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

Study report

Version 1 of 04 October 2023

[redacted]
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Study information

Title	*Maternal and Newborn Safety profile of Progestogens in EARLY pregnancy (PEARLY)*
Protocol No.	*DYDR5007*
Date of last version of the final study report	*04-October-2023*
EU PAS register number	*EUPAS43631*
ClinicalTrials.gov Identifier	*NCT05186779*
Active Ingredient(s)	*Dydrogesterone*
Name of Finished Product	*Duphaston*
Name of Sponsor	*Abbott Products Operations AG* *Hegenheimermattweg 127, 4123 Allschwil*
Joint PASS	*No*
Countries of study	*Brazil, China, Russia, Türkiye*
First subject enrolled	*30-December-2021*
Date of early termination	*22-June-2023*
Author	[redacted] *(ZEG Berlin)* *Invalidenstrasse 115, 10115 Berlin, Germany* [redacted] *t:* [redacted]

Table of contents

1. List of abbreviations

ART	assisted reproductive technology
AT	as treated
CI	confidence interval
EDC	Electronic data capture
EDD	estimated date of delivery
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ePRO	electronic patient reported outcomes
EU PAS	European Union Electronic Register of Post-Authorization Studies
FU1	follow-up 1 questionnaire
GCD	Global Clinical Director
GMD	Global Medical Director
HCP	health care professionals
IVF	in vitro fertilization
LPS	luteal phase support
N/A	not applicable
NC-FET	natural cycle frozen embryo transfer
MAH	market authorization holder
OR	odds ratio
OTC	over the counter
PASS	post-authorization safety study
PEARLY	Maternal and Newborn Safety Profile of Progestogens in EARLY Pregnancy
SMAC	Safety, Monitoring and Advisory Council
SMP	safety management plan
UK	United Kingdom
US(A)	United States (of America)
ZEG Berlin	Berlin Center for Epidemiology and Health Research (Zentrum für Epidemiologie und Gesundheitsforschung)

2. Investigator

[redacted]
Berlin Center for Epidemiology and Health Research
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3. Other responsible parties

Study conduct was overseen by an independent safety, monitoring and advisory council (SMAC). ZEG Berlin was accountable to the SMAC in all scientific matters, with the oversight of Abbott. Members of the SMAC received remuneration of expenses and an honorarium to compensate for the loss of potential earnings during their work for the SMAC according to Abbott's Fair Market Value. The members were not involved in the operational conduct of the study or received any additional payments.

Safety Monitoring and Advisory Council Members:

- [redacted] (US, Chair)
- [redacted] (Sweden)
- [redacted] (Canada)
- [redacted] (UK)
- [redacted] (UK)

4. Milestones

The following milestones were defined in the latest protocol version (V03-00 as of 27 October 2022). Due to challenges in recruitment the sponsor took the decision to terminate the study on 22-June-2023.

Milestone	Planned date	Actual date	Comments
Global ethics approval	September 2021	28-September-2021	Subsequent ethics approvals were obtained in Russia (25-November-2021), Türkiye (23-August-2022), and China (02 November 2022).
Registration at the EU PAS register	October 2021	16-November-2021	Registration at ENCePP registry October 2021; award letter issued 16 November 2021
Start of data collection (first patient in)	December 2021	30-December-2021	
Study interim/progress report 1	October 2023	N/A	Early study termination on 22-June-2023. First, and final, study report issued in October 2023.
Study interim/progress report 2	October 2024	N/A	
Study interim/progress report 3	October 2025	N/A	
End of data collection (last patient last follow-up)	March 2026	15-August-2023	Entry of study data in Electronic Data Capture (EDC) system was deactivated for study participants and health care practitioners (HCPs)
Database lock	July 2026	15-August-2023	
Final report of study results	October 2026	06-October-2023	Abbreviated report finalization

ENCePP: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; EU PAS: European Union Electronic Register of Post-Authorization Studies; N/A: not applicable.

5. Rationale and background

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

6. Research question and objectives

The primary objective was to assess the rate of major malformations in fetuses and newborns by indication and by exposure to progestogens in the first trimester of pregnancy with a focus on dydrogesterone versus non-dydrogesterone-containing treatments. This study aimed to accurately characterize and describe users of progestogens in early pregnancy including past gynecological and obstetric history, indication for progestogen use, type of progestogen use, and detail of the course of pregnancy, birth outcome and newborn health. A comparison of live birth rates and rate of malformations in fetuses and newborns was based on the indication area (recurrent pregnancy loss[1], bleeding in early pregnancy[2] or IVF/ART) and the treatment (dydrogesterone, other progestogens, and other treatments[3]).

[1] Habitual miscarriage

[2] Threatened miscarriage

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

7. Protocol Amendments and updates

Number	Date	Section of study protocol	Amendment update or reason
V01-00	16-July-2021	N/A	First version
V02-00	11-October-2021	• Section 3: Rationale and background • Section 5.2.2.1 Inclusion criteria • Section 5.7.3 Interim analyses	Amendments as per recommendation by the Global Ethics Committee
V02-01	16-June-2022	• Global clinical director (GCD) and global medical director (GMD) on page 1 and 2 • Sponsor representative on protocol signature page (on page 2)	• Updated as the earlier GCD and GMD are no longer associated with sponsor • Updated as the earlier signatory is no longer associated with sponsor
V03-00	27-October-2022	• Abstract • 2. Milestones • 5.2. Setting • 5.2.2.1 Inclusion criteria • 5.5. Study size • Section 7: Management and reporting of adverse events/adverse reactions	• Change inclusion criteria age from 18 to 35 years to 18 to 40 years • Update protocol to be in line with the PEARLY SMP • Change in study geography (closure of Russia), added Appendix 5

GCD: global clinical director; GMD: global medical director; N/A: not applicable; SMP: study management plan.

8. Research methods

8.1. Study design

This multinational, prospective, active surveillance, registry study followed two cohorts and included study participants who were pregnant and seeking any type of medical treatment, including dydrogesterone and other progestogens, for either (A) recurrent pregnancy loss and/or bleeding in early pregnancy or (B) as IVF/ART support. Pregnant women not taking progestogen and who were advised an alternative non-medical treatment, in the context of bleeding in early pregnancy, recurrent pregnancy loss, or undergoing natural cycle frozen embryo transfer (NC-FET) were also included in this study. Eligible study participants were recruited via an international network of prescribing HCPs in participating countries with the aim to collect data related to maternal safety and newborn safety in women prescribed progestogens during early pregnancy.

Study participants were followed from early pregnancy until 6–12 weeks after giving birth. All malformations were captured via direct contacts with the study participants. Study participants were sent online questionnaires via the electronic patient reported outcomes (ePRO) solution provided by Medidata. Major malformations reported by the study participants were validated by the Berlin Center for Epidemiology and Health Research (ZEG Berlin) via relevant source documents and if necessary, via contacting the treating HCPs.

The total study duration was planned for approximately four years including recruitment and follow-up.

8.2. Setting

The study was conducted by ZEG Berlin, with the oversight of Abbott. The study was divided into two phases: a baseline survey, which includes an initial consultation at baseline with recruiting HCPs and completion of a baseline questionnaire by the study participant, and a follow-up phase, which included two follow-up contacts directly with the study participant at approximately 24 weeks of gestation and 6 to 12 weeks after the initial estimated date of delivery (EDD).

The study was planned to take approximately four years and included the recruitment and follow-up of approximately 11,000 study participants.

Participating countries were Brazil, China, Türkiye and Russia.

8.3. Subjects

Pregnant women aged 18 to 40 who were treated with progestogens, including dydrogesterone, or other treatment for (Cohort A) recurrent pregnancy loss and/or bleeding in early pregnancy or as (Cohort B) IVF/ART support were included in the study. Study participants were only recruited after the decision on treatment was made. Additionally, study participants were recruited in different geographical areas where dydrogesterone was marketed.

8.4. Variables

The primary variable of interest was the rate of major malformations in fetuses and newborns. Data were collected on treatment, treatment indication, risk factors and potential confounding factors for malformations.

8.5. Data sources and measurement

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

8.6. Study size

Two independent cohorts were considered in the analysis:
(Cohort A) study participants with bleeding in early pregnancy and/or recurrent pregnancy loss, **and**
(Cohort B) study participants receiving IVF/ART.

Sample size calculations for both cohorts were similar and based on an incidence proportion of major malformations at birth of 200 per 10,000 births for both indications. Assuming a drop-out rate of 20% and a rate of major malformation in fetal newborns of 0.02, sample size calculations showed that approximately 5,500 study participants per cohort were statistically sufficient (power = 90%, one-sided α = 0.025) to exclude a 2.0-fold risk (odds ratio; OR) in the dydrogesterone cohort. The total number of study participants was planned to be 11,000 across all geographical study sites.

8.7. Statistical methods

The analyses originally planned were described in the Statistical Analysis Plan (SAP V01-00, November 23, 2022). This final report does not include statistical analyses or multivariable modeling. Absolute frequencies were used to report enrollment of study participants, reasons for early discontinuation and/or failed screening, the number of study participants who met inclusion/ exclusion criteria and completed the baseline questionnaire. Cohort distribution and treatment prescribed at study entry were presented using absolute frequencies.

9. Results

Global ethics approval was obtained from the Berliner Ärztekammer on 28-September-2021. Subsequent ethics approvals were obtained in Russia (25-November-2021), Türkiye (23-August-2022), and China (02-November-2022). Due to challenges in recruitment, the decision to terminate the study was taken on 22-June-2023. Participants were recruited in Russia and Türkiye; however, recruitment in Brazil and China had not been initiated by the time of study termination.

At the time of study close, a total of 113 women were enrolled in the study, of which 83 met the inclusion and exclusion criteria and 54 women completed their baseline questionnaires.

Seven (7) women answered the follow-up 1 questionnaire (i.e., at least one question was answered). Of which, five (5) women were treated for IVF/ART support, one woman was treated for bleeding in early pregnancy, and one woman was treated for recurrent pregnancy loss and bleeding in early pregnancy.

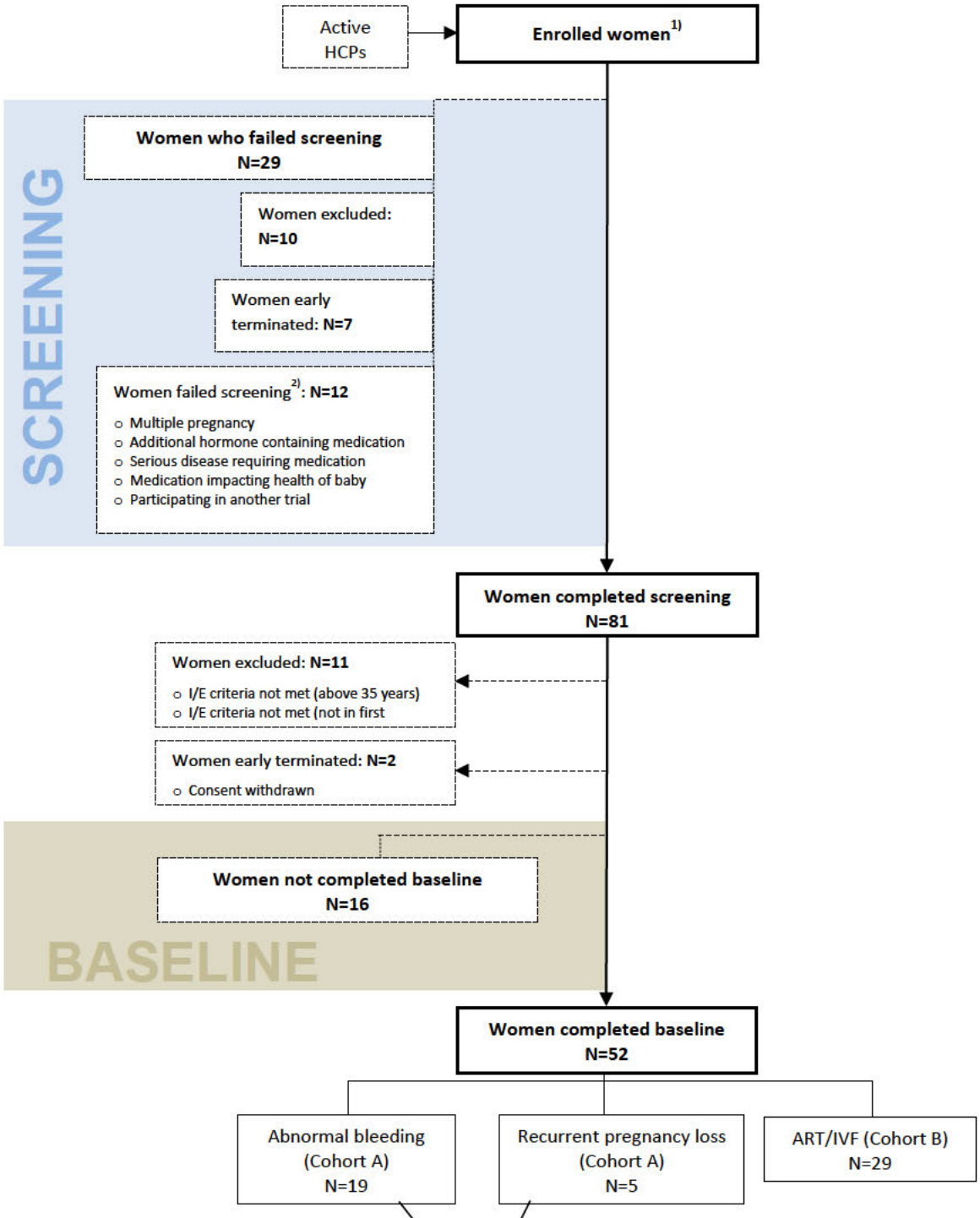
No major malformations (primary outcome) in fetuses or newborns were detected during the observation period. A list of adverse events/reactions is presented in Section 9.6.

9.1. Participants in Türkiye

	Number
Number of active HCPs	8
Number of enrolled women[1]	**110**
Women who failed screening	**29**
thereof status excluded	10
of which	
Duplicate	2
Inclusion/Exclusion criteria not completed	8
thereof status early terminated	7
of which	
Consent withdrawn	7
thereof status failed screening[2]	12
of which	
Multiple pregnancy	3
Additional hormone containing medication	3
Serious disease requiring medication	1
Medication impacting health of baby	4
Participating in another trial	1
Women who completed screening	**81**
thereof status excluded	11
of which[3]	
Inclusion/Exclusion criteria not met (above 35 years)	6
Inclusion/Exclusion criteria not met (not in first trimester)	5
thereof status early terminated	2
of which	
Consent withdrawn	2
Women who did not complete baseline	**16**
Women who completed baseline	**52**
of which	
Dydrogesterone only	6
Dydrogesterone Combination Therapy	2
Non-dydrogesterone (i.e., other progesterone)	40
Other/No treatment	4
thereof ART/IVF	29
thereof Abnormal bleeding	18
thereof Recurrent pregnancy loss	4
thereof Abnormal bleeding & recurrent pregnancy loss	1

[1]ICF completed by patient and HCP
[2] Women may have more than one reason; two women did not specify reason
[3]Based on the protocol inclusion/exclusion criteria, women were excluded post-screening based on answer provided in the baseline questionnaire

Figure 1: Flowchart of study participants in Türkiye



Treatment	Abnormal bleeding		Recurrent pregnancy loss	ART/IVF	Total
Dydrogesterone Only	2		2	2	6
Dydrogesterone Combination	1		0	1	2
Non-dydrogesterone	14	1	1	24	40
Other/No treatment	1		1	2	4**All**
	18	**1**	**4**	**29**	**52**

1)ICF completed by patient and HCP; 2)Women may have more than on reason; Abbreviations: HCP=Health Care Practitioner; I/E=Inclusion/Exclusion;

9.2. Participants in Russia

	Number
Number of active HCPs	1
Number of enrolled women[4]	**3**
Women who failed screening	**1**
thereof status excluded	1
of which	
Inclusion/Exclusion criteria not completed	1
Women who completed screening	**2**
Women who completed baseline	**2**
of which	
Non-dydrogesterone (i.e., other progesterone)	2
thereof ART/IVF	1
thereof Abnormal bleeding	1

ART: assisted reproductive technology; HCP: health care professionals; IVF: in vitro fertilization.

9.3. Descriptive data

N/A

9.4. Outcome data

N/A

9.5. Main results

N/A

9.6. Adverse events/adverse reactions

Subject ID	Time-point	Date of Report	Term	Serious criteria	Treatment	Cohort
12000020008	*FU1*	*25.06.2023*	Influenza	Not serious	Non-dydrogesterone	ART/IVF
12000020010	*FU1*	*10.08.2023*	Gestational diabetes	Serious	Non-dydrogesterone	ART/IVF
12000060003	*FU1*	*15.02.2023*	Urinary tract infection	Not serious	Non-dydrogesterone	ART/IVF

[4] ICF completed by patient and HCP

10. Discussion

N/A

11. Conclusion

One hundred thirteen subjects were enrolled in the PEARLY study between 30-December-2021 (FPI) and 15-August-2023. Challenges in enrollment resulted in the termination of the study in June 2023. Due to limited follow-up activities, follow-up data should be considered as a quantitative assessment only.

12. References

N/A