

# 640385, a Novel HIV-1 Protease Inhibitor (PI): Safety and Pharmacokinetics (PK) of 640385 Following Repeat Administration with and without Ritonavir (RTV) in Healthy Subjects

## Introduction

GW640385X (640385, 385) is a novel PI in development for treatment of PI-resistant HIV. 640385 was shown to be more potent than lopinavir (LPV), amprenavir (APV), nelfinavir (NFV) and indinavir (IDV) against a panel of 55 PI-resistant clinical isolates with an average of 8 PRO mutations per virus. *In vitro* 640385 IC50s ranged from 0.1–14.9nM against these isolates, 80% of which had an IC50 at or below 0.8nM (28ng/mL when corrected for protein binding)<sup>2,5</sup>. The low oral bioavailability of 640385 in humans can be overcome by co-administration of low dose ritonavir (RTV); plasma 640385 exposure increased ~30-fold following single dose administration with RTV 100mg<sup>5</sup>.

The objectives of this study (HPR10003) were to assess the safety, tolerability and pharmacokinetics (PK) of 640385 following repeat administration with and without RTV in healthy subjects.

## Methods

### Study Design

Double-blind, randomized, placebo controlled, escalating, repeat oral administration study in six cohorts of healthy male and female subjects (n=10 subjects per cohort, 8 active and 2 placebo). The protocol was approved by the Covance IRB and all subjects provided written informed consent prior to taking part in the study.

### PO Doses Studied (2 weeks duration, administered in fed state)

- 640385 800mg BID n=10 (8 active/2 placebo)
- 640385 100mg/RTV 100mg QD n=9 (8/1)
- 640385 250mg/RTV 100mg QD n=9 (7/2)
- 640385 50mg/RTV 100mg BID n=10 (8/2)
- 640385 150mg/RTV 100mg BID n=10 (8/2)
- 640385 300mg/RTV 100mg BID n=10 (8/2)

### Study Procedures

- Safety assessments
  - Physical Exam on Days -1 and 16.
  - Vital Signs on Days 1 through 16.
  - Clinical Laboratory Tests (Hematology, Clinical Chemistry, Urinalysis, Lipid Panel) on Days -1, 2, 4, 7, 10, 13, 15, and 16.
  - Holter Monitoring (from -1h to 24h post dose) Days 1 and 15.
  - ECGs (predose and 1, 2, 4, 6, 8, 12, and 24h post dose) on Days 1 and 15.
  - AE Assessment on Days -1 through 16.
- PK assessments
  - Blood samples were collected to 24h post dose on Days 1 and 15, and AM predose samples were collected on Days 3-14.

### Sample Analysis

- Plasma 640385 and RTV concentrations were determined by a validated LC/MS/MS method.
- Linear ranges: 640385 1-1000ng/mL, RTV 10-10000ng/mL.

### PK Analysis

- PK parameters were determined by non-compartmental methods on nominal time data using WinNonLin 4.1 (Pharsight Corp).

### Statistical Analysis

- PK parameters were summarized by cohort using descriptive statistics.

## Results

### Demography

Table 1. Demographic Data

N	Sex	Race	Age <sup>1</sup> (y)	Weight <sup>1</sup> (kg)	Height <sup>1</sup> (cm)	BMI <sup>1</sup> (kg/m <sup>2</sup> )
58	M 47 (81%) F 11 (19%)	W 43 (74%) B 11 (19%) H 3 (5%) O 1 (2%)	36 (19, 55)	76.8 (51.6, 94.3)	176 (154, 188.5)	25.7 (19.2, 19.6)

### Safety

#### Hemodynamics and ECG

- There were no clinically significant changes in blood pressure, heart-rate or ECG measurements.

#### Adverse Events

- No serious adverse events (SAEs) were reported in this study.
- There were no drug-related withdrawals from any of the Cohorts receiving 640385/RTV.
- Of the 47 subjects who received 640385/RTV, 16 (34%) experienced at least one adverse event (AE) thought to be related to the study drug. These AEs were all Grade 1 and most commonly included: GI symptoms, headache, and dizziness/fatigue.
- Of the 10 subjects enrolled in the Cohort that received 640385 alone (800mg), 3 subjects experienced a diffuse, erythematous macular rash that appeared on Days 5, 10, and 10, respectively. 2 of these subjects received 640385 and 1 received placebo. All three subjects were withdrawn from the study and the rashes resolved within 2 days.
- There were no rashes seen in any of the other Cohorts.
- This observation is similar to APV where the incidence of rash appears higher without RTV boosting<sup>1</sup>.

#### Laboratory Safety Data

- 4 of 8 subjects receiving 640385 50mg/RTV 100mg BID had asymptomatic, Grade 1 elevations of TSH on routine labs drawn on Day 15. These abnormalities returned to baseline over 2-3 weeks.
- There were no clinically significant trends in free T3 and T4 values associated with the elevated TSH results.
- On retrospective testing, 2 of the 4 subjects with TSH elevations were found to be positive for thyroid peroxidase antibodies (TPOAbs).
- In subsequent Cohorts, subjects were screened for TPOAbs, and those with positive titers were excluded from the study.
- No other TSH abnormalities were observed in the subsequent Cohorts.

### 640385 Pharmacokinetics

Table 2. Median (range) Day 15 Plasma 640385 PK Parameters By Regimen

640385/RTV Regimen	N	AUC(0-τ) <sup>1</sup> (ng.h/mL)	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (h)	C <sub>τ</sub> <sup>1</sup> (ng/mL)
800mg BID	6	221 (74, 402)	54 (15, 113)	3.8 (1.5, 5.0)	3.1 (1.1, 5.6)
100/100mg QD	8	1939 (1119, 2478)	247 (175, 302)	3.8 (2.5, 5.0)	17 (6.3, 45)
250/100mg QD	6	2489 (1772, 4486)	398 (291, 609)	4.0 (2.5, 4.0)	18 (9.6, 32)
50/100mg BID	8	1175 (620, 1985)	154 (100, 249)	4.5 (3.0, 6.0)	61 (27, 120)
150/100mg BID	8	2145 (763, 3049)	346 (141, 420)	4.5 (3.5, 5.0)	104 (36, 217)
300/100mg BID	8	2735 (2244, 7329)	463 (366, 998)	4.0 (2.5, 6.0)	132 (83, 387)

1. τ=12h for BID regimens and 24h for QD regimens

Figure 1. Median Day 15 Plasma 640385 Concentration Time Profiles

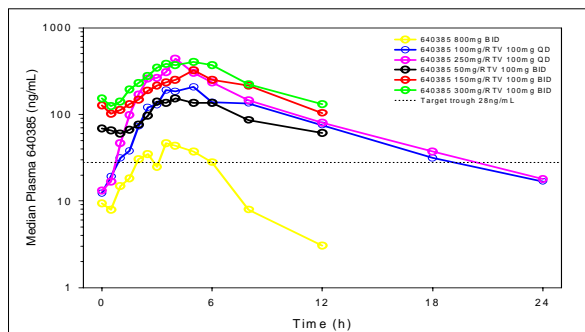
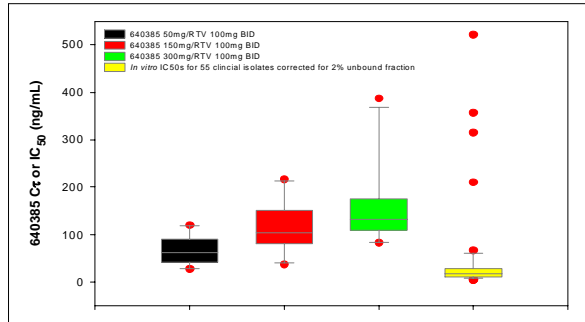


Figure 2. Summary of 640385 Day 15 C<sub>12</sub> values following administration of 640385/RTV BID shown with Protein Binding Adjusted *in vitro* IC<sub>50</sub>s for 55 Clinical Isolates



### 640385 PK Summary

- 640385 was readily absorbed following administration of 640385 and 640385/RTV with similar t<sub>max</sub> values on Days 1 and 15.
- Dose adjusted median Day 15 640385 AUC(0-12) values were 85-, 52- and 33-fold higher following 640385 50mg/RTV 100mg BID, 150mg/RTV 100mg BID, and 300mg/RTV 100mg BID, respectively, than the median Day 15 640385 AUC(0-12) following 640385 800mg BID alone, which is consistent with the boost effect of RTV 100mg on single dose 640385<sup>5</sup>.
- All 640385/RTV BID regimens achieved median C<sub>τ</sub> values above the 28ng/mL target trough concentration.
- Administration of 640385 800mg BID alone and in QD regimens with RTV resulted in 640385 exposures below the estimated 640385 target for resistant virus; 640385/RTV QD regimens may provide sufficient exposure to inhibit WT virus (estimated target 4ng/mL).
- Estimated median (range) C<sub>τ,actual</sub>/C<sub>τ,target</sub> ratios were 2.2 (1-4.3), 3.7 (1.3-7.8) and 4.7 (3-13.8) following 640385 50mg/RTV 100mg BID, 640385 150mg/RTV 100mg BID, and 640385 300mg/RTV 100mg BID, respectively.
- All subjects receiving 640385 300mg/RTV 100mg BID had Day 15 C<sub>12</sub> values above 56ng/mL (the 90<sup>th</sup> percentile of protein binding adjusted IC<sub>50</sub>s from 55 clinical isolates).
- Although no PM dose was administered, median Day 15 Plasma 640385 C<sub>24</sub> values were 49ng/mL and 36ng/mL following 640385 150mg/RTV 100mg and 300mg/RTV 100mg BID, respectively.
- Day 15 640385 AUC(0-τ) and C<sub>max</sub> following administration of 640385/RTV BID regimens increased less than proportional to dose.
- Accumulation of 640385 following 640385/RTV BID regimens ranged from 2-5-fold relative to Day 1 exposures.
- 640385 steady state appeared to have been achieved by Day 15.

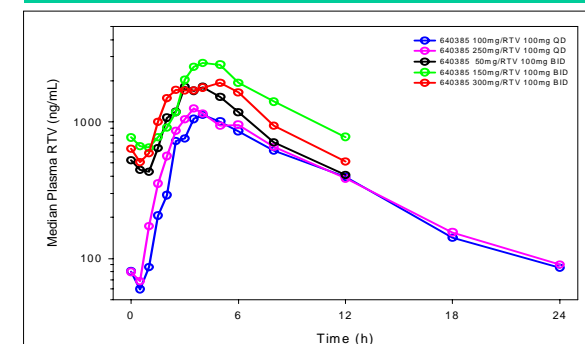
### RTV Pharmacokinetics

Table 3. Median (range) Day 15 Plasma RTV PK Parameters By Regimen

640385/RTV Regimen	N	AUC(0-τ) <sup>1</sup> (ng.h/mL)	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (h)	C <sub>τ</sub> <sup>1</sup> (ng/mL)
100/100mg QD	8	9809 (5119, 19146)	1389 (541, 2240)	3.5 (2.5, 6.0)	85 (48, 244)
250/100mg QD	6	9958 (7287, 22547)	1271 (967, 2889)	3.8 (3.5, 5.0)	90 (48, 261)
Placebo/100mg QD	3	5133 (3415, 9146)	985 (396, 672)	4.0 (3.5, 5.0)	31 (30, 145)
50/100mg BID	8	11464 (6189, 26700)	1960 (714, 3638)	3.0 (1.5, 5.0)	407 (272, 1147)
150/100mg BID	8	18803 (10257, 26637)	2771 (1465, 4878)	4.0 (3.0, 5.0)	776 (330, 1205)
300/100mg BID	8	13890 (8873, 28531)	2162 (1599, 4360)	4.0 (2.5, 6.0)	512 (201, 1196)
Placebo/100mg BID	6	9251 (6387, 12792)	1414 (1045, 1976)	4.0 (3.0, 5.0)	398 (194, 547)

1. τ=12h for BID regimens and 24h for QD regimens

Figure 3. Median Day 15 Plasma RTV Concentration Time Profiles



### RTV PK Summary

- Plasma RTV exposures following co-administration with 640385 exceeded those following co-administration with placebo. RTV AUC(0-τ) following 640385/RTV 100mg BID regimens was similar to that following RTV 100mg/IDV 800mg BID<sup>6</sup> and higher than observed with LPV/RTV<sup>1,3</sup> and APV/RTV<sup>7</sup>.
- Accumulation of RTV following 640385/RTV BID regimens ranged from 4-6-fold relative to Day 1 exposures.
- RTV steady-state appeared to have been achieved by Day 15.

## Conclusions

- Short-term repeat administration of 640385 and 640385/RTV was generally safe and well tolerated.
- Consistent with single dose data<sup>5</sup>, co-administration of RTV 100mg with 640385 significantly increased plasma 640385 exposure following repeat administration.
- All 640385/RTV BID regimens studied achieved median 640385 C<sub>τ</sub> values above the 28ng/mL estimated target for resistant virus.
- 640385/RTV BID regimens will be investigated in clinical studies of HIV infected subjects.

## References

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