ I took note of the registry data privacy notice.
In case I provide the contact details of my physician, I authorize
- the registry coordinator to contact my physician and
- my physician to provide further information on my pregnancy and its outcome to this registry

B. Information for physicians in EEA countries (except Liechtenstein) and the UK (reporting environment):

Thank you for your interest in participating in this registry. Before you continue and enter your patient's data, it is important for you to understand why this registry was set-up and what participation means for you.

Who is responsible for the creation of this registry?
This joint pregnancy registry is set-up on request of the European Health Authorities by the following pharmaceutical companies as joint data controllers

- Aristo Pharma GmbH
- Aspen Healthcare Malta Limited
- BIOGARAN
- ELPEN Pharmaceutical Co. Inc
- Exeltis Pharmaceuticals Holding, S.L.
- Farmitalia s.r.l
- HELM AG
- Mylan
- Hexal AG
- STADA Arzneimittel AG
- Zentiva Group, a.s.

The registry is managed on behalf of these companies by DADA Consultancy B.V. (registry coordinator), located in the Netherlands, who can be reached at [redacted] for questions related to this registry. For any other request (i.e. medical inquiry, quality complaint, adverse drug reactions) the company from which you purchased your product needs to be contacted.

What is a pregnancy registry and what is the purpose of this registry?
A pregnancy registry is a voluntary prospective program designed to collect and evaluate medical information on pregnancies and outcomes reported, following exposure to a pharmaceutical product. Since there is little data regarding pregnancies exposed to ulipristal 30 mg, the collection of further data has been requested by European Health Authorities to continuously monitor the safety profile of ulipristal during pregnancy. The aforementioned companies established this registry to collect information on any pregnancy exposed to ulipristal 30 mg, e.g. unrecognized pregnancy before intake, or treatment failure.

It is important to know that your identity and the identity of your patient will remain strictly confidential and the personal/professional information will only be known to the electronic system. Your email address will also be requested and will be used only within the electronic system, through which you will receive automated emails that will allow you to complete additional information in the online questionnaire.

The registry coordinator (DADA Consultancy B.V.) manages the electronic system and will have access to your personal/professional information. However, the information will only be used for the correct handling and linking of data in the electronic system and will remain strictly confidential.

Why have I been approached about this registry?
If you have been contacted either via the electronic system based on information provided by a pregnant woman that has been exposed to ulipristal and is your patient, the woman in question has provided us with your contact details and has given her consent for us to request follow-up data on her pregnancy directly from you.

How is patient's confidentiality ensured?
The pregnancy registry will only collect patients' initials, dates of birth and email addresses that will allow the electronic system to link data originating from the same patient. Patients' identities will not be forwarded to pharmaceutical companies.

Information on how your and your patient`s data is being processed and protected can be found in the registry data privacy notice: [link to privacy notice]

Entering data on behalf of your patient
Please note that patients are not required to sign an Informed Consent Form attesting they accept their data to be collected in the framework of this registry. However, before enrolment in the registry, you should inform each patient of the objective and the content of the registry. Patients should be reassured that any information used would be handled in an anonymous manner in order to preserve confidentiality.

If you are a healthcare professional and intend to report a patient's pregnancy after exposure to Ulipristal 30 mg bought in Switzerland or Liechtenstein, please contact [redacted] for directions before submitting data to the registry.

☐ I took note of the registry data privacy notice

☐ I have informed my patient of the objective and content of the registry, and my patient has released me from the medical secrecy in order to enter data into the registry on her behalf.

C. Information for physicians in Switzerland and Liechtenstein (email text):

Subject: Ulipristal Pregnancy Registry – Information for data entry

Dear Dr. [Healthcare Professional's name],

We, DADA Consultancy, are contacting you in the name of the Marketing Authorization Holders (MAHs) who market ulipristal 30 mg tablets in Switzerland and Liechtenstein. DADA has been contracted by the MAHs of generic ulipristal 30 mg tablets to set-up and run a registry for reports of pregnancies after use of one of their ulipristal 30 mg products, which is a Health Authority obligation to market the product.

We are contacting you via this email because you have indicated that you intend to report a patient's pregnancy after exposure to an ulipristal 30 mg tablet from a generic company bought in Switzerland or Liechtenstein. For the reporting of pregnancy cases in the EU, a joint pregnancy registry was set-up and is available online. For the reporting of Swiss or Liechtenstein pregnancy cases, an individualized registry link is required.

Before you sign up via the link below, please note that patients are not required to sign an Informed Consent Form attesting they accept their data to be collected in the framework of this registry. However, before enrolment in the registry, you should inform each patient of the objective and the content of the registry. Patients should be reassured that any information used would be handled in an anonymous manner in order to preserve confidentiality.

By signing up via the link below, please be aware that you confirm that you have:

- read and accept the attached privacy notice
- informed your patient of the objective and content of the registry, and your patient has released you from the medical secrecy in order to enter data into the registry on her behalf.

If you agree with the above, please sign up to report your patient's pregnancy and its outcome in the registry via this link:
https://public.smart-trial.co/#/public/5e14831f3b75ff282caff3c0/5e1714cc3b75ff282cef640c/6373646c192906b9aacf9ecc/signup?lang=en

The above link can be used for signing up for the registry and initial data entry. After sign up, you will receive an automated email containing another link leading to the case you reported. If you wish to provide more information at a later date, you can follow this case-specific link in the automated email to enter the additional data.

If your patient is still pregnant at the time you enter information in the registry or if you do not provide information on the pregnancy outcome, the electronic system will send you an automated email 10 weeks after you initially have entered information, and at the expected delivery date, asking you to complete the missing information. We may send you up to four reminders. If your patient has asked you not to provide further information you can ignore the emails.

For more information on the registry, please find attached the Information for physicians in Switzerland and Liechtenstein. If you have further questions regarding the registry, please contact [redacted]. For any other request (i.e. medical inquiry, quality complaint, adverse drug reactions) the company from which your patient purchased her product needs to be contacted.

Thank you for your collaboration,
The Ulipristal Registry Study Team

Annex 6. List of medicinal products relevant for this PASS

DIAPILL 30 mg comprimido recubierto con película EFG
Ecinq
Elperil®
Evante 30 mg compressa rivestita con film
Evante 30 mg filmomhulde tablet
EVANTE 30 mg compressa rivestita con film
Femke
Femke 30 mg comprimate filmate
Femke 30 mg filmomhulde tablet
Femke 30 mg Filmtablette
Femke 30 mg tablett, filmdrasjert
Femke Mylan filmovertrukne tabletter 30 mg
Kruidvat noodanticonceptie ulipristal, 30 mg filmomhulde tablet
Lencya
Lencya 30 mg – Filmtabletten
Misstala 30 mg, tabletka powlekana
Ulipristal 30 mg film-coated tablet
Ulipristal acetate Aristo 30 mg potahovaná tableta
ULIPRISTAL ACETATE BIOGARAN 30 mg, comprimé pelliculé
ULIPRISTAL ACETATE EXELTIS 30mg, comprimé pelliculé
Ulipristal acetate Hexal 30 mg – Filmtabletten
ULIPRISTAL ACETATE Viatris 30 mg, comprimé pelliculé
Ulipristal Acetate Rowex 30 mg Film-coated Tablets
Ulipristal acetate Sandoz
Ulipristal acetate Sandoz 30 mg apvalkotās tabletes
Ulipristal acetate Sandoz 30 mg plėvele dengta tableté
Ulipristal Aristo 30 mg compressa rivestita con film
Ulipristal Aristo 30 mg comprimido revestido por película
Ulipristal Aristo 30 mg comprimidos recubiertos con película EFG
Ulipristal Aristo 30 mg filmomhulde tablet
Ulipristal Aristo 30 mg Filmtablette
Ulipristal Aristo 30 mg tabletka powlekana
ULIPRISTAL Viatris 30 mg comprimido recubierto con película EFG
Ulipristal Mylan 30 mg filmomhulde tablet
Ulipristal Sandoz
Ulipristal STADA 30 mg comprimido recubierto con película EFG
Ulipristalacetaat Exeltis 30 mg filmomhulde tablet
Ulipristalacetaat HTP Noodanticonceptie 30 mg, filmomhulde tablet
Ulipristalacetaat Sandoz 30 mg, filmomhulde tablet
Ulipristalacetat AL 30 mg Filmtablette
Ulipristalacetat STADA 30 mg Filmtablette
Ullanesse, Filmtabletten
Ullionce 30 mg Filmtablette