P185 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

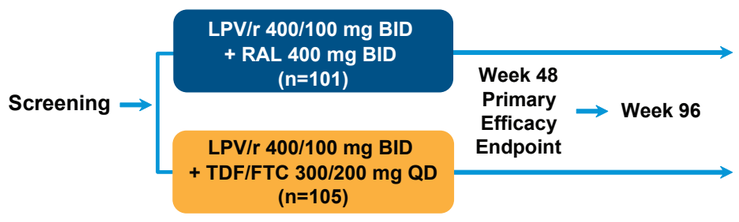
- Standard therapy for HIV-1 infected, antiretroviral-naïve patients, consists of a protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitor, integrase strand transfer inhibitor, or CCR5 inhibitor + 2 nucleoside reverse transcriptase inhibitors (NRTIs)
- For those whom NRTI-containing 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 was 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

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



*3 subjects were randomized but not dosed.

- 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 and a sample for HIV-1 drug resistance genotyping were collected within 4 weeks. If the rebound was confirmed by an HIV-1 RNA level >400 copies/mL, genotypic resistance testing was performed on the sample collected for confirmation
  - 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
- Longitudinal Resistance Testing and Phylogenetic Analysis – Reverse transcriptase (RT), protease (PR), and integrase (IN) genotyping using population-based sequencing techniques was performed at multiple time points on plasma HIV-1 stored samples from the subject with LPV/r and RAL resistance. Sequencing data was confirmed by Abbott Diagnostics (Abbott Park, IL) using the ViroSeq HIV-1® Genotyping System v2.0 and nested RT-PCR amplification of full-length IN.
- IN phenotypes and IN replication capacity (RC) data was obtained using PhenoSense® Integrase (Monogram Biosciences, San Francisco, CA)

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 plasma 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 CD4⁺ T-cells/mm³ (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.

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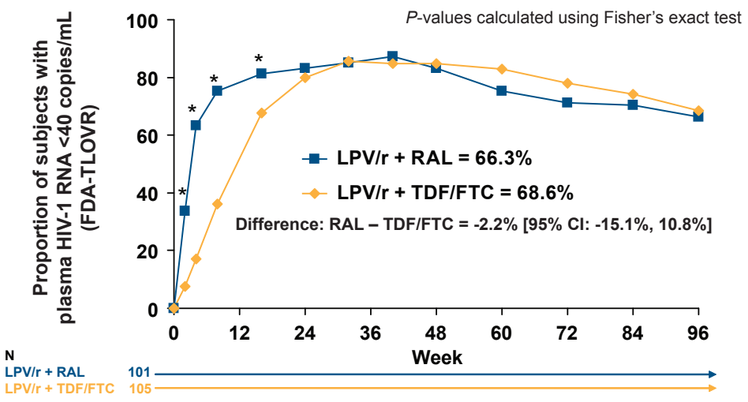
Results, cont.

Efficacy

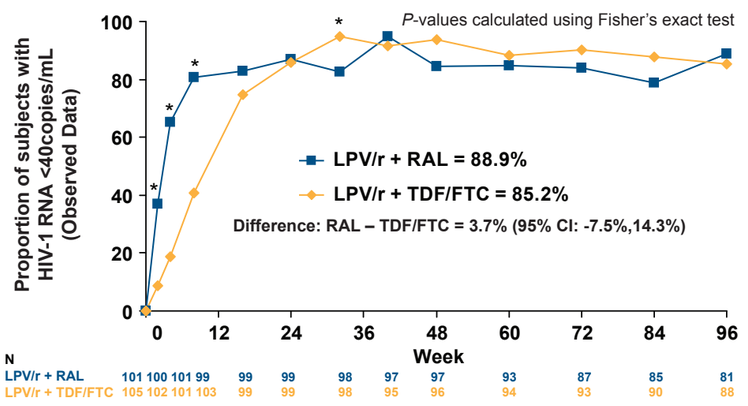
- Met primary endpoint of noninferiority
  - The primary endpoint for this study was: plasma HIV-1 RNA <40 copies/mL at week 48 (FDA-TLOVR)
  - FDA-TLOVR week 48: LPV/r + RAL = 83.2%, LPV/r + TDF/FTC = 84.8%
  - P=0.850, difference -1.6%, 95% exact confidence interval (CI) -12.0%, 8.8%
  - Safety and tolerability were similar at week 48
- At week 96 using the FDA-TLOVR algorithm, 66.3% of subjects in the LPV/r + RAL group and 68.6% of subjects in the LPV/r + TDF group 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).
- Statistically significantly more subjects in the LPV/r + RAL group achieved virologic suppression (FDA-TLOVR) at weeks 2, 4, 8 and 16 compared with the LPV/r + TDF/FTC group (weeks 2, 4 and 8 P<0.001, week 16 P=0.038)
- Week 96 FDA-TLOVR response for subjects with baseline plasma HIV-1 RNA ≥100,000 copies/mL: LPV/r + RAL = 6/15, LPV/r + TDF/FTC = 10/19 (Table 3)
- Week 96 observed data response for subjects with baseline plasma HIV-1 RNA ≥100,000 copies/mL: LPV/r + RAL = 8/10, LPV/r + TDF/FTC =12/15
- There were no differences between treatment groups in immunologic recovery as measured by CD4⁺ T-cell counts (Figure 4)

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



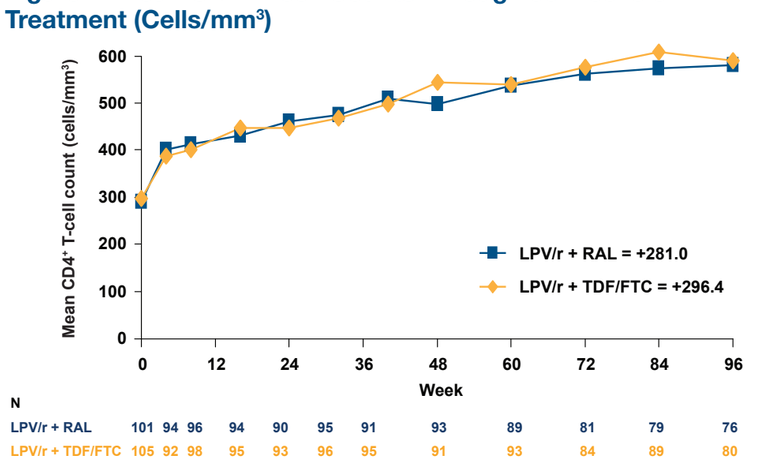
*Statistically significant difference between groups: weeks 2, 4, 8 P<0.001; week 16 P=0.038.

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.

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



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.

Table 3. Description of Subject Disposition through 96 weeks for Subjects with Baseline Plasma HIV-1 RNA ≥100,000 copies/mL

	Baseline Plasma HIV-1 RNA (copies/mL)	Responder, Non-responder (Rebound), Never Suppressed, or Other*	Study week subject became non-responder or completed study (as a responder)
		LPV/r + RAL (n=15)	
1	108776	Other (Adverse event/HIV-related event)	0
2	162025	Non-responder (Rebound)	61.3
3	171091	Responder	Completed study
4	180848	Never suppressed	0
5	183935	Non-responder (Rebound)	47.4
6	200578	Never suppressed	0
7	260270	Responder	Completed study
8	399012	Responder	Completed study
9	414040	Non-responder (Rebound)	95.1
10	447529	Responder	Completed study
11	497339	Responder	Completed study
12	663236	Responder	Completed study
13	670398	Other (Withdrew consent)	72.0
14	904592	Non-responder (Rebound)	70.7
15	1101476	Non-responder (Rebound)	82.7
		LPV/r + TDF/FTC (n=19)	
1	106526	Other (Adverse event/HIV-related event)	0
2	116768	Other (Withdrew consent)	84.0
3	117213	Responder	Completed study
4	127490	Non-responder (Rebound)	39.9
5	129978	Responder	Completed study
6	136370	Responder	Completed study
7	144544	Responder	Completed study
8	159575	Non-responder (Rebound)	72.0
9	169903	Responder	Completed study
10	230790	Non-responder (Rebound)	60.6
11	265737	Other (Withdrew consent)	60.0
12	296677	Responder	Completed study
13	312069	Other (Discontinued due to insufficient viral response)	0
14	364471	Non-responder (Rebound)	97.1
15	370591	Responder	Completed study
16	391793	Responder	Completed study
17	588872	Responder	Completed study
18	598821	Never suppressed	0
19	1037837	Responder	Completed study

*Response determined using FDA-TLOVR algorithm.

Results, cont.

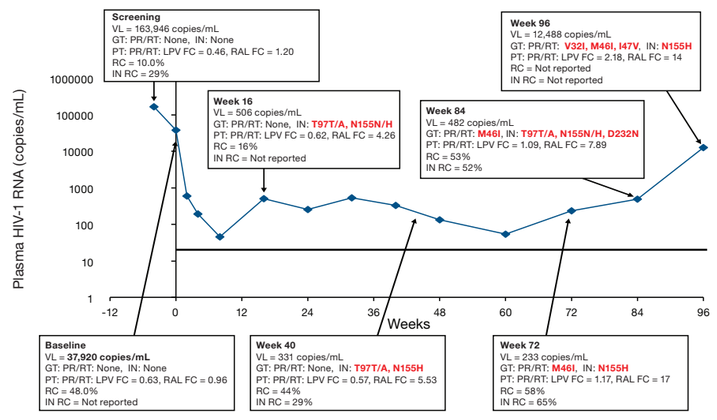
- A total of 13 subjects (8 LPV/r + RAL and 5 LPV/r + TDF/FTC) met protocol-defined criteria for resistance testing
- The baseline plasma HIV-1 RNA levels and resistance mutations indentified for these subjects are shown in Table 4
  - FTC RAM was detected in 1 subject (week 40)
  - RAL RAMs without 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
- Ten of the subjects had baseline plasma HIV-1 RNA <100,000 copies/mL, while 3 subjects had baseline HIV-1 RNA ≥100,000 copies/mL

Table 4. Baseline Plasma HIV-1 RNA Levels for Subjects who had Protocol-Defined Genotype Testing and Resistance Mutations Occurring through Week 96

	LPV/r + RAL		LPV/r + TDF/FTc	
	Baseline plasma HIV-1 RNA (copies/mL)	Resistance Mutations	Baseline plasma HIV-1 RNA (copies/mL)	Resistance Mutations
1	158,467	IN: G140/S, Q148/H (Day 458)	695,767	No Resistance Detected
2	70,618	No Resistance Detected	312,069	RT: M184V (Day 281)
3	37,920	PI: V32I, M46I, I47V (Day 672) IN: N155H (Day 112)	37,337	No Resistance Detected
4	28,449	No Resistance Detected	25,903	No Resistance Detected
5	20,821	IN: N155/H, G163/R (Day 337)	14,626	No Resistance Detected
6	18,069	No Resistance Detected		
7	15,758	No Resistance Detected		
8	5,350	No Resistance Detected		

- Both LPV/r and RAL resistance-associated mutations were detected in one subject who never achieved viral suppression (Figure 5)
- Longitudinal resistance analysis in this subject revealed a RAL resistance-associated mutation at week 16, followed by a period of intermittent viremia and selection of LPV/r resistance-associated mutations at week 72

Figure 5. HIV-1 RNA Levels for Subject with LPV/r and RAL Resistance-Associated Mutations



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 5)
- 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 6)
- There were no statistically significant differences in the mean change from baseline to week 96 in lipid parameters (Table 7)

Table 5. 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 6. 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)
(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 7. 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.

Conclusions

- LPV/r + RAL virologic efficacy was comparable to LPV/r + TDF/FTC
  - Proportion of subjects responding at week 96 [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/mm³
  - LPV/r + TDF/FTC: +296.4 cells/mm³
- 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%
  - Adverse event 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%

Disclosures

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