Characterization of the Effect of Upadacitinib on the Pharmacokinetics of Bupropion, a Sensitive Cytochrome P450 2B6 Probe Substrate

Mohamed-Eslam F. Mohamed, Mukul Minocha**, Sheryl Trueman, Tian Feng, Jeffrey Enejosa, Ogert Fisniku, and Ahmed A. Othman**

Abstract
This phase 1 study characterized the effect of multiple doses of upadacitinib, an oral Janus kinase 1 selective inhibitor, on the pharmacokinetics of the cytochrome P450 (CYP) 2B6 substrate bupropion. Healthy subjects (n = 22) received a single oral dose of bupropion 150 mg alone (study period 1) and on day 12 of a 16-day regimen of upadacitinib 30 mg once daily (study period 2). Serial blood samples for measurement of bupropion and hydroxybupropion plasma concentrations were collected in each study period. The central values (90% confidence intervals) for the ratios of change were 0.87 (0.79-0.96) for bupropion maximum plasma concentration (Cmax), 0.92 (0.87-0.98) for bupropion area under the plasma-concentration time curve from time 0 to infinity (AUCinf), 0.78 (0.72-0.85) for hydroxybupropion Cmax, and 0.72 (0.67-0.78) for hydroxybupropion AUCinf when administered with, relative to when administered without, upadacitinib. After multiple-dose administration of upadacitinib 30 mg once daily, upadacitinib mean ± SD AUC0-24 was 641 ± 177 ng·h/mL, and Cmax was 83.3 ± 30.7 ng/mL. These results confirm that upadacitinib has no relevant effect on pharmacokinetics of substrates metabolized by CYP2B6.

Keywords
upadacitinib, CYP2B6, bupropion, Janus kinase inhibitor, pharmacokinetics, drug interaction

Upadacitinib is an oral Janus kinase (JAK) 1 selective inhibitor recently approved by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and other regulatory agencies for the treatment of moderate to severe rheumatoid arthritis (RA). Upadacitinib is also currently under development for the treatment of several other inflammatory diseases including psoriatic arthritis, ankylosing spondylarthritis, atopic dermatitis, Crohn’s disease, and ulcerative colitis.1 Upadacitinib potently inhibits JAK1 and is less potent against the other isoforms (JAK2, JAK3, and tyrosine kinase).2 The selectivity of upadacitinib against JAK1 may offer an improved benefit-risk profile in patients with inflammatory conditions compared with less selective JAK inhibitors.3 Upadacitinib doses of 15 and 30 mg once daily using the extended-release formulation were evaluated in global phase 3 studies in RA.4 Results from the phase 3 studies demonstrated that upadacitinib 15 mg once daily maximized efficacy and provided the optimal benefit-risk in RA, which supported approval of 15 mg once daily as the recommended upadacitinib dose in RA.4-11

Upadacitinib is a nonsensitive substrate of cytochrome P450 (CYP) 3A, and approximately 20% of the upadacitinib dose is eliminated unchanged in urine.12 Administration of upadacitinib with the strong CYP3A inhibitor ketoconazole increased upadacitinib Cmax and AUC by 70% and 75%, respectively, whereas...
the administration of multiple doses of rifampin (a broad CYP inducer) decreased upadacitinib C_max and AUC by approximately 50% and 60%, respectively. Upadacitinib did not inhibit or induce the activity of CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at clinically relevant concentrations, but in vitro studies demonstrated an increase in CYP2B6 mRNA expression at concentrations higher than those that are clinically relevant. In a healthy volunteers study, chronic dosing of upadacitinib 30 mg once daily (a dose that is twice the recommended dose in RA) showed a limited effect on CYP3A activity (26% decrease in exposures of midazolam, a sensitive CYP3A substrate) and no relevant effects on CYP1A2, CYP2C9, CYP2C19, or CYP2D6 activity. A follow-up drug interaction study demonstrated no impact of upadacitinib on exposure of levonorgestrel and ethinylestradiol, 2 oral contraceptives that are substrates of CYP3A, confirming a lack of clinical relevance of the observed small effect of upadacitinib on midazolam exposure.

Given that patients with inflammatory conditions often have other comorbidities, it is expected that upadacitinib will be concomitantly administered with drugs metabolized by different CYP enzymes, including CYP2B6. Bupropion, a drug used for the treatment of depression and smoking cessation, is metabolized to the active metabolite hydroxybupropion primarily by CYP2B6. Therefore, assessing the effect of upadacitinib on the pharmacokinetics of bupropion can inform the potential for the in vivo effect of upadacitinib on CYP2B6. The objective of this clinical study was to evaluate the effect of repeated dosing of upadacitinib 30 mg once daily using the extended-release formulation on the pharmacokinetics of bupropion.

Methods

The study protocol and informed consent form were approved by Quorum Institutional Review Board (Seattle, Washington). Informed consent was obtained from the subjects prior to performing any study-related procedures. The study was conducted at the AbbVie Clinical Pharmacology Research Unit (Grayslake, Illinois) in accordance with Good Clinical Practice guidelines and ethical principles that have their origin in the Declaration of Helsinki.

Subjects

Healthy male and female subjects between 18 and 55 years of age inclusive were enrolled based on screening results from a medical history, physical examination, clinical laboratory profile, and electrocardiogram (ECG) evaluations. Subjects must not have consumed any prescription medication (prescription or over the counter) or herbal supplements within 14 days, tobacco or nicotine-containing products within 180 days, or investigational drugs within 6 weeks prior to first study drug dose or 5 half-lives, whichever is longer. Use of any known inhibitors or inducers of drug-metabolizing enzymes within 30 days prior to study start and through the course of the study was prohibited.

Study Design

In this single-center, open-label, 2-period, single-sequence -over study, subjects received a single dose of 150 mg bupropion using the extended-release formulation (InvaGen Pharmaceuticals Inc., Hauppauge, New York) alone (study period 1) and on day 12 of a 16-day regimen of upadacitinib 30 mg once daily (study period 2) using the extended-release formulation. Bupropion was administered in the morning after a minimum 10-hour fast and 4 hours prior to lunch. Subjects were confined to the study site and supervised for 24 days. The study design schematic is shown in Figure 1.

Pharmacokinetic Assessments and Bioanalysis

Serial blood samples for the measurement of bupropion and hydroxybupropion plasma concentrations were collected prior to dosing and 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, and 120 hours after the morning dose on day 1 in study period 1 and on day 12 in study period 2. Serial blood samples for the measurement of upadacitinib plasma concentrations were collected prior to dosing and 1.5, 3, 4, 6, 8, 12, and 24 hours after the morning dose on day 11 in study period 2 to determine upadacitinib steady-state plasma exposure.

Plasma samples for upadacitinib were analyzed using a validated assay developed by AbbVie Inc. (Lake County, Illinois). Plasma samples for bupropion and hydroxybupropion were analyzed using a validated assay developed by inVentiv Health Clinitec, Inc. (Quebec, Canada). For the bupropion and hydroxybupropion assay, the analyte of interest was extracted by liquid-liquid extraction from a 50-μL sample volume. Chromatographic separation was achieved using an ACE 3 C18 column (3 μm, 4.6 × 30 mm) and isocratic conditions with a mobile phase consisting of 65/35 water:methanol, ammonium formate 1 mM, acetic acid 0.2% (v/v). An API 4000 mass spectrometer (AB Sciex, Framingham, Massachusetts) employing electrospray ionization in positive ion mode was used to monitor the analyte. Multiple-reaction monitoring (MRM) transitions were m/z 240 → 184 for bupropion, 256.1 → 167 for hydroxybupropion, and m/z 251 → 169.1 for the internal standard (threohydroxybupropion-d3). For bupropion the lower limit of quantification (calibration range) was 0.05 ng/mL (0.05-250 ng/mL), and...
interassay precision and accuracy/bias as demonstrated by the performance of the quality control samples were ≤4.17% and between −2.94% and −0.16%, respectively. For hydroxybupropion the lower limit of quantification (calibration range) was 5 ng/mL (5-800 ng/mL), and interassay precision and accuracy/bias as demonstrated by the performance of the quality control samples were ≤3.88% and between −3.84% and 2.38%, respectively.

For the upadacitinib assay, a sample volume of 50 μL was combined with the internal standard (upadacitinib-d4), and the analyte of interest extracted by salt-assisted liquid-liquid extraction. A portion of the supernatant was transferred and combined with water prior to submission for analysis. Chromatographic separation was achieved using a Thermo Aquasil C18 column (3 μm, 2.1 × 50 mm) and isocratic conditions with a mobile phase consisting of 30/70/0.1 (v/v/v) acetonitrile/water/formic acid. An API 5500 mass spectrometer (AB Sciex, Framingham, Massachusetts) employing electrospray ionization in positive ion mode was used to monitor the analyte. MRM transitions were m/z 381 → 256 for upadacitinib and 385 → 260 for the internal standard (upadacitinib-d4). The lower limit of quantification (calibration range) was 0.0506 ng/mL (0.0506-101 ng/mL), and interassay precision and accuracy/bias as demonstrated by the performance of the quality control samples were ≤5.9% and between −0.8% and 1.9%, respectively.

Pharmacokinetic Analyses
Pharmacokinetic parameters for bupropion, hydroxybupropion, and upadacitinib were estimated using noncompartmental methods with Phoenix WinNonlin version 6.4 (Pharsight, A Certara Company, St. Louis, Missouri). Bupropion and hydroxybupropion pharmacokinetic parameters included the maximum observed plasma concentration (Cmax), time to reach Cmax (Tmax), the area under the plasma concentration-time curve (AUC) from 0 to last measurable point (AUCt) and from 0 to infinity (AUCinf), and the terminal-phase elimination half-life (t1/2). Upadacitinib pharmacokinetic parameters included Cmax, Tmax, and AUC from time 0 to 24 hours after dose (AUC0-24).

Statistical Analyses of the Pharmacokinetic Parameters
To evaluate the effect of multiple doses of upadacitinib on bupropion and hydroxybupropion, a repeated-measures analysis was performed for the natural logarithms of Cmax and AUC for bupropion using data from study period 1, day 1 and study period 2, day 12. The model had study period as a fixed effect. The within-subject variability was accounted for using the repeated statement for the effect of study period. The bioavailability of the combination regimen containing upadacitinib and bupropion (study period 2, day 12) relative to that of the bupropion-alone regimen (study period 1, day 1) was assessed by point estimates and corresponding 90% confidence intervals obtained from the repeated-measures analysis of the natural logarithms of Cmax and AUC. These confidence intervals were obtained by taking the antilogarithm of the upper and lower limits of confidence intervals for the difference of the least-squares means on the logarithmic scale within the framework of the repeated-measures analysis.

All statistical tests were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina). For the repeated-measures analysis, SAS procedure PROC MIXED was used.

Safety Monitoring
Routine safety evaluations, which included adverse event monitoring, physical examinations, vital sign measurements, ECG assessments, and clinical laboratory tests (hematology, chemistry, and urinalysis) were performed throughout the course of the study.
Table 1. Subject Demographics (n = 22)

|                  | Mean ± SD    | Min-Max     |
|------------------|--------------|-------------|
| Age (years)      | 41.1 ± 9.7   | 26-56<sup>a</sup> |
| Weight (kg)      | 76.3 ± 14.0  | 55.9-99.7   |
| Height (cm)      | 172.0 ± 10.8 | 154.5-192.6 |
| BMI (kg/m<sup>2</sup>) | 25.6 ± 2.6  | 20.1-29.3   |
| Sex              | 16 men (73%), 6 women (27%) |
| Race             | 12 white (54.5%), 7 black (32%), 1 Asian (4.5%), 2 multiple (9%) |

SD, standard deviation; BMI, body mass index.
<sup>a</sup>All subjects were 18-55 years of age at screening.

Results

**Subject Disposition**

Twenty-two healthy subjects (6 women and 16 men) with a mean ± SD age of 41 ± 10 years and a mean body mass index of 25.6 ± 2.6 kg/m<sup>2</sup> were enrolled and completed the study (Table 1).

**Pharmacokinetics**

The mean bupropion and hydroxybupropion plasma concentrations-versus–time profiles when administered with and without 30 mg of upadacitinib once daily are presented in Figure 2 and a summary of the bupropion and hydroxybupropion pharmacokinetic parameters is shown in Table 2. The results of the repeated-measures analysis to assess the effect of chronic dosing of upadacitinib coadministration on bupropion and hydroxybupropion exposures are shown in Table 3.

Administration of bupropion on day 12 of a 16-day multiple-dose regimen (30 mg once daily using the extended-release formulation) of upadacitinib had no relevant effect on bupropion exposures (C<sub>max</sub> or AUC). The central values for C<sub>max</sub> and AUC ratios when bupropion was administered with, relative to when administered without, upadacitinib were 0.87 and 0.92, respectively, for bupropion with the 90% confidence interval for bupropion AUC ratio falling within the default 0.8 to 1.25 equivalence boundaries, and 0.78 and 0.72, respectively, for hydroxybupropion. After multiple-dose administration of upadacitinib 30 mg once daily, upadacitinib mean ± SD AUC<sub>0-24</sub> was 641 ± 177 ng·h/mL, C<sub>max</sub> was 83.3 ± 30.7 ng/mL, and median T<sub>max</sub> was 3 hours.

**Safety and Tolerability**

There was no pattern to the types of adverse events (AEs) that were reported. The majority of the treatment-emergent AEs were mild in severity, and no subject discontinued because of AEs. One subject reported an asymptomatic decrease in neutrophil count on the last day of dosing, considered by the investigator as having a reasonable possibility of a relationship to upadacitinib, which returned to normal levels 8 days later. No other clinically significant laboratory abnormalities or changes in vital signs were observed during the course of the study.

**Discussion**

In this clinical study, administration of multiple doses of upadacitinib 30 mg once daily had no relevant effect on bupropion AUC and C<sub>max</sub> with the 90% confidence intervals for the ratios for change in bupropion AUC within the no-effect boundaries of 0.8 to 1.25. Hydroxybupropion exposures (AUC<sub>inf</sub>) were 28% lower when administered with upadacitinib, which is within the range of reported inter- and intrasubject variability in hydroxybupropion exposures and is not expected to be clinically relevant. Overall, these results demonstrate the lack of relevant effect of upadacitinib administration on the pharmacokinetics of CYP2B6-sensitive substrates and were the basis for recommending no dose adjustment of CYP2B6 substrates when coadministered with upadacitinib in the US prescribing information and the European Summary of Product Characteristics for upadacitinib.

Bupropion is metabolized to hydroxybupropion primarily by CYP2B6, with a minor contribution from CYP3A<sup>15,20,27</sup> and to threohydrobupropion and erythro hydrobupropion by carbonyl reductases. It has also been reported that CYP2C19 contributes to bupropion metabolism and that glucuronidation enzymes contribute to hydroxybupropion metabolism.<sup>21,22,29,30</sup> Changes in hydroxybupropion have been used as a marker for CYP2B6 activity;<sup>23,31</sup> however, plasma concentrations of hydroxybupropion were reported to be elimination — rather than formation — limited, which limits the selectivity of using changes in hydroxybupropion as a measure for CYP2B6 activity.<sup>32,33</sup> A true decrease in hydroxybupropion exposure may result from a decrease in its formation or an increase in elimination. In vitro, upadacitinib was not an inhibitor or inducer of drug-metabolizing enzymes, including CYP2B6, at clinically relevant concentrations.<sup>15</sup> In addition, a cocktail clinical drug interaction demonstrated that upadacitinib 30 mg once daily had no effect on OH-omeprazole-to-omeprazole AUC ratio, indicating lack of effect on CYP2C19. Upadacitinib resulted in a relatively small decrease in midazolam exposures (decrease in midazolam AUC and C<sub>max</sub> by 26%).<sup>16</sup> Therefore, the mechanism for this slight difference in hydroxybupropion exposure (with vs without upadacitinib) is not fully understood based on prior in vivo and in vitro assessments and is not expected to be clinically relevant because it is within the range of variability in hydroxybupropion exposures (~20% to 50%).
bupropion is not considered a selective probe substrate for CYP2B6, the lack of relevant effect of upadacitinib on bupropion and the apparent limited effect on hydroxybupropion observed in this study indicates lack of relevant effect of upadacitinib on CYP2B6. At the present time, no specific CYP2B6 in vivo probe substrates are known.\textsuperscript{54}

In the current study, a upadacitinib dose of 30 mg once daily was evaluated, which is twice the FDA- and EMA-approved dose of upadacitinib (15 mg once
Table 2. Mean ± SD Pharmacokinetic Parameters of Bupropion and Hydroxybupropion Following Administration of Bupropion Alone and on Day 12 of a 16-Day Regimen of 30 mg Upadacitinib Once Daily

| Pharmacokinetic Parameters (Units) | Study Period 1, Day 1: Bupropion 150 mg Alone (n = 22) | Study Period 2, Day 12: Upadacitinib 30 mg Once Daily + Bupropion 150 mg (n = 22) |
|------------------------------------|--------------------------------------------------------|----------------------------------------------------------------------------------|
| Cmax (ng/mL)                       | 83.5 ± 26.2 | 72.9 ± 20.8 |
| Tmax (h)                           | 5.0 (3.0-10.0) | 5.0 (3.0-8.0) |
| AUCt (ng·h/mL)                     | 869 ± 271 | 795 ± 210 |
| AUCinf (ng·h/mL)                   | 898 ± 281 | 826 ± 215 |
| t1/2 (h)                           | 26.0 ± 7.3 | 26.3 ± 8.4 |

Bupropion pharmacokinetic parameters

| Pharmacokinetic Parameters (Units) | Study Period 1, Day 1: Bupropion 150 mg Alone (n = 22) | Study Period 2, Day 12: Upadacitinib 30 mg Once Daily + Bupropion 150 mg (n = 22) |
|------------------------------------|--------------------------------------------------------|----------------------------------------------------------------------------------|
| Cmax (ng/mL)                       | 336 ± 150 | 264 ± 121 |
| Tmax (h)                           | 10.0 (5.0-24.0) | 10.0 (6.0-24.0) |
| AUCt (ng·h/mL)                     | 15 000 ± 7290 | 11 000 ± 5480 |
| AUCinf (ng·h/mL)                   | 15 900 ± 8040 | 11 500 ± 5730 |
| t1/2 (h)                           | 25.1 ± 6.8 | 23.9 ± 5.6 |

Hydroxybupropion pharmacokinetic parameters

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SD, standard deviation; Cmax, maximum observed plasma concentration; Tmax, time to Cmax; AUCt, area under the curve to the last measurable concentration; AUCinf, AUC from zero to infinity; t1/2, terminal phase elimination half-life

Medians (minimum through maximum).

Results from this study further support the lack of clinically relevant effects of upadacitinib on the pharmacokinetics of concomitant medications, which is consistent with previously reported clinical drug interaction studies.16,17

Conclusions

Upadacitinib has no relevant effect on the pharmacokinetics of drug substrates metabolized by CYP2B6. No dose adjustment is recommended for drugs metabolized by CYP2B6 when coadministered with upadacitinib.

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Data-Sharing Statement

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 unlisd 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 (SAP) and execution of a data-sharing agreement (DSA). 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.

Conflicts of Interest

Drs. Mohamed, Trueman, Feng, Enejosa, and Fisniku are employees of AbbVie and may hold AbbVie stock. Drs. Minocha and Othman are former AbbVie employees and may hold AbbVie stock.

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**Table 3.** Point Estimates and 90% Confidence Intervals for the Pharmacokinetic Parameters of Bupropion, Hydroxybupropion, and Hydroxybupropion-to-Bupropion Ratio When Bupropion Is Administered on Day 12 of 16-Day Multiple-Dose Regimen of Upadacitinib Relative to When Administered Alone

| Regimens Test Versus Reference | Pharmacokinetic Parameter | Central Value<sup>a</sup> | Ratio of Central Values | 90% Confidence Interval<sup>d</sup> |
|-------------------------------|---------------------------|---------------------------|------------------------|----------------------------------|
| Bupropion                     |                           |                           |                        |                                  |
| Period 2, day 12 versus period 1, day 1<sup>b</sup> | C<sub>max</sub> | 69.3 | 79.8 | 0.868 | 0.787-0.957 |
|                              | AUC<sub>t</sub>           | 763 | 830 | 0.919 | 0.868-0.974 |
|                              | AUC<sub>inf</sub>         | 794 | 859 | 0.924 | 0.873-0.979 |
| Hydroxybupropion              |                           |                           |                        |                                  |
| Period 2, day 12 versus period 1, day 1<sup>b</sup> | C<sub>max</sub> | 239 | 306 | 0.783 | 0.723-0.847 |
|                              | AUC<sub>t</sub>           | 9970 | 13700 | 0.726 | 0.676-0.780 |
|                              | AUC<sub>inf</sub>         | 10500 | 14500 | 0.721 | 0.671,0.775 |
| Hydroxybupropion-to-bupropion metabolic ratio |                            |                           |                        |                                  |
| Period 2, day 12 versus period 1, day 1<sup>b</sup> | C<sub>max</sub> | 3.45 | 3.83 | 0.902 | 0.811-1.004 |
|                              | AUC<sub>t</sub>           | 13.1 | 16.5 | 0.790 | 0.739-0.844 |
|                              | AUC<sub>inf</sub>         | 13.2 | 16.9 | 0.780 | 0.731-0.832 |

<sup>a</sup>C<sub>max</sub>, maximum observed plasma concentration; AUC<sub>t</sub>, area under the curve to the last measurable concentration; AUC<sub>inf</sub>, AUC from zero to infinity.

<sup>b</sup>Antilogarithm of the least-squares means for logarithms.

<sup>c</sup>Antilogarithm of the difference (test minus reference) of the least-squares means for logarithms.

<sup>d</sup>Antilogarithm of the end points of confidence intervals for the difference of logarithms means.

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