ABX464 Decreases Total HIV DNA in PBMCs When Administered During 28 Days to HIV-infected Virologically Suppressed Patients

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Background
ABX464 is a first-in-class antiviral drug candidate for the treatment of patients with HIV infection. It is an orally available small molecule that blocks HIV replication through an entirely novel mechanism, inhibition of Rev activity.

Practical data in two humanized mice showed that ABX464 monotherapy had an antiviral effect, which remained sustained after treatment interruption.1 A prior food-effect study demonstrated a 3.4-fold decrease in parent drug exposure when administered with food with no significant impact on the active glucoronide metabolite.2 A Phase IIa study demonstrated dose-dependent viral load reductions in treatment-naive HIV subjects and good safety and tolerability.3

Objectives
ABX464-004 is a multi-center, randomized, double-blind, placebo-controlled Phase IIa trial to compare the safety of ABX464 given at a fixed dose to placebo in fully controlled HIV-infected patients treated with boosted darunavir/r (DRV/r)/fostartavir (PI) or DRV/r/cobicistat (CCIT) monotherapy (high drug barrier and lower potency for driving interactions).

Primary endpoint:
• Evaluate the safety of ABX464 vs placebo when administered on top of boosted PI DRV

Secondary endpoints:
• Evaluate long-lasting effect of ABX464 on viral load after treatment stop (Day 28) using time-to-oviral rebound vs placebo
• Evaluate HIV reservoir (total HIV DNA in PBMCs) vs placebo from Day 0 to Day 28

Methods
• Multi-center, randomized, double-blind, placebo-controlled Phase IIa trial conducted in Spain, Belgium, and France
• Patients with HIV viral load <50 copies/mL or DRV/r or DRV/CCIT therapy for at least 8 weeks were enrolled. Patients were required to be fully suppressed (<50 copies/mL) for at least 6 months prior to enrollment and randomized to receive either ABX464 or placebo (PBO) in a 1:1 allocation plus in Day 28 for 28 days
• At the end of 28 days all treatment was interrupted.
• HIV-1 viral load was regularly measured and ART reintroduced when viral load was >1000 copies/mL.
• Blood samples were taken at Day 0 and Day 28 to measure the potential effect of ABX464 on the HIV reservoir (total HIV DNA in PBMCs).
• Response was defined as a >5% reduction in HIV DNA of at least 50 copies/MONO in PI and a relative decrease >25%.
• All analyses were performed blinded with respect to the treatment groups

Results
Table 1. Baseline Demographics

<table>
<thead>
<tr>
<th>Event (n %)</th>
<th>Placebo (n = 10)</th>
<th>ABX464 (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (&gt;100°C)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Abnormality</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Renal</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Liver</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Abdominal pain</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Abdominal pain</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Abdominal pain</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Table 2. Summary of Treatment Emergent Adverse Events (AEs)

<table>
<thead>
<tr>
<th>Event (n %)</th>
<th>Placebo (n = 10)</th>
<th>ABX464 (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Rash</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anosmia</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Headache</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Table 3. ABX464-004 Efficacy Analysis

<table>
<thead>
<tr>
<th>Total subjects included, n (%)</th>
<th>Placebo (n = 10)</th>
<th>ABX464 (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response (n %)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Complete (n %)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Next Steps
• ABX464-005 study is ongoing.
• ABX464 given in addition to triple therapy.
• The first cohort is being enrolled and evaluated, followed by the second cohort given during 28 days on the reservoir in blood and in gut tissue.
• A protocol amendment has been submitted with longer ABX464 treatment (84 days) in order to
• Study the further decay of the HIV reservoir beyond 28 days
• Potentially increase the response rate
• Confirm the impact of ABX464 on tissue HIV reservoir

Conclusions
ABX464 was well tolerated in fully suppressed patients on boosted DRV.
• The most common drug-related AEs were abdominal pain and headache. One subject experienced a grade 3 fatigue, all other events were grade 1 or 2.
• There were no serious adverse events reported in either ABX464 group.
• A mean decrease of 186 (38%) copies of HIV DNA/Mono PBMCs was demonstrated in ABX464 responders.
• Despite the important decrease of the HIV reservoir, this was not yet sufficient to delay the time to viral load rebound.
• A mean decrease of 87 and 67 copies of HIV DNA/Mono PBMCs was observed in the placebo and ABX464 non-responders cohort, respectively. No responders were observed in the placebo group.
• To our knowledge this is the first time a signal has been observed demonstrating the reduction of HIV in reservoirs in patients with any therapy category.
• Further clinical trials with longer treatment duration are needed to more fully understand the mechanisms and implications of these findings.

References

Acknowledgements
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