ansm
Agence nationale de sécurité du médicament et des produits de santé

Summary of Final Report	SFR

1	Sponsor: Inserm – ANRS: French National Institute of Health and Medical Research – French National Agency for Research on AIDS and Viral Hepatitis	
2	Name of experimental drug(s): Celsentri®	
3	Name of active ingredient(s): maraviroc (MVC)	
4	Full title of study: Phase III clinical trial of the efficacy of maraviroc, in combination with standard antiretroviral treatments in HIV-infected patients diagnosed at a late stage with an AIDS-defining infection and/or a CD4 count < 200/mm^3 (ANRS 146 OPTIMAL)	
5	Investigator(s)[1]: Coordinating investigator: Prof. Yves LEVY Joint coordinating investigator: Prof. Jean-Daniel LELIEVRE Coordinating investigator in Spain: Dr Frederico PULIDO Coordinating investigator in Italy: Dr Giuseppe TAMBUSSI Number of principal investigators in the trial: 50	
6	Study locations and centres[2]: 25 centres in Metropolitan France; 20 in Spain; 5 in Italy	
7	Publications[3]: Oral presentation at IAS 2017 – ANRS 146 – GeSIDA 7211 OPTIMAL phase III trial: maraviroc plus cART in advanced HIV1-infected individuals – Y. Levy, J.-D. Lelièvre, L. Assoumou, E. Aznar, F. Pulido, G. Tambussi, M. Crespo, A. Meybeck, J.-M. Molina, F. Cardon, C. Delaugerre, R. Lancar, L. Béniguel, D. Costagliola, on behalf of the ANRS 146 – GeSIDA 7211 study group/	
8 8.1 8.2	**Duration of study:** - date of first enrolment: 25/10/11 - date of end of participation of the last individual enrolled in the study: 31/03/16	9. Clinical testing phase: Phase III
10	**Primary and secondary objectives** **Primary objective:** To demonstrate the clinical benefit of the adjunction of MVC to a combination of antiretroviral therapy in naïve and late diagnosed HIV-1 infected patients. A late diagnosis during the natural course of HIV-1 infection is defined by an AIDS-Defining-Events (ADE) and/or an absolute number of T CD4+ lymphocytes ≤ 200/mm3. The clinical benefit is the reduction of the occurrence of a composite outcome consisting of new ADE, Non B or C events, serious non-AIDS events, IRIS and death. **Secondary objective:** 1. To compare MVC to PBO arm for each component of the primary composite end point and other major outcomes 2. Impact of CCR5 tropism on primary and major secondary end points 3. Immunological evaluation 4. Virological evaluation 5. Pharmacology substudy 6. Safety of the strategy 7. Cost-effectiveness analysis	
11	**Methods:** This is an European, multicentre, randomized, versus placebo, double-blind, phase III trial, conducted in France, Spain and Italy, comparing two strategies to treat patients with late diagnosis of HIV. **Group 1:** Patients will receive cART optimized regimen according to the recommended regimen as first line of treatment in most commonly used guidelines, without MVC, but with PBO orally twice a day. The number of pills will be adapted accordingly to the combined cART regimen. **Group 2:** Patients will receive cART optimized regimen according to the recommended regimen as first line of treatment in most commonly used guidelines with MVC at the following dose: 150 mg orally twice a day for patients receiving a PI Ritonavir-boosted regimen (except Fosamprenavir), 300 mg orally twice a day for patients receiving a Fosamprenavir Ritonavir-boosted regimen or 600 mg orally twice a day for patients receiving EFV-based regimen.	
12 12.1 12.2	**Number of individuals who volunteered for the study:** - planned number of individuals: 408 - number of individuals analysed: 409 (207 in the placebo group and 202 in the maraviroc group)	
13	**Eligibility criteria** Patients will be included if they fulfill the following criteria.	

[1] If the study is multicentre, indicate the name(s) of the coordinating investigator(s) and the total number of investigators.
[2] State the number of study location(s) and centre(s) (if different from the number of locations).
[3] Specify in the following order: names of authors, title of publication, name of journal, year, volume number and page numbers.

	Inclusion criteria • Confirmed HIV-1 infection (positive ELISA and Western Blot tests or positive ELISA and Immunoblot or positive ELISA and positive viral load); • Adult patients (age >= 18 years); • CD4+ T lymphocytes <= 200/mm3 and/or previous AIDS-defining-illness at W-2 or W-4; • Patient naïve from any antiretroviral; • In women, use of a contraceptive method, and lack of actual pregnancy; • Patients with a coverage from social health; • After informed consent. **Exclusion criteria** • Current pregnancy, lack of contraceptive method, breast-feeding; • Current active tuberculosis (either suspected, diagnosed); • Ongoing malignancies except cutaneous Kaposi's sarcoma. Patients with a previous cancer considered as cured for at least 6 months could be included in the study; • Current or previous severe cardiac failure[a], chronic respiratory disease[b], renal[c] or liver insufficiency; any life-threatening organ failure; • Cognitive impairment, psychiatric disorders, severe depressive affects, inadapted behavior; • Use of cytostatic drugs, immunosuppressive agents, steroids. Treatment with steroids can be authorized if they are given for less than two months as adjuvant treatment for opportunistic infections; • PMN < 750/mm3, platelets < 50,000/mm3, haemoglobin < 10 g/dL; ASAT, ALAT or bilirubin > 2.5 ULN; lipase > 2 ULN, serum creatinine > 1.5 ULN; proteinuria > 1g/L; INR abnormal (Note: normal INR values are included between 0.8 and 1.3)[d]; • Current or previous, during the 3 last months, use of immunomodulatory agents (G-CSF, IL-2, GM-CSF, interferons, pentoxifylline); • Hypersensitivity to peanut and /or soy products. a: if a severe cardiac failure is suspected, an echocardiography should be performed (ejection fraction < 45% should not be included in the trial). b: Patients having a Chronic Obstructive Pulmonary Disease can not be included in the trial. c: Renal insufficiency defined by creatinine clearance < 60/mL. d: Patients taking anticoagulant can be included in the trial.
14	Experimental drug(s) studied[5] (name, dose, route of administration and lot numbers): • Maraviroc (Celsentri®): 150 mg x 2/d, i.e. 1 tablet twice a day by mouth. Lot numbers: 09-074233 (exp; 31/01/2014), 11-004705 (exp: 31/08/2016). • Maraviroc (Celsentri®): 300 mg x 2/d, i.e. 1 tablet twice a day by mouth, or 600 mg x 4/d, i.e. 2 tablets twice a day by mouth. Lot numbers: 08-070686 (exp: 31/08/2013), 10-083001 (exp: 31/05/2015), 11-004704 (exp: 31/10/2016), 13-110726 (exp: 30/09/2018). • Placebo: 150 mg x 2/d, i.e. 1 tablet twice a day by mouth. Lot numbers: 08-064059 (exp: 31/10/2012), 11-004265 (exp: 31/03/2016), 12-000277 (exp: 31/01/2017). • Placebo: 300 mg x 2/d, i.e. 1 tablet twice a day by mouth, or 600 mg x 4/d, i.e. 2 tablets twice a day by mouth. Lot numbers: 07-055902 (exp: 31/03/2012), 11-005868 (exp: 30/04/2016), 11-005556 (exp: 30/04/2016), 11-005868 (exp: 30/04/2016).
15	Duration of treatment[6]: 72 weeks
16	Reference experimental drug(s)[7] (name, dose, route of administration and lot numbers), where applicable: NA
17 17.1	**Evaluation criteria** **<u>Efficacy endpoint</u>** The main criteria is to assess a reduction in a new clinical event. The latter is a composite criteria encompassing the occurrence of either: o <u>New ADE</u> (opportunistic events consistent with the 1993 CDC expanded surveillance definition plus additional events associated with immunosuppression in the patient population targeted for enrolment) o <u>Non B or C</u>: ▪ Aspergillosis, invasive, ▪ Bartonellosis, includes bacillary angiomatosis and peliosis hepatis, ▪ Chagas disease (American trypanosomiasis) of the central nervous system (CNS), ▪ Leishmaniasis, visceral (kala-azar), ▪ Lymphoma, Hodgkin's, ▪ Lymphoma, non-Hodgkin's, other cell type,

[5] Repeat the section if the study involves more than one experimental drug.
[6] Specify, where relevant, for each experimental drug, the maximum period of treatment for the individual who volunteered for the study.
[7] Repeat the section if the study involves more than one reference experimental drug.

- Microsporidiosis, chronic intestinal (> 1 month's duration),
- Nocardiosis,
- Penicillium marneffei, extrapulmonary,
- Pneumocystis jiroveci, extrapulmonary,
- Rhodococcus equi disease,
- Severe infections: defined by sepsis with bacteremia requiring overnight hospitalisation, or pneumonia requiring overnight hospitalisation.

o Serious non-AIDS events :
- Cardiovascular disease (CVD): myocardial infarction, stroke, coronary revascularization,
- Chronic end stage renal disease (ESRD),
- Liver failure,
- Non-AIDS-defining cancers except basal and squamous cell skin cancers,
- IRIS,

o All causes of mortality (related or not to AIDS)

o Grade 4 events

17.2 **Safety endpoint:**

o Virological criteria:

Percentage of patients with a plasma HIV-1 RNA < 400 copies/mL and <50 copies/mL at W0, W4, W8, W12, W24, W36, W48, W60, W72,

Virological failure is defined by a plasma viral load> 400 copies / mL after the S24 visit confirmed on a second sample taken 15 days later

Resistance testing performed in patients with detectable plasma HIV-1 RNA during the study (on the second sample with HIV-1 RNA > 400 copies/ml after week 24),

o Immunological Criteria:

Absolute number of T $CD4^+$ lymphocytes at W4, W8, W12, W24, W36, W48, W60, W72,

Percentage of patients with > 200 $CD4^+$ T lymphocytes at W4, W8, W12, W24, W36, W48, W60, W72

o Clinical event:

Frequency of serious adverse events and serious adverse events (SAEs) related to trial treatment

Frequency of study withdrawn or treatment withdrawn

17.3 **Other:**

o Virological endpoint:

- Tropism testing performed by Tropisme Test Toulouse at baseline (W0) on plasma HIV-1 RNA and in patients with detectable plasma HIV-1 RNA during the study (on the first sample with HIV-1 RNA > 1000 copies/ml after week 24),
- **Virological study (for 100 patients enrolled in France):**

  - HIV-1 DNA in PBMC (peripheral blood mononuclear cells) at W0, W24, W72 (whole blood samples),

  - Tropism testing by genotypic analysis of the V3 loop to investigate (1) the correlation with virology response at W0 on plasma HIV RNA, and (2) the tropism evolution in patients with undetectable viral load at W0, W24, W72 on HIV-1 DNA.
- **Seminal compartment sub-study (for 20 patients in each group):**

  - HIV viral load will be determined at W0, W24,

o Immunological endpoint:

- Phenotypic analysis of $CD4^+$ T lymphocytes, $CD8^+$ T lymphocytes (naïve, central memory cells, and cytotoxic cells) and evolution of markers of immune activation (expression of HLA-DR and CD38 on CD4 and CD8 T cells) at W0, W8, W24, W60 (substudy),
- Seric markers of immune activation (inflammation): Hs-CRP, fibrinogen, IL-6, IL-1-beta, IFN-alpha, d-dimers, SAA and sCD14 at W0, W8, W24, W60 (substudy),
- Density of CCR5 and CXCR4 expression at W0, W8, W24 (substudy),
- Expression of homing receptors on CD4 T lymphocytes (% of cells $CD4^+a4b7^+CCR9^+$) at W0, W8, W24 (substudy),
- Evaluation of HIV-1 and recall-antigen specific immune responses by Intra-Cellular Staining (ICS) at W0, W24 (substudy).

o Pharmacokinetic (PK) endpoints:

PK analysis:

- Determinations of MVC trough plasma concentration of MVC (Cmin; 12 ± 2 hours after the last drug intake) at W4 and W24 in 50 patients randomized in Group 2* in France using UPLC-MS/MS,

	• Distributions of MVC Cmin by dosing regimen and according to the associated PI Ritonavir-boosted or EFV, • Between and within patients variability of MVC Cmin, ▪ Substudy in 25 patients in each group to calculate the: • Steady-state plasma area under curve (AUC) of MVC at W4 based on the determination of 0h, 1h, 3h, 6h, 8h, 12h post dose concentrations of MVC, • Average of MVC concentration at W4 (Cave = AUC/12h), • Free fraction AUC (unbound to plasma protein) of MVC at W4, ▪ Determination of MVC Cmin for study discontinuations (before the end point) (adverse events, virological failure, etc.), ▪ Determination of MVC seminal at W24 in a subgroup of 20 patients from Group 2, **Pharmacokinetic-Pharmacodynamic (PK-PD) relationship:** ▪ Relationship between MVC Cmin at W4 and W24 and virological response at W8, W12, W36, W48, W60 and W72 in 50 patients randomized in Group 2* in France, ▪ Percentage of patients with a MVC Cmin ≥ 50 ng/mL by dosing group in 50 patients randomized in Group 2 in France, ▪ Relationship between MVC Cave (free and total) at W4 and virological response at W24, W36, W48, W60 and W72 in a subgroup of 25 patients, ▪ Relationship between MVC Cmin (free and total) at W4 and virological response at W24, W36, W48, W60 and W72 in a subgroup of 25 patients, ▪ Analysis of MVC Cmin in patients demonstrating changes of their tropism results according to the genotype or/and the Tropisme Test Toulouse, ▪ Relationship between MVC Cmin at W24 in seminal plasma and virological response in seminal and blood plasma at W0 and W24 in a subgroup of patients. * Samples will be stored for patients from Group 1 & 2 and retrospectively analyzed for Group 2 only. ▪ Drug-drug interactions by determination of associated PI Ritonavir-boosted or EFV plasma concentrations in 50 patients randomized in Group 2 in France using UPLC-MS/MS, **Safety of the strategy,** **Cost-effectiveness study**
18	**Statistical analyses:** The primary endpoint was analysed on an intention to treat (ITT) basis. All randomly assigned participants were included in the ITT population, except those who never received the study treatment. The number of participants enrolled and the flow chart for the study are shown in Figure 1. The characteristics of the participants at enrolment are described overall and by treatment arm. The primary endpoint is the occurrence of severe morbidity (new AIDS event, other HIV-related infections, serious events unrelated to HIV, IRIS and death). The primary endpoint and its components were compared between the 2 groups using the Kaplan-Meier estimator and the Cox proportional hazards model. In a post hoc analysis, using a Poisson regression model, we evaluated the treatment effect according to the study period (0-24 versus 24-72 weeks). A subgroup analysis was also performed. The variables studied were as follows: the family of the third antiretroviral agent (protease inhibitor, NNRTI or INI), the country of enrolment (France, Spain or Italy), participant age (<40 versus ≥40 years), sex, geographic origin (Sub-Saharan Africa or other), CD4 count at enrolment (≥50 versus <50/mm^3), viral load at enrolment (<100,000, 100,000-500,000 or >500,000 copies/mL), tobacco use (no versus yes), presence of R5 viral tropism (no versus yes), history of AIDS event (yes versus no) and CD4/CD8 count ratio at enrolment (<0.10; 0.10-0.30; >0.30) The proportion of participants with a viral load <50 copies/mL at each follow-up point was estimated using the snapshot approach. Fisher's exact test was to compare the two groups at W48 and W72. The analysis was also stratified by initial viral load (<100,000, 100,000-500,000 or >500,000 copies/mL). In the snapshot approach, failure was defined by a viral load >50 copies/mL at the assessment visit or by withdrawal from the trial or trial treatment before the visit, regardless of the reason. The evolution of CD4 T lymphocyte count over time was compared between the 2 groups using a mixed linear model with random effects. The proportion of participants with at least one serious adverse event and the proportion of those who withdrew from the trial or trial treatment was compared between the 2 groups using Fisher's exact test. The evolution of the immunological parameters, the total and free residual concentration of drugs (mean of all measurements for each participant) and the area under the curve for total and free concentration of the drugs were compared between the 2 groups using the nonparametric Mann-Whitney-Wilcoxon test. Generally speaking, quantitative variables are described by their medians, minima and maxima. For qualitative variables, numbers and percentages per category or mode are given. Statistical tests are two-sided with a 5% risk level. For analysis of the immunological substudy, the significance threshold was

set at 0.01 to allow for the multiplicity of tests. The analysis was performed using SAS® statistical analysis software, version 9.4, and STATA SE, version 13.

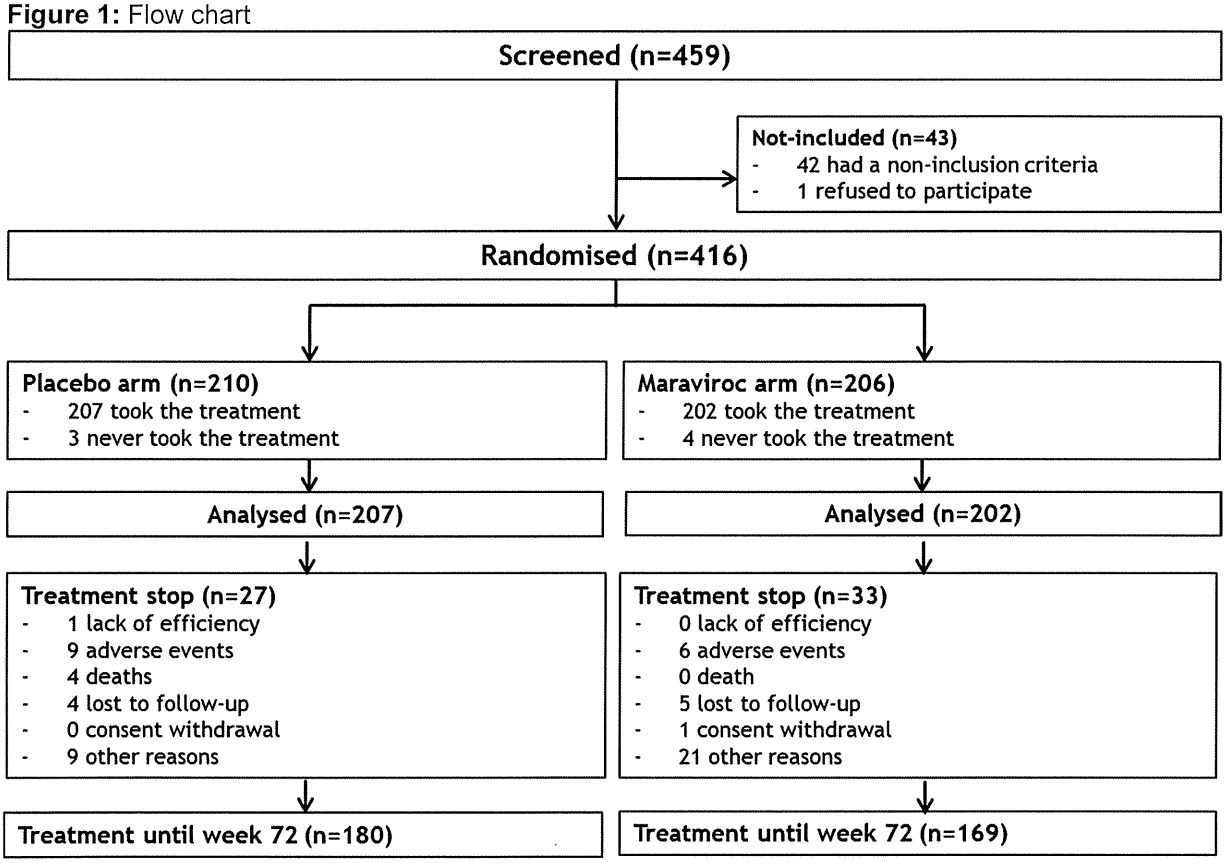
19 **Summary – conclusions from the study**

- Distribution of patients

Between October 2011 and November 2014, 459 patients from 50 centres in 3 European countries (France, Spain and Italy) were preselected to participate in the study. 43 were ineligible or refused to participate in the trial after signing consent, and 416 were randomly assigned, including 7 who never took the trial treatment. Ultimately, 409 patients received at least one dose of the experimental treatment, and were included in the ITT population: 207 in the Placebo group and 202 in the Maraviroc group.

During follow-up, 60 participants stopped taking the study treatment: 27 in the Placebo group and 33 in the Maraviroc group.

Figure 1: Flow chart



- Patient characteristics at enrolment

Characteristics of the 409 participants are shown in Table 1 below. They were mainly men (85%), half were men who had sex with men, the median age was 42 years (range: (21-74) and 15% were from Sub-Saharan Africa. At enrolment, 9.5% of participants had been diagnosed HIV positive for <15 days, 40.9% for 15 days to 1 month, and 49.6% for >1month. The median plasma HIV viral load at enrolment was 5.4 $\log_{10}$ copies/mL) (1.9-6.7), the CD4 T lymphocyte count was 80 cells/µL (0-308), and 42% of participants had an AIDS-defining event.

Table 1: Patient characteristics at enrolment

Variable		Placebo (n=207)	Maraviroc (n=202)	Total (n=409)
Age, year	Median [Min, Max]	42 [21-74]	42 [21-70]	42 [21-74]
Sex	Male	173 (83.6%)	174 (86.1%)	347 (84.8%)
Origin				
	Caucasian	156 (75.4%)	143 (70.8%)	299 (73.1%)
	Sub-Saharan Africa	34 (16.4%)	27 (13.3%)	61 (14.9%)
	Asia	3 (1.4%)	3 (1.5%)	6 (1.5%)
	Other	14 (6.8%)	29 (14.4%)	43 (10.5%)
Transmission group				
	Homosexual	102 (49.3%)	104 (51.5%)	206 (50.3%)
	Heterosexual	90 (43.5%)	81 (40.1%)	171 (41.8%)

	Intravenous drug user	3 (1.4 %)	5 (2.5%)	8 (2.0%)
	Other	12 (5.8 %)	12 (5.9%)	24 (5.9%)
Time from diagnosis of HIV infection to enrolment				
	<15 days	21 (10.3%)	17 (8.6%)	38 (9.5%)
	>15 days to 1 month	86 (42.4%)	78 (39.4%)	164 (40.9%)
	>1 month	96 (47.3%)	103 (52.0%)	199 (49.6%)
Viral load at enrolment (copies/mL)	Median [Min, Max]	279,206 [2,850-4,810,000]	230,602 [78-5,363,308]	244,964 [78-5,363,308]
Viral load at screening				
	$<10^5$ copies/mL	54 (26.1%)	54 (27.0%)	108 (26.5%)
	10^5-$5x10^5$ copies/mL	88 (42.5%)	98 (49.0%)	186 (45.7%)
	$>5x10^5$ copies/mL	65 (31.4%)	48 (24.0%)	113 (27.8%)
R5 tropism at enrolment				
	No	59 (29.1%)	75 (37.9%)	134 (33.4%)
	Yes	144 (70.9%)	123 (62.1%)	267 (66.6%)
CD4 cells/µL at enrolment*	Median [Min, Max]	85 [0-308]	77 [3-236]	80 [0-308]
CD4 cells/µL at screening				
	<50 /µL	82 (39.6%)	78 (38.6%)	160 (39.1%)
	50 /µL-200 /µL	121 (58.5%)	116 (57.4%)	237 (58.0%)
	>200 /µL	4 (1.9%)	8 (4.0%)	12 (2.9%)
CD4/CD8 ratio at enrolment				
	Median [Min, Max]	0.12 [0-0.84]	0.11 [0.01-0.56]	0.11 [0-0.84]
	<0.10	87 (42.2%)	90 (45.0%)	177 (43.6%)
	0.10-0.30	99 (48.1%)	91 (45.5%)	190 (46.8%)
	>0.30	20 (9.7%)	19 (9.5 %)	39 (9.6%)
AIDS-defining event at screening		83 (40.1%)	87 (43.1%)	170 (41.6%)
Time from screening to initiation of treatment (days)	Median [Min, Max]	8 [2-82]	8 [2-40]	8 [2-82]

19.1

- Results of efficacy assessment:

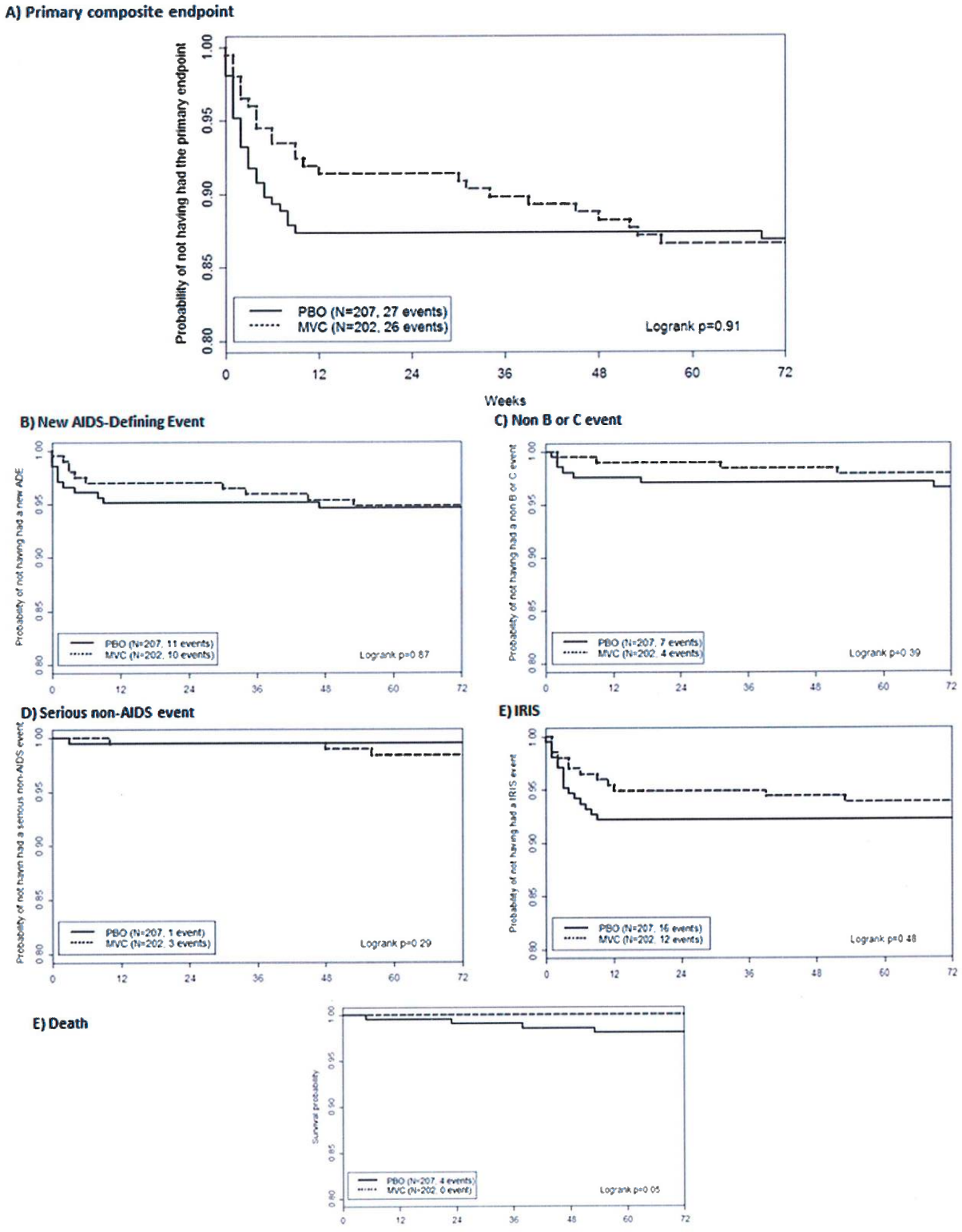
During the 72 weeks of follow-up, a total of 74 events were reported in 53 participants: 42 events in 27 participants in the Placebo group, and 32 events in 26 participants in the Maraviroc group. The incidence of the first event was estimated at 11.2 per 11 person-years in the Placebo group versus 11.1 per 100 person-years in the Maraviroc group, with a hazard ratio of 0.97 (95% confidence interval [95% CI], 0.57-1.67, P=0.91). (Figure 2A)

The hazard ratios for each component of the primary endpoint were:

- 0.94 (95% CI: 0.40-2.21, P=0.89) for new AIDS events,
- 0.59 (95% CI: 0.17-2.01, P=0.40) for serious non-B/C events,
- 3.15 (95% CI: 0.33-30.3, P=0.32) for serious events unrelated to AIDS,
- 0.76 (95% CI: 0.36-1.62, P=0.48) for IRIS.

Four participants died in the placebo group, and none died in the maraviroc group (Logrank, P=0,05) (Figure 2B, C, D, E, F).

Figure 2: Primary criterion and secondary criteria of efficacy

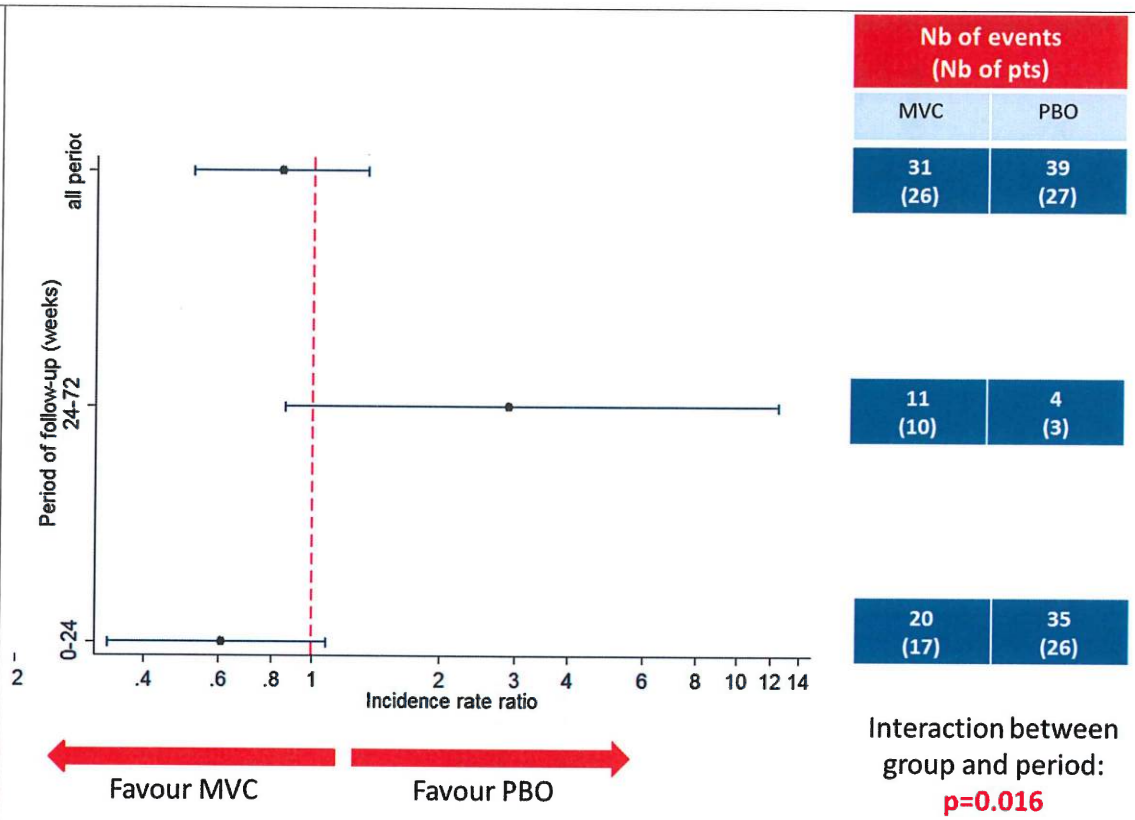


A post hoc Poisson regression analysis showed that the incidence rate ratio (IRR) of the 2 groups differed significantly between the 0-24 week and 24-72 week periods, with IRRs of 0.61 (95% CI: 0.33-1.08) for the 0-24 week period and 2.90 (95% CI: 0.86-12.49) for the 24-72 week period (p=0.016) (Figure 3).

Subgroup analysis did not show any significant difference in treatment effect in the different subgroups evaluated, except for age, with a slightly harmful effect in individuals over 40 years: hazard ratio (HR) of 0.50 (95% CI: 0.21-1.19) for individuals <40 years and 1.60 (95% CI: 0.77-3.32) in individuals ≥40 years (p=0.040).

Figure 3: Post hoc Poisson regression analysis

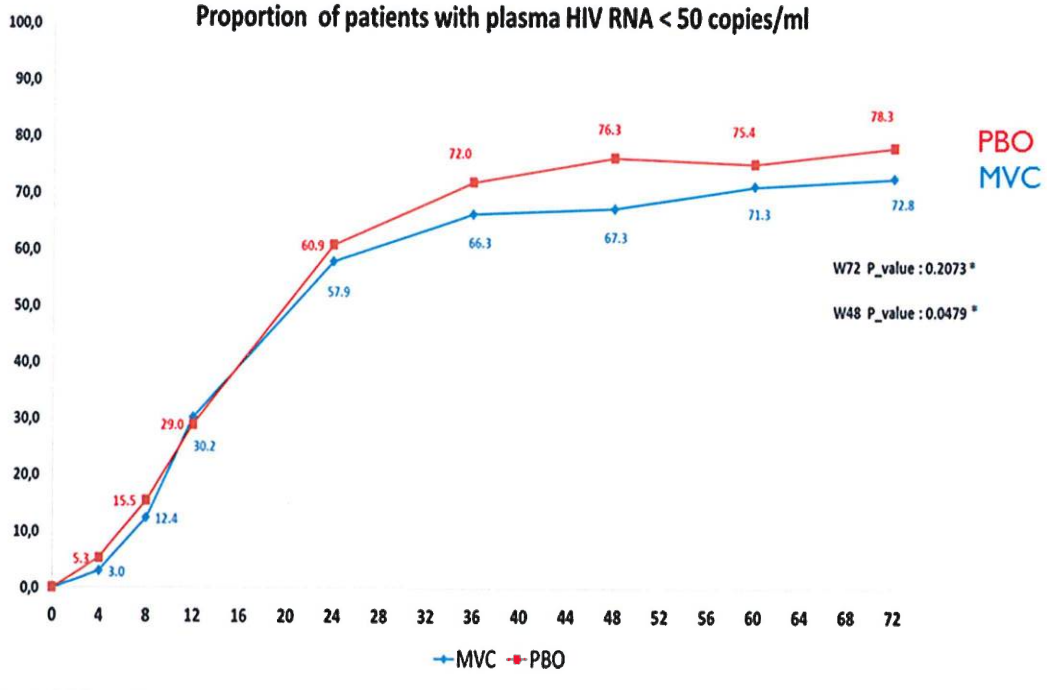
19.2



- Results of safety assessment:

Figure 4 shows the proportion of participants with a viral load <50 copies/mL on the study treatment over time, according to the snapshot method. The success rate was 76.3% in the placebo group versus 67.3% in the maraviroc group at W48 (p=0.048). It was 78.3% versus 72.8% at W72 (p=0.207). In participants with an initial viral load of >500,000 copies/mL, the success rate was clearly lower at W48 in the maraviroc group compared with the placebo group (53.3% versus 73.1%, p=0.043). This difference was no longer significant at W72 (68.9% versus 76.1%, p=0.514).

Figure 4: Proportion of participants with a viral load <50 copies/mL on trial treatment at each follow-up point over time (snapshot method)

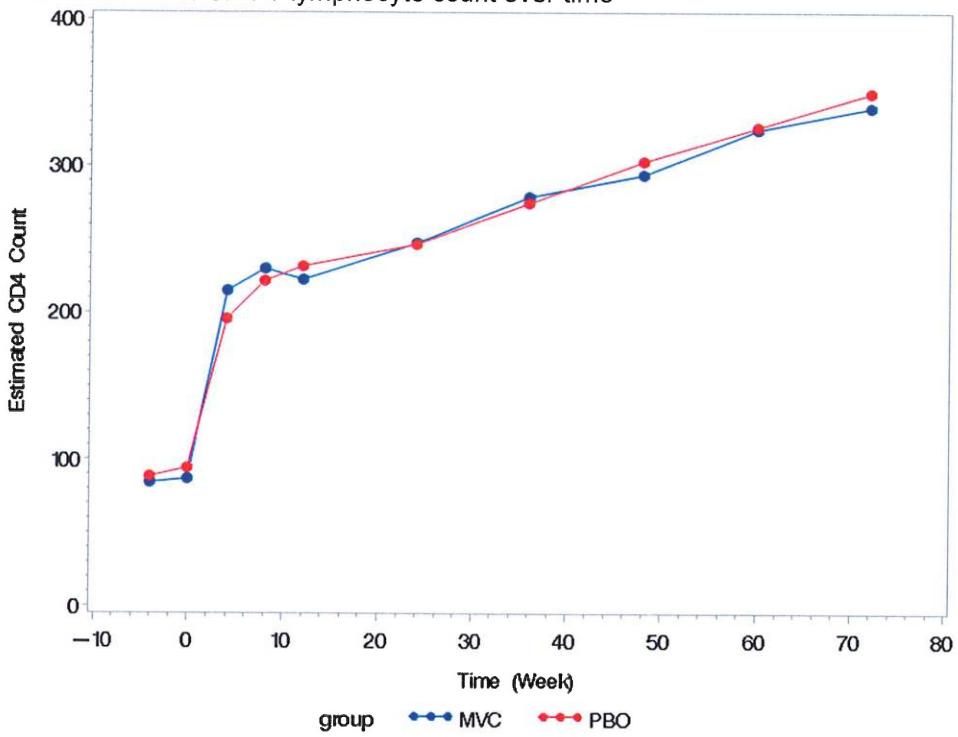


In all, 18 participants (11 in the PBO arm and 7 in the MVC arm) showed 2 successive viral load values >400 copies/mL) at a given time after W24. Genotypic resistance tests showed an acquisition of resistance mutations conferring resistance to the antiretroviral drugs in 5 of the 14 participants for whom

genotype sequence was obtained: 4 in the placebo group and 1 in the maraviroc group. Viral tropism also switched from R5 to R5X4 for 2 other participants in the maraviroc group.

Figure 5 shows the evolution of CD4 T lymphocyte count over time. The gain in CD4 at W72 was similar in the 2 groups, with a gain of +258.3±8.9/µL in the placebo group versus +254.2±9.2/µL in the maraviroc group, p=0.746.

Figure 5: Evolution of CD4 T lymphocyte count over time



Participant safety was also assessed in terms of frequency of serious adverse events (SAEs). In all, 154 serious adverse events occurred in the trial, in 110 participants: 80 SAEs in 52 participants in the placebo group, 66 SAEs in 51 participants in the maraviroc group, and 8 SAEs occurred in participants who did not receive the experimental treatment. Of the 66 events that occurred in the maraviroc group, 25 were considered by the investigator or sponsor to be linked to the trial treatment. 4 pregnancies were reported during the trial, and no neonatal disease was reported. In the course of the trial, 4 deaths were reported in the placebo group and none in the maraviroc group (Figure 2F).
The frequency of withdrawal from the trial or trial treatment was similar in the 2 groups: 11.6% in the placebo group versus 16.8% in the maraviroc group (p=0.156).

Other results:
The evolution of HIV DNA expressed as copies per million PBMC or as copies/mL was not significantly different between the 2 groups at W24 and W72 (Table 2).

Table 2: Evolution of HIV DNA at W24 and W48

	HIV DNA log_{10} copies/mL			HIV DNA log_{10} copies/million PBMC		
	PBO	**MVC**	**P value**	**PBO**	**MVC**	**P value**
W0	3.6(2.4-4.4)	3.5(2.3-4.4)	0.35	3.8(2.7-4.5)	3.7(2.3-4.7)	0.25
W24-W0	-0.3(-0.9-0.8)	-0.2(-2.4-1.9)	0.21	-0.4(-1.4-0.4)	-0.4(-1.2-0.6)	0.45
W72-W0	-0.4(-1.4-1)	-0.3(-1.0-1.6)	0.18	-0.5(-1.6-0.6)	-0.4(-1.4-0.5)	0.20

No impact of viral tropism detected at enrolment was demonstrated on virological response.
HIV-1 DNA-based analysis of the evolution of tropism in individuals with undetectable viral loads at W0, W24 and W72 is underway.
The seminal substudy was planned for 40 participants; however, only 5 samples were obtained at W0 and 6 at W24, with only 3 participants for whom there were samples at W0 and W24. Because of the small number of samples collected, no analysis was performed.

19.3

Analysis of the parameters of the immunological substudy showed no difference between the placebo and maraviroc groups in the behaviour of these parameters, namely phenotypic analysis of the $CD4^+$ and $CD8^+$ T lymphocytes, evolution of immune activation markers, serum markers of activation (inflammation), density of CCR5 and CXCR44 expression, expression of "homing" receptors on CD4+ T lymphocytes, and assessment of the specific immune responses to HIV-1 and recall antigen by

	intracellular labelling. The pharmacological substudy was planned for 50 participants. However, only 34 participated. The total and free residual concentration of maraviroc was similar, depending on the nature of the 3rd antiretroviral agent received (inducers, inhibitors or neutral). The total and free residual concentrations of the other drugs were similar in both groups. The pharmacokinetic substudy carried out at W4 in 32 participants showed no significant difference between the 2 groups in the elimination of the drugs over time. The areas under the curve of the total and free maraviroc concentrations at 12 h were respectively 2,655 (range: 358-7,981) and 1,295 (range: 139-2,915 **- Conclusion:** The results of this placebo-controlled randomised trial show that adding maraviroc to standard combined antiretroviral therapies had no impact on the risk of occurrence of infections / serious events or mortality, or on immunological and virological parameters in HIV-1 infected individuals diagnosed at a late stage. However, a post hoc analysis showed that maraviroc might have had a beneficial effect on the occurrence of clinical events during the first 6 months of use, which subsequently disappeared.
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