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A phase 2, open label study of the safety, antiretroviral activity and pharmacokinetics of 3BNC117 during a short analytical treatment interruption in HIV-infected subjects

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Confidentiality Statement

Statement of Compliance

The clinical trial will be conducted in compliance with the protocol, with the International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), and with 45 CFR 46 and 21 CFR 50, 56 and 312. All protocol investigators have completed Protection of Human Subjects Training.

1.1 Design

The proposed study is a Phase II, open label study to evaluate the antiretroviral activity and safety of two and four 3BNC117 infusions in HIV-infected subjects on combination antiretroviral therapy, during a brief analytical treatment interruption. The study will also obtain additional data on its pharmacokinetic profile.

After meeting enrollment criteria eight subjects with 3BNC117 sensitive virus (< 2μg/ml IC_{50}) enrolled in Group A to receive two intravenous infusions of 3BNC117, administered at 30 mg/kg on day 0 and day 21 (Group A). Eight additional subjects with 3BNC117 sensitive virus (< 2μg/ml IC_{50}) will be enrolled to receive four intravenous infusions of 3BNC117, administered at 30 mg/kg on day 0, day 14, day 28 and day 42 (Group B). As 3BNC117 has not been administered four times to single individuals to date, Group B will be started with a mini cohort (n=3). Safety will be assessed by the SMC 1 week after the second dose, as well as 2 weeks after the fourth dose in the mini cohort, before proceeding with further infusions and enrollment.

Antiretroviral therapy will be discontinued on day 2 for 12 weeks after the first 3BNC117 infusion (week 12). We project screening 50 subjects in order to achieve 16 evaluable subjects. In case of drop-outs an over-enrollment of 10% will be allowed.

The same ART regimen will be resumed at week 12. ART regimen will be resumed sooner if plasma HIV-1 RNA level is ≥ 200 copies/ml or if CD4+ count drops < 350 cells/μl and either result is confirmed upon repeat measurement during the next weekly scheduled visit. If plasma HIV-1 RNA level is ≥ 1,000 copies/ml, the participant will be asked to return for a repeat measurement prior to the next scheduled visit, and ART will be resumed if results are confirmed. ART will also be resumed early if the participant becomes pregnant, or if otherwise clinically indicated. If ART regimen is resumed before completion of 3BNC117 infusions, further 3BNC117 infusions will not be performed. All subjects will be followed weekly until week 12 for safety assessments and for monitoring plasma HIV-1 RNA levels. CD4+ T cell counts will be monitored every 2 weeks until week 12. After week 12 subjects will be followed as outlined in the Time of Events Schedule (Appendix A).

Subjects will be offered a continuation of the treatment interruption through week 36, coordinated with their primary care physician as long as viral rebound does not occur. In the extension phase of the study subjects will return for follow up every week, while off ART. ART resumption will follow same criteria as detailed above.

The subjects' primary care physician will be consulted on any changes in antiretroviral treatment. In addition, non-research results will be communicated to the subjects' primary care physician after each study visit during all phases of the study. Safety and PK assessments will be performed at multiple time points following 3BNC117 infusions (see Appendix A). Subjects will be followed for 36 weeks from enrollment.

1.2 Analysis of Antiretroviral effects, Safety and Pharmacokinetics

Primary Objectives:

1. 3BNC117's effect on virologic rebound:

A one sided less Binomial Test with Clopper-Pearson confidence interval at 95% for rate of rebound will allow us to determine the population probability for the "occurrence of rebound", with 95% of statistical significance level (Clopper, C.; Pearson, E. S. (1934)).

Kaplan-Meier estimator will be used to address the second variable, "time to rebound" (Kaplan, E. L.; Meier, P. (1958).

2. 3BNC117's safety and tolerability profile in HIV-infected subjects with suppressed viremia during an analytical treatment interruption:

The number and percentage of subjects experiencing one or more AEs will be summarized by relationship to study drug, and severity. AEs will be summarized by the number and percentage of subjects who experienced the event, according to system organ class (SOC) and preferred term. AEs will also be summarized by severity grade and by relationship to study drug according to the DAIDS AE Grading Table (see Appendix B). The CTCAE v4.03 grading scale will be used for reporting and grading adverse events related to infusion reactions and cytokine release syndromes in all groups.

The changes in hematology, chemistry, and other laboratory values will be summarized descriptively. Changes will be calculated relative to the values collected at baseline.

3. 3BNC117's pharmacokinetic profile in HIV-infected subjects with suppressed viremia during an analytical treatment interruption:

Pharmacokinetic parameters will be calculated using standard non-compartmental analysis methods. Pharmacokinetic parameters, including AUC, Cmax, T½, Tmax and others will be summarized. A 95% two tails matched pairs T-test will be used to compare 3BNC117 serum levels before and after each antibody infusion. Pharmacokinetic parameters will be examined to correlate exposure with safety and pharmacodynamic parameters. Variance based on population intrinsic factors such as weight and gender will be explored.

Secondary and Exploratory Objectives:

1. The range of 3BNC117 serum levels at which virologic rebound occurs:

For each participant the time to rebound and the concentration of 3BNC117 at the time of rebound will be determined and summarized using confidence intervals.

2. Compare the rate and time to rebound between groups:

A Fisher exact test will allow us to contrast the rate of rebound between groups and Kruskal–Wallis one-way analysis of variance will be used to compare the mean time to rebound. For both tests a 95% significance level will be assumed.

3. Host immune responses:

A 95% repeated measures ANOVA F-test will be used to compare the following variables, at baseline, 2 weeks after the last infusion, at weeks 12 and 36:

- serum levels of inflammation markers, such as: C-reactive protein, D-dimers, IL-6 and soluble CD-14.
- CD8+ T cell expression of activation markers such as: HLA-DR, CD38 and PD-1.
- HIV gag and env-specific T and B cell immune responses will be evaluated by intracellular cytokine staining and ELISA.

4. Antiretroviral effects:

A 95% repeated measures ANOVA F-test will be used to compare the following variables, before as well as 8 weeks after the first infusion if viral rebound does not occur:

- levels of plasma HIV-1 RNA by single copy assay;
- levels of cell-associated HIV-1 RNA and DNA;

5. Other measurements:

The frequency and levels of anti-3BNC117 antibodies after each 3BNC117 infusion will be calculated and displayed in tables.

Genotyping of HIV isolates will be performed in the Laboratory of Molecular Immunology by reverse transcription followed by PCR amplification and sequencing of HIV envelope genes. This will allow us to phylogenetically compare viruses grown from PBMCs collected from subjects while on ART to rebound viruses collected after treatment interruption and analyze the induction of escape mutations. In addition, amplified HIV envelope genes will be cloned and produced in pseudoviruses in order to test for resistance to 3BNC117 by TZM-bl neutralization assay. Results will be descriptive.

Continuous data will be summarized by descriptive statistics, including the sample size, mean, standard deviation, median and range. Categorical data will be summarized by the number and percentage of subjects. If necessary Log2 of variables will be used.

1.3 Sample Size Considerations

The confidence interval calculation is based on one of the primary objectives of this study "Evaluate the effect of two or four infusions of 3BNC117 at 30 mg/kg in delaying virologic rebound and maintaining viral suppression during a short analytical treatment

interruption". As such, the primary outcome is the occurrence of rebound during treatment interruption.

In study group A, 5 out 7 participants who received 2 infusions of 3BNC117 have experienced viral rebound to date. Eight participants will be enrolled in the new study group B and will be administered four 3BNC117 infusions at days 0, 14, 28 and 42.

A one-sided upper confidence interval will be constructed for the probability of rebound in study group B using the Clopper-Pearson method. As such, a sample size of 8 HIV-infected individuals will allow the rejection of the null hypothesis (rate = 1) with 80% power for an effect size equal or higher than 0.18, if at least 4 out of 8 participants enrolled in study group B do not experience viral rebound by week 8. The one-sided 95% Clopper-Pearson confidence intervals calculated for a varying number of observed rebounds are presented in **Table 1**. If 5 or more participants in group B experience viral rebound prior to study week 6 [2 weeks after the third 3BNC117 infusion], additional participants will not undergo ATI.

Table 1. Upper bound Confidence Interval
for a sample size of n=8 (Study Group B)

Number of Rebounds	UCI
0	0.3694
1	0.5265
2	0.6509
3	0.7551
4	0.843
5	0.9148
6	0.9682
7	0.9968
8	1

We will compare days from date of ART interruption to viral rebound in group A to group B. Given a standard deviation (SD) of 10 (days), enrolling 7 or 8 patients in each of the two arms, will have 80% power to detect ≥ 15 days difference in time to viral rebound at a 5% significance level (Davey et al., 1999, Rothenberger et al., 2015).

The safety population will include all subjects who receive a 3BNC117 infusion. A baseline measurement and at least one laboratory, vital sign, or other safety-related measurement obtained after at least one dose of study treatment may be required for inclusion in the analysis of a specific safety parameter.

All adverse events will be reported, grouped as to whether or not they qualify as SAEs, their severity grading, and their relationship to the antibody, as judged by the study investigators. If none of the subjects experiences a moderate adverse event related to 3BNC117 (n=16), the 95% upper confidence bound for the rate of adverse events in the population is 20.6%.

Two tail matched pairs T- test will be used to compare 3BNC117 serum levels before and after each antibody infusion. For two tail matched pairs T- Test, a sample size of 16 subjects in the group allows to detect an effect size of 0.75, with 80% power and 95% confidence.

For repeated measures ANOVA F-test, a sample size of 16 subjects in the group allows to detect an effect size of 0.46, with 80% power and 95% confidence. (to compare variables of antiretroviral effects and immune responses, before first infusion, at 2 weeks after last infusion, at week 12 and week 36.

2 Data and Sample Storage

The Principal Investigator will oversee how the data are collected, entered, and protected. All study data will be collected by the clinical study staff using designated source documents and entered onto the appropriate electronic case report forms (eCRFs). Data collection forms (DCFs) will be provided by EMMES^{TM} for use as source documents as appropriate. All study data must be verifiable to the source documentation. All source documents will be kept in a locked facility at the clinical site and remain separate from volunteer identification information (name, address, etc.) to ensure confidentiality. All medical records (when not being reviewed by the research team) will be kept under lock and key in the Medical Record Department of the hospital with access limited to the appropriate RUH personnel. Source documentation will be available for review to ensure that the collected data are consistent with the eCRFs.

All eCRFs and laboratory reports will be reviewed by the clinical team, who will ensure that they are accurate and complete.

All research samples will have a unique identifier. The site PI will be responsible for ensuring project compliance, data analysis and entry, regulatory monitoring, and coordination of the activities of the entire study team. Standard GCP practices will be followed to ensure accurate, reliable and consistent data collection.

Source documents include, but are not limited to:
- Signed Informed Consent Documents
- Dates of visits including date of 3BNC117 infusions
- Documentation of any existing conditions or past conditions relevant to eligibility
- Reported laboratory results
- All adverse events
- Concomitant medications