SUMMARY OF STUDY RESULTS

EudraCT number: 2019-002032-84

Sponsor Protocol Code: ELYS-CS01

Name and Address of Sponsor:

Disphar International B.V., Winkelskamp 6, 7255 PZ Hengelo (Gld), The Netherlands

Full title of the study:
Evaluating the Use of a Progesterone Receptor Modulator for Cervical Ripening at Full Term Pregnancy – a Randomized, Double-blind, placebo controlled Study (LUCYNA)

Investigational Product: Mifepristone tbl. 75 and 150 mg

Indication: Cervix Ripening in Full-term Pregnancy

Initiation Date: 30 January 2020 (FPI)
End of study: 4 July 2022 (early termination)

Main objective of the study:

The primary objective of the study is to compare the efficacy of Mifepristone tablet 150 mg with placebo in cervix ripening in full-term pregnancy 48 hours after baseline

Study design:

A comparative, randomised, double-blind, multicentre Phase II clinical study with 2 parts:

Part I – a double-blind, randomized, placebo-controlled, two-arm, parallel-group design

Eligible subjects at Week 40 + 5 days of pregnancy were randomized with 1:1 allocation ratio into two groups:

- Test Group: Mifepristone tablet 150 mg at baseline
- Control Group: placebo

All subjects were monitored at hour 24 and 48 hours after the baseline (vital signs, gynaecological examination – Bishop Score). This was not applicable if delivery started in the meantime.
If the labour did not start until Week 41 + 0 (48 hours after the baseline), subjects uderwent the further cervical ripening and/or induction with Dilapan-S or Prostin E2 (depending on the actual Bishop Score).

After the delivery all subjects and infants were followed-up daily for three days.

A post-study follow-up was performed in infants of all subjects at their age of 5 months: local paediatricians were contacted, adverse events were recorded and a questionnaire on health condition was completed.

Part II – a double-blind, single-arm part of the study

All subjects received the same dose of Mifepristone – 75 or 300 mg depending on the results of the interim analysis after Part I.

All procedures were identical as those in the Test Group of the Part I.

Primary end-point:

Gain in Bishop score at 48 hours from baseline

Secondary end-points:

- Rate of subjects with Bishop score gain ≥ 2
- Change in Bishop Score after 24 hours
- Time to vaginal delivery
- Rate of spontaneous vaginal delivery (without any assistance other than mifepristone or placebo in the control group)
- Rate of Caesarean sections
- Rate of subjects treated with Dilapan-S
- Rate of subjects treated with Prostin E2
- Mean dose of oxytocine
- Adverse events - subjects
- Adverse events - infants
- Consumption of analgesics

Clinical sites:

1. Fakultní nemocnice Brno, Gynekologicko-porodnická klinika (CZ)
2. Nemocnice milosrdných bratří Brno (CZ)
3. Fakultní nemocnice Olomouc, Porodnicko Gynekologická Klinika (CZ)

Planned number of subjects: 150 (100 subjects in Part I, 50 subjects in Part II)
Number of enrolled subjects: 136 (95 subjects in Part I, 41 subjects in Part II)

Progress of the study:

A total of 95 of the 100 planned subjects were enrolled in the Part I (due to Covid-related enrolment difficulties). After the end of Part I an interim analysis has been performed, IDMC chose based on the results the dose of 300 mg Mifepristone for Part II in a blinded regimen.

In the second part, 41 out of 50 planned subjects were enrolled before the expiry date of the IMP - 30 June 2022.

Sponsor decided to early terminate the study after the IMP had expired since a new supply of IMP would take a long time to prepare. This is an exploratory study, in the opinion of the sponsor a slightly lower number of subjects will not affect the results of the study.

Results:

The primary efficacy endpoint was the gain in the Bishop Score at 48 hours from baseline if recorded in the CRF. If the BS could not be determined at 48 hours due to early labour or delivery, the maximum achievable score was to be used for BS at 48 h.

<u>Interim analysis after the end of Part I:</u>

Results show that the gain in BS at 48 h ranged from 0 to 11 with a median of 3 for both treatment groups. The mean gain was greater for treatment with Mifepristone 150 mg - „B“ (4.4) as compared to treatment with placebo - „A“ (4.0). The point estimate of the treatment difference (A-B) was -

0.4 with a 2-sided 95% confidence interval -1.8 to +1.1. The confidence interval did not exclude a value of 0 which means that the treatment difference is not statistically significant at the α=0.05 level of significance. The null hypothesis of equality could not be rejected.

Gain in Bishop Score at 48 h (Part I)*

	Treatment A N = 46	Treatment B N = 49	Total N = 95
BS Difference from Baseline at 48 h			
Minimum	0	0	0
1st Quartile	1.0	2.0	1.0
Mean (SD [1])	4.0 (3.5)	4.4 (3.6)	4.2 (3.5)
Median	3.0	3.0	3.0
3rd Quartile	6.0	8.0	6.5
Maximum	11	11	11
Total N [2]	46	49	95
Treatment Difference (A-B)			
Point Estimate		-0.4	
95% CI [3]		-1.8 - 1.1	

Analysis population: ITT Dataset: DELIVERY Data version: 2021-07-25

** „A" = placebo, „B" = Mifepristone 150mg*

Interim analysis after the end of Part II:

Results show that the gain in BS at 48 h ranged from 0 to 12 with a median of 3 for both treatment groups pooled. The mean gain was greater in the Mifepristone group (5.32) as compared to the placebo group (4.0). The point estimate of the treatment difference (Mifepristone - placebo) was 1.2 with a 2-sided 95% confidence interval from -0.4 to +2.9. The treatment difference seems to be clinically relevant and practically important.

Gain in Bishop Score at 48 h (Part II):*

	Mifepristone 300 N = 39	Placebo N = 46	Total N = 85
BS Difference from Baseline at 48 h			
Minimum	0	0	0
1st Quartile	1.0	1.0	1.0
Mean (SD [1])	5.3 (4.2)	4.0 (3.5)	4.6 (3.8)
Median	5.0	3.0	3.0
3rd Quartile	9.0	6.0	9.0
Maximum	12	11	12
Total N [2]	39	46	85
Treatment Difference (Mifepristone - Placebo)			
Point Estimate		1.2	
95% CI [3]		-0.4 - 2.9	

Analysis population: ITT Dataset: DELIVERY Data version: 2022-08-25

Complete analyses are currently not yet available.

Adverse events information:

Subjects: no AEs
Infants:
There were 5 infants experiencing AEs in Mifepristone 150 mg group , 4 infants experiencing AEs in the Mifepristone 300 mg group and 3 in placebo group. No AE was considered related to treatment. One infant in the Mifepristone 150 mg group experienced AE considered by the investigator to be serious. No AE was of severe intensity.

Overview of AEs (infants):

	SAE	Intensity	Causality	Resolved
Mifepristone 150 mg				
Grunting	no	mild	unlikely	yes
Asphyxia neonatorum	yes	mild	unrelated	yes
Transitory fever	no	mild	unrelated	yes
Hyperbilirubinaemia, ABO incompatibiliy	no	mild	unrelated	yes
Subfebrile	no	mild	unrelated	yes
Mifeprisotone 300mg				
Stagnant cyanosis in the face	no	mild	unrelated	yes
Neonatal arrythmias	no	mild	unrelated	yes
Interventricular septal defect	no	mild	unrelated	yes
Cephalohematoma post vacuumextraction		mild	unrelated	yes
Placebo				
Right side cephalohematoma	no	mild	unrelated	yes
Peripherial paresis of brachial plex	no	mild	unlikely	ongoing
Febrile	no	mild	unrelated	yes