Merck & Co., Inc. Study Synopsis

1. **Proprietary Drug Name**:	2. **Generic Drug Name**:	3. **Therapeutic area and FDA-approved indications**:
Crixivan	Indinavir sulfate	HIV Infection

4. **Name of Sponsor/Company**:	Merck & Co., Inc.
5. **Title of Study**:	A Multicenter, Double-Blind, Randomized, One-Year Study to Evaluate the Safety and Activity of MK-0639 Administered in Combination With Zidovudine and 3TC™ Versus Zidovudine and 3TC™ Versus MK-0639 Monotherapy for the Treatment of HIV Infection (Eighth-Year Extension) - No NCT # available (PN 035-50)
6. **Study Investigators/Study Center(s)**:	Multicenter, U.S.

7. **Studied Period (years)**: *(Date of first enrollment) (date of last completed)*	8. **Phase of development**:
28-Apr-1995 to June-2003 (eight years); however report is on six-year data.	IIb

9. Primary Hypotheses and Secondary Hypothesis:

Primary:

Administration of MK-0639 in combination with zidovudine and lamivudine for a cumulative duration of up to 404 weeks will be generally safe and well tolerated based on the incidence of serious, drug-related adverse events.

10. **Study Design/ Methodology**:	Open-label 48-week extension (cumulative Study Weeks 357 through 404).

11. Number of Patients (planned and analyzed):

Up to 34 patients, who had participated in Protocol 035 for a total of 356 weeks and who were tolerating the study drug regimens, willing to comply with protocol requirements and procedures, and willing to keep scheduled extension study visits were planned. Thirty-three patients actually entered the current study after completing 356 weeks of study therapy.

12. **Diagnosis and main criteria for inclusion**:	HIV-1 seropositive zidovudine-experienced (≥6 months) male or female patients 18 years of age or older who had CD4 cell counts between 50 and 400 cells/mm^3 and serum viral RNA levels ≥20,000 copies/mL at study entry. In order for a patient to continue in Protocol 035-50, the patient needed to complete 356 weeks in Protocol 035-41.

13. Test product and reference therapy (if applicable); dose and mode of administration; batch number:	Patients received orally capsules or tablets of: Indinavir 800 mg q8h and lamivudine/zidovudine combination 150/300 mg b.i.d..
14. Duration of treatment:	Additional 48-weeks of Open-label therapy.
15. Criteria for Evaluation:	**Efficacy:** Evaluated using two surrogate markers: CD4 cell counts and serum viral RNA. **Safety:** Evaluated by tabulating all adverse experiences, serious adverse experiences, serious drug-related adverse experiences, adverse experiences relating to nephrolithiasis, and clinically significant laboratory abnormalities.
16. Statistical methods:	**Safety:** The safety of MK-0639 will be assessed through the evaluation of adverse experiences with particular focus on estimating the incidence of serious, drug-related clinical and laboratory adverse experiences. **Efficacy:** Antiviral effect will be evaluated by changes in the immunological (CD4 cell count) and virological (serum viral RNA) surrogate markers of activity. Summary statistics will be tabulated and/or graphically displayed to show the profile of CD4 cell count and serum viral RNA values and/or changes by study week. The proportion of patients with viral RNA below 500 copies/mL by the AMPLICOR™ assay and 50 copies/mL by the Ultradirect assay will be estimated. Confidence intervals will be used to make inference from the sample to the population.

17. Summary: Originally, 33 subjects were randomized to receive zidovudine, lamivudine, and indinavir. The subjects were 31 (94%) men and two (6%) women; 26 (79%) white, two (6%) black, three (9%) hispanic, and two (6%) other. At baseline, subjects had taken zidovudine for a median of 28 months, had a median serum HIV-1 RNA of 41,900 copies/ml (range, 7550–219,040), a median CD4 cell count of 133 x 10^6 cells/l (range, 35–433) and 25 of 32 (78%) had genotypic evidence of zidovudine resistance. Two subjects substituted stavudine for zidovudine during the study. Of the 33 subjects, 16 (48%) discontinued study therapy before 6 years: seven for increased HIV-1 RNA levels (at weeks 58, 79, 118, 123, 134, 137, and 148), two for contraindicated medications (rifampin, week 8; chemotherapy for Kaposi's sarcoma, week 32), four for nephrolithiasis/urinary tract obstruction (at weeks 157, 171, 182, and 221); one for nausea (week 4), and two for patient request (at weeks 127 and 269). Questionnaire data were obtained for 12 of 16 subjects who discontinued the study. Of the others, one moved, one refused, one was not available, and one died without further information available. No subjects died while participating in the study. Three subjects were known to have died after study discontinuation: one with Kaposi's sarcoma died 9 months later of disseminated disease; one who discontinued at week 137 because of increased HIV RNA levels died 6 weeks later of a myocardial infarction; and one who discontinued at week 4 for nausea died

subsequently (date/cause of death unknown).

Antiretroviral activity:

The proportions of contributing subjects who had HIV-1 RNA , 500 and , 50 copies/ml, respectively, were 78% and 75% at 1 year, 78% and 66% at 2 years, 68% and 65% at 3 years, 58% and 55% at 4 years, 58% and 48% at 5 years, and 53% (16 of 30 subjects) and 47% (14 of 30 subjects) at 6 years (Fig. 1). Overall, the group had a median reduction in HIV-1 RNA levels from baseline of 2.0 log10 copies/ml, sustained through 6 years. In total, 10 subjects experienced virological failure on the study: six in year 1, three in year 3, and one in year 6. The median increases in CD4 cell counts from baseline were 155 (1 year), 209 (2 years), 230 (3 years), 219 (4 years), 298 (5 years), and 268 x 10^6 cells/l (6 years).

Of the 12 subjects with post-study questionnaire data, four who had virological failure on the study regimen and three who discontinued the study regimen owing to adverse events subsequently had HIV-1 RNA, 500 copies/ml at 5–6 years on other antiretroviral regimens; four subjects had HIV-1 RNA . 500 copies/ml and one had no post-study virological data available. Subjects took 12 different post-study antiretroviral regimens.

Adverse events

Four subjects experienced serious drug-related adverse events related to nephrolithiasis, and three of them required urinary tract stenting. Two of these four also experienced other serious, drug-related adverse events (generalized pain; abdominal pain). In total, 14 of 33 (42%) had at least one episode of nephrolithiasis over 5 years. The incidence rate is 17 patients with nephrolithiasis events per 100 patient-years of follow-up. Of 17 subjects assessed at approximately 6 years, 10 (59%) fulfilled the definition of lipodystrophy.

18. Date of the report:	19-Feb-08
19. Contact:	Merck National Service Center 1.800.672.6372