Study Synopsis

1. Proprietary Drug Name	2. Generic Drug Name	3. Therapeutic Area/ Indication
CRIXIVAN®	Indinavir Sulfate	Infectious Disease/HIV

4. Name of Sponsor/Company: Merck & Co., Inc., Whitehouse Station, New Jersey, USA

5. Title of Study: A Multicenter, Open-Label, Randomized Study to Compare the Efficacy and Safety of Indinavir 800 mg b.i.d. Plus Ritonavir 100 mg b.i.d. Plus Two NRTIs vs. Nelfinavir 1250 mg b.i.d. Plus Two NRTIs in HIV-1 Seropositive Patients Who Have Failed Or Are Intolerant to an NNRTI Containing Regimen (Protocol 112)

6. Study Investigators/Study centre(s): A total of 38 centers in the United States participated in the study.

Number of Patients Entered by Investigator

Site number	IDV/RTV 800/100 mg bid (N=48)	NFV 1250 mg bid (N=49)	Total (N=97)
112002	2	0	2
112004	1	0	1
112007	1	1	2
112009	2	1	3
112012	1	1	2
112014	1	0	1
112016	1	2	3
112019	1	1	2
112020	1	0	1
112023	0	1	1
112026	2	2	4
112027	0	1	1
112029	0	1	1
112037	1	1	2
112038	1	1	2
112042	1	0	1
112043	1	2	3
112044	1	0	1
112049	1	1	2
112051	0	1	1
112052	7	8	15

112062	1	0	1
112065	0	1	1
112066	1	1	2
112067	1	1	2
112068	1	0	1
112071	8	8	16
112073	0	1	1
112075	1	0	1
112076	1	0	1
112080	1	2	3
112084	1	0	1
112088	0	1	1
112089	1	2	3
112090	0	1	1
112095	1	1	2
112096	2	1	3
112099	2	4	6

7. Study period (years): 11-Jan-2001 to 30-May-2003

8. Phase of development: IIb

9. Primary Hypothesis

In HIV-1 infected patients who have failed or are intolerant to an NNRTI-containing regimen, indinavir 800 mg plus ritonavir 100 mg b.i.d. plus 2 NRTIs will be at least as effective as nelfinavir 1250 mg b.i.d. plus 2 NRTIs with respect to the proportion of patients with plasma viral RNA < 400 copies/mL after 24 weeks of randomized therapy. Indinavir plus ritonavir will be considered at least as effective as nelfinavir if the lower bound of the 95% confidence interval for the difference in proportions (indinavir/ritonavir minus nelfinavir) excludes differences as large as -12 percentage points.

If the above can be established, the following will be evaluated:

In HIV-1 infected patients who have failed or are intolerant to an NNRTI-containing regimen, indinavir 800 mg plus ritonavir 100 mg b.i.d. plus 2 NRTIs will be superior to nelfinavir 1250 mg b.i.d. plus 2 NRTIs with respect to the proportion of patients with plasma viral RNA < 400 copies/mL after 24 weeks of randomized therapy. Indinavir plus ritonavir will be considered superior to nelfinavir if the lower bound of the 95% confidence interval for the difference in proportions (indinavir/ritonavir minus nelfinavir) is greater than 0 and the upper bound of the confidence interval is greater than 12 percentage points.

Secondary Hypothesis

1. In HIV-1 infected patients who have failed or are intolerant to an NNRTI-containing regimen, indinavir 800 mg plus ritonavir 100 mg b.i.d. plus 2 NRTIs will be at least as effective as nelfinavir 1250 mg b.i.d. plus 2 NRTIs with respect to the proportion of patients with plasma viral RNA < 400 copies/mL after 48 weeks of randomized therapy. Indinavir plus ritonavir will be considered at least as effective as nelfinavir if the lower bound of the 95% confidence interval for the difference in proportions (indinavir/ritonavir minus nelfinavir) excludes differences as large as -12 percentage points.

If the above can be established, the following will be evaluated:

In HIV-1 infected patients who have failed or are intolerant to an NNRTI-containing regimen, indinavir 800 mg plus ritonavir 100 mg b.i.d. plus 2 NRTIs will be superior to nelfinavir 1250 mg b.i.d. plus 2 NRTIs with respect to the proportion of patients with plasma viral RNA < 400 copies/mL after 48 weeks of randomized therapy. Indinavir plus ritonavir will be considered superior to nelfinavir if the lower bound of the 95% confidence interval for the difference in proportions (indinavir/ritonavir minus nelfinavir) is greater than 0 and the upper bound of the 95% confidence interval is greater than 12 percentage points.

2. The proportion of patients with plasma viral RNA < 50 copies/mL in the indinavir 800 mg/ritonavir 100 mg b.i.d. treatment group will be similar to that observed in the nelfinavir 1250 mg b.i.d. treatment group.
3. The changes from baseline in CD4 cell counts in the indinavir 800 mg/ritonavir 100 mg b.i.d. treatment group will be similar to that observed in the nelfinavir 1250 mg b.i.d. treatment group.
4. The two regimens will have a similar safety/tolerability profile, as judged by (a) the incidence of patients with serious, drug-related adverse experiences and (b) the incidence of patients that discontinue study due to drug-related adverse experiences.

10. **Study Design/Methodology**: Multicenter, open-label, randomized, 48-week two-treatment, parallel study with non-inferiority (nested superiority) design. Patients were stratified based on NNRTI failure vs. intolerability to NNRTIs.

11. Number of patients (planned and analyzed):
There were 330 patients planned and 97 patients enrolled. Enrollment was difficult as new therapies became available during the course of the study. The study was stopped after the 18-month planned enrollment period because of slow enrollment.

12. Diagnosis and main criteria for inclusion:
Adult patients must have been HIV-1 seropositive. Patients must have initially responded to, then subsequently failed, an NNRTI regimen, or they had never responded to an NNRTI regimen, or they were intolerant to an NNRTI. Patients who failed or had never responded to an NNRTI regimen must have had a pre-study viral load $\geq$ 2,000 copies/mL. Patients who were intolerant to an NNRTI regimen could enroll with any viral load. Patients must have had a CD4 count $\geq$50 cells/mm^3.

13. Test and reference therapy (if applicable) product, dose and mode of administration, batch number:

Patients were stratified by NNRTI use and randomized to receive one of the following treatments:

Group 1: indinavir 800 mg plus ritonavir 100 mg b.i.d. plus 2 NRTIs*

Group 2: nelfinavir 1250 mg b.i.d. plus 2 NRTIs*

* The choice of NRTIs was determined by the investigator based on the results of the phenotypic and genotypic susceptibility or based on previous history of previous antiretroviral therapy. When using history to chose NRTI therapy, agent (s) were to be selected that had a different susceptibility pattern from other drugs to which the patient had been exposed, when possible.

14. **Duration of treatment**: 48 weeks

15. Criteria for evaluation:

Efficacy: CD4 cell counts and plasma viral RNA were measured at screen 1, Pre-treatment- Day 1, Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, and 48.

Safety: Physical examination and laboratory tests of blood and urine were performed at screen 2, Pre-treatment – Day 1, Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, and 48. A chest x-ray was done before the study.

16. **Statistical methods**: The primary efficacy analysis was based on the intent-to-treat approach, which included all randomized patients in the groups to which they were randomly assigned, regardless of their adherence with the entry criteria, the treatment they actually received, and subsequent withdrawal from treatment or deviation from the protocol.

1)Percentage of Patients with Plasma Viral RNA Below Specified Levels

The proportion of patients with vRNA below the specified levels was to be estimated for each treatment group at each time point, along with corresponding 95% confidence intervals. Treatment differences and 95% confidence intervals were also estimated at each time point.

Estimation was done using three different approaches. The primary approach was "Model Based," which applied a simple generalized estimating equation (GEE) model. This GEE model-based approach estimated the proportions of patients responding based on the observed data, with the therapy-related withdrawals counted as failures (i.e., vRNA above specified level), missing completely at random assumed for other patients with missing data, and an assumed autoregressive AR(1) correlation among the repeated measurements over time. A second approach was "Data As Observed" and used all observed data, i.e., ignoring dropouts. A third approach was the "Dropout=Failure" approach, where all missing values due to dropouts were assumed to be failures.

2) Changes from Baseline in Plasma Viral RNA and CD4 Cell Counts

In the analysis of the changes from baseline in vRNA and absolute CD4 cell counts, changes were calculated for each patient, and routine summary statistics were provided at each time point. A "Model Based" approach was used, where values that were missing due to therapy-related discontinuations were imputed using the last observation carried forward (LOCF) method. Estimation was done using a generalization of analysis of covariance, which allows for correlation and non-constant variability in longitudinal data. An AR(1) covariance structure was used, and the model was fit to the data using the method of restricted maximum likelihood (REML).

Estimation was also done using data as observed, with an analysis of covariance model including terms for treatment and the baseline covariate. Ninety-five percent confidence intervals about the differences between treatment groups in the changes from baseline were calculated at each time point.

17. SUMMARY

Patient Accounting

Although expected to enroll approximately 330 patients, this study was discontinued early due to poor enrollment. Ninety-seven (97) patients were randomized, with 48 randomized to indinavir/ritonavir and 49 randomized to nelfinavir (Table 1).

Table 1

Patient Accounting

	IDV/RTV 800/100 mg bid		NFV 1250 mg bid		Total	
	n	%	n	%	n	%
SCREENING FAILURES					55	
RANDOMIZED	48		49		97	
Male (age range)	37	(28 to 73)	35	(21 to 62)	72	(21 to 73)
Female (age range)	11	(28 to 62)	14	(25 to 64)	25	(25 to 64)
COMPLETED	24	(50.0)	26	(53.0)	50	(51.5)
DISCONTINUED	24	(50.0)	23	(46.9)	47	(48.4)
clinical AE	9	(18.7)	3	(6.1)	12	(12.3)
laboratory AE	3	(6.2)	0	(0.0)	3	(3.1)
lack efficacy	1	(2.1)	4	(8.2)	5	(5.2)
lost to follow-up	5	(10.4)	5	(10.2)	10	(10.3)
pat. discont. for other	2	(4.2)	0	(0.0)	2	(2.1)
pat. Moved	0	(0.0)	3	(6.1)	3	(3.1)
pat. withdrew consent	2	(4.2)	6	(12.2)	8	(8.2)
protocol dev	2	(4.2)	2	(4.1)	4	(4.1)

EFFICACY RESULTS:

At baseline, 12.5% of indinavir/ritonavir patients and 16.3% of nelfinavir patients had vRNA < 400 copies/mL. From the model based approach at Week 24, 63.0% of indinavir/ritonavir patients and 60.9% of nelfinavir patients had vRNA < 400 (Table 2). The estimated treatment difference was 2.1% with a 95% confidence interval of -19.0 to 23.1. By Week 48, this treatment difference decreased to 0.6% (48.7% for indinavir/ritonavir versus 48.1% for nelfinavir, CI = -22.9% to 24.0%).

Table 2
Percentage Of Patients with viral RNA < 400 Copies/mL (Amplicor Assay)
Model Based Approach

	Treatment							
	Indinavir+Ritonavir			Nelfinavir				
Time Point	N*	%	(95% CI)	N*	%	(95% CI)	Estimated Difference	95% CI)+
Week 0	48	12.5	(5.7,25.2)	49	16.3	(8.4,29.4)	-3.8	(-17.8,10.1)
Week 2	43	38.9	(25.9,53.6)	44	31.3	(19.8,45.7)	7.5	(-11.8,26.9)
Week 4	44	55.4	(41.0,69.0)	44	51.8	(37.8,65.6)	3.6	(-16.7,23.9)
Week 8	45	65.7	(51.0,77.9)	45	54.2	(39.8,67.9)	11.5	(-8.4,31.5)
Week 12	43	64.1	(49.2,76.7)	41	61.5	(46.8,74.3)	2.6	(-17.3,22.5)
Week 16	39	55.8	(40.5,70.1)	39	60.0	(45.2,73.3)	-4.3	(-25.3,16.7)
Week 20	38	64.8	(49.1,77.8)	37	63.8	(48.4,76.8)	1.0	(-19.7,21.7)
Week 24	39	63.0	(47.4,76.3)	35	60.9	(45.5,74.5)	2.1	(-19.0,23.1)
Week 32	38	44.6	(30.0,60.2)	33	59.9	(44.1,73.9)	-15	(-37.1,6.6)
Week 40	37	52.3	(36.7,67.4)	34	49.5	(33.7,65.4)	2.8	(-20.0,25.6)
Week 48	36	48.7	(33.3,64.3)	30	48.1	(31.8,64.8)	0.6	(-22.9,24.0)

N*: Number of patients with available data at indicated time point.
CI=Confidence Interval
(95% CI)+: The 95% CI interval for estimated difference of proportions is generated from the delta method applied to GEE estimates.

Using the data-as-observed approach, the Week 24 estimates were 80.6% for indinavir/ritonavir and 66.7% for nelfinavir (Table 3). The treatment difference was 14.0% (CI = -7.7% to 33.8%).

Table 3
Percentage of Patients with viral RNA < 400 Copies/mL (Amplicor Assay)
Data As Observed

	Treatment							
	Indinavir+Ritonavir			Nelfinavir				
Time Point	n / N1*	%	(95% CI)	n / N2*	%	(95% CI)	Estimated Difference	(95% CI)+
Week 0	6/48	12.5	(4.7,25.2)	8/49	16.3	(7.3,29.7)	-3.8	(-18.2,10.7)
Week 2	17/39	43.6	(27.8,60.4)	13/41	31.7	(18.1,48.1)	11.9	(-9.0,31.5)
Week 4	24/42	57.1	(41.0,72.3)	23/43	53.5	(37.7,68.8)	3.7	(-16.8,23.7)
Week 8	30/43	69.8	(53.9,82.8)	25/44	56.8	(41.0,71.7)	12.9	(-7.1,31.6)
Week 12	28/39	71.8	(55.1,85.0)	25/38	65.8	(48.6,80.4)	6.0	(-14.3,25.7)
Week 16	23/33	69.7	(51.3,84.4)	23/36	63.9	(46.2,79.2)	5.8	(-16.0,26.6)
Week 20	24/30	80.0	(61.4,92.3)	22/32	68.8	(50.0,83.9)	11.3	(-10.6,31.5)
Week 24	25/31	80.6	(62.5,92.5)	22/33	66.7	(48.2,82.0)	14.0	(-7.7,33.8)
Week 32	17/26	65.4	(44.3,82.8)	20/30	66.7	(47.2,82.7)	-1.3	(-25.1,22.2)
Week 40	19/23	82.6	(61.2,95.0)	18/30	60.0	(40.6,77.3)	22.6	(-2.4,43.1)
Week 48	17/23	73.9	(51.6,89.8)	16/23	69.6	(47.1,86.8)	4.3	(-20.9,28.9)

N*: Number of patients with available data at indicated time point.
CI=Confidence Interval
(95% CI)+: The 95% CI interval for estimated difference of proportions is generated by the Wilson's Score Method.

From the dropout=failure approach, the estimates were 52.1% for indinavir/ritonavir and 44.9% for nelfinavir, with a treatment difference of 7.2% (CI = -12.3% to 25.9%) (Table 4).

Table 4

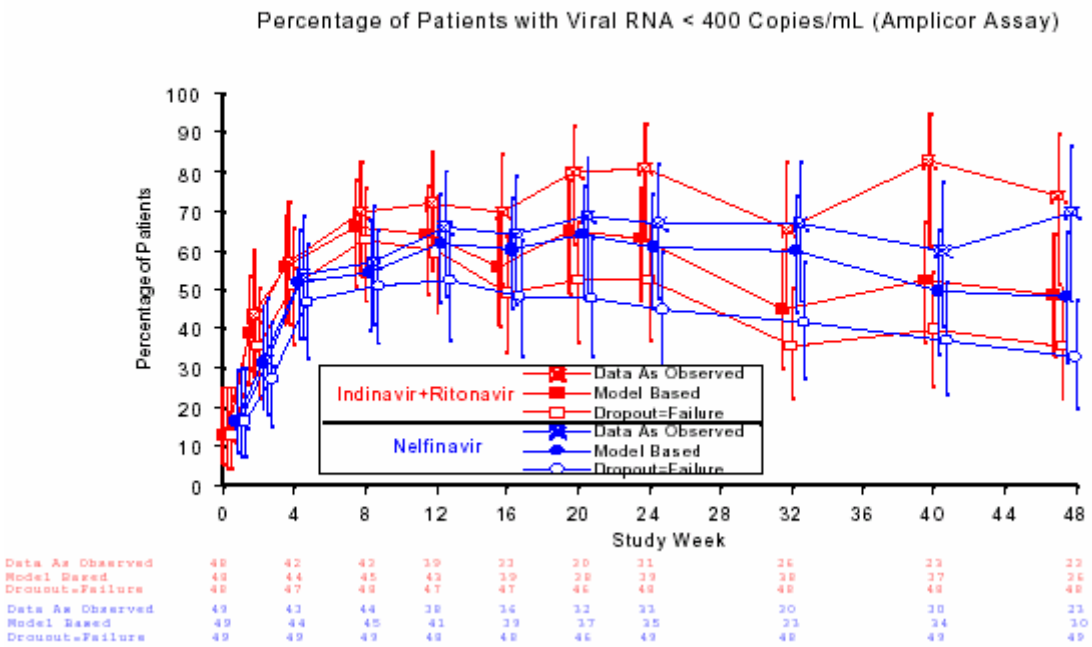
Percentage of Patients with viral RNA < 400 Copies/mL (Amplicor Assay)
Dropout=Failure Approach

Time Point	Indinavir+Ritonavir n / N1*	%	(95% CI)	Nelfinavir n / N2*	%	(95% CI)	Estimated Difference	(95% CI)+
Week 0	6/48	12.5	(4.7,25.2)	8/49	16.3	(7.3,29.7)	-3.8	(-18.2,10.7)
Week 2	17/48	35.4	(22.2,50.5)	13/48	27.1	(15.3,41.8)	8.3	(-10.0,26.0)
Week 4	24/47	51.1	(36.1,65.9)	23/49	46.9	(32.5,61.7)	4.1	(-15.3,23.1)
Week 8	30/48	62.5	(47.4,76.0)	25/49	51.0	(36.3,65.6)	11.5	(-8.0,29.8)
Week 12	28/47	59.6	(44.3,73.6)	25/48	52.1	(37.2,66.7)	7.5	(-12.1,26.3)
Week 16	23/47	48.9	(34.1,63.9)	23/48	47.9	(33.3,62.8)	1.0	(-18.4,20.3)
Week 20	24/46	52.2	(36.9,67.1)	22/46	47.8	(32.9,63.1)	4.3	(-15.5,23.7)
Week 24	25/48	52.1	(37.2,66.7)	22/49	44.9	(30.7,59.8)	7.2	(-12.3,25.9)
Week 32	17/48	35.4	(22.2,50.5)	20/48	41.7	(27.6,56.8)	-6.2	(-24.7,12.8)
Week 40	19/48	39.6	(25.8,54.7)	18/49	36.7	(23.4,51.7)	2.8	(-16.0,21.4)
Week 48	17/48	35.4	(22.2,50.5)	16/49	32.7	(19.9,47.5)	2.8	(-15.6,21.0)

N*: Number of contributing Patients
CI=Confidence Interval
(95% CI)+: The 95% CI interval for estimated difference of proportions is generated by the Wilson's Score Method.

The three approaches are compared graphically in Figure 1

Figure 1



Data As Observed	48	42	42	39	33	30	31	26	33	33
Model Based	48	44	45	43	39	38	39	38	37	36
Dropout=Failure	48	47	48	47	47	46	48	48	48	48
Data As Observed	49	43	44	38	36	32	33	30	38	33
Model Based	49	44	45	41	39	37	35	33	34	30
Dropout=Failure	49	49	49	48	48	46	49	48	49	49

At baseline, 6.2% of indinavir/ritonavir patients and 10.2% of nelfinavir patients had vRNA < 50 copies/mL. From the model based approach at Week 24, 50.3% of indinavir/ritonavir patients and 46.4% of nelfinavir patients had vRNA < 50 (Table 5). The estimated treatment difference was 3.9% with a 95% confidence interval of -18.4% to 26.1%

Table 5

Percentage of Patients with viral RNA < 50 Copies/mL (Ultra-Sensitive Assay)
Model Based Approach

	Treatment							
	Indinavir+Ritonavir			Nelfinavir				
Time Point	N*	%	(95% CI)	N*	%	(95% CI)	Estimated Difference	(95% CI)+
Week 0	48	6.2	(2.0,17.7)	49	10.2	(4.3,22.3)	-4.0	(-14.9,6.9)
Week 2	45	8.5	(3.2,20.7)	45	15.6	(7.9,28.5)	-7.1	(-20.0,5.9)
Week 4	44	15.7	(7.7,29.3)	45	22.5	(12.8,36.5)	-6.8	(-22.7,9.1)
Week 8	45	37.4	(24.7,52.1)	45	28.2	(17.1,42.8)	9.1	(-10.0,28.3)
Week 12	43	45.4	(31.4,60.1)	41	39.4	(26.3,54.2)	6.0	(-14.6,26.6)
Week 16	39	41.9	(27.9,57.3)	39	50.0	(35.2,64.8)	-8.1	(-29.6,13.4)
Week 20	38	43.6	(29.3,59.1)	37	47.2	(32.4,62.6)	-3.6	(-25.5,18.3)
Week 24	39	50.3	(35.2,65.2)	35	46.4	(31.2,62.2)	3.9	(-18.4,26.1)
Week 32	38	31.7	(19.1,47.8)	33	41.7	(27.1,57.9)	-10	(-31.6,11.7)
Week 40	37	40.1	(26.0,56.1)	34	28.1	(15.6,45.2)	12.0	(-9.7,33.6)
Week 48	36	39.6	(25.3,55.9)	30	32.0	(18.2,50.0)	7.6	(-15.2,30.3)

N*: Number of patients with available data at indicated time point.
CI=Confidence Interval
(95% CI)+: The 95% CI interval for estimated difference of proportions is generated from the delta method applied to GEE estimates.

Using the data-as-observed approach, the Week 24 estimates were 64.5% for indinavir/ritonavir and 48.5% for nelfinavir (Table 6). The treatment difference was 16.0% (CI = -7.9% to 37.5%).

Table 6

Percentage of Patients with viral RNA < 50 Copies/mL (Ultra-Sensitive Assay)
Data As Observed

Time Point	Treatment: Indinavir+Ritonavir n / N1*	%	(95% CI)	Treatment: Nelfinavir n / N2*	%	(95% CI)	Estimated Difference	(95% CI)+
Week 0	3/48	6.3	(1.3,17.2)	5/49	10.2	(3.4,22.2)	-4.0	(-16.2,8.1)
Week 2	4/39	10.3	(2.9,24.2)	7/41	17.1	(7.2,32.1)	-6.8	(-22.3,9.0)
Week 4	7/42	16.7	(7.0,31.4)	10/43	23.3	(11.8,38.6)	-6.6	(-23.3,10.6)
Week 8	17/43	39.5	(25.0,55.6)	13/44	29.5	(16.8,45.2)	10.0	(-9.7,28.7)
Week 12	20/39	51.3	(34.8,67.6)	16/38	42.1	(26.3,59.2)	9.2	(-12.6,29.8)
Week 16	17/33	51.5	(33.5,69.2)	19/36	52.8	(35.5,69.6)	-1.3	(-23.6,21.2)
Week 20	16/30	53.3	(34.3,71.7)	15/32	46.9	(29.1,65.3)	6.5	(-17.5,29.4)
Week 24	20/31	64.5	(45.4,80.8)	16/33	48.5	(30.8,66.5)	16.0	(-7.9,37.5)
Week 32	12/26	46.2	(26.6,66.6)	13/30	43.3	(25.5,62.6)	2.8	(-21.8,27.2)
Week 40	15/23	65.2	(42.7,83.6)	10/30	33.3	(17.3,52.8)	31.9	(4.8,53.2)
Week 48	14/23	60.9	(38.5,80.3)	10/23	43.5	(23.2,65.5)	17.4	(-10.7,42.0)

N*: Number of patients with available data at indicated time point.
CI=Confidence Interval
(95% CI)+: The 95% CI interval for estimated difference of proportions is generated by the Wilson's Score Method.

From the dropout=failure approach, the estimates were 41.7% for indinavir/ritonavir and 32.7% for nelfinavir, with a treatment difference of 9.0% (CI = -9.9 to 27.1) (Table 7).

Table 7

Percentage of Patients with viral RNA < 50 Copies/mL (Ultra-Sensitive Assay)
Dropout=Failure Approach

Time Point	Treatment: Indinavir+Ritonavir n / N1*	%	(95% CI)	Treatment: Nelfinavir n / N2*	%	(95% CI)	Estimated Difference	(95% CI)+
Week 0	3/48	6.3	(1.3,17.2)	5/49	10.2	(3.4,22.2)	-4.0	(-16.2,8.1)
Week 2	4/48	8.3	(2.3,20.0)	7/49	14.3	(5.9,27.2)	-6.0	(-19.3,7.4)
Week 4	7/48	14.6	(6.1,27.8)	10/49	20.4	(10.2,34.3)	-5.8	(-21.0,9.6)
Week 8	17/48	35.4	(22.2,50.5)	13/49	26.5	(14.9,41.1)	8.9	(-9.3,26.4)
Week 12	20/48	41.7	(27.6,56.8)	16/49	32.7	(19.9,47.5)	9.0	(-9.9,27.1)
Week 16	17/48	35.4	(22.2,50.5)	19/49	38.8	(25.2,53.8)	-3.4	(-21.8,15.4)
Week 20	16/47	34.0	(20.9,49.3)	15/46	32.6	(19.5,48.0)	1.4	(-17.2,19.9)
Week 24	20/48	41.7	(27.6,56.8)	16/49	32.7	(19.9,47.5)	9.0	(-9.9,27.1)
Week 32	12/48	25.0	(13.6,39.6)	13/48	27.1	(15.3,41.8)	-2.1	(-19.3,15.3)
Week 40	15/48	31.3	(18.7,46.3)	10/49	20.4	(10.2,34.3)	10.8	(-6.6,27.5)
Week 48	14/48	29.2	(17.0,44.1)	10/49	20.4	(10.2,34.3)	8.8	(-8.4,25.4)

N*: Number of contributing Patients
CI=Confidence Interval
(95% CI)+: The 95% CI interval for estimated difference of proportions is generated by the Wilson's Score Method.

Viral RNA decreased from baseline, as seen in the $\log_{10}$ vRNA values over time. In the model based approach at Week 24, mean values were 2.67 and 2.82, which is a change from baseline of -1.07 and -1.03 in the indinavir/ritonavir and nelfinavir groups, respectively (Table 8). The treatment difference was -0.04, with a 95% confidence interval of -0.37 to 0.29. At Week 48, the treatment difference was -0.34 (CI = -0.69 to 0.01).

Table 8

Mean Change From Baseline from Baseline for Log10 HIV RNA (Amplicor Assay)
Model Based Approach

		Baseline			Treatment		Change			VS. Nelfinavir	
Time Point	Treatment	N	Mean	SD	Mean	SD	Mean	SE	95% CI	DIFF	95% CI
Week 2	Indinavir+Ritonavir	39	3.79	0.90	2.92	0.62	-0.88	0.12	(-1.11,-0.65)	-0.03	(-0.34,0.28)
	Nelfinavir	41	3.96	1.04	3.05	0.73	-0.85	0.11	(-1.07,-0.63)		
Week 4	Indinavir+Ritonavir	42	3.83	0.83	2.85	0.84	-0.97	0.11	(-1.20,-0.75)	-0.02	(-0.33,0.28)
	Nelfinavir	43	3.94	1.04	2.89	0.80	-0.95	0.11	(-1.16,-0.74)		
Week 8	Indinavir+Ritonavir	43	3.79	0.85	2.78	0.84	-1.00	0.11	(-1.23,-0.78)	-0.05	(-0.36,0.26)
	Nelfinavir	44	3.85	1.01	2.86	0.88	-0.96	0.11	(-1.17,-0.74)		
Week 12	Indinavir+Ritonavir	42	3.81	0.88	2.84	0.97	-0.96	0.11	(-1.19,-0.74)	0.11	(-0.20,0.42)
	Nelfinavir	39	3.94	1.04	2.79	0.77	-1.07	0.11	(-1.29,-0.85)		
Week 16	Indinavir+Ritonavir	38	3.80	0.86	2.75	0.81	-0.93	0.12	(-1.16,-0.70)	0.11	(-0.21,0.43)
	Nelfinavir	37	3.91	1.07	2.81	0.72	-1.04	0.11	(-1.26,-0.82)		
Week 20	Indinavir+Ritonavir	36	3.76	0.84	2.66	0.75	-1.08	0.12	(-1.31,-0.84)	-0.08	(-0.41,0.25)
	Nelfinavir	34	3.93	1.06	2.87	0.87	-0.99	0.12	(-1.22,-0.77)		
Week 24	Indinavir+Ritonavir	38	3.75	0.82	2.67	0.77	-1.07	0.12	(-1.30,-0.83)	-0.04	(-0.37,0.29)
	Nelfinavir	35	3.84	1.02	2.82	0.77	-1.03	0.12	(-1.26,-0.79)		
Week 32	Indinavir+Ritonavir	37	3.75	0.83	2.69	0.80	-1.07	0.12	(-1.31,-0.83)	-0.18	(-0.52,0.16)
	Nelfinavir	32	3.83	1.04	2.91	0.87	-0.89	0.12	(-1.12,-0.65)		
Week 40	Indinavir+Ritonavir	34	3.75	0.84	2.52	0.63	-1.15	0.12	(-1.40,-0.91)	-0.27	(-0.61,0.07)
	Nelfinavir	34	3.84	1.03	2.94	0.85	-0.88	0.12	(-1.12,-0.64)		
Week 48	Indinavir+Ritonavir	35	3.77	0.85	2.66	0.74	-1.14	0.12	(-1.38, -0.89)	-0.34	(-0.69, 0.01)
	Nelfinavir	30	3.85	1.07	2.97	0.87	-0.79	0.13	(-1.04, -0.54)		

N: Number of contributing patients
Change: Mean and SE are estimates from the longitudinal analysis model including a term for the baseline covariate.
VS. Nelfinavir: Diff is the estimated difference of Indinavir+Ritonavir - Nelfinavir.

CD4 cell counts increased from baseline, with mean Week 24 increases of 50.84 cells for the indinavir/ritonavir group and 64.15 cells for the nelfinavir group in the model-based approach (Table 9). The treatment difference was -13.31, with a 95% confidence interval of -87.32 to 60.70. At Week 48, the mean increases from baseline were 127.12 cells for the indinavir/ritonavir group and 73.22 cells for the nelfinavir group, with a treatment difference of 53.90 (CI = -25.18 to 132.98).

Table 9

Mean Change From Baseline from Baseline for CD4 Cell Counts
Model Based Approach

Time Point	Treatment	Baseline N	Baseline Mean	Baseline SD	Treatment Mean	Treatment SD	Change Mean	Change SE	Change 95% CI	VS. Nelfinavir DIFF	VS. Nelfinavir 95% CI
Week 2	Indinavir+Ritonavir	38	412.3	271	453.4	292	42.50	24.9	(-6.59,91.60)	30.27	(-40.37,100.91)
	Nelfinavir	40	374.7	254	388.6	311	12.23	25.9	(-38.86,63.33)		
Week 4	Indinavir+Ritonavir	41	416.4	277	421.1	265	12.03	24.2	(-35.76,59.83)	-23.28	(-92.32,45.77)
	Nelfinavir	42	359.5	229	398.5	248	35.31	25.4	(-14.81,85.43)		
Week 8	Indinavir+Ritonavir	43	422.8	275	464.1	249	41.44	24.0	(-5.94,88.83)	2.00	(-66.69,70.69)
	Nelfinavir	43	362.1	251	403.0	266	39.44	25.3	(-10.58,89.47)		
Week 12	Indinavir+Ritonavir	42	427.3	277	509.0	305	82.22	24.2	(34.46,129.99)	45.62	(-24.42,115.67)
	Nelfinavir	38	388.9	254	427.6	243	36.60	26.1	(-14.91,88.11)		
Week 16	Indinavir+Ritonavir	39	434.0	281	508.4	292	72.53	24.7	(23.64,121.41)	10.29	(-81.95,61.37)
	Nelfinavir	36	374.6	267	465.3	300	82.82	26.7	(30.17,135.46)		
Week 20	Indinavir+Ritonavir	34	422.4	291	502.2	317	78.07	25.7	(27.32,128.81)	-4.67	(-78.78,69.44)
	Nelfinavir	33	370.2	256	435.8	248	82.74	27.5	(28.49,136.99)		
Week 24	Indinavir+Ritonavir	38	438.6	283	491.3	320	50.84	25.5	(0.37,101.30)	13.31	(-87.32,60.70)
	Nelfinavir	36	378.5	260	442.9	280	64.15	27.5	(9.76,118.54)		
Week 32	Indinavir+Ritonavir	37	438.1	287	538.7	322	99.53	25.9	(48.44,150.62)	2.32	(-73.95,78.59)
	Nelfinavir	30	352.4	245	455.2	258	97.21	28.8	(40.34,154.09)		
Week 40	Indinavir+Ritonavir	35	450.1	291	535.3	314	84.30	26.3	(32.33,136.27)	-0.74	(-77.21,75.72)
	Nelfinavir	34	372.5	266	461.1	278	85.04	28.5	(28.69,141.39)		
Week 48	Indinavir+Ritonavir	34	451.6	296	578.6	326	127.12	26.7	(74.30,179.94)	53.90	(-25.18,132.98)
	Nelfinavir	29	387.0	280	457.5	278	73.22	29.9	(14.11,132.34)		

N: Number of contributing patients
Change: Mean and SE are estimates from the longitudinal analysis model including a term for the baseline covariate.
VS. Nelfinavir: Diff is the estimated difference of Indinavir+Ritonavir - Nelfinavir.

SAFETY RESULTS:

Nearly all patients experienced at least one clinical adverse experience (92% in indinavir/ritonavir group and 86% in the nelfinavir group) (Table 10). Many experiences were considered drug-related, with a total of 69% of patients in the indinavir/ritonavir group and 45% of the patients in the nelfinavir group reporting at least one adverse experience considered to be drug-related by the investigator. In the indinavir/ritonavir group, 2 patients had adverse events of renal calculus, 2 had nephrolithiasis, 1 patient had a ureteric calculus, and 1 patient had a kidney stone. No patient in the nelfinavir group had an adverse event of kidney stone or nephrolithiasis.

Table 10
Clinical Adverse Experience Summary

	IDV/RTV 800/100 mg bid (N=48)		**NFV 1250 mg bid (N=49)**	
	N	(%)	n	(%)
Number (%) of patients:				
With one or more adverse experiences	44	(91.7)	42	(85.7)
With no adverse experience	4	(8.3)	7	(14.3)
With drug-related adverse experiences†	33	(68.8)	22	(44.9)
With serious adverse experiences	8	(16.7)	5	(10.2)
With serious drug-related adverse experiences	4	(8.3)	1	(2.0)
Who died	1	(2.1)	1	(2.0)
Discontinued due to adverse experiences	9	(18.8)	3	(6.1)
Discontinued due to drug-related adverse experiences	9	(18.8)	2	(4.1)
Discontinued due to serious adverse experiences	3	(6.3)	2	(4.1)
Discontinued due to serious drug-related adverse experiences	3	(6.3)	1	(2.0)

† Determined by the investigator to be possibly, probably or definitely drug related.

There were 4 patients (8.3%) with serious drug-related clinical adverse experiences in the indinavir/ritonavir group, compared to 1 patient (2.0%) in the nelfinavir group. This treatment difference of 6.3% was not statistically significant (CI = -3.7% to 17.6%, p=0.204) (Table 11). Nine patients (18.8%) discontinued due to a drug-related adverse experience in the indinavir/ritonavir group, compared to 2 patients (4.1%) in the nelfinavir group. This treatment difference of 14.7% was statistically significant (CI = 1.8 to 28.2%, p=0.028).

Table 11
Clinical Adverse Experience Risk Difference

Clinical Adverse Experience	Indinavir+Ritonavir n	Indinavir+Ritonavir %	Nelfinavir n	Nelfinavir %	Difference (95% CI)+	P-Value@
Serious Drug-Related Adverse Experience	4	8.3%	1	2.0%	6.3 (-3.7,17.6)	0.204
Discontinued due to Drug-Related AE	9	18.8%	2	4.1%	14.7 (1.8,28.2)	0.028

(95% CI)+: The 95% CI interval for estimated difference of proportions is generated by the Wilson's Score Method.
@ P-values are from Fisher's Exact tests.

There were 35% in the indinavir/ritonavir group and 23% in the nelfinavir group who experienced at least one laboratory adverse laboratory event (Table 12). These were generally related to blood chemistries, with increases in aspartate aminotransferase (AST; 8% in each treatment group) and bilirubin (13% in the indinavir/ritonavir group and 0% in the nelfinavir group).

Table 12

Laboratory Adverse Experience Summary

	IDV/RTV 800/100 mg bid (N=48) n	(%)	NFV 1250 mg bid (N=49) n	(%)
Number (%) of patients:				
With at least one laboratory test postbaseline	48		48	
With one or more adverse experiences	17	(35.4)	11	(22.9)
With no adverse experience	31	(64.6)	37	(77.1)
With drug-related adverse experiences†	12	(25.0)	6	(12.5)
With serious adverse experiences	0	(0.0)	0	(0.0)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	3	(6.3)	0	(0.0)
Discontinued due to drug-related adverse experiences	2	(4.2)	0	(0.0)
Discontinued due to serious adverse experiences	0	(0.0)	0	(0.0)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably or definitely drug related.

‡ The percent = number of patients within the laboratory adverse experience category / number of patients with one or more laboratory tests postbaseline.

18. Date of the report: September 6, 2005
19. Contact: Sponsor National Service Center (1-800-672-6372)