Received: 14 December 2021 | Revised: 11 February 2022 | Accepted: 26 February 2022

DOI: 10.1111/cts.13265

ARTICLE

Evaluation of the potential for pharmacokinetic interaction between tirabrutinib and levonorgestrel/ethinyl estradiol in healthy female volunteers

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Funding information
The study was funded by Gilead Sciences Inc (Foster City, CA) including provision of study drug

Abstract

Tirabrutinib (TIRA), a potent and nonreversible oral Bruton tyrosine kinase inhibitor, is evaluated for treatment of certain hematological malignancies and inflammatory diseases. A drug–drug interaction study to evaluate the effect of TIRA on the pharmacokinetics of the oral contraceptive levonorgestrel (LEVO)/ethinyl estradiol (EE) was conducted in healthy female participants ($N = 26$). Participants received a single dose of LEVO (150 mcg)/EE (30 mcg) alone (reference), and on day 12 of a 15-day regimen of TIRA 160 mg once-daily (test). Intensive blood sampling for determination of LEVO, EE, and TIRA plasma concentrations was conducted, and safety was assessed throughout the study. Pharmacokinetic interactions were evaluated using 90% confidence intervals (CIs) of the geometric least squares mean (GLSM) ratios of the test versus reference treatments. The GLSM (90% CI) ratios of area under the concentration-time curve from zero to infinity (AUC_{inf}; LEVO: 0.95, 95% CI: 0.88–1.03, EE: 1.10, 95% CI: 1.05–1.16) and maximum plasma concentration (C_{max}; LEVO: 0.85, 95% CI: 0.74–0.98, EE: 1.07, 95% CI: 0.98–1.18) were within the prespecified 0.70 to 1.43 no effect bounds; and the AUC ratios met the stricter 0.80 to 1.25 equivalence bounds. Study treatments were generally well-tolerated. In conclusion, co-administration with TIRA did not alter the exposure of LEVO/EE, and accordingly LEVO/EE containing oral contraceptives can serve as a contraception method for participants on TIRA 160 mg (or lower) daily doses.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Tirabrutinib (TIRA) is a Bruton tyrosine kinase inhibitor developed for treatment of certain hematological malignancies and inflammatory diseases. Due to

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teratogenic potential of TIRA, enrollment of women of childbearing age is contingent upon the use of highly effective contraception.

WHAT QUESTION DID THIS STUDY ADDRESS?

The study evaluated the potential effect of TIRA 160 mg once-daily regimen on the exposure of a hormonal oral contraceptive containing levonorgestrel (LEVO) and ethinyl estradiol (EE).

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

TIRA 160 mg once daily did not have any clinically relevant impact on the exposures of LEVO and EE.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Combination oral contraception containing LEVO and EE can be allowed as a highly effective form of contraception during administration of TIRA at 160 mg once daily or lower daily doses.

INTRODUCTION

Tirabrutinib (TIRA) is a potent and nonreversible oral Bruton tyrosine kinase (BTK) inhibitor.[1,2] BTK plays key roles in multiple pathways in diverse cell populations that may underlie the pathogenesis of inflammatory diseases and specific B-cell malignancies. As an oral BTK inhibitor, TIRA (Velexbru®) is approved in Japan for recurrent or refractory primary central nervous system lymphoma, Waldenström macroglobulinemia, and lymphoplasmacytic lymphoma.[3] TIRA is also currently in development for B-cell hematologic malignancies and has been evaluated in certain autoimmune/inflammatory diseases.

In embryo-fetal toxicology studies in rats, increased numbers of fetal skeletal malformations and increased visceral and skeletal developmental variations were seen at the highest dose tested (600 mg/kg/day).[4] As such, pregnant women are excluded from TIRA clinical studies. Additionally, inclusion of women of childbearing age in TIRA clinical trials is contingent upon the use of highly effective nonhormonal contraception methods. Hormonal contraceptives, especially combinations of an estrogen and a progestin, are among the most commonly used methods of family planning/pregnancy prevention worldwide.[5,6] Cytochrome P450 (CYP) enzymes, including CYP3A, and non-CYP enzymes, are involved in the metabolism of estrogen and progestins.[7,8] Data from a previous drug–drug interaction (DDI) study showed ~ 20% reduction in midazolam exposure when co-administered with TIRA 320 mg once daily regimen, indicating the potential for weak to moderate induction of CYP3A at the 320 mg TIRA dose.[4] TIRA doses up to 160 mg once daily were considered for evaluation in treatment of chronic spontaneous urticaria[9] whose prevalence is high among women compared with men, especially younger women.[10,11] Thus, it is important to understand the effects of TIRA on the pharmacokinetics of hormonal oral contraceptives prior to allowing them as part of a highly effective contraceptive regimen in clinical studies.

The objective of this study was to evaluate the effect of concomitant administration of TIRA 160 mg once-daily on the exposure of ethinyl estradiol (EE) and levonorgestrel (LEVO), a representative combination oral contraceptive, when co-administered with TIRA. EE is the most common form of estrogen in combined oral contraceptives. LEVO is the most frequently prescribed progestin in combined oral contraceptives[8] and is also used in other forms of contraception including progestin-only implants, progestin-containing intrauterine devices, and progestin-only emergency contraception.

METHODS

Study participants

Eligible participants were non-pregnant, non-lactating, non-smoking women of 18 to 45 years of age with a body mass index (BMI) between 19 and 30 kg/m^2. Major inclusion criteria included healthy participants, based on medical history/physical examinations/laboratory evaluations, normal or clinically insignificant 12-lead electrocardiogram (ECG), normal renal function defined as creatinine clearance greater than 90 ml/min, and no evidence of HIV, hepatitis B virus, or hepatitis C virus infection. Hormonal contraceptives, including oral, implanted, patches or coils with hormonal contraceptives, were to be discontinued for at least 30 days prior to enrollment. Participants were excluded if they had used any investigational compound or any prescription or over-the-counter medication within 1 month or injectable contraceptives within 9 months of study drug dosing.

Exclusion criteria also included treatment with systemic steroids, immunosuppressant therapies, or chemotherapeutic agents within 3 months of study screening.

The study protocol and informed consent were approved by the study center's institutional review board, and participants provided written consent before study participation. This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki (including the 2013 amendment) and in compliance with all current International Conference on Harmonization Good Clinical Practice Guidelines (2018).

Study design

This study was a phase 1, open-label, single-center, fixed-sequence study to characterize the effect of multiple doses of 160 mg once-daily TIRA on the pharmacokinetics of a representative combined hormonal oral contraceptive medication, EE/LEVO, in healthy women.

Each participant received a single dose of oral contraceptive (30 mcg EE/150 mcg LEVO; Portia (Teva Pharmaceuticals USA, Inc., North Wales, PA) administered on day 1 (treatment A; reference) followed by TIRA (160 mg) administered once-daily for 15 days after a week of washout (i.e., TIRA treatment started on day 8) with a single dose of 30 mcg EE/150 mcg LEVO administered on the twelfth day of TIRA dosing (treatment B; test; Figure 1). All study drugs were administered in the morning within 5 min of completion of a standard moderate-fat breakfast. All participants were confined to the study center beginning at admission (day −1) until the completion of assessments (day 24), discharged on day 24, and followed up by telephone on day 29 (±2). A total of 26 healthy women were enrolled and 23 of them completed both study treatment A and treatment B.

Pharmacokinetic evaluation

Intensive pharmacokinetic sampling occurred relative to the morning dose of study drug. Samples were collected on the days of the oral contraceptive dosing (study days 1 and 19) at predose (≤5 min before dose), 0.5, 1, 1.5, 2, 4, 6, 8, 12, 18, 24, 36, 48, 72, 96, and 120 h postdose.

Timing of blood sample collection was based on known pharmacokinetic profiles for each analyte. Blood samples were collected in a Vacutainer Plus plastic sterile tube (Becton Dickinson, Franklin Lakes, NJ) containing K2-EDTA and were inverted several times to ensure mixing of the blood and anticoagulant. Tubes were kept on ice within 5 min of collection until centrifugation. The tubes were centrifuged for 10 min at 1000 ***g*** in a refrigerated centrifuge (4°C) to harvest plasma within 30 min of blood collection. Plasma samples were kept frozen at −70°C until analysis.

Bioanalytical procedures

Concentrations of TIRA, LEVO, and EE in plasma samples were determined by validated bioanalytical methods that included high performance liquid chromatography coupled with a tandem mass spectrometry (HPLC-MS/MS) and used isotopically labeled internal standards (IS): [$^2H_5$]-TIRA, [$^2H_6$]-LEVO, and [$^2H_4$]-EE, respectively. For LEVO and EE, methods were validated, and samples analyzed at Syneos Health Clinique (Québec, QC, Canada); for TIRA, the method was validated, and samples were analyzed at Syneos Health (Princeton, NJ). Validations met the expectations presented in the US Food and Drug Administration (FDA) guidance for bioanalytical method validation,[12] and all samples were analyzed within storage stability durations established during the method validations. Calibration curve ranges were 1.00 to 2000 ng/ml for TIRA, 10.0 to 10,000 pg/ml for LEVO, and 1.00 to 200 pg/ml for EE.

For determination of TIRA, 0.50 µl plasma sample aliquots were spiked with IS and processed by protein precipitation by addition of 250 µl of 4% (v:v) ammonium hydroxide in acetonitrile. The resulting supernatant was subjected to analysis by HPLC-MS/MS. TIRA:IS peak area ratios obtained from of a set of eight calibration standards analyzed in each run were subjected to weighted ($1/x^2$, where x is nominal concentration) linear least-squares regression to generate a calibration curve equation, which was then used to calculate concentrations of TIRA in a given sample from the TIRA:IS peak area ratio obtained for that sample.

For determination of LEVO, 500-µl plasma sample aliquots were spiked with IS and processed by liquid–liquid extraction; LEVO and its IS present in the extract were

Study Day	1	2-7	8-18	19	20-22
Treatment	A	Washout	B	B	B
	Oral Contraceptive		TIRA	TIRA + Oral Contraceptive	TIRA

Oral Contraceptive (30 mcg Ethinyl Estradiol/150 mcg Levonorgestrel); TIRA, Tirabrutinib (160mg, QD)

FIGURE 1 Study design schematic

then subjected to analysis by HPLC-MS/MS. LEVO:IS peak area ratios obtained from of a set of eight calibration standards analyzed in each run were subjected to weighted ($1/x^2$, where x is nominal concentration) linear least-squares regression to generate a calibration curve equation, which was then used to calculate concentrations of LEVO in a given sample from the LEVO:IS peak area ratio obtained for that sample.

For determination of EE, 600-µl plasma sample aliquots were spiked with IS and processed by liquid–liquid extraction; EE and its IS present in the extract were then derivatized with dansyl chloride and subjected to analysis by HPLC-MS/MS. The EE:IS peak area ratios obtained from of a set of eight calibration standards analyzed in each run were subjected to weighted ($1/x^2$, where x is nominal concentration) linear least-squares regression to generate a calibration curve equation, which was then used to calculate concentrations of EE in a given sample from the EE:IS peak area ratio obtained for that sample.

Safety assessments

Safety was evaluated by assessment of clinical laboratory tests, including hematology profile, chemistry profile, urinalysis, physical examinations, and vital signs. A review of medications was performed at screening, baseline, on days with pharmacokinetic sampling, and at various times during the study. Participants were monitored for adverse events (AEs) throughout the study and follow-up.

Pharmacokinetic analyses

Pharmacokinetic parameters were estimated using Phoenix WinNonlin 6.4 software (Certara, L.P., Princeton, NJ) using standard noncompartmental methods. Samples with concentrations below the limit of quantitation of the bioanalytical assays occurring prior to the achievement of the first quantifiable concentration were assigned a concentration value of zero, and at all other time points were treated as missing data in the noncompartmental analyses. Pharmacokinetic parameters for LEVO and EE included area under plasma concentration versus time curve extrapolated to infinity (AUC_{inf}) and area under the concentration versus time curve from time zero to the last quantifiable concentration (AUC_{last}), maximal concentration (C_{max}), time to C_{max} (T_{max}), and terminal half-life ($t_{1/2}$). Pharmacokinetic parameters for TIRA included area under the concentration- time curve over the dosing interval (AUC_{tau}), C_{max}, T_{max}, and $t_{1/2}$.

Statistical analyses

A sample size of 20 evaluable participants was projected to achieve at least 90% power, such that the 90% confidence interval (CI) for the geometric least squares mean (GLSM) ratio of LEVO and EE AUC_{inf}, AUC_{last}, and C_{max} in test (treatment B) versus reference (treatment A) treatments would be within 0.70 to 1.43, if the true GLSM ratio was 1.0. This was assuming an SD of differences of no more than 0.525 on a natural logarithm scale. An analysis of variance (ANOVA) using a mixed-effects model with treatment, sequence, and period as a fixed effects and participant within sequence as a random effect[13] was fitted to the natural logarithmic transformation of pharmacokinetic parameters for each analyte (EE and LEVO), respectively. Participants whose predose concentrations exceeded 5% of C_{max} value were excluded from statistical analysis. Two-sided 90% CIs were calculated for the ratio of GLSM of primary pharmacokinetic parameters (AUC_{inf}, AUC_{last}, and C_{max}) between test (TIRA and oral contraceptive) versus reference (oral contraceptive alone) treatments for each analyte.

RESULTS

Participant demographics

All 26 participants received a single dose of oral contraceptive on day 1. Three participants discontinued prior to treatment B. Most participants were White (65%; $n = 17$) followed by Black (31%; $n = 8$), and Others (4%; $n = 1$). At baseline, the mean age was 30 years (range: 19 to 45 years), the mean bodyweight was 64.4 kg (range: 41.5–81.0 kg), mean BMI was 23.9 kg/m^2 (range: 18.9–29.6 kg/m^2).

Pharmacokinetics

Effect of TIRA on LEVO pharmacokinetics

The mean (SD) LEVO plasma concentrations versus time profiles after administration of the oral contraceptive alone or in combination with TIRA are presented in Figure 2. Corresponding LEVO pharmacokinetic parameters, GLSM ratio, and 90% CIs are presented in Table 1. Administration of the oral contraceptive with TIRA resulted in similar LEVO AUC_{inf}, AUC_{last}, and C_{max} compared with administration of the oral contraceptive alone. The 90% CIs of the GLSM ratios were contained within the prespecified no effect bounds (0.70–1.43); and the 90% CIs of the GLSM ratios for LEVO AUC_{inf} and AUC_{last} were within the stricter 0.80 to 1.25 bioequivalence bounds. Median $t_{1/2}$ of LEVO was similar for both treatments.

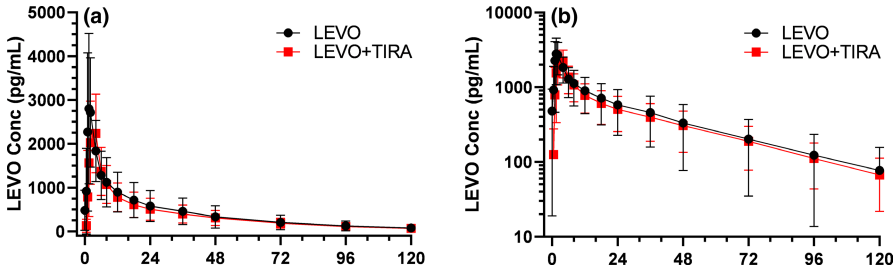

FIGURE 2 Mean (SD) plasma concentrations versus time profiles of levonorgestrel (LEVO) following administration of LEVO (150 mcg)/ethinyl estradiol (30 mcg) alone ($N = 26$) or in combination with 160 mg once daily tirabrutinib (TIRA; $N = 23$). (a) Linear scale; (b) semilogarithmic scale

TABLE 1 Levonorgestrel plasma pharmacokinetic parameters and statistical comparisons following administration of levonorgestrel/ethinyl estradiol (oral contraceptive) alone or with tirabrutinib

Levonorgestrel pharmacokinetic parameter	Mean (%CV)		GLSM ratio (90% CI)
	Oral contraceptive (Reference)($N = 26$)	Oral contraceptive + tirabrutinib (Test)($N = 23$)	Oral contraceptive + tirabrutinib vs. oral contraceptive[b]
AUC_{inf}, ng.h/ml	50.4 (64.2)	46.6 (44.2)	0.95 (0.88, 1.03)
AUC_{last}, ng.h/ml	47.2 (61.3)	43.4 (43.4)	0.94 (0.86, 1.01)
C_{max}, ng/ml	3.35 (44.2)	2.77 (35.3)	0.85 (0.74, 0.98)
T_{max}, h[a]	1.50 (1.00, 2.00)	4.00 (2.00, 4.00)	–
$t_{1/2}$, h[a]	26.5 (23.1, 30.9)	29.1 (24.0, 36.4)	–

Abbreviations: AUC_{inf}, area under the plasma concentration–time curve extrapolated to infinity; AUC_{last}, area under the plasma concentration–time curve from time 0 to the last quantifiable concentration; C_{max}, maximum concentration; CI, confidence interval; %CV, percent coefficient of variation; GLSM, geometric least squares mean; $t_{1/2}$, half-life; T_{max}, time to maximum concentration.

[a]Presented as median (first quartile and third quartile).

[b]Two participants predose concentrations exceeded 5% of C_{max} value for the reference treatment, and their corresponding PK parameters from the reference period were excluded from the statistical comparisons.

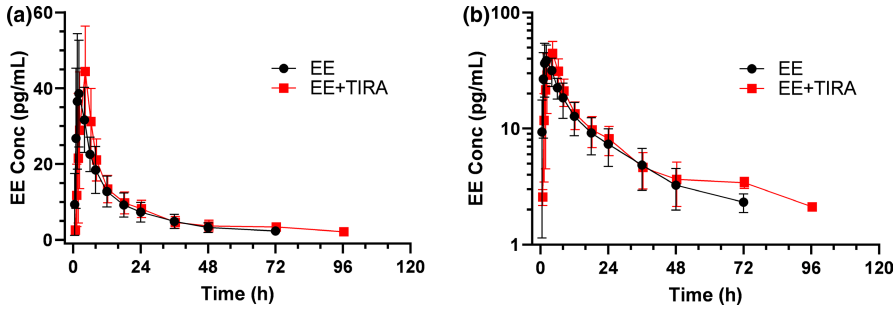

FIGURE 3 Mean (SD) plasma concentrations versus time profiles of ethinyl estradiol (EE) following administration of levonorgestrel (150 mcg)/EE (30 mcg) alone ($N = 26$) or in combination with 160 mg once daily tirabrutinib (TIRA; $N = 23$). (a) Linear scale; (b) semilogarithmic scale

Effect of TIRA on EE pharmacokinetics

The mean (SD) EE plasma concentrations versus time profiles after administration of the oral contraceptive alone or in combination with TIRA are presented in Figure 3. Corresponding EE pharmacokinetic parameters, GLSM ratio, and 90% CIs are presented in Table 2. Administration of the oral contraceptive with TIRA resulted in similar EE AUC_{inf}, AUC_{last}, and C_{max} compared with administration of oral contraceptive alone. The 90% CI of the GLSM ratios

TABLE 2 Ethinyl estradiol plasma pharmacokinetic parameters and statistical comparisons following administration of levonorgestrel/ethinyl estradiol (oral contraceptive) alone or with tirabrutinib

Ethinyl estradiol pharmacokinetic parameter	Mean (%CV)		GLSM ratio (90% CI)
	Oral contraceptive (Reference)($N = 26$)	Oral contraceptive + tirabrutinib (Test)($N = 23$)	Oral contraceptive + tirabrutinib vs oral contraceptive[b]
AUC_{inf}, pg.h/ml	557 (36.7)	616 (30.6)	1.10 (1.05, 1.16)
AUC_{last}, pg.h/ml	488 (41.2)	536 (30.9)	1.09 (1.04, 1.14)
C_{max}, pg/ml	45.1 (29.8)	47.9 (25.3)	1.07 (0.98, 1.18)
T_{max}, h[a]	1.00 (1.00, 1.25)	1.00 (1.00, 1.00)	–
$t_{1/2}$, h[a]	33.7 (28.4, 37.7)	37.1 (32.2, 41.8)	–

Abbreviations: AUC_{inf}, area under the plasma concentration–time curve extrapolated to infinity; AUC_{last}, area under the plasma concentration–time curve from time 0 to the last quantifiable concentration; C_{max}, maximum concentration; CI, confidence interval; %CV, percent coefficient of variation; GLSM, geometric least squares mean; $t_{1/2}$, half-life; T_{max}, time to maximum concentration.

[a]Presented as median (first quartile, third quartile).

[b]One participant's predose concentrations exceeded 5% of C_{max} value for the reference treatment, and her corresponding pharmacokinetic parameters from the reference period were excluded from the statistical comparisons.

for EE AUC_{inf}, AUC_{last}, and C_{max} were within the strict bioequivalence bounds (0.80 to 1.25). Median $t_{1/2}$ of EE was similar for both treatments.

Steady-state pharmacokinetics of TIRA

At steady-state, the mean (percent coefficient of variation) TIRA plasma AUC_{tau} and C_{max} were 3170 (34) ng.h/ml and 564 (28) ng/ml, respectively. The median T_{max} and $t_{1/2}$ were 4.0 h and 3.8 h, respectively.

Safety

Study treatments were generally well-tolerated. There were no grade 3 or 4 AEs and no participant prematurely discontinued the study drug due to an AE. Following treatment A, AEs were reported for 13 participants (50%). AEs considered related to EE/LEVO were reported in eight participants (30.8%) where the most commonly reported oral contraceptive-related AEs were intermenstrual bleeding (11.5%, 3 participants) and dizziness (7.7%, 2 participants). Following treatment B, AEs were reported for 21 participants (91.3%). AEs considered related to TIRA included dermatitis (39.1%, 9 participants), nausea (30.4%, 7 participants), and headache (26.1%, 6 participants). AEs considered related to EE/LEVO following treatment B were dysmenorrhea (26.1%, 6 participants) and heavy menstrual bleeding (21.7%, 5 participants). All treatment-emergent AEs were grade 1 or grade 2.

Eleven participants (44%) in treatment A and 21 participants (91.3%) experienced a graded treatment-emergent laboratory abnormality. Most treatment-emergent laboratory abnormalities were grade 1 or grade 2 in severity. Grade 3 hyperkalemia was observed in one participant during treatment B on study day 19. There were no reported symptoms and potassium levels were observed to be within normal reference range for all preceding and subsequent evaluations in this participant. Overall, there were no clinically significant trends in laboratory abnormalities, vital sign measurements, or ECG recordings.

DISCUSSION

Combination oral contraceptives containing LEVO and EE are among the safe and highly effective contraception choices available to women of child-bearing age.[14] DDIs involving oral contraceptives as victim drugs could lead to unintended pregnancies and even teratogenicity if the perpetrator drug has teratogenic potential. TIRA has shown embryo-fetal toxicity in rats and weak-to-moderate CYP3A induction in a clinical study, albeit at the 320 mg once daily TIRA dose. This warranted characterization of the potential pharmacokinetic interaction between TIRA at the highest dose considered for evaluation in inflammatory diseases (160 mg once daily)[9] and LEVO/EE to inform LEVO/EE potential use as a safe and a highly effective oral contraception method in women of childbearing potential in TIRA clinical studies.

Results of this study demonstrated that TIRA has no clinically relevant effect on the exposures of LEVO and EE at the 160 mg once daily dose. The 90% CIs of the GLSM ratios of AUC_{inf}, AUC_{last}, and C_{max} of EE and AUC_{inf} and

AUC_{last} of LEVO were within the default bioequivalence bounds (0.80–1.25). The lower 90% CI bound of LEVO C_{max} GLSM ratio extended slightly below the bioequivalence bound but was within the prespecified no effect bounds of 0.70 to 1.43. The prespecified no-effect criteria, which correspond to 30% difference in exposure on the log scale, were deemed adequate because the trough concentrations of LEVO with the 150 mcg once daily dose provide adequate buffer above the reported minimum pharmacological threshold plasma concentration of LEVO efficacy.[15,16] Additionally, the sample size of the study was not selected to demonstrate strict bioequivalence on all the pharmacokinetic parameters.

Although clinical data indicated weak induction of CYP3A with TIRA 320 mg dose,[4] no clinically relevant impact on the pharmacokinetics of either LEVO or EE was observed with TIRA 160 mg once daily dose. In addition to the lower TIRA dose evaluated in the study, it is noteworthy that CYP3A is not the major contributor toward LEVO and EE clearance.[7,17]

LEVO is one of the most prescribed progestin in the United States as well as globally.[8] Furthermore, LEVO is used as progestin only pill and emergency contraception, and thus the current study could inform the impact on the alternate types of contraception containing LEVO. TIRA was dosed daily at the maximum dose that was considered for clinical evaluation for treatment of chronic spontaneous urticaria. The duration of dosing (11 days) of TIRA prior to examining the potential interaction with oral contraceptives on day 12 would ensure attainment of the maximum induction of inducible metabolic enzymes. Continuation of dosing of TIRA through the collection of pharmacokinetic samples for oral contraceptives ensures characterizing maximum effect (any induction or unsuspected inhibition), if any, of TIRA on these oral contraceptives. The systemic exposures of TIRA on day 12 were within the expected steady-state range for 160 mg dose informed by prior clinical studies for TIRA.[18,19]

All reported AEs were mild, and there were no discontinuations due to AEs. Overall, the combination of TIRA and oral contraceptives was well-tolerated in this single-dose assessment of LEVO and EE. In summary, the study findings support LEVO and EE containing combination oral contraceptive can be used as a highly effective form of contraception when administered concomitantly with TIRA 160 mg once daily or lower doses.

ACKNOWLEDGMENTS

The authors warmly thank Nicholas Piquet (Syneos Health Clinique, Québec, QC, Canada) and Stephanie Recklau (Syneos Health, Princeton, NJ) for bioanalytical sample analyses.

CONFLICT OF INTEREST

G.C., Y.G., A.M., T.T., and A.A.O. are employees of, and may own stock in, Gilead Sciences Inc. C.N. was an employee of Gilead Sciences at the time of study and may own stocks in Gilead Sciences.

AUTHOR CONTRIBUTIONS

G.C., C.N., Y.G., A.M., T.T., and A.O. wrote the manuscript. C.N. and A.O. designed the research. C.N., G.C., T.T., and A.O. performed the research. G.C., Y.G., T.T., and A.O. analyzed the data.

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How to cite this article: Cherala G, Nelson C, Guo Y, Mathur A, Tarnowski T, Othman AA. Evaluation of the potential for pharmacokinetic interaction between tirabrutinib and levonorgestrel/ethinyl estradiol in healthy female volunteers. *Clin Transl Sci*. 2022;15:1492-1499. doi: 10.1111/cts.13265