The Journal of Clinical Pharmacology
2019, 59(4) 510–516

DOI: 10.1002/jcph.1350

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

Mohamed-Eslam F. Mohamed, PhD[1], Sheryl Trueman, PhD[1], Tian Feng, PhD[2], Alan Friedman, MD[3], and Ahmed A. Othman, PhD, FCP[1]

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

[1]Clinical Pharmacology and Pharmacometrics, AbbVie, North Chicago, IL, USA
[2]Data and Statistical Sciences, AbbVie, North Chicago, IL, USA
[3]Immunology Development, AbbVie, North Chicago, IL, USA

Submitted for publication 13 September 2018; accepted 8 November 2018.

Corresponding Author:
Ahmed A. Othman, PhD, FCP, AbbVie, 1 North Waukegan Road, North Chicago, IL, 60064
Email: ahmed.othman@abbvie.com

Dr. Ahmed A. Othman is a Fellow of the American College of Clinical Pharmacology

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_{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.

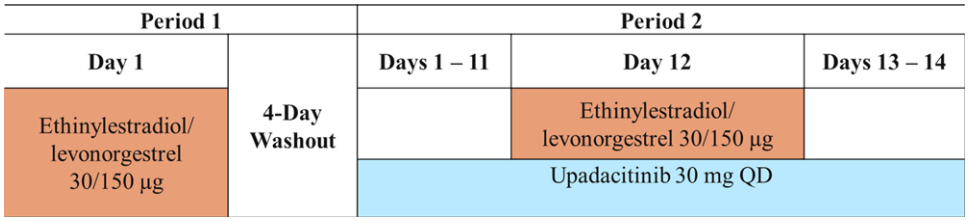

Figure 1. Study design schematic.

Pharmacokinetics

Ethinylestradiol and levonorgestrel plasma concentrations were analyzed by noncompartmental methods using Phoenix WinNonlin (version 6.2, Pharsight Corp., Mountain View, California). C_{max}, median time to maximum plasma concentration (T_{max}), AUC from time zero to the time of last measureable concentration ($AUC_{0\text{-}t}$), the AUC from time zero to infinity (AUC_{inf}), 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_{max} for ethinylestradiol. This value was selected based upon the results from Menon et al,[34] and the largest value of variation of C_{max} 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_{max} 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_{max} 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_{max} 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^2 (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_{max}, $AUC_{0\text{-}t}$, and AUC_{inf} 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_{max}, $AUC_{0\text{-}t}$, and AUC_{inf} 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. In

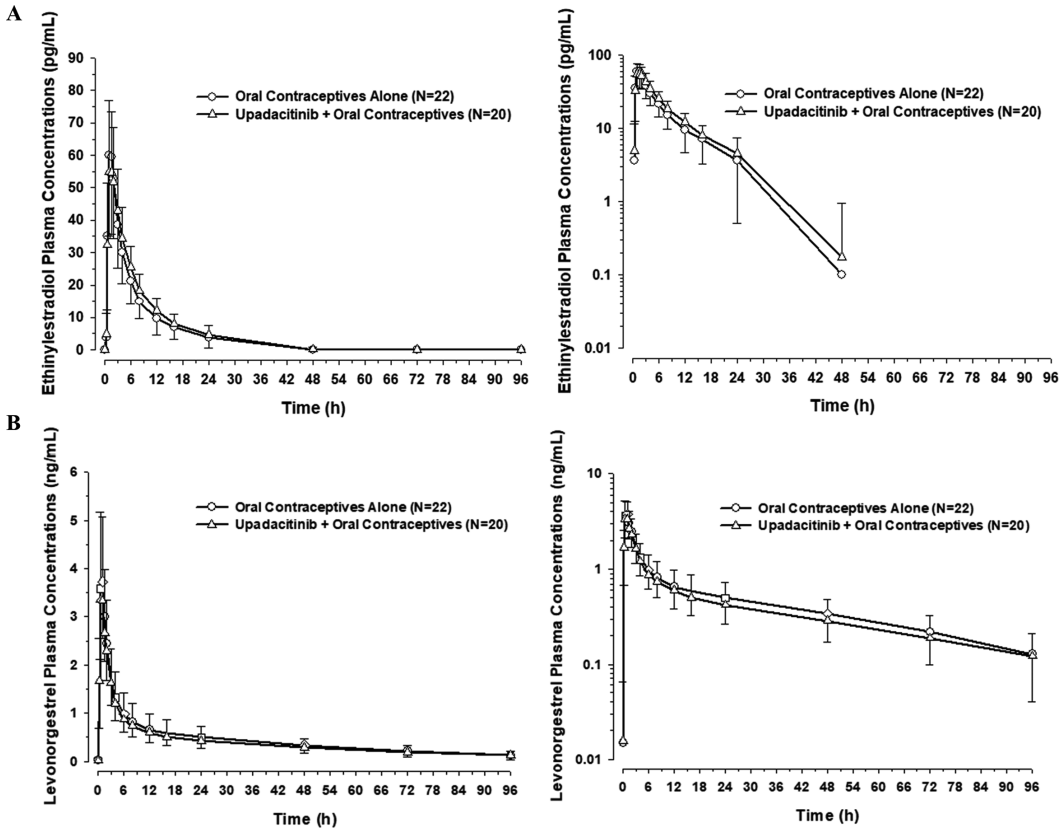

Figure 2. Mean ± SD (A) ethinylestradiol and (B) levonorgestrel plasma concentration vs time profiles following administration of a single dose of 0.03-mg ethinylestradiol and 0.15-mg levonorgestrel alone and with repeated once-daily doses of 30-mg upadacitinib.

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.[35] The high prevalence of oral contraceptive use and the contribution of CYP3A to the metabolism of oral contraceptives[36] 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 0.03/0.15 mg (N = 22)	Period 2/Day 14: Upadacitinib 30 mg QD + Ethinylestradiol/ Levonorgestrel 0.03/0.15 mg (N = 20)
Ethinylestradiol		
C_{max} (pg/mL)	62.7 ± 24.3	59.0 ± 20.5
T_{max}[a] (h)	1.5 (1.0–2.0)	1.5 (1.0–3.0)
$AUC_{0\text{-}t}$ (pg · h/mL)	378 ± 154	426 ± 137
AUC_{inf} (pg · h/mL)	441 ± 193	492 ± 166
$t_{1/2}$[b] (h)	7.0 (3.4)	7.7 (2.4)
Levonorgestrel		
C_{max} (ng/mL)	3.9 ± 1.4	3.7 ± 1.15
T_{max}[a] (h)	0.8 (0.5–2.0)	0.8 (0.5–2.0)
$AUC_{0\text{-}t}$ (ng · h/mL)	43.0 ± 18.4	38.7 ± 12.1
AUC_{inf} (ng · h/mL)	51.7 ± 22.0	49.5 ± 20.4
$t_{1/2}$[b] (h)	33.1 (12.4)	37.1 (15.1)

$AUC_{0\text{-}t}$, area under the plasma drug concentration–time curve from time zero to the time of last measureable concentration; AUC_{inf}, area under the plasma drug concentration–time curve from time zero to infinity; C_{max}, maximum plasma concentration; QD, once daily; $t_{1/2}$, terminal half-life; T_{max}, median time to maximum plasma concentration.

[a]Median (minimum to maximum).

[b]Harmonic mean (pseudo-standard deviation).

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

			Central Value		Ratio of Central Values	
Compound	Regimens Test vs Reference	Pharmacokinetic Parameter	Test	Reference	Point Estimate	90% Confidence Interval
Ethinylestradiol	Period 2, day 12 vs period 1, day 1	C_{max}	55.3	57.9	0.955	0.893–1.022
		AUC_{0-t}	390	348	1.121	1.043–1.205
		AUC_{inf}	445	402	1.108	1.036–1.186
Levonorgestrel	Period 2, day 12 vs period 1, day 1	C_{max}	3.59	3.74	0.961	0.873–1.059
		AUC_{0-t}	36.3	39.6	0.916	0.828–1.014
		AUC_{inf}	45.5	47.6	0.955	0.851–1.071

AUC_{0-t}, area under the plasma drug concentration–time curve from time zero to the time of last measureable concentration; AUC_{inf}, area under the plasma drug concentration–time curve from time zero to infinity; C_{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_{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

Acknowledgments

AbbVie contributed to the study design, research, and interpretation of data, and the writing, review, and approval of the publication.

Funding

The study was funded by AbbVie.

Declaration of Conflicting Interest

All authors are employees and shareholders of AbbVie.

References

1. Parmentier JM, Voss J, Graff C, et al. In vitro and in vivo characterization of the JAK1 selectivity of upadacitinib (ABT-494). *BMC Rheumatology*. 2018;2(1):23.

2. O'Shea JJ. Jaks, STATs, cytokine signal transduction, and immunoregulation: are we there yet? *Immunity*. 1997;7(1):1–11.
3. Murray PJ. The JAK-STAT signaling pathway: input and output integration. *J Immunol*. 2007;178(5):2623–2629.
4. Guschin D, Rogers N, Briscoe J, et al. A major role for the protein tyrosine kinase JAK1 in the JAK/STAT signal transduction pathway in response to interleukin-6. *EMBO J*. 1995;14(7):1421–1429.
5. Schindler C, Levy DE, Decker T. JAK-STAT signaling: from interferons to cytokines. *J Biol Chem*. 2007;282(28):20059–20063.
6. Maini RN, Taylor PC, Szechinski J, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum*. 2006;54(9):2817–2829.
7. Neurath MF, Finotto S. IL-6 signaling in autoimmunity, chronic inflammation and inflammation-associated cancer. *Cytokine Growth Factor Rev*. 2011;22(2):83–89.
8. Cutolo M. The kinase inhibitor tofacitinib in patients with rheumatoid arthritis: latest findings and clinical potential. *Ther Adv Musculoskelet Dis*. 2013;5(1):3–11.
9. Norman P. Selective JAK inhibitors in development for rheumatoid arthritis. *Expert Opin Investig Drugs*. 2014;23(8):1067–1077.
10. Genovese MC, Smolen JS, Weinblatt ME, et al. Efficacy and safety of ABT-494, a selective JAK-1 inhibitor, in a phase IIb study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Arthritis Rheumatol.* 2016;68(12):2857–2866.
11. Kremer JM, Emery P, Camp HS, et al. A phase IIb study of ABT-494, a selective JAK-1 inhibitor, in patients with rheumatoid arthritis and an inadequate response to anti-tumor necrosis factor therapy. *Arthritis Rheumatol.* 2016;68(12):2867–2877.
12. Sandborn WJ, Feagan BG, Panes J, et al. Safety and efficacy of ABT-494 (upadacitinib), an oral Jak1 inhibitor, as induction therapy in patients with Crohn's disease: results from Celest. *Gastroenterology*. 2017;152(5):S1308–S1309.
13. AbbVie. A multicenter, randomized, double-blind, placebo-controlled study of ABT-494 for the induction of symptomatic and endoscopic remission in subjects with moderately to severely active Crohn's disease who have inadequately responded to or are intolerant to anti-TNF therapy (Celest Study) [ClinicalTrials.gov identifier NCT02365649]. https://clinicaltrials.gov/ct2/show/NCT02365649?term=NCT02365649&rank=1. Accessed January 3, 2018.
14. AbbVie. A phase 3 study to compare ABT-494 to abatacept in subjects with rheumatoid arthritis on stable dose of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) who have an inadequate response or intolerance to biologic DMARDs (SELECT-CHOICE) [ClinicalTrials.gov Identifier NCT03086343]. https://clinicaltrials.gov/ct2/show/NCT03086343?term=NCT03086343&rank=1. Accessed January 3, 2018.
15. AbbVie. A study comparing ABT-494 monotherapy to methotrexate (MTX) monotherapy in subjects with rheumatoid arthritis (RA) who have an inadequate response to MTX (SELECT-MONOTHERAPY) [ClinicalTrials.gov identifier NCT02706951]. https://clinicaltrials.gov/ct2/show/NCT02706951?term=NCT02706951&rank=1. Accessed January 3, 2018.
16. AbbVie. A study comparing ABT-494 to placebo and to adalimumab in participants with psoriatic arthritis who have an inadequate response to at least one non-biologic disease modifying anti-rheumatic drug (SELECT - PsA 1) [ClinicalTrials.gov identifier NCT03104400]. https://clinicaltrials.gov/ct2/show/NCT03104400?term=NCT03104400&rank=1. Accessed January 3, 2018.
17. Guttman-Yassky E, Silverberg JI, Thaci D, Hong C-H, Mohamed M-E, Othman AA. Primary results from a phase 2b, randomized, placebo-controlled trial of upadacitinib for patients with atopic dermatitis [abstract 6533]. In: American Academy of Dermatology Annual Meeting, San Diego, CA; February 2018: 16–20.
18. Genovese MC, Fleischmann R, Combe B, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. *Lancet*. 2018;391:P2513–2524.
19. Burmester GR, Kremer JM, Van den Bosch F, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2018;391:P2503–2512.
20. AbbVie. A study comparing ABT-494 to placebo in participants with active psoriatic arthritis who have a history of inadequate response to at least one biologic disease modifying anti-rheumatic drug (SELECT - PsA 2) [ClinicalTrials.gov identifier NCT03104374]. https://clinicaltrials.gov/ct2/show/NCT03104374?term=NCT03104374&rank=1. Accessed January 3, 2018.
21. AbbVie. A study to evaluate ABT-494 in adult subjects with moderate to severe atopic dermatitis [ClinicalTrials.gov identifier NCT02925117]. https://clinicaltrials.gov/ct2/show/NCT02925117?term=NCT02925117&rank=1. Accessed January 3, 2018.
22. AbbVie. A study to evaluate the safety and efficacy of ABT-494 for induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis [ClinicalTrials.gov identifier NCT02819635]. https://clinicaltrials.gov/ct2/show/NCT02819635?term=NCT02819635&rank=1. Accessed January 3, 2018.
23. Abbvie. A multicenter, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of upadacitinib in subjects with active ankylosing spondylitis (SELECT Axis 1). [ClinicalTrials.gov identifier NCT03178487]. https://clinicaltrials.gov/ct2/show/NCT03178487?term=NCT03178487&rank=1. Accessed April 9, 2018.
24. Mohamed MF, Zeng J, Marroum PJ, Song IH, Othman AA. Pharmacokinetics of upadacitinib with the clinical regimens of the extended-release formulation utilized in rheumatoid arthritis phase 3 trials [published online ahead of print April 24, 2018]. *Clin Pharmacol Drug Dev*. doi: 10.1002/cpdd.462.
25. Klunder B, Mohamed MF, Othman AA. Population pharmacokinetics of upadacitinib in healthy subjects and subjects with rheumatoid arthritis: analyses of phase I and II clinical trials. *Clin Pharmacokinet*. 2018;57(8):977–988.
26. Mohamed MF, Jungerwirth S, Asatryan A, Jiang P, Othman AA. Assessment of effect of CYP3A inhibition, CYP induction, OATP1B inhibition, and high-fat meal on pharmacokinetics of the JAK1 inhibitor upadacitinib. *Br J Clin Pharmacol*. 2017;83(10):2242–2248.
27. Johnson S, Pion C, Jennings V. Current methods and attitudes of women towards contraception in Europe and America. *Reprod Health*. 2013;10:7.
28. Dunaway A. What types of birth control are available? *JAAPA*. 2008;21(3):63–64.

29. Zhang H, Cui D, Wang B, et al. Pharmacokinetic drug interactions involving 17alpha-ethinylestradiol: a new look at an old drug. *Clin Pharmacokinet*. 2007;46(2):133–157.
30. Lello S, Cavani A. Ethynilestradiol 20 mcg plus levonorgestrel 100 mcg: clinical pharmacology. *Int J Endocrinol*. 2014;2014:102184.
31. Davis AR, Westhoff CL, Stanczyk FZ. Carbamazepine coadministration with an oral contraceptive: effects on steroid pharmacokinetics, ovulation, and bleeding. *Epilepsia*. 2011;52(2):243–247.
32. Barditch-Crovo P, Trapnell CB, Ette E, et al. The effects of rifampin and rifabutin on the pharmacokinetics and pharmacodynamics of a combination oral contraceptive. *Clin Pharmacol Ther*. 1999;65(4):428–438.
33. Reimers A, Brodtkorb E, Sabers A. Interactions between hormonal contraception and antiepileptic drugs: Clinical and mechanistic considerations. *Seizure*. 2015;28:66–70.
34. Menon S, Riese R, Wang R, et al. Evaluation of the effect of tofacitinib on the pharmacokinetics of oral contraceptive steroids in healthy female volunteers. *Clin Pharmacol Drug Dev*. 2016;5(5):336–342.
35. United States Food and Drug Administration. Guidance for industry: drug interaction studies - study design, data analysis, implications for dosing, and labeling recommendations. 2012. https://www.xenotech.com/regulatory-documents/2012/2012_guidance.aspx. Accessed 16 November 2018.
36. Mosher WD, Jones J. Use of contraception in the United States: 1982–2008. *Vital Health Stat 23*. 2010(29):1–44.
37. Prueksaritanont T, Chu X, Gibson C, et al. Drug-drug interaction studies: regulatory guidance and an industry perspective. *AAPS J*. 2013;15(3):629–645.
38. Imai H, Kotegawa T, Tsutsumi K, et al. The recovery time-course of CYP3A after induction by St John's wort administration. *Br J Clin Pharmacol*. 2008;65(5):701–707.
39. Akbar M, Berry-Bibee E, Blithe DL, et al. FDA public meeting report on "drug interactions with hormonal contraceptives: public health and drug development implications." *J Clin Pharmacol*. 2018;58:1655–1665.