

## H-4059

## THE EFFECT OF UGT2B7 INHIBITION ON THE STEADY-STATE PHARMACOKINETICS OF UK-453,061 AFTER MULTIPLE-DOSE ADMINISTRATION IN HEALTHY MALE SUBJECTS

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## Abstract

**Background:** UK-453,061 is a next-generation NNRTI currently in clinical development for treatment of HIV-1. Previous studies have indicated that UK-453,061 is cleared by cytochrome P450 and glucuronidation-mediated pathways. *In vitro* experiments with recombinant UGTs indicate a major role for 2B7 in glucuronide formation of UK-453,061. This study used valproic acid (VPA), a potent inhibitor of UGT2B7, to investigate the effect of drug-induced UGT2B7 inhibition on the steady-state pharmacokinetics (PK) of UK-453,061.

**Methods:** 14 healthy male subjects were enrolled into an open-label, randomized, placebo-controlled, two-period crossover study. Subjects participated in two 8-day treatment periods separated by a 14-day washout period. All subjects received UK-453,061 (500 mg QD) on Days 1-7 during both treatment periods and were randomized to receive VPA (1000 mg QD) on Days 1-7 in one period and placebo (QD) on Days 1-7 in the other. Blood samples for PK analysis were taken pre-dose on Days 1-7 and at various times up to 24 hours post-dose on Day 7. Safety was assessed throughout the treatment period and at follow-up. Natural log-transformed  $AUC_{0-24h}$  and  $C_{max}$  were analyzed using a mixed-effect model.

**Results:** For UK-453,061, steady-state  $AUC_{0-24h}$  and  $C_{max}$  ratios of adjusted geometric treatment means [%] (UK-453,061 + VPA/UK-453,061 + placebo) were 125.1% (90% CI: 115.7%, 135.4%) and 102.5% (90% CI: 90.8%, 115.5%), respectively. There were no serious or severe adverse events and no clinically significant laboratory abnormalities.

**Conclusions:** Co-administration of VPA with UK-453,061 increased the  $AUC_{0-24h}$  and  $C_{max}$  of UK-453,061 by approximately 25% and 3%, respectively, suggesting that inhibition of UGT2B7 is not associated with a marked change in the PK of UK-453,061. UK-453,061 appeared to be well tolerated in both the presence and absence of VPA.

## Introduction

UK-453,061 is a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) currently in clinical development for the treatment of HIV/AIDS. UK-453,061 has demonstrated potent activity against both wild-type and clinically relevant drug-resistant viruses.<sup>1</sup> *In vitro* studies indicate that UK-453,061 is cleared by cytochrome P450 and glucuronidation-mediated pathways.<sup>2</sup> Experiments with recombinant UDP-glucuronosyltransferase (UGT) enzymes indicate a major role for UGT2B7 in the glucuronide formation of UK-453,061.

## Objectives

- To investigate the effects of UGT2B7 inhibition, mediated by valproic acid (VPA), on the pharmacokinetics (PK) of multiple oral doses of UK-453,061.
- To investigate the safety and tolerability of co-administration of UK-453,061 with VPA.

## Methods

- The protocol was reviewed and approved by an independent ethics committee and all volunteers gave written informed consent.
- Study A5271026 was an open-label, randomized, placebo-controlled, two-period, crossover study.
- 14 healthy male subjects were enrolled.
- Screening was conducted up to 28 days prior to the first dose.
- Subjects received two 8-day treatments, with oral doses of UK-453,061 500 mg QD plus VPA 1000 mg QD or placebo QD.

- Minimum 14-day washout period.
- Blood samples for PK analysis were collected pre-dose on Days 1 to 7 and at various times from 0.5 to 24 hours post-dose on Day 7.
- Follow-up visit was conducted 10–14 days after the final dose.
- Safety laboratory tests were performed at screening, Day 0, and Day 8 of each study period, and at follow-up.
- The investigator obtained and recorded all observed or volunteered adverse events, the severity (mild, moderate, or severe) of the events, and the investigator's opinion of the relationship to the study drug.
- Natural log-transformed  $AUC_{0-24h}$  and  $C_{max}$  were analyzed using a mixed-effect model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals (CIs) were obtained from the model. The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. UK-453,061 administered alone is the Reference treatment and UK-453,061 + VPA in co-administration is the Test treatment.
- The mixed-effect model was implemented using SAS Proc Mixed, with REML estimation method and Kenward-Roger degrees of freedom algorithm.

## Results

- Inhibition of UGT2B7 by co-administration of VPA with UK-453,061 increased the  $AUC_{0-24h}$  and  $C_{max}$  of UK-453,061 by 25% and 3%, respectively (Table 1).

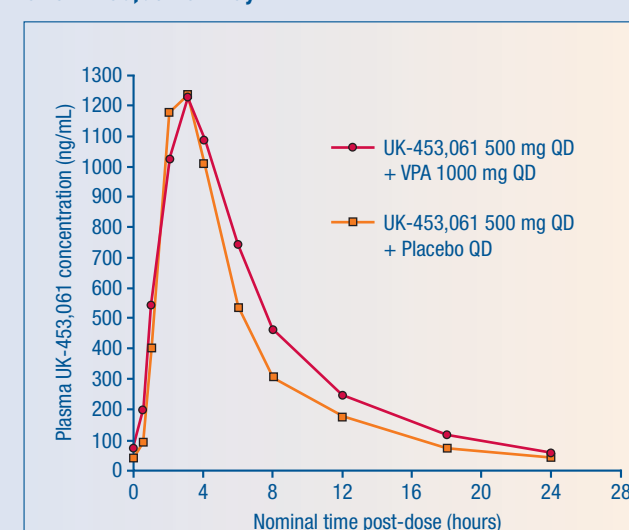
Table 1. Effect of VPA on UK-453,061 steady-state pharmacokinetics

	UK-453,061 (500 mg QD) + VPA (1000 mg QD)	UK-453,061 (500 mg QD) + placebo	Ratio of adjusted geometric means (90% CI) (%) <sup>a</sup>
$AUC_{0-24h}$ <sup>a</sup> (ng.hr/mL)	9383	7498	125.1 (115.7, 135.4)
$C_{max}$ <sup>a</sup> (ng/mL)	1327	1295	102.5 (90.8, 115.5)
$C_{min}$ <sup>a</sup> (ng/mL)	62	38	-
$T_{max}$ <sup>b</sup> (hr)	3.0	3.0	-

<sup>a</sup>Geometric mean; <sup>b</sup>median; <sup>c</sup>UK-453,061 + VPA/UK-453,061 + placebo QD, once daily; VPA, valproic acid

- UK-453,061  $T_{max}$  was unaffected by the inhibition of UGT2B7 by co-administration of VPA (Figure 1).

Figure 1. Effect of VPA on the median plasma concentration of UK-453,061 on Day 7



- Co-administration of UK-453,061 and VPA appeared to be well tolerated. There were no serious or severe adverse events and no discontinuations from the study.

- There were more adverse events considered treatment-related while subjects were receiving UK-453,061 + VPA than while receiving UK-453,061 + placebo (Table 2). All adverse events were either mild or moderate in intensity.

Table 2. Treatment-emergent adverse events

	UK-453,061 (500 mg QD) + VPA (1000 mg QD) N=14	UK-453,061 (500 mg QD) + placebo N=14
<i>All causalities (treatment-related)</i>		
Number of AEs	12 (6)	5 (3)
Subjects with AEs	6 (4)	5 (3)

AE, adverse event; QD, once daily; VPA, valproic acid

- No adverse event occurred in more than two subjects (Table 3).

Table 3. Incidence of adverse events

	UK-453,061 (500 mg QD) + VPA (1000 mg QD) N=14	UK-453,061 (500 mg QD) + placebo N=14
<i>MedDRA preferred term, all causalities (treatment-related)</i>		
Headache	2 (1)	0
Vessel puncture-site hematoma	2 (0)	0
Nausea	1 (1)	2 (2)
Upper respiratory tract infection	0	2 (0)
Blood bilirubin increased	1 (1)	1 (1)
Anorexia	1 (1)	0
Vomiting	1 (1)	0
Hyperhidrosis	1 (1)	0
Gastroenteritis	1 (0)	0
Back pain	1 (0)	0
Lethargy	1 (0)	0

QD, once daily; VPA, valproic acid

## Conclusions

- Inhibition of UGT2B7 by VPA is not associated with a marked change in the PK of UK-453,061, thus no dose modifications are necessary when UK-453,061 is co-administered with potent inhibitors of UGT2B7.
- Co-administration of UK-453,061 and VPA appeared to be well tolerated.

## References

- Mori J et al. Abstract presented at the 15<sup>th</sup> Conference on Retroviruses and Opportunistic Infections, Boston, MA, February 3-6, 2008; Abs F-134.
- Davis J et al. Abstract presented at the 9<sup>th</sup> International Workshop on Clinical Pharmacology of HIV Therapy, New Orleans, LA, USA, 2008.

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