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Absence of Drug-Drug Interaction of Anastrozole on Levonorgestrel Delivered Simultaneously by an Intravaginal Ring: Results of a Phase 2 Trial

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Abstract

Intravaginal rings (IVRs) are an established option for continuous administration of drugs in women. The combination of anastrozole (ATZ) and levonorgestrel (LNG) in an IVR with an intended 4-week wearing period has been considered for long-term treatment of endometriosis-associated pelvic pain. A randomized, parallel-group, multicenter phase 2b study to assess the efficacy and safety of different dose combinations in women with symptomatic endometriosis has recently been performed. This paper will focus on the investigation of pharmacokinetic (PK) effects of ATZ on LNG using data collected from this study. Two hundred sixteen patients were randomized to the treatment group with IVRs releasing LNG 40 μg/day alone or in combination with ATZ 300 μg/day, 600 μg/day, or 1050 μg/day for 12 weeks. PK blood samples were taken before dosing and before IVR replacement or removal (days 28, 56, and 84). The primary PK parameter was the plasma concentration in apparent steady state of ATZ and LNG at the end of each IVR wearing period. Results of PK analysis demonstrate that ATZ concentrations increased proportionally with increasing dose (geometric mean values of 7.85, 15.48, and 22.61 μg/L at 300, 600, and 1050 μg/day nominal release, respectively). All point estimates for LNG concentration in apparent steady state ratios between the mono and combination IVR groups were close to 1, and the 90% confidence interval limits were in the 0.80 to 1.25 range (1.01 [0.85-1.19], 1.03 [0.88-1.20], 0.94 [0.80-1.10]). In conclusion, our data indicate there is no evidence of drug-drug interaction of ATZ on LNG.

Keywords

clinical pharmacology, drug delivery, drug-drug interactions, gynecology, pharmacokinetics and drug metabolism, women's health

Endometriosis is a chronic, painful inflammatory disease affecting up to 10% of women of reproductive age, and up to 50% of women with infertility.[1,2] Despite available treatments, the loss of efficacy and side effects observed over time have created an unmet need for effective medical therapies with favorable safety profiles for the long-term treatment of endometriosis. This study investigates the drug-drug interaction (DDI) potential of various doses of the aromatase inhibitor anastrozole (ATZ) on a fixed low dose of levonorgestrel (LNG) delivered simultaneously via intravaginal rings (IVRs) for the treatment of endometriosis-associated pelvic pain. While ATZ is applied with the intention to inhibit endometriotic estrogen production, low-dose LNG aims to provide effective contraception to prevent the unwanted embryotoxic effects of ATZ.[3] LNG is a well-characterized drug product approved for use as a contraceptive in various delivery systems: progestin-only pill (eg, Norgeston, corresponding to Microlut in other countries), subcutaneous implant (Jadelle), or intrauterine system (Mirena).[4–6]

A phase 1 study has been completed in Europe investigating pharmacokinetics, pharmacodynamics, and the safety and tolerability of ATZ/LNG in healthy, ovulating women aged 18 to 35 years.[3] Participants were randomized equally to use IVRs releasing 1 of 3 ATZ/LNG dose combinations (ATZ 500 μg/day + LNG 20 μg/day, ATZ 1000 μg/day + LNG 30 μg/day, or ATZ 1500 μg/day + LNG 40 μg/day). These doses are the nominal in vitro daily drug release rates at the end of the 28-day wearing period and are used to denote the different treatment groups. In addition, actual in vitro release rates were measured

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for all batches for the defined intervals. Treatment duration in this phase 1 study was 56 days with an IVR change conducted after 28 days. Data on safety obtained in this study showed that treatment with the administered IVR containing different doses of ATZ and LNG was well tolerated. From a pharmacokinetic (PK) point of view, it is important to note that the exposure of LNG was stable over the entire treatment period (starting 1 week after the first IVR insertion). In particular, the plasma concentration at the end of each 4-week wearing period (concentration at apparent steady state [C_{ss}]) was almost identical in the individual subjects.[3] Overall, the same trend was observed for ATZ. However, consistent with the higher ATZ in vitro release rates observed at the beginning of the release period, plasma concentration declined slightly over time.[3] Furthermore, there was no observed daily fluctuation of LNG or ATZ plasma concentrations following administration via an IVR.[7] Consequently, a single blood sample taken at a defined time period during the wearing period of the IVR allowed for the calculation of C_{ss} for both LNG and ATZ.

Simulations using pharmacometric approaches showed that LNG doses of 40 μg/day combined with ATZ 300, 600, or 1050 μg/day reached anticipated plasma concentrations for both drugs. As a result, these doses were selected for the phase 2 dose-finding study.[8] It should be noted that for these simulations it was anticipated that there would be no effect of ATZ on LNG. However, potential DDIs have not been clinically investigated to date, as an IVR administering only LNG was not included in the phase 1 program. As both drugs are intended to be used in a fixed combination, the knowledge on potential DDI (ie, relevant for the contraceptive efficacy) is essential.[9] To address the question of whether ATZ affects the plasma concentration of LNG and subsequently may jeopardize the contraceptive efficacy, various strategies were considered. An innovative method to optimize the development process was implemented by incorporating this objective into the phase 2 dose-finding study, the results of which are described in this paper. All details of this phase 2b study are summarized in the corresponding study synopsis, while only the relevant information for the DDI investigation is summarized in this paper.[10] Consequently, no efficacy or safety data are reported in this paper. However, this data will be published in a separate paper.

Methods

The study protocol (EudraCT number 2013-005090-53; National Clinical Trial number NCT02203331) was approved by the corresponding competent authorities, independent site ethics committee, and institutional review boards. All patients provided written informed consent prior to participating in the study. The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles established in the Declaration of Helsinki and the International Council for Harmonization guidelines.

Study Design

This investigation was a multicenter, randomized, double-blind, double-dummy, placebo and active-controlled, parallel-group study conducted with 117 participating sites in the United States, Europe, and Japan. The study comprised 3 different periods: screening (with a duration of at least 28 days to a maximum of 60 days), treatment (12 weeks = 84 days with IVR changes every 28 days), and a follow-up (28 days).

Four of 6 dose groups received an IVR releasing either LNG as a monotherapy or in 1 of 3 ATZ/LNG dose combinations:

- LNG 40 μg/day
- ATZ 300 μg/day + LNG 40 μg/day
- ATZ 600 μg/day + LNG 40 μg/day
- ATZ 1050 μg/day + LNG 40 μg/day

The dose per day for ATZ and LNG reflects nominal doses based on an intended in vitro release rate at the end of the 28-day wearing period. The PK evaluation included data from these 4 dose groups. It should be noted that in addition to the 4 dose groups previously described, 2 more dose groups were also included in the study consisting of a leuprorelin/leuprolide acetate (3-month depot injection of 11.25 mg) group and a placebo group.[10,11] As leuprorelin/leuprolide acetate was added to benchmark efficacy of the IVR to an active approved comparator, and a placebo was added to control for known placebo effects on pain, both groups were excluded in the evaluation of potential DDI.

Patients

Subjects participating in the study consisted of premenopausal women aged ≥18 years with endometriosis (confirmed by laparoscopy or laparotomy) and suffering from moderate to severe endometriosis-associated pelvic pain. Excluding endometriosis, these women were considered to be in otherwise good general health as supported by their medical history, physical and gynecological examinations, and laboratory test results obtained for inclusion in the study. Use of a nonhormonal barrier method (ie, spermicide-coated condoms) for contraception was required from the screening visit until the end of the study.

Key exclusion criteria included conditions/diseases that could compromise the function of the body systems and could result in altered absorption,

excessive accumulation, impaired metabolism, or altered excretion of the non-study drug; use of nonstudy oral, vaginal, or transdermal hormonal contraception; use of drugs inducing or inhibiting metabolizing liver enzymes; or regular use of vaginal medication (eg, spermicides, antibiotics).

Treatments

All patients in the PK analysis set received an IVR (active drug) and an injection (placebo) administered between the second and fifth days of the subjects' menstrual bleeding. The initial IVRs were inserted by a gynecologist. Every 4 weeks a new IVR was inserted by the subject or the investigator. Subjects were trained on the correct application of the IVR and on the procedure to be performed if loss of the IVR occurred. Reserve IVRs (corresponding to their randomized treatment) were distributed to each subject in the event IVR replacement was required. Any removal and reinsertion of the IVR between visits was to be recorded by the subject.

The IVRs were made of silicone elastomer with an outer diameter of 54 mm and a cross-sectional diameter of 5 mm as described previously.[3,7,12] The outer surface of the ring is covered with an elastomeric membrane controlling drug release. The core of the ring is composed of individual elastomer segments including 1 containing ATZ, 1 containing LNG, and several segments without drug. The size of the segment containing LNG was consistent between IVRs, while segments containing ATZ maintained varied lengths corresponding to different release rates. The actual in vitro release rates for ATZ and LNG for the different IVR batches used in the current study were assessed.

Pharmacokinetics

Blood samples for PK analysis were taken before the start of treatment (predose sample) and before IVR replacement or removal (days 28, 56, and 84). A time window of ± 2 days for IVR replacement was allowed.

Plasma concentrations of ATZ and LNG were determined using validated liquid chromatography–tandem mass spectrometry methods.[7] Quality control and calibration samples were analyzed concurrently. For ATZ and LNG, the lower limit of quantification (LLOQ) was 0.10 μg/L and 0.01 μg/L, respectively. Quality control samples for ATZ above LLOQ were determined with an accuracy of 98.5% to 105.0% and a precision of 2.43% to 5.02%. Quality control samples for LNG above LLOQ were determined with an accuracy of 97.3% to 103.0% and a precision of 1.23% to 4.68%. The C_{ss} was calculated as the median of all measured values under treatment with ATZ and/or LNG (days 28, 56, and 84) provided that at least 2 of these values were greater than the LLOQ.

Table 1. Demographics and Mean (SD) Baseline Characteristics (PKS)

	LNG 40 μg/day	ATZ 300 μg/day + LNG 40 μg/day	ATZ 600 μg/day + LNG 40 μg/day	ATZ 1050 μg/day + LNG 40 μg/day
n	49	50	54	49
Race				
White	35 (71.4%)	36 (72.0%)	42 (77.8%)[a]	34 (69.4%)
Black	4 (8.2%)	1 (2.0%)	1 (1.9%)[a]	2 (4.1%)
Asian	10 (20.4%)	13 (26.0%)	11 (20.4%)[a]	12 (24.5%)
Age (years)	33.12 (7.58)	33.28 (8.88)	34.13 (5.65)	34.14 (7.70)
Weight (kg)	67.34 (15.12)	70.21 (19.40)	66.00 (19.30)	67.95 (16.99)
BMI (kg/m^2)	24.20 (4.52)	25.98 (6.88)	23.72 (6.14)	25.14 (5.43)

ATZ, anastrozole; BMI, body mass index; LNG, levonorgestrel; PKS, pharmacokinetic analysis set; SD, standard deviation.
[a]Not reported for 1 subject.

Statistical Analysis

Unless otherwise specified, the PK data are presented using geometric means (coefficient of variation [%CV]). A one-way analysis of variance was performed on the logarithmized PK parameter C_{ss} for LNG to assess DDI between LNG and ATZ. Point estimates and 90% confidence intervals (CIs) were determined for the geometric mean ratio of C_{ss} between each of the combination treatments and the LNG-only treatment cohort to serve as a reference.

The study was planned with 53 participants per treatment arm, which was based on efficacy considerations rather than pharmacokinetics.

Results

Patients

In total, 605 women were screened for all 6 dose groups in this study, with 319 subjects randomized to all treatment groups and 272 patients having completed the study treatment. Focusing on the relevant 4 groups described in this manuscript, 213 patients were randomized, with 180 having completed treatment. The PK analysis set consisted of subjects with valid PK measurements and included 49 subjects from the LNG 40 μg/day group, 50 subjects from the ATZ 300 μg/day + LNG 40 μg/day group, 54 subjects from the ATZ 600 μg/day + LNG 40 μg/day group, and 49 subjects from the ATZ 1050 μg/day + LNG 40 μg/day group.

Overall, demographic parameters were well balanced between the treatment groups (Table 1). Subjects were predominantly white and of non-Hispanic or Latino ethnicity (98.5% overall).

Intravaginal Rings

For the IVR, the dose administered per day of ATZ and LNG reflected nominal doses based on an intended in vitro release rate of ATZ 300, 600, and 1050 μg/day

Table 2. Summary Statistics of C_{ss} of ATZ (μg/L)

Dose Group	n	Geometric Mean (μg/L)	%CV
ATZ 300 μg/day + LNG 40 μg/day	41	7.85	35.96
ATZ 600 μg/day + LNG 40 μg/day	51	15.48	26.11
ATZ 1050 μg/day + LNG 40 μg/day	47	22.61	58.15

ATZ, anastrozole; C_{ss}, concentration in apparent steady state; CV, coefficient of variation; LNG, levonorgestrel.

and LNG 40 μg/day at the end of the 28-day intended wearing period. The average actual in vitro release rates for ATZ 300, 600, and 1050 μg/day on day 28 were 290, 596, and 941 μg/day, respectively. Only the highest ATZ dose group had an observed release rate slightly below the nominal intended value (10.4%). For LNG, actual in vitro release rates of 39 μg/day (LNG 40 μg/day; ATZ 1050 μg/day + LNG 40 μg/day), 41 μg/day (ATZ 600 μg/day + LNG 40 μg/day) and 43 μg/day (ATZ 300 μg/day + LNG 40 μg/day) have been measured. All these actual in vitro LNG release rates were similar and very close to the intended nominal value of 40 μg/day. As mentioned previously, the nominal doses are used to describe the treatment groups.

Pharmacokinetics of ATZ

Plasma concentrations of ATZ were above the LLOQ in the majority of samples taken during treatment with ATZ. The determination of C_{ss} was planned to be based on at least 2 concentration values during treatment. However, PK samples for a few patients were taken only at the end of the last treatment (day 84) and as a result, C_{ss} could not be calculated as primary PK parameter for all patients. Nevertheless, data from at least 41 patients in each dose group could be evaluated. As expected, C_{ss} of ATZ was positively correlated with increasing dose levels (see Table 2 and Figure 1).

To investigate dose proportionality in an explorative way, the dose normalized C_{ss} values were calculated. For this purpose, the actual daily ATZ release rates of the IVR batches were used (ie, 290 μg/day, 596 μg/day, and 941 μg/day). Geometric mean values of 0.027 L^{-1}, 0.026 L^{-1}, and 0.024 L^{-1} were obtained for the IVRs delivering LNG together with nominal 300, 600, and 1050 μg ATZ/day, respectively. Therefore, overall exposure of ATZ increased in a proportional manner in the presence of a low dose of LNG.

Pharmacokinetics of LNG

Ideally, PK samples should have been taken before dosing as well as at the end of week 4 (day 28), week 8 (day 56) and week 12 (day 84). As previously described for ATZ, a few patients had PK samples collected during only the last treatment week. As a result, C_{ss} could not always be calculated. Nevertheless, C_{ss} could be determined based on at least 2 values for a minimum of 40 subjects per group.

Summary statistics of LNG are provided in Table 3 and graphically displayed in Figure 2. LNG concentrations were comparable between the LNG-only and ATZ/LNG IVR groups.

Before the start of treatment (predose samples), several subjects (n = 29) had LNG concentrations above the LLOQ. In the majority of cases, these patients had reported the use of LNG containing contraceptives prior to enrollment in the study.

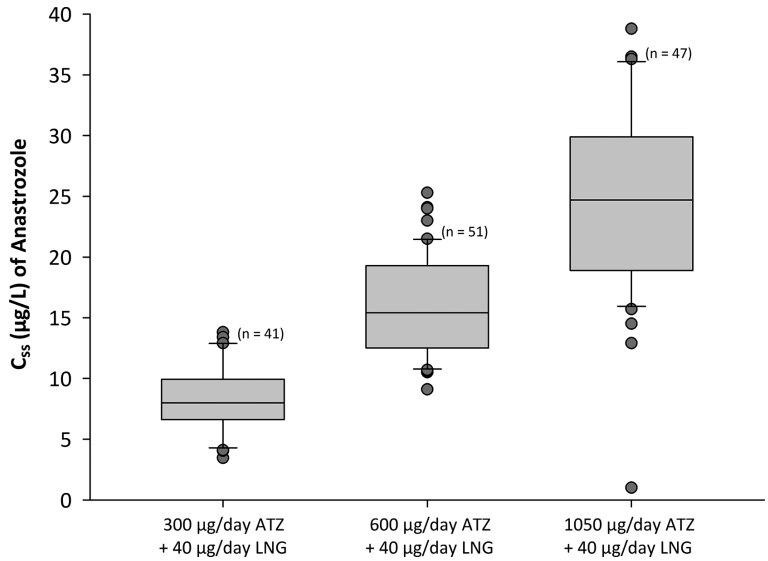

Figure 1. Box plot for C_{ss} of ATZ (μg/L) by treatment. Box: 25th to 75th percentile; horizontal line: median; whiskers (error bars): 10th to 90th percentile; any value more extreme is plotted separately. ATZ, anastrozole; C_{ss}, concentration in apparent steady state.

Table 3. Summary Statistics of C_{ss} of LNG (μg/L)

Dose Group	n	Geometric Mean (μg/L)	%CV
LNG 40 μg/day	45	0.35	64.08
	44[a]	0.33	46.50
ATZ 300 μg/day + LNG 40 μg/day	40	0.33	48.80
ATZ 600 μg/day + LNG 40 μg/day	51	0.34	50.78
ATZ 1050 μg/day + LNG 40 μg/day	47	0.31	54.60

ATZ, anastrozole; C_{ss}, concentration in apparent steady state; CV, coefficient of variation; LNG, levonorgestrel.
[a]Excluding the subject identified as outlier.

Table 4. 90% Confidence Intervals Based on ANOVA of C_{ss} of LNG

Ratio	Outlier	Lower Limit	Geom. LS-Mean	Upper Limit
ATZ 300 μg/day + LNG	Excluded	**0.85**	**1.01**	**1.19**
40 μg/day vs LNG 40 μg/day	Included	0.79	0.95	1.14
ATZ 600 μg/day + LNG	Excluded	**0.88**	**1.03**	**1.20**
40 μg/day vs LNG 40 μg/day	Included	0.82	0.97	1.15
ATZ 1050 μg/day + LNG	Excluded	**0.80**	**0.94**	**1.10**
40 μg/day vs LNG 40 μg/day	Included	0.74	0.89	1.06

ANOVA, analysis of variance; ATZ, anastrozole; C_{ss}, concentration in apparent steady state; LNG, levonorgestrel, LS-mean, least squares mean; PK, pharmacokinetic.

One subject of interest (treatment group mono-LNG IVR) whose LNG concentrations exceeded the range of 0.3 μg/L observed in almost all other subjects, had a C_{ss} value of 4.54 μg/L based on LNG concentrations of 9.79 μg/L, 4.54 μg/L, and 4.04 μg/L measured on day 28, day 56, and day 84, respectively. This 31-year-old subject had 2 births. The subject was not trying to conceive and had been wearing Mirena for 3 months prior to the study (removed before IVR insertion, LNG concentration 0.75 μg/L). No use of sex hormones was recorded during the study. The reason for increased LNG could not be established, but it cannot be excluded that she had taken prohibited LNG-containing medication during participation in the study. This subject was not excluded from the PK analysis set, and therefore this outlier is clearly identified in Figure 2. As a result, there is a definitive impact on the variability in this dose group as the %CV increased from 46.50% to 64.08%. To further investigate this finding (LNG reference group), 2 analyses of variance were performed with and without this subject included.

To assess DDI of ATZ on LNG, the C_{ss} of LNG groups with ATZ/LNG IVRs were compared to the corresponding C_{ss} of the mono-LNG IVR group by determining point estimates and 90%CIs for the given ratios. The point estimates and 90%CIs for these ratios were calculated and are provided in Table 4. No evidence of DDI was detected as the point estimates for ratios in C_{ss} between the combination and monotherapy IVR groups were close to 1 with 90%CI limits consistently in the 0.80 to 1.25 range.

Discussion

This paper discusses the DDI potential of a fixed-dose combination of simultaneously delivered ATZ and LNG, which is of crucial importance to achieve the envisaged effects of both drugs.[9] It is known from in vitro studies that ATZ inhibits cytochrome P450 (CYP) 1A2, 2C8/9, and 3A4, and that the oxidative

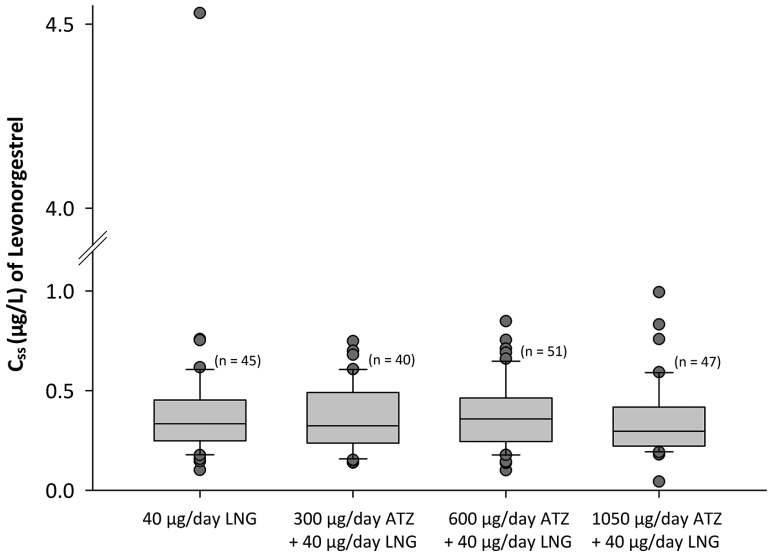

Figure 2. Box plot for C_{ss} of LNG (μg/L) by treatment. Box: 25th to 75th percentile; horizontal line: median; whiskers (error bars): 10th to 90th percentile; any value more extreme is plotted separately. C_{ss}, concentration in apparent steady state; LNG, levonorgestrel.

metabolism of LNG is catalyzed by CYP3A4.[4,13] Therefore, inhibition of CYP3A4 by ATZ may impact the metabolic clearance of LNG in vivo. Clinical studies with antipyrine and warfarin have shown that ATZ at a dose of 1 mg did not significantly inhibit the mixed CYP-mediated metabolism of these drugs.[13] However, due to the high relevance of contraceptive efficacy of this combined product, the potential effect of ATZ on the contraceptive hormone LNG required further investigation in vivo. A typical way to investigate potential DDI would be a crossover phase 1 design (eg, an LNG monotherapy IVR compared to ATZ/LNG combination IVRs).[14] Considering the route of administration as well as the long half-life of ATZ (approximately 50 hours[13,15]), this investigation would require adequate washout periods. We have chosen another way to investigate the effect of ATZ on LNG by including a corresponding objective into the phase 2b study. Regardless, PK sampling in the phase 2 study would have been included to allow population PK evaluations for exposure-response modeling and compliance requirements. Regarding the latter, there was no indication that subjects were noncompliant with the study drug based on results from the PK analysis. No DDI of ATZ on LNG was detected, as the point estimates for ratios in C_{ss} between the mono and combination IVR groups were close to 1 with 90%CI limits consistently in the 0.80 to 1.25 range, which is typically used in bioequivalence studies.[14] Although not conducted in a highly controlled phase 1 setting (including intraindividual comparisons) typically applied in bioequivalence or DDI studies, the results of this phase 2 study strongly indicate no DDI of ATZ on LNG. Consequently, no further PK phase 1 studies are warranted for investigation of DDI potential. With regards to a potential effect of LNG on ATZ, it should be noted that the LNG dose is fixed to 40 μg/day based on modeling and simulation data.[8]

The observed plasma concentrations of ATZ and LNG were in the expected range for this study. Furthermore, these are the first PK data sets generated for this product within the relevant patient populations. In a previous phase 1 study involving healthy young subjects, the geometric mean concentrations of ATZ (1000 μg/d) and LNG (40 μg/d) prior to IVR removal were 21.8 μg/L and 0.34 μg/L, respectively.[3] This is very similar to the exposure data in the present study of ATZ (22.6 μg/L for ATZ 1050 μg/day; see Table 2) and LNG (range, 0.31-0.34 μg/L for LNG 40 μg/day; see Table 3). In this context, it should be noted that the demographics of the included study populations were much more diverse (including approximately 23% Japanese patients). As shown in Tables 2 and 3, the overall %CV for the PK parameter C_{ss} of ATZ and LNG is in the range of 26.11% to 58.15% and 46.50% to 54.60%, respectively. As this is a global phase 2b study performed in more than 100 study sites throughout the United States, Europe, and Japan, more variability was expected as compared to phase 1 studies involving 1 or 2 individual centers. The %CV for the ATZ and LNG at 40 μg/day seen in the phase 1 study evaluating concentration prior to removal of the second IVR is 27.5% to 53.6% and 36.0%, respectively.[3] Therefore, the variability of the PK parameter in the phase 2b study is acceptable to allow robust conclusions. In this context, the impact of the patient with an unexpectedly high LNG concentration in the LNG monotherapy group should be considered. Although this outlier increased the interindividual variability in this reference group, the overall conclusion of DDI remained unaffected. It cannot be excluded that she had taken prohibited LNG-containing medication during participation in the study in contrast to other subjects with predose sample values above the LLOQ. As indicated by these values, some patients had taken LNG-containing oral contraceptives prior to the start of treatment. Such prior medication was allowed according to the protocol. No impact on the outcome of this study is expected when such contraceptives were discontinued with the start of study medication. The earliest PK sample was taken 28 days after IVR insertion, and this washout is sufficient considering an elimination half-life of 13 to 20 hours for LNG.[4,5]

In the current study, 3 samples per patient were collected during the treatment phase of 84 days, having always been collected at the end of the IVR wearing period (days 28, 56, and 84). The intraindividual variability of the concentration at the end of the wearing period for consecutive IVRs is of particular relevance for the analysis design of this study. The median value of these samples was predefined as the PK parameter C_{ss} for statistical evaluation to control for random fluctuations of the measured concentration within a subject. This methodology is feasible as long as there are no systematic effects between time points. A mixed linear model on the logarithmized PK parameters with a fixed-effects treatment time point nested under treatment, and a random subject parameter did not show any significant time point effect ($P = .29$ for LNG; $P = .72$ for ATZ). As a result, the chosen PK parameter C_{ss} is considered reliable for this study.

Conclusion

In this globally conducted clinical phase 2 study, up to 4 PK plasma samples per patient were collected and provided sufficient data for various PK analyses. The expected systemic exposure for ATZ and LNG delivered from IVRs was achieved in the entire study population in all regions. As ATZ concentrations were

shown to increase proportionally with the administered dose and always in the presence of the same low dose of LNG, a clear separation between groups with regard to the systemic exposure was observed. There was no evidence of DDI of ATZ on LNG at any of the ATZ doses investigated. The PK data obtained in this phase 2b study made additional dedicated phase 1 studies on the DDI of both compounds superfluous, indicating the value of considering development programs holistically.

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Author Contributions

All authors contributed significantly to the study conception and design. All the authors were involved in revising the manuscript for important intellectual content and approving the final version for publication.

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Conflicts of Interest

R.N., U.M., S.K., J.H., and H.S. are employees of Bayer AG. H.S. is a named inventor on EP 2 552 404 B1, a patent application relating to this work.

Data Availability Statement

Availability of the data underlying this publication will be determined according to Bayer's commitment to the European Federation of Pharmaceutical Industries and Associations/ Pharmaceutical Research and Manufacturers of America Principles for Responsible Clinical Trial Data Sharing. This pertains to scope, time point, and process of data access. As such, Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States and European Union as necessary for conducting legitimate research.

Interested researchers can visit www.clinicalstudydata request.com to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the Study Sponsors section of the portal.

Data access will be granted to anonymized patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

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