Clinical Development of ABX464, drug candidate for HIV Functional Cure

Jean-Marc Steens· MD

Chief Medical Officer ABIVAX
• GSK
• ABIVAX
ABX464 is a first-in-class orally available antiviral small molecule that blocks HIV replication by preventing Rev-mediated export of unspliced HIV-1 transcripts to the cytoplasm.
ABX464 shows long-lasting viral load reduction vs. HAART in tg mice

Preclinical efficacy data in a transgenetic (humanized) mouse model*

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With ABX464, HIV viral titres remain low compared to existing therapies

These data suggest control of HIV by the immune system

*adapted from: Campos et al., Retrovirology 2015, 12:30
ABX464: Mechanism of Action

Molecular target:

Activity:

Biological effects:

• Enhanced viral RNA splicing and Prevention of REV mediated export of long viral RNA

• Hypotheses being investigated:
  1. Generation of neoantigens and initiation of immune response
  2. Cytotoxicity for reservoir cells by peptides related to viral RNA
  3. Generation of deficient virus

Outcome:

HIV: Reduction of viral load

HIV: Sustained biological control of viral load

HIV and other inflammatory diseases: Dampening of inflammation

Observed outcome:

In vitro ✓

In vivo ✓

Note: *Italic characters = hypotheses*
ABX464, by binding to the CBC 80/20 complex, enhances pre-mRNA splicing, resulting in the generation of novel HIV-derived RNA species and in increased expression of the anti-inflammatory miR-124

Audrey Vautrin\textsuperscript{2,3}, Laurent Manchon\textsuperscript{2,3}, Aude Garcel\textsuperscript{2}, Noëlie Campos\textsuperscript{2}, Karim Chebli\textsuperscript{1}, Didier Scherrer\textsuperscript{2}, Hartmut Ehrlich\textsuperscript{2}, and Jamal Tazi*
ABX464 Mechanism of Action

• The findings substantiate a mechanism of action for ABX464 that starts with CBC 80/20 binding and enhancement of mRNA splicing which leads to the following:
  – Viral load reduction and elimination of HIV from the latent reservoir through immune response to putative new peptides generated by viral RNA splicing
  – A negligible effect of ABX464 on cellular splicing
  – ABX464 upregulates the anti-inflammatory miR-124, caused by splicing of long non-coding RNA (Inc RNA 599-205)
ABX464 Clinical Profile

• ABX464 has acceptable safety profile, patient exposure > 180 patients
• ABX464 has antiviral properties ( study 003 )
• Two independent studies showed that reduction of HIV DNA in blood from HIV well suppressed patients is feasible ( study 004 / 005 )
• Single copy assay showed reduction in residual viremia
• Mir124 is being overexpressed in tissue
• Phase IIB is being planned in US / EU based on these data, supported by investigators and SAB
ABX464-004: Study Scheme

Vandekerckhove et al. ABX464 Decreases Total HIV DNA and Integrated HIV DNA in PBMCs When Administered During 28 Days to HIV-infected Virologically Suppressed Patients. EACS October 26 2017
Total HIV PBMC DNA Change: Day 0 - 28

Vandekerckhove et al, ABX464 Decreases Total HIV DNA and Integrated HIV DNA in PBMCs When Administered During 28 Days to HIV-infected Virologically Suppressed Patients EACS October 26 2017

SD, standard deviation
ABX464-005 Study

**Title:** An Open-Label Study of the Safety, Pharmacokinetics, and Pharmacodynamics of ABX464 in HIV-1 Seronegative and Seropositive Adults

**Primary objective:**
To evaluate the distribution of ABX464 and its main metabolite (N-Glu) in various compartments in HIV-1 Seronegative and Seropositive adult subjects

**Secondary objectives:**
To evaluate the safety of ABX464 administered once daily at one dose, alone in HIV-uninfected subjects and in combination with ARTs in HIV-1 infected adult subjects;
To evaluate the effect of ABX464 on the HIV reservoir cells in HIV-infected adult subjects;
To evaluate the effect of ABX464 on the control of the viral load and the CD4+/CD8+ in HIV-infected adult subjects
ABX464-005: Cohort 1

**COHORT 1 (N=12)**
HIV-infected subjects
- VL<50 copies/ml
- Current CD4 > 600 cells/mm³
- CD4 nadir > 250 cells/mm³
- Post primary VL ≤ 100,000 copies/ml
- Over 12 months Rx with DTG or RAL plus TDF/FTC or ABC/FTC

**Tissue sampling**

**Day 0**
**Day 28**
**Day 56**

**ABX464 150 mg orally daily for 28 days**
**ABX-005: Sampling**

**Peripheral blood**
- Systemic safety
  - haematology
  - renal
  - hepatic
- PK (up to 8h post dose)
- Peripheral CD4+ T cell purification
  - HIV DNA
  - HIV RNA
- Plasma viremia

**Rectal tissue**
- PK
- MMC
  - HIV DNA
  - HIV RNA
- Flow cytometry
- Proteome
- Transcriptome

**Rectal secretions**
- Microbiome
ABX464-005: Baseline Demographics

11 male participants were recruited

Age: Mean 45.0 (median 48.0, range 29-55) years
Ethnicity: 11 white
Nadir CD4: Mean 515 (median 501, range 279-810 cells/mm$^3$)
CD4 T cells: Mean 911 (median 812, range 582-1420 cells/mm$^3$)
ABX464-005: Safety

- No SAEs
- No grade 3 or higher AEs
- 59 Grade 1 or 2 AEs, (45 (76.3%) related, 14 (23.7%) unrelated)
- 2 withdrawals due to AEs (Related)
  - G1 abdominal pain, hyperlipasemia, headache, and G2 hyperamylasemia
  - G1 headache, myalgia, asthenia, insomnia, and backache
- 1 temporary discontinuation due to AE (Related)
  - G1 headache
- Most common AEs (>30%)
  - nausea, myalgia, back pain, headache
ABX464-005: HIV DNA

HIV-DNA reservoir in CD4+ T cells from PBMCs at Baseline and Day 28

P = 0.0078
• All participants had <50 copies of HIV RNA at study enrollment
• LOQ = 0.5 HIV RNA copies/mL
• Residual viremia was detected in 5 participants
• In 4 participants there was a decrease between d0 and d28; one participant did not attend for d28 sampling
• 9/9 patients either decreased (n=4) or maintained their residual pVL suppressed from d0 to d28

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase</td>
<td>0/9</td>
</tr>
<tr>
<td>Decrease</td>
<td>4/9</td>
</tr>
<tr>
<td>Stable</td>
<td>5/9</td>
</tr>
</tbody>
</table>

n = 9
ABX464-005: miRNA-124

- miRNA124 is an ‘anti-inflammatory’ microRNA
- All participants (n=7) had over-expression of miRNA124 in rectal biopsies
- Mean ratio between d0 and d28: + 9.27*

* Estimation based on the quantity of the target DNA template (amplicon) doubles every cycle.
ABX464-005: Conclusions

• Dosing was associated with adverse events that led to discontinuation of 2 study participants. All symptoms and biochemical abnormalities normalized upon drug withdrawal. There were no SAEs
• Exposure to 150 mg of ABX464 for 28 days was associated with a significant decrease in HIV-1 DNA in CD4+ T cells from baseline
• A decrease in residual plasma viremia was measured at D28 in some patients who still had residual plasma viremia at d0. CD4 T cell counts were stable
• MicroRNA 124 was over expressed at d28 versus d0
• Overall, these data confirm the decrease in PBMC HIV-1 DNA seen in responding participants in the ABIVAX-004 study and support the continued development of ABX464 as a component of cure eradication strategies
ABX464: Next Steps

- ABX464-005 second cohort
  - A protocol amendment for the second cohort has been implemented with daily ABX464 50 mg over 84 days in order to
    - Assess safety with a lower dose
    - Study the potential decay of the HIV reservoir beyond 28 days
    - Assess the impact of ABX464 on tissue HIV reservoir
  - Top line data available in July 2018

- ABX464-006 (planned)
  - Evaluate time needed to achieve maximal reduction of HIV reservoir in chronically infected well suppressed HIV patients

- ABX464-007 (planned)
  - Evaluate time needed to achieve maximal reduction of HIV reservoir in early treated well suppressed HIV patients
ABX464 – 006 study design

<table>
<thead>
<tr>
<th>Screening</th>
<th>Treatment Phase (48 weeks) (Double-blinded treatment phase / monthly visits)</th>
<th>Treatment Alleviation Phase (Applicable to responder patients receiving ABX464 at W48)</th>
<th>ARTs reintroduction and Follow-up</th>
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<td>Total HIV DNA high (≥ 200 copies/million of PBMCs)</td>
<td>ABX464 50 mg (N=40)</td>
<td>ABX464 Alone (50mg or 100mg)</td>
<td>Follow-up visits every 14 days after antiviral therapy reintroduction until the viral load has returned to undetectable levels</td>
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<td>Weekly Visits until viral rebound (max. 3 months)</td>
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What data should Phase IIB studies provide us

• Can HIV DNA be suppressed to the lowest level possible
• How long does this take
• Is the response dependent on HIV reservoir at baseline
• Is the response dependent on dose (50 versus 100 mg)
• Do “early treated” HIV patients have a faster decline
• Are inflammatory markers (which ??) influenced
• Is there any evidence of immune reaction leading to long term HIV DNA suppression
• Is HIV DNA suppression sufficient or are functional assays needed before treatment interruption
• What % of patients are eligible for treatment interruption
• Exploratory outcome of treatment interruption
THANK YOU