

INVESTIGATOR SITES FOR PROTOCOL NUMBER T20-301/NV16054

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SYNOPSIS OF PROTOCOL NUMBER T20-301/NV16054

TITLE	A phase III open-label, randomized, active-controlled study assessing the efficacy and safety of T-20/Ro 29-9800 (HIV-1 fusion inhibitor) in combination with an optimized background regimen, versus optimized background regimen alone, in patients with prior experience and/or prior documented resistance to each of the three classes of approved antiretrovirals (nucleoside reverse transcriptase, non-nucleoside reverse transcriptase and protease inhibitors).		
SPONSORS	Hoffmann-La Roche Inc., Nutley, NJ Trimeris Inc., Durham, NC	CLINICAL PHASE	III
INDICATION	Treatment of HIV-1 / AIDS		
OBJECTIVES	<p>Primary</p> <ol style="list-style-type: none">To demonstrate that a deliverable dose of 90 mg b.i.d. of T-20/Ro 29-9800 (corresponding to the 100 mg nominal dose studied in phase I/II) added to an Optimized Background (OB) regimen* provides an additional drop in plasma HIV-1 RNA of at least 0.5 log₁₀ copies/mL compared to the OB regimen alone at week 24, as measured by the difference between the two treatment arms in the mean changes from baseline in plasma HIV-1 RNA at week 24. <p>*For definition of OB regimen, see under COMPARATOR "DRUG", DOSE/ROUTE/REGIMEN.</p> <ol style="list-style-type: none">To demonstrate the durability of efficacy of T-20/Ro 29-9800 plus OB regimen, as measured by the percentage of patients who responded with viral load of a) <50 copies/mL, b) 50-400 copies/mL, c) ≥1 log₁₀ decrease from baseline but >400 copies/mL, and d) virological failure at week 24, and maintain response in each category or better at week 48. <p>Secondary</p> <ol style="list-style-type: none">To evaluate the percentage of patients with > 1.0 log₁₀ drop in plasma HIV-1 RNA, plasma HIV-1 RNA < 400 copies/mL (or < 50 copies/mL) at week 24 and week 48.To compare the safety of T-20/Ro 29-9800 plus OB regimen, to OB regimen alone, at 24 and 48 weeks of treatment.To evaluate the pharmacokinetics of T-20/Ro 29-9800 in triple class experienced and/or resistant patients.To compare the health-related quality of life (HRQL) domains derived from the MOS-HIV instrument of T-20/Ro 29-9800 plus OB versus OB alone.		
TRIAL DESIGN	<p>This is a randomized, open-label, active-controlled, parallel group, multicenter trial, assessing patients with prior experience and/or prior documented resistance to each of the three classes of approved ARVs.</p> <p>Patients will be randomized to receive one of the following treatments for 48 weeks:</p> <ul style="list-style-type: none">- Optimized Background (OB)- OB + T-20/Ro 29-9800, 90 mg SQI b.i.d.		

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NUMBER OF SUBJECTS	<p>A total of 525 patients will be randomized at a ratio of 1:2::OB (175 patients):OB+T-20/Ro 29-9800 (350 patients).</p> <p>Patients will be enrolled at approximately 48 centers in the USA, Canada, Mexico, and Brazil.</p>
TARGET POPULATION	<p>Patients must be HIV-1 infected adults or adolescents (≥ 16 years of age) with HIV-1 RNA $\geq 5,000$ copies/ml.</p> <p>Patients must have prior experience (for at least 6 months) and/or prior documented resistance to each of the 3 classes of approved antiretrovirals as follows:</p> <ul style="list-style-type: none">- nucleoside reverse transcriptase inhibitors (≥ 1 member of the class),- non-nucleoside reverse transcriptase inhibitors (≥ 1 member of the class), and- protease inhibitors (≥ 2 members of the class, taken either sequentially or concomitantly for a total of at least 6 months). <p>In order to achieve balance across the treatment groups, eligible patients will be stratified with respect to 1) screening viral load ($<40,000$ or $\geq 40,000$ copies/mL) and 2) use of any of the allowed newly approved/investigational antiretrovirals (versus non-use).</p> <p>Subsequently, patients will be randomized to one of the following two treatment groups, using a 1:2 ratio: OB : OB + T-20/Ro 29-9800, respectively.</p>
LENGTH OF STUDY	<p>58 weeks (6 weeks of screening, 48 weeks of treatment, 4 weeks of follow-up).</p> <p><u>Optional treatment extension:</u> at the end of the 48 weeks of treatment, patients will be allowed to a) roll-over and receive OB + T-20/Ro 29-9800 (for patients receiving OB regimen alone) or b) continue taking OB + T-20/Ro 29-9800 (for patients already receiving OB + T-20/Ro 29-9800), for a maximum of an additional 48 weeks (+ 4 weeks safety follow-up period), or until 12 weeks after commercial availability of T-20/Ro 29-9800 in the country in which they are treated, whichever comes first.</p> <p>All patients will be followed in this study for a maximum of 100 weeks from their initial baseline visit date.</p>
INVESTIGATIONAL PRODUCT(S) DOSE/ ROUTE/ REGIMEN	<p>T-20/Ro 29-9800 HIV-1 fusion inhibitor, 90 mg SQI b.i.d. (deliverable dose)</p>

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COMPARATOR "DRUG"
DOSE/ ROUTE/ REGIMEN

The OB regimen will be chosen by the physician and patient, based on the patient's prior treatment history, the screening GT/PT antiretroviral resistance testing, and any prior GT/PT antiretroviral resistance testing (if available). **Prior or current laboratory abnormalities, including triglycerides and cholesterol, should also be taken into account when selecting the OB regimen.** The drugs in the OB regimen will be chosen from among the currently approved antiretrovirals and permitted **newly approved**/investigational antiretrovirals available in the countries where the study will be implemented, and must consist of 3 to 5 drugs, including no more than one **newly approved**/investigational agent. Investigational agents may be obtained through expanded access.

Ritonavir at doses ≤ 200 mg/day will not be counted as one of the protease inhibitors, in either a "pre-study" regimen or the study OB regimen, but must be recorded in the case report form. Combination tablets (e.g., Combivir, Trizivir) will be counted and recorded as separate antiretroviral drugs in either a "pre-study" regimen or the study OB regimen.

For the purposes of this study, **newly approved**/investigational antiretroviral agents will be considered as **newly approved**/investigational for the duration of the trial, even after their commercial availability in the country in which the patient is treated.

ASSESSMENTS OF:

- EFFICACY

Primary:

- Viral load (plasma HIV-1 RNA) will be measured by using Amplicor HIV-1 Monitor assay.

Secondary:

- CD4 and CD8 T-lymphocyte counts,
- AIDS defining events,
- Death of any cause during specified study periods,
- Summary scores of physical function and mental health domain derived from the MOS-HIV instrument.

- SAFETY

Adverse events, clinical laboratory tests (hematology, blood chemistry, urinalysis), anthropometric measurements, DEXA and CT scan (for patients participating in the metabolic sub-study), and vital signs.

- TOLERABILITY

Premature withdrawals due to adverse events; local injection site reactions.

- OTHER PARAMETERS

Detectable antibodies to gp41 cross-reacting with T-20/Ro 29-9800, genotypic and/or phenotypic antiretroviral resistance, adherence to antiretroviral regimen; pharmacokinetics, Karnofsky score, and subcutaneous injections survey.

- PHARMACOKINETICS/
PHARMACODYNAMICS

All patients randomized to T-20/Ro 29-9800 will have sparse pharmacokinetic sampling: 7 samples per patient will be collected: 2 samples per visit on week 1, week 8, and week 24, and one additional sample at week 48.

- QUALITY OF LIFE/
PHARMACOECONOMICS

MOS-HIV instrument

PROCEDURES (summary):

Patients must be on a current "pre-study" antiretroviral regimen in which medications and doses have remained unchanged; this "pre-study" regimen may be no antiretroviral therapy at all. Patients must have documentation of a plasma HIV-1 RNA level $\geq 5,000$ copies/mL (by any method) measured at least 4 weeks after the initiation of their "pre-study" antiretroviral regimen, but no more than 6 months prior to the first screening visit (Screen 1).

During the first screening visit, Screen 1, (42 to 21 days prior to baseline), samples for HIV-1 genotypic/phenotypic (GT/PT) resistance testing and for plasma HIV-1 RNA measurement will be obtained for each patient. Plasma HIV-1 RNA will be measured using the Roche Amplicor HIV-1 Monitor assay. Plasma HIV-1 RNA from the first screening visit must be $\geq 5,000$ copies/mL.

Prior to the second screening visit, the investigator must have received the patient's viral GT/PT antiretroviral resistance testing and viral load results from Screen 1.

During the second screening visit, Screen 2, (14 to 7 days prior to baseline), the investigator and patient will discuss and select the patient's OB regimen to be initiated at baseline (consisting of 3 to 5 drugs, including no more than one **newly approved**/investigational drug, chosen from the approved antiretrovirals and allowed **newly approved**/investigational antiretrovirals listed in Appendices 1 and 2), based on the patient's prior treatment history as well as the results from the Screen 1 GT/PT antiretroviral resistance testing, and prior GT/PT antiretroviral resistance testing (if available). **Prior or current laboratory abnormalities, including triglycerides and cholesterol, should also be taken into account when selecting the OB regimen.** A sample for plasma HIV-1 RNA measurement will again be obtained for each patient. Plasma HIV-1 RNA will be measured using the Roche Amplicor HIV-1 Monitor assay. Patients must have a plasma HIV-1 RNA level that is $\geq 5,000$ copies/mL, and that is not decreased from the Screen 1 viral load by more than $1.0 \log_{10}$.

Patients must continue on their current, stable "pre-study" antiretroviral regimen (unchanged medications and doses) until baseline. Patients must not wash out prior to GT/PT or between GT/PT and randomization, since it could negatively impact on the genotypic and phenotypic assay results and the baseline viral load value, which in turn would affect the choice of drugs in the OB regimen or the assessment of efficacy. Should a patient change his/her current "pre-study" antiretroviral regimen at any time before baseline, his/her subsequent viral load measurements will be invalidated. He/she may re-enter the 6-week screening period on one occasion, after at least 4 weeks on a stable "pre-study" antiretroviral regimen (with unchanged medications and doses).

After fulfilling all inclusion / exclusion criteria, committing to their OB regimen, and having all OB drugs in hand, patients will be randomized at a ratio of 1:2 to one of the following two treatment groups: OB or OB + T-20/Ro 29-9800 b.i.d. (one third of the patients will be randomized to the OB regimen arm, and two thirds of the patients will be randomized to T-20/Ro 29-9800 + OB regimen). The time window between randomization and baseline should be no more than two working days (48 working hours). Patients will receive their first doses of OB medications and T-20/Ro 29-9800 at the baseline visit or within one working day (24 working hours), after all study procedures have been performed.

Patients will continue on their assigned treatment for 48 weeks. Changes to the OB regimen (irrespective of randomization to OB alone or OB + T-20/Ro 29-9800) are permitted only for toxicity management or if the patient meets criteria for virological failure (see section 5.5).

Rules for changing the OB regimen for toxicity management, and the criteria for virological failure are identical for the two treatment arms.

Treatment interruption (of OB or OB + T-20/Ro 29-9800) is not permitted during the primary treatment period (from initial randomization to meeting criteria for virological failure, or to week 48, whichever occurs first), except for toxicity management as per protocol (see sections 7.3.1 and 7.3.2). Treatment intensification is not permitted during the primary treatment period (from initial randomization to meeting criteria for virological failure, or to week 48, whichever occurs first).

Patients will be seen for evaluation of efficacy and safety at weeks 1, 2, and 4, every 4 weeks through week 24, and then every 8 weeks through week 48. In addition, efficacy only will be evaluated at weeks 6, 10 and 14. Patients may also be seen at additional visits during the study for plasma HIV-1 RNA measurements to potentially confirm virological failure.

Patients initially randomized to the OB arm who meet the criteria for virological failure as described in section 5.5., and who switch to OB + T-20/Ro 29-9800 after week 8 will be followed under a new ("switch") schedule of assessments (see Table 5 of protocol). Patients will be encouraged to change their OB regimen at the time of switch. See section 5.6 for details.

Patients initially randomized to the OB+T-20/Ro 29-9800 arm who meet the criteria for virological failure as described in section 5.5. may continue to receive OB + T-20/Ro 29-9800 if the patient and the physician feel that there is sufficient benefit. Patients will be encouraged to change their OB regimen after week 8 if they choose to continue on OB + T-20/Ro 29-9800 despite meeting the criteria for virological failure. See section 5.7 for details.

Patients on OB or OB + T-20/Ro 29-9800 arm who meet the criteria for virological failure as described in section 5.5, but who do not wish to either switch to T-20/Ro 29-9800 (for patients initially randomized to OB arm) or continue with T-20/Ro 29-9800 (for patients initially randomized to OB + T-20/Ro 29-9800) will be allowed to remain in the study for a maximum of one month.

After week 48, all patients will be allowed to a) roll-over and receive OB + T-20/Ro 29-9800 (for patients receiving OB regimen alone) or b) continue taking OB + T-20/Ro 29-9800 (for patients already receiving OB + T-20/Ro 29-9800), for a maximum of 48 additional weeks (+ 4 week safety follow-up) or until 12 weeks after commercial availability of T-20/Ro 29-9800 in the country in which they are treated, whichever comes first. Please refer to section 5.8. for details.

All patients will be followed in this study for a maximum of 100 weeks from their initial baseline visit date.

STATISTICAL ANALYSES

Primary efficacy analysis

Week 24

The primary analysis will be on intent-to-treat population. For patients who meet virological failure criterion or withdraw prematurely, the mean of their last two observations (prior to or on the day of the 2nd confirmation sample or premature withdrawal sample) will be carried forward (LOCF) to the planned analysis time points (i.e., week 8 and week 24).

An analysis of covariance model will be used to analyze the transformed HIV-1 RNA data. The model will include the following terms: stratum (four strata of screening viral load category and

use of any allowed **newly approved**/investigational antiretroviral drugs combinations), treatment, treatment by stratum interaction, and the covariate (the phenotypic sensitivity score). If there is a significant treatment by stratum interaction effect, a simple analysis of covariance model only includes treatment and phenotypic sensitivity score will also be used to analyze the viral load data within each stratum. The same analysis will be repeated on restrict treated patient (RTP) population.

Also in order to assess the impact of the choice of LOCF method for handling dropouts, additional cohort analyses for patients who complete 2, 4, 8, 16, and 24 weeks of treatment will be performed.

Week 48

In order to compare the durability of viral suppression, a chi-square test will be used to test the equality of the two multinomial distributions of patients who maintained or improved their responder status **between week 24 and week 48 based on ITT population. If the overall test is significant, then the percent of patients who maintain in each of the following category will be tested at the α level of 0.05: a) < 50 copies/mL, b) < 400 copies/mL, and c) $\geq 1.0 \log_{10}$ reduction from baseline.**

The same analysis will be repeated on restrict treated patient (RTP) population.

For secondary efficacy analysis, exploratory analyses, subgroup analysis, and safety data analysis, see protocol, section 8.