

Clinical Study Synopsis

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Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer Healthcare AG	
Study Number:	13180 NCT00754871	
Study Phase:	I	
Official Study Title:	A double-blind, randomized, dose-controlled study to evaluate pharmacodynamic properties of four oral doses of dienogest (DNG) in 100 healthy young female volunteers over a period of two cycles up to a maximum of 72 days	
Therapeutic Area:	Women's Healthcare	
Test Product		
Name of Test Product:	Dienogest (Visanne, BAY86-5258)	
Name of Active Ingredient:	Dienogest (DNG)	
Dose and Mode of Administration:	Four doses were tested: 0.5 mg, 1 mg, 2 mg and 3 mg, oral administration	
Reference Therapy/Placebo		
Reference Therapy:	Not applicable.	
Dose and Mode of Administration:	Not applicable	
Duration of Treatment:	two cycles up to a maximum of 72 days	
Studied period:	Date of first subjects' first visit:	23 SEP 2008
	Date of last subjects' last visit:	10 SEP 2009
Study Center(s):	One center in The Netherlands	
Methodology:	See below: Criteria for evaluation	

<p>Indication/ Main Inclusion Criteria:</p>	<p>Healthy female subjects, age 18 – 35 years (smokers not older than 30 years, inclusive), ovulatory pre-treatment cycle</p>
<p>Study Objectives:</p>	<p><u>Overall:</u> to evaluate the pharmacodynamic characteristics of dienogest after administration of four doses DNG for 2 cycles up to a maximum of 72 days.</p> <p><u>Primary:</u> Not applicable.</p> <p><u>Secondary:</u> Not applicable</p>
<p>Evaluation Criteria:</p>	<p><u>Overall:</u></p> <ul style="list-style-type: none"> • 6-step grading of ovarian activity according to Hoogland (based on follicle size measurements (by transvaginal ultrasound TVU) and serum estradiol and progesterone concentrations) • Course of serum estradiol levels (E2), progesterone and the gonadotropins (follicle-stimulating hormone (FSH), luteinizing hormone (LH)) • Effects on the cervix and the cervical mucus (Insler Score) • Endometrial thickness (by TVU) • mRNA expression profile of endometrial biopsies using a pre-defined candidate biomarker panel and a hypothesis-free search <p>Additionally:</p> <ul style="list-style-type: none"> • Dose-response regarding pharmacodynamic parameters (i.e. Hoogland score, endometrial thickness and hormone concentrations) <p><u>Efficacy (Primary):</u> Not applicable.</p> <p><u>Efficacy (Secondary):</u> Not applicable.</p> <p><u>Safety:</u></p> <ul style="list-style-type: none"> • Medical and gynecological history, medication history • Physical and gynecological examination including TVU and cervical cytological smear • Standard safety laboratory analyses in blood and urine complemented by urine pregnancy tests; body weight; blood pressure; heart rate; bleeding pattern; additional TVU parameters / findings, e.g. ovarian cysts • Documentation of adverse events / concomitant medication

	<p><u>Pharmacokinetics(PK):</u> Analyses of DNG concentration in serum Population PK: to estimate the individual $AUC_{\tau,ss}$ as a measure of individual exposure for the subsequent exposure-response analysis</p> <p><u>Other:</u> Not applicable.</p>
<p>Statistical Methods:</p>	<p><u>Overall:</u> All pharmacodynamic analyses were considered as exploratory analyses. The Hoogland score and Insler score were analyzed by treatment and time point using frequency tables. Dose response relationship was assessed for the maximum of Hoogland score/Insler score.</p> <p>For endogenous hormone concentrations (E2, progesterone, LH and FSH), summary parameters (C_{max}, t_{max}, C_{av}) were calculated.</p> <p>For follicle size and endometrium thickness, maximum follicle size / endometrium thickness, time to maximum and average endometrium thickness / follicle size were calculated for each subject over the treatment period, per cycle (including pre-treatment) and treatment group.</p> <p>Changes of mRNA levels from biopsy day (BD) in the pre-treatment period to BD in the treatment period as well as the dependency of these changes were investigated. Therefore, in a first step paired tests were applied. Linear models were utilized to test for dose-dependency.</p> <p>Nonlinear regression methods were applied to explore the relationship between DNG pharmacokinetics and pharmacodynamics.</p> <p><u>Efficacy (Primary):</u> Not applicable.</p> <p><u>Efficacy (Secondary):</u> Not applicable.</p> <p><u>Safety:</u> All safety variables were analyzed according to the variable type: descriptive statistics (number of non-missing data, number of missing data, arithmetic mean, standard deviation, minimum, 1st quartile, median, 3rd quartile and maximum) were provided for continuous data, frequency tables for categorical data.</p>

	<p><u>Pharmacokinetics:</u> Measured serum concentrations of DNG were listed for each subject and each visit day with descriptive statistics for all treatments (e.g. range: minimum - maximum). Population PK: PK data were evaluated by means of nonlinear mixed-effects models using NONMEM.</p> <p><u>Other:</u> Not applicable.</p>
<p>Number of Subjects:</p>	<p>Planned: 25 subjects per treatment group (per protocol set: 20 subjects) Analyzed per group: Full analysis set (FAS): 25 subjects (DNG 0.5 mg), 27 (DNG 1 mg), 25 (DNG 2 mg), 25 (DNG 3 mg) Per protocol set (PPS): 21 (DNG 0.5 mg), 23 (DNG 1 mg), 20 (DNG 2 mg), 23 (DNG 3 mg) Reasons for non-inclusion in the PPS were mostly irregular/not complete intake of study medication</p>
<p>Study Results</p>	
<p>Results Summary — Subject Disposition and Baseline</p>	
<p>199 female subjects were screened, and 104 subjects were randomized at 1 center. Of these, 102 subjects started intake of study drug, and 2 subjects discontinued their participation prior to receiving study drug, i.e. were randomized but not treated. 92 subjects completed the study drug administration whereas 10 subjects prematurely discontinued study medication. Overall, 85 subjects completed the study course inclusive the follow-up period, and further 7 subjects discontinued their participation after drug intake was completed before the end of the study.</p> <p>102 female subjects with an average age of 22.6 years and mean body mass index of 22.4 kg/m² were treated in the study. Ninety subjects were Caucasians, 3 were Blacks, one was Hispanic, one was Asian and 7 had another ethnicity.</p>	
<p>Results Summary — Efficacy</p>	
<p>During the treatment period, two subjects (one each in the 0.5 mg and 1 mg group) had an ovulation during the first treatment phase (day 1 – 36) and three (two in the 0.5 mg and one in the 1 mg group) during the second phase (after day 36), whereas none of the women had an ovulation in the two higher dose groups (PPS). Only one subject was classified as having a luteinized unruptured follicle (Hoogland score 5) in the second treatment phase after administration of 0.5 mg DNG. Regarding the maximum Hoogland score for the complete treatment period, 16 out of 21 subjects (76%) in the 0.5 mg group and 18 out of 23 subjects (78%) in the 1 mg group had a Hoogland score \geq 4 (i.e. at least follicle-like structure $>$ 13 mm and estradiol $>$ 27.2 pg/mL). After administration of 2 mg and 3 mg DNG Hoogland score 4 was found in 10 out of 20 subjects (50%) and in 7 out of 23 subjects (30%) respectively.</p>	

During the treatment period, the Insler score was only assessed if a follicle-like structure > 13 mm was measured. This was the case in 53 out of 87 women (60.9%), most often in the two lower dose groups. Only 2 subjects (2.3% of all subjects) receiving 0.5 mg DNG had an Insler score of 9, about 15% of all subjects a value between 6 and 8 and the majority of all subjects (43.5%) Insler scores below 6.

The hormone levels of FSH during treatment were basically unchanged as compared with pre-treatment values.

Regarding LH, mean maximum values were clearly decreased after study drug intake in comparison to pre-treatment. The graphical display shows more constant levels without peak values. Differences between the dose groups were not found.

The increase of progesterone during the second half of the pre-treatment cycle was clearly suppressed by the study drug.

A significant difference between the two low and high doses was found for estradiol. While still high C_{max} values for subjects of the 0.5 mg and 1 mg group were reached (C_{max}: 252 and 212 pg/mL respectively, complete treatment period), 2 and 3 mg DNG decreased the C_{max} values to 79 pg/mL respective 54 pg/mL (pre-treatment: 247 pg/mL). Mean average estradiol values (C_{av}) were between 30 pg/mL (higher dose groups) and approximately 80 pg/mL (lower dose groups).

No decrease of the maximum follicle size was observed in the two lower dose groups when comparing pre-treatment and treatment values. However, large interindividual differences have to be taken into consideration as single subjects reached follicle sizes above 60 mm. The mean maximum follicle sizes of the two higher dosage groups were distinctly decreased in comparison to pre-treatment. All individual values of these two groups were < 30 mm, 75% were below 20 mm (2 mg group) respectively 14 mm (3 mg group) in all dose groups.

The endometrial thickness was reduced during the treatment period, reaching a mean value of about 6 mm, compared with about 10 mm in the pre-treatment cycle, each on the biopsy day. During treatment, endometrium remained small.

The endometrial biomarker panel (LNG Classifier) clearly shows a progestogenic effect at all DNG dose levels (0.5, 1, 2 and 3 mg) which is indicative for a change in endometrial receptivity as complement to ovulation inhibition. In contrast to central/ovarian function, there is no clear dose dependency. In particular, women in dose groups 0.5 and 1 mg, who still had ovulations, show full effects at the endometrial level.

Results Summary — Safety

No deaths were reported during the study. Two serious adverse events (SAEs) were reported: ankle fracture and loss of consciousness (probably because she was drugged in a discotheque) which both resulted in hospitalization. None of these findings was assessed as study-drug related. Five subjects withdrew prematurely from the study because of the following 6 treatment emergent adverse events (TEAEs): ankle fracture (also reported as SAE), headache, mood swings, prolonged menstrual bleeding and genital and pelvic pain. All 6 but one TEAE (ankle fracture) were assessed as being related to the study drug. In total, 546 TEAEs were documented in 101 (24 subjects with 0.5 mg DNG, 27 subjects with 1 mg DNG, 25 subjects with 2 mg DNG and 25 subjects with 3 mg DNG) out of 102 (99.0%) subjects.

The most frequently occurring TEAEs by subject were:

- headache (47 subjects, 46.1%:
13 subjects with 0.5 mg DNG, 11 with 1 mg DNG, 8 with 2 mg DNG, 15 with 3 mg DNG),
- nasopharyngitis (41 subjects, 40.2%:
14 subjects with 0.5 mg DNG, 3 with 1 mg DNG, 12 with 2 mg DNG, 12 with 3 mg DNG),
- dysmenorrhoea (30 subjects, 29.4%:
5 subjects with 0.5 mg DNG, 12 with 1 mg DNG, 6 with 2 mg DNG, 7 with 3 mg DNG) and
- influenza (26 subjects, 25.5%:
9 subjects with 0.5 mg DNG, 8 with 1 mg DNG, 5 with 2 mg DNG, 4 with 3 mg DNG).

Forty-one TEAEs were rated as 'severe', the categories with the most frequent severe TEAEs were gastrointestinal disorders, infections and infestations and nervous system disorders. 183 of 546 TEAEs in 74 subjects were study drug-related. The most frequently occurring study drug-related TEAEs were headache (35 subjects), dysmenorrhoea (12 subjects), nausea (9 subjects) and acne (9 subjects).

Furthermore, at the final visit two subjects had positive pregnancy test results. Both women had received the complete amount of study medication as planned. Pregnancy tests were positive 3 respectively 6 weeks after last study medication intake. One further woman was excluded from the study because of a pregnancy at screening (exclusion criteria).

The number of clinically relevant changes in laboratory values was relatively low.

The statistics regarding bleeding pattern were similar for all 4 treatment groups. No different pattern was recognizable by increasing DNG doses.

Blood pressure, heart rate and body weight were unremarkable during the course of the study.

Results Summary — Pharmacokinetics

Concentration measurements were widely distributed within the whole dosing interval of 24 hours. Serum concentrations of DNG increased with increasing dose between 0.5 and 3 mg of DNG. The scatter plots of individual DNG serum concentrations versus time after last dose administration showed a rapid increase of the concentrations and a biphasic decline after reaching peak concentrations at around 1 – 2 hours after administration. The $AUC_{\tau,SS}$ was a good predictor for the PD response with regard to maximum follicle size and Hoogland Score. For the median DNG exposure observed in the 2 mg dose group of about 620 $\mu\text{g}\cdot\text{h/L}$, the probability to achieve a Hoogland Score ≤ 2 is about 50%.

Results Summary — Other

Not applicable.

Conclusion(s)

The administration of 0.5, 1, 2 or 3 mg DNG for up to 72 days in healthy, young women was well tolerated. No unexpected adverse events occurred. The two SAEs (ankle fracture, loss of consciousness) were not regarded as study drug related. Five subjects discontinued their participation due to AEs (fracture of the ankle (SAE), headache, mood swing, prolonged menstrual bleeding, genital and pelvic pain) which all are known after DNG treatment except for the fracture of the ankle. No clinically relevant changes of the laboratory values occurred which were attributed to the study drug.

A dose-dependent effect on the ovarian activity was observed. Only single ovulations occurred in the 0.5 and 1 mg group and an even better suppression was found in the 2 and 3 mg group. The probability of follicle-like structures ≤ 13 mm (i.e. Hoogland score 1 or 2) grows from less than 20% at 0.5 mg DNG to over 70% at 3 mg DNG. A Hoogland score of 5 or 6 (i.e. luteinized unruptured follicle or ovulation) occurs with a probability $\leq 5\%$, if the DNG dose is 2 mg or above. The average estradiol levels showed clear differences between the two lower dose groups (Cav: 80 pg/mL) and the two higher dose groups (Cav: 30 – 40 pg/mL). An Insler score below 9 indicating contraceptive effects was observed in all but 2 subjects in the 0.5 mg group. The endometrial biomarker panel (LNG Classifier) clearly showed a progestogenic effect at all DNG dose levels, but no clear dose dependency. Besides the dose-dependent effect on ovarian activity, also a clear concentration effect relationship was observed.

In conclusion, an effect of the study drug on most of the pharmacodynamic parameters was found. Differences within the 4 doses were mostly detectable between the two lower (0.5 and 1 mg) and the two higher doses (2 and 3 mg).

Publication(s):	None
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