Lopinavir/ritonavir (LPV/r) Combined with Raltegravir (RAL) or Tenofovir/Emtricitabine (TDF/FTC) in Antiretroviral-Naïve Subjects: 96-Week Efficacy and Safety Results of the PROGRESS Study

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Background

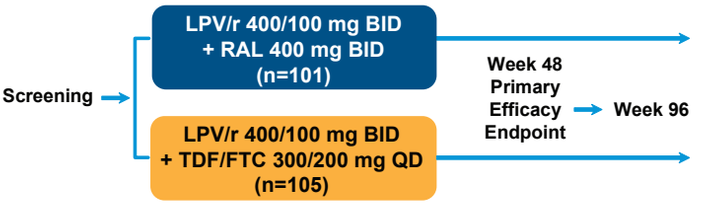
- Standard therapy for HIV-1 infected, antiretroviral-naïve patients, consists of a Protease Inhibitor (PI), Non-Nucleoside Reverse Transcriptase Inhibitor, Integrase Strand Transfer Inhibitor, or CCR5 Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
- For those whom NRTI-containing combinations may not be the best option, a NRTI-sparing regimen may offer an alternative therapeutic approach
- The SPARTAN study and the ACTG 5262 study have recently raised questions over the safety and efficacy of ATV+RAL and DRV+ritonavir+RAL, respectively
- **The PROGRESS trial is the first study designed to test the efficacy and safety of LPV/r and RAL in antiretroviral-naïve subjects**

Methods

Study Design

- The PROGRESS study is a randomized, open-label, multicenter trial comparing the safety, tolerability and antiviral activity of LPV/r when administered in combination with RAL to LPV/r when administered in combination with TDF/FTC in ARV-naïve, HIV-1-infected subjects for 96 weeks. The study design is shown in Figure 1.
- Subjects were randomized in a 1:1 ratio to receive either LPV/r 400/100 mg BID plus RAL 400 mg BID or LPV/r 400/100 mg BID plus a fixed dose combination of TDF/FTC 300/200 mg QD
- Main Inclusion Criteria for PROGRESS
  - HIV-1 infection
  - ARV-naïve
  - Plasma HIV-1 RNA >1000 copies/mL
  - Any CD4$^+$ T-cell count
  - Susceptibility to LPV/r, TDF and FTC assessed by HIV-1 genotyping at screening
- RAL resistance testing was not routinely performed at baseline, nor was RAL resistance at baseline an exclusion criterion, however, baseline samples were archived for RAL baseline resistance testing in the case of virologic failure
- Resistance testing was performed at time of virologic failure if any of the following criteria were met
  - Beginning at week 8, if plasma HIV-1 RNA level was ≥40 copies/mL and at the previous visit the plasma HIV-1 RNA was <40 copies/mL, confirmatory plasma HIV-1 RNA level >400 copies/mL repeated within 4 weeks
  - If plasma HIV-1 RNA increased >0.5 $\log_{10}$ copies/mL above study nadir and >400 copies/mL on two consecutive measurements obtained at least 14 days apart or
  - If plasma HIV-1 RNA never reached <400 copies/mL by week 24
- Resistance testing for LPV/r, TDF and FTC was performed using ViroSeq HIV-1 (Abbott Laboratories, Abbott Park, IL) and resistance testing for RAL was performed using GeneSeq HIV (Monogram Biosciences, San Francisco, CA)
- Resistance was specified by the 2010 IAS-USA panel

Figure 1. LPV/r + RAL vs. LPV/r + TDF/FTC in Treatment-Naive Subjects: PROGRESS Study Design*



*3 subjects were randomized but not dosed.

Results

Baseline Demographics and Subject Disposition

- No statistical differences were observed with regards to baseline demographics and HIV disease characteristics (Table 1)
- There were no significant differences between the treatment groups in the number of subjects who discontinued or in the reasons for discontinuation (Table 2)
- The most common reason for premature discontinuation was lost to follow-up, followed by adverse event or HIV-related event and withdrawal of consent
- Both LPV/r + RAL and LPV/r + TDF/FTC treatments were generally well tolerated as indicated by the low incidence of discontinuations due to adverse events

Table 1. Baseline Demographics and HIV Disease Characteristics

Variable	LPV/r + RAL (N=101)	LPV/r + TDF/FTC (N=105)	Total (N=206)
Males, n (%)	88 (87.1)	86 (81.9)	174 (84.5)
Race			
White, n (%)	74 (73.3)	81 (77.1)	155 (75.2)
Black, n (%)	22 (21.8)	22 (21.0)	44 (21.4)
Other, n (%)	5 (4.9)	2 (1.9)	7 (3.4)
Mean age ± SD, years	39.8 ± 9.9	39.4 ± 11.2	39.6 ± 10.6
Mean BL HIV-1 RNA, log_{10} copies/mL (range)*	4.24 (2.0 – 6.0)	4.25 (2.7 – 6.0)	4.25 (2.0 – 6.0)
Mean BL CD4⁺ T-cells/µL (range)	289.3 (5 – 668)	297.6 (5 – 743)	293.5 (5 – 743)

*Plasma HIV-1 viral loads determined using automated, quantitative RT-PCR assay (Abbott RealTime HIV-1 assay®).
Groups were compared using one-way ANOVA for continuous variables and Fisher's exact test for categorical variables.

Table 2. Subject Disposition at Week 96

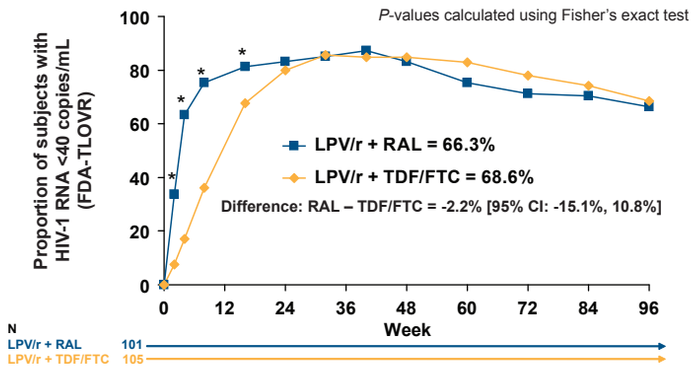
Reasons for Discontinuations	LPV/r + RAL (N=101) n (%)	LPV/r + TDF/FTC (N=105) n (%)	Total (N=206) n (%)
All Reasons*	19 (18.8)	15 (14.3)	34 (16.5)
Lost to Follow-Up	9 (8.9)	3 (2.9)	12 (5.8)
AE/HIV-related Event	5 (5.0)	4 (3.8)	9 (4.4)
Withdrew Consent	2 (2.0)	4 (3.8)	6 (2.9)
Virologic Failure	1 (1.0)	2 (1.9)	3 (1.5)
Other†	2 (2.0)	1 (1.0)	3 (1.5)
Noncompliance†	1 (1.0)	0 (0)	1 (0.5)
Pregnancy	0 (0)	1 (1.0)	1 (0.5)

*P>0.05 for LPV/r +RAL vs. LPV/r + TDF/FTC comparison for each reason based on Fisher's exact test.
†1 LPV/r + RAL subject discontinued for two reasons: Noncompliance and Other.

Efficacy

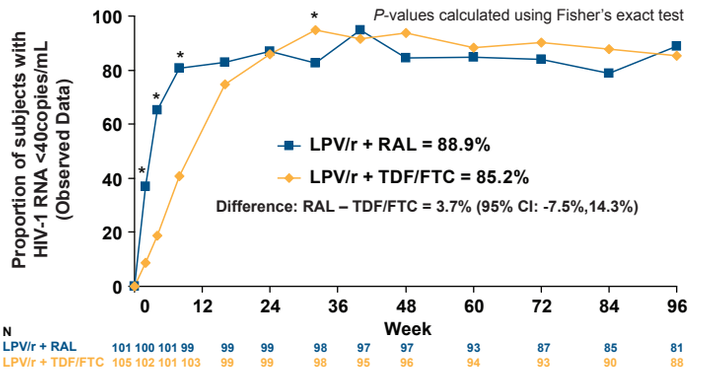
- Met primary endpoint of noninferiority
  - The primary endpoint for this study was: plasma HIV-1 RNA <40 copies/mL at week 48 (FDA-TLOVR)
  - FDA-TLOVR week 48: LPV/r + RAL=83.2%, LPV/r + TDF/FTC=84.8%
  - P=0.850, difference -1.6%, 95% exact confidence interval (CI) -12.0%, 8.8%
  - Safety and tolerability were similar at week 48
- At week 96 using the FDA-TLOVR primary endpoint, 66.3% in the LPV/r + RAL and 68.6% in the LPV/r + TDF were virologically suppressed (HIV-1 RNA <40 copies/mL) (Figure 2). The proportion of responders at week 96 was also similar between treatment groups for the observed data analysis (Figure 3).
- Week 96 FDA-TLOVR response for subjects with BL plasma HIV-1 RNA ≥100,000 copies/mL: LPV/r + RAL= 6/15, LPV/r + TDF/FTC= 10/19
- Week 96 observed data response for subjects with BL plasma HIV-1 RNA ≥100,000 copies/mL: LPV/r + RAL= 8/10, LPV/r + TDF/FTC= 12/15
- Statistically significantly more subjects in LPV/r + RAL group achieved virologic suppression (FDA-TLOVR) at weeks 2, 4, 8 and 16 compared with LPV/r + TDF/FTC group (weeks 2, 4 and 8 P<0.001, week 16 P=0.038)
- Early differences in the proportion of subjects achieving HIV-1 viral loads of <40 copies/mL between treatment groups did not appear to be associated with differences in immunologic recovery as measured by CD4⁺ T-cell counts (Figure 4)

Figure 2. Proportion of Subjects Responding at Week 96 (FDA-TLOVR)



*Statistically significant difference between groups: weeks 2, 4, 8 P<0.001; week 16 P=0.038.

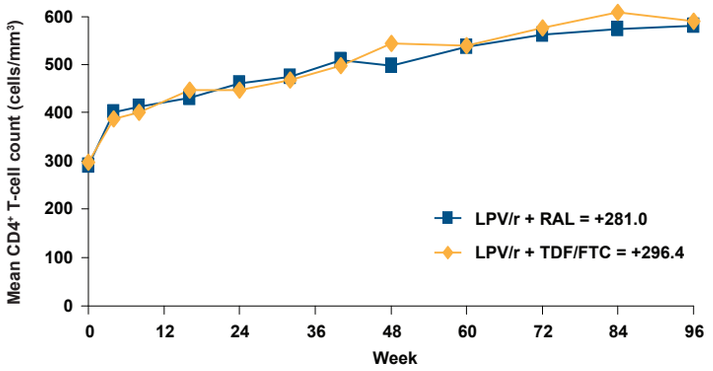
Figure 3. Proportion of Subjects Responding at Week 96 (Observed Data Analysis)



*Statistically significant difference between groups: weeks 2, 4, 8 P<0.001; week 32 P=0.011.

Results

Figure 4. Mean CD4⁺ T-cell Counts Through 96 Weeks of Treatment (Cells/mm³)



N											
LPV/r + RAL	101	94	96	94	90	95	91	93	89	81	79	76
LPV/r + TDF/FTC	105	92	98	95	93	96	95	91	93	84	89	80

P>0.100 for difference between treatment groups in change from baseline at all time points using one-way ANOVA;
P<0.001 for CD4⁺ T-cell count increase from baseline to each visit within each treatment group at all time points using one-way ANOVA.

- Thirteen subjects (8 LPV/r + RAL and 5 LPV/r + TDF/FTC) met the protocol-defined criteria for resistance testing
  - FTC RAM was detected in 1 subject (week 40)
  - RAL RAMs without LPV/r RAMs were detected in 2 subjects (weeks 48 and 65)
  - RAL (week 16) and LPV/r (week 72) RAMs were detected in 1 subject

Safety and Adherence

- No statistically significant differences between groups for the incidence of moderate to severe treatment-related adverse events occurring in ≥2% in either treatment group (Table 3)
- The proportion of subjects with Grade 3+ laboratory abnormalities in creatine phosphokinase was statistically significantly greater in the LPV/r + RAL group; no other statistically significant difference in Grade 3+ laboratory abnormalities occurred between arms (Table 4)
- There were no statistically significant differences in the mean change from baseline to week 96 in lipid parameters (Table 5)
- Adherence was similar between treatment groups regardless of adherence measure (Table 6)

Table 3. Number and % of Subjects with Moderate or Severe Drug-Related Adverse Events*

	LPV/r + RAL (N=101) n (%)	LPV/r + TDF/FTC (N=105) n (%)
Any adverse event	31 (30.7)	36 (34.3)
Diarrhea	8 (7.9)	17 (16.2)
Hypercholesterolaemia†	10 (9.9)	7 (6.7)
Hypertriglyceridaemia†	9 (8.9)	5 (4.8)
Alanine Aminotransferase Increased	3 (3.0)	1 (1.0)
Hyperlipidaemia	3 (3.0)	1 (1.0)
Asthenia	0 (0)	3 (2.9)
Regurgitation	0 (0)	3 (2.9)

*Occurring in ≥2.0% in either treatment group.
†Hypercholesterolaemia includes blood cholesterol increased, hypertriglyceridaemia includes blood triglycerides increased.
P>0.05 for LPV/r + RAL vs. LPV/r + TDF/FTC comparison for each adverse event based on Fisher's exact test.

Table 4. Number and % of Subjects with Grade 3+ Laboratory Values*

	LPV/r + RAL (N=101) n (%)	LPV/r + TDF/FTC (N=105) n (%)
Creatine Phosphokinase (CPK) (>4x ULN)†	20 (19.8)	9 (8.7)
Creatine Phosphokinase (CPK) (>10x ULN)†	10 (9.9)	3 (2.9)
Cholesterol (>7.77 mmol/L)	17 (16.8)	14 (13.5)
Triglycerides (>8.475 mmol/L)	10 (9.9)	5 (4.8)
Lipase (>2x ULN)	4 (4.0)	8 (7.7)
SGPT/ALT(>5x ULN)	5 (5.0)	3 (2.9)
SGOT/AST (>5x ULN)	5 (5.0)	3 (2.9)
Calculated Creatinine Clearance (<50 mL/min)	1 (1.0)	4 (3.8)
Neutrophils (<0.75 x 10^9/L)	0	4 (3.8)
Calcium (<1.75 mmol/L)	2 (2.0)	0
Magnesium (<0.5 mmol/L)	2 (2.0)	0

*Occurring in ≥2.0% in either treatment group.
†*P*<0.05 for LPV/r + RAL vs. LPV/r + TDF/FTC comparison based on Fisher's exact test.

Table 5. Mean Change in Lipid Levels at Week 96

Variable		LPV/r + RAL N=82	LPV/r + TDF/FTC N=90
LDL:HDL ratio	Baseline	2.64	2.57
	Week 96	2.60	2.51
	Mean change	-0.04	-0.06
HDL mmol/L	Baseline	0.99	1.07
	Week 96	1.33	1.33
	Mean change	+0.35	+0.26
LDL mmol/L	Baseline	2.53	2.61
	Week 96	3.24	3.15
	Mean change	+0.72	+0.54
Total Cholesterol mmol/L	Baseline	4.25	4.40
	Week 96	5.36	5.20
	Mean change	+1.11	+0.81
Triglycerides mmol/L	Baseline	1.43	1.40
	Week 96	2.53	2.25
	Mean change	+1.10	+0.85

P>0.05 for difference between treatment groups in mean change at all time points using one-way ANOVA.

Table 6. Adherence via MEMS Data: 96 Weeks

Time Period	Adherence Measure	LPV/r + RAL N=76 (Mean %)	LPV/r + TDF/FTC N=84 (Mean %)
Baseline to Week 96	Taking Compliance	68.5	71.2
	Correct Dosing	55.1	59.4
	Timing Compliance	46.9	50.1

P>0.100 for each measure based on Wilcoxon rank sum test to test for differences between groups in the distribution of subjects' adherence rates.

Conclusions at 96 Weeks

- **LPV/r + RAL virologic efficacy was comparable to LPV/r + TDF/FTC**
  - Proportion of subjects responding [FDA-TLOVR, *P*=0.767]
    - LPV/r + RAL: 66.3%
    - LPV/r + TDF/FTC: 68.6%
- **Similar mean increases in $CD4^+$ T-cell counts at week 96 (*P*=0.598)**
  - LPV/r + RAL: +281.0 cells/mm^3
  - LPV/r + TDF/FTC: +296.4 cells/mm^3
- **Both regimens were generally well tolerated with few study drug-related discontinuations**
  - Discontinuations for AEs or HIV-related events: LPV/r + RAL = 5.0% and LPV/r + TDF/FTC = 3.8%
  - AE profile and laboratory abnormalities were generally similar with the exception of percent of subjects with CPK elevations: LPV/r + RAL = 19.8% and LPV/r + TDF/FTC = 8.7%

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