NEAT 001/ANRS 143

Randomised comparative trial in HIV-infected antiretroviral naïve subjects: darunavir/r + tenofovir/ emtricitabine vs. darunavir/r + raltegravir

Copenhagen CTU Newsletter #5, April 2013

Introduction

Many thanks to all of you for the great achievements and for your involvement in the NEAT001/ANRS143 trial.

Results of the W48 interim analysis were presented on 30 January 2013 to the IDMC members. The IDMC had no safety concerns and recommended to continue the trial follow-up as planned. The Trial Steering Committee (TSC) met on 13 February 2013 and decided to follow the IDMC recommendations.

A new protocol amendment (amendment 5) will be submitted in all countries in the next few months.

Week 48 Interim Analysis

Many thanks to all for your efforts in entering data and resolving inconsistencies in the eCRF for the completion of this analysis.

At data extraction for the interim analysis (8/9 December 2012):

- 94% of participants had reached 48 weeks
- 85 % of participants had reached 64 weeks
- 8220 clinic visits completed (96 % of those due to date)

Recommendation of the IDMC

The NEAT 001/ANRS 143 Independent Data Monitoring Committee (IDMC) held their fourth meeting on 30 January 2013. In the closed session, they reviewed the closed report which considered data from the study up to the 7th December 2013 with the primary analysis limited to the first 48 weeks as well as over the entire follow-up. They had **no safety concerns,** saw no reason for the trial to stop or be modified in any way and recommended to **continue the study as planned.**

The IDMC welcomed the substantial improvement and timeliness of the review of the events by the ERC.

The IDMC noted that the protocol mentions two definitions of clinical equivalence between the two arms, one in terms of the hazard ratio and the other in terms of the absolute difference in the proportion of failures by week 96. Given that the primary event rate may be lower than had been projected it would be wise for the TSC to specify which will be the more important comparison whilst still blinded to the outcome by arm.

IMPORTANT - DATA COLLECTION

Reminder on the completeness of data (for more details, please refer to the study manual):

Please complete the visit of all participants as soon as possible and no later than 2 weeks after the visit.

As soon as you get HIV-1 RNA results or any other data is available, please do not wait for other results and enter these data in the eCRF immediately.

Please lock all the pages after completion to allow for the coding of events and medication and sending of queries (lock even if pages are not completely fulfilled).

Queries are posted on the e-CRF on a monthly basis, they are signalled by a blinking orange question mark on the home page of the e-CRF. Please make sure to check and address these queries regularly.

PHARMACOVIGILANCE

Declaration of SAEs has to be done **within 24 hours** after being aware of the event. This is a regulatory obligation which means that data should immediately be entered in the eCRF. SAE form must be signed by a clinician and the box “report this SAE” ticked - An email will be automatically sent to the ANRS pharmacovigilance department, if the report box is not ticked, the declaration is not done. If no clinician is available, the SAE should be reported within 24 hours anyway and the clinician

Reaction of the TSC

The Trial Steering Committee replied to the IDMC that they will follow the recommendations of the IDMC and continue to monitor closely the blinded trial data and report to the IDMC as necessary. After appreciation of the methodological aspects related to each definition, the clinicians on the TSC recommended to base the primary analysis on the absolute difference in proportion. The analysis based on the Hazard Ratio (time-to-event analysis) will be performed as a secondary analysis.
As a consequence the TMT will prepare a substantial amendment to the protocol (see below).

Amendment 5

The principal modification is to clarify the definition of the non-inferiority margin used in the final analysis (see above). In the previous protocol version, two definitions of non-inferiority between the arms were used (hazard ratio and absolute difference in the proportion of failures). These two approaches could give discordant results with regards to non-inferiority in the final analysis. While still blinded to arms, The TSC decided to use the definition based on the absolute difference in proportions in the primary analysis of the primary endpoint. The analysis based on the hazard ratio will be performed as a secondary analysis.
Amendment 5 will be submitted in all countries participating in the NEAT 001/ANRS 143 Trial during the month of April 2013

TRIAL Close-out Procedure

All participants must be followed until week 96 visit of the last randomised participant, which is expected to happen on 2 August 2013. **Follow-up in the trial should be completed also for those participants who have discontinued the trial drugs or have reached an endpoint.**

A last study visit should thus be scheduled for all participants on or after 2 August 2013.To allow for a timely study close-out while keeping the workload manageable for the study sites, the final patient visits should be scheduled in the **window from August 2, 2013 to September 15, 2013** ideally, and 30 September 2013 at the latest.
Please inform the participants enrolled at your site about the expected end date of the trial.

Please complete and return the form provided by your CTU to log final visit date per patient, and contact your CTU if you anticipate any problems to organise all final visits of your patients within those two months.

A last series of on-site monitoring is to be scheduled between 15 September and 1 December 2013.

Once monitoring is complete (monitoring visit done and all queries resolved), CTUs will remotely monitor the pages to allow for your signature in the eCRF. We anticipate that this process should be achieved by end of December 2013 to allow the Stat Center to start analyses in the first month of 2014.

must sign the form ASAP.

TRIAL SUBSTUDIES

Pharmacogenetics sub-study:

Please remember that the written consent form can be signed at any visit during the trial. It is important that as many participants as possible participate in the pharmacogenetics sub-study. If the consent for the pharmacogenetics study has not been obtained at enrolment, please try to re-discuss this sub-study with the participant at any later stage during the trial.

Patient questionnaires and CRF neurocognitive:

Please regularly send the completed patient questionnaires and neurocognitive CRF to your local CTU, they will then forward them to the coordinating CTU.

POSSIBLE ROLL-OVER

We are conducting discussions to propose an extension of the follow-up (2 years) for the well-controlled “Darunavir/r + Raltegravir” patients and we will inform you at the latest by mid-April whether this will be implemented.

Management team: François Raffi, Anton Pozniak **Legal sponsor:** ANRS
Chair of the trial steering committee: Eric Sandström, full list of members here
CTUs: AMC (The Netherlands), CMG-EC U897 (France), MRC (United Kingdom), **CHIP, (Denmark)**