Comparable HIV-1 Viral Suppression and Immunologic Recovery of White and Non-White Antiretroviral-Naïve Subjects Taking Lopinavir/ritonavir (LPV/r) Tablets + Tenofovir Disoproxil Fumarate (TDF) and Emtricitabine (FTC) through 48 Weeks

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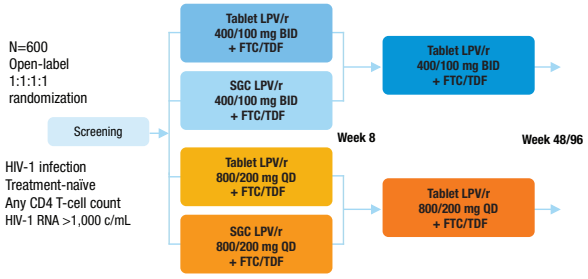
Background

- Worldwide, non-white patients account for the vast majority of HIV infections. In 2007, out of a total of 33.2 million people living with HIV, 22.5 million lived in sub-Saharan Africa.[1]
- Increasing numbers of African Americans and Hispanics are living with HIV compared to any other ethnic group in the United States. Although African Americans represent approximately 13% of the population, they accounted for 48% of new HIV or AIDS diagnoses in 2005. Hispanics, who comprise about 14% of the population, accounted for 18% of new diagnoses.[2]
- Virologic and immunologic status at time of clinical presentation as well as response to combination antiretroviral therapy may vary by race.[3]
- Previous studies have found no major effect of race on the outcome of HAART therapy for HIV-1 infected patients.[4,5] Lopinavir/ritonavir (LPV/r) soft-gel capsules (SGC) dosed once daily (QD) or twice daily (BID) for 48 weeks, along with QD disoproxil fumarate (TDF) and emtricitabine (FTC), demonstrated similar virologic and immunologic responses regardless of race.[4]
- The current analysis was conducted to assess the virologic and immunologic response of non-white vs. white antiretroviral-naïve subjects receiving LPV/r tablets in combination with TDF and FTC.

Objective

- To assess and compare 48-week safety and efficacy between subjects self-reporting as white vs. non-white with respect to virologic response, CD4+ T-cell increase, adverse events (AEs) and laboratory abnormalities in study M05-730.
- The M05-730 study design is shown in Figure 1.

Figure 1. Study Design for Study M05-730



Methods

- Study M05-730 is an ongoing 96-week Phase 3, open-label, randomized, multi-center, multi-country study that enrolled antiretroviral (ARV)-naïve subjects with HIV-1 RNA ≥ 1000 copies/mL and any CD4+ T-cell count.
- 664 ARV-naïve HIV-1 infected subjects were dosed after being randomized 1:1:1:1 to LPV/r QD SGC, BID SGC, QD tablet, or BID tablet for 8 weeks.
- All subjects received emtricitabine (FTC) 200 mg QD and tenofovir disoproxil fumarate (TDF) 300 mg QD.
- At Week 8, all subjects receiving LPV/r SGC were switched to the tablet formulation while maintaining their same randomized dosing schedule (QD vs. BID).
- Subjects were evaluated every 2 weeks through Week 16, every 8 weeks through Week 48, then every 12 weeks through Week 96.
- Efficacy Analyses
  - Primary efficacy endpoint: Proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48, using an intent-to-treat, noncompleter=failure (ITT, NC=F) approach comparing QD and BID groups. The pre-specified non-inferiority margin was 12%.
  - Secondary analyses included the mean change from baseline in CD4+ T-cell count and the emergence of viral resistance through 48 weeks.
- Race was determined based on the subject's selection of race at time of study entry. Selections of choice were: white, black, Asian, American Indian/Alaska Native, and other. Subjects were included as white if they selected only white; all other subjects were included as non-white.
- 48-week safety and efficacy between subjects self-reporting as white vs. non-white with respect to virologic response, CD4+ T-cell increase, adverse events (AEs) and laboratory abnormalities were compared.
- Therapy preference for subjects who switched from the SGC to tablet formulation at Week 8 was assessed. Subjects were asked to choose which formulation they preferred: Kaletra Tablets, Kaletra Soft Gel Capsules, or equal preference for Kaletra Tablets and Soft Gel Capsules.

Results

- 664 ARV-naïve HIV-1 infected subjects were randomized and dosed.
- Overall, in the M05-730 primary efficacy analysis at Week 48, 77% of QD-treated and 76% of BID-treated subjects achieved a viral load <50 copies/mL by ITT, NC=F analysis.[8]
- The difference in response rates (QD *minus* BID) and 95% CI was 1% (–5% to 8%), which confirmed the non-inferiority of the QD regimen to the BID regimen, as the lower bound of the confidence interval was within the pre-specified margin of –12%. The on-treatment data confirmed this finding.[8]
- Overall, similar mean increases from baseline in CD4+ T-cell count at Week 48 were observed in the QD and BID treatment groups (186 and 197 cells/mm^3, respectively; p=0.350).[8]

Results: Baseline Demographics

- There were a total of 165 non-white subjects. The majority of these subjects were black (73.3%). The remaining non-white subjects included Asian (12.1%), American Indian/Alaskan Native (3.6%), and other (10.9%).
- Baseline demographics for this analysis are shown in Table 1, comparing white vs. non-white subjects, in the BID and QD arms.
- Mean baseline CD4+ T-cell counts were significantly different between white (224.7 cells/mm^3) and non-white (187.6 cells/mm^3) subjects, p=0.002.
- The mean baseline HIV-1 RNA was higher in white subjects (5.03 $\log_{10}$ c/mL) than in non-white subjects (4.88 $\log_{10}$ c/mL), p=0.014.
- Mean baseline LDL cholesterol levels were lower in non-whites compared to whites (p=0.007).

Results: Baseline Demographics

Table 1. Baseline Demographics

Variable	Non-White (QD) N=74	White (QD) N=259	Non-White (BID) N=91	White (BID) N=240	Non-White Overall N=165	White Overall N=499
Age (years)						
Mean ± SD*	36.7 ± 9.63	39.0 ± 9.69	37.9 ± 10.57	39.3 ± 9.78	37.4 ± 10.14	39.1 ± 9.72
Weight (kg)						
Mean ± SD†	74.6 ± 22.40	74.5 ± 16.02	75.8 ± 18.02	72.0 ± 12.36	75.2 ± 20.1	73.3 ± 14.4
HIV-1 RNA (log_{10} copies/mL)						
Mean ± SD‡	4.84 ± 0.653	4.96 ± 0.654	4.92 ± 0.737	5.10 ± 0.622	4.88 ± 0.700	5.03 ± 0.642
<5, n (%)	40 (54.1)	133 (51.4)	41 (45.1)	97 (40.4)	81 (49.1)	230 (46.1)
≥5, n (%)	34 (45.9)	126 (48.6)	50 (54.9)	143 (59.6)	84 (50.9)	269 (53.9)
CD4+ T-cell (cells/mm^3)§						
Mean ± SD‖	187.7 ± 125.99	224.4 ± 125.31	187.5 ± 130.39	225.0 ± 140.21	187.6 ± 128.05	224.7 ± 132.57
<50, n (%)	10 (13.5)	24 (9.3)	17 (18.7)	36 (15.0)	27 (16.4)	60 (12.0)
50 – <200, n (%)	34 (45.9)	82 (31.8)	33 (36.3)	67 (27.9)	67 (40.6)	149 (29.9)
≥200, n (%)	30 (40.5)	152 (58.9)	41 (45.1)	137 (57.1)	71 (43.0)	289 (58.0)
Mean Lipids mmol/L (mg/dL)						
Total cholesterol (TC)	3.932 (152.0)	4.036 (156.1)	3.884 (150.2)	4.011 (155.1)	3.906 (151.0)	4.024 (155.6)
Triglycerides (TG)	1.670 (147.9)	1.716 (151.9)	1.658 (146.9)	1.793 (158.8)	1.663 (147.3)	1.753 (155.3)
LDL cholesterol¶	2.393 (92.5)	2.561 (99.0)	2.331 (90.1)	2.510 (97.1)	2.359 (91.2)	2.537 (98.1)
HDL cholesterol	1.045 (40.2)	1.031 (39.9)	1.040 (40.2)	1.003 (38.8)	1.042 (40.3)	1.018 (39.4)
LDL:HDL ratio	2.579	2.758	2.718	2.670	2.656	2.716

* p=0.045 for non-white vs. white subjects overall.
† p=0.033 for non-white vs. white subjects BID.
‡ p=0.025 and p=0.014 for non-white vs. white subjects BID and overall, respectively.
§ p=0.017 and p=0.003 for the difference between non-white vs. white subjects QD and overall, respectively, in distribution of baseline CD4+ T-cell values: <50, 50 – <200 or ≥200 cells/mm^3.
‖ p=0.027, p=0.028, and p=0.002 for non-white vs. white subjects QD, BID and overall, respectively.
¶ p=0.050 and p=0.007 for non-white vs. white subjects BID and overall, respectively.

Results: Subject Disposition

- Subject disposition at Week 48 is shown in Table 2.
- There were no statistically significant differences between non-white and white subjects with regards to reasons for discontinuation.

Table 2. Subject Disposition at Week 48

Variable	Non-White (QD) N=74	White (QD) N=259	Non-White (BID) N=91	White (BID) N=240	Non-White Overall N=165	White Overall N=499
Subjects discontinued, n (%)						
Any reason	12 (16.2)	37 (14.3)	18 (19.8)	37 (15.4)	30 (18.2)	74 (14.8)
Adverse event	3 (4.1)	13 (5.0)	1 (1.1)	9 (3.8)	4 (2.4)	22 (4.4)
Withdrew consent	1 (1.4)	15 (5.8)	4 (4.4)	9 (3.8)	5 (3.0)	24 (4.8)
Lost to follow-up	2 (2.7)	8 (3.1)	7 (7.7)	10 (4.2)	9 (5.5)	18 (3.6)
Nonadherence	2 (2.7)	3 (1.2)	3 (3.3)	6 (2.5)	5 (3.0)	9 (1.8)
Death	0	2 (0.8)	1 (1.1)	0	1 (0.6)	2 (0.4)
Virologic failure	1 (1.4)	1 (0.4)	2 (2.2)	3 (1.3)	3 (1.8)	4 (0.8)
Other	3 (4.1)	6 (2.3)	2 (2.2)	6 (2.5)	5 (3.0)	12 (2.4)

Results: Efficacy

- There was no difference in the overall proportion of white and non-white subjects achieving HIV-1 RNA <50 copies/mL at Week 48: 77% vs. 75.2%, respectively, p=0.672 (Figure 2).
- Furthermore, there were no differences between whites and non-whites in virologic response at Week 48 when stratifying subjects by baseline CD4+ T-cell counts (Figure 3a) or BL viral load (<100,000 or ≥100,000 c/mL—Figure 3b).

Figure 2. Proportion of Subjects with HIV-1 RNA <50 copies/mL at Week 48 (ITT, NC=F Analysis)

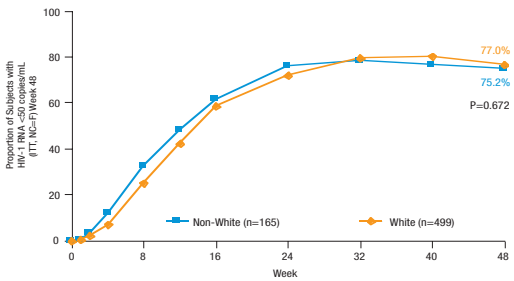
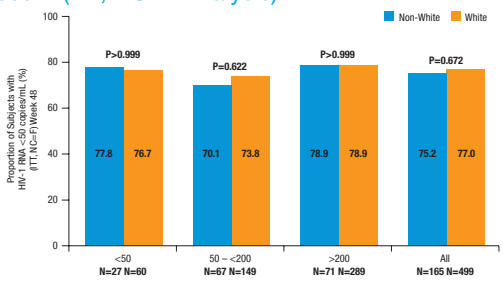


Figure 3a. Proportion of Subjects with HIV-1 RNA <50 copies/mL at Week 48 by Baseline CD4+ T-cell count (ITT, NC=F Analysis)



Results: Efficacy

Figure 3b. Proportion of Subjects with HIV-1 RNA <50 copies/mL at Week 48 by Baseline Viral Load (ITT, NC=F Analysis)

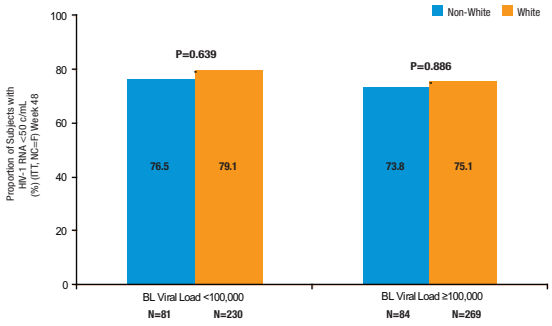
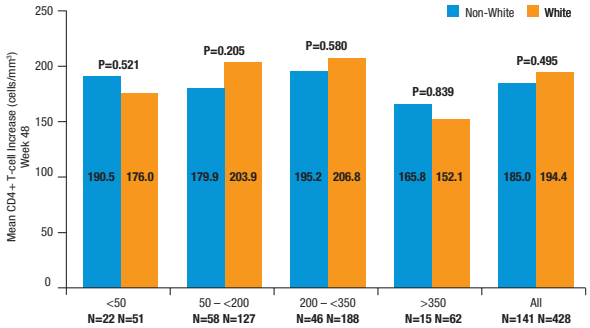


Figure 4. Mean CD4+ T-cell Increase from Baseline to Week 48 by Baseline CD4+ T-cell Counts



- There was no difference in mean increase in CD4+ T-cell counts at Week 48 between non-white and white subjects: 185 vs. 194 cells/mm^3, respectively (p=0.495).
- Mean increases in CD4+ T-cell count at Week 48 were similar between race groups regardless of baseline CD4+ T-cell count (Figure 4).

Results: Safety

- Gastrointestinal adverse events were the most commonly occurring events in both white and non-white subjects (Table 3). Two gastrointestinal events occurred in ≥ 5% of the subjects in any race/dose group.
- One adverse event was noted in a significantly higher proportion of non-white compared to white subjects (anorexia, p=0.049). This event occurred in a low percentage of the study cohort (1.8% and 0.2%, respectively).
- The overall rate of moderate to severe diarrhea in this study was approximately 16%. White subjects experienced moderate to severe diarrhea at a rate of 17.8%, while non-white subjects experienced moderate to severe diarrhea less frequently (9.7%, p=0.014).
- No statistically significant differences were noted between non-white and white subjects, overall and within QD or BID groups, for mean changes from baseline at Week 48 in total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL) or LDL:HDL ratio (Table 4).
- Statistically significant differences were noted for high density lipoprotein cholesterol (HDL), between non-white and white subjects overall (p<0.001), for QD dosing (p=0.007), and for BID dosing (p=0.018).

Table 3. Moderate to Severe Study Drug-Related Adverse Events Occurring in ≥5.0% of Subjects in Any Race/Dose Group

Adverse Event	Non-White (%)			White (%)		
	QD N=74	BID N=91	Overall N=165	QD N=259	BID N=240	Overall N=499
Diarrhea*	9.5	9.9	9.7	18.5	17.1	17.8
Nausea	9.5	6.6	7.9	6.6	5.0	5.8

* p=0.014 for white vs. non-white subjects overall.

Table 4. Mean Change from Baseline at Week 48 in Lipid Parameters by Race and Dosing Group

Variable*	Non-White (QD) N=66	White (QD) N=229	Non-White (BID) N=76	White (BID) N=204	Non-White Overall N=142	White Overall N=433
TC mmol/L (mg/dL)	+0.821 (+31.7)	+0.731 (+28.3)	+0.958 (+37.0)	+0.868 (+33.6)	+0.895 (+34.6)	+0.795 (+30.7)
TG mmol/L (mg/dL)	+0.298 (+26.4)	+0.565 (+50.0)	+0.739 (+65.5)	+0.711 (+62.9)	+0.534 (+47.3)	+0.634 (+56.2)
HDL† mmol/L (mg/dL)	+0.267 (+10.3)	+0.165 (+6.4)	+0.245 (+9.5)	+0.167 (+6.5)	+0.255 (+9.9)	+0.166 (+6.4)
LDL mmol/L (mg/dL)	+0.203 (+7.8)	+0.121 (+4.7)	+0.219 (+8.5)	+0.249 (+9.6)	+0.212 (+8.2)	+0.181 (+6.9)
LDL:HDL ratio mmol/L (mg/dL)	–0.488	–0.407	–0.427	–0.207	–0.455	–0.314

* N-values per race/dosing group may differ slightly across variables.

† p=0.007, p=0.018, p<0.001 for non-white vs. white subjects for QD, BID, and overall, respectively.

Table 5. Grade 3/4 Laboratory Abnormalities of Interest through Week 48

- At Week 48, there were no significant differences between race groups in terms of Grade 3/4 abnormalities of transaminases, total cholesterol, triglycerides and creatinine clearance regardless of dosing regimen (Table 5).

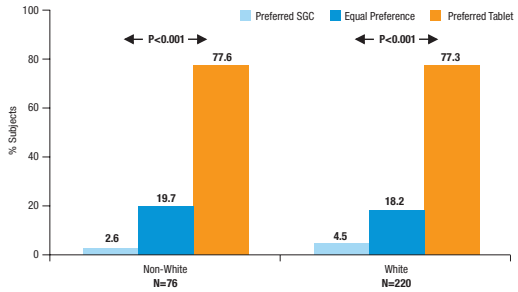
Variable*	Non-White (QD) N=74	White (QD) N=259	Non-White (BID) N=90	White (BID) N=237	Non-White Overall N=164	White Overall N=496
SGOT/AST >5 x ULN, n (%)	0	4 (1.5)	2 (2.2)	5 (2.1)	2 (1.2)	9 (1.8)
SGPT/ALT >5 x ULN, n (%)	1 (1.4)	3 (1.2)	1 (1.1)	3 (1.3)	2 (1.2)	6 (1.2)
Cholesterol >300 mg/dL, n (%)	2 (2.7)	11 (4.2)	2 (2.2)	8 (3.4)	4 (2.4)	19 (3.8)
Triglycerides >750 mg/dL, n (%)	1 (1.4)	9 (3.5)	6 (6.7)	14 (5.9)	7 (4.3)	23 (4.6)
CrCL <50 ml/min, n (%)	3 (4.1)	4 (1.5)	3 (3.3)	5 (2.1)	6 (3.7)	9 (1.8)

* N-values per race/dosing group may differ slightly across variables.

Results: Patient Preference

- The patient preference questionnaire administered at Week 12 demonstrated that both non-white and white subjects who switched from the SGC to the tablet formulation at Week 8 overwhelmingly preferred the tablet formulation (Figure 5).
- Of those subjects who switched from the SGC to the tablet formulation at Week 8, 78% of non-white subjects and 77% of white subjects preferred the tablet over the SGC (p<0.001 for both). Only 3% of non-white subjects and 5% of white subjects preferred the SGC over the tablet.

Figure 5. LPV/r SGC vs. Tablet Formulation Preference Survey by Race at Week 12



Summary

- There was no difference in the efficacy of an LPV/r-based regimen dosed QD or BID at 48 weeks in antiretroviral-naïve non-white vs. white subjects.
- In addition, as was noted for the overall study population[7], within subgroups defined by baseline CD4+ T-cell count and BL HIV RNA levels, similar proportions of non-white and white subjects achieved HIV-1 RNA <50 copies/mL at Week 48.
- As previously noted with LPV/r-based ARV therapy, within subgroups defined by baseline CD4+ T-cell count, mean CD4+ T-cell count increases at Week 48 were similar for non-white and white subjects.[8]
- Despite having lower baseline HIV-1 viral loads, non-white subjects had lower baseline CD4+ T-cell counts compared to white subjects (mean: 187.6 vs. 224.7 cells/mm^3, respectively, p=0.002).
- Previous data report that non-white subjects tend to present later for HIV testing and treatment.[5] As a result, these subjects may have lower CD4+ T-cell counts at presentation.[5,6] While later presentation may explain the lower CD4+ T-cell counts, the potential causes for lower HIV-1 viral loads are less clear.
- LPV/r was well tolerated in non-whites and white subjects. The overall rate of moderate to severe diarrhea for the study was approximately 16%. Given that whites made up the majority of the study population, it is not surprising that they experienced moderate to severe diarrhea rates similar to the overall study population. Non-whites, however, experienced moderate to severe diarrhea less frequently than whites.
- Mean baseline LDL cholesterol levels were lower in non-whites compared to whites. At Week 48, mean change in TC, TG, and LDL was similar for non-white and white subjects, with no mean increase in the LDL:HDL for either group. Non-white subjects had a significantly greater mean increase in HDL compared to white subjects.
- Both non-white and white subjects overwhelmingly preferred the tablet formulation over the SGC. The reasons associated with patient preference were not collected, but may include the lack of refrigeration, diminished food effect, and possible tolerability effects not detected by the standardized adverse event assessment performed during a clinical trial. Data from this study are consistent with previous studies that demonstrated patient preference for the tablet formulation after switching from the SGC.[9-11]

Conclusions

- A LPV/r-based regimen dosed QD or BID provides similar virologic efficacy and immunologic recovery in both non-white and white subjects, regardless of baseline CD4+ T-cell count or viral load.
- The LPV/r safety profile was similar between races for both QD and BID dosing.
- The patient preference questionnaire demonstrated that subjects overwhelmingly preferred the tablet formulation over the SGC, regardless of race.

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