2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
HRA Pharma
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Volume:

Page:</td><td>(For National Authority Use only)</td></tr>
<tr><td>Name of Finished Product: CDB-2914</td><td colspan="2" rowspan="2"></td></tr>
<tr><td>Name of Active Ingredient: Ulipristal Acetate</td></tr>
<tr><td colspan="3">Title of Study: A Prospective, Randomized, Single Blind, Multicenter Study to Compare the Efficacy, Safety and Tolerability of CDB-2914 with Levonorgestrel as Emergency Contraception Within 120 Hours of Unprotected Intercourse</td></tr>
<tr><td colspan="3">Investigators:
<table>
<tr><td>UK/Ireland Site</td><td>Investigators</td><td>USA Site</td><td>Investigators</td></tr>
<tr><td>01</td><td>Pr Anna Glasier (CI) /Dr. Sharon Cameron</td><td>21-22</td><td>Dr. Paul Fine</td></tr>
<tr><td>02</td><td>Dr. Susan Logan</td><td>23-26</td><td>Dr. Jennifer Traught-Van Horn</td></tr>
<tr><td>03</td><td>Dr. Audrey Brown</td><td>27-28</td><td>Dr. Scott Spear</td></tr>
<tr><td>06</td><td>Dr. Asha Kasliwal</td><td>29-34</td><td>Dr. Laszlo Sogor</td></tr>
<tr><td>07-08</td><td>Dr. Anne Webb</td><td>35-37</td><td>Dr. Savita Ginde</td></tr>
<tr><td>09</td><td>Pr. Judith Stephenson</td><td>38-42</td><td>Dr. William Casale</td></tr>
<tr><td>10</td><td>Dr. Charlotte Porter</td><td>43-44</td><td>Dr. Deb Nucatola</td></tr>
<tr><td>11</td><td>Dr. Cynthia Harper</td><td></td><td></td></tr>
<tr><td>13</td><td>Dr. Caroline Hunter</td><td></td><td></td></tr>
<tr><td>14</td><td>Dr. Shirley McQuade</td><td></td><td></td></tr>
</table></td></tr>
<tr><td colspan="3">Study site(s): Thirty five (35) active sites participated and enrolled subjects in this study; UK (10), Ireland (1), US (24).</td></tr>
<tr><td colspan="3">Publication (reference): Not applicable</td></tr>
<tr><td colspan="2">Study period (years):
Date of first enrolment: 09 April 2007
Date of last completed: 02 April 2009</td><td>Study Phase: Phase 3</td></tr>
<tr><td colspan="3">Objectives: Primary objective:
• To provide evidence that the pregnancy rate observed after taking CDB-2914 (30 mg) within 72 hours of unprotected intercourse (UPI) is statistically significantly lower than the estimated expected pregnancy rate in the absence of emergency contraception (EC).

Secondary objectives:
• To provide evidence that the pregnancy rate observed after taking CDB-2914 (30 mg) within 120 hours of UPI is statistically significantly lower than the estimated expected pregnancy rate in the absence of emergency contraception
• To provide evidence that the pregnancy rate observed after taking CDB-2914 (30 mg) within 72 hours of UPI is statistically significantly lower than 4% considered as the clinical irrelevance threshold
• To provide evidence that the pregnancy rate observed after taking CDB-2914 (30 mg) within 120 hours of UPI is statistically significantly lower than 4% considered as the clinical irrelevance threshold</td></tr>
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- To provide evidence that the non-inferiority of CDB-2914 (30 mg) versus levonorgestrel (1.5 mg) as emergency contraception within 72 hours of UPI. Should non-inferiority be demonstrated, superiority was tested
- To provide evidence that the non-inferiority of CDB-2914 (30 mg) versus levonorgestrel (1.5 mg) as EC within 120 hours of UPI. Should non-inferiority be demonstrated, superiority would be tested
- To evaluate the trend in pregnancy rates over time since intercourse of CDB-2914 (30 mg) to levonorgestrel (1.5 mg)
- To assess the contraceptive effectiveness (prevented fraction) between treatment groups
- To assess the impact of CDB-2914 (30 mg) on the menstrual cycle compared to levonorgestrel (1.5 mg)
- To evaluate the safety and tolerability profile of CDB-2914 (30 mg) in comparison to levonorgestrel (1.5 mg)

Methodology: This was a prospective, single-blind, randomized, multicenter, 2-arm parallel comparative study designed to evaluate the efficacy, safety and tolerability of a single dose of CDB-2914 (30 mg) compared to levonorgestrel (1.5 mg) administered for EC within 120 hours after UPI. Subjects who requested EC within 120 hours after UPI at a participating study site and who met the inclusion/exclusion criteria were enrolled into the study after they signed informed consent forms (ICF). A total of up to three visits were scheduled over the course of the study. The first visit occurred on Day 1 and included the screening and treatment phases. At Day 1, a high sensitivity urinary pregnancy (HSUP) test was performed and a blood sample was taken and stored for serum β-hCG pregnancy testing, in case a pregnancy was detected during the study. Follow-up was initially to be done from home and the protocol was later amended to allow follow-up visit at the clinical sites.

At the second visit (first follow-up visit; 5-7 days after expected onset of menses) a HSUP test was performed:

1) If the HSUP test was positive, a serum β-hCG pregnancy test was performed; if positive, the frozen pre-treatment serum was also analyzed to verify whether the subject was pregnant prior to treatment. A transvaginal ultrasound was then scheduled.
2) If the HSUP test was negative and menses had resumed, study completion procedures were performed.
3) If the HSUP test was negative but menses had not resumed, a second follow-up visit was scheduled one week later.

If a second follow-up visit was required (12-14 days after expected onset of menses), the procedures from the first follow-up visit were repeated. If the HSUP test was negative and menses had not resumed, a serum β-hCG pregnancy test was performed and amenorrhea follow-up was initiated.

Safety was evaluated by adverse events, change in menstrual cycle length during the treatment cycle compared to baseline, incidence and duration of intermenstrual / vaginal bleeding, incidence of amenorrhea and pregnancy follow-up.

Number of patients (planned and analyzed): A total of 2044 subjects were planned to be enrolled in this study, taking into account expected lost-to-follow-up and subjects enrolled between 72 and 120 hours. To demonstrate non-inferiority of CDB-2914 to levonorgestrel within 72 hours of UPI, a sample size of 1654 subjects was estimated to be needed. Overall, 2321 were screened and 2221 were treated for analysis.

Diagnosis and main criteria for inclusion: Women presenting for EC within 120 hours of UPI, 16 years or more in UK (except Northern Ireland), 17 years or more in Northern Ireland (UK) and 18 years or more in Ireland and US, with regular cycle length (24 to 35 days).

Women presenting more than 72 hours after intercourse were eligible for inclusion only if they declined the insertion of an Intra-Uterine Device (IUD) for EC or had contraindications to IUD insertion.

Test product, dose and mode of administration, batch number: The study medication, a single oral dose of CDB-2914 (30 mg) was administered immediately after all eligibility criteria (including current pregnancy status) were verified. Subjects took the study medication in the presence of the clinical staff.

Two different batch numbers were used for the European sites as these sites began recruitment before the US sites.

Duration of treatment: A single tablet was taken orally (within 120 hours of UPI).

Reference therapy, dose and mode of administration: The reference therapy for this study was a single oral dose of Levonelle® 1500 (1.5 mg).

Criteria for evaluation:

Primary Efficacy: The primary efficacy parameter was the pregnancy rate (%), calculated as the number of subjects being pregnant after administration of EC, divided by the number of subjects administered EC.

Secondary Efficacy: The secondary efficacy parameter was the pregnancy prevented fraction, defined as the number of prevented pregnancies divided by the number of expected pregnancies:

- Number of prevented pregnancies = Number of expected pregnancies - Number of observed pregnancies
- The number of expected pregnancies was determined based on conception probabilities by cycle day of intercourse (Trussell et al. 1998)

Safety: Adverse events, change in menstrual cycle length during treatment cycle compared to baseline, incidence of amenorrhea, incidence and duration of intermenstrual / vaginal bleeding, and pregnancy follow-up.

Statistical methods: The primary efficacy analysis was performed on the mITT population and these subjects had to meet the following criteria:

- Randomized and received study drug
- Had at least one UPI in the current cycle before enrollment
- Participated for the first time in the current study
- Known pregnancy status using high sensitivity urinary pregnancy (HSUP) test after emergency contraception intake (not lost-to-follow-up at follow-up Visits 1 & 2)
- 35 years of age or younger
- If pregnant, without pregnancy identified as having started before EC intake (as measured by pre-treatment serum β-hCG level and gestational age confirmed by transvaginal ultrasound) or as "not compatible" with an EC failure, based on independent evaluation.

The final analyses were performed using the Lan DeMets' alpha spending function approach, O'Brien-Flemming spending function and an information fraction of 1200/1654 = 0.72. The critical value for the final analysis $z_{0.025}$ = 2.0056 (instead of 1.96) which corresponds to a nominal alpha of 0.02245 and a cumulated exit probability of 0.05 for a one-sided test or to a nominal alpha of 0.0449 for a two-sided test.

The 95% confidence interval (CI) of the pregnancy rate was constructed using the Agresti-Coull method. The logistic regression was used to investigate the trend of pregnancy rate using SAS macros for the Spline Cubic Estimation; also the logistic regression was used to estimate the odds ratios for some cofactors. The Chi-squared test was used for sensitivity analysis to confirm results obtained from the primary efficacy analysis.

The primary efficacy analysis compared the pregnancy rate observed after administration of EC within 72 hours to the estimated expected pregnancy rate in the absence of emergency contraception. The observed pregnancy rate was considered to be statistically significantly lower than the expected pregnancy rate if the upper bound of the 2-sided 95% CI of the observed pregnancy rate was below the expected pregnancy rate.

The main secondary efficacy analysis compared the upper bound of the observed pregnancy rate to the clinically irrelevant threshold of 4%. The non-inferiority of CDB-2914 versus levonorgestrel as EC was concluded if the upper bound of the 95% CI of the odds ratio of pregnancy in the CDB-2914 group and the levonorgestrel group is lower than the non-inferiority margin of 1.6. Superiority was established if the upper bound of the 95% CI of the odds ratio is below 1.0.

Safety was evaluated by incidence of adverse events and laboratory safety parameters. Effects on the menstrual cycle were described by comparing the treatment menstrual cycle length to the average cycle length and by examining incidence of intermenstrual bleeding.

Summary - Conclusions

Efficacy Results: The primary efficacy analysis demonstrated that for subjects treated within 72 hours with CDB-2914 the observed pregnancy rate of 1.51% (95% CI; 0.62%, 3.32%) was statistically significantly lower than the expected pregnancy rate of 5.63%. The 95% CI upper limit of the observed pregnancy rate was lower than the clinical irrelevance threshold of 4% which is considered clinically meaningful for an emergency contraception method. In addition, the 95% CI upper limit of the odds ratio of the observed pregnancy rate in the CDB-2914 group vs. levonorgestrel was lower than the non-inferiority margin 1.6. The results are consistent across all analysis populations studied (mITT, ITT completers, mITT2, ITT and Per Protocol). The results are robust and conclusive in demonstrating the efficacy of CDB-2914 in preventing pregnancy when taken within 72 hours after UPI.

There was also a statistically significantly lower pregnancy rate within 120 hours of UPI in the mITT population with an observed pregnancy rate of 1.60% and 2.67% for the upper bound of the 95% CI compared to an expected pregnancy rate of 5.72%. This result was supported by an analysis of the trend in pregnancy rates up to 120 hours provided by estimates of the probabilities of pregnancy from the time of UPI to treatment assessed at various time intervals.

CDB-2914 compared favorably to levonorgestrel in all of the analyses, meeting the prespecified criteria for non-inferiority and trending toward better efficacy in all analyses.

Overall efficacy results are presented in the Table below.

	Pregnancy Rate [95% CI]		OR [95% CI]
	CDB-2914	Levonorgestrel	
0-72h mITT (n= 1694)	1.78% (1.04%, 2.98%)	2.59% (1.68%, 3.94%)	0.68 (0.35, 1.31)
0-120h mITT (n= 1893)	1.60% (0.93%, 2.67%)	2.62% (1.75%, 3.89%)	0.59 (0.31, 1.14)

Safety Results: Overall, 597 (54.1%) of the CDB-2914-treated subjects (ITT population) experienced 1506 AEs, of which 675 (44.8%) were considered treatment related; while 626 (56.0%) of the levonorgestrel-treated subjects experienced 1629 AEs, of which 752 (46.2%) were considered treatment related. The majority of the AEs (CDB-2914, 93.9%; levonorgestrel, 94.0%) were mild or moderate in intensity and resolved spontaneously.

The most frequently experienced AEs associated with CDB-2914 by MedDRA coded Preferred Term were headache (19.3%); dysmenorrhea (12.9%) and nausea (12.8%). Abdominal pain, either general (5.1%), upper (3.4%), or lower (1.9%) was also frequently experienced. The pattern and frequency of AEs was similar for levonorgestrel.

Seven serious adverse events were reported during the study (CDB-2914, urinary tract infection, right contact lens related corneal ulcer and dizziness; levonorgestrel, vomiting blood stained fluid, molar

pregnancy, ruptured ovarian cyst and kidney stones). Only dizziness (CDB-2914) and molar pregnancy (levonorgestrel) were considered possibly related to the study drug. Two CDB-2914 treated subjects were discontinued from the study due to an adverse event (vomiting, ovarian cyst) and only vomiting was considered related to the study drug.

The percentage of subjects who experienced at least one AE was comparable in the ITT population and in the population ≤ 35 years (mITT); Repeated Enrollers did not experience AEs more frequently than other populations. The safety profile (type of events, characteristics) was also comparable within the different analysis populations.

Treatment with CDB-2914 was associated with a mean increase of 2.1 days in the menstrual cycle length compared to a mean reduction of 1.2 days with levonorgestrel from the historical average length for the ITT population as reported by the subjects. The average duration of bleeding was 5.2 days for CDB-2914 treated subjects and 5.6 days for levonorgestrel treated subjects. This duration corresponded to a minimal change of 0.5 day and 0.8 day, respectively, from the pre-study average duration. The majority of these subjects (64.0%) had regular menstrual volume, while 33.8% had menses with heavy bleeding, similar to that of levonorgestrel. Post treatment, 95 (8.6%) CDB-2914 and 117 (10.5%) levonorgestrel treated subjects experienced inter-menstrual bleeding other than menses, the majority of which was described as spotting.

Pregnancy occurred in fifty subjects (CDB-2914, 20; levonorgestrel, 30), of whom 35 (CDB-2914, 14; levonorgestrel, 21) elected to have an induced abortion, 8 (CDB-2914, 4; levonorgestrel, 4) reported spontaneous abortion, 4 (CDB-2914, 1; levonorgestrel, 3) decided to carry the pregnancy to term and 3 in the other category (CDB-2914, 1; levonorgestrel, 2) included one molar pregnancy (levonorgestrel groupe), one lost to follow-up and one subject who did not make a decision by database lock. At the time of database lock, 4 pregnancies were still ongoing.

Conclusion: This large multicenter international study demonstrated that a single 30 mg dose of CDB-2914 as emergency contraception whether administered within 72 or 120 hours after UPI, statistically significantly lowered the observed pregnancy rate compared to the expected pregnancy rate in the absence of EC. The reduction in pregnancy rate was clinically relevant.

The efficacy of CDB-2914 was also supported by an analysis of the trend in pregnancy rates up to 120 hours based upon estimates of the probability of pregnancy from the time of UPI to treatment assessed at various time intervals.

CDB-2914 was well tolerated by the majority of subjects with adverse events associated with the treatment similar in type, severity and frequency to the already marketed active comparator drug levonorgestrel. Importantly, no new safety issues arose in this study where 1,104 subjects received treatment.

CDB-2914 did not show a clinically significant impact on menstrual cycle length. The majority of the treated subjects had no change in duration of menstrual bleeding. Only a small proportion of subjects experienced post treatment intermenstrual vaginal bleeding, which was mostly light bleeding/spotting.

This study demonstrates that CDB-2914 is a safe and effective EC with no apparent loss of effectiveness if taken up to 120 hours after UPI. This represents a clinically important and significant improvement with respect to currently available methods.

Date of the report: 5Oct2009