Pharmacokinetics, Safety, and Tolerability of the NS5A Inhibitor, ABT-267 in Healthy Caucasian, Japanese, and Chinese Subjects


Abbott Laboratories, Global Pharmaceutical R&D, Abbott Park, USA.

*ex-Abbott employee

7th International Workshop on Clinical Pharmacology of Hepatitis Therapy
27 - 28 June 2012, Cambridge MA, USA
Session 4: Clinical Pharmacology - Adherence and Exposure Response on Wednesday 27 June
Abs # O_02A
Disclosure Statement

• All authors (except Dr Gulati) are Abbott employees and may hold Abbott stock or options

• Dr Gulati is an ex-Abbott employee

• The design, study conduct, analysis, and financial support of the clinical trials were provided by Abbott. Abbott participated in the interpretation of data, review, and approval of the presentation.

• This presentation contains information on the investigational product ABT-267
Background

• ABT-267 is an HCV NS5A inhibitor being dosed once-daily (QD) in Phase 2 studies

• ABT-267 has linear PK across a wide range of doses and a long $t_{1/2}$ making it suitable for once daily dosing. (Dumas, EASL 2011)

• Administration with a CYP3A inhibitor showed a minimal to modest increase in exposure (Dumas, EASL 2011)

• Following monotherapy in Genotype 1 HCV infected treatment naïve subjects, ABT-267 showed potent antiviral activity (Lawitz, EASL 2012) – Viral load decreased by 3 log following 3-days of monotherapy

• ABT-267 is being evaluated with other DAAs as part of interferon free regimens in treatment naïve and experienced Genotype 1 HCV infected subjects
Objective and Study Design

- Blinded, sequential, multiple-ascending dose (MAD) study to assess the safety, tolerability, and pharmacokinetics of ABT-267 under non-fasting conditions in healthy adult Han Chinese, Japanese, and Caucasian subjects.

- Each group consisted of 8 subjects per ethnic group (24 total subjects per group) randomized in a 3:1 ratio to receive ABT-267 or placebo.

![Diagram showing the study design with two groups: Group 1 (N=24) receiving ABT-267 25 mg QD on Day 1 and 7, and Group 2 (N=24) receiving ABT-267 200 mg QD on Day 1 and 7.]
## Demographics

<table>
<thead>
<tr>
<th></th>
<th>Han Chinese 25 mg/kg N = 6</th>
<th>Japanese 25 mg/kg N = 6</th>
<th>Caucasian 25 mg/kg N = 6</th>
<th>Han Chinese 200 mg/kg N = 6</th>
<th>Japanese 200 mg/kg N = 6</th>
<th>Caucasian 200 mg/kg N = 6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>37.5 ± 8.22 (27 – 46)</td>
<td>38.5 ± 10.7 (27 – 53)</td>
<td>36.5 ± 12.6 (23 – 55)</td>
<td>39.8 ± 5.74 (33 – 46)</td>
<td>41.8 ± 12.8 (22 – 55)</td>
<td>36.3 ± 11.6 (22 – 51)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>70.7 ± 5.75 (62 – 80)</td>
<td>66.5 ± 8.17 (57 – 76)</td>
<td>77.2 ± 10.7 (60 – 90)</td>
<td>71.5 ± 9.29 (59 – 81)</td>
<td>66.2 ± 9.22 (51 – 78)</td>
<td>76.0 ± 9.98 (62 – 86)</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>169 ± 5.64 (162 – 175)</td>
<td>172 ± 8.67 (161 – 183)</td>
<td>175 ± 7.53 (165 – 186)</td>
<td>173 ± 6.77 (163 – 181)</td>
<td>169 ± 9.13 (155 – 178)</td>
<td>178 ± 6.02 (170 – 188)</td>
</tr>
<tr>
<td><strong>Male Sex, n (%)</strong></td>
<td>6 (100.0)</td>
<td>5 (83.3)</td>
<td>5 (83.3)</td>
<td>6 (100.0)</td>
<td>5 (83.3)</td>
<td>6 (100.0)</td>
</tr>
</tbody>
</table>
ABT-267 Pharmacokinetic Parameters across Ethnicities at Steady State (Day 7)

- In the Han Chinese group, the ABT-267 Cmax and AUC central values were approximately 47% and 35% higher, respectively, relative to the Caucasian group.
- In the Japanese group, the ABT-267 Cmax and AUC central values were approximately 38% and 50% higher, respectively, relative to the Caucasian group.
- $T_{1/2}$ of ABT-267 was comparable across ethnicities (23 to 31 hours).
- Accumulation ratio following multiple dosing was 30-40%.
Safety Summary

• The ABT-267 25 and 200 mg doses tested were generally well tolerated by all subjects regardless of ethnicity

• No deaths, other serious adverse events or discontinuations due to adverse events were reported in this study

• All adverse events in the ABT-267 dose groups and the placebo group were assessed by the investigator as mild in severity

• The majority of adverse events were assessed by the investigator as not related to study drug

• No clinically significant vital signs, ECG or laboratory measurements were observed during the course of the study for any dose group or ethnicity. There were no apparent differences among the ethnicities for the doses tested with respect to safety

• The proportion of subjects reporting at least one treatment-emergent adverse event was greater for the placebo group (6/12, 50.0%) relative to all ABT-267 dose groups and ethnicities combined (14/36, 38.9%)

• The adverse event assessed as possibly related was somnolence (one Japanese subject, ABT-267 25 mg). The adverse event assessed as probably related was headache (one Caucasian subject, ABT-267 200 mg)
Conclusions

• ABT-267 was safe and well tolerated across the 3 ethnicities following multiple dosing at the 25 and 200 mg QD doses for 7 days

• ABT-267 exposures were 35% to 50% higher in Chinese and Japanese subjects relative to Caucasians

• These increases in exposures do not warrant a change in dose in Chinese and Japanese subjects
Multiple-dose Pharmacokinetics and Safety Following Coadministration Of ABT-450/r, ABT-267 and ABT-333 in Caucasian, Japanese and Chinese Subjects


*ex-Abbott employee

Abbott Laboratories, Global Pharmaceutical R&D, Abbott Park, USA.

7th International Workshop on Clinical Pharmacology of Hepatitis Therapy
27 - 28 June 2012, Cambridge MA, USA
Session 4: Clinical Pharmacology - Adherence and Exposure Response on Wednesday 27 June
Abs # O_02B
Disclosure Statement

• All authors (except Dr Gulati) are Abbott employees and may hold Abbott stock or options

• Dr Gulati is an ex-Abbott employee

• The design, study conduct, analysis, and financial support of the clinical trials were provided by Abbott. Abbott participated in the interpretation of data, review, and approval of the presentation

• This presentation contains information on the investigational products ABT-450/r, ABT-267 and ABT-333
Background

• ABT-267 is an HCV NS5A inhibitor dosed once-daily (QD) in Phase 2 clinical studies

• ABT-333 is a non-nucleoside inhibitor of HCV NS5B polymerase dosed twice a day (BID) in Phase 2 clinical studies

• ABT-450, identified as a lead compound by Abbott and Enanta, is a potent HCV NS3/4A protease inhibitor that is co-administered with ritonavir (ABT-450/r) and dosed once-daily (QD) in Phase 2 clinical studies

• ABT-450/r and ABT-333 have been co-administered in HCV GT1 infected subjects for 12 weeks with ribavirin (Poordad et al, EASL 2012)
  – 93-95% of treatment-naïve subjects infected with HCV genotype 1 achieved SVR$_{12}$
  – No virologic failures occurred among treatment-naïve subjects who completed study drug treatment
  – 47% of previous non-responders achieved SVR$_{12}$
Why is ABT-450 Dosed with Ritonavir?

ABT-450 dose = 300 mg

- Significant PK boosting allows for QD administration at lower ABT-450 doses while potentially improving the resistance profile.

Cmax $\uparrow$ 28-fold
AUC $\uparrow$ 48-fold
$C_{12}$ $\uparrow$ 200-fold
$C_{24}$ $\uparrow$ 340-fold
$T\frac{1}{2}$ $\uparrow$ from 3 hrs to 5 hrs

Matias T, et al. EASL 2011; 06-10 December 2011
Open-label, multiple dose study to assess the safety, tolerability, and pharmacokinetics of ABT-450/r + ABT-267 ± ABT-333 under non-fasting conditions in healthy Chinese, Japanese and Caucasian subjects.
## Demographics

<table>
<thead>
<tr>
<th></th>
<th>Han Chinese</th>
<th>Japanese</th>
<th>Caucasian</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>(N = 30)</td>
<td>(N = 30)</td>
<td>(N = 30)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>34.2 ± 8.77</td>
<td>31.2 ± 10.5</td>
<td>38.2 ± 10.0</td>
</tr>
<tr>
<td>(Min - Max)</td>
<td>(23.0 - 55.0)</td>
<td>(21.0 - 55.0)</td>
<td>(21.0 - 55.0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.6 ± 8.40</td>
<td>68.7 ± 9.57</td>
<td>78.2 ± 13.3</td>
</tr>
<tr>
<td>(Min - Max)</td>
<td>(55.0 - 87.0)</td>
<td>(49.0 - 87.0)</td>
<td>(56.0 - 106)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173 ± 6.92</td>
<td>172 ± 8.47</td>
<td>177 ± 6.77</td>
</tr>
<tr>
<td>(Min - Max)</td>
<td>(159 - 184)</td>
<td>(155 - 189)</td>
<td>(167 - 190)</td>
</tr>
<tr>
<td>Male Sex</td>
<td>29 (96.7%)</td>
<td>28 (93.3%)</td>
<td>29 (96.7%)</td>
</tr>
</tbody>
</table>
NS5A Inhibitor: ABT-267
Comparison of **ABT-267** AUC When Co-dosed with ABT-450/r: Chinese vs. Japanese vs. Caucasians

Arm 1: ABT-450 250 mg + ABT-267 25 mg
Arm 2: ABT-450 200 mg + ABT-267 25 mg
Arm 3: ABT-450 150 mg + ABT-267 25 mg + ABT-333 400 mg

Fold increases are for Chinese and Japanese over Caucasians subjects.
Protease Inhibitor: ABT-450
Comparison of **ABT-450** AUC When Co-dosed with ABT-267: Chinese vs. Japanese vs. Caucasians

<table>
<thead>
<tr>
<th>Arm</th>
<th>ABT-450/r</th>
<th>ABT-405 AUC (ng*hr/ml)</th>
<th>Fold Increases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1</td>
<td>250/100</td>
<td>~ 1.2x Caucasians</td>
<td></td>
</tr>
<tr>
<td>Arm 2</td>
<td>200/100</td>
<td>~ 2.7x Caucasians</td>
<td></td>
</tr>
<tr>
<td>Arm 3</td>
<td>150/100</td>
<td>~ 2.5x Caucasians</td>
<td></td>
</tr>
</tbody>
</table>

Fold increases are for Chinese and Japanese over Caucasians subjects.
NS5B Inhibitor: ABT-333
Comparison of **ABT-333** AUC When Co-dosed with ABT-267 and ABT-450: Chinese vs. Japanese vs. Caucasians

Arm 3: ABT-450 150 mg + ABT-267 25 mg + ABT-333 400 mg

Fold increases are for Chinese and Japanese over Caucasians subjects.
Safety and Tolerability
Safety Summary

• All treatments tested were generally well tolerated by all subjects; there was no pattern to the adverse events and no ethnicity response was noted

• Following combination dosing, the most common adverse events noted in more than two subjects
  – aphthous stomatitis (n=3), nausea (n=3) [ABT-267 + ABT/450/r]
  – Constipation (n=3), dizziness, (n=3) [ABT-267 + ABT-450/r + ABT-333]

• Grade 3 bilirubin elevations that were transient, asymptomatic, self-limited and not associated with ALT or AST elevations were observed in 6 of 18 subjects at the highest dose of ABT-450/r (250/100 mg QD); seen with or without ABT-267 25 mg QD across all 3 ethnicities
  – The elevations are consistent with the pattern observed when ABT-450/r is dosed alone and is probably due to potent inhibition of the transporter OATP1B1 observed in vitro with ABT-450

• Other laboratory abnormalities were infrequent all Grade 1, and not considered clinically significant
Conclusions

• The 2 and 3 DAA combinations of ABT-450/r + ABT-267 ± ABT-333 were safe and well tolerated following multiple dosing in healthy subjects

• Irrespective of the combination of co-administered drugs assessed in this study (two DAAs or three DAAs), ABT-267, ritonavir and ABT-333 exposures in Chinese and Japanese subjects were comparable to Caucasian subjects

• ABT-450 exposures in Japanese and Chinese subjects were comparable to Caucasian subjects when 250/100 ABT-450/r was co-administered with 25 mg ABT-267

• However, when a lower dose of 200/100 mg ABT-450/r was administered with 25 mg ABT-267, ABT-450 exposures in Japanese and Chinese subjects were 1.5- to 3-fold of Caucasians exposures though differences in Japanese exposures were not statistically significant

• At steady state, when co-administered with 25 mg ABT-267 and 400 mg BID ABT-333 for 21 days, 150 mg ABT-450 exposures in Chinese and Japanese subjects were ~2.5-fold of exposures in Caucasian subjects