Robert C. Stevens
Dept R48U, Bldg AP30-3
Abbott Laboratories
200 Abbott Park Road
Abbott Park, IL 60064
robert.stevens@abbott.com

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Abstract 2.14

SOKRATES: Prospective Clinical Trials to Investigate the Evolution of Protease Resistance During Lopinavir/ritonavir Treatment

R.C. Stevens, P. Cernohous, M. King, D. Kempf, N. Travers, J. Moseley, K. Grebner, and S. Brun; Abbott Laboratories, Abbott Park, IL, USA

BACKGROUND

Lopinavir/ritonavir (Kaletra™, LPV/r) is a novel protease inhibitor (PI) that achieves lopinavir trough concentrations >75-fold above the protein binding-adjusted IC_{50} of LPV relative to wild type virus when dosed at 400/100 mg BID. This high ratio of LPV trough concentrations to IC_{50} (referred to as the inhibitory quotient or IQ) provides a formidable pharmacologic barrier to the emergence of viral resistance in antiretroviral (ARV)-naïve patients.[1] Indeed, in 508 ARV-naïve patients enrolled in Phase II/III trials with LPV/r for a median duration of 97 weeks (range, 0-250 weeks) there has been no evolution of genotypic or phenotypic resistance to LPV observed to date[2-5] (Table 1).

Table 1. Clinical Trials Supporting Absence of Evolution of Resistance to LPV in ARV-Naïve Patients During LPV/r Therapy

Study	Age Group	N	Duration	Reference
M97-720 (Phase II)	Adults	100	4 Years[2]	Murphy, 2002
M98-863 (Phase III)	Adults	326	96 Weeks[3]	Kempf, 2003
M98-940 (Phase II)	Pediatric	44	72 Weeks[4]	Cahn, 2001
M00-056 (Phase II)	Adults	38	72 Weeks[5]	Feinberg, 2002

LPV/r demonstrated superior efficacy to nelfinavir (when dosed with d4T/3TC) in a randomized, double-blind Phase III clinical trial (Study M98-863) in ARV-naïve patients (Figure 1).[6] Through 96 weeks of therapy, no evidence of primary resistance to LPV (defined as any primary or active site mutation in protease) was detected in any of 51 Kaletra-treated patients with detectable viral load for whom genotype was available (Table 2). In contrast, 48% of rebound isolates with genotype available from nelfinavir-treated patients displayed primary resistance to nelfinavir (emergence of D30N and/or L90M) or displayed substantially reduced (>6.8-fold) susceptibility to nelfinavir in the absence of either primary mutation. Moreover, through 96 weeks, patients on LPV/r demonstrated a significantly lower cumulative probability of resistance in protease and reverse transcriptase (Figure 2).[3,7,8]

Figure 1. Study M98-863; LPV/r vs. NFV: Time to Loss of Virologic Response

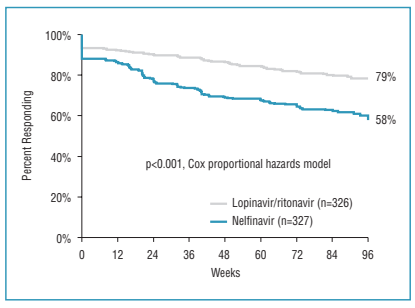


Figure 2. Study M98-863; LPV/r vs. NFV: Cumulative Probability of Resistance Development Across Total Study Population

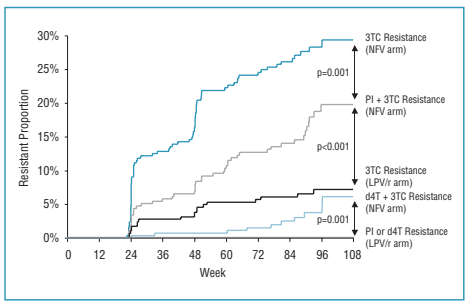


Table 2. Summary of Resistance Analysis of LPV/r vs. Nelfinavir in ARV-Naïve Patients in Study M98-863 Through Week 96[7,8]

	LPV/r	Nelfinavir	p-value
Number of patients enrolled	326	327	
Patients with HIV RNA >400 copies/mL	74 (23%)	113 (35%)	
Genotype available	51/74 (69%)	96/113 (85%)	
PI resistance[a]	0/51 (0%)	46/96 (48%)	<0.001
3TC resistance	19/51 (37%)	79/96 (82%)[b]	<0.001

[a] LPV resistance defined as the emergence of any primary or active site mutation in protease (amino acids 8, 30, 32, 46, 47, 48, 50, 82, 84, or 90) and confirmed by phenotypic analysis. NFV resistance defined as the emergence of the D30N or L90M mutation in protease, or the emergence of the M46I/L mutation in protease with confirmed reduced phenotypic susceptibility to NFV.
[b] Previous results' that reported 78 of 96 patients with 3TC resistance did not include one isolate with a M184T mutation that demonstrated >100-fold phenotypic resistance to 3TC.

The objectives of the SOKRATES trials are to further define rates and patterns of PI resistance in patients receiving LPV/r as first or second PI-based therapy and to evaluate potential salvage regimens.

METHODS

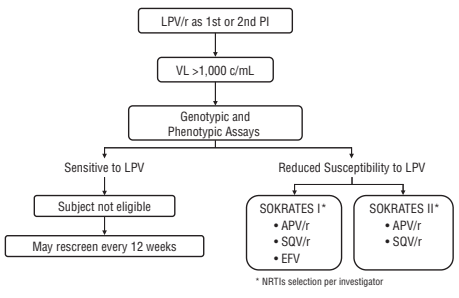
SOKRATES (Salvage of Kaletra Resistance) is a prospective, open-label, study involving 112 sites in 14 countries. Planned enrollment is 24 patients (SOKRATES I) and 16 patients (SOKRATES II) for a 48-week duration. As an adjunct to these two studies, patients who are currently on LPV/r as either a first or second PI containing regimen at each of the participating sites are being followed prospectively to identify evolution of resistance.

Eligibility criteria for SOKRATES

- Minimum of 16 weeks of treatment with LPV/r as initial (SOKRATES I) or second (SOKRATES II) PI-based therapy.
- Confirmed HIV RNA rebound to >1,000 copies/mL or lack of suppression below 1,000 copies/mL after 16 weeks of treatment.
- Reduced phenotypic susceptibility to LPV (defined as >10-fold increase in IC_{50} relative to wild type HIV).

Once LPV resistance is identified, patients are switched to efavirenz (SOKRATES I only), saquinavir/ritonavir (SQV/r), or amprenavir/ritonavir (APV/r), based on phenotypic susceptibility, along with 2 nucleoside analogues (Figure 3).

Figure 3. SOKRATES I and II Study Design



RESULTS

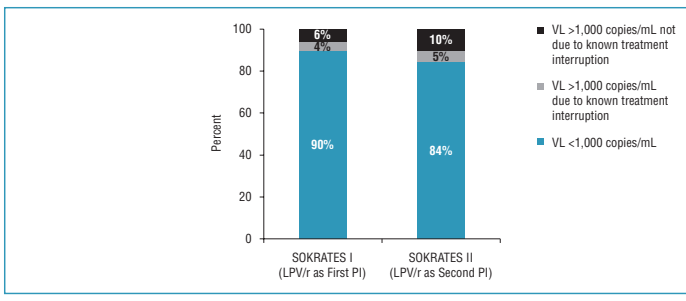
Of the 48 study sites providing data for the registry of patients, 467 and 429 patients received LPV/r as their first or second PI, respectively (Table 3).

Table 3. LPV/r Exposure in SOKRATES Patients

	SOKRATES I (LPV/r as first PI)	SOKRATES II (LPV/r as second PI)
Number of Patients	467	429
Median time on LPV/r (weeks)	57	55
Range of time on LPV/r (weeks)	18-197	16-213

- As of their most recent data, 419 (90%) and 362 (84%) subjects had HIV RNA <1,000 copies/mL in SOKRATES I and II, respectively, while 48 (10%) and 67 (16%) subjects had HIV RNA >1,000 copies/mL in SOKRATES I and II, respectively (Figure 4).
- Twenty of the 48 SOKRATES I HIV RNA elevations were due to known treatment interruptions while 23/67 SOKRATES II HIV RNA elevations were the result of known treatment interruptions.

Figure 4. Categorization of Most Recent HIV RNA Values for SOKRATES I and II



- Three and 16 patients met criteria to be screened for SOKRATES I and II, respectively. For patients with HIV RNA >1,000 copies/mL (not due to known treatment interruptions), absence of a pre LPV/r genotype was the most common reason for not being screened.
- No viral isolates from patients screened for SOKRATES I demonstrated any new primary or active site mutations in protease, consistent with phase II/III LPV/r clinical trial data listed in Table 1.
- Viral isolates from 6 patients screened for SOKRATES II demonstrated evolution of resistance to LPV. The protease mutations for these patients are listed in Table 4. Patient B had a screening phenotype based on evolution of one primary (V32I) and one secondary (M46I) mutation, but there was no fold-change in LPV susceptibility. Only two patients met entry criteria for salvage therapy based on phenotypic susceptibility. Patient C is being evaluated for salvage therapy with SQV/r. Patient D is receiving SQV/r (800 mg/200 mg BID) based on resistance testing.

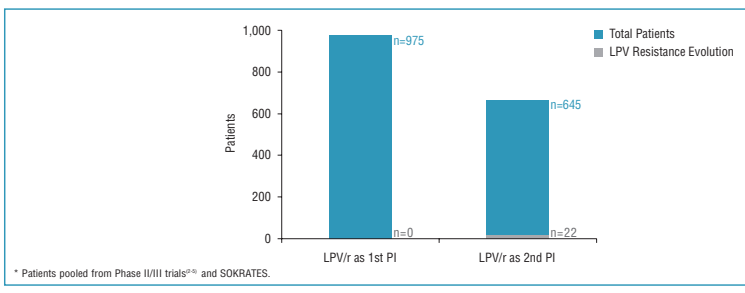
Table 4. Genotypic and Phenotypic Results from Patients Screened for SOKRATES II

Patient	Protease Mutations[a]	Number of Mutations Associated with LPV Resistance	Fold-Change in PI Susceptibility[b] LPV	APV	SQV
A	**L10I** T12K I15V M36L S37D **M46I F53L I54V** I62V **L63P** C67F H69R **A71V** I72T **V82A** N88D **L90M** Q92K	8	70.0	3.5[c]	55.0
B	I15I/V L19I V32I/M/V **M36I** S37N R41K **M46I**/M **L63P**/L	3	0.8	0.9	0.6
C	V32I **M36I** S37N R41K **M46I I47A/V L63P** K70K/E **A71V V82A**/V **L90M**/L I93L	7	38.0	14.0	1.4[d]
D	**L10I** T12I I15V L19V **K20R** V32 **M36I** S37N **M46I I47V I54M** I62V **L63P A71T** I72E **V82T** I85V	9	98.0	27.0	1.7[e]
E	**L10F L24I L33F** S37N P39Q R41K K43T **M46L I54V** D60E I62V **L63P A71V** V77I/V **V82A**	8	73.0	9.3	6.0
F	**L10V** I15V **K20R** E35D **M36I** S37E/D **M46**M/**L G48V I50I/V I54A/V** Q58Q/E I62V **L63P** C67S/C **A71T/I/A/V V82T/A I84I/V** I93L	10	202.0	9.9	545.5

[a] Mutations in boldface indicate mutations associated with reduced susceptibility or attenuated response to LPV.[9-11]
[b] Susceptibility was defined as a less than 10, 8 and 4 fold change in phenotypic susceptibility to LPV, APV and SQV, respectively.
[c] Patient A was eligible, but was hospitalized for an opportunistic infection and died before enrollment.
[d] Patient C is eligible for enrollment in SOKRATES II and is being evaluated for salvage therapy with SQV/r.
[e] Patient D enrolled in the SOKRATES II study and is receiving SQV/r (800 mg/200 mg BID) based on resistance testing.

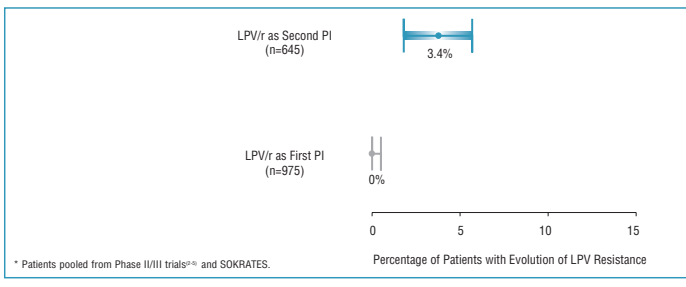
- Combining available data from phase II/III trials (Table 1) and SOKRATES, the observed rate of LPV resistance was 0/975 (0%) patients (99% CI, 0% to 0.5%) in patients receiving LPV/r as a first PI and 22/645 (3.4%) patients (99% CI, 1.8% to 5.7%) when LPV/r is used as a second PI (Figures 5 and 6).

Figure 5. Incidence of LPV Resistance Evolution*



* Patients pooled from Phase II/III trials[2-5] and SOKRATES.

Figure 6. Observed Rates of LPV Resistance with 99% CI*



* Patients pooled from Phase II/III trials[2-5] and SOKRATES.

CONCLUSIONS

- Development of protease inhibitor resistance during viral load rebound when LPV/r is used as initial PI-based therapy has not been observed to date and is likely a rare event based on the sample size available for evaluation.
- Among patients using LPV/r as their second PI-based regimen, evolution of resistance to LPV was significantly higher (3.4%) than in those using LPV/r as their first PI-based regimen.
- Screening is ongoing for SOKRATES.

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