Evaluation of The Food Effect On a Drospirenone Only Contraceptive Containing 4 mg Administered With and Without High-Fat Breakfast

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Abstract

Background:

The objective of the present trial was to assess the difference in pharmacokinetics of an oral test preparation containing 4 mg drospirenone. under fasting conditions compared to food intake after single dose administration.

Methods:

Open label, single centre, two-treatment, two-sequence, crossover study in 24 healthy female volunteers, with duration of 1 day per sequence and with a real wash-out period of 14 days to investigate the relative bioavailability of DRSP with both forms of administration. The 90% confidence intervals were calculated for the intra-individual ratio (test with food vs. without food) of the pharmacokinetic endpoints $AUC_{(0\text{-}72h)}$ and C_{max} of drospirenone.

Results:

The 90% CI calculated by means of ANOVA-log for the endpoint, intra-individual ratio (Test 'A' = with food intake) vs. Test 'B' = without food intake) of AUC(0-72h) of drospirenone was between 104.72% and 111.36%. The 90% CI calculated by means of ANOVA- log for the endpoint intra-individual ratio (Test 'A' vs. Test 'B') of C_{max} of drospirenone was between 118.58% and 141.10%.

The mean relative bioavailability of the Test with food 'A' compared to the Test without food 'B' after single dose administration based on the endpoints $AUC_{(0\text{-}72h)}$ was 107.99%; for the endpoint C_{max} it was 129.35%.

Conclusions:

The rate of absorption, based on the endpoint Cmax of drospirenone was increased by about 30% under fed conditions which differs to a COC containing 0,02 mg EE and 3 mg drospirenone in a 24/4 regimen where the rate of absorption was reduced by about 40% for both components.

Implications: Our results suggest that the food intake has no impact on the absorption of 4 mg drospirenone in the management for contraception.

This raises up the contraceptive efficacy as no interference with food is expected in real life use when consuming the oral formulation

1. Introduction

Estrogen-free pills are safe regarding cardiovascular diseases as they do not increase the risk of thromboembolic or stroke events in comparison to contraceptives containing estrogens [1, 2]. Traditional progestin-only pills (POPs) are associated with an unpredictable bleeding pattern, and stringent daily timing and missed pill rules that might affect contraceptive reliability. A new generation of estrogen-free pill containing 4 mg of drospirenone (DRSP) has been developed to improve these aspects.

Data from a human mass balance study indicate that DRSP is extensively metabolized, as only trace amounts of DRSP were excreted unchanged in urine and feces. In human plasma, the two major metabolites of DRSP that have been identified are the acid form of DRSP generated by opening of the lactone ring and the 4,5-dihydro-drospirenone-3-sulfate form [3]. Both metabolites are formed independently of the CYP pathways [3].

Drospirenone is also rapidly absorbed following oral administration. Serum drospirenone concentrations are linearly related to the amount of drospirenone in a single oral dose with a mean bioavailability of 76%.

Circulating drospirenone binds serum proteins to an extent of nearly 98.5% but does not bind SHBG or corticosteroid-binding globulin (CBG) [4,5,6]. Unlike drospirenone, other progestins such as norethindrone, levonorgestrel, desogestrel and gestodene all have binding affinities to SHBG, resulting in less availability of SHBG for androgen binding [7].

Drospirenone binds to aldosterone receptors in the kidney, blocking the effects of aldosterone and resulting in moderately increased sodium and water excretion [6, 8, 9, 10, 11]. Drospirenone also binds the androgen receptor (AR) in peripheral tissues, blocking the effects of testosterone [6, 8, 9, 11].

Drospirenone is metabolized in the liver to the acid conjugate and 4,5-dihydrodrospirenone-3- sulfate, which are formed independently of the cytochrome P450 system. These main plasma metabolites are considered pharmacologically inactive and excreted in urine or feces, with almost complete excretion occurring 10 days after administration of single and multiple dose regimens. Plasma levels decline biophysically with a plasma distribution phase half-life of 2 h and a terminal disposition half-life of 30-34 h [4].

These data confirmed the in-vitro results with the assumption that CYP3A4 inhibitors should have no significant effect on the pharmacokinetics (PK) of DRSP, as the latter is not a substrate of CYP3A4 in-vitro [12] and led to the conclusion that only a minor part of the DRSP metabolism is catalyzed by CYP3A4 and other CYP isoenzymes (unpublished data on file [reports B186, AY74, A166], Bayer, Berlin, Germany). Recent studies have found a PK interaction between CYP3A4 inhibitors and DRSP. Co-administration of boceprevir (Victrelis®, Merck Sharp & Dohme), a protease inhibitor used to treat chronic hepatitis C, with a combined oral contraceptive (COC) containing DRSP and ethinyl estradiol (EE) (Yaz®, Bayer) resulted in a 2-fold increase in DRSP exposure [13]. A subsequent study investigated the potential interaction between the potent CYP3A4 inhibitor ketoconazole and the above-mentioned COC and found a 2.68-fold increase of DRSP exposure in the DRSP with EE group when ketoconazole was co-administered [3].

Another study could show that DRSP alone exhibits a lower accumulation ratio than together with EE. The extent of systemic exposure at steady-state is about 32% less with the new formulation (AUC(0-24h), steady-state geometric mean ratio: 77.8%; 90% confidence interval: 74.6%–81.1%). These results suggest that metabolic pathways of DRSP can be inhibited by EE resulting in higher DRSP plasma concentrations in DRSP/EE formulations than in a DRSP-alone formulation and that the enzymes CYP3A4 and SULT1A1 may play a role [14].

The main objective of the present trial was to assess the food effect on an oral contraceptive containing 4 mg of non-micronized drospirenone after single dose administration one under fasting conditions and after food intake (i.e., 30 minutes after the start of a standard high-fat breakfast) both in two different periods, at least 14 days apart.

2. Materials And Methods

2.1 Study design

We conducted an open-label, controlled, crossover, 2-treatment, 2-period, 2-sequence, monocentre study at the Sector for Bioequivalence Trials at MHAT Tokuda Hospital, (Sofia, Bulgaria) between Januar and Februar 2013 (EudraCT-No: 2011-002396-42. Each study period lasted 5 days, including two hospitalizations of approximately 24 h (days 0 to 1) and 4 out-patient visits.

The concentration of total (i.e., free, and protein-bound) DRSP was determined using liquid chromatography and double-sector mass spectrometry [LC/MS/MS] in accordance with the respective recommendation for determination of

DRSP in PK studies [15].

DRSP was analyzed by the bioanalytical division of Anapharm Europe using the analytical method SOP ANE 5199.05 entitled “Determination of Drospirenone in Human EDTA Plasma over a Concentration Range of 0.25 to 100 ng/mL using a LC/MS/MS Method”. The method involved a solid-phase extraction procedure with reversed phase 60 mg cartridges and subsequent derivatization with Girard-P solution. DRSP and internal standard were measured by reversed phase high-performance liquid chromatography coupled to a tandem mass spectrometry detector (LC/MS/MS). The calibration range at on-line validation was 0.25-99.80 ng/mL. The lowest calibrator (and thus the limit of quantification) was 0.25 ng/mL. The on-line validation based on quality control samples at four concentration levels (0.75, 35.00, 75.00, 8.00 ng/mL) for DRSP measured twice per analytical run showed an inter-assay precision of 2.17-6.72% coefficient of variation (CV). All samples from the same subject were measured in a single analytical run to eliminate the influence of the inter-assay imprecision of the assessment [15, 16, 17].

2.2. Ethical conduct, study approval and timelines.

We performed the study in accordance with Good Clinical Practice (GCP), local requirements and the Declaration of Helsinki. The Bulgarian Drug Agency and the local ethics committee at MHAT Tokuda Hospital (Sofia, Bulgaria) approved the study, and all subjects gave written informed consent.

Studied period:

Date of first enrolment: 15-JAN-2013 date of first subject dosed: 20-JAN-2013

Date of last completion: 06-FEB-2013 (last regular final visit), on 22-FEB-2013, additional control visit in 1 subject.

Trial registration number: EudraCT-No: 2012-004309-28. https://www.clinicaltrialsregister.eu

The posted result-related information is made public through the EU Clinical Trials Register of Eudra Pharm in accordance with the Commission guidance documents set out under Section 1, i.e., only result-related information on non-paediatric Phase-I clinical trials is not made public.

Subjects and treatments

We conducted the study in pre-menopausal Caucasian women, aged between 18 and 40 years, with a body mass index of $\geq$18.5 to $\leq$30 kg/m^2. The women were required to be physically and mentally healthy based on medical and standard laboratory examinations, non-smokers since at least 6 months (confirmed by urine cotinine test) and had to be using an effective non-hormonal method of contraception. According to the final version of the study protocol (dated 08-Oct-2012) 24 healthy pre-menopausal female volunteers were randomized and completed both study periods according to protocol.

The investigator administered the study medication to each volunteer in a random way a single oral dose of 4 mg drospirenone on two single occasions. Each dosing was performed in the morning of day 1 between 8:00 and 8:46 a.m. and thus either under fasting conditions (at least 10 hours overnight fasting) or after food intake (i.e., 30 minutes after the start of the standard high-fat breakfast) after check for exclusion criteria and diet, restrictions, and adverse event.

A second medical professional supervised the intake. On each day of administration and/or blood sampling, the identity of the subject was compared with their national identity card.

In 2 study periods, the subjects received an oral dose of 4 mg DRSP, with a wash-out period of 14 days between study periods.

The investigator administered the dose according to randomization (Figure 1) with the subjects standing, and on days 1 subjects had to remain in an upright position (walking, sitting, or standing) for 5 h after drug administration.

2.3. Sample size

We calculated the sample size based on residual variance data for the area under the concentration/time curve (AUC) (15%) and observed maximum concentration (C_{max}) (20%) obtained in a preceding pilot PK study. Twenty-four (24) subjects were enrolled and dosed so that, and all 24 subjects completed the study, which was considered to provide at least 80% power at 5% alpha for an equivalence test with a geometric mean ratio of up to 1.05 and the corresponding confidence interval (CI) within the limits of 80-125%.

Pharmacokinetic endpoints

The following pharmacokinetic endpoints were defined for drospirenone:

AUC(0-72h) Area under the concentration/time curve, calculated by the trapezoidal rule from time 0 h to 72h:

Cmax Observed maximal concentration after administration

tmax Observed time point of maximal concentration

The highest concentration really measured and the time at which it was registered in any given volunteer was regarded as Cmax and tmax, respectively. In cases with two or more identical concentration maxima at different time points the first one was always regarded as tmax.

If differences between the planned and real blood sampling times (time deviations) were observed after the administration of the test product the real time intervals were used for the purpose of calculation of the pharmacokinetic endpoints.

In case of missing samples because of not coming to visit or in case of drop-out subject all available plasma samples of this subject had to be analysed in the bioanalytical center and the results were to be presented in the study report as concentrations and individual graphics. No dropouts and no missing samples were recorded in the present study. The PK/BA evaluations had to be done as far as possible for the concrete individual case.

All endpoints listed above were determined in a model-independent way according to the algorithm of the program NC_PKP.sas.

All pharmacokinetic endpoints had to be determined in a model-independent way. The highest concentration really measured and the time at which it has been registered after each dose in any given volunteer was regarded as Cmax and tmax respectively.

The primary endpoints in the present trial were AUC(0-72h) and Cmax of drospirenone. These endpoints had to undergo descriptive and comparative statistical evaluation.

Secondary endpoint was tmax of drospirenone and had to undergo descriptive statistical evaluation.

2.4. Statistics

Descriptive statistical evaluation provided the arithmetic and geometric means, standard deviation, CV, minimum, maximum, and median of the following: safety and demographic data of all randomized subjects, blood concentrations per subject/treatment for all randomized subjects and PK endpoints for all randomized subjects.

We performed the analysis of variance of log-transformed data according to a general linear model (GLM-ANOVA). Fixed factors in the model were sequence, treatment, period and subject within sequence.

We carried out the biostatistical evaluation using SAS for Windows version 9.2 (Statistical Analysis System, SAS-Institute, Cary NC, USA).

For the pharmacokinetic endpoints a descriptive statistical evaluation for all PK endpoints after single dose administration with and without food intake was performed. A parametric method (ANOVA-log) for the primary endpoints AUC(0-72h) and Cmax of drospirenone was carried out.

A 90% confidence interval (CI) for the ratio (Test with food vs. Test without food) for the primary endpoints AUC(0-72h) and Cmax of drospirenone was used with following fixed factors in the model: sequence, treatment, period, volunteer within sequence. A non-parametric method (Hauschke et al. 1990) for tmax of drospirenone was used.

A descriptive statistical evaluation was used for the evaluation of the safety.

We selected the 90% CI in accordance with the Committee for Medicinal Products for Human Use (CHMP) Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), dated 20 January 2010, stating that in "studies to determine bioequivalence after a single dose, the parameters to be analyzed are $AUC_{(0-t)}$, or, when relevant, $AUC_{(0-72h)}$ and C_{max}, and that for these parameters the 90% CI for the ratio of the test and reference products should be contained within the acceptance interval of 80.00-125.00%. For studies to determine bioequivalence of immediate-release formulations at steady-state, $AUC_{(0-\tau)}$ and $C_{max,ss}$ should be analyzed using the same acceptance interval as stated above." [18]

3. Results

3.1. Subject disposition

We questioned a total of 35 pre-menopausal female subjects with respect to the inclusion and exclusion criteria and performed standard clinical and laboratory screening at the entry examination. Eleven of the 35 enrolled subjects were screened but not randomized (see Figure 1). The demographic data of all randomized subjects (n=24) are summarized in Table 1.

The 24 study-completers were exposed to a single oral dose of DRSP 4 mg. The actual wash-out phase between both study periods was 14 days.

Pharmacokinetics

A total number of 24 volunteers completed the trial according to the protocol. The samples of 24 study completers were analyzed. The statistical evaluation was based on the data of 24 volunteers.

The concentration-time curves of drospirenone after administration of an oral single dose of 4 mg drospirenone under fasting and food conditions are to be found in the figures 2 and 3 (linear and semilogarithmic).

The evaluation of bioavailability of the endpoints AUC(0-72h) and Cmax of drospirenone was based on a parametric method (ANOVA-log). The 90% CI for the intra-individual ratios (Test with food 'A' vs. Test without food 'B') for AUC(0-72h) and Cmax of drospirenone are presented in table 2.

The 90% CI calculated by means of ANOVA-log for the endpoint, intra-individual ratio (Test 'A' vs. Test 'B') of AUC(0-72h) of drospirenone was between 104.72% and 111.36%. The 90% CI calculated by means of ANOVA- log for the endpoint intra-individual ratio (Test 'A' vs. Test 'B') of Cmax of drospirenone was between 118.58% and 141.10% (see table 3).

The mean relative bioavailability of the Test with food 'A' compared to the Test without food 'B' after single dose administration based on the endpoints AUC(0-72h) was 107.99% and for the endpoint Cmax it was 129.35%

3.2. Adverse events

No serious AEs or unexpected AEs occurred during the study.

4. Discussion

The evaluation of the relative bioavailability in this study was based on a parametric method (ANOVA-log) for the pharmacokinetic endpoints AUC(0-72h) and Cmax of drospirenone after food intake and under fasting conditions. The 90% CI calculated by means of ANOVA-log for the endpoint, intra-individual ratio (Test 'A' vs. Test 'B') of AUC(0-72h) of drospirenone was between 104.72% and 111.36%. The 90% CI calculated by means of ANOVA-log for the endpoint intra-individual ratio (Test 'A' vs. Test 'B') of Cmax of drospirenone was between 118.58% and 141.10%.The mean relative bioavailability of the Test with food 'A' compared to the Test without food 'B' after single dose administration based on the endpoints AUC(0- 72h) was 107.99% and for the endpoint Cmax it was 129.35%.The single dose administration of 4 mg non micronized drospirenone taken after a standard high-fat breakfast has a relative bioavailability of 107.99 % for AUC(0-72h).

The rate of absorption, based on the endpoint Cmax of drospirenone was increased by about 30% under fed conditions which differs from information reported in the US Prescribing Information of YAZ® (tablets containing drospirenone and ethinyl estradiol). According to the latter the rate of absorption of drospirenone in the combination with ethinyl estradiol following single administration of a formulation similar to YAZ® was slower under fed (high fat meal) conditions with the serum Cmax being reduced by about 40% for both components.

EE is an inhibitor of CYP3A4 [16, 17, 18] and our findings are in line with those previously reported by Kasserra et al. 2015 [19] and Wiesinger et al. 2015 [3]; however, the present study could not determine which metabolic pathway is responsible for the observed increased exposure to DRSP when co-administered with EE. Contradictory in-vitro data leave doubt as to whether CYP3AA inhibition is the main contributor or not.

Considering the metabolic pathway of DRSP, sulfotransferases in addition to CYP3A4 are a possible target for a drug-drug interaction between the 2 steroids. Rohn et al. [20] and Rohn-Glowacki [21] recently explored the potent inhibition by EE of human sulfotransferase 1A1 (SULT1A1), the major xenobiotic sulfating isoform in the liver. The isoforms of greatest interest in these studies were SULT1E1, known to sulfate EE at nanomolar levels (Falany et al., 1995, [22], Falany and Falany, 1997 [23]), and SULT1A2, which has the most similar loop 1 aa sequence including Ile89 identical to SULT1A1. The inhibition of SULT1E1 sulfation activity by EE would be competitive since it is known to be a substrate.

Possible explanations for the different effect of food on the test product as compared to literature data might be the following:

1. The fact that the data related to YAZ® refer to a combination of drospirenone with ethinyl oestradiol. The food effect might be different for the combination as compared to the single component

2. The fact that completely different galenic formulations were investigated. Differences in the formulation might also lead to a difference in the effect of food.

3. Our results may also be due to the non-micronized formulation of the DRSP 4 mg tablets.

The observed differences neither affect inhibition of ovulation [24] nor the clinical efficacy that was demonstrated in 2 European and 1 US clinical trial [].

The non-existing absorption of the drospirenone only pill between food intake and non-food intake is at least an increase in the safety profile of this non micronized drospirenone formulation as constant hormonal levels are garneted independent of the consumers habits in real life.

Abbreviations

DRSP = Drospirenone

AUC = Area Under the Curve

Cmax = Observed Maximal Concentration after Administration

Tmax = Observed Time Point of Maximal Concentration

POP = Progestin Only Pill

CYP = Cytochrome P

SHBG = Sexual Hormone Binding Globuline

CBG = Corticosteroid-Binding Globulin

AR = Androgene Receptore

PK = Pharmakokinetics

COC = Combined Oral ContraceptiveDocosapentanoic Acid

EE = Ethinyl Estradiol

LC/MS/MS = Liquid Chromatography Coupled to a Tandem Mass Spectrometry Detector

SULT1A1 = Sulfotransferase 1A1

Declarations

Conflict of interest

Authors: P.-A. Regidor, W. Richter, R. Koytchev, V. Kirkov, E. Colli

All authors have completed the Unified Competing Interest form.

W. Richter, R. Koytchev are employed by Cooperative Clinical Drug Research and Development AG, Hoppegarten, Germany. V. Kirkov is employed at the Sector for Bioequivalence Trials at MHAT Tokuda Hospital Sofia AD, Bulgaria.

E. Colli and P.-A. Regidor are employees of Exeltis Healthcare.

There are no other financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

Funding

The study was sponsored by LEON FARMA, S.A., Spain.

Ethics approval and consent to participate:

We performed the study in accordance with Good Clinical Practice (GCP), local requirements and the Declaration of Helsinki. The Bulgarian Drug Agency and the local ethics committee at MHAT Tokuda Hospital (Sofia, Bulgaria) approved the study, and all subjects gave written informed consent.

Trial registration number: EudraCT-No: 2012-004309-28

Consent for publication

Patients consent of publication and authors consent of publication is given.

Consent for publication from participants for manuscripts that include information or images that could lead to the identification of study participants.

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

W. Richter, R. Koytchev are employed by Cooperative Clinical Drug Research and Development AG, Hoppegarten, Germany. V. Kirkov is employed at the Sector for Bioequivalence Trials at MHAT Tokuda Hospital Sofia AD, Bulgaria.

E. Colli and P.-A. Regidor are employees of Exeltis Healthcare.

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Authors' contributions

Pedro Antonio Regidor: Responsible for writing and data collection

W. Richter: Responsible for the data evaluation

R. Koytchev. Responsible for the study design

V. Kirkov: Responsible for the clinical data

E. Colli: Responsible for the scientific design

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Not applicable

A written informed consent was obtained from all participants that were enrolled in the clinical trial.

References

1. Medical eligibility criteria for contraceptive use, 5th ed. 2015. World Health Organization. ISBN 978 92 4 154915 8.
2. Lidegaard Ø, Løkkegaard E, Jensen A, Skovlund CW, Keiding N. Thrombotic stroke and myocardial infarction with hormonal contraception. N Engl J Med 2012; 366(24):2257–2266.
3. Wiesinger H, Berse M, Klein S, Gschwend S, Höchel J, Zollmann F, Schütt B. Pharmacokinetic interaction between the CYP3A4 inhibitor ketoconazole and the hormone drospirenone in combination with ethinylestradiol or estradiol: Br J Clin Pharmacol 2015; 80(6): 1399–1410.
4. Yaz (drospirenone and ethinyl estradiol) [prescribing information]. Berlex,Inc., Montville, NJ, USA, October (2006).
5. Yasmin (drospirenone and ethinyl estradiol) [prescribing information]. Berlex, Inc., Montville, NJ, USA, October (2005).
6. Krattenmacher R: Drospirenone: pharmacology and pharmacokinetics of a unique progestogen. Contraception 62(1), 29–38 (2000).
7. Kuhnz W, Blode H, Zimmermann H: Pharmacokinetics of exogenous natural and synthetic estrogens and antiestrogens. In: Handbook of Experimental Pharmacology. Oettel M, Schillinger E (Eds), Springer- Verlag, Berlin, Germany, 261–320 (1999).
8. Fuhrmann U, Krattenmacher R, Slater EP et al.: The novel progestin drospirenone and its natural counterpart progesterone: biochemical profile and antiandrogenic potential. Contraception. 54(4), 243–251 (1996).
9. Sitruk-Ware R: Pharmacology of different progestogens: the special case of drospirenone. Climacteric 8(3), 4–12 (2005).
10. Oelkers W: Drospirenone – a new progestogen with antimineralocorticoid activity, resembling natural progesterone. Eur. J. Contracept. Reprod. Health Care 5(3), 17–24 (2000).
11. Muhn P, Krattenmacher R, Beier S, Elger W, Schillinger E: Drospirenone: a novel progestogen with antimineralcorticoid and antiandrogenic activity. Pharmacological characterization in animal models. Contraception 51(2), 99–110 (1995).
12. US Food and Drug Administration. Center for Drug Evaluation and Research: NDA 21676 - Clinical pharmacology and biopharmaceutics review(s) 2006. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021676s000_CLINPHARMR.pdf (last accessed 28 July 2015).
13. Treitel M, Marbury T, Preston RA, Triantafyllou I, Feely W, O'Mara E, Kasserra C, Gupta S, Hughes EA. Single-dose pharmacokinetics of boceprevir in subjects with impaired hepatic or renal function. Clin Pharmacokinet. 2012 Sep

1;51(9):619-28.

14. Richter WH, Koytchev R, Kirkov V, Merki G, Colli E, Regidor PA. Comparative pharmacokinetic estimates of drospirenone alone and in combination with ethinyl estradiol after single and repeated oral administration in healthy females. Contraception 2020; 101: 137–143.
15. FDA Draft Guidance on Drospirenone and Ethinyl Estradiol. Recommended Mar 2009; Revised Nov 2013. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm118167.pdf.
16. Zhang H, Cui D, Wang B, Han Y, Balimane P, Yang Z, Sinz M, Rodrigues AD. Pharmacokinetic drug interactions involving 17alpha-ethinylestradiol: a new look at an old drug. Clin Pharmacokinet 2007; 46: 133–157.
17. Chang S, Chen C, Yang Z, Rodrigues AD. Further assessment of 17alpha-ethinyl estradiol as an inhibitor of different human cytochrome P450 forms in vitro. Drug Metab Dispos 2009; 37: 1667–1675.
18. Lin H, Kent UM, Hollenberg PF. Mechanism-based inactivation of cytochrome P450 3A4 by 17 alpha-ethynylestradiol: evidence for heme destruction and covalent binding to protein. J Pharmacol Exp Ther 2002; 301: 160–167.
19. Kasserra C, Hughes E, Treitel M, Gupta S, O'Mara E. Clinical pharmacology of boceprevir: Metabolism, excretion, and drug-drug interactions: 18th Conference on Retroviruses and Opportunistic Infections (CROI), Boston, MA, 2011. 2011. Available at http://www.natap.org/2011/CROI/ croi_11.htm (last accessed 11 May 2015).
20. Rohn KJ, Cook IT, Leyh TS, Kadlubar SA, Falany CN. Potent inhibition of human sulfotransferase 1A1 by 17α-ethinylestradiol: role of 3'-phosphoadenosine 5'-phosphosulfate binding and structural rearrangements in regulating inhibition and activity. Drug Metab Dispos. 2012 Aug;40(8):1588–95.
21. Rohn-Glowacki KJ, Falany CN. The potent inhibition of human cytosolic sulfotransferase 1A1 by 17α-ethinylestradiol is due to interactions with isoleucine 89 on loop 1. Horm Mol Biol Clin Investig. 2014 Dec;20(3):81–90.
22. Falany CN, Krasnykh V, and Falany JL. Bacterial expression and characterization of a cDNA for human liver estrogen sulfotransferase. J Steroid Biochem Mol Biol. 1995; 52:529–539.
23. Falany JL, Falany CN. Regulation of estrogen activity by sulfation in human MCF-7 breast cancer cells. Oncol Res. 1997; 9:589–596.
24. Duijkers IJM, Heger-Mahn D, Drouin D, Colli E, Skouby S. Maintenance of ovulation inhibition with a new progestogen-only pill containing drospirenone after scheduled 24-h delays in pill intake. Contraception. 2016 Apr;93(4):303–309.
25. Palacios S, Colli E, Regidor PA. Multicenter, phase III trials on the contraceptive efficacy, tolerability and safety of a new drospirenone-only pill. Acta Obstet Gynecol Scand. 2019;98: –1557. DOI: 10.1111/aogs.13688.
26. Kimble T, Burke A, Barnhart K, Colli E, Archer D, Westhoff C. 2020. A 1-year prospective, open-label, single-arm, multicenter, phase 3 trial of the contraceptive efficacy and safety of the oral progestin-only-pill, drospirenone 4 mg, using a 24/4-day regimen. Contraception X.

Tables

Table 1. Patient's characteristics

(n=24)	Mean ± SD	Min – Max
Age [years]	30.5 ± 5.5	19.0 - 39.0
Height [cm]	161.5 ± 6.2	153.0 - 172.0
Weight [kg]	62.6 ± 10.8	49.5 - 87.3
BMI [kg/m^2]	23.9 ± 3.4	19.2 - 29.5
male : female	0 : 24	

Table 2: Pharmacokinetic endpoints of drospirenone after an oral single dose of 4 mg drospirenone administered after food intake and under fasting conditions (arithmetic mean, geometric mean, SD, CV, lower and upper ranges, median, n = 24)

DROSPIRENONE							
TEST 'A' (with food)							
Variable	**geom. mean**	**arithm. mean**	**SD**	**CV**	**range**	**median**	**N**
AUC(0-72h) [ng*h/mL]	479.28	487.93	96.00	19.7	311.46 - 733.36	462.40	24
Cmax [ng/mL]	34.98	36.19	9.83	27.1	20.60 - 59.39	35.42	24
tmax [h]	2.698	2.896	1.343	46.4	2.000- 8.000	2.500	24
TEST 'B' (without food)							
Variable	**geom. mean**	**arithm. mean**	**SD**	**CV**	**range**	**median**	**N**
AUC(0-72h) [ng*h/mL]	443.83	452.38	91.13	20.1	303.76 - 671.67	438.23	24
Cmax [ng/mL]	27.04	27.53	5.17	18.8	17.99 - 35.02	28.24	24
tmax [h]	3.944	4.063	0.958	23.6	2.500 - 6.000	4.500	24

Table 3: 90% confidence intervals of drospirenone.

DROSPIRENONE (n=24)				
Variable	**method**	**point estimator**	**confidence intervals**	**CV(%)**
AUC(0-72h) (Ratio TEST 'A' with food vs. TEST 'B' without food)	ANOVA-log	107.99%	104.72% - 111.36%	6.21%
Cmax (Ratio TEST 'A' with food vs. TEST 'B' without food)	ANOVA-log	129.35%	118.58% - 141.10%	17.68%

Figures

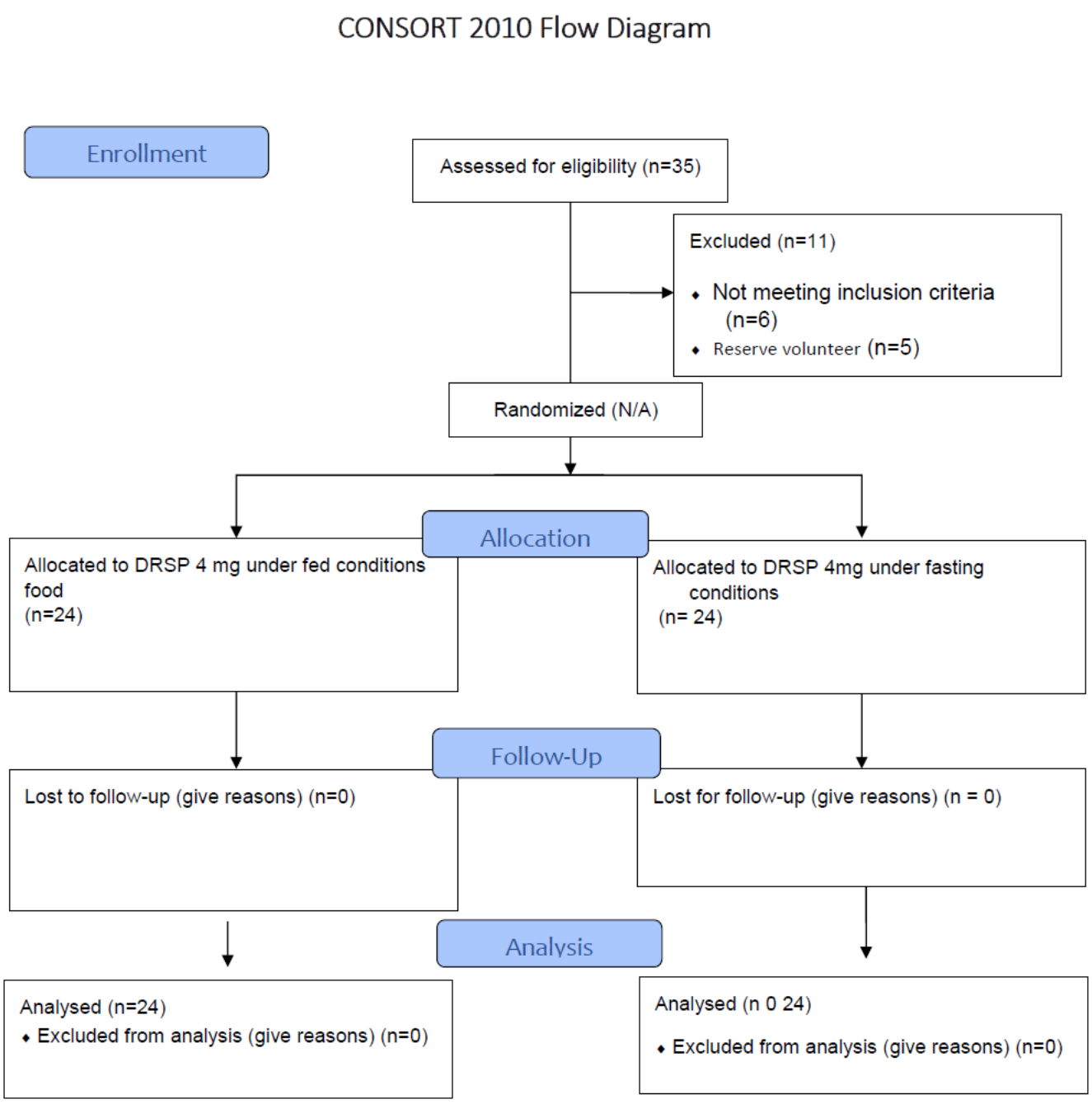

Figure 1

Flow diagram of the patients enrolled in the clinical trial.

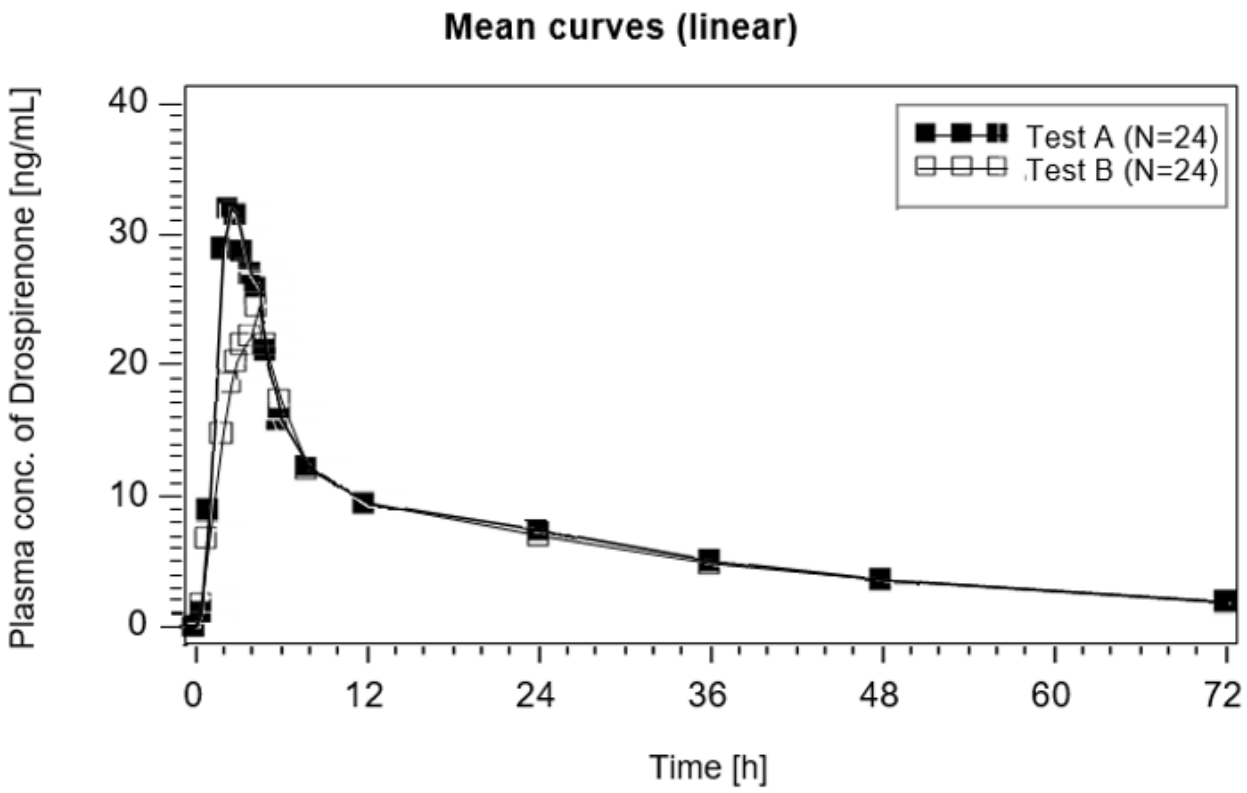

Figure 2

Mean drospirenone plasma concentration-time profile (linear) after single dose of 4 mg drospirenone administered after food intake ‘A’ and under fasting conditions ‘B’

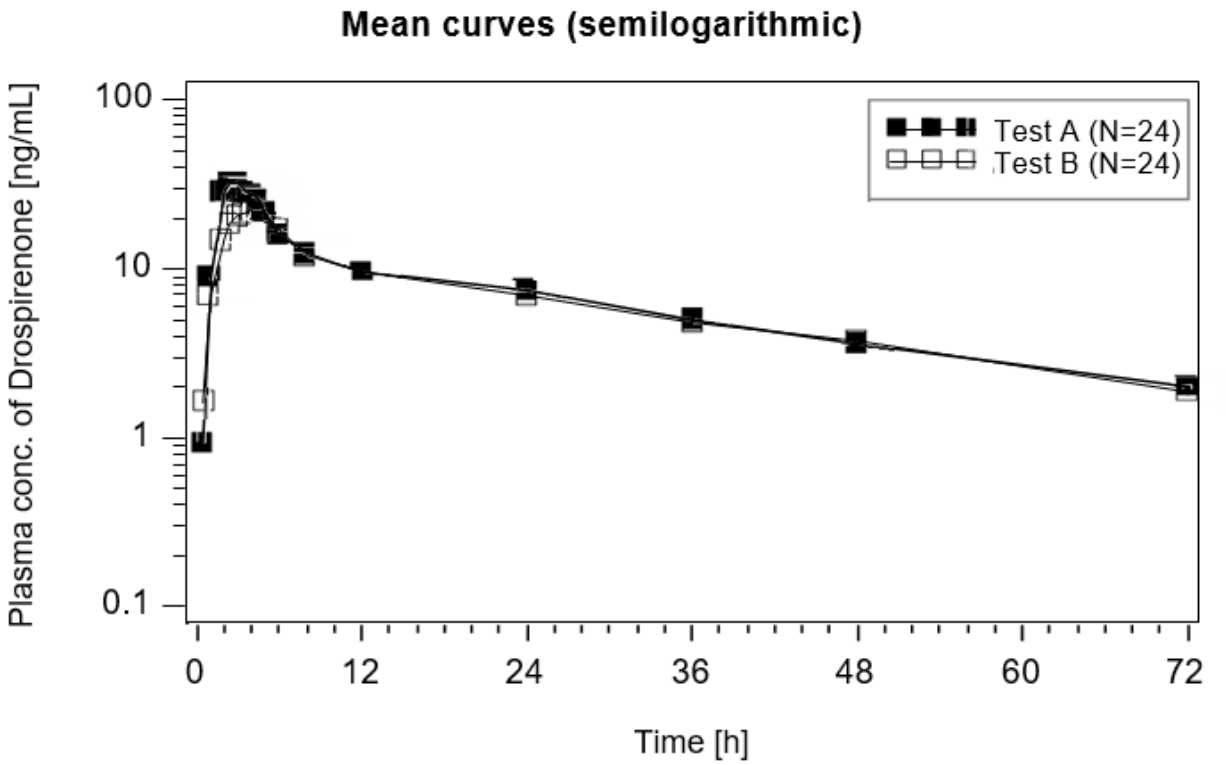

Figure 3

Mean drospirenone plasma concentration-time profile (semilogarithmic) after single dose of 4 mg drospirenone administered after food intake ‘A’ and under fasting conditions ‘B’

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010checklist.docx