The JAK1 Inhibitor Upadacitinib Has No Effect on the Pharmacokinetics of Levonorgestrel and Ethinylestradiol: A Study in Healthy Female Subjects

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Abstract

Upadacitinib is a novel selective oral Janus kinase 1 (JAK) inhibitor being developed for treatment of several inflammatory diseases. Oral contraceptives are anticipated to be a common concomitant medication in the target patient populations. This study was designed to evaluate the effect of multiple doses of upadacitinib on the pharmacokinetics of ethinylestradiol and levonorgestrel in healthy female subjects. This phase I, single-center, open-label, 2-period crossover study evaluated the effect of multiple doses of 30 mg once daily extended-release upadacitinib on the pharmacokinetics of a single oral dose of ethinylestradiol/levonorgestrel (0.03/0.15 mg; administered alone in period 1 and on day 12 of a 14-day regimen of upadacitinib in period 2) in 22 healthy female subjects. The ratios (90% confidence intervals) for maximum plasma concentration and area under the plasma drug concentration–time curve from time zero to infinity following administration of ethinylestradiol/levonorgestrel with upadacitinib compared with administration of ethinylestradiol/levonorgestrel alone were 0.96 (0.89–1.02) and 1.1 (1.04–1.19), respectively, for ethinylestradiol, and 0.96 (0.87–1.06) and 0.96 (0.85–1.07), respectively, for levonorgestrel. The harmonic mean terminal half-life for ethinylestradiol (7.7 vs 7.0 hours) and levonorgestrel (37.1 vs 33.1 hours) was similar in the presence and absence of upadacitinib. Ethinylestradiol and levonorgestrel were bioequivalent in the presence and absence of upadacitinib. Therefore, upadacitinib can be administered concomitantly with oral contraceptives containing ethinylestradiol or levonorgestrel.

Keywords

ABT-494, drug interaction, ethinylestradiol, levonorgestrel, upadacitinib

Upadacitinib (ABT-494) is a selective Janus kinase (JAK) inhibitor that potently inhibits JAK1 but is less potent against the other JAK isoforms.¹ The JAK/STAT (signal transducers and activators of transcription) pathway is involved in the regulation of not only innate immunity and adaptive immune mechanisms but also inflammatory responses. Therefore, this pathway has been targeted for the development of treatments for immunologic disorders.² The JAK enzyme family comprises 4 members: JAK1, 2, 3, and tyrosine kinase 2 (Tyk2).³–⁵ Inhibition of JAK1 signaling inhibits interleukin-6 proinflammatory signaling, which is considered to be a major contributor to clinical efficacy in immunologic disorders.⁶,⁷ In contrast, JAK2 downstream signaling cascade regulates interleukin-3, interleukin-5, erythropoietin, thrombopoietin expression, which contributes to erythropoiesis and myelopoiesis.⁸,⁹ Upadacitinib enhanced selectivity against JAK1 has the potential to offer an improved benefit-risk profile in patients with inflammatory diseases. Upadacitinib has demonstrated robust efficacy and acceptable safety in several phase 2 and phase 3 studies in patients with rheumatoid arthritis (RA) as well as in phase 2 studies in patients with Crohn’s disease and atopic dermatitis.¹⁰–¹⁹ Upadacitinib is also being evaluated for the treatment of psoriatic arthritis, ulcerative colitis, and ankylosing spondylitis.²⁰–²³

Upadacitinib is being administered in the form of an extended-release formulation, which is administered in phase 3 studies in rheumatoid arthritis at doses of

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15 mg and 30 mg once daily (QD). The pharmacokinetics of upadacitinib are characterized by biexponential disposition, with a harmonic mean terminal half-life of 9 to 14 hours, and a median time to maximum plasma concentration of 2 to 4 hours following administration of the extended-release formulation.\(^{24,25}\) No significant accumulation occurs upon multiple QD dosing with upadacitinib extended-release formulation, and steady state is achieved by day 4. Upadacitinib is a nonsensitive substrate for cytochrome P450 (CYP) 3A; coadministration of upadacitinib following multiple doses of the strong CYP3A inhibitor ketoconazole resulted in an increase in upadacitinib area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C\(_{\text{max}}\)) by 75% and 70%, respectively.\(^{26}\) The majority (>60%) of the administered upadacitinib dose is eliminated in urine and feces as unchanged upadacitinib. Based on the in vitro and physiologically based pharmacokinetic analyses, upadacitinib was not expected to have clinically relevant effects on the pharmacokinetics of substrates of CYP enzymes or transporters at the doses evaluated in phase 3 studies in RA (data on file at AbbVie).

Hormonal contraceptives are among the most widely used methods of contraception.\(^{27}\) Therefore, it is anticipated that upadacitinib will be used by patients who concomitantly use hormonal contraceptives. Multiple forms of hormonal contraceptives are available that use estrogen and progestin steroids individually or in combination.\(^{28}\) The estrogen ethinylestradiol and the progestin levonorgestrel are among the most commonly prescribed contraceptives and both are metabolized through CYP3A, sulfotransferases, and uridine 5′-diphospho-glucuronosyltransferases.\(^{29,30}\) Drugs that have pharmacokinetic interactions with oral contraceptives can potentially result in failure of contraception through induction of metabolism or increased incidence of the side effects through inhibition of metabolism.\(^{31-33}\) Given the wide use of hormonal contraceptives, this study was conducted to characterize any potential effect of upadacitinib on ethinylestradiol and levonorgestrel pharmacokinetics to inform safety of coadministration in patients.

**Methods**

**Study Participants**

The study protocol and informed consent form were approved by the Institutional Review Board (Vista Medical Center East Institutional Review Board, Waukegan, Illinois) prior to the initiation of any screening or study-specific procedures. Written informed consent was obtained from each individual participating in the study. The study was conducted at the AbbVie Clinical Pharmacology Research Unit in accordance with Good Clinical Practice guidelines and the ethical principles that have their origin in the Declaration of Helsinki.

The study was conducted in healthy female subjects (N = 22) between the ages of 18 and 55 years and with a body mass index of 18 to 29.9 kg/m\(^2\), inclusive. Subjects were excluded if they had used oral contraceptives or oral hormone replacement within 30 days, implanted hormonal contraceptives within 6 months, injectable contraceptives within 12 months, or topical controlled-delivery contraceptives or hormonal coils within 3 months prior to initial study drug administration. Additional exclusion criteria were use of any known inhibitors or inducers of drug metabolizing enzymes within 30 days of the first dose of study drug, use of tobacco or nicotine-containing products within 6 months prior to the administration of the study drug, or history of alcohol abuse.

**Clinical Study Design**

This was a phase 1, single-center, open-label, 2-period study designed to evaluate the effect of multiple doses of upadacitinib on the pharmacokinetics of ethinylestradiol and levonorgestrel (Figure 1). During period 1, subjects received a single dose of ethinylestradiol/levonorgestrel (0.03/0.15 mg) on day 1 after an overnight fast followed by a washout period of 4 days. During period 2, subjects received multiple doses of upadacitinib 30 mg administered once daily using the extended-release upadacitinib formulation for 14 days (days 1–14, with exception of day 12, under nonfasting conditions). On study day 12 of period 2, upadacitinib was coadministered with a single dose of ethinylestradiol/levonorgestrel (0.03/0.15 mg) after an overnight fast.

**Pharmacokinetic Sampling**

Blood samples for the measurements of ethinylestradiol and levonorgestrel in plasma were collected prior to (0 hour) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72, and 96 hours after the combined oral contraceptive administration on day 1 of period 1 and on day 12 of period 2.

Plasma concentrations of ethinylestradiol and levonorgestrel (norgestrel) were determined using a validated high-performance liquid chromatography with tandem mass spectroscopy detection method at PPD (LLC, Richmond, Virginia). The lower limit of quantitation was 2 pg/mL for ethinylestradiol and 50 pg/mL for norgestrel. The mean accuracy (absolute % difference from theoretical) of the analytical method was 1.6% for ethinylestradiol and 1.8% for norgestrel and the coefficient of variation values (as a measure for precision) were 4.1% and 4.6% for ethinylestradiol and norgestrel, respectively.
Pharmacokinetics
Ethinylestradiol and levonorgestrel plasma concentrations were analyzed by noncompartmental methods using Phoenix WinNonlin (version 6.2, Pharsight Corp., Mountain View, California). C<sub>max</sub>, median time to maximum plasma concentration (T<sub>max</sub>), AUC from time zero to the time of last measureable concentration (AUC<sub>0-t</sub>), the AUC from time zero to infinity (AUC<sub>inf</sub>), and terminal half-life were determined for ethinylestradiol and levonorgestrel.

Statistical Analyses
Statistical analysis was performed using SAS software, version 9.3 (SAS Institute Inc., Cary, North Carolina). Sample size was determined through a power calculation. The calculation assumed an intrasubject error term variance of 0.025 for the natural logarithm of C<sub>max</sub> for ethinylestradiol. This value was selected based upon the results from Menon et al.,<sup>34</sup> and the largest value of variation of C<sub>max</sub> and AUC for ethinylestradiol and levonorgestrel was used for the calculation. For the assessment of the effect of upadacitinib on ethinylestradiol and levonorgestrel, complete data from 19 subjects would have provided a power of 98.5% to detect at least a 25% increase (20% decrease) in the central value of ethinylestradiol/levonorgestrel C<sub>max</sub> for coadministration of ethinylestradiol and levonorgestrel with multiple doses of upadacitinib relative to ethinylestradiol and levonorgestrel alone.

To assess the effect of upadacitinib on the plasma exposures of ethinylestradiol and levonorgestrel, repeated measures analyses were performed for the natural logarithms of C<sub>max</sub> and AUC values when the oral contraceptives were administered alone (period 1, day 1) and with upadacitinib (period 2, day 12). The point estimates and 90% confidence intervals (CIs) for the ratio of C<sub>max</sub> and AUC central values on period 2, day 12 to period 1, day 1 were obtained by taking the antilogarithm of the point estimates and confidence limits of the differences in least squared means on the logarithmic scale obtained from the repeated measures analysis.

Safety
Safety was assessed for all subjects throughout the study based on monitoring of treatment-emergent adverse events, serious adverse events, hematology, blood chemistry, vital signs, electrocardiograms, and physical examinations.

Results
Disposition and Demographics
A total of 22 female subjects were enrolled in the study, and 20 subjects completed both periods 1 and 2. The subjects enrolled in the study had mean age of 41.1 years (range, 21–53), mean weight of 72.7 kg (range, 58–84), mean body mass index of 26.6 kg/m<sup>2</sup> (range, 19–30), and mean height of 165 cm (range, 156–174). One subject discontinued the study in period 1 (prior to upadacitinib administration) due to an adverse event. A second subject withdrew consent in period 1 for non–study-related reasons.

Pharmacokinetics
Mean ethinylestradiol and levonorgestrel plasma concentration vs time profiles following administration of single doses of 0.03-mg ethinylestradiol and 0.15-mg levonorgestrel alone and on day 12 of a 14-day regimen of upadacitinib 30 mg QD are shown in Figure 2. The mean pharmacokinetic parameters for ethinylestradiol/levonorgestrel alone and following administration of repeated upadacitinib 30 mg QD are shown in Table 1. Ethinylestradiol and levonorgestrel pharmacokinetic parameters were similar when the oral contraceptives were administered alone compared to after repeated 30-mg QD doses of upadacitinib.

The point estimates for the 90%CIs for the effect of upadacitinib on ethinylestradiol and levonorgestrel pharmacokinetic parameters are shown in Table 2. The 90%CIs for the central values of ethinylestradiol C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>inf</sub> were within the default no-effect equivalence boundaries of 0.8 to 1.25. Similarly, the 90%CIs for the central values of levonorgestrel C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>inf</sub> were within the default no-effect equivalence boundary of 0.8 to 1.25.

Safety
No serious adverse events that led to discontinuation after upadacitinib study drug administration or deaths were reported during the study. The majority of adverse events were mild in severity, and there was no clinically relevant pattern to the reported adverse events.
period 1, one female subject had an upper respiratory tract infection that led to premature discontinuation after receiving ethinylestradiol/levonorgestrel and before upadacitinib administration. The adverse event was assessed by the investigator as having “no reasonable possibility” of being related to ethinylestradiol and levonorgestrel. In period 2, the only adverse event reported by more than one subject was a headache after coadministration of upadacitinib with ethinylestradiol/levonorgestrel. In period 2, the treatment-emergent adverse events were not considered to have a reasonable possibility of being related to upadacitinib administration.

**Discussion**

Metabolic drug-drug interactions can impact the pharmacokinetics of concomitant medications, which can lead to reduction in efficacy or safety concerns. The high prevalence of oral contraceptive use and the contribution of CYP3A to the metabolism of oral contraceptives and upadacitinib motivated the evaluation of the effect of repeated doses of upadacitinib on the pharmacokinetics of single-dose ethinylestradiol/levonorgestrel (0.03/0.15 mg, respective dose).

Table 1. Pharmacokinetic Parameters of Ethinylestradiol and Levonorgestrel Following Administration of 0.03-mg Ethinylestradiol and 0.15-mg Levonorgestrel Alone and Following Repeated Administration of Upadacitinib 30 mg QD

| Pharmacokinetic Parameters (Units) | Period 1/Day 1: Ethinylestradiol/Levonorgestrel (N = 22) | Period 2/Day 14: Upadacitinib 30 mg QD + Ethinylestradiol/Levonorgestrel (N = 20) |
|-----------------------------------|----------------------------------------------------------|----------------------------------------------------------------------------------|
| Cmax (pg/mL)                      | 62.7 ± 24.3                                              | 59.0 ± 20.5                                                                      |
| Tmax (h)                          | 1.5 (1.0–2.0)                                            | 1.5 (1.0–3.0)                                                                    |
| AUC0-t (pg · h/mL)                | 378 ± 154                                                | 426 ± 137                                                                        |
| AUCinf (pg · h/mL)                | 441 ± 193                                                | 492 ± 166                                                                        |
| t1/2 (h)                          | 7.0 (3.4)                                                | 7.7 (2.4)                                                                        |
| Cmax (ng/mL)                      | 3.9 ± 1.4                                                | 3.7 ± 1.15                                                                       |
| Tmax (h)                          | 0.8 (0.5–2.0)                                            | 0.8 (0.5–2.0)                                                                    |
| AUC0-t (ng · h/mL)                | 43.0 ± 18.4                                              | 48.7 ± 12.1                                                                      |
| AUCinf (ng · h/mL)                | 51.7 ± 22.0                                              | 49.5 ± 20.4                                                                      |
| t1/2 (h)                          | 33.1 (12.4)                                              | 37.1 (15.1)                                                                      |

AUC0-t, area under the plasma drug concentration–time curve from time zero to the time of last measurable concentration; AUCinf, area under the plasma drug concentration–time curve from time zero to infinity; Cmax, maximum plasma concentration; QD, once daily; t1/2, terminal half-life; Tmax, median time to maximum plasma concentration.

*Median (minimum to maximum).*

**Figure 2.** Mean ± SD (A) ethinylestradiol and (B) levonorgestrel plasma concentration vs time profiles following administration of a single dose of 0.03-mg ethinylestradiol and 0.15-mg levonorgestrel alone and with repeated once-daily doses of 30-mg upadacitinib.
Table 2. Point Estimate and 90% Confidence Intervals for the Effect of Repeated Doses of Upadacitinib 30 mg QD on Ethinylestradiol and Levonorgestrel Pharmacokinetic Parameters

| Compound   | Regimens Test vs Reference | Pharmacokinetic Parameter | Central Value | Ratio of Central Values |
|------------|----------------------------|----------------------------|---------------|-------------------------|
|            |                            |                            | Test          | Reference               | Point Estimate | 90% Confidence Interval |
| Ethinylestradiol | Period 2, day 12 vs period 1, day 1 | $C_{\text{max}}$           | 55.3          | 57.9                    | 0.955         | 0.893–1.022             |
|            |                            | AUC$_0$-$\text{t}$         | 390           | 348                     | 1.121         | 1.043–1.205             |
|            |                            | AUC$_{\text{inf}}$         | 445           | 402                     | 1.108         | 1.036–1.186             |
| Levonorgestrel | Period 2, day 12 vs period 1, day 1 | $C_{\text{max}}$           | 3.59          | 3.74                    | 0.961         | 0.873–1.059             |
|            |                            | AUC$_0$-$\text{t}$         | 36.3          | 39.6                    | 0.916         | 0.828–1.014             |
|            |                            | AUC$_{\text{inf}}$         | 45.5          | 47.6                    | 0.955         | 0.851–1.071             |

AUC$_{0}$-$\text{t}$, area under the plasma drug concentration–time curve from time zero to the time of last measurable concentration; AUC$_{\text{inf}}$, area under the plasma drug concentration–time curve from time zero to infinity; $C_{\text{max}}$, maximum plasma concentration; QD, once daily.

Results from this study indicate that upadacitinib has no effect on the exposures of ethinylestradiol or levonorgestrel. The 90% CIs for the AUCs and $C_{\text{max}}$ of ethinylestradiol and levonorgestrel when administered with repeated doses of 30-mg QD upadacitinib relative to when administered alone were within the default no-effect bioequivalence boundaries of 0.8 to 1.25. These results are consistent with the predicted lack of clinically relevant effect of upadacitinib at the relevant doses in RA on CYP enzymes based on in vitro data and physiologically based pharmacokinetic analyses (data on file at AbbVie).

This study was designed in accordance to the recommendations set forth by the US Food and Drug Administration’s guidance for drug interaction studies. 35,37 The 30-mg QD dose is the highest dose currently being evaluated in the RA phase 3 trials and is the evaluated dose in this study. In the case of induction, the attainment of steady state for an extended duration is important to observe any delayed effect on enzyme activity. 38 On days 1 through 11 in period 2, the upadacitinib 30-mg once-daily formulation was administered alone. A single dose of ethinylestradiol/levonorgestrel (0.03/0.15 mg) was coadministered with the upadacitinib 30-mg once-daily formulation on the morning of day 12 of period 2 to ensure ample time for maximum potential enzyme induction or inhibition to occur. Upadacitinib was also dosed on days 13 and 14 in period 2 ensure continued effect of any potential effect of upadacitinib through the entirety of exposure to the oral contraceptives.

The study aim was to evaluate whether upadacitinib affects the pharmacokinetics of ethinylestradiol and levonorgestrel; therefore, administration of a single dose, rather than multiple doses, of the oral contraceptives was considered sufficient to capture potential for pharmacokinetic interaction. 39

Conclusions

The results of this study suggest that contraceptive drugs containing ethinylestradiol or levonorgestrel can be safely coadministered with upadacitinib without any concern about a potential pharmacokinetic interaction.

Data Sharing

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and statistical analysis plan and execution of a data sharing agreement. Data requests can be submitted at any time, and the data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html

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Declaration of Conflicting Interest

All authors are employees and shareholders of AbbVie.

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