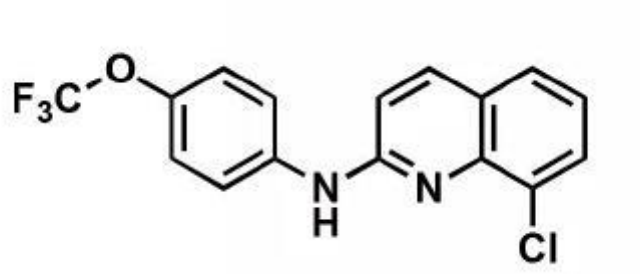
Clinical Development of ABX464, drug candidate for HIV Functional Cure



Jean-Marc Steens, MD

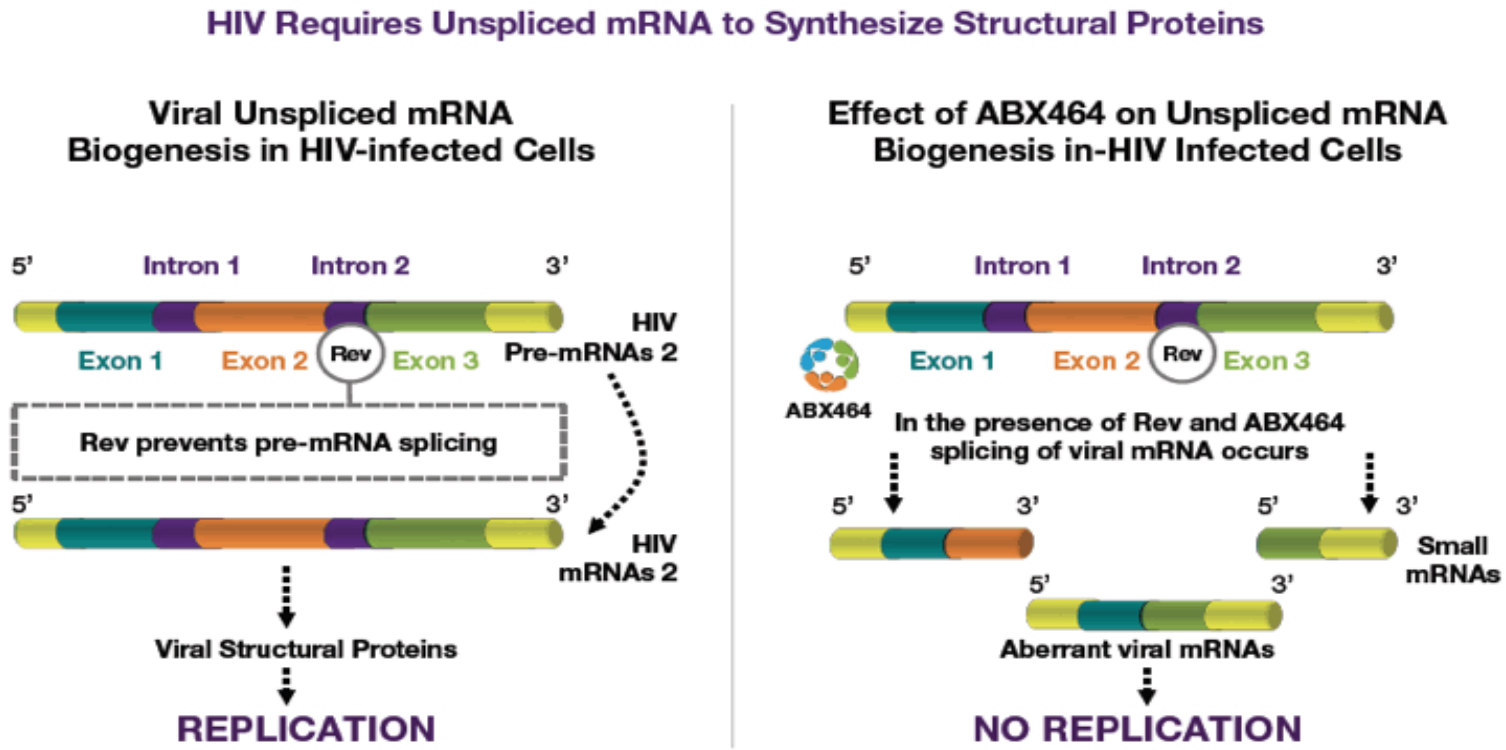
Chief Medical Officer ABIVAX

DECLARATION OF CONFLICT OF INTEREST

- GSK
- ABIVAX

ABX464: Mechanism of Action

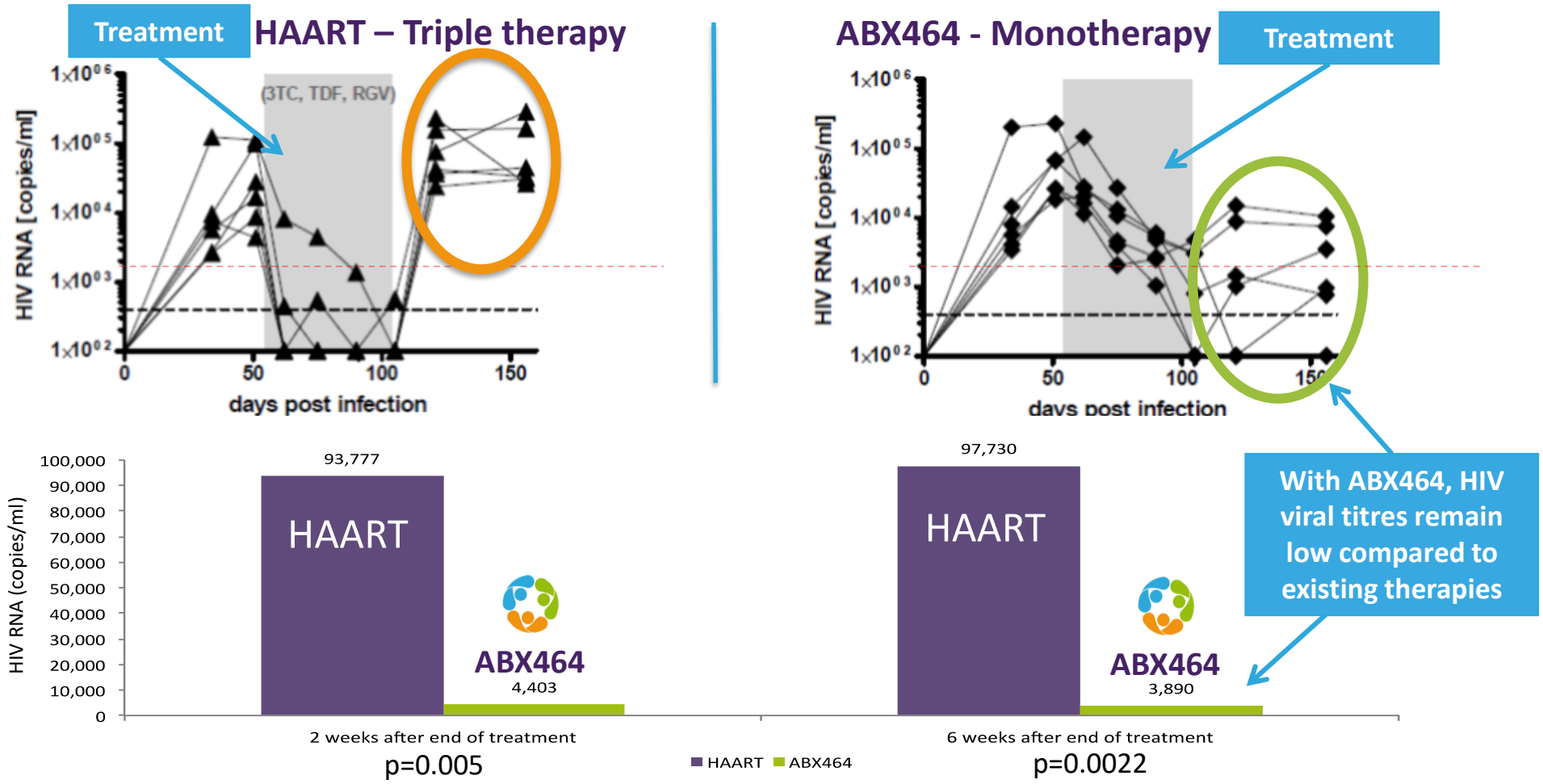
ABX464 is a first-in-class orally available antiviral small molecule that blocks HIV replication by preventing Rev-mediated export of unspliced HIV-1 transcripts to the cytoplasm



Campos Long lasting control of viral rebound with a new drug ABX464 targeting Rev - mediated viral RNA biogenesis. Retrovirology. 2015 Apr 9

ABX464 shows long-lasting viral load reduction vs. HAART in tg mice

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



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:

CBC 80/20

Activity:

Conformational change of CBC Complex → Enhanced RNA splicing

Biological effects:

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

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

1. Enhanced splicing of a long, non-coding RNA, leading to miR124 upregulation
2. Cytokine modulation

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 Mechanism of action

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[2,3], Laurent Manchon[2,3], Aude Garcel[2], Noëlie Campos[2], Karim Chebli[1], Didier Scherrer[2], Hartmut Ehrlich[2], and Jamal Tazi[1*]

Poster 15

16th European Meeting on HIV and Hepatitis Treatment Strategies and Antiviral Drug Resistance
Rome, Italy
30 May–1 June, 2018

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)

Poster 15

16th European Meeting on HIV and Hepatitis Treatment Strategies and Antiviral Drug Resistance
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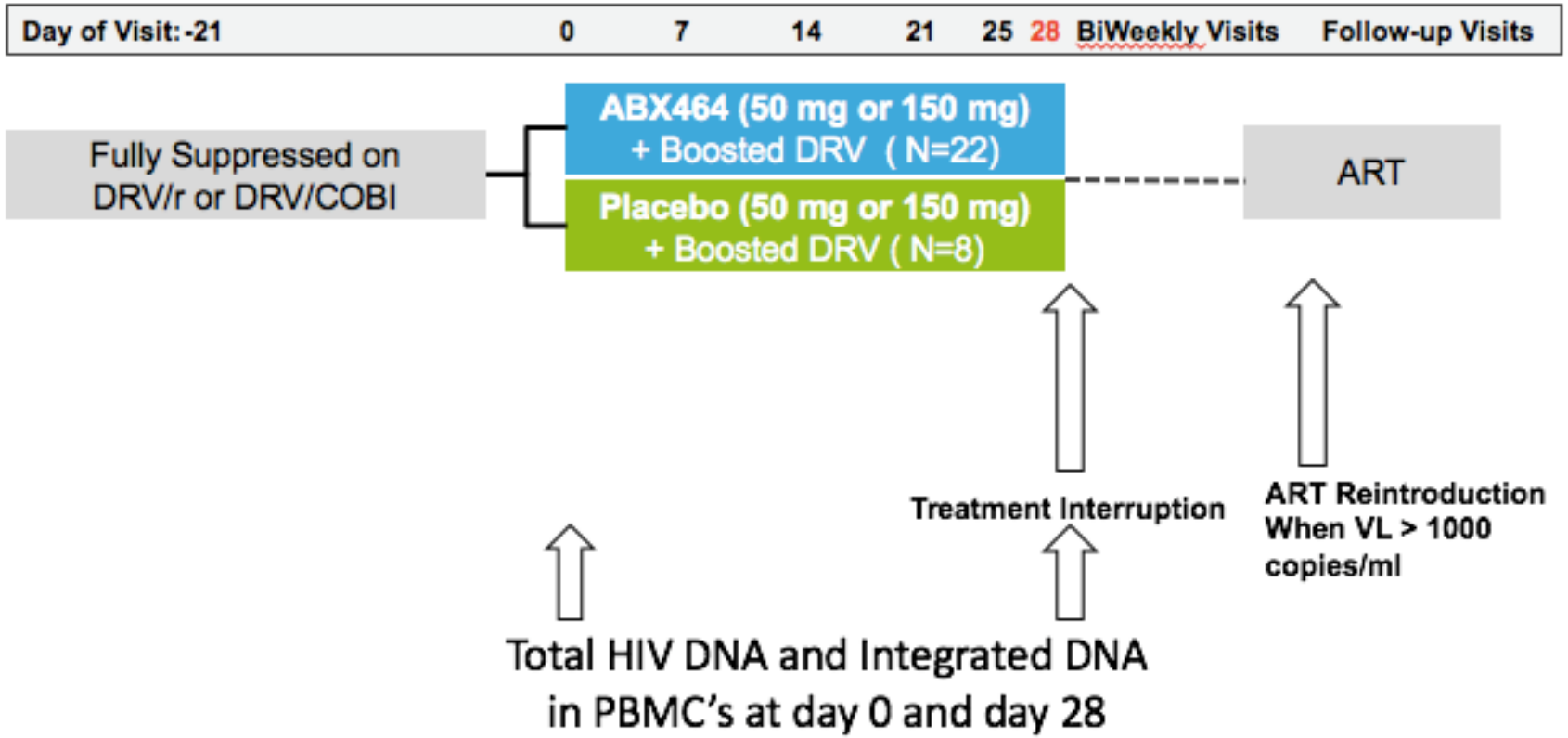
ABX464 Clinical Profile

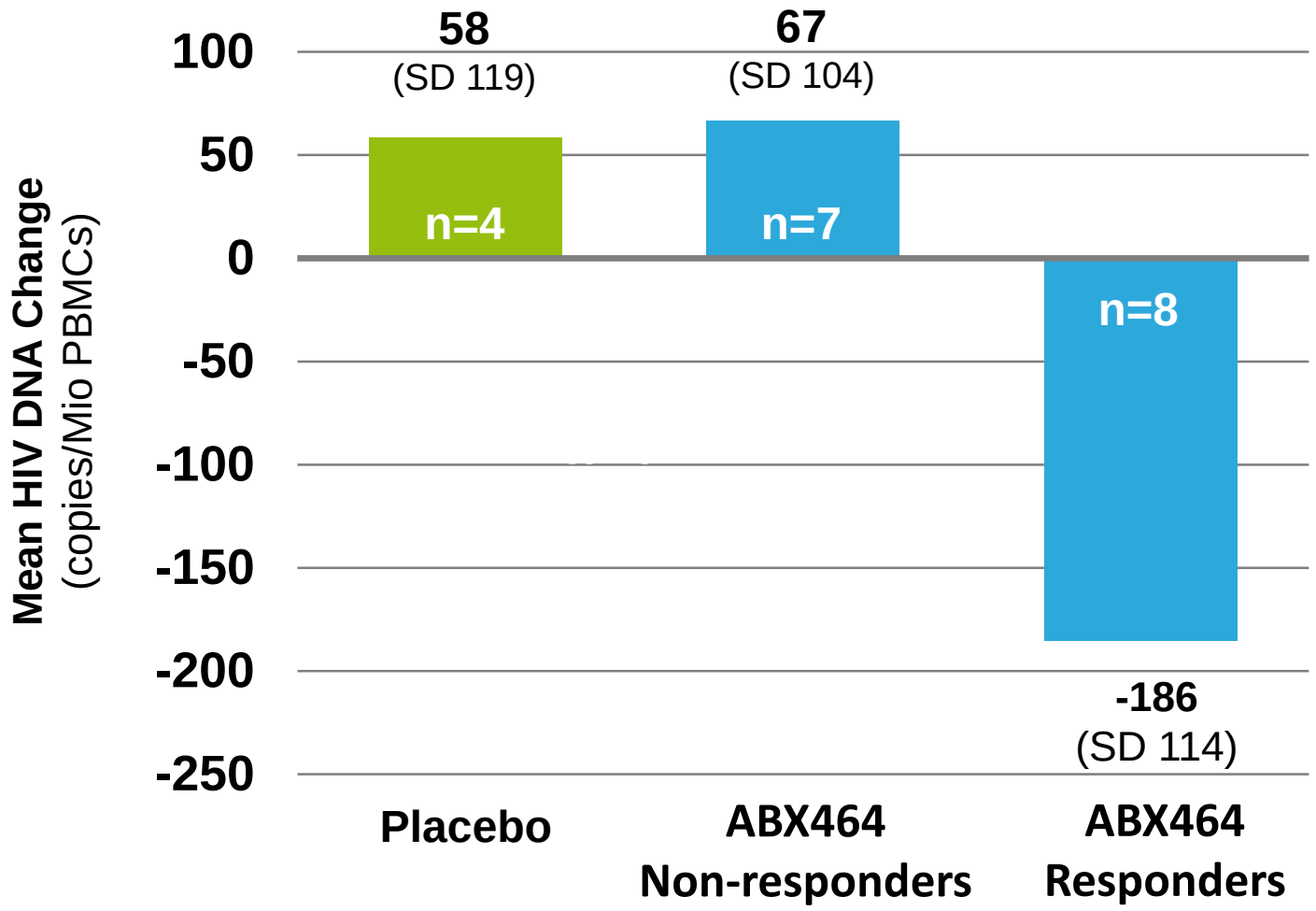
- ABX464 has acceptable safety profile, patient exposure
  - > 180 patients
- ABX464 has antiviral properties (study 003)
- Two independent studies showed that reduction of HIV DNA in blood from HIV well suppressed patients is feasible (study 004 / 005)
- Single copy assay showed reduction in residual 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



SD, standard deviation

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

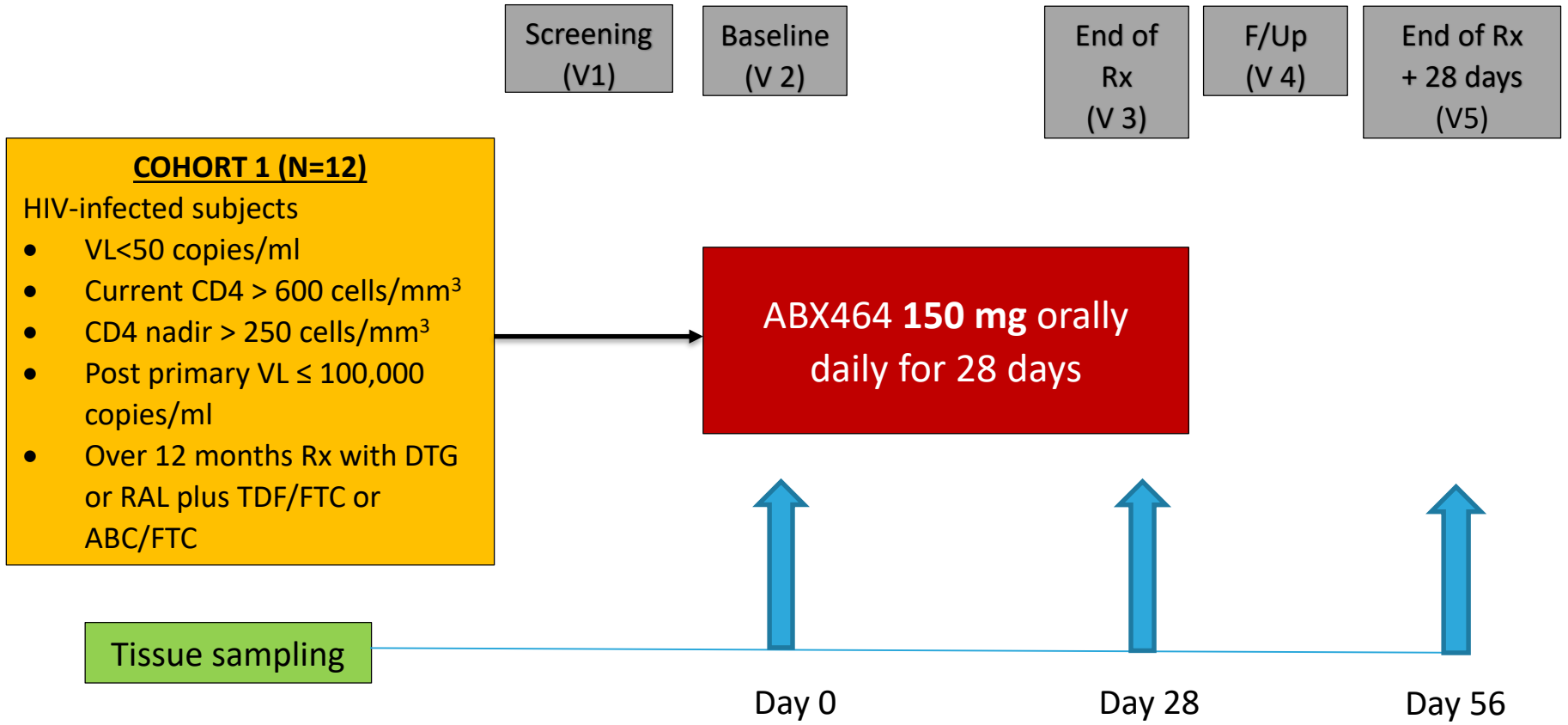
ABX464-005 Study

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



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

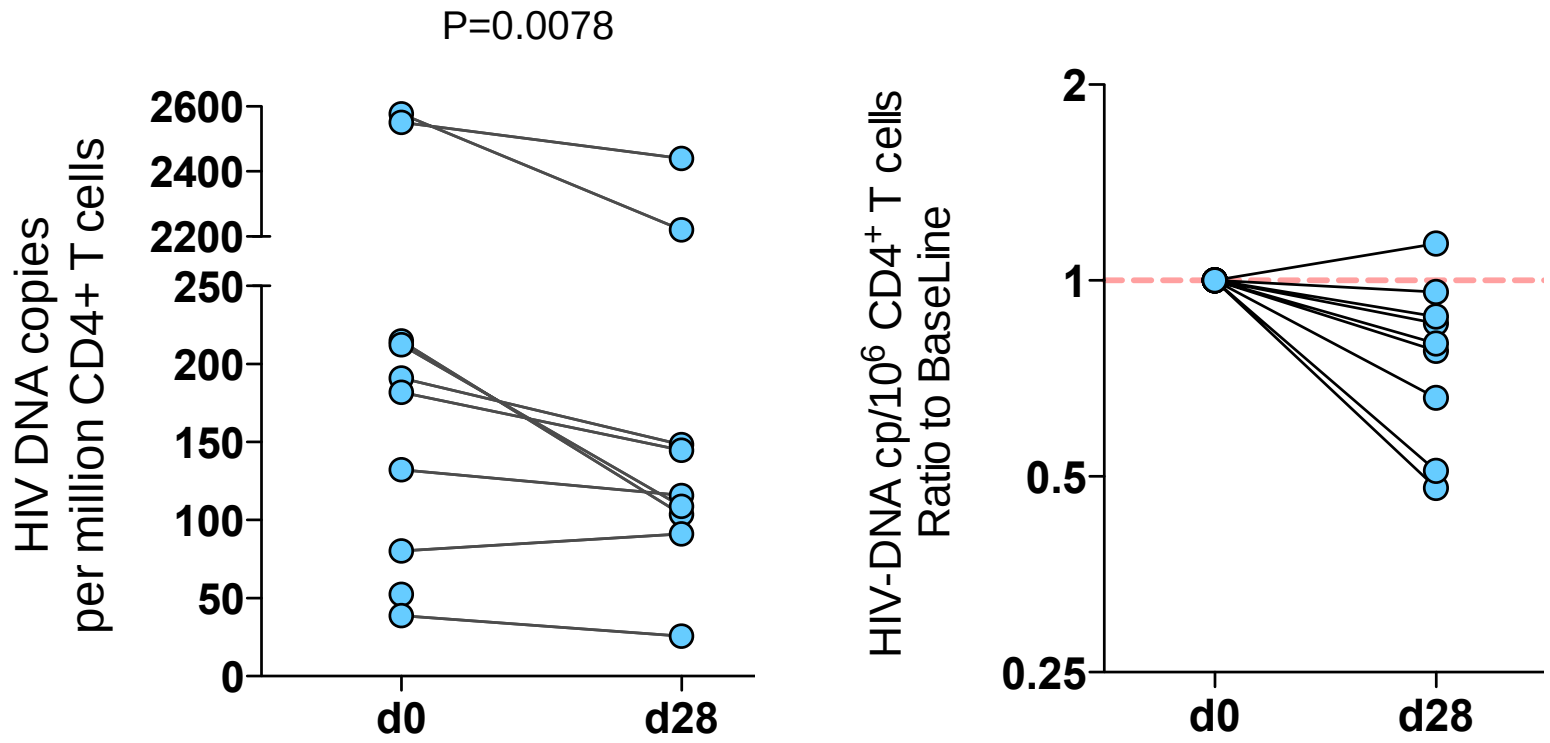
Age:	Mean 45.0 (median 48.0, range 29-55) years
Ethnicity:	11 white
Nadir CD4:	Mean 515 (median 501, range 279-810 cells/mm^3)
CD4 T cells:	Mean 911 (median 812, range 582-1420 cells/mm^3)

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

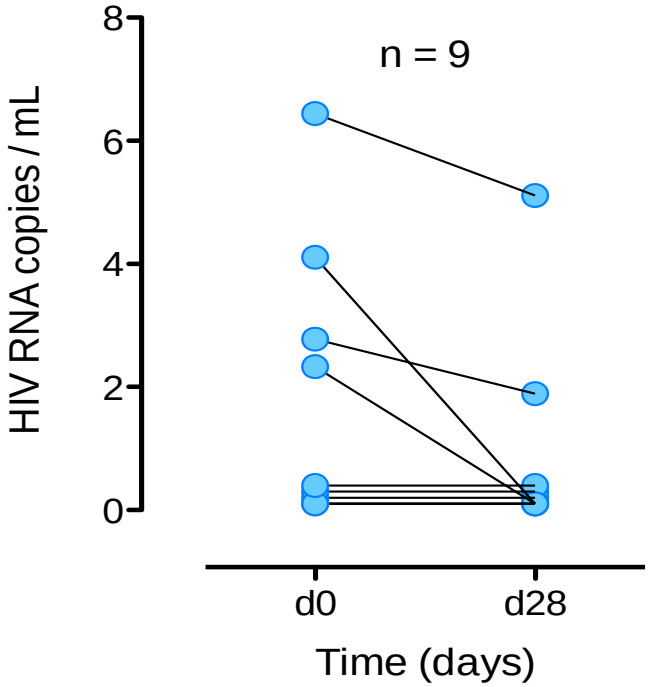
ABX464-005: HIV DNA

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



ABX464-005: Residual Plasma HIV Viremia by SCA

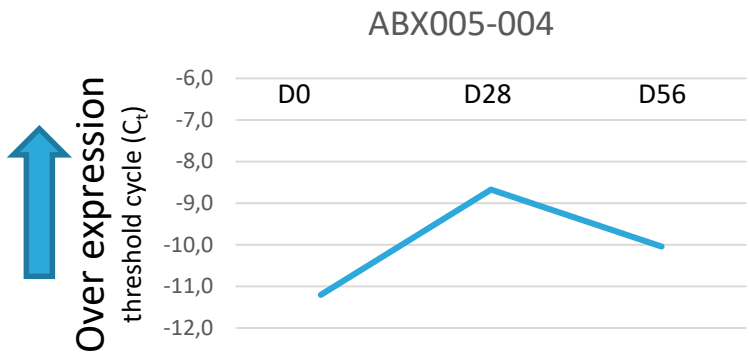
- All participants had <50 copies of HIV RNA at study enrollment
- LOQ = 0.5 HIV RNA copies/mL
- Residual viremia was detected in 5 participants
- In 4 participants there was a decrease between d0 and d28; one participant did not attend for d28 sampling
- 9/9 patients either decreased (n=4) or maintained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

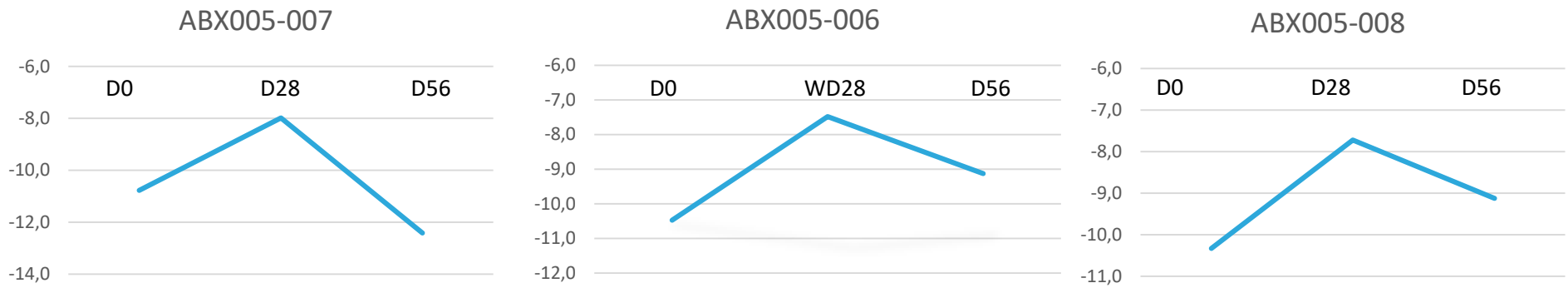


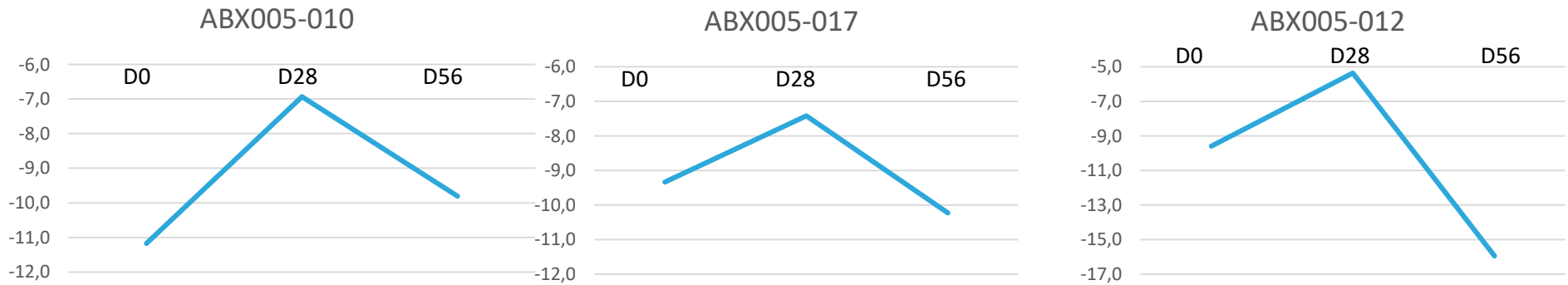
Increase	0/9
Decrease	4/9
Stable	5/9

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.

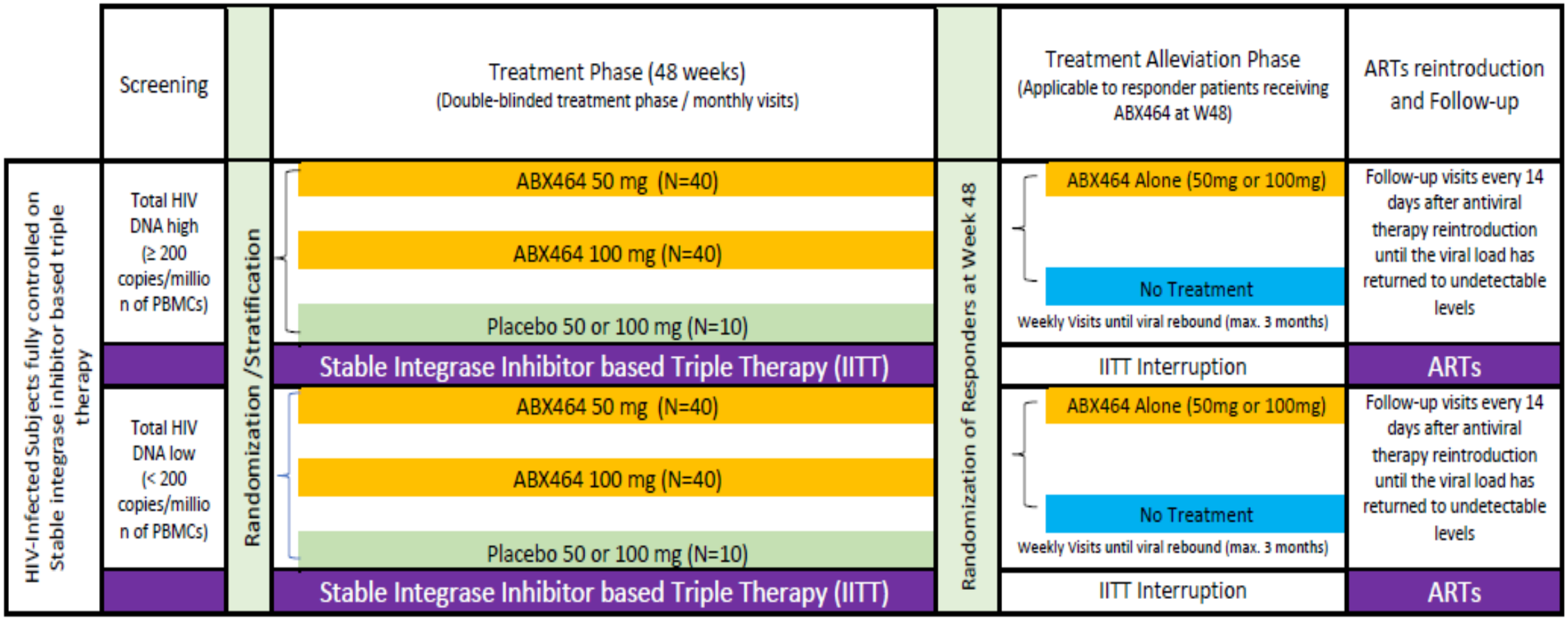
ABX464-005: Conclusions

- 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



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