Impact of Baseline Resistance on Virologic Outcome with Once-Daily (QD) or Twice-Daily (BID) Lopinavir/ritonavir (LPV/r) through 48 Weeks of Combination Antiretroviral Therapy in Treatment-Experienced, HIV-1-Infected Subjects

PE7.3/3

Martin S. King, Adebayo A. Lawal, Linda M. Fredrick, Thomas J. Podsadecki, Barry M. Bernstein

Abbott, Abbott Park, IL USA

12th European AIDS Conference • 11-14 November 2009 • Cologne, Germany

Corresponding author: Adebayo A. Lawal, M.D., Abbott, 200 Abbott Park Rd., Abbott Park, IL 60064-6146 USA; Tel: +1-847-937-2735; Fax: +1-847-938-3711; E-mail: adebayo.lawal@abbott.com

Background

- Lopinavir/ritonavir (LPV/r), a coformulated HIV-1 protease inhibitor (PI), has been used extensively in treating both antiretroviral-naïve and treatment-experienced HIV-1-infected patients. Originally approved for twice-daily (BID) dosing of both treatment-naïve and experienced subjects, LPV/r has also been approved in the US, Europe and many other countries for once-daily (QD) dosing of treatment-naïve individuals.
- Prior studies in antiretroviral-naïve subjects indicated that QD dosing of LPV/r offered similar efficacy, safety, and tolerability as BID administration[1, 2]
- Study M06-802 was designed to test the antiviral activity, safety, and tolerability of LPV/r when dosed QD or BID in HIV-1-infected subjects with prior antiretroviral treatment[3]
- Individuals with antiretroviral experience may harbor HIV-1 virus with mutations in reverse transcriptase and protease
- Resistance-associated mutations have been shown to impact susceptibility to antiretroviral agents and treatment response[4-6]

Objective

To evaluate the influence of baseline resistance mutations on efficacy in antiretroviral-experienced subjects treated with LPV/r dosed QD and BID

Methods

Study Design

- Study M06-802 was a Phase 3, randomized, open label trial that included antiretroviral-experienced subjects failing their current regimen with plasma HIV-1 RNA >1000 copies/mL[3]
- If study participation was deemed appropriate by the investigator based on subject treatment history and results of genotypic resistance testing obtained at the screening visit, subjects were randomized to receive LPV/r tablets either QD (800/200 mg) or BID (400/100 mg) with at least 2 investigator-selected, locally available nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)

Efficacy

- The primary efficacy endpoint was virologic response as analyzed using an intent-to-treat, time-to-loss of virologic response (ITT-TLOVR) algorithm
- Additionally, antiviral efficacy was assessed using a dropouts-as-censored approach, which censored non-responders whose reason for failure was unlikely to be related to their virologic response (early discontinuations and subjects with a final HIV-1 RNA level <50 copies/mL)
- Logistic regression was used to evaluate the relationship between the number of baseline mutations and virologic response

Resistance

- Protease resistance mutations were defined according to 4 lists
  - Lists 1 and 2 are derived from in vitro and clinical data for general protease inhibitor-associated resistance mutations[4, 5, 7]
    - List 1: L10F/I/R/V, K20M/R, L24I, V32I, L33F, M36I, M46I/L, I47V/A, G48V, I50V, F53L, I54 (any change), A71V/T, G73S, V82A/F/T/S, I84V, L90M
    - List 2: Any change at: D30, V32, M36, M46, I47, G48, I50, F53, I54, G73, V82, I84, N88, L90
  - List 3 reflects the US LPV/r prescribing information and clinical data on mutations specifically associated with resistance to LPV/r[6, 8]
    - List 3: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, I84V
  - List 4 is based on the original lopinavir mutation score (LMS) and is provided in the EMEA Summary of Product Characteristics[4, 9]
    - List 4: L10F/I/R/V, K20M/R, L24I, M46I/L, F53L, I54L/T/V, L63P, A71I/L/T/V, V82A/F/T, I84V, L90M
- NRTI resistance-associated mutations were derived from the IAS-USA panel[7]

Results

Subjects

- Similar numbers of subjects were randomized and treated with LPV/r QD (N=300) or BID (N=299); baseline demographics were comparable between treatment groups, except that subjects in the BID-dosed group had a higher mean baseline CD4+ T-cell count (Table 1)
- Subjects had similar patterns of prior antiretroviral treatment
  - 94 subjects (16%) were NNRTI-naïve (Table 1)
  - Overall, 189 subjects (32%) had a history of triple-class experience (prior use of NRTIs, NNRTIs, and PIs)
  - Based on genotypic resistance screening at baseline, 29 subjects (5%) showed at least possible evidence of resistance to LPV

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	QD N=300	BID N=299	Total N=599
Gender, n (%)			
Male	197 (66%)	196 (66%)	393 (66%)
Female	103 (34%)	103 (34%)	206 (34%)
Race, n (%)			
White	158 (53%)	150 (50%)	308 (51%)
Black	104 (35%)	104 (35%)	208 (35%)
Other	38 (13%)	45 (15%)	83 (14%)
Ethnicity, n (%)			
Hispanic	98 (33%)	105 (35%)	203 (34%)
Non-Hispanic	202 (67%)	194 (65%)	396 (66%)
Mean (range) baseline HIV-1 RNA, $\log_{10}$ copies/mL	4.26 (1.7-6.6)	4.26 (1.7-6.5)	4.26 (1.7-6.6)
Mean (range) baseline CD4+ T-cell count, cells/μL*	239.3 (4-754)	268.3 (5-952)	253.9 (4-952)
Prior antiretroviral therapy, n (%)			
NRTI	299 (100%)	297 (99%)	596 (99%)
NNRTI	264 (88%)	241 (81%)	505 (84%)
PI	140 (47%)	136 (46%)	276 (46%)
Number of baseline PI mutations, mean (range)			
List 1	1.1 (0-6)	1.2 (0-7)	1.2 (0-7)
List 2	0.9 (0-6)	1.0 (0-6)	0.9 (0-6)
List 3	0.8 (0-4)	0.9 (0-5)	0.9 (0-5)
List 4	1.1 (0-7)	1.2 (0-7)	1.1 (0-7)

*N= 275 (QD), 279 (BID), *P*=0.047 (between-groups comparison based on one-way ANOVA)

- Background NRTI usage on study was comparable between treatment arms
  - The number of active background NRTIs was similar between groups; the majority of subjects, 63% of QD- and BID-dosed subjects each, were susceptible to at least 2 NRTIs in the background regimen
  - The most common background regimen consisting of 2 NRTIs was tenofovir DF (TDF) with either emtricitabine (FTC) or lamivudine (3TC), used by 89 QD subjects (30%) and 71 BID subjects (24%)
  - The most common regimen consisting of 3 NRTIs, employed by 43 QD subjects (15%) and 51 BID subjects (17%), included TDF and zidovudine with either FTC or 3TC

Efficacy

- The primary efficacy endpoint at 48 weeks revealed non-inferior antiviral activity of LPV/r dosed QD as compared to BID in treatment-experienced subjects
  - By ITT-TLOVR analysis, 55.3% of QD and 51.8% of BID subjects had HIV-1 RNA <50 copies/mL[3]
  - Other intent-to-treat and on-treatment analyses also demonstrated similar antiviral activity with LPV/r QD and BID[3]
- Virologic response remained comparable between dosing groups when analyzed in subjects stratified by the number of active NRTIs at baseline (Table 2)

Table 2. Virologic Efficacy (ITT-TLOVR) at Week 48 by Number of Active NRTIs at Baseline

Number of active NRTIs	Proportion of subjects with HIV-1 RNA <50 copies/mL, n/N (%)			*P* value (QD vs. BID)
	QD	BID	Overall	
<2	64/110 (58%)	74/109 (68%)	138/219 (63%)	0.162
2	96/175 (55%)	77/170 (45%)	173/345 (50%)	0.085
>2	6/15 (40%)	4/19 (21%)	10/34 (29%)	0.276

- Response rates at Week 48 were not statistically significantly different between treatment groups in the few subjects with at least possible evidence of resistance to LPV/r at baseline (QD: 58%, N=12; BID: 29%, N=17; *P*=0.148)
- Response rates were higher in the QD group versus the BID group in subjects with ≥2 prior protease regimens (Table 3)

Table 3. Antiviral Efficacy (ITT-TLOVR) at Week 48 Based on Number of Previous Protease Inhibitor Treatments

Number of prior protease inhibitor treatments	Proportion of subjects with HIV-1 RNA <50 copies/mL, n/N (%)			*P* value (QD vs. BID)
	QD	BID	Overall	
0	90/164 (55%)	105/164 (64%)	195/328 (59%)	0.115
1	44/77 (57%)	33/70 (47%)	77/147 (52%)	0.250
≥2	32/59 (54%)	17/65 (26%)	49/124 (40%)	0.002

Results

Relationship between Baseline Protease Inhibitor-associated Resistance Mutations and Virologic Response

- The impact of the number of baseline mutations on response was comparable between QD and BID LPV/r dosing, and outcomes were similar when analyzed by both ITT-TLOVR and dropouts-as-censored methods
  - For List 1, a tendency for virologic response to be associated with the number of baseline mutations was observed (*P*=0.054); efficacy was similar in subjects with 4 or fewer List 1 mutations at baseline (Table 4)

Table 4. Virologic Response at Week 48 by Dropouts-as-censored Analysis in Subjects with List 1 Protease Inhibitor-associated Resistance Mutations at Baseline

Number of List 1 Mutations[a]	Proportion of subjects with HIV-1 RNA <50 copies/mL, n/N (%)			OR[b] (95% CI)	*P* value[c]
	QD	BID	Overall		
0	59/85 (69%)	53/79 (67%)	112/164 (68%)	0.872	0.054
1	69/111 (62%)	63/107 (59%)	132/218 (61%)	(0.758, 1.002)	
2	29/46 (63%)	26/45 (58%)	55/91 (60%)		
3	8/12 (67%)	8/13 (62%)	16/25 (64%)		
4	4/7 (57%)	8/11 (73%)	12/18 (67%)		
5+	2/7 (29%)	4/9 (44%)	6/16 (38%)		

[a]L10F/I/R/V, K20M/R, L24I, V32I, L33F, M36I, M46I/L, I47V/A, G48V, I50V, F53L, I54 (any change), A71V/T, G73S, V82A/F/T/S, I84V, L90M
[b]OR (95% CI): odds ratio (95% confidence interval) per additional mutation
[c]*P* value comparing number of mutations with response, based on logistic regression chi-square test

  - The number of mutations from List 2 was not associated with virologic suppression (Table 5)

Table 5. Virologic Response at Week 48 by Dropouts-as-censored Analysis in Subjects with List 2 Protease Inhibitor-associated Resistance Mutations at Baseline

Number of List 2 Mutations[a]	Proportion of subjects with HIV-1 RNA <50 copies/mL, n/N (%)			OR[b] (95% CI)	*P* value[c]
	QD	BID	Overall		
0	71/103 (69%)	58/94 (62%)	129/197 (66%)	0.965	0.682
1	71/118 (60%)	73/117 (62%)	144/235 (61%)	(0.815, 1.143)	
2	15/26 (58%)	13/25 (52%)	28/51 (55%)		
3	8/14 (57%)	12/19 (63%)	20/33 (61%)		
4+	6/7 (86%)	6/9 (67%)	12/16 (75%)		

[a]Any change at: D30, V32, M36, M46, I47, G48, I50, F53, I54, G73, V82, I84, N88, L90
[b]OR (95% CI): odds ratio (95% confidence interval) per additional mutation
[c]*P* value comparing number of mutations with response, based on logistic regression chi-square test

  - Virologic response was significantly associated with the number of baseline mutations according to List 3 (*P*=0.031); responses were similar for subjects with 2 or fewer baseline List 3 mutations (Table 6)

Table 6. Virologic Response at Week 48 by Dropouts-as-censored Analysis in Subjects with List 3 Protease Inhibitor-associated Resistance Mutations at Baseline

Number of List 3 Mutations[a]	Proportion of subjects with HIV-1 RNA <50 copies/mL, n/N (%)			OR[b] (95% CI)	*P* value[c]
	QD	BID	Overall		
0	74/105 (71%)	62/98 (63%)	136/203 (67%)	0.810	0.031
1	67/107 (63%)	62/106 (59%)	129/213 (61%)	(0.669, 0.981)	
2	26/43 (61%)	30/46 (65%)	56/89 (63%)		
3	3/9 (33%)	7/10 (70%)	10/19 (53%)		
4+	1/4 (25%)	1/4 (25%)	1/4 (25%)		

[a]L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, I84V
[b]OR (95% CI): odds ratio (95% confidence interval) per additional mutation
[c]*P* value comparing number of mutations with response, based on logistic regression chi-square test

  - There was no significant effect of the number of baseline protease inhibitor-associated mutations from List 4 on virologic response (Table 7)

Table 7. Virologic Response at Week 48 by Dropouts-as-censored Analysis in Subjects with List 4 Protease Inhibitor-associated Resistance Mutations at Baseline

Number of List 4 Mutations[a]	Proportion of subjects with HIV-1 RNA <50 copies/mL, n/N (%)			OR[b] (95% CI)	*P* value[c]
	QD	BID	Overall		
0	55/94 (59%)	45/73 (62%)	100/167 (60%)	0.929	0.331
1	71/106 (67%)	78/120 (65%)	149/226 (66%)	(0.801, 1.078)	
2	31/43 (72%)	22/39 (56%)	53/82 (65%)		
3	9/12 (75%)	8/15 (53%)	17/27 (63%)		
4+	5/13 (38%)	9/17 (53%)	14/30 (47%)		

[a]L10F/I/R/V, K20M/R, L24I, M46I/L, F53L, I54L/T/V, L63P, A71I/L/T/V, V82A/F/T, I84V, L90M
[b]OR (95% CI): odds ratio (95% confidence interval) per additional mutation
[c]*P* value comparing number of mutations with response, based on logistic regression chi-square test

Results

Relationship between Baseline NRTI-associated Resistance and Virologic Response

- Virologic response was higher among subjects with an M184V/I mutation in reverse transcriptase compared to those with wild-type virus at codon 184, although the response rate of the QD group appeared to be less affected by this mutation than the BID group (Table 8)
- The effect of M184V/I on virologic response remained statistically significant after adjustment for the number of protease inhibitor mutations, the number of active NRTIs, and adherence (data not shown)

Table 8. Virologic Response at Week 48 Based on Dropouts-as-censored Analysis, by Presence of M184V/I Mutation at Baseline

Mutation	Proportion of subjects with HIV-1 RNA <50 copies/mL, n/N (%)			*P* value (QD vs. BID)
	QD	BID	Overall	
M184 wild type	42/74 (57%)	33/82 (40%)	75/156 (48%)	0.039
M184V/I	129/194 (66%)	129/182 (71%)	258/376 (69%)	0.360
P value (M184V/I vs. wild type)	0.138	<0.001	<0.001	

Summary

- Enrollment of Study M06-802 was designed to mirror clinical practice where physicians design an antiretroviral regimen based on treatment history, genotypic resistance testing and interpretation, and local availability of antiretroviral agents
- LPV/r dose frequency did not affect antiviral efficacy, regardless of the number of baseline mutations. This finding may reflect, in part, the high LPV trough concentrations achieved with both QD and BID dosing relative to viral IC50, even in subjects with up to 2-3 protease mutations.
- Baseline 3TC/FTC resistance, as conferred by the presence of M184V/I, appeared to enhance virologic response rates. This effect is consistent with the hypothesis that M184V imparts reduced viral fitness, rendering the virus hypersusceptible to other antiretroviral agents[10]; however, the effect of this mutation on treatment outcome requires further exploration.
- The only statistically significant association between the number of baseline protease inhibitor-associated resistance mutations and virologic response was seen with LPV-specific mutations in List 3[6]
  - Efficacy was similar within and across treatment groups in subjects with fewer than 3 baseline mutations from List 3; the number of subjects with 3 or more mutations was insufficient to draw further conclusions

Conclusion

The impact of baseline protease resistance mutations is similar whether LPV/r is dosed QD or BID in treatment-experienced subjects

Acknowledgements

This study is registered with ClinicalTrials.gov (NCT00358917). The authors wish to acknowledge Rafael Rivero, MD (Abbott), for critical review of the poster content, and Elaine M. Smith, PhD (Abbott), for assistance in writing the poster.

Disclosures

Abbott provided financial support for this study. All authors are employees of Abbott and may hold Abbott stock or options.

References

1. Molina JM, Podsadecki TJ, Johnson MA, et al. A lopinavir/ritonavir-based once-daily regimen results in better compliance and is non-inferior to a twice-daily regimen through 96 weeks. *AIDS Res Hum Retroviruses*. 2007;23:1505-1514.
2. Gathe J, da Silva BA, Cohen DE, et al. A Once-Daily Lopinavir/Ritonavir-Based Regimen Is Noninferior to Twice-Daily Dosing and Results in Similar Safety and Tolerability in Antiretroviral-Naive Subjects Through 48 Weeks. *J Acquir Immune Defic Syndr.* 2009;50:474-481.
3. Zajdenverg R, Badal-Faesen S, Andrade-Villanueva J, et al. Lopinavir/ritonavir (LPV/r) tablets administered once- (QD) or twice-daily (BID) with NRTIs in antiretroviral-experienced HIV-1 infected subjects: Results of a 48-week randomized trial (Study M06-802). Paper presented at: 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention; 19-22 July 2009; Cape Town, South Africa.
4. Kempf DJ, Isaacson JD, King MS, et al. Identification of genotypic changes in human immunodeficiency virus protease that correlate with reduced susceptibility to the protease inhibitor lopinavir among viral isolates from protease inhibitor-experienced patients. *J Virol.* 2001;75:7462-7469.
5. Mo H, King MS, King K, Molla A, Brun S, Kempf DJ. Selection of resistance in protease inhibitor-experienced, human immunodeficiency virus type 1-infected subjects failing lopinavir- ritonavir-based therapy: mutation patterns and baseline correlates. *J Virol.* 2005;79:3329-3338.
6. King MS, Rode R, Cohen-Codar I, et al. Predictive genotypic algorithm for virologic response to lopinavir-ritonavir in protease inhibitor-experienced patients. *Antimicrob Agents Chemother.* 2007;51:3067-3074.
7. Johnson VA, Brun-Vézinet F, Clotet B, et al. Update of the Drug Resistance Mutations in HIV-1: December 2008. *Top HIV Med.* 2008;16:138-145.
8. Abbott Laboratories. Kaletra Tablets and Oral Solution, Full Prescribing Information. October 2008; http://www.rxabbott.com/pdf/kaletratabpi.pdf.
9. European Medicines Agency. Kaletra Product Information, Summary of Product Characteristics. August 2009; http://www.emea.europa.eu/humandocs/PDFs/EPAR/kaletra/emea-combined-h368en.pdf.
10. Miller V, Stark T, Loeliger AE, Lange JM. The impact of the M184V substitution in HIV-1 reverse transcriptase on treatment response. *HIV Med.* 2002;3:135-145.