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NEAT 001/ANRS 143

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

Copenhagen CTU Newsletter #4, September 2012

All participants reached week 42!

We are delighted to inform you that the last patient enrolled in the trial has reached the W48 follow-up visit in August 2012

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

Results of the W32 interim analysis, requested by the Independent Data Monitoring Committee (IDMC), were presented on 11 June 2012 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 3 July 2012 and decided to follow the IDMC recommendations.

Information about the Core Trail Week 32 Interim Analysis

Many thanks to all for your efforts in entering data and resolving inconsistencies in the eCRF for this analysis. At data extraction for the interim analysis (4th May 2012):

- 94% of participants had reached 32 weeks
- 59 % of participants had reached 48 weeks
- 22% of participants had reached 64 weeks
- 6739 clinic visits completed (96 % of those due to date)

Recommendation of the IDMC

The NEAT 001/ANRS 143 IDMC held their third meeting at the MRC Clinical Trials Unit in London on 11 June 2012. In the closed session, they reviewed the unblinded data, including a 32-week analysis. 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**.

IDMC noted the time lag between events reported and adjudication and reporting by the Endpoint Review Committee (ERC). They acknowledge that the Trial Management Team is in the process of identifying the reasons for such a lag and addressing them and hope for much improvement in this regard by the time of their next review, in February 2013, when all patients have reached their W48. In case of an event qualifying for ERC review (see protocol section 13.5), we thus kindly ask you to **send all source documentation needed for ERC review as soon as possible to your CTU**.

Copenhagen CTU Information

On behalf of the Copenhagen CTU we wish to thank the sites in our region for your continuous efforts to make the NEAT001 study a success. As we are approaching the last year of patient follow-up, and particularly the next interim analysis, we would like to emphasis some important operational matters that we encourage all site staff to pay extra attention to:

VL >50 cp/ml by W32 or at any time after W32: the virological response to trial treatment is a very important endpoint in the NEAT001 trial. To ensure the statistical integrity of the study design it is crucial you call in your patient for a 'repeat VL' should the result be VL >50 cp/ml at any time after W32. This is also critical in cases where the VL 'slightly' excedes the protocol defined limit of 50 cp/ml. As previously mentioned in this newletter 'repeat VL' should preferably be done within 10 to 28 days.

Patient questionnaires: please make sure to regularly send completed patient questionnaires and neurocognitive substudy CRFs to the CPH CTU. It is of crucial importance that all due questionnaires are keyed in the database before the next upcoming interim analysis.

Study IMP: as earlier announced in a central email from CHIP (8 August 2012) the sponsor has requested all sites to make an estimation of IMP needed to finalize the trial in September 2013. We kindly ask those of you who have not yet provided this information to your local monitor (deadline 31 August 2012) to do so at your earliest convenience.

Expected last study visit: please inform your patients that the expected 'last study visit' will be between 2 August 2013 and 30 September 2012. All patients will be followed until the last patient in the study has attended the W96 visit. This means most patients will have a limited number of additional follow-up visits every 3-4 months after their W96 visit.

On-site monitor visit: please assist your local monitor to arrange the 2nd NEAT monitor visit between Sep-Oct 2012.

IMPORTANT

Trial Steering Committee Concerns

Low number of repeat VL test after virological faliure: The TSC is concerned by the low number of patients in virological failure with no repeat tests of viral load recorded or with repeat tests performed out of the defined window (10 to 28 days). We thus remind you that, even after having modified the primary endpoint in the new protocol version, HIV-1 RNA must be retested between 10 and 28 days if at any point after HIV-1 RNA < 50 c/ml it is recorded as ≥ 50 c/ml. Please make sure that all procedures are in place

Preparation for Week 48 Interim Analysis

As defined in the protocol, an interim analysis is planned when all patients have reached W48. The last patient's W48 visit was in August 2012.
In order to prepare for this analysis, we kindly remind you that all data, and especially data up to W48 should be entered in the eCRF as soon as possible, **all pages have to be locked** and all **queries** (from CTUs and Data Management center) **resolved**.
Once all pages will be locked and all queries will be resolved, CTUs will remotely monitor the pages to **allow for the site PI's signature** in the eCRF. We anticipate that this process should be achieved by November 2012 to allow the Stat Center to start analyses.
Please note that no results will be presented publically before the end of the trial in 2013.
Please complete the visit of all participants as soon as possible and no later than two weeks after the visit, until the end of the trial follow-up in August 2013.

Pharmacovigilance

Declaration of SAEs has to be done within 24 hours after being aware of the event. This is a regulatory obligation - for more detail follow link.

Data completeness

Please see the reminder for issues related to data completeness.

Trial Close-out

All participants will be followed until week 96 visit of the last randomised participant which is expected to happen on 2 August 2013. Fore more datail follow link.

Sub-study Information

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

Site PI to sign eCRF: once the 2nd on-site monitor visit has taken place, all queries have been resolved and all pages locked by the site, the local monitor will remotely monitor each eCRF page by turning the page to 'status monitored'. At this point the site PI will enter the eCRF using his/her personal password, equivalent to an electronic signature, and sign all pages turned to 'status monitored'. Please refer to the eCRF guide or contact your local monitor for further guidance.

Delayed reporting of SAE's: Serious Adverse Events must be reported within 24h of site awareness. In a past report from the sponsor's pharmacoviglilance department you have been informed that an uacceptable number of SAE's reported in our region did not comply with this regulatory obligation. We are very pleased to see the situation has much approved since our last email alert regarding this matter, however, we kindly ask all study staff to always bear this requirement in mind in the future.

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: The trial committees (IDMC and TSC) are concerned about the low number of patient questionnaires received at the coordinating CTU which centralises questionnaires from all countries. Please regularly send the completed patient questionnaires and neurocognitive CRF to your local CTU, they will then forward them to the coordinating CTU.

Bone sub-study: DPlease inform your CTU if you have any difficulties to enter the DXA results in the eCRF..

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)**