

## Safety of Abacavir (ABC)+Lamivudine (3TC)-based HAART in ART-Naïve HIV-Infected Subjects With and Without Hepatitis B (HBV) and/or Hepatitis C (HCV) Co-Infection

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### Introduction

The interactions between hepatitis viruses and HIV are complex and clinically important. Co-infection with HIV accelerates HCV-related liver damage and progression to end stage liver disease. Similarly, HBV DNA levels are higher in HIV-infected patients and HIV may increase the risk of HBV-associated morbidity and mortality. Although antiretroviral therapy (ART) is beneficial for HBV and/or HCV co-infected subjects, hepatitis increases their risk for ART-associated hepatotoxicity.

A fixed dose combination (FDC) tablet of two antiretrovirals, abacavir (Ziagen<sup>®</sup>, ABC) and lamivudine (Epivir<sup>®</sup>, 3TC) was developed to reduce pill burden and dosing frequency. This improved dosing convenience may lead to improved adherence and potentially better clinical outcomes. The efficacy and tolerability of ABC + 3TC have been previously demonstrated in ART-naïve subjects.<sup>1, 2</sup> The objective of the analyses described here was to assess the safety and tolerability over 48 weeks of treatment with ABC + 3TC based HAART in HIV-1 infected ART naïve adults with and without HBV and/or HCV co-infection.

### Methods

- Data from 1985 ART-naïve, HIV-infected subjects participating in 4 large, randomized clinical trials using ABC+3TC once daily (QD) or twice daily (BID) in combination with EFV or protease inhibitors (PI) were used for this analysis.
- Subjects with co-infection were allowed to enroll in these 4 trials if their infection was not clinically relevant within the last 6 months, and if ALT and AST levels were below a Grade 3 (<5 x ULN) within 28 days of screening.
- Safety data over >48 weeks of ART for patients with HBV (baseline positive HBV-SAg) and/or HCV (baseline positive anti-HCV) co-infection were compared to those of subjects without co-infection using meta-analysis method. Descriptive statistics were summarized for subjects with and without HBV and/or HCV co-infection.

## Results

- The percentage of subjects with HBV and/or HCV co-infection was 15 to 25% in these 4 large clinical trials using ABC+3TC. Of 1985 subjects participating, 389 (20%) were HBV and/or HCV co-infected. Baseline demographics and disease characteristics were comparable between subjects with and without (1596 subjects) HBV/HCV co-infection.
- The median number of days of exposure to ABC + 3TC in these 4 clinical trials was 337 to 421 days for non co-infected subjects compared to 321 to 428 days for co-infected subjects. 75 to 81% of non co-infected subjects participating in these 4 clinical trials received at least 24 weeks of ABC + 3TC therapy, compared with 68 to 80% of co-infected patients.
- The Baseline ALT/AST values, the changes from BL in AST and ALT and the proportion of patients developing Grade 2–4 AST and ALT elevations for non co-infected and co-infected subjects are shown in **Tables 1 to 3**.

*Table 1. Baseline ALT and AST Values (Median (Q1, Q3; N))*

	No HBC and/or HCV	HBV and/or HCV
ALT (u/L)	26.5 (17.9, 38.5; 1579)	42.1 (26.6, 64.7; 383)
AST (u/L)	27.2 (21.7, 35.7; 1572)	39.7 (20.6, 60.1; 383)

- As expected, median Baseline (BL) ALT and AST levels were higher in co-infected subjects than in those without co-infection (*Table 1*).

*Table 2. Change from BL in ALT and AST at Week 48 (Median (Q1, Q3; N))*

	No HBC and/or HCV	HBV and/or HCV
ALT (u/L)	-3.9 (-15.9, 3.0; 1181)	-1.6 (-14.2, 26.8; 254)
AST (u/L)	-5.4 (-12.6, -0.4; 1174)	-4.7 (-20.0, 11.3; 246)

- Subjects in both the co-infected and non co-infected groups who completed at least 48 weeks had a median decrease in ALT and AST (*Table 2*).

*Table 3. Treatment Emergent Grade 2-4 ALT/AST*

	<b>No HBC and/or HCV N=1596 n (%)</b>	<b>HBC and/or HCV N=389 n (%)</b>
<b>ALT</b>	<b>20 (1.3%)</b>	<b>41 (10.5%)</b>
<b>AST</b>	<b>21 (1.3%)</b>	<b>33 (8.5%)</b>

- The number of subjects with Grade 2-4 ALT or AST elevations through 48 weeks of therapy was small (*Table 3*):
  - 41 co-infected subjects experienced a new treatment-emergent Grade 2-4 ALT elevation through 48 weeks of ART.
  - 33 co-infected subjects experienced a new treatment-emergent Grade 2-4 AST elevation through 48 weeks of ART.

*Table 4. Adverse Events*

- The overall incidence of Adverse Events (AEs) was similar between the two groups with 95% (1524/1596) and 90% (352/389) for subjects without co-infection and with co-infection, respectively.

	<b>No HBC and/or HCV N=1596 n (%)</b>	<b>HBV and/or HCV N=389 n (%)</b>	<b>P value*</b>
<b>Grade 2-4 AEs</b>	<b>1135 (71)</b>	<b>275 (71)</b>	<b>0.9</b>
<b>Drug-related AEs</b>	<b>1135 (71)</b>	<b>272 (70)</b>	<b>0.6</b>
<b>* By two-sided Fisher's exact test.</b>			

- Through 48 weeks of ART, similar proportions of co-infected subjects and non co-infected subjects reported grade 2-4 AEs and drug related AEs (*Table 4*).

Table 5. AEs for Co-infected Subjects (CNA30021)

- The incidence of specific AEs in co-infected subjects was comparable between subjects taking ABC once daily (OAD) and those taking ABC twice daily (BID).

	ABC OAD (N=71)	ABC BID (N=62)
<b>Overall AEs</b>	<b>62 (87)</b>	<b>54 (87)</b>
<b>ALT</b>	<b>5 (7%)</b>	<b>8 (13%)</b>
<b>AST</b>	<b>6 (8%)</b>	<b>4(6%)</b>

## Discussion

Co-infection prevalence has become significant in the developed world (~ 25%), particularly in southern Europe, and is becoming more problematic in some individual countries.<sup>3</sup> Treatment with boosted HAART has been associated with slower progression to fibrosis for hepatitis co-infected patients.<sup>4</sup> Therefore, comparative safety data, especially with regard to hepatic toxicity of specific nucleoside-based HAART in HIV and HBV/HCV co-infected patients, is particularly pertinent.

An earlier analysis of the randomised phase of SOLO<sup>5</sup> demonstrated that both FPV and NFV in combination with ABC + 3TC had a favourable effect with a modest reduction in median ALT and AST levels in both HBV/HCV co-infected and non co-infected patients. By Week 48 around 20-25% of co-infected subjects in both the FPV and NFV arms experienced grade 3/4 elevations in ALT and AST (mostly ALT). It was suggested that some of these elevations might be due to the natural history of hepatitis infection or to immune reconstitution leading to HBV immune mediated response with ALT flares.

The present analysis combining data from 3 additional trials shows that the favourable median change from baseline in ALT and AST observed in SOLO was also seen in one additional study with FPV and NFV and in 2 large studies with EFV. New Grade 2-4 ALT and AST elevations through 48 weeks of ART were relatively uncommon, being observed in 10.5% (41/389) and 8.5% (33/389) of co-infected subjects compared to 1.3% (20/1596) and 1.3% (21/1596) in non co-infected subjects, respectively. There were no differences in the incidence of Grade 2-4 AEs or drug-related AEs between the co-infected and non co-infected subjects through 48 weeks of ART.

This 48 week analysis shows that ABC + 3TC in combination with PIs and EFV is well tolerated in patients with hepatitis B/C co-infection with a similar median reduction in AST/ALT and a similar rate of Grade 2-4 AEs and drug-related AEs compared to non-co-infected subjects. Grade 2-4 increases in AST/ALT were more common in co-infected subjects but were likely due to the natural history of hepatitis B or C infection.

## Conclusion

- In subjects treated with ABC+3TC based HAART, there was no significant difference in the incidence and/or type of AEs, grade 2-4 AEs or drug-related AEs, regardless of whether subjects were HBV and/or HCV co-infected or not.
- Relatively few co-infected subjects experienced new treatment-emergent Grade 2-4 ALT or AST toxicities through 48 weeks of ART.
- In addition, the incidence of specific adverse events in co-infected subjects did not differ between subjects taking ABC QD and those taking ABC BID.

## References

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