# 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)

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## Background

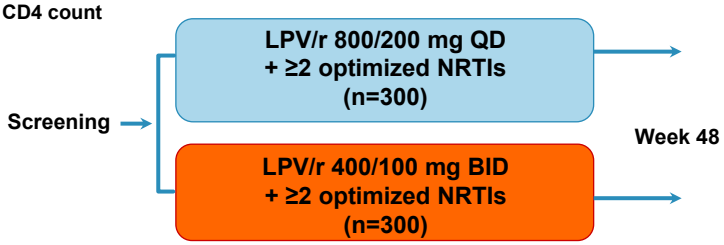
- LPV has demonstrated durable antiviral activity and favorable safety profile in antiretroviral-naïve and experienced subjects
- LPV/r has been approved for QD use in treatment-naïve patients in the US and many other countries since 2005[1-3]
  - Once-daily dosing has been shown to increase adherence[4-6]
  - Increased adherence to HIV treatment is a strong predictor of clinical outcomes[7]
- M06-802 is the first study of LPV/r tablet dosed QD in treatment-experienced patients

1. Kaletra US prescribing Information, 2009; 2. Johnson MA *et al, JAIDS*, 2006;43:153-160;
3. Gathe JR *et al, JAIDS*, 2009;50:474-481; 4. Stone VE, *et al. JAIDS* 2004; 36: 808-816;
5. Molina JM *et al, Drugs* 2008; 68 (5): 567-578; 6. Molina JM *et al, AIDS Research and Human Retroviruses,* 2007: 23 (12) 1505–1514; 7. Paterson DL *et al, Ann Intern Med*. 2000; 133:21-30

## LPV/r QD *vs* BID in Treatment-Experienced Subjects M06-802 Study Design

**Inclusion Criteria**

- HIV-1 infection
- ARV-experienced, lopinavir-naïve
- HIV-1 RNA >1000 c/mL on treatment regimen unchanged for ≥12 weeks
- Based on genotypic and treatment history, investigator considers LPV/r plus ≥2 NRTIs to be an appropriate treatment option
- Any CD4 count




- Primary endpoint: HIV-1 RNA <50 copies/mL at Week 48 (ITT TLOVR)
- Noninferiority assessed by 95% CI for the difference (QD *minus* BID) using a -12% threshold



## Baseline Demographics and HIV Disease Characteristics*

| Variable | LPV/r QD (n=300) | LPV/r BID (n=299) | Total (n=599) | *P* value |
|---|---|---|---|---|
| Males, n (%) | 197 (66) | 196 (66) | 393 (66) | NS |
| Females, n (%) | 103 (34) | 103 (34) | 206 (34) | NS |
| Caucasian, n (%) | 158 (53) | 150 (50) | 308 (51) | NS |
| Black, n (%) | 104 (35) | 104 (35) | 208 (35) | NS |
| Hispanic/Latino, n (%) | 98 (33) | 105 (35) | 203 (34) | NS |
| Mean age, years (SD) | 40.4 (9.2) | 40.8 (8.6) | 40.6 (8.9) | NS |
| Mean BL HIV-1 RNA#, $\log_{10}$ copies/mL (range) | 4.26 (1.7 – 6.6) | 4.26 (1.7 – 6.5) | 4.26 (1.7 – 6.6) | NS |
| Mean BL CD4, cells/µL (range) | 239 (4 – 754) | 268 (5 – 952) | 254 (4 – 952) | 0.047 |

* Excludes randomized but not dosed, n=1
# 2 subjects QD and 3 subjects BID with baseline HIV-1 RNA ≤50 copies/mL

## Proportion of Subjects Having Received ≥1 Prior Agent by Antiretroviral Class

| | LPV/r QD (N=300) n (%) | LPV/r BID (N=299) n (%) |
|---|---|---|
| Any prior ARV | 300 (100) | 299 (100) |
| NRTI | 299 (99.7) | 297 (99.3) |
| NNRTI | 264 (88.0) | 241 (80.6) |
| Protease Inhibitor | 140 (46.7) | 136 (45.5) |
| 1 prior PI | 77 (25.7) | 70 (23.4) |
| 2 prior PIs | 46 (15.3) | 49 (16.4) |
| 3 prior PIs | 11 (3.7) | 13 (4.3) |
| 4 prior PIs | 2 (0.7) | 3 (1.0) |
| Entry inhibitor | 4 (1.3) | 0 |
| Fusion inhibitor | 1 (0.3) | 2 (0.7) |



## Subject Disposition at Week 48

| Reasons for Discontinuations | LPV/r QD (N=300) n (%) | LPV/r BID (N=299) n (%) | Total (N=599) n (%) |
|---|---|---|---|
| All Reasons* | 66 (22.0) | 69 (23.1) | 135 (22.5) |
| AE/HIV-related Event† | 14 (4.7) | 22 (7.4) | 36 (6.0) |
| Withdrew Consent | 8 (2.7) | 8 (2.7) | 16 (2.7) |
| Lost to Follow-Up | 23 (7.7) | 17 (5.7) | 40 (6.7) |
| Noncompliance | 13 (4.3) | 17 (5.7) | 30 (5.0) |
| Death | 2 (0.7) | 3 (1.0) | 5 (0.8) |
| Virologic Failure | 12 (4.0) | 10 (3.3) | 22 (3.7) |
| Other | 6 (2.0) | 4 (1.3) | 10 (1.7) |
| On Treatment at Week 48 | 234 (78.0) | 230 (76.9) | 464 (77.5) |

* *P* >0.100 for all comparisons QD vs BID
†1 subject in each group discontinued due to an HIV-related event; 7 (QD) and 6 (BID) subjects discontinued for diarrhea

## Adherence Monitoring Through Week 24 With MEMS® Monitors (Pill Bottle Caps)

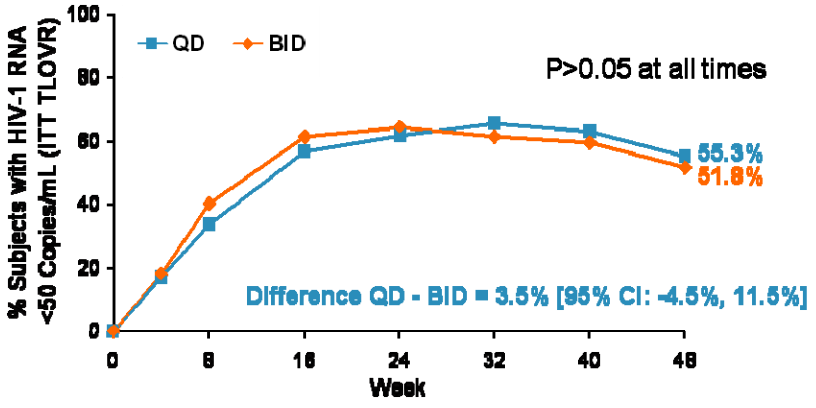
- Consistent with prior studies in naïve subjects (M02-418[1] and M05-730[2]), QD dosing of LPV/r provided a significant benefit with regard to adherence over BID dosing in treatment-experienced subjects

| Time Period | Adherence measure | LPV/r QD (mean %) | LPV/r BID (mean %) | P-value |
|---|---|---|---|---|
| **Baseline to Week 8** (N=256 QD, N=265 BID) | **Taking compliance** | **89.6** | **84.5** | **<0.001** |
| | **Correct dosing** | **84.6** | **75.2** | **<0.001** |
| | **Timing compliance** | **72.3** | **65.5** | **0.030** |
| **Baseline to Week 24** (N=251 QD, N=255 BID) | **Taking compliance** | **84.4** | **78.1** | **0.003** |
| | **Correct dosing** | **79.6** | **68.1** | **<0.001** |
| | **Timing compliance** | **65.8** | **58.2** | **0.014** |

1. Johnson MA *et al, JAIDS*, 2006;43:153-160; 2. Gathe JR *et al, JAIDS*, 2009;50:474–481

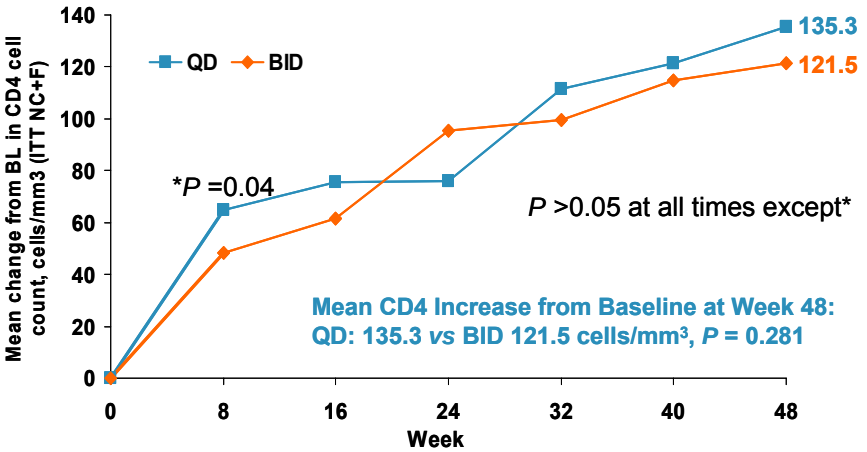


## Primary Efficacy Endpoint at Week 48 Proportion of Subjects Responding (ITT TLOVR)




**Demonstrating non-inferiority of LPV/r QD to BID in treatment-experienced subjects**

## Mean CD4+ T-cell Count Change from Baseline to Week 48 (cells/mm$^3$)






## Virologic Response by Number of LPV Resistance Mutations at Baseline†‡

| Number of Mutations in Protease | Number of Subjects (%) LPV/r QD N=300 | LPV/r BID N=299 |
|---|---|---|
| 0 | 74/105 (70.5) | 62/98 (63.3) |
| 1 | 67/107 (62.6) | 62/106 (58.5) |
| 2 | 26/43 (60.5) | 30/46 (65.2) |
| 3 or more | 4/13 (30.8) | 8/14 (57.1) |

† LPV-associated mutations: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82/A/C/F/S/T, and I84V[1]; ‡ Dropout-as-censored endpoint

- **In subjects with 0-2 LPV-associated mutations, response was similar within and across dosing groups**
  - Because of the small number of subjects with significant PI resistance at baseline, there are insufficient data to draw firm conclusions on the use of LPV/r QD in patients with ≥3 LPV-associated mutations
- **Emergence of new protease resistance mutations in subjects with inadequate virologic suppression was uncommon**
  - No difference in changes in protease between the LPV/r QD and BID dosing groups

1. King MS *et al, AAC* 2007; 51(9): 3067–3074

## Number and % of Subjects with Moderate or Severe Drug-related Adverse Events Occurring in ≥2%*

| | LPV/r QD (N=300) n (%) | LPV/r BID (N=299) n (%) | *P* value |
|---|---|---|---|
| **Any Adverse Event** | 82 (27.3) | 76 (25.4) | NS |
| **GI Disorders** | | | |
| Diarrhea | 42 (14.0) | 33 (11.0) | NS |
| Nausea | 8 (2.7) | 22 (7.4) | 0.009 |
| Abdominal pain | 6 (2) | 1 (0.3) | NS |
| Abdominal pain (upper) | 2 (0.7) | 6 (2.0) | NS |
| Vomiting | 6 (2.0) | 8 (2.7) | NS |
| **Metabolism and Nutrition Disorders** | | | |
| Hypercholesterolemia | 7 (2.3) | 4 (1.3) | NS |

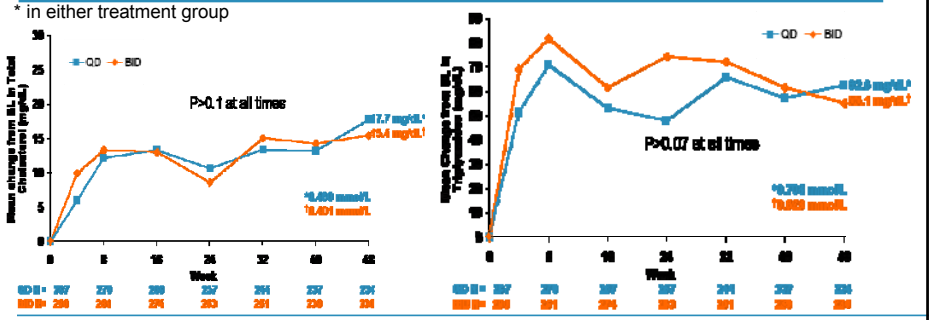
* in either treatment group



## Number and % of Subjects with Potentially Clinically Significant Laboratory Values ≥5%*

| | LPV/r QD (N=300) n (%) | LPV/r BID (N=299) n (%) |
|---|---|---|
| **CPK >4x ULN** | 13/293 (4.4) | 16/295 (5.4) |
| **Total Cholesterol >7.8 mmol/L (300 mg/dL)** | 19/293 (6.5) | 22/295 (7.5) |
| **Triglycerides >8.475 mmol/L (750 mg/dL)** | 14/293 (4.8) | 19/295 (6.4) |

* in either treatment group



## Study Conclusions

- **Through 48 weeks, LPV/r dosed QD or BID had similar efficacy in treatment-experienced subjects**
  - LPV/r dosed QD was non-inferior to BID – Proportion of subjects responding at Week 48 [FDA ITT TLOVR]: QD: 55.3% and BID: 51.8%, *P*=0.412
  - Consistent with results obtained with LPV/r SGC dosed BID in recent comparative studies in experienced patients
  - Similar mean increases in CD4+ T-cell counts at Week 48 (QD: 135 *vs* BID: 121 cells/mm$^3$, *P*>0.05)
- **Through 24 weeks, QD dosing of LPV/r resulted in higher treatment compliance than BID dosing**
- **Generally well tolerated with few study drug-related discontinuations**
  - Discontinuations for AEs 34/599: QD 13/300 (4.3%), BID 21/299 (7.0%)
  - AE profile generally similar across dosing groups
  - No clinically significant difference in laboratory abnormalities



## M06-802: Acknowledgements

- The authors express their gratitude to **the patients and their families** for their participation and support during the study
- To the **investigators**, **co-investigators** and **clinical research personnel** who worked on this study at 193 sites in 17 countries around the world
- And to the **M06-802 Study Team** at Abbott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