ANRS 12313 Namsal

Un essai ouvert randomisé de phase III pour évaluer le dolutégravir par rapport à l'éfavirenz 400 mg, tous deux combinés au fumarate de ténofovir disoproxil + lamivudine pour la prise en charge initiale des adultes infectés par le VIH dans les contextes à ressources limitées

Promoteur	Inserm-ANRS
Début des inclusions	11 Juillet 2016
Statut des inclusions	Terminé
Fin d'étude	30 Juillet 2021
Nombre de participants	613 participants

Objectifs *Principal : Évaluer la non-infériorité du DTG par rapport à l'EFV 400, à la fois combiné avec le TDF/XTC et administré une fois par jour comme traitement de première ligne pour les adultes infectés par le VIH-1 naïfs d'antirétroviraux provenant de pays à ressources limitées*

Secondaires :

- Comparer la réponse immuno-virologique entre les deux associations médicamenteuses de première intention sur 24 et 48 semaines
- Comparer l'incidence des décès et des affections associées au VIH entre les deux combinaisons de médicaments de première ligne sur 48 semaines
- Comparer le taux d'émergence de la résistance aux médicaments entre les deux combinaisons de médicaments de première ligne sur 48 semaines
- Évaluer et comparer la durabilité, l'innocuité et la tolérabilité des deux combinaisons de médicaments de première ligne sur 48 semaines
- Pour évaluer l'observance du traitement sur 48 semaines
- Évaluer l'évolution de la qualité de vie liée à la santé dans les deux bras sur 48 semaines

Sommaire

A – Les résultats globaux de la recherche

Title	**ANRS 12313 – NAMSAL**
Complete title	**ANRS 12313 – NAMSAL** - **N**ew **A**ntiretroviral and **M**onitoring **S**trategies in HIV-infected **A**dults in **L**ow-Income Countries: A phase III randomized, open label, trial to evaluate Dolutegravir (DTG) versus Efavirenz 400 mg (EFV 400), both combined with Tenofovir Disoproxil Fumarate (TDF) + Emtricitabine or

	Lamivudine (XTC) for the initial management of HIV infected adults in resource-limited settings.
Number Registration	Number registration on ClinicalTrials.gov**: NCT02777229**
Ethics	**CNERSH** initial ethics clearance (Cameroonian Ethics Committee) 2015/11/658/CE/CNRSH/SP – **November 12th, 2015**
Regulatory	○ **DROS** Authorization (Cameroonian Regulatory Administration) D3064/L/MINSANTE/SG/DROS/TMC **N°631-09-16 – February 4th, 2016** ○ **CNIL** Number Registration (French Agency of Data Protection) **N°916455**
Sponsor and Co-funder	**INSERM – ANRS | MIE** : Agence nationale de recherches sur le SIDA et les hépatites virales | Maladies infectieuses émergentes, Agence autonome de l'Inserm (Institut national de la santé et de la recherche médicale), Paris, France. National Agency for Research on AIDS and Viral Hepatitis | Emerging infectious diseases, Autonomous Agency of Inserm (National Institute of Health and Medical Research), Paris, France.
Funder	**UNITAID**: Innovation in Global Health, Global Health Campus, Geneva, Switzerland, Geneva, Switzerland
Coordinating Investigators	○ **Prof. Eric Delaporte** – Coordinating Investigator – TransVIHMI: Université de Montpellier-IRD-INSERM, Montpellier, France ○ **Dr. Charles Kouanfack** – Co-coordinating Investigator – Site ANRS of Cameroon, Hôpital Central de Yaoundé, Yaoundé, Cameroon
Trial phase	Phase III
Countries	Cameroun, Yaoundé
Investigation sites	Central Hospital, Military Hospital, District of the Cité Verte Hospital
Study duration	From July 2016 to July 2021
Enrolment	11 July 2016 – First participant 18 July 2017 – Last participant
Follow-up	30 July 2021 – Last participant (for Namsal) 18 February 2022 – Last participant contacted for no-opposition to TRIO (sub-study to Namsal)
Study design	Randomized, open-label trial. Patients was be randomized 1:1 to one of the two treatment groups: ○ DTG + TDF/XTC ○ EFV 400 + TDF/XTC All randomized patients were followed for 192 weeks.
Study population	HIV-1 infected Age ≥ 18 years ARV naïve, including < 7 days of cumulative prior ARV therapy at any time prior to study entry Viral load ≥ 1000 copies/ml
Primary objective	To assess the non-inferiority of DTG versus EFV 400 both combined with TDF/XTC and given once a day as first-line treatment for antiretroviral-naive HIV-1 infected adults from resource-limited countries
Secondary objectives	○ To compare the immuno-virological response between the two first-line drug combinations over 24 and 48 weeks ○ To compare the incidence of death and HIV-associated conditions between the two first-line drug combinations over 48 weeks ○ To compare the rate of emergence of drug resistance between the two first-line drug combinations over 48 weeks ○ To evaluate and compare the durability, safety and tolerability of the two first-line drug combinations over 48 weeks ○ To assess adherence to treatment over 48 weeks ○ To assess the change in health-related quality of life in both arms over 48 weeks
Numbers of exposed subjects	○ Estimate of cumulative: **606 patients (303 per arm**) ○ Subjects analyzed: **613 patients (DTG: 313; EFV400: 303)**
Primary endpoint	Proportion of patients with VL<50 copies/mL at week 48 (FDA snapshot algorithm)

Secondary endpoints	○ Immuno-viral response ▪ % of patients with VL< 50 copies/mL at week 24 (FDA snapshot algorithm) ▪ % of patients with VL< 200 copies/mL at week 24 and week 48 (FDA snapshot algorithm) ▪ Time to virologic failure ▪ Changes in CD4-cell count from baseline to week 48 ○ Time to death or to disease progression ○ Resistance ▪ % of patients with at least one major drug resistance mutation ▪ % of patients with dual class resistance mutation ▪ % of patients with NNRTI, INI and NRTI resistance mutation ○ Toxicity ▪ Time to first toxicity failure ▪ Incidence of first grade 3 or 4 clinical adverse event ▪ Incidence of first grade 3 or 4 laboratory adverse event ▪ Incidence of adverse events (AE) and serious adverse event (SAE) ○ Tolerance • Time to treatment discontinuation and causes of treatment discontinuation • Change from baseline to week 48 in hemoglobin, creatinine, estimated glomerular filtration rate (Cockroft and MDRD study equations), AST, ALT, glucoses and lipids ○ Adherence to treatment and retention in care endpoints: ▪ % of patients defaulting clinic schedule; ▪ Mean adherence level overall ○ Mean change in quality-of-life questionnaires scores over 48 weeks
Inclusion criteria	○ HIV-1 infected ○ Age ≥ 18 years ○ ARV naïve, including 7 days of cumulative prior ARV therapy at any time prior to study entry ○ Viral load ≥ 1000 copies/ml ○ For women of childbearing potential: acceptance to use effective contraceptive methods ○ Provision of written informed consent
Non-inclusion criteria	○ Infection with HIV-1 group O, N, P ○ Infection or co-infection with HIV-2 ○ Absolute neutrophil count (ANC) < 500 cells/mm3 ○ Hemoglobin < 7.0 g/dL ○ Platelet count < 50,000 cells/mm3 ○ AST and/or ALT > 5 x ULN ○ Calculated creatinine clearance < 50 mL/min ○ Active opportunistic or severe disease not under adequate control ○ For women of childbearing age: Pregnancy/breastfeeding ○ History or presence of allergy and/or contraindications to the trial drugs or their components ○ Severe psychiatric illness ○ Severe hepatic failure NB: Patients co-infected with tuberculosis (TB), receiving a TB treatment and with stable clinical condition was not be excluded.
Statistical methods	The proportion of patients with viral load < 50 copies/mL at week 48 was be analyzed using the FDA Snapshot algorithm. Treatment difference adjusted for baseline viral load was be calculated and non-inferiority was be tested with a 10% margin using 95% confidence interval. A gatekeeping procedure was be used to sequentially test the primary endpoint for non-inferiority and superiority at the two-sided level 0.05 if non-inferiority is demonstrated. All other endpoints were tested for superiority.

Sub-studies	○ Clinical Trial Extension until 96 weeks ▪ To assess the non-inferiority of DTG versus EFV 400 both combined with TDF/XTC and given once a day as first-line treatment for antiretroviral-naive HIV-1 infected adults from resource-limited countries ▪ To compare the immuno-virological response between the two first-line drug combinations over 96 weeks ▪ To compare the incidence of death and HIV-associated conditions between the two first-line drug combinations over 96 weeks ▪ To compare the rate of emergence of drug resistance between the two first-line drug combinations over 96 weeks ▪ To evaluate and compare the durability, safety and tolerability of the two first-line drug combinations over 96 weeks ▪ To assess adherence to treatment over 96 weeks ▪ To assess the change in health-related quality of life in both arms over 96 weeks ○ Post-trial follow-up as prospective cohort follow-up until 192 weeks and TRIO: Long-term evaluation of risk-benefit for Dolutegravir in three randomized trials ▪ To assess the non-inferiority of DTG versus EFV 400 both combined with TDF/XTC and given once a day as first-line treatment for antiretroviral-naive HIV-1 infected adults from resource-limited countries ▪ To compare the immuno-virological response between the two first-line drug combinations over 192 weeks ▪ To compare the incidence of death and HIV-associated conditions between the two first-line drug combinations over 192 weeks ▪ To compare the rate of emergence of drug resistance between the two first-line drug combinations over 192 weeks ▪ To evaluate and compare the durability, safety and tolerability of the two first-line drug combinations over 192 weeks ▪ To assess adherence to treatment over 192 weeks ▪ To assess the change in health-related quality of life in both arms over 192 weeks
Knowledge generated	○ Dolutegravir-Based or Low-Dose Efavirenz-Based Regimen for the Treatment of HIV-1, NAMSAL ANRS 12313 Study Group, Kouanfack C., Mpoudi-Etame M., Omgba Bassega P., Eymard-Duvernay S., Leroy S., Boyer S., Peeters M., Calmy A., et Delaporte E. N. Engl. J. Med., vol. 381, no 9, p. 816 826, 29 2019. doi: 10.1056/NEJMoa1904340. ○ Dolutegravir-based and low-dose efavirenz-based regimen for the initial treatment of HIV-1 infection (NAMSAL): week 96 results from a two-group, multicentre, randomised, open label, phase 3 non-inferiority trial in Cameroon, Calmy A., Tovar Sanchez T., Kouanfack C., Mpoudi-Etame M., Leroy S., Perrineau S., Lantche Wandji M., Tetsa Tata D., Omgba Bassega P., Abong Bwenda T., Varloteaux M., Tongo M., Mpoudi-Ngolé E., Montoyo A., Mercier N., LeMoing V., Peeters M., Reynes J., Delaporte E., et New Antiretroviral and Monitoring Strategies in HIV-infected Adults in Low-Income Countries (NAMSAL) ANRS 12313 Study Group, Lancet HIV, vol. 7, no 10, p. e677 e687, oct. 2020. doi: 10.1016/S2352-3018(20)30238-1. ○ Cost-Utility Analysis of a Dolutegravir-Based Versus Low-Dose Efavirenz-Based Regimen for the Initial Treatment of HIV-Infected Patients in Cameroon (NAMSAL ANRS 12313 Bousmah M.-A.-Q., Nishimwe M. L., Tovar-Sanchez T., Lantche Wandji M., Mpoudi-Etame M., Maradan G., Omgba Bassega P., Varloteaux M., Montoyo A., Kouanfack C., Delaporte E., Boyer S., et New Antiretroviral and Monitoring Strategies in HIV-infected Adults in Low-Income Countries (NAMSAL) ANRS 12313 Study Group, Trial), Pharmacoeconomics, déc. 2020. doi: 10.1007/s40273-020-00987-3. ○ 16 Communications to international conferences (Oral presentations and posters)

Conclusions

Efficacy conclusions

The primary endpoint was the proportion of patients with HIV viral load (VL) < 50 copies/mL at week 48 (window 42 – 54) using the FDA snapshot algorithm. HIV viral load (VL) < 50 copies/mL was also analysed at weeks 96 and 192.

In ITT analysis, Dolutegravir-based regimen was noninferior to an EFV400-based reference regimen with regard to viral suppression at week 48 (difference between treatment groups was 5.5 percentage points; 95% confidence interval [CI] was −1.6 to 12.7; thus, meeting the criterion for noninferiority [P<0.001] but not for superiority [P = 0.13]). Dolutegravir-based regimen was associated with a low risk of acquiring drug-resistance mutations, compared to a low-dose Efavirenz–based regimen. Viral suppression was impaired in participants with a high baseline viral load (VL >100 000 copies/mL), few participants expected quickly viral suppression.

At week 96, the noninferiority was also demonstrated confirming Dolutegravir robustness in this high-risk population, as the risk of acquiring new resistance was lower, as well as the impaired in patients starting ART with a high baseline viral load and that this effect was not due to a delayed viral suppression time.

After 192 weeks of follow up, the durability of the Dolutegravir efficacy was demonstrated and was more important in participants with a high baseline viral load unlike EFV400-based regime, any acquiring new resistance was associated to Dolutegravir-based regimen.

Safety Conclusions

The trial was monitoring reinforced with the viral load and the close monitoring of pregnant women due to WHO DOLUTEGRAVIR signal concerning the risk of neural tube malformations on May 18th 2018 and until the end of the trial on July 31st 2021.

Letters to investigators to inform them about the signal and about the new contraindication of EFAVIRENZ were sent. Convocation for all females in age of childbearing treated by DTG to explain the risk of malformations and the importance of effective contraception was performed. In case of pregnancy EFV and DTG concentration levels were assessed at each study visit to monitor pharmacokinetic impact of pregnancy. Pregnant women were monitored with regular visits with the gynecologist and regular ultrasound scanners (up to 4 during the pregnancy) realized by a trained radiologist. The risk of neural tube defect under DTG treatment for which safety measures were implemented was kept but a significant decreased of this risk was noted: 0.30 % compared to 0.9% initially declared.

The trial benefice/risk ratio wasn't modified at the time of this safety report. Inclusions and follow-up of participants in the trial has been completed.

Overall Conclusions

This was an open-label, multicenter, randomized, phase 3 non inferiority trial conducted in Cameroon over 48 weeks, extended until 192 weeks, with the objective of evaluating the efficacy and safety of new therapeutic combinations for the treatment of adults infected with HIV-1 in real conditions of low-income countries.

The regimens compared were the Dolutegravir 50 mg, an integrase inhibitor, with interesting properties in terms of efficiency and especially resistance versus the low dose Efavirenz, a reduction in dosage of preferential treatment in order to reduce the side effects of this molecule without loss of efficacy.

A total of 613 participants were enrolled and followed-up during four years. Results of the main endpoint (48 weeks) demonstrated the noninferiority of Dolutegravir versus low dose of Efavirenz. Superiority was not demonstrated. The outcomes supports the WHO recommendations to initiate ART with a Dolutegravir-based regimen, and with low-dose-Efavirenz-based regimen as an alternative.

Viral suppression was impaired in participants with a high baseline viral load but was reached significantly faster in the Dolutegravir group. Dolutegravir was associated with a low risk of acquiring drug-resistance mutations and with a significantly weight gain in women.

Those outcomes were confirmed at the 96 weeks. At 192 weeks of follow up, outcomes showed the durability of the efficacy and safety of both regimes, suggesting the reinforcement of the cardiovascular and metabolic monitoring of the adults infected with HIV-1 treated with Dolutegravir or low-dose-Efavirenz.

B – Réutilisation secondaire des données et des échantillons

Cette section concerne les participants ayant été inclus dans la recherche et ayant accepté la réutilisation de leurs données et/ou de leurs échantillons. Via son site internet et le présent document, le promoteur de la recherche vous informe des projets liés à la réutilisation secondaire de vos données et/ou de vos échantillons.

B1. Pour les projets non initiés ou en cours listés ci-dessous uniquement, vous avez la possibilité de vous opposer à l'utilisation secondaire de vos échantillons et/ou données. Pour cela, vous devez écrire un e-mail à l'adresse suivante dpo@inserm.fr en renseignant le nom de l'essai et le titre du projet pour lequel vous refusez la réutilisation de vos données et/ou échantillons dans la limite d'une semaine avant la date prévisionnelle de réalisation du projet.

Projets non initiés : *Non applicable*

Projets en cours : *Non applicable*

B2. Pour les projets terminés, il n'est pas possible de s'y opposer.

Projets terminés

Titre du projet	TRIO évaluation à long terme du rapport bénéfice / risque du Dolutégravir dans trois essais randomisés « NAMSAL, ADVANCE, DOLPHIN-2 ».
Résumé du projet	Objectif principal : Évaluer l'efficacité, la tolérance et la sécurité du DTG et d'autres nouveaux ARV comme l'EFV 400 en combinaison avec TDF/XTC en traitements de 1ère ligne pendant le suivi post-essai chez l'adulte naïf de traitement antirétroviral (ARV) infecté par le VIH-1 vivant dans des pays à ressources limitées Objectifs secondaires : • Comparer la réponse immuno-virologique au cours du suivi post-essai • Comparer la morbidité, la mortalité et la progression de la maladie pendant le suivi post-essai • Comparer le risque d'apparition de résistances aux ARV pendant le suivi post-essai • Évaluer et comparer la durabilité, la sécurité d'utilisation et les risques de toxicité des deux 1ères lignes pendant le suivi post-essai • Évaluer l'observance au traitement pendant le suivi post-essai • Évaluer les changements de qualité de vie pendant le suivi post-essai • Évaluer des marqueurs cardio-vasculaires et métaboliques pendant le suivi post-essai • Évaluer qualitativement la procédure fin d'essai
Dates de début de réalisation du projet	Démarrage pendant le suivi post-essai des participants de Namsal
Destinataires des données en France	Inserm-ANRS
Destinataire des données à l'étranger	Les données cliniques issues des participants de NAMSAL seront poolées et partagée avec l'Université de Liverpool qui coordonne l'étude TRIO.
Identité et responsable du traitement	Inserm-ANRS
Catégorie de données	Étude poolée, des statistiques descriptives simples seront utilisées à la fois pour l'efficacité et l'innocuité à S144 et S192, développant les résultats à long terme des deux paramètres du critère de jugement principal évalué à S48 (non-infériorité et mage de 10%, algorithme snapshot). Statistiques descriptives simples pour l'étude des marqueurs cardio-vasculaires et métaboliques chez une sub-cohorte d'environ 5% de participants NAMSAL en cours de suivi post-essai.
Résultats globaux du projet	Analyses des résultats en cours