5th March 2014

Executive Summary of NEAT 001/ANRS 143 Trial Results

Introduction and study design

NEAT 001/ANRS 143 was a large phase III, open-label, multicentre, randomised controlled trial designed to assess whether initiation of antiretroviral therapy (ART) with a regimen consisting of an Integrase Inhibitor and a boosted Protease Inhibitor (PI) would be non-inferior to the standard Nucleotide reverse transcriptase inhibitor (NtRTI) plus boosted PI regimen.

The trial participants were enrolled from 78 clinical sites across 15 countries (Austria, Belgium, Denmark, France, Germany, Great Britain, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Spain and Sweden) between October 2010 and October 2011 and follow up continued until August 2013 when the last enrolled participant completed their week 96 visit.

Participants were HIV-1 positive, ART-naïve, 18 years or older, have HIV-1 RNA >1000 copies/ml and CD4≤500 cells/mm^3, HBs Ag negative and have no major IAS-USA resistance mutations. They were randomised 1:1 to either

- Raltegravir (RAL) 400mg BD and ritonavir-boosted darunavir (DRV/r) 800mg+100mg QD (RAL+DRV/r)

- Tenofovir/Emtricitabine (TDF/FTC) fixed daily combination QD and DRV/r 800mg+100mg QD (TDF/FTC+DRV/r) (control arm).

Randomisation was stratified by country and participation in a virology/immunology substudy.

The primary outcome was time from randomisation to virological or clinical failure, defined as the first occurrence of any of the following components of the composite primary endpoint:

Virological

1. Change of any component of the initial randomised regimen before week 32 because of documented insufficient virological response, defined as HIV RNA reduction <1 log_{10} copies/ml by week 18 or HIV RNA ≥400 copies/ml at week 24 (confirmed by a subsequent measurement)

2. Failure to achieve virological response by week 32 (defined as HIV RNA ≥50 copies/ml at week 32, confirmed by a subsequent measurement)
3. HIV RNA ≥50 copies/ml (confirmed by a subsequent measurement) at any time after week 32

Clinical

4. Death due to any cause
5. Any new or recurrent AIDS defining event, confirmed by the Endpoint Review Committee (ERC)
6. Any new serious non-AIDS defining event, confirmed by the ERC

Major secondary endpoints included safety, changes in CD4 and HIV RNA, time to discontinuation of randomised regimen for any reason and for treatment-limiting adverse events, time to virological failure, time to clinical failure, and genotypic resistance.

The primary analysis assessed whether the upper bound of the two-sided 95% confidence interval (CI) of the absolute difference in proportions of participants with virological or clinical failure between the two arms at week 96, estimated by Kaplan-Meier methods and adjusted for stratification factors, was at most 9%, which was the pre-defined non-inferiority margin. The two arms were compared as randomised according to the intention-to-treat principle.

Results

The trial enrolled 805 participants with 401allocated to RAL+DRV/r and 404 to TDF/FTC+DRV/r.

Baseline characteristics

Baseline characteristics were well balanced between the arms and overall 88% patients were male, median age was 38 years (IQR 31-46), and 82% of the participants were Caucasian. In terms of likely mode of HIV transmission, 71% were homosexual/bisexual, 25% heterosexual, 3% injecting drug users and 1% infected with HIV by blood/blood products. 38/805 (5%) patients had CDC Stage C disease and 12% had stage B. Median HIV-1 RNA at baseline was 4.77 $\log_{10}$ c/ml, with 32% participants having ≥100000 c/ml, and 6% with ≥500000 c/ml. Median CD4 count was 333 (IQR 253-399) cells/mm^3 and 16% had <200 cells/mm^3, and 4% were positive for HCV serology.

Follow up

Participants were followed up for a minimum of 96 weeks and the trial continued until the last patient enrolled had their week 96 visit in August 2013. 363 participants (91%) of the RAL+DRV/r arm completed 96 weeks (10 withdrew, 24 were lost to follow up and 4 died) compared to 382 participants (95%) in the FTC/TDF+DRV/r arm (7 withdrew, and 15 were lost to follow up). Median follow up in both arms was 123 weeks (Inter-quartile range (IQR) 112-133 weeks), with 368 (87%) in the RAL+DRV/r arm and 366 (91%) in the FTC/TDF+DRV/r completing follow up to the end of trial.

Treatment received

Overall 800/805 (99%) participants started antiretroviral treatment and of those known to have started, 98% started within 3 days of randomisation, and all but 2 participants started on their randomised regimen. This gave 398/401 starting their randomised regimen in the RAL+DRV/r arm and 400/404 in the TDF/FTC+DRV/r arm.

Primary endpoint analysis

The proportion of participants meeting the primary endpoint by 96 weeks (estimated by Kaplan Meier methods adjusting for stratification factors and) was 17.4% in the RAL+DRV/r arm compared to 13.7% in the TDF/FTC+DRV/r arm, a difference of 3.7% (95% CI -1.1, 8.6%) demonstrating non-inferiority according to the pre-specified margin of 9%.

In total during the entire follow-up until the end of the trial in August 2013, 137 participants met the primary endpoint, 76/401 (19%) in the RAL+DRV/r arm and 61/404 (15.3%) in the TDF/FTC+DRV/r arm. These are presented by component in Table 1 below.

Table 1: Primary endpoint broken down by components.

	RAL +DRV/r	TDF/FTC +DRV/r
Number of participants	401	404
Number that met primary endpoint	76 (19%)	61 (15.3%)
1. Regimen change for insufficient response		
a) <1 log10 c/ml HIV RNA reduction W18	1	0
b) HIV RNA ≥400 at W24	1	0
2. HIV RNA ≥50 c/ml at W32	27	28
3. HIV RNA ≥50 c/ml after W32	32	22
4. Death	3	1
5. AIDS event	5	3
6. SNAIDS event	7	7

Secondary endpoint analyses

The proportion of participants who met the virological failure components by 96 weeks, estimated with Kaplan Meier methods adjusting for stratification factors was 15.4% in the RAL+DRV/r arm compared to 11.8% in the TDF/FTC+DRV/r arm, which gave an adjusted difference of 3.6% (95% CI -0.8, 8.1%). The proportion of participants meeting the primary endpoint in the per protocol population (censoring follow-up at the first time when any component of the randomised regimen was discontinued for any reason for more than 30 days) was 15.3% in the RAL+DRV/r arm and 12.6% in the TDF/FTC + DRV/r arm which gave an adjusted difference of 2.7% (95% CI -1.8, 7.3%). Including treatment discontinuation for any reason to the primary endpoint as an outcome gave proportions meeting the outcome as 22.8% in the RAL+DRV/r arm and 19.5% in the TDF/FTC +DRV/r arm with a difference of 3.3% (95% CI -1.9, 8.4%).

Mean CD4 increases at 96 weeks were +268 cells/mm^3 (95% CI 250, 285) in the RAL+DRV/r arm compared to +266 cells/mm^3 (95% CI 249, 283) in the TDF/FTC+DRV/r arm. The percentage of participants with HIV RNA <50 c/ml out of those with HIV RNA tests at 96 weeks was 89% in the RAL+DRV/r arm compared to 93% in the TDF/FTC+DRV/r arm.

Subgroup analyses

Pre-specified subgroup analyses were performed with subgroups defined by baseline HIV RNA (<100,000 c/ml or ≥100,000 c/ml) and CD4 (<200 cells/mm^3 or ≥200 cells/mm^3). The proportion of participants meeting the primary endpoint at 96 weeks in the two arms was similar in those with baseline HIV RNA <100,000 with 7% in each arm and a difference of 0.2% (95% CI -3.9%, 3.5%). This was compared to a difference of 9.4% (95% CI -0.05%, 19.3%) in the subgroup of participants with HIV RNA ≥100,000 c/ml with the proportion meeting the endpoint in the RAL+DRV/r arm at 36% and 27% in the TDF/FTC+DRV/r arm and test for homogeneity gave p=0.09. Proportions meeting the endpoint were similar between the arms for those with CD ≥200 cells/mm^3 with 13.6% in the RAL+DRV/r arm and 12.2% in the TDF/FTC+DRV/r arm, with a difference of 1.4% (95%CI -3.4%, 6.3%). This was found to be significantly different (p=0.02) from those with CD<200 cells/mm^3 at baseline as the proportions meeting the endpoint in this group were 39% in the RAL+DRV/r arm and 21.3% in the TDF/FTC+DRV/r arm with a difference of 17.7% (95% CI 4.7-30.8%).

Resistance

There were 66 participants in the RAL+DRV/r arm who met protocol defined virological failure and 52 in the TDF/FTC +DRV/r arm. Out of these participants 33 in the RAL+DRV/r arm met the criteria in the protocol for genotype testing (a single HIV RNA > 500 copies at or after week 32) and 9 in the TDF/FTC+DRV/r arm. These participants along with 3 and 6 in the RAL+DRV/r arm and TDF/FTC+DRV/r arm respectively who just met the criteria were identified for testing. 28/36 of those in the RAL+DRV/r arm and 13/15 of the TDF/FTC+DRV/r arm had a genotype test done. 5 major resistance mutations were found, all the in the RAL+DRV/r arm and all N155H for Integrase. K65R for NRTI resistance was also found in the RAL+DRV/r arm although there is no evidence that the patient received an NRTI regimen prior to the test.

Safety

Adverse events

There were 89 serious adverse events (SAEs) (from 73 participants) in the RAL+DRV/r arm and 75 SAEs (from 61 participants) in the TDF/FTC+DRV/r arm. These included 5 deaths (4 in the RAL+DRV/r arm (Burkitt's lymphoma, DRESS syndrome, melanoma, suicide) and 1 in the TDF/FTC+DRV/r arm (overdose of morphine)), 12 life-threatening events (8 in the RAL+DRV/r arm (creatine phosphokinase (CK) increase (n=5), hepatitis, Hodgkin's lymphoma, pancreatitis) and 4 in the TDF/FTC+DRV/r arm (CK increase (n=2), myocardial infarction, gamma-glutamyltransferase increase)), 127 hospitalisation events (67 in the RAL+DRV/r arm and 60 in TDF/FTC+DRV/r arm) and 20 other medical condition events (10 per arm). The rate per 100 person years was 10.2 in the RAL+DRV/r arm and 8.3 in the TDF/FTC+DRV/r arm, p=0.17).

There were no significant differences in incidence rates for: grade 4 adverse events (AEs) (2.1 in RAL+DRV/r vs 1.0 in TDF/FTC+DRV/r p=0.09), grade 3 or 4 AEs (9.6 in RAL+DRV/r vs 7.4 in TDF/FTC+DRV/r p=0.16), grade 3 or 4 treatment-modifying AEs (1.0 in RAL+DRV/r vs 0.6 in TDF/FTC+DRV/r p=0.53) or any grade treatment-modifying AEs (4.2 in both arms p=0.82).

Laboratory results and toxicity

Mean changes from baseline in fasting lipids at 96 weeks were 0.9mmol/l for total cholesterol, 0.5mmol/l for LDL-cholesterol, 0.2mmol/l for HDL, -0.7 for triglycerides and 0.0 for total cholesterol/HDL-cholesterol ratio in the RAL+DRV/r arm. These were statistically significantly different from the changes in the TDF/FTC+DRV/r arm for total cholesterol 0.5mml/l (p<0.001), LDL-cholesterol 0.4mmol/l (p=0.02), HDL-cholesterol 0.1mmol/l (p<0.001) but no evidence of a difference for changes in triglycerides -0.8mmol/l (p=0.15) and total cholesterol/HDL-cholesterol ratio 0.0mmol/l (p=0.7). Mean change in creatinine

clearance (eGFR, Cockroft-Gault formula) from baseline at 96 weeks was +0.9 ml/min in the RAL+DRV/r arm compared to -3.8 ml/min in the TDF/FTC+DRV/r arm (p=0.02) but no grade 2-4 toxicities were found in either arm. The proportion of participants with grade 3 or 4 CK elevation was 6.2% in the RAL+DRV/r arm compared to 5.0% in the TDF/FTC+DRV/arm, and the proportion with ALT elevation was 3.0% vs 1.0% in the RAL+DRV/r arm and TDF/FTC+DRV/r arm respectively.

Summary

NEAT 001/ANRS 143 was a well-powered, randomised controlled trial run successfully across 15 countries and 78 sites.

The trial showed that twice daily RAL was well tolerated and had comparably efficacy to once daily TDF/FTC when co-administered with once daily DRV/r over 96 weeks in first-line ARV therapy. The proportions meeting the primary endpoint at 96 weeks, calculated using Kaplan Meier and adjusted for stratification factors, were 17.4% in the RAL+DRV/r arm compared to 13.7% in the TDF/FTC+DRV/r arm with a difference of 3.7% (95% CI -1.1, 8.6%). This demonstrated non-inferiority as the upper bound of 8.6% is below the 9% pre-defined limit. In a planned subgroup analysis of the outcome for participants with low CD4 at baseline (<200cells/mm^3) there is some evidence that RAL+DRV/r was inferior to TDF/FTC+DRV/r.

There was comparable safety between the 2 strategies with similar rates per 100 person years of SAEs, grade 3 or 4 AEs, and AEs leading to treatment modification. Treatment emergent resistance was seen in 5/28 in RAL+DRV/r arm compared to 0/13 in TDF/FTC+DRV/r arm in participants with available genotype at failure.

In conclusion RAL+DRV/r represent an alternative option to TDF/FTC+DRV/r for first-line therapy, particularly in participants with CD4 ≥200 cells/mm^3.

Acknowledgements

We would like to thank everyone who has contributed to the success of this study, including:

All the study participants,

Inserm-ANRS, Paris, France (trial sponsor),

*European Commission (*NEAT EC Project, contract nr LSHP-CT-2006-037570*),*

Trial Development Team: C. Allavena, A. Antinori, J. Arribas, B. Autran, A. Babiker, M. Boffito, G. Chêne, N. Dedes, A. Horban, R. Murri, D. Pillay, A. Pozniak, F. Raffi, L. Richert, S. Vella,

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All TSC, IDMC and ERC members

Merck, Janssen and Gilead for funding, drug supplies and support,

And the NEAT 001/ANRS 143 Study group.