ABBREVIATED CLINICAL STUDY REPORT

Study Title:	**ROCKET II** - **R**andomized **O**pen Label Switch for **C**holesterol Elevation on **K**ivexa + Kaletra **E**valuation **T**rial A Phase 4, Open Label, Randomized, Controlled Study to Assess the Effect on Lipid Profile of Switching a Stable HAART Regimen of fixed dose Abacavir/Lamivudine (Kivexa) Plus Lopinavir/Ritonavir (Kaletra), to Emtricitabine/Tenofovir Disoproxil Fumarate (Truvada) Plus Lopinavir/Ritonavir (Kaletra) in Adult HIV-1 Infected Subjects With Raised Cholesterol
Name of Test Drug:	Truvada® (emtricitabine/tenofovir disoproxil fumarate)
Dose and Formulation:	Fixed-dose film-coated tablet containing emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg
Indication:	HIV-1 Infection
Sponsor:	Gilead Sciences Europe Ltd. 2 Roundwood Avenue, South Building, Stockley Park, Uxbridge, UB11 1AZ, United Kingdom
Study No.:	GS-EU-164-0206
Phase of Development:	Phase 4
IND No.: **EudraCT No.:**	Not applicable 2008-002043-16
Study Start Date: **Study End Date:**	29 September 2008 (First Subject Screened) 19 October 2009 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Prof. Dr. Georg Behrens, MD Affiliation: [redacted] PPD [redacted]
Gilead Responsible Medical Monitor:	Name: Florian Abel, MD Telephone: PPD Fax: PPD
Report Date:	18 March 2010

CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS

Gilead Sciences Europe Ltd.
2 Roundwood Avenue, South Building, Stockley Park,
Uxbridge, UB11 1AZ, United Kingdom

Title of Study:

ROCKET II - **R**andomized **O**pen Label Switch for **C**holesterol Elevation on **K**ivexa + Kaletra **E**valuation **T**rial

A Phase 4, Open Label, Randomized, Controlled Study to Assess the Effect on Lipid Profile of Switching a Stable HAART Regimen of fixed dose Abacavir/Lamivudine (Kivexa) Plus Lopinavir/Ritonavir (Kaletra), to Emtricitabine/Tenofovir Disoproxil Fumarate (Truvada) Plus Lopinavir/Ritonavir (Kaletra) in Adult HIV-1 Infected Subjects With Raised Cholesterol

Investigators: Multicenter

Study Centers: Subjects were enrolled at 29 centers: 10 centers in Spain, 10 centers in Italy, 6 centers in Germany, and 3 centers in Austria.

Publications: None

Study Period:

29 September 2008 (first subject screened)
19 October 2009 (last subject observation)

Phase of Development: Phase 4

Objectives:

The primary objective of this study was as follows:

- To determine if switching the nucleoside reverse transcriptase inhibitor (NRTI) backbone from Kivexa to Truvada leads to a reduction in fasting total cholesterol at 12 weeks.

The secondary objectives of this study were as follows:

- Evaluation of fasting metabolic parameters (e.g., low-density lipoprotein [LDL], high-density lipoprotein [HDL], non-HDL cholesterol, triglycerides, and cholesterol ratios).
- Evaluation of efficacy and safety by assessing adverse events (AEs), clinical laboratory tests, physical examinations and vital signs at every visit.
- Evaluation of changes in the 10-year risk factor for coronary heart disease (CHD) outcomes.

Methodology: This was a Phase 4, open-label, randomized, multicenter, controlled study to assess the effect on lipid profile of switching from a stable highly active antiretroviral therapy (HAART) regimen of Kivexa + Kaletra to Truvada + Kaletra in adult human immunodeficiency virus type 1 (HIV-1) infected subjects with raised cholesterol.

Subjects were randomized 1:1 to either switch to Truvada + Kaletra (Group 1) or remain on Kivexa + Kaletra (Group 2). Concomitant lipid regulating therapy was permitted but had to be stable for ≥ 12 weeks prior to screening and had to remain stable throughout the treatment phase of the study.

Postbaseline assessments were completed during visits at Weeks 4 and 12.

Number of Subjects (Planned and Analyzed):
Planned: 160
Analyzed: 85 (intent-to-treat [ITT] analysis set: 42 Truvada, 43 Kivexa; treated analysis set 43 Truvada, 42 Kivexa). Recruitment was lower than anticipated, likely in part due to data becoming available regarding cardiovascular risks with abacavir treatment.

Diagnosis and Main Criteria for Inclusion: HIV-1 infected adults, virologically suppressed (HIV-1 ribonucleic acid [RNA] < 50 copies/mL at screening and for ≥ 12 weeks prior to screening) on a stable HAART regimen of Kivexa + Kaletra for ≥ 24 weeks prior to screening, with documented confirmed raised total cholesterol ≥ 5.2 mmol/L (≥ 200 mg/dL) for the last 2 consecutive tests (at least 4 weeks apart), and with fasted total cholesterol ≥ 5.2 mmol/L (≥ 200 mg/dL) at screening.

Duration of Treatment: 12 weeks

Test Product, Dose, Mode of Administration, and Batch No.: Truvada (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg), 1 tablet, orally, once-daily. It was recommended that Truvada tablets were taken with food. (Subjects also continued to take Kaletra, orally, as prescribed).

Truvada Lot Numbers: C361621 for all subjects except 1 who received drug from commercial supply.

Reference Therapy, Dose, Mode of Administration, and Batch No.: Kivexa (abacavir [as sulfate] 600 mg/lamivudine 300 mg), orally, once-daily. (Subjects also continued to take Kaletra, orally, as prescribed).

Criteria for Evaluation:

Efficacy: Metabolic endpoints were assessed by monitoring fasting lipid profiles. Virologic efficacy was assessed by monitoring plasma HIV-1 RNA levels. Immunologic efficacy was assessed by monitoring CD4 and CD8 cell counts and percentages.

Safety: Safety was assessed by monitoring AEs, clinical laboratory tests, and physical examinations including vital signs and body weight. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 12.

Outcomes Research: Changes in the 10-year risk for CHD outcomes were assessed using Framingham risk score.

Statistical Methods:

Efficacy: The ITT analysis set was used for analyses of fasting lipid parameters, HIV-1 RNA, CD4, and CD8 endpoints. The ITT analysis set included subjects who were randomized, received at least one dose of study drug, and had at least one postbaseline observation. Subjects were grouped by treatment assigned.

The primary endpoint was the change from baseline in fasting total cholesterol at Week 12. The primary analysis of the primary endpoint was based on the ITT analysis set and used last postbaseline observation carried forward [LOCF] methodology. Changes from baseline were analyzed within each treatment group using a Wilcoxon signed rank test, and differences between treatment groups were analyzed using a Wilcoxon rank sum test. The difference (Truvada versus Kivexa) in least squares means (LSM) and the 95% confidence interval (CI) for the difference were calculated using analysis of variance with treatment as the factor. A secondary analysis of the primary endpoint was based on observed data (i.e., no imputation for missing). Two sensitivity analyses were also conducted for the primary endpoint: 1 using LOCF methodology in the treated analysis set (which included subjects who were randomized and received at least 1 dose of study drug grouped according to the study drug received) and 1 using LOCF methodology in the ITT analysis excluding data for 1 subject in the Truvada group who started/modified lipid-lowering medication during the study. Other fasting lipid parameters were analyzed in a similar manner to the primary endpoint.

The proportions of subjects with plasma HIV-1 RNA < 50, < 200, and < 400 copies/mL at Week 12 were compared between treatment groups using Fisher's Exact test. The exact 95% CIs were estimated based on unconditional exact methods using inverted 2 one-sided tests with the standardized statistic. The p-values and 95% CIs were based on the proportions of subjects in 2 response categories: success (HIV-1 RNA less than the specified level) and failure (HIV-1 RNA equal or above the specified level). The following methods were used for treating missing values in calculating proportions: missing = failure, LOCF, and missing = excluded.

For CD4 and CD8 cell counts and percentages, absolute values and change from baseline were summarized at Weeks 4 and 12. Differences between treatment groups in change from baseline were tested using the Wilcoxon rank sum test at Week 12.

Safety: All safety analyses were based on the treated analysis set and were summarized using descriptive statistics by treatment group according to the study drug received. Data collected up to the date of last dose of study drug plus 30 days were included in safety analyses.

Outcomes Research: The observed values and changes from baseline at Week 12 in the 10-year risk for CHD outcomes were summarized by treatment group using the treated analysis set. The change from baseline was tested using the Wilcoxon signed rank test within treatment group and was compared between treatment groups using the Wilcoxon rank sum test. Numbers and percentages of subjects with CHD risk in the categories of < 10%, 10% to 20%, and > 20% were summarized at baseline and Week 12. Shifts between categories from baseline to Week 12 were summarized.

SUMMARY – RESULTS:

A total of 85 subjects were randomized and received at least 1 dose of study drug. Forty-two subjects were randomized to receive Truvada and 43 subjects were randomized to continue Kivexa. One subject who was randomized to continue Kivexa received Truvada, therefore 43 subjects received Truvada and 42 subjects received Kivexa. Eighty-one subjects completed the study. Reasons for discontinuation in the randomized analysis set were protocol violation (2 subjects in the Kivexa group), AE (1 subject in the Truvada group), and withdrawal of consent (1 subject in the Kivexa group).

There were no clinically relevant differences in demographic and baseline characteristics between the Truvada and Kivexa groups in either the randomized or treated analysis sets. Subjects were predominantly male (77.6%) and white (89.4%) with a mean age of 44.6 years (range 26 to 74 years). Mean (standard deviation [SD]) fasting total cholesterol at baseline was 6.47 (0.980) mmol/L. Subjects had been receiving Kivexa for a mean (SD) of 2.6 (1.6) years.

Efficacy Results: In the primary analysis (LOCF, ITT analysis set) of fasting total cholesterol, the difference between groups (Truvada minus Kivexa) for the change from baseline to Week 12 was −0.82 mmol/L (95% CI −1.22, −0.43); the difference was statistically significant ($p < 0.001$). In the Truvada group, there was a statistically significant decrease from baseline to Week 12 in fasting total cholesterol (median change −0.73 mmol/L, $p < 0.001$), while in the Kivexa group there was no statistically significant change from baseline to Week 12 in fasting total cholesterol (median change −0.01 mmol/L, $p = 0.75$). Results were similar to those for the primary analysis when assessed according to the secondary analysis based on observed data; for the sensitivity analysis using the treated analysis set; and for the sensitivity analysis of the ITT set excluding 1 subject in the Truvada group who started/modified lipid-lowering medication during the study.

Results of analyses of secondary fasting lipid parameters were similar to those for fasting total cholesterol. For each parameter (LOCF, ITT analysis set), there was a statistically significant decrease from baseline to Week 12 in the Truvada group while there was no statistically significant change from baseline to Week 12 in the Kivexa group. Differences between groups (Truvada minus Kivexa, mean [95% CI]) for the changes from baseline to Week 12 in secondary fasting lipid parameters were statistically significant for LDL cholesterol (−0.46 mmol/L [−0.77, −0.15], $p = 0.010$), HDL cholesterol (−0.10 mmol/L [−0.20, 0.00], $p = 0.029$), and non-HDL cholesterol (−0.72 mmol/L [−1.08, −0.37], $p < 0.001$), but not for triglycerides or total/HDL cholesterol ratio.

Virologic suppression and immunologic control were maintained in subjects who switched therapy to Truvada or who remained on Kivexa.

Safety Results: Truvada was well tolerated in this study. No subjects died. Serious adverse events (SAEs) were reported for 1 subject in each treatment group; no SAE was considered related to study drug or study regimen by the investigator. One subject discontinued study drug due to an AE (sarcoma for a subject in the Truvada group that was also reported as an SAE). At least one AE was reported for 44.2% of subjects (19 subjects) in the Truvada group and 26.2% of subjects (11 subjects) in the Kivexa group. There were no notable differences between groups in the incidences of any AEs. AEs considered related to study drug (Truvada or Kivexa) were reported for 2 subjects in the Truvada group (gastritis, renal pain, and pruritus, each reported for 1 subject [renal pain and pruritus were reported for the same subject]) and for 1 subject (blood cholesterol increased) in the Kivexa group. AEs considered related to study regimen (Truvada + Kaletra or Kivexa + Kaletra) were reported for 4 subjects in the Truvada group and for 2 subjects in the Kivexa group. Grade 3 AEs were reported for 2 subjects in the Truvada group and for 1 subject in the Kivexa group; no Grade 4 AEs were reported. No Grade 3 AEs were considered related to study drug (lipids increased for 1 subject in the Truvada group was considered related to study regimen).

Renal pain, reported for 1 subject in the Truvada group, was the only AE reported in the renal and urinary disorders system organ class. The event was nonserious, Grade 1 in severity, and considered related to study drug by the investigator. No fractures or other bone events, or AEs of skin hyperpigmentation were reported.

There were no clinically relevant changes from baseline in median values for hematology and (nonlipid) chemistry parameters in either group during the study (including renal parameters: serum creatinine, serum phosphorus, estimated creatinine clearance [using the Cockcroft-Gault method], and estimated glomerular filtration rate [using the Modification of Diet in Renal Disease formula]). The profile of laboratory abnormalities reported was similar in the 2 groups, with the exception of treatment-emergent Grade 3 elevations in cholesterol that were reported for 6 subjects in the Kivexa group compared to zero subjects in the Truvada group.

There were no clinically relevant differences between treatment groups for the changes from baseline in body weight, body mass index, or vital signs.

Outcomes Research Results: The difference between groups (Truvada minus Kivexa) for the change from baseline to Week 12 in the 10-year risk for CHD outcomes was statistically significant ($p = 0.027$). While the median change was zero in both groups, mean (SD) changes were –0.7% (2.42) in the Truvada group and 0.5% (2.51) in the Kivexa group. The change from baseline to Week 12 was statistically significant in the Truvada group ($p = 0.034$) but not in the Kivexa group ($p = 0.33$). Categorical summaries showed some evidence for clinically meaningful improvement (shift from a higher risk category to a lower risk category) in the 10-year risk for CHD outcomes at Week 12 in the Truvada group, compared to no marked change in the Kivexa group.

CONCLUSIONS: The conclusions of Study GS-EU-164-0206 are as follows:

- In virologically suppressed HIV-1 infected subjects with raised cholesterol, switching the NRTI backbone from Kivexa to Truvada led to a reduction in fasting total cholesterol and other fasting lipid parameters (LDL cholesterol, HDL cholesterol, triglycerides, non-HDL cholesterol, and total/HDL cholesterol ratio). For all fasting lipid parameters, statistically significant decreases from baseline were seen at Week 12 in the Truvada group.
- HIV-1 infected subjects who switched their NRTI backbone from Kivexa to Truvada maintained virologic and immunologic control.
- Truvada was generally safe and well tolerated in this study. No deaths or SAEs considered related to study drug were reported, and only 1 subject who received Truvada discontinued due to an AE (sarcoma that was reported as an SAE). There were no clinically relevant differences in AEs, clinical laboratory tests, or vital signs between the Truvada and Kivexa groups with the exception of treatment-emergent Grade 3 elevations in cholesterol that were reported for 6 subjects in the Kivexa group compared to zero subjects in the Truvada group.
- In virologically suppressed HIV-1 infected subjects with raised cholesterol, switching the NRTI backbone from Kivexa to Truvada led to a statistically significant reduction in the 10-year risk for CHD outcomes as assessed using Framingham risk score.