Statistical Analysis Plan

ADVICE: Attenuation of D-dimer using Vorapaxar to target Inflammatory and Coagulation Endpoints

A double blind randomised comparison of vorapaxar versus placebo for the treatment of HIV associated inflammation and coagulopathy in patients with well controlled HIV replication

Protocol Registration Number: NCT02394730

Version 1, 13 November 2017

ADVICE Statistical Analysis Plan

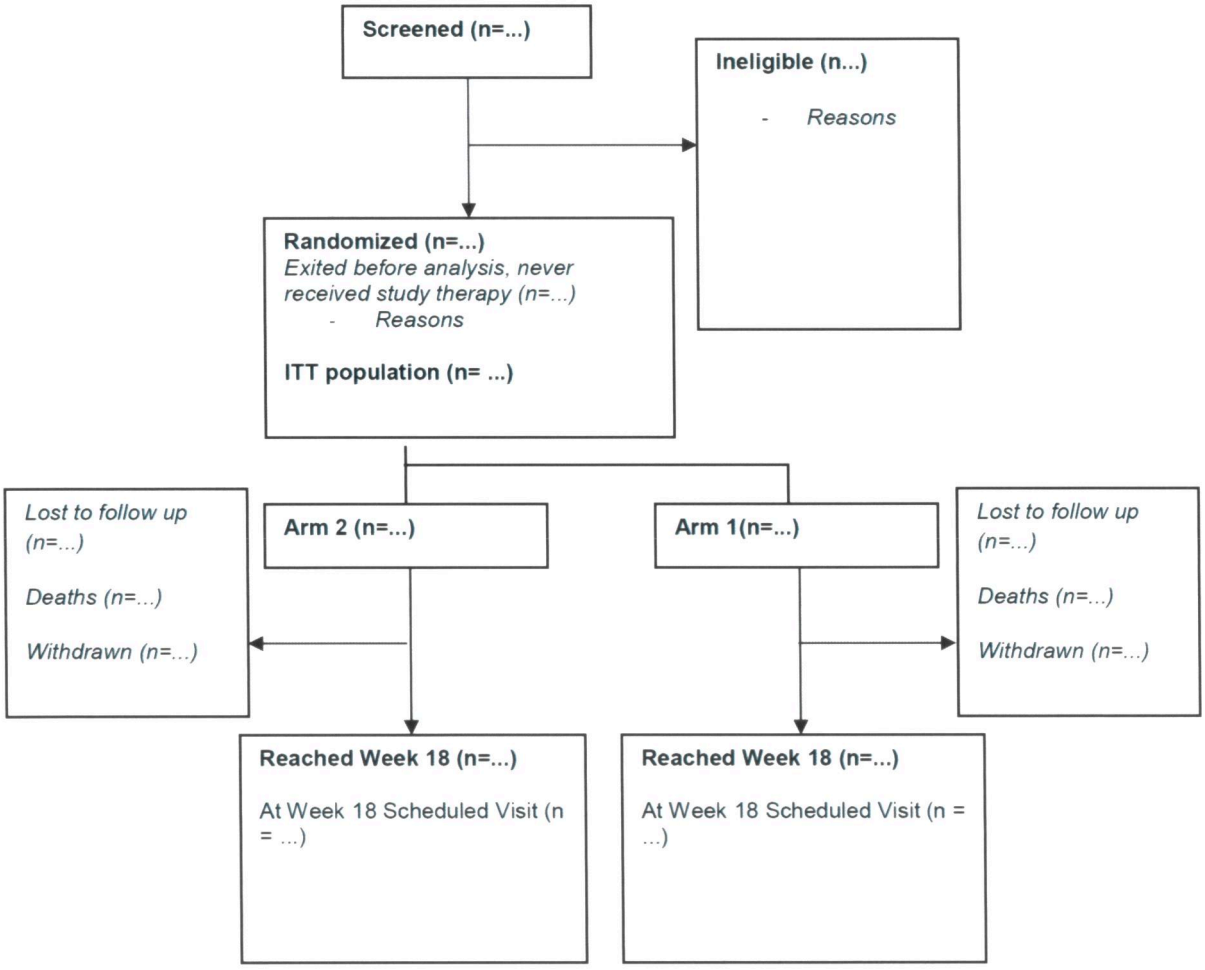
The final statistical analysis will be performed when all randomised participants have completed follow-up to week 18, or have permanently stopped trial follow-up, and all data have been entered into the study database, data cleaned and database locked.

1. STUDY POPULATIONS

1.1 Subject Disposition

The disposition of participants will be described by the following diagram (Figure 1).

Figure 1. Patient disposition



1.2 Protocol Violations

Number, proportion and reason for any protocol violations and variations will be described by randomization arm. For this purpose we will report any enrolment event that contravenes an inclusion criterion and/or meets an exclusion criterion, and any event that could potentially affect either the primary endpoint or ongoing patient safety.

1.3 Definition of Populations for Analysis

All endpoints will be analysed using a modified Intention to Treat (mITT) approach.

We will include all randomised participants who received any study drug and had any study follow-up. All available follow-up data will be included, regardless of whether the participant remained on study drug.

Sensitivity analyses based on different study populations for analysis may be considered including:

- mITT last observation carried forward for participants who stopped study follow-up
- per protocol – censoring data at time of stopping trial drug

But given the known excellent trial follow-up, these analyses are not currently thought necessary.

1.4 Summary of Numbers Analyzed

Number of participants contributing data to each study visit according to mITT will be summarized by randomised treatment.

Changes, if any, to participants antiretroviral treatment during the study will also be summarized.

2. EVALUATION OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS

2.1 Demographics and Baseline Characteristics

Participant demographic and baseline characteristics (Table 2), ascertained at time of study enrolment, will be reported by randomization treatment. Continuous variables will be presented as mean and standard deviation (SD), median, 25^{th}, 75^{th} percentile, minimum and maximum value. Categorical variables will be presented as number and percent. Baseline is defined as the date of randomisation, without exception.

No formal statistical tests will be performed to evaluate potential between-group differences at baseline. If there are important imbalances in baseline characteristics, which are both clinically important and related to the primary endpoint, then analyses will be performed and presented

4. EVALUATION OF PRIMARY AND SECONDARY EFFICACY ENDPOINTS

4.1 Primary Endpoint

The primary endpoint is changes in log10 d-dimer from baseline (week 0) to the average of weeks 8 and 12.

4.2 Secondary Endpoints

Virologic measures

- Proportion of participants in each treatment group with plasma HIV-1 RNA <50 copies/mL at week 12 and week 18

Immunologic measures

- Differences between treatment groups in mean change from baseline in CD4+ cell counts at week 12
- Differences between treatment groups in mean change from baseline in CD4+ cell counts at week 18
- Differences between treatment groups in mean change from baseline in CD8+ cell counts at week 12
- Differences between treatment groups in mean change from baseline in CD8+ cell counts at week 18

Activation/Coagulation measures of interest

- Percentage of patients in each treatment group with d-dimer <165ng/mL at week 8 and week 12
- Percentage of patients in each treatment group with d-dimer >165ng/mL at week 18
- Differences between treatment groups in mean change from baseline log10 d-dimer at week 18
- Differences between treatment groups in mean change from baseline log10 hs-CRP to the average of week 8 and week 12
- Differences between treatment groups in mean change from baseline log10 hs-CRP at week 18
- Differences between treatment groups in mean change from baseline log10 IL-6 to the average of week 8 and week 12
- Differences between treatment groups in mean change from baseline log10 IL-6 at week 18
- Differences between treatment groups in mean change from baseline log10 sCD14 to the average of week 8 and week 12
- Differences between treatment groups in mean change from baseline log10 sCD14 at week 18
- Differences between treatment groups in mean change from baseline log10 sCD163 to the average of week 8 and week 12
- Differences between treatment groups in mean change from baseline log10 sCD163 at week 18

Immunopathegenesis measures

- Differences between treatment groups in mean change from baseline in percent total CD4 cells expressing PAR-1 at week 12

- Differences between treatment groups in mean change from baseline in percent total CD8 cells expressing PAR-1 at week 12

4.3 Statistical analysis

All efficacy endpoints will be summarised by randomised treatment and study visit. Continuous measures will be summarised as means and standard deviations, categorical measures as n and percent.

Formal statistical comparisons between randomised treatment arms will use repeated measures regression methods as appropriate to continuous and binary data. Precise models to be used will depend on data and fit to model assumptions, but *a priori* choice will be generalised estimating equations with robust standard errors. Initial analyses will be unadjusted comparison of randomised treatments with baseline value only as a covariate, but further adjusted analyses may be performed as needed.

Further regression modelling may be performed to explore how primary and secondary activation and coagulation endpoints evolve over time.

4.4 Exploratory Efficacy analyses

If an effect of randomised treatment is seen on the primary endpoint, then exploratory analyses will be performed assessing correlations between changes in d-dimer and changes in PAR-1 expression. Regression models will also be used to assess the extent to which differences in changes in d-dimer between randomised treatments are attenuated through adjustment for PAR-1 expression.

These analyses will be on a subset of participants for whom PAR-1 expression data are available. It is accepted that this will result in lower power, and results will be interpreted cautiously.

5 EVALUATION OF SAFETY PARAMETERS

Evaluation of safety parameters in participants who receive at least one dose of study therapy and attend at least one visit post randomisation with no imputation for missing data.

5.2 Adverse Events

Bleeding adverse events
Total number of participants with Type 1, 2, 3, 4 or 5 bleeding episodes using BARC criteria. Bleeding episodes will be summarised by type and randomised treatment.

Serious Adverse Events
Total number of participants with any Serious Adverse Event (SAE) and the cumulative incidence of SAEs. SAEs will be summarised by randomised treatment and relationship to study drug.

Adverse events
Total number of participants with any Adverse event (AE) and the cumulative incidence of AEs. All AEs, and grade 3 or 4 AEs, will be summarised by MeDRA group term, relationship to study drug and randomised treatment.

Laboratory adverse events
Total number of participants with laboratory or biochemical adverse events, according to DAIDS criteria, in particular renal function measured by the CKD-EPI estimate of creatinine clearance. Laboratory AEs will be summarised by grade and randomised treatment.

Statistical analysis of adverse event data
The proportion of patients with adverse events will be compared between randomised treatments using chi-square tests, Fisher's exact test or similar as appropriate to the data. Differences in proportions of patients with events by randomised treatments will be summarised as 95% confidences intervals.

5.3 Serious non-AIDS events (SNAEs), AIDS, pregnancies and deaths

Occurrences of any of the above events will be summarized by randomized treatment.

6 *A PRIORI* DEFINED SUBGROUP ANALYSES

There are no pre-planned subgroups analyses