This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2.0 SYNOPSIS

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC Vicriviroc, 30 mg tablet HIV	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: Efficacy and Safety of Vicriviroc (SCH 417690) in HIV-Infected Treatment-Naive Subjects — P04875

PROTECTION OF HUMAN SUBJECTS: This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. For study audit information see [16.1.8].

INVESTIGATOR(S)/STUDY CENTER(S): 39 centers in Germany, Guatemala, Honduras, Italy, Portugal, Puerto Rico, South Africa, Spain, and the United States of America.

PUBLICATION(S): None

PRIMARY THERAPY PERIOD: 21 JAN 2008 – 27 OCT 2010 **CLINICAL PHASE:** 2b

DURATION OF TREATMENT: The planned study treatment duration for all subjects was 96 weeks. Study participants in the vicriviroc (VCV) arm who completed 96 weeks of treatment could continue in the open-label VCV extension phase, during which they received VCV until the sponsor terminated the clinical development of VCV.

OBJECTIVE(S): Primary Objective: To evaluate the virologic efficacy of VCV combined with ritonavir-boosted Reyataz™ in human immunodeficiency virus (HIV)-infected treatment-naïve subjects.

Secondary Objectives: To assess the long-term safety and tolerability of VCV, and to explore the relationship of plasma drug concentrations (pharmacokinetics) to virologic response.

STUDY STATUS: The study was terminated early, after the Sponsor discontinued the development of vicriviroc for the treatment of HIV in June 2010. The final analysis was performed after early termination of the study, when 63 of 218 randomized subjects had completed 96 weeks of study treatment (database lock was 06 DEC 2010). This abbreviated clinical study report presents a complete final safety analysis. A previous abbreviated clinical study report (CSR), dated 28 Jul 2009, summarized safety results from an interim analysis conducted at Week 24 of study Stage 1.

STUDY DESIGN: This clinical study report presents final results of an open-label 96-week two stage study of VCV in treatment-naïve adults infected with CCR5-tropic HIV-1 (hereinafter referred to as HIV). The report also summarizes data for 28 subjects who received VCV during an Open Label Extension phase. The study was conducted in conformance with Good Clinical Practice. During a screening period, subjects were confirmed to be eligible, treatment naïve (per protocol), and to meet international or local recommendations for initiation of antiretroviral therapy (ART).

In Stage 1 of the study, subjects were randomized to receive either VCV 30 mg or Truvada™ (tenofovir [TDF] and emtricitabine [FTC]; control arm) once daily, each in combination with ritonavir-boosted atazanavir (ATV/r) for 96 weeks. Randomization was stratified by entry (Screening) viral load (< or ≥100,000 copies/mL). When the enrolled subjects from Stage 1 had completed 24 weeks of treatment or discontinued, a formal pre-planned interim analysis was conducted and the results were presented to an independent Data Safety Monitoring Board (DSMB) to ensure the safety of study participants. Based upon the results of the Week 24 interim analysis (presented in a previous abbreviated CSR), the DSMB recommended enrollment of Stage 2. Randomization for Stage 2 was stratified by baseline viral load < or ≥100,000 copies/mL and baseline CD4 count < or ≥200 cells/mm^3.

Subjects who had dual/mixed or X4-tropic virus at the Baseline visit in the Monogram Trofile™ assay were discontinued from the study regardless of their treatment assignments at the time

that results became available. These subjects were excluded from the efficacy analyses. Subjects who developed intolerance to any component of the treatment arms were evaluated by investigators for possible discontinuation from the study. Other reasons for discontinuation included: (1) an inadequate virologic response (defined as <1.0 $\log_{10}$ decrease in HIV RNA compared with the baseline value at the end of 8 weeks of treatment, confirmed within 4 weeks on retesting); (2) virologic failure (defined as ≥0.5 $\log_{10}$ increase in HIV RNA at or after Week 8, confirmed on retesting within 4 weeks, compared with the prior value); (3) viral rebound (defined as those who, at any time during the study, had achieved viral suppression of <50 copies/mL HIV RNA and who on two consecutive subsequent measurements had HIV RNA >50 copies/mL); or (4) confirmed HIV coreceptor phenotype shift to X4 or R5/X4 with a corresponding significant drop in CD4 count (an absolute drop in CD4 count of >100 cells/mm^3 or a drop of >30% below the baseline value) at or after Week 8. At the time of discontinuation, subjects were to have testing for viral tropism and susceptibility, as well as genotyping and phenotyping of their HIV isolates.

After study completion, study participants were offered VCV through a protocol extension until termination of drug development. Subjects who discontinued from the study were offered prospective follow-up in a registry (P04999) with sponsor-supported testing for HIV tropism and monitoring of clinical events. These patients were to be treated as medically appropriate by their primary medical providers.

The primary efficacy and safety analysis was performed when subjects from both study stages had completed 48 weeks of treatment or discontinued. Pursuant to Amendment 3, a final analysis was to be performed when all subjects completed 96 weeks of randomized treatment or discontinued; the final analysis was performed when the Sponsor discontinued development of VCV for HIV and terminated the study.

SUBJECT/PATIENT DISPOSITION: A total of 218 subjects were randomized, including 109 subjects in each treatment arm. Randomization resulted in similar demographics across treatment arms in the Double-blind Treatment Phase. The median age was 37 years (range 18-70 years). Sixty-six percent of subjects were men and 34% were women. Racial and ethnic minorities were well represented, and 39% of subjects came from outside of North America and Western Europe.

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Disposition of Subjects Following Randomized Treatment Assignment (All Randomized Subjects, 96-Week Treatment Phase)

Subject Status	Number (%) of Subjects		
	VCV + ATV/r n=109	Truvada + ATV/r n=109	Total n=218
Randomized	109 (100)	109 (100)	218 (100)
Treated	109 (100)	108 (99)	217 (100)
Completed	30 (28)	33 (30)	63 (29)
Discontinued	79 (72)	75 (69)	154 (71)
Adverse Event	9 (8)	1 (1)	10 (5)
Treatment Failure [a]	3 (3)	3 (3)	6 (3)
Progression of Disease (AIDS-defining Event)	0	0	0
Protocol-Defined Clinical Event [b]	1 (1)	0	1 (<1)
Lost to Follow-Up	7 (6)	7 (6)	14 (6)
Investigator Discontinued Subject	0	0	0
Patient Moved or Relocated	0	1 (1)	1 (<1)
Subject Withdrew Consent	2 (2)	5 (5)	7 (3)
Noncompliance	4 (4)	2 (2)	6 (3)
Administrative	53 (49)	56 (51)	109 (50)
Did not Meet Protocol Eligibility	0	0	0
Randomized but not Treated	0	1 (1)	1 (<1)

AIDS = acquired immunodeficiency syndrome; ATV/r =ritonavir-boosted atazanavir; DM = dual/mixed; VCV = vicriviroc; X4 = CXCR4-tropic.

[a] As determined by investigators guided by prespecified virologic failure criteria.

[b] DM/X4 virus detected at Baseline.

Twenty-eight subjects continued on VCV during an open-label extension between 08 JAN 2010 and study termination on 27 OCT 2010. All 28 subjects discontinued for administrative reasons when the sponsor terminated the study. The median age of the 28 subjects was 40 years (range 21-57 years); 71% were men and 29% were women.

DOSAGE/FORMULATION NOS.: Vicriviroc maleate 30-mg tablets were administered orally QD from batch numbers [redacted] see [16.1.6]). Truvada™ (Emtriva™ [emtricitabine 200 mg] and Viread™ [tenofovir disoproxil fumarate 300 mg]) was administered orally in one 200-mg/300-mg combination tablet QD (lot numbers were [redacted] In addition, all subjects received Reyataz™ (atazanavir or ATV), depending on regional availability, as either two 150-mg capsules QD (lot numbers [redacted] or one 300-mg capsule QD (lot numbers were [redacted] plus ritonavir in one 100-mg capsule QD (lot numbers were [redacted]

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DIAGNOSIS/INCLUSION CRITERIA: Eligible subjects were adults with documented CCR5-tropic HIV infection who met International AIDS Society (IAS), Department of Health and Human Services (DHHS), or local recommendations for initiation of ART and who had a cumulative lifetime ART exposure of ≤4 weeks (with the exception of prophylaxis to prevent mother-to-child transmission); and screening laboratory assessments of HIV RNA ≥2000 copies/mL, CD4 cell count ≥100 cells/mm^3 (or as specified by local treatment guidelines), platelet count ≥75,000/μL, hemoglobin ≥8 g/dL, serum creatinine <2.0 mg/dL (154 μmol/L), and aspartate and alanine aminotransferase (AST, ALT or SGOT, SGPT) levels ≤3 times the upper limit of normal (ULN). Eligible subjects had no active opportunistic infection or malignancy and no seizure disorder requiring ongoing anti-seizure therapy and were not at risk for seizures, in the judgment of the investigator.

EVALUATION CRITERIA: The study was descriptive in nature, and no formal hypothesis testing (ie, p-values) was planned.

Efficacy: The primary efficacy endpoint was the mean change from baseline in log_{10} HIV RNA at Week 48. The key secondary efficacy endpoint was the proportion of subjects with plasma HIV RNA <50 copies/mL at Week 48.

Other Secondary Endpoints:

- Mean change from baseline in CD4 count at Weeks 24, 48, and 96;
- Mean change from baseline in log_{10} HIV RNA at Weeks 24 and 96;
- Proportion of subjects with plasma HIV RNA <50 copies/mL at Weeks 24 and 96;
- Proportion of subjects with <400 copies/mL of HIV RNA at Weeks 24, 48, and 96;
- Proportion of subjects with at least 1 log_{10} HIV RNA reduction from baseline at Weeks 24, 48, and 96.

Safety: Monitoring of safety included, but was not limited to, physical examination, laboratory abnormalities, CD4/CD8 count, susceptibility testing, adverse events (AEs), AIDS-defining conditions (ADEs), and detection of X4 tropism of HIV isolates.

STATISTICAL PLANNING AND ANALYSIS:

Efficacy: The efficacy analysis was based on the Modified Intent-To-Treat (MITT) population, which included all subjects who were randomized and received at least one dose of study drug (excluding subjects whose viral tropism was not CCR5 only by the Monogram Trofile™ ES assay at the Baseline/Randomization visit). Data were summarized according to the treatment group assigned regardless of adherence to study protocol.

The primary efficacy variable (mean change from baseline value in log_{10} HIV RNA) was analyzed in an analysis of variance (ANOVA) model with treatment and stratification factors as covariates. Stratification factors were baseline HIV RNA (<100,000 vs ≥100,000 copies/mL) and baseline CD4 counts (<200 vs ≥200/mm^3). A 95% confidence interval around the primary efficacy endpoint for each treatment as well as the difference between the two treatment arms were constructed based on the ANOVA model.

The change in CD4 count was analyzed in an analogous ANOVA model, with treatment and baseline viral load (< or ≥100,000 copies/mL) as covariates. The proportion of subjects achieving virologic response (<50 copies/mL, <400 copies/mL, ≥1 log_{10} reduction from baseline value) were analyzed in a logistic regression model adjusting for treatment and stratification factors. The odds ratios for each virologic response comparing the two treatments and 95% confidence intervals were provided based on the logistic analyses.

To facilitate interpretation of data, the following data imputation logic was used. Missing data in log_{10} HIV RNA and CD4 values were imputed by taking the average of the values immediately preceding and following the missing values. Further, where the proportion of subjects reaching below the limit of quantitation (LOQ) could not be determined due to missing HIV RNA counts, the imputed HIV RNA values were compared with the LOQ of 50 copies/mL and 400 copies/mL to determine individual successes or failures of these endpoints. The

method of Last Observations Carried Forward (LOCF) and repeated measure mixed modeling of longitudinal data were also used to assess sensitivity of the above methodologies.

Safety: The incidence of AEs was summarized by body system and by severity and relation to study drug. The incidence and timing of ADEs and the proportion of subjects with detectable CXCR4-tropism were summarized by treatment arm. Laboratory data were listed, and values outside the normal ranges were flagged. Abnormal findings on physical exams were also listed. The safety analysis was evaluated in all treated subjects, which comprised all subjects who had taken at least one dose of study medication. Subjects were analyzed according to the actual treatment received, regardless of treatment group assignment.

An independent, external DSMB reviewed study data on a regular basis to ensure continued safety of the participants. An independent committee of HIV experts reviewed data from any reported ADEs to ensure a consistent evaluation of these events.

Interim Analyses: Two interim analyses were performed at Weeks 24 and 48 of Stage 1. The first planned interim analysis occurred when all 95 subjects from Stage 1 had completed 24 weeks of randomized treatment or discontinued; this analysis was presented in a previous abbreviated clinical study report. The purpose of this interim analysis was to ensure the safety of study participants. The results of the Week 24 interim analysis were reviewed by an independent DSMB. Based upon results of the Week 24 interim analysis, the study proceeded into Stage 2, in which an additional 123 subjects were enrolled into a 96-week treatment period. A second interim analysis was performed on 08 Sep 2009 after the first 80 subjects enrolled in Stage 1 completed 48 weeks of treatment or discontinued. A complete evaluation of all primary and secondary efficacy and safety parameters took place based on all available data in the second interim analysis. No concerns were raised.

A final interim analysis was performed on 02 Jun 2010 when subjects enrolled in Stage 2 of the study had completed 24 weeks of treatment or discontinued. No concerns were raised.

RESULTS:

Efficacy: This abbreviated CSR is primarily a safety report. A brief summary of primary and key secondary efficacy results at Week 48 and final outcomes at Week 96 is provided. The VCV and Truvada treatment arms had similar reductions in plasma HIV RNA. The 95% CI for the between-treatment differences in the primary endpoint, using the least-squares mean $\log_{10}$ change from baseline HIV-RNA at Week 48, included zero. A similar proportion of subjects in the VCV and Truvada treatment arms had HIV-RNA levels below 50 copies/mL at Week 48 and Week 96. The 95% CIs for odds ratios (VCV vs. Truvada) included unity.

Tabulated summaries and graphical representations of efficacy analyses are provided in Section 14.2. Listings of individual efficacy data are provided in Section 16.2.6.

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Summary of Primary and Key Secondary Efficacy Endpoints at Week 48 and Final Outcomes at Week 96 (mITT Population)

LS Mean log_{10} Change from Baseline HIV-RNA (SE)						
Time Point	Type of Analysis	VCV + ATV/r N=108		Truvada + ATV/r N=108		LS Mean Difference (95% CI) [c]
Baseline [a]	N/A	108	4.66 (0.64)	108	4.63 (0.62)	N/A
TW 48	ANOVA, NC=F [b]	108	-2.40 (0.11)	108	-2.56 (0.11)	0.16 (-0.14, 0.46)
TW 96	ANOVA, NC=F [b]	46	-2.22 (0.21)	48	-2.37 (0.20)	0.15 (-0.43, 0.74)
Proportion of Subjects with Plasma HIV RNA <50 copies/mL (%)						
Time Point	Type of Analysis	VCV + ATV/r N=108		Truvada + ATV/r N=108		Odds Ratio (95% CI) [d]
Baseline	N/A	0/108		0/108		N/A
TW 48	LR, NC=F [e]	82/108 (75.93)		90/108 (83.33)		0.63 (0.32, 1.23)
TW 96	LR, NC=F [e]	32/46 (69.57)		35/48 (72.92)		0.81 (0.32, 2.05)

ANOVA = analysis of variance; ATV/r = ritonavir-boosted atazanavir; CI = confidence interval; LS = least squares; MITT = modified intent to treat; NC=F = noncompleter equals failure; SE = standard error; TW = Treatment Week; VCV = vicriviroc.

Note: The mITT population included all treated subjects with R5-tropic HIV at baseline by Monogram assay (n=216).

Note: The ANOVA and LR models were adjusted for treatment and stratification factors: baseline HIV RNA (<100,000 vs ≥100,000 copies/mL) and baseline CD4 counts (<200 vs ≥200/mm^3).

[a] Means are raw means with standard deviations for baseline values and LS means with standard errors for the changes from baseline.

[b] Missing values of change from baseline were imputed using the geometric mean of immediately preceding and following non-missing values, and in any other cases, missing values were imputed as zero.

[c] LS mean difference for VCV – Truvada.

[d] Cochran-Mantel-Haenszel estimator of odds ratio (VCV vs Truvada) adjusted for stratification factors.

[e] Missing values of HIV-RNA were imputed using the geometric mean of immediately preceding and following non-missing values, and in any other cases, missing values were imputed as baseline value.

Source Data: Section 14.2.1.1, Section 14.2.2.1.

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Safety:

Summary of Adverse Events (All Treated Subjects, 96-Week Treatment Phase)

Adverse Events	VCV + ATV/r n=109 Total Exposure Years = 141.05 n (%)	Rate [a]	Truvada + ATV/r n=108 Total Exposure Years = 146.53 n (%)	Rate [a]
Treatment-emergent AE	107 (98)	75.86	100 (93)	68.25
Treatment-related AE	33 (30)	23.40	37 (34)	25.25
Any serious AE [b]	13 (12)	9.22	12 (11)	8.19
Grade 3 or 4 Treatment-emergent AE	18 (17)	12.76	16 (15)	10.92
AEs that led to discontinuation [b,c]	9 (8)	6.38	1 (1)	0.68
Deaths [b,c]	0	0.00	0	0.00

AE = adverse event, ATV/r =ritonavir-boosted atazanavir, VCV = vicriviroc.

[a] Rate = Incidence / 100 person-years.

[b] All events are reported, regardless of whether or not they were treatment-emergent.

[c] Including AIDS-defining events.

Source Data: Section 14.3.1.1.1.

During the Open Label Extension Phase, 6 (21%) of 28 subjects reported treatment-emergent AEs; none was considered treatment related. The exposure-adjusted rate of treatment-emergent events was similar to that reported during the 96-Week Treatment Phase (68 vs 75 per 100 person-years of VCV exposure, respectively). No serious or Grade 3 or 4 AE was reported, and no AE led to discontinuation or resulted in death during the Open Label Extension Phase.

Vicriviroc was generally well tolerated and safe in this treatment-naïve population. The most commonly reported AEs during the 96-week treatment phase were disorders related to bilirubin metabolism, presumably related to atazanavir, and the aggregated rates for these terms were comparable between study arms.

Malignancy was infrequently reported (2% in each arm during the 96-week treatment phase) and generally considered unrelated to study drug. Rates of hepatotoxicity, dyslipidemia, and infection (upper respiratory and HSV) were not increased in VCV recipients in comparison with Truvada recipients. Cardiovascular events were rare (1% per arm during the 96-week treatment phase), not serious, and not considered related to study drug.

Most subjects began the study with normal safety laboratory parameters. Abnormalities on study, with the exception of increased total bilirubin, were infrequent and usually limited to single grade changes.

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CONCLUSIONS:

The following conclusions can be drawn from this study:

- VCV showed efficacy at Week 48 comparable to Truvada, when administered in combination with ritonavir-boosted atazanavir to individuals with CCR5-tropic HIV.
- VCV was generally well tolerated. Rates of serious adverse events were similar between the treatment arms. A small proportion of subjects discontinued for adverse events, mainly due to the atazanavir component of treatment.