Table 16: Post-Therapy Microbiological Response: All Subjects with Community-Acquired Pneumonia by Population Type
(Protocol LOFBIV-PCAP-001) (per Applicant)

Population	N	Microbiological Eradication [a,b] n/N	(%)
Intent-to-Treat Subjects with an Admission Pathogen	468	408/468 [c]	(87.2)
Microbiologically Evaluable Subjects	398	383/398 [c]	(96.2)

[a] Numbers shown in parentheses are percentages for that category.
[b] Microbiological eradication = eradicated + presumed eradicated; Microbiologic persistence = persisted + unknown.
[c] Subject 59005 (——— admission pathogen: *M. pneumoniae*) is classified in this table as having a Post-Therapy microbiologic response of presumed eradicated, corrected from the listed response of unknown. He became microbiologically evaluable after a second post-therapy visit on 12/29/97. The data collected at this time replaces the unknown response of the first post-therapy visit, which was conducted on 12/22/97, the last day of therapy. When compared to his admission and On-Therapy clinical evaluations, there are no clinically significant differences between the clinical responses collected at the two post-therapy evaluations.
Adapted from Applicant's Table 31b, NDA 20-634 SE1-008 Vol. 25.3, p. 202

Of the 398 patients who were evaluable for microbiological efficacy, 383 (96%) had a response reported as eradicated (eradicated + presumed eradicated), 15 (4%) were scored as microbiological persistence. The results for microbiological efficacy at Post-Therapy stratified by study center are presented in Table 17. Three study centers enrolled over 50% of the microbiologically evaluable population with one of these 3 centers contributing over 30%.

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Table 17: Microbiologic Eradication Rates Five to Seven Days Post-Therapy for Each Study Center: Subjects Evaluable for Microbiologic Efficacy per Applicant (Protocol LOFBIV-PCAP-001)

	Levofloxacin						
Investigator	N	Eradicated[a,b]		Persisted[b]		Unknown[b]	
det	2	2	(100.0%)	0	(0.0%)	0	(0.0%)
	11	10	(90.9%)	1	(9.1%)	0	(0.0%)
	2	2	(100.0%)	0	(0.0%)	0	(0.0%)
	11	11	(100.0%)	0	(0.0%)	0	(0.0%)
	4	4	(100.0%)	0	(0.0%)	0	(0.0%)
	38	37	(97.4%)	1	(2.6%)	0	(0.0%)
	5	5	(100.0%)	0	(0.0%)	0	(0.0%)
	122	118	(96.7%)	4	(3.3%)	0	(0.0%)
	10	10	(100.0%)	0	(0.0%)	0	(0.0%)
	7	7	(100.0%)	0	(0.0%)	0	(0.0%)
	7	6	(85.7%)	1	(14.3%)	0	(0.0%)
	47	46	(97.9%)	1	(2.1%)	0	(0.0%)
	2	2[c]	(100.0%)	0	(0.0%)	0[c]	(0.0%)
	9	9	(100.0%)	0	(0.0%)	0	(0.0%)
	3	3	(100.0%)	0	(0.0%)	0	(0.0%)
	2	2	(100.0%)	0	(0.0%)	0	(0.0%)
	3	3	(100.0%)	0	(0.0%)	0	(0.0%)
	13	13	(100.0%)	0	(0.0%)	0	(0.0%)
	19	16	(84.2%)	3	(15.8%)	0	(0.0%)
	7	6	(85.7%)	1	(14.3%)	0	(0.0%)
	8	8	(100.0%)	0	(0.0%)	0	(0.0%)
	19	17	(89.5%)	2	(10.5%)	0	(0.0%)
	14	14	(100.0%)	0	(0.0%)	0	(0.0%)
	8	8	(100.0%)	0	(0.0%)	0	(0.0%)
	2	2	(100.0%)	0	(0.0%)	0	(0.0%)
	3	3	(100.0%)	0	(0.0%)	0	(0.0%)
	3	3	(100.0%)	0	(0.0%)	0	(0.0%)
	3	3	(100.0%)	0	(0.0%)	0	(0.0%)
	5	5	(100.0%)	0	(0.0%)	0	(0.0%)
	5	5	(100.0%)	0	(0.0%)	0	(0.0%)
	4	3	(75.0%)	1	(25.0%)	0	(0.0%)
Total	398	383[c]	(96.2%)	15	(3.8%)	0[c]	(0.0%)

[a] Eradication of all pathogens isolated for a subject at admission. Eradicated = eradicated + presumed eradicated

[b] Numbers shown in parentheses are percentages for that category.

[c] Subject 59005 (admission pathogen: *M. pneumoniae*) is classified in this table as having a Post-Therapy microbiologic response of presumed eradicated, corrected from the clinical study data base entry of unknown. He became microbiologically evaluable after a second post-therapy visit on 12/29/97. The data collected at this time replaces the unknown response of the first post-therapy visit, which was conducted on 12/22/97, the last day of therapy. When compared to his admission and On-Therapy clinical evaluations, there are no clinically significant differences between the clinical responses collected at the two post-therapy evaluations.

Applicant's Table 19, from NDA 20-634 SE1-008, Vol. 25.3, p. 183

The Applicant also analyzed microbiological eradication rates by age (<65 vs. ≥65 years), sex, and race (white, black, and other). The microbiological eradication rates observed in these strata within the microbiologically evaluable population were comparable to what was observed in the analysis of the microbiologically evaluable patients.

Eradication Rates by Pathogen

The Applicant analyzed the microbiological eradication rates by pathogen for the microbiologically evaluable population. The results are summarized in Table 18. The microbiological eradication rates (eradication + presumed eradication) at the Post-Therapy assessment for patients with *S. pneumoniae* as a respiratory pathogen were 97% (126/130). For the patients with *S. pneumoniae* isolated from blood, the eradication rate was 100% at the Post-Therapy visit.

Table 18: Microbiologic Eradication Rates Five to Seven Days Post-Therapy Summarized by Pathogen Category and Pathogen: Subjects Evaluable for Microbiological Efficacy per Applicant
(Protocol LOFBIV-PCAP-001) (per Applicant)

Pathogen Category / Pathogen[a]	Levofloxacin N[b]	Eradicated	
Respiratory pathogens			
Streptococcus pneumoniae	130	126	(96.9%)
Haemophilus influenzae	58	57	(98.3%)
Staphylococcus aureus	18	17	(94.4%)
Moraxella (Branhamella) catarrhalis	15	15	(100.0%)
Haemophilus parainfluenzae	14	14	(100.0%)
Klebsiella pneumoniae	12	12	(100.0%)
Escherichia coli	11	11	(100.0%)
Pseudomonas aeruginosa	10	9	(90.0%)
Enterobacter cloacae	6	6	(100.0%)
Streptococcus pyogenes	6	5	(83.3%)
Haemophilus parahemolyticus	5	5	(100.0%)
Blood pathogens			
Streptococcus pneumoniae	25	25	(100.0%)
Atypical pathogens			
Mycoplasma pneumoniae	182	179[c]	(98.4%)
Chlamydia pneumoniae	84	82	(97.6%)
Legionella pneumophila	37	34	(91.9%)

[a] The most prevalent pathogens (N≥5) are presented in this summary for each pathogen category.

[b] N=number of subjects who had that pathogen, alone or in combination with other pathogens.

[c] Subject 59005 [redacted] admission pathogen: *M. pneumoniae*) is classified in this table as having a Post-Therapy microbiologic response of presumed eradicated, corrected from the clinical study data base entry of unknown. He became microbiologically evaluable after a second post-therapy visit on 12/29/97. The data collected at this time replaces the unknown response of the first post-therapy visit, which was conducted on 12/22/97, the last day of therapy. When compared to his admission and On-Therapy clinical evaluations, there are no clinically significant differences between the clinical responses collected at the two post-therapy evaluations.

Adapted from Applicant's Table 20, NDA 20-634 SE1-007, Vol. 25.3, p. 185

Eradication Rates by Severity of Infection

The Applicant also summarized the Post-Therapy eradication rates for the microbiologically evaluable population stratified by disease severity (Table 19). The rates for microbiologic eradication were 96 to 97% for patients with either severe or mild/moderate disease.

Table 19: Microbiologic Eradication Rates at Post-Therapy (5 to 7 days post-therapy) Summarized by Severity of Infection: Subjects Evaluable for Microbiologic Efficacy (Protocol LOFBIV-PCAP-001) (per Applicant)

	Levofloxacin						
	N	Eradicated[a]		Persisted[a]		Unknown[a]	
Severe							
Total severe by pathogen	225	219	(97.3%)	6	(2.7%)	0	(0.0%)
Total severe by subject	121	117	(96.7%)	4	(3.3%)	0	(0.0%)
Mild/moderate							
Total mild/moderate by pathogen	424	412[b]	(97.2%)	12	(2.8%)	0[b]	(0.0%)
Total mild/moderate by subject	277	266[b]	(96.0%)	11	(4.0%)	0[b]	(0.0%)
Overall total							
Total by pathogen	649	631[b]	(97.2%)	18	(2.8%)	0[b]	(0.0%)
Total by subject	398	383[b]	(96.2%)	15	(3.8%)	0[b]	(0.0%)

[a] Numbers shown in parentheses are percentages for that category.

[b] Subject 59005 (; admission pathogen: *M. pneumoniae*) is classified in this table as having a Post-Therapy microbiologic response of presumed eradicated, corrected from the clinical study data base entry of unknown. He became microbiologically evaluable after a second post-therapy visit on 12/29/97. The data collected at this time replaces the unknown response of the first post-therapy visit, which was conducted on 12/22/97, the last day of therapy. When compared to his admission and On-Therapy clinical evaluations, there are no clinically significant differences between the clinical responses collected at the two post-therapy evaluations.

Adapted from Applicant's Table 21, NDA 20-634 SE1-007, Vol. 25.3, p. 186

Superinfection

In the intent-to-treat population, 4 patients presented with superinfections at the Post-Therapy visit. Three of these 4 patients had *C. difficile* (toxin) identified from stool (pseudomembranous colitis) as their superinfecting pathogen. The other patient had a mucoid strain of *P. aeruginosa* from a respiratory culture that was susceptible to levofloxacin on *in vitro* testing.

Other infections that were identified in patients while on study therapy that did not meet the protocol definition of superinfection or new infection included the following. Five subjects received treatment for moniliasis (Pt. No. 1032, 1069, 8009, 8012, and 55004). One patient developed cellulitis (Pt. No. 8011).

MO Comment: Note that the categories of New Infector and Superinfector are microbiological definitions. Hence the five patients with moniliasis and the patient

with cellulitis (as clinically diagnosed infections) do not meet the Applicant's protocol specified definition of New Infector or Superinfector. Clinical events (without an associated microbiological isolate) other that the patient's pneumonia would be captured as adverse events.

Post-Study Microbiologic Response

Patients who were evaluable for microbiological efficacy and were scored as clinical cure or improved at the Post-Therapy evaluation were to return for a Post-Study assessment 21 to 28 days after completing therapy. The Applicant's summary notes that of the 398 microbiologically evaluable patients, Post-Study assessments were available for 345 patients (39 were scored as unknown and 14 were scored as failure at the Post-Therapy visit). For the 345 patients for whom Post-Study assessments were made, 331 of 345 (96%) were scored as microbiological eradications and 14 of 345 (4%) were scored as microbiological relapse. In the patients considered to have microbiological relapse, no acquisition of resistance to levofloxacin was reported.

MO Comment: Note that in the category of Post-Therapy microbiological response, a total of 15 patients were scored as "persisted" at the Post-Therapy assessment. In the Applicant's summary of Post-Study assessments, a total of 14 patients are scored as persisted at the Post-Therapy assessment. The one patient difference is the result of Pt. No. 19013 who was scored as clinically improved and microbiological persisted at Post-Therapy. At Post-Study this patient was scored as clinical relapse and microbiological relapse. Because the patient was scored as microbiological persistence at Post-Therapy this patient is best carried forward as a microbiological failure (persistence at the Post-Therapy visit). Because the patient did not achieve eradication or presumed eradication at the Post-Therapy assessment, the patient should not be eligible for the category of relapse at subsequent assessments. The effect of this difference in scoring of this one patient does not influence the overall conclusions from the data.

Patients with CAP due to *Streptococcus pneumoniae*

One of the objectives of LOFBIV-PCAP-001 was to study the safety and efficacy of levofloxacin in the treatment of CAP due to resistant *S. pneumoniae*. The Applicant provided a summary of the data for patients with CAP due to *S. pneumoniae* in the LOFBIV-PCAP-001 Study Report. Because the data for levofloxacin for the treatment of CAP due to PRSP and PISP are presented in detail in the Integrated Summary of Efficacy for LEVAQUIN for the Treatment of CAP due to PRSP (within this document), only the Applicant's key tables on CAP due to *S. pneumoniae* from Study LOFBIV-PCAP-001 are presented within this section of the review.

Intent-to-Treat Population

The Applicant tabulated the clinical and microbiological response rates for patients who had *S. pneumoniae* as their admission isolate within the intent-to-treat population (Table 20). Six patients in the ITT population were scored as clinical failure and microbiological persistence at the Post-Therapy evaluation. The Admission and Post-Therapy isolates for 5 of these 6 patients were susceptible to levofloxacin. No susceptibility information was available for the 6th patient. Of the 5 patients for whom susceptibility results were available for their *S. pneumoniae* isolates, 1 patient had PISP isolated at the Post-Therapy assessment (this patient's admission isolate was PSSP).

Table 20: Post-Therapy Clinical and Microbiological Responses of *Streptococcus pneumoniae* Isolates to Levofloxacin by Susceptibility to Penicillin: Intent-to-Treat Subjects (Protocol LOFBIV-PCAP-001) (per Applicant)

		Clinical Response						Microbiological Response					
Penicillin Susceptibility	N[a]	Success[a,b]		Failure[a]		Unable to Evaluate[a]		Eradicated[a,b]		Persisted[a]		Unknown[a]	
Susceptible	109	102	(93.6%)	5	(4.6%)	2	(1.8%)	95	(87.2%)	5	(4.6%)	9	(8.3%)
Intermediate	26	26	(100.0%)	0	(0.0%)	0	(0.0%)	26	(100.0%)	0	(0.0%)	0	(0.0%)
Resistant	5	5	(100.0%)	0	(0.0%)	0	(0.0%)	5	(100.0%)	0	(0.0%)	0	(0.0%)
Not available	15	14	(93.3%)	1	(6.7%)	0	(0.0%)	14	(93.3%)	1	(6.7%)	0	(0.0%)
Total	**155**	**147**	**(94.8%)**	**6**	**(3.9%)**	**2**	**(1.3%)**	**140**	**(90.3%)**	**6**	**(3.9%)**	**9**	**(5.8%)**

[a] Values represent the number of subjects. Numbers shown in parentheses are percentages for that category.
[b] Clinical success=cured + improved. Microbiological eradication=eradicated + presumed eradicated.

Adapted from Applicant's Table 9a, NDA 20-634 SE1-008, Vol. 25.3, p. 165

Clinically and Microbiologically Evaluable Population

The Applicant also tabulated the clinical and microbiological response rates for both the clinically evaluable and microbiologically evaluable populations (Table 21). Note that the clinically and microbiologically evaluable populations for patients with *S. pneumoniae* (as their admission isolate) were identical.

Table 21: Post-Therapy Clinical and Microbiological Responses of *Streptococcus pneumoniae* Isolates to Levofloxacin by Susceptibility to Penicillin: Subjects Evaluable for Microbiological Efficacy
(Protocol LOFBIV-PCAP-001) (per Applicant)

		Clinical Response						Microbiological Response					
Penicillin Susceptibility	N[a]	Success[a,b]		Failure[a]		Unable to Evaluate[a]		Eradicated[a,b]		Persisted[a]		Unknown[a]	
Susceptible	95	91	(95.8%)	4	(4.2%)	0	(0.0%)	91	(95.8%)	4	(4.2%)	0	(0.0%)
Intermediate	26	26	(100.0%)	0	(0.0%)	0	(0.0%)	26	(100.0%)	0	(0.0%)	0	(0.0%)
Resistant	5	5	(100.0%)	0	(0.0%)	0	(0.0%)	5	(100.0%)	0	(0.0%)	0	(0.0%)
Not available	14	14	(100.0%)	0	(0.0%)	0	(0.0%)	14	(100.0%)	0	(0.0%)	0	(0.0%)
Total	**140**	**136**	**(97.1%)**	**4**	**(2.9%)**	**0**	**(0.0%)**	**136**	**(97.1%)**	**4**	**(2.9%)**	**0**	**(0.0%)**

[a] Values represent the number of subjects. Numbers shown in parentheses are percentages for that category.
[b] Clinical success=cured + improved. Microbiologic eradication=eradicated + presumed eradicated.

Adapted from Applicant's Table 9b, NDA 20-634 SE1-008, Vol. 25.3, p. 165

Post-Therapy Microbiologic and Clinical Response by Severity and Age

Severity

The Applicant analyzed the Post-Therapy clinical and microbiological response rates for patients with *S. pneumoniae* stratified by disease severity at Admission and penicillin susceptibility (Table 22). The rates for clinical and microbiological response are similar across the different strata with the lowest response rates observed of 91% in the group of patients with CAP due to PSSP of severe grade at baseline.

Table 22: Post-Therapy Clinical and Microbiological Responses of *Streptococcus pneumoniae* Isolates to Levofloxacin Stratified by Severity and Susceptibility to Penicillin: Subjects Evaluable For Microbiologic Efficacy
(Protocol LOFBIV-PCAP-001) (per Applicant)

		Clinical Response[a]						Microbiologic Response[a]					
Penicillin Susceptibility	N	Success		Failure		Unable to Evaluate		Eradicated		Persisted		Unknown	
Susceptible	**95**	**91**	**(95.8)**	**4**	**(4.2)**	**0**	**(0.0)**	**91**	**(95.8)**	**4**	**(4.2)**	**0**	**(0.0)**
Severe	35	32	(91.4)	3	(8.6)	0	(0.0)	32	(91.4)	3	(8.6)	0	(0.0)
Mild/Moderate	60	59	(98.3)	1	(1.7)	0	(0.0)	59	(98.3)	1	(1.7)	0	(0.0)
Intermediate	**26**	**26**	**(100.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**26**	**(100.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Severe	13	13	(100.0)	0	(0.0)	0	(0.0)	13	(100.0)	0	(0.0)	0	(0.0)
Mild/Moderate	13	13	(100.0)	0	(0.0)	0	(0.0)	13	(100.0)	0	(0.0)	0	(0.0)
Resistant	**5**	**5**	**(100.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**5**	**(100.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Severe	4	4	(100.0)	0	(0.0)	0	(0.0)	4	(100.0)	0	(0.0)	0	(0.0)
Mild/Moderate	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)	0	(0.0)
Not Available	**14**	**14**	**(100.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**14**	**(100.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Severe	7	7	(100.0)	0	(0.0)	0	(0.0)	7	(100.0)	0	(0.0)	0	(0.0)
Mild/Moderate	7	7	(100.0)	0	(0.0)	0	(0.0)	7	(100.0)	0	(0.0)	0	(0.0)
Total	**140**	**136**	**(97.1)**	**4**	**(2.9)**	**0**	**(0.0)**	**136**	**(97.1)**	**4**	**(2.9)**	**0**	**(0.0)**
Severe	59	56	(94.9)	3	(5.1)	0	(0.0)	56	(94.9)	3	(5.1)	0	(0.0)
Mild/Moderate	81	80	(98.8)	1	(1.2)	0	(0.0)	80	(98.8)	1	(1.2)	0	(0.0)

[a] Values represent the number of subjects. Numbers shown in parentheses are percentages for [redacted] category.

Adapted from Applicant's Table 13a, NDA 20-634 Vol. 25.3, p. 172

Age

The Applicant also analyzed the Post-Therapy clinical and microbiological response rates for the clinically and microbiologically evaluable population stratified by age (<65 years-of-age versus ≥65 years-of-age) and by susceptibility to penicillin (Table 23.) The response rates across the different age and susceptibility strata were similar. The lowest observed response rate of 94% was observed in the group of patients 65 years of age or older with CAP due to PSSP.

Table 23: Post-Therapy Clinical and Microbiological Responses of *Streptococcus pneumoniae* Isolates to Levofloxacin Stratified by Age and Susceptibility to Penicillin: Subjects Evaluable for Microbiological Efficacy (Protocol LOFBIV-PCAP-001) (per Applicant)

		Clinical Response[a]						Microbiological Response[a]					
Penicillin Susceptibility	N	Success		Failure		Unable to Evaluate		Eradicated		Persisted		Unknown	
Susceptible	**95**	**91**	**(95.8)**	**4**	**(4.2)**	**0**	**(0.0)**	**91**	**(95.8)**	**4**	**(4.2)**	**0**	**(0.0)**
<65	59	57	(96.6)	2	(3.4)	0	(0.0)	57	(96.6)	2	(3.4)	0	(0.0)
≥65	36	34	(94.4)	2	(5.6)	0	(0.0)	34	(94.4)	2	(5.6)	0	(0.0)
Intermediate	**26**	**26**	**(100.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**26**	**(100.0)**	**0**	**(0.0)**	**0**	**(0.0)**
<65	12	12	(100.0)	0	(0.0)	0	(0.0)	12	(100.0)	0	(0.0)	0	(0.0)
≥65	14	14	(100.0)	0	(0.0)	0	(0.0)	14	(100.0)	0	(0.0)	0	(0.0)
Resistant	**5**	**5**	**(100.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**5**	**(100.0)**	**0**	**(0.0)**	**0**	**(0.0)**
<65	5	5	(100.0)	0	(0.0)	0	(0.0)	5	(100.0)	0	(0.0)	0	(0.0)
Not Available	**14**	**14**	**(100.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**14**	**(100.0)**	**0**	**(0.0)**	**0**	**(0.0)**
<65	9	9	(100.0)	0	(0.0)	0	(0.0)	9	(100.0)	0	(0.0)	0	(0.0)
≥65	5	5	(100.0)	0	(0.0)	0	(0.0)	5	(100.0)	0	(0.0)	0	(0.0)
Total	**140**	**136**	**(97.1)**	**4**	**(2.9)**	**0**	**(0.0)**	**136**	**(97.1)**	**4**	**(2.9)**	**0**	**(0.0)**
<65	85	83	(97.6)	2	(2.4)	0	(0.0)	83	(97.6)	2	(2.4)	0	(0.0)
≥65	55	53	(96.4)	2	(3.6)	0	(0.0)	53	(96.4)	2	(3.6)	0	(0.0)

[a] Values represent the number of subjects. Numbers shown in parentheses are percentages for that category.

Adapted from Applicant's Table 13b, NDA 20-634 Vol. 25.3, p. 173

Superinfection for Patients with CAP due to *Streptococcus pneumoniae*

In the group of patients who had *S. pneumoniae* isolated at admission, none presented with superinfections during the study.

Post-Study Microbiologic and Clinical Response for Patients with CAP due to *Streptococcus pneumoniae*

Patients with *S. pneumoniae* as their admission isolate who were evaluable for microbiological efficacy and were scored as clinical cure or improved at the Post-Therapy evaluation were to return for a Post-Study assessment 21 to 28 days after completing therapy.

Of the 136 patients scored as clinical success at Post-Therapy, 125 had clinical data available from the Post-Study visit. The clinical response results for the other 11 patients at Post-Study were unknown. Of these 125 patients, 122 were considered to be clinical successes,

3 were clinical relapses. The relapse isolates for two patients were susceptible to penicillin, erythromycin, and levofloxacin. Susceptibility results for the relapse isolate from the third patient were unknown. The clinical success rate at Post-Study (carrying Post-Therapy failures forward, n=4) was 122/129 (95%).

Of the 136 patients scored as microbiological eradications at Post-Therapy, 124 had microbiological assessments at the Post-Study visit. The microbiologic response results for the other 12 patients at the Post-Study evaluation were unknown. Of these 124 patients, 121 remained as microbiologic eradications and 3 presented with microbiological relapse. The relapse isolates for two patients were susceptible to penicillin, erythromycin, and levofloxacin. Susceptibility results for the relapse isolate from the third patient were unknown. The microbiological eradication rate at Post-Study (carrying Post-Therapy failures forward, n=4) was 121/128 (95%).

Summary of Applicant's Analysis of Efficacy for All Subjects with Community-Acquired Pneumonia

The Applicant's clinical and microbiological response rates for all subjects with CAP are summarized in Table 24 for the intent-to-treat, clinically evaluable, and microbiologically evaluable populations.

Table 24: Applicant's Intent-to-Treat, Post-Therapy And Post-Study Clinical and Microbiological Responses: All Subjects with Community-Acquired Pneumonia (Protocol LOFBIV-PCAP-001)

Response Time of Assessment Population	Clinical Success[a,b] or Microbiological Eradication Rate[a,c]	
Clinical Response		
Intent-to-treat subjects	605/655	(92.4%)
Post-Therapy		
Clinically evaluable subjects	511/532	(96.1%)
Microbiologically evaluable subjects	384/398	(96.5%)
Post-Study		
Clinically evaluable subjects[e]	442/483	(91.5%)
Microbiologically evaluable subjects[e]	334/364	(91.8%)
Microbiological Response		
Intent-to-treat subjects with an admission pathogen	408/468[d]	(87.2%)
Post-Therapy		
Microbiologically evaluable subjects	383/398[d]	(96.2%)
Post-Study		
Microbiologically evaluable subjects[e]	331/360	(91.9%)

[a] Numbers shown in parentheses are percentages for that category.
[b] Clinical success = cured + improved; Clinical failure = failed + unable to evaluate.
[c] Microbiological eradication = eradicated + presumed eradicated; Microbiological persistence = persisted + unknown.
[d] Subject 59005 (——— admission pathogen: *M. pneumoniae*) is classified in this table as having a Post-Therapy microbiologic response of presumed eradicated, corrected from the listed response of unknown. He became microbiologically evaluable after a second Post-Therapy visit on 12/29/97. The data collected at this time replaces the unknown response of the first Post-Therapy visit, which was conducted on 12/22/97, the last day of therapy. When compared to his admission and on-therapy clinical evaluations, there are no clinically significant differences between the clinical responses collected at the two Post-Therapy evaluations.
[e] For the evaluable populations at Post-Study the denominators include all patients who were evaluable at Post-Study and patients who were failures at the Post-Therapy assessment (failures are carried forward.

Adapted from Applicant's Table 31b, NDA 20-634 SE1-008 Vol. 25.3, p. 202, Applicant's Attachment 13.3 NDA 20-634 SE1-008 Vol. 25.4, p. 14, Applicant's Attachment 7.3 and 8.3 NDA 20-634 SE1-008 Vol. 25.3, p. 314 and p. 321, respectively

The results for clinical and microbiological response at the Post-Study assessments are comparable to the results observed at the earlier assessment (Post-Therapy). The clinical success rates in the clinically evaluable population are corroborated by the clinical success rates in the microbiologically evaluable population. For those patients experiencing clinical or microbiological failure/persistence or relapse no acquisition of resistance was reported. The efficacy results observed in Study LOFBIV-PCAP-001 for the treatment of CAP are similar to what was observed in the original NDA clinical studies of CAP.

Medical Officer's Efficacy Analysis

In the Applicant's protocol specified evaluability criteria, Post-Therapy assessments could occur as soon as 2 days post-therapy and up to 10 days post-therapy. The protocol specified Post-Therapy visit window was 5-7 days post-therapy. Post-Therapy evaluations occurring prior to the 5th day post-therapy may not allow sufficient time for drug to clear and for clinical manifestations of disease to recrudesce. In order to address this concern, the MO requested that the Applicant re-analyze the LOFBIV-PCAP-001 efficacy data using the protocol-specified windows of 5-7 days post-therapy for the Post-Therapy assessment and 21-28 days post-therapy for the Post-Study assessment. The results of this re-analysis of the efficacy data comprise the MO Efficacy Analysis that follows. In addition there were several patients for whom the MO disagreed with the Applicant's evaluability or response determinations. In the MO Efficacy analysis these patients are scored based on the MO's review of the efficacy data. These patients are discussed in the MO Comments within the preceding section in which the Applicant's Efficacy analysis is reviewed.

In the MO Efficacy analysis, clinical response and microbiological response for Post-Therapy and Post-Study were determined. The efficacy results were also tabulated by study center and severity of illness. The results in the MO Efficacy analysis were consistent with the Applicant's Efficacy results with the exception that the evaluable populations were smaller in the MO Efficacy analysis (as would be expected because of the more stringent windows for Post-Therapy and Post-Study evaluability). For the purposes of brevity and because the conclusions from the Applicant's Efficacy analysis and MO Efficacy analysis are comparable, only the key summary tables from the MO Efficacy analysis will be presented.

Post-Therapy Clinical Response Rates, MO Efficacy Analysis

The clinical response rates at the Post-Therapy assessment in patients evaluable for clinical efficacy were, cured 270/403 (67.0%) and improved 111/403 (27.5%) for a clinical success rate of 381/403 (94.5%). Review of the by center clinical response rates did not reveal any marked disparities in response rates considering the small number of patients that were enrolled at many of the centers. The clinical response rates at the Post-Therapy assessment were also stratified by severity of illness. Similar to what was observed in the Applicant's Efficacy analysis, a greater proportion of patients with mild/moderate disease achieved cure at the Post-Therapy assessment while a greater proportion of patients with severe disease were scored as improved at Post-Therapy. Similar proportions of patients achieved clinical success (cured or improved) in the severe and mild/moderate disease categories.

MO Comment: The similar clinical success rates at the Post-Therapy time point suggests that similar proportions of patients showed evidence of a response but that recovery to the state of "cure" requires a longer period of time in patients with severe disease. This observation is consistent with what would be expected physiologically for patients with severe pneumonia.

The clinical success rate in the population of patients evaluable for microbiological efficacy was 284/298 (95.3%) corroborating the clinical response rates observed in the population of patients evaluable for clinical efficacy.

The clinical response rates at Post-Therapy in the patients evaluable for clinical efficacy summarized by admission pathogen are presented in Table 25. The response rates for *Streptococcus pneumoniae* were 74/106 (69.8%) cured and 28/106 (26.4%) improved for a clinical success rate of 102/106 (96.2%). The clinical response rates by pathogen for the clinically evaluable patients with *Streptococcus pneumoniae* obtained from blood cultures were 10/19 (52.6%) cured and 9/19 (47.4%) improved for a success rate of 19/19 (100.0%).

Table 25: Clinical Response Post-Therapy Summarized by Pathogen Category and Prevalent Pathogens: Patients Evaluable for Clinical Efficacy Whose Post-Therapy Evaluation Was Done Five to Seven Days After Completion of Therapy (Protocol LOFBIV-PCAP-001) (MO Efficacy Analysis)

Pathogen Category	Levofloxacin			
Pathogen(s)[a]	N[b]	Cured[c]	Improved[c]	Failed[c]
Respiratory cultures				
Streptococcus pneumoniae	106	74 (69.8%)	28 (26.4%)	4 (3.8%)
Haemophilus influenzae	48	29 (60.4%)	18 (37.5%)	1 (2.1%)
Staphylococcus aureus	16	11 (68.8%)	4 (25.0%)	1 (6.3%)
Moraxella (Branhamella) catarrhalis	12	5 (41.7%)	7 (58.3%)	0 (0.0%)
Haemophilus parainfluenzae	11	8 (72.7%)	3 (27.3%)	0 (0.0%)
Klebsiella pneumoniae	8	4 (50.0%)	4 (50.0%)	0 (0.0%)
Escherichia coli	7	5 (71.4%)	2 (28.6%)	0 (0.0%)
Blood cultures				
Streptococcus pneumoniae	19	10 (52.6%)	9 (47.4%)	0 (0.0%)
Atypical pathogens				
Mycoplasma pneumoniae	126	96 (76.2%)	27 (21.4%)	3 (2.4%)
Chlamydia pneumoniae	62	44 (71.0%)	16 (25.8%)	2 (3.2%)
Legionella pneumophila	29	19 (65.5%)	7 (24.1%)	3 (10.3%)

[a] The most prevalent pathogens (N≥5) are presented in this summary for each pathogen category.
[b] N=number of subjects who had that pathogen, alone or in combination with other pathogens.
[c] Numbers shown in parentheses are percentages for that category.

Post-Study Clinical Response Rates

In order to remain in the evaluable population in the MO Efficacy Analysis of Post-Study clinical response rates, patients were required to have their Post-Therapy assessment 5-7 days post-therapy and their Post-Study assessment within the protocol specified Post-Study visit window of 21-28 days post-therapy. Patients who were assessed as clinical cures or clinically improved at the Post-Therapy assessment were eligible to return for a Post-Study visit. Of the 381 clinically evaluable patients assessed as clinical cure or improved at the Post-Therapy visit, 288 had a Post-Study visit that occurred within the protocol specified 21 to 28 day window.

> **MO Comment:** Note that in the MO Efficacy Analysis, Patients 4018, 28063, and 52013 had Post-Therapy and Post-Study visits that occurred within the protocol specified windows. As noted previously in this review, different from the Applicant's assessment of clinical response at Post-Study, the MO considered these three patients evaluable at Post-Study. The Post-Study clinical response for these three patients was scored as relapse and their Post-Study microbiological response was scored as presumed relapse in the MO Efficacy Analysis. The numbers in the MO Efficacy Analysis reflect these changes, as compared to the Applicant's database.

The Post-Study clinical response rates for the clinically evaluable population are presented in Table 26. The clinical response rates at Post-Study for the clinically evaluable population were 246/310 (79.4%) cured, 20/310 (6.5%) improved, 7/310 (2.3%) relapse (Note: in the denominator, failures are carried forward from Post-Therapy, n=22).

Table 26: Clinical Response Post-Study (21-28 days post-therapy) for the Clinically Evaluable and Microbiologically Evaluable Populations
(Protocol LOFBIV-PCAP-001) (MO Efficacy Analysis)

	Levofloxacin					
Population	N	Cured[a]	Improved[a]	Relapse[a]	Failure at Post-Therapy[a]	Unable to Evaluate[a]
Clinically Evaluable at Post-Study	310	246 (79.4%)	20 (6.5%)	7 (2.3%)	22 (7.1%)	15 (4.8%)
Microbiologically Evaluable at Post-Study	231	183 (79.2%)	19 (8.2%)	5 (2.2%)	14 (6.1%)	10 (4.3%)

[a] Numbers shown in parentheses are percentages for that category.

MO Comment: The clinical success rate at Post-Study in the microbiologically evaluable population corroborates the findings in the clinically evaluable population.

The Post-Study clinical responses in the clinically evaluable population were stratified by severity of infection (Table 27). A smaller percentage of the patients with severe disease achieved cure at the Post-Study visit compared to those with mild/moderate disease. Also notable is the slightly higher percentage of patients with severe disease scored as improved, relapse, or unable to evaluate, compared to those with mild/moderate disease, although the numbers are quite small.

Table 27: Clinical Response Post-Study Summarized by Severity of Infection: Patients Evaluable for Clinically Efficacy Whose Post-Therapy Evaluation was Done Five To Seven Days After Completion of Therapy and Post-Study Visit Was 21 to 28 Days After Completion of Therapy (Protocol LOFBIV-PCAP-001) (MO Efficacy Analysis)

	Levofloxacin					
Severity of Infection	N	Cured[a]	Improved[a]	Relapse[a]	Failure at Post-Therapy[a]	Unable to Evaluate[a]
Severe	82	58 (70.7%)	9 (11.0%)	5 (6.1%)	5 (6.1%)	5 (6.1%)
Mild/moderate	227	188 (82.8%)	11 (4.8%)	2 (0.9%)	16 (7.0%)	10 (4.4%)
Total	309	246 (79.6%)	20 (6.5%)	7 (2.3%)	21 (6.8%)	15 (4.9%)

[a] Numbers shown in parentheses are percentages for that category.

The Post-Study clinical response rates by pathogen for the clinically evaluable population are presented in Table 28. The clinical response rates for clinically evaluable patients at the Post-Study assessment with *S. pneumoniae* were 72/83 (86.7%) cured, 4/83 (4.8%) improved.

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Table 28: Clinical Response Post-Study Summarized by Pathogen Category and Prevalent Pathogens: Subjects Evaluable for Clinical Efficacy Whose Post-Therapy Evaluation Was Done Five to Seven Days After Completion of Therapy and Post-Study Visit Was 21 to 28 Days After Completion of Therapy (Protocol LOFBIV-PCAP-001) (MO Efficacy Analysis)

	Levofloxacin								
Pathogen Category Pathogen(s)[a]	N[b]	Cured[c]		Improved[c]		Relapse[c]		Unable to Evaluate[c]	
Respiratory cultures									
Streptococcus pneumoniae	83	72	(86.7%)	4	(4.8%)	2	(2.4%)	5	(6.0%)
Haemophilus influenzae	37	28	(75.7%)	5	(13.5%)	0	(0.0%)	4	(10.8%)
Moraxella (Branhamella) catarrhalis	11	8	(72.7%)	1	(9.1%)	0	(0.0%)	2	(18.2%)
Staphylococcus aureus	11	9	(81.8%)	0	(0.0%)	1	(9.1%)	1	(9.1%)
Haemophilus parainfluenzae	10	8	(80.0%)	1	(10.0%)	0	(0.0%)	1	(10.0%)
Klebsiella pneumoniae	8	6	(75.0%)	2	(25.0%)	0	(0.0%)	0	(0.0%)
Blood cultures									
Streptococcus pneumoniae	12	8	(66.7%)	3	(25.0%)	1	(8.3%)	0	(0.0%)
Atypical pathogens									
Mycoplasma pneumoniae	95	81	(85.3%)	8	(8.4%)	1	(1.1%)	5	(5.3%)
Chlamydia pneumoniae	47	38	(80.9%)	4	(8.5%)	1	(2.1%)	4	(8.5%)
Legionella pneumophila	20	15	(75.0%)	1	(5.0%)	0	(0.0%)	4	(20.0%)

[a] The most prevalent pathogens (N≥5) are presented in this summary for each pathogen category.
[b] N=number of subjects who had that pathogen, alone or in combination with other pathogens.
[c] Numbers shown in parentheses are percentages for that category.

Post-Therapy Microbiological Response, MO Efficacy Analysis

The MO Efficacy analysis microbiological eradication rates by patient in the microbiologically evaluable population at the Post-Therapy assessment are presented in Table 29. Of the 298 microbiologically evaluable patients at Post-Therapy, 283 (95%) achieved microbiologic eradication at Post-Therapy.

Table 29: Microbiologic Eradication Rate by Patient in the Microbiologically Evaluable Population For Patients Whose Post-Therapy Evaluation Was Done Five to Seven Days After Completion of Therapy (Protocol LOFBIV-PCAP-001) (MO Efficacy Analysis)

	Levofloxacin						
Population	N	Eradicated[a]		Persisted		Unknown	
Microbiologically Evaluable Patients	298	283[b]	(95.0%)	14	(4.7%)	1[b]	(0.3%)

[a] Eradication of all pathogens isolated for a subject at admission. Eradicated = eradicated + presumed eradicated
[b] Subject 59005 (admission pathogen: *M. pneumoniae*) is classified in this table as having a Post-Therapy microbiologic response of presumed eradicated, corrected from the clinical study data base entry of unknown. He became microbiologically evaluable after a second post-therapy visit on 12/29/97. The data collected at this time replaces the unknown response of the first post-therapy visit, which was conducted on 12/22/97, the last day of therapy. When compared to his Admission and On-Therapy clinical evaluations, there are no clinically significant differences between the clinical responses collected at the two post-therapy evaluations.

MO Comment: The rates for microbiological eradication and persistence (for the evaluable for microbiological efficacy population) at Post-Therapy were similar to the rates observed in the Applicant's analysis.

The Post-Therapy microbiological eradication rates by pathogen at Post-Therapy in the microbiologically evaluable population are similar to what was observed in the Applicant's Efficacy Analysis but the population of evaluable patients is smaller in the MO Efficacy Analysis (Table 30).

Table 30: Microbiologic Eradication Rates Post-Therapy Summarized by Method of Evaluation and Pathogen, for Microbiologically Evaluable Subjects Whose Post-Therapy Evaluation Was Done Five to Seven Days After Completion of Therapy (Protocol LOFBIV-PCAP-001) (MO Efficacy Analysis)

Pathogen Category / Pathogen[a]	Levofloxacin N[b]	Eradicated	
Respiratory cultures			
Streptococcus pneumoniae	106	102	(96.2%)
Haemophilus influenzae	48	47	(97.9%)
Staphylococcus aureus	16	15	(93.8%)
Moraxella (Branhamella) catarrhalis	12	12	(100.0%)
Haemophilus parainfluenzae	11	11	(100.0%)
Klebsiella pneumoniae	8	8	(100.0%)
Escherichia coli	7	7	(100.0%)
Blood cultures			
Streptococcus pneumoniae	19	19	(100.0%)
Serology cultures			
Mycoplasma pneumoniae	125	122[c]	(97.6%)
Chlamydia pneumoniae	62	60	(96.8%)
Legionella pneumophila	29	26	(89.7%)

[a] The most prevalent pathogens (N≥5) are presented in this summary for each pathogen category.
[b] N=number of subjects who had that pathogen, alone or in combination with other pathogens.
[c] Subject 59005 <— admission pathogen: *M. pneumoniae*) is classified in this table as having a Post-Therapy microbiologic response of presumed eradicated, corrected from the clinical study database entry of unknown. He became microbiologically evaluable after a second post-therapy visit on 12/29/97. The data collected at this time replaces the unknown response of the first post-therapy visit, which was conducted on 12/22/97, the last day of therapy. When compared to his admission and on-therapy clinical evaluations, there are no clinically significant differences between the clinical responses collected at the two post-therapy evaluations.

MO Comment: The Post-Therapy microbiologic eradication rates by pathogen and by patient, stratified for severity of illness, were also examined. The rates were similar for patients with mild/moderate or severe infection.

Post-Study Microbiological Eradication

The Post-Study microbiological eradication rates by patient are presented in Table 31. Of the 231 microbiologically evaluable patients at Post-Study, 200 (86.6%) achieved microbiologic eradication.

Table 31: Microbiologic Eradication Rates Post-Study for Each Study Center: Subjects Evaluable for Microbiologic Efficacy Whose Post-Therapy Evaluation Was Done Five to Seven Days After Completion of Therapy and Post-Study Visit Was 21 to 28 Days After Completion of Therapy (Protocol LOFBIV-PCAP-001) (MO Efficacy Analysis)

Population	Levofloxacin								
	N	Eradicated[a]		Relapse		Failure at Post-Therapy[a,b]		Unknown	
Microbiologically Evaluable Patients	231	200	(86.6%)	5	(2.2%)	14	(6.1%)	12[c]	(5.2%)

[a] Eradication of all pathogens isolated for a subject at admission. Eradicated = eradicated + presumed eradicated

[b] These subjects were clinical failures at Post-Therapy and as per protocol were not to return for a Post-Study evaluation.

[c] Subjects 4017 (—— admission pathogen: *H. influenzae*) and 16001 —— admission pathogen: *C. pneumoniae*) are classified in this table as having a Post-Study microbiologic response of unknown, corrected from the clinical study data base entry of presumed eradicated.

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The Post-Study microbiological eradication rates by pathogen are presented in Table 32. The Post-Study eradication rates for *S. pneumoniae* from a respiratory culture was 76/83 (91.6%) and for *S. pneumoniae* from a blood culture was 11/12 (91.7%).

Table 32: Microbiologic Eradication Rates Post-Study Summarized by Pathogen Category and Pathogen: Subjects Evaluable for Microbiologic Efficacy Whose Post-Therapy Evaluation Was Done Five to Seven Days After Completion of Therapy And Post-Study Visit Was 21 to 28 Days After Completion of Therapy (Protocol LOFBIV-PCAP-001) (MO Efficacy Analysis)

Pathogen Category / Pathogen[a]	Levofloxacin N[b]	Eradicated	Relapse	Unknown	Failure at Post-Therapy[c]
Respiratory cultures					
Streptococcus pneumoniae	83	76 (91.6%)	2 (2.4%)	1 (1.2%)	4 (4.8%)
Haemophilus influenzae	37	33[d] (89.2%)	0 (0.0%)	3[d] (8.1%)	1 (2.7%)
Moraxella (Branhamella) catarrhalis	11	9 (81.8%)	0 (0.0%)	2 (18.2%)	0 (0.0%)
Staphylococcus aureus	11	9 (81.8%)	1 (9.1%)	0 (0.0%)	1 (9.1%)
Haemophilus parainfluenzae	10	9 (90.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)
Klebsiella pneumoniae	8	8 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood cultures					
Streptococcus pneumoniae	12	11 (91.7%)	1 (8.3%)	0 (0.0%)	0 (0.0%)
Serology cultures					
Mycoplasma pneumoniae	95	87 (91.6%)	1 (1.1%)	4 (4.2%)	3 (3.2%)
Chlamydia pneumoniae	47	42[d] (89.4%)	1 (2.1%)	2[d] (4.3%)	2 (4.3%)
Legionella pneumophila	20	16 (80.0%)	0 (0.0%)	1 (5.0%)	3 (15.0%)

[a] The most prevalent pathogens (N≥5) are presented in this summary for each pathogen category.
[b] N=number of subjects who had that pathogen, alone or in combination with other pathogens.
[c] These subjects were clinical failures at Post-Therapy and as per protocol were not to return for Post-Study evaluations.
[d] Subjects 4017 (⟵ admission pathogen: *H. influenzae*) and 16001 ⟵ admission pathogen: *C. pneumoniae*) are classified in this table as having a Post-Study microbiologic response of unknown. corrected from the clinical study data base entry of presumed eradicated.

The Post-Study microbiological eradication rates stratified by severity of infection were also examined. Eradication rates were similar for patients with severe or mild/moderate disease. However, a slightly higher relapse rate at Post-Study was observed in patients with severe disease (5% vs. 0.5%).

Summary of the MO Efficacy Analysis

The MO Efficacy analysis was done primarily to examine the response rates when using the strict protocol-specified windows for the Post-Therapy and Post-Study visit. The population of evaluable patients is smaller in the MO Efficacy analysis, as would be expected because of the more restrictive windows. The response rates in the categories for which analyses were

performed are similar between the Applicant's Efficacy Analysis and the MO's Efficacy Analysis. The response rates for the MO Efficacy Analysis are summarized in Table 33.

MO Comment: In Table 33, the summary table of clinical and microbiological response rates at Post-Therapy and Post-Study for the MO Efficacy Analysis, failures at Post-Therapy are carried forward as failures at the Post-Study assessment.

Table 33: MO Efficacy Analysis: Post-Therapy and Post-Study Clinical and Microbiologic Responses: All Subjects with Community-Acquired Pneumonia Whose Post-Therapy Evaluation Was Done Five to Seven Days After Completion of Therapy (Protocol LOFBIV-PCAP-001) (MO Efficacy Analysis)

Response Time of Assessment Population	Clinical Success[a,b] or Microbiologic Eradication Rate[a,c] (Post-Therapy)	
Clinical Response		
Post-Therapy		
Clinically evaluable subjects	381/403	(94.5%)
Microbiologically evaluable subjects	284/298	(95.3%)
Post-Study		
Clinically evaluable subjects[e]	266/310	(85.8%)
Microbiologically evaluable subjects[e]	202/231	(87.4%)
Microbiologic Response		
Post-Therapy		
Microbiologically evaluable subjects	283/298[d]	(95.0%)
Post-Study		
Microbiologically evaluable subjects[e]	200/231	(86.6%)

[a] Numbers shown in parentheses are percentages for that category.
[b] Clinical success = cured + improved; Clinical success rate = (cured+improved)/(cured+improved+failure) Clinical failure = failed + unable to evaluate.
[c] Microbiologic eradication = eradicated + presumed eradicated; Microbiologic persistence = persisted + unknown.
[d] Subject 59005 ——— admission pathogen: *M. pneumoniae*) is classified in this table as having a Post-Therapy microbiologic response of presumed eradicated, corrected from the listed response of unknown. He became microbiologically evaluable after a second post-therapy visit on 12/29/97. The data collected at this time replaces the unknown response of the first post-therapy visit, which was conducted on 12/22/97, the last day of therapy. When compared to his admission and on-therapy clinical evaluations, there are no clinically significant differences between the clinical responses collected at the two post-therapy evaluations.
[e] For the evaluable populations at Post-Study the denominators include all patients who were evaluable at Post-Study and patients who were failures at the Post-Therapy assessment (failures are carried forward).

Overall Summary of Efficacy Results from LOFBIV-PCAP-001

The efficacy rates demonstrated in the Study LOFBIV-PCAP-001 are similar to what was observed in the two pivotal clinical trials that were submitted in support of the community-

acquired pneumonia (CAP) indication in the original NDA. The efficacy rates for the treatment of CAP due to *S. pneumoniae* were similar to the overall response rates for community-acquired pneumonia (of all causes) and consistent with the observed rates in the original NDA CAP studies.

This study was only able to enroll 5 patients with CAP due to PRSP despite exceeding the study's planned enrollment. At the time the study was designed, it was anticipated that the study would enroll 15 patients with CAP due to PRSP. In order to augment the number of cases of CAP due to PRSP (and PISP), the Applicant provided additional clinical data from other clinical studies of CAP. The review of this additional data is discussed in the later sections of this review and discussed in an Integrated Summary of Efficacy for LEVAQUIN® for the Treatment of CAP due to PRSP.

Safety

Patients Evaluable for Safety

All patients who received at least one dose of study-drug and had post-admission safety data were included in the safety analysis. Twenty-five of the 655 patients enrolled in the study were lost to follow-up. Of these 25 patients, 5 provided no safety data and therefore were excluded from the safety analysis. Six hundred and fifty patients were evaluable for safety.

The Applicant analyzed the extent of levofloxacin exposure in the ITT population. Most patients (83%) received between 7 to 14 days of therapy as prescribed by the study protocol. Of the remaining 17%, 6% received therapy beyond 14 days, 7% less than 7 days, and 4% received therapy of unknown duration. The mean duration of therapy was 11.7 days and the range of therapy duration was 1 to 29 days. The mean duration of time that patients received oral levofloxacin was 10.9 days and 3.0 days for i.v. levofloxacin.

Adverse Events

Reports of treatment emergent adverse events occurring between study admission and the Post-Therapy visit were collected. In addition, information about serious adverse events that occurred after the Post-Therapy visit and within 30 days of study completion were also summarized by the Applicant, but not included in the tabulations of adverse events. The Applicant also summarized information on deaths that occurred within 3 months of study completion.

Of the 650 subjects that were evaluable for safety, 347 (53%) reported at least one treatment-emergent adverse event (regardless of relationship to study drug). The treatment-emergent adverse events that were reported by at least 2% of patients are summarized in Table 34.

Table 34: Incidence of Frequently Reported (≥2%)[a] Treatment-Emergent Adverse Events Summarized by Preferred Term: Subjects Evaluable for Safety (Protocol LOFBIV-PCAP-001)

Body System Preferred Term	Number (%) of Subjects Levofloxacin (N=650)
All body systems	**347 (53.4%)**
Central & peripheral nervous system disorders	
Headache	47 (7.2%)
Psychiatric disorders	
Insomnia	45 (6.9%)
Anxiety	13 (2.0%)
Gastrointestinal system disorders	
Nausea	56 (8.6%)
Diarrhea	42 (6.5%)
Constipation	29 (4.5%)
Vomiting	20 (3.1%)
Abdominal pain	16 (2.5%)
Body as a whole - general disorders	
Chest pain	14 (2.2%)
Resistance mechanism disorders	
Moniliasis	15 (2.3%)

[a] Preferred term reported by ≥2% of subjects.
Adapted from Applicant's Table 30 from NDA 20-634 SE1-008, Vol. 25.3, p. 207

Drug-related treatment-emergent adverse events (AEs) were classified as those AEs that were considered by the investigator to be related to study drug (probably or definitely related to study drug). Seven percent of patients evaluable for safety (44/650) experienced drug-related adverse events. Of these 44 drug-related AEs, 57% (25/44) were considered mild, 39% (17/44) were considered moderate, and 5% (2/44) were considered of marked severity. Most of the specific drug-related adverse events were reported in less than 1% of patients. Those drug-related adverse events that were reported in at least 1% of patients are tabulated below (Table 35).

Table 35: Incidence of Drug-Related Treatment-Emergent Adverse Events (frequency ≥1%)[a] Summarized by Preferred Term: Subjects Evaluable for Safety (Protocol LOFBIV-PCAP-001)

Body System Preferred Term	Number (%) of Subjects Levofloxacin (N=650)
All body systems	**44 (6.8%)**
Psychiatric disorders	
Insomnia	9 (1.4%)
Gastrointestinal system disorders	
Nausea	12 (1.8%)
Reproductive Disorders, Female (N = 271)	
Vaginitis	3 (1.1%)

[a] Preferred term reported by ≥1% of patients.
Adapted from Applicant's Attachment 20, from NDA 20-634 SE1-008, Vol. 25.4, pp. 84, 85

The frequency of reporting of treatment-emergent adverse events were analyzed by sex, race, and age. AEs (all causality) were reported more commonly by women (59%) than men (49%). This difference is mainly derived from differences in the categories of gastrointestinal disorders (women 31%; men 20%) (nausea, vomiting, and diarrhea) and reproductive system disorders (women 4%; men <1%) (vaginitis in women). AEs were reported less frequently among Black (40%) than among Caucasian (58%) and other (55%) racial groups. AE reporting rates were comparable for patients less than 64 years-of-age and for those 65 years-of-age and older.

Adverse Events of Marked Severity

The AEs of marked severity are tabulated in Table 36. Fifty-five patients reported AEs of marked severity. Thirty-three of these 55 AEs were judged to have serious adverse events (includes deaths). Study drug was discontinued in 16 of the 55 patients experiencing AEs of marked severity. The AE that led to discontinuation of study drug was considered serious in 15 of these 16 patients. Of the 55 patients with adverse events of marked severity, 2 reported events (allergic reaction and abnormal hepatic function) that were considered related to study drug (probably or definitely related to study drug). The narratives for these 2 patients are provided following Table 36. Both patients were discontinued from study therapy because of these adverse events.

Table 36: Subjects with Adverse Events of Marked Severity (Protocol LOFBIV-PCAP-001)

Subject Number	Age	Sex	Adverse Event	Study Day of Onset	Duration of Event (Days)	Relationship to Study Drug[a]	Duration of Therapy (Days)	Outcome
1016	69	F	Angina pectoris[b]	21	Unknown	None	14	Persisted
1038	81	M	Respiratory insufficiency[c,d]	2	2	None	2	Death
			Urinary tract malformation	2	1	None		Death
1056	46	F	Condition aggravated[c,d]	1	2	None	1	Death
1064	55	M	Respiratory insufficiency	4	2	None	14	Disappear
1069	72	F	Dyspnea[d]	4	18	None	14	Death
			Moniliasis	10	12	Possible		Death
			Agitation	16	Unknown	None		Death
3038	41	M	Dyspnea[c,d]	2	1	None	1	Death
			Emphysema[c,d]	2	1	None		Death
3047[e]	29	M	Diarrhea[b,c]	10	Unknown	None	9	Disappear
4002	50	M	Condition aggravated[b,c]	2	Unknown	None	2	Persisted
4009	82	M	Heart block[b]	10	2	Remote	11	Disappear
4030[e]	79	M	Aortic stenosis[b]	6	Unknown	None	14	Persisted
4037	70	M	Coma hypoglycemic[b]	13	Unknown	Remote	13	Persisted
4053[e]	71	M	Purpura thrombocytopenic[b]	21	Unknown	Possible	14	Persisted
7021	49	M	Tooth disorder	3	3	None	10	Disappear
8004	79	F	Stupor	7	1	None	10	Disappear
8011	66	F	Cellulitis[b,c]	2	Unknown	None	5	Persisted
8012[e,g]	63	M	Dysphagia	1	15	None	9	Disappear
			Moniliasis	17	7	None		Death
			Granulocytopenia[d,g]	22	2	None		Death
9017	78	M	Cardiac failure[b]	6	5	None	15	Disappear
10002	60	F	Dehydration[b,c]	2	3	Remote	4	Disappear
			Diarrhea[b,c]	2	3	Possible		Disappear
			Vomiting[c]	2	3	Remote		Disappear
11006	62	F	Fever	2	2	None	14	Disappear
			Dyspnea	16	16	None		Disappear
16003	32	F	Arthralgia	1	2	None	10	Disappear
			Dystonia	1	2	None		Disappear
18004	76	M	Edema peripheral	6	Unknown	None	10	Persisted
19008	78	F	Condition aggravated[b]	19	Unknown	Remote	10	Persisted
20004	38	F	Cardiac failure[b,c]	2	16	None	1	Disappear
			Respiratory insufficiency[b,c]	2	16	None		Disappear
21002[e]	79	M	Somnolence[b]	5	3	None	14	Disappear
22001	76	M	Myelomatosis multiple[b]	3	Unknown	None	14	Persisted
25005[e]	56	F	Hepatic function abnormal[e,f]	3	21	Probable	3	Disappear
27003	60	F	Arthralgia	4	4	None	14	Disappear
27008	33	M	Headache	10	1	Possible	13	Disappear
			Headache	12	1	Possible		Disappear
28006	72	M	Hypotension	2	3	None	2	Death
			Cardiac failure[c,d]	3	2	None		Death
			Myocardial infarction[c,d]	3	2	None		Death
28027	57	F	Nausea[b]	3	5	Possible	14	Disappear
28041	59	F	Injury	18	Unknown	None	14	Persisted
28043	37	F	Chest pain	4	1	None	14	Disappear
28050	62	M	Pulmonary carcinoma[b]	19	Unknown	None	14	Persisted
28055[e]	42	F	Respiratory insufficiency[d]	14	16	None	14	Death
			GI hemorrhage	19	3	Remote		Disappear
28065	51	M	Leg pain	10	14	None	15	Disappear
			Edema	11	13	None		Disappear

[a] Based on investigator's assessment.
[b] Serious adverse event (see Table 38).
[c] Subject discontinued therapy due to this adverse event (see Table 39).
[d] Subject died as a result of the adverse event(s) (see Table 37).
[e] Subject also had at least one treatment-emergent, markedly abnormal laboratory value (see Table 43).
[f] Subject 25005 had elevated alkaline phosphatase, AST, ALT, and LDH.
[g] This adverse event occurred after the Post-Therapy visit; however, it inadvertently was included in the clinical study database.

Adapted form Applicant's Table 35, NDA 20-634 SE1-008, Vol. 25.3, pp. 209, 210

Table 36: Subjects with Adverse Events of Marked Severity (Continued)
(Protocol LOFBIV-PCAP-001)

Subject Number	Age	Sex	Adverse Event	Study Day of Onset	Duration of Event (Days)	Relationship to Study Drug[a]	Duration of Therapy (Days)	Outcome
51003	80	M	Myocardial infarction[b,c]	3	1	Remote	2	Death
51010	48	F	Diarrhea	1	Unknown	Possible	14	Persisted
51017	23	F	Asthma[d]	2	3	None	3	Disappear
51019[e]	84	F	Intestinal obstruction[b,f]	29	1	None	2	Death
51023	82	M	Ataxia[c,d]	1	1	Possible	1	Disappear
			Confusion[c,d]	1	1	Possible		Disappear
53013	80	F	Angina pectoris	4	6	Possible	8	Disappear
55001[e]	68	F	Respiratory depression[b]	8	14	Remote	16	Death
55002	24	F	Confusion[c,d]	8	2	Possible	8	Disappear
55004[g]	78	M	Chest pain	2	3	Remote	14	Death
55005	72	M	Confusion	2	30	Possible	1	Disappear
			Convulsions[c,d]	2	1	Possible		Disappear
			Arthralgia	4	Unknown	Remote		Persisted
55007	22	F	Insomnia	1	3	Possible	9	Disappear
55010	37	M	Confusion[c,d,h]	1	3	Possible	2	Disappear
			Convulsions grand mal[c,d]	1	3	Remote		Disappear
			Hepatic function abnormal[h]	2	Unknown	Remote		Persisted
55013[e]	74	M	Depression	2	34	Remote	14	Disappear
55020	81	M	Arthralgia	1	22	Remote	14	Disappear
			Gout	1	22	Remote		Disappear
55021	61	F	Chest pain	3	4	Remote	13	Disappear
55028	37	F	Embolism pulmonary[b]	15	1	None	10	Death
56009	37	F	Allergic reaction[c,d]	1	3	Definite	1	Disappear
56010	48	F	Leg pain	6	4	None	14	Disappear
56011	20	F	Migraine	10	2	Possible	14	Disappear
			Nausea	10	2	None		Disappear
59002	83	M	Eczema	1	Unknown	Possible	10	Persisted

[a] Based on investigator's assessment.
[b] Subject died as a result of the adverse event(s) (see Table 37).
[c] Subject discontinued therapy due to this adverse event (see Table 39).
[d] Serious adverse event (see Table 38).
[e] Subject also had at least one treatment-emergent, markedly abnormal laboratory value (see Table 43).
[f] This adverse event occurred after the Post-Therapy visit; however, it inadvertently was included in the clinical study database.
[g] Subject died as a result of another adverse event (see Table 37)
[h] Subject 55010 had elevated AST, ALT, and LDH.

Adapted form Applicant's Table 35, NDA 20-634 SE1-008, Vol. 25.3, pp. 209, 210

Subject 25005 (Abnormal hepatic function): This 56-year-old Black woman had a history of hypertension, anorexia, fibroid tumors, right nephrectomy, and non-insulin dependent diabetes mellitus. Levofloxacin i.v. 500 mg q24h was administered for the treatment of pneumonia for a total of 3 days before the subject was discontinued from study therapy. On Day 1, the subject experienced mild diarrhea, which resolved within one day. She developed mild muscle ache in her back and legs and marked asymptomatic chemical hepatitis 2 days later. Study drug administration was discontinued permanently with a concurrent change of diagnosis from pneumonia to tuberculosis. On Day 4, the subject experienced mild nausea, which resolved within one day. On Day 7, liver enzymes were elevated (AST: 160 U/L, admission: 32 U/L, normal range: 9-34 U/L; ALT: 692 U/L, admission: 28 U/L, normal range: 6-34 U/L, T.Bili 0.3 mg/dL, admission 0.5 mg/dL). Resolution of abnormal hepatic function occurred on Day 21. At the time of the adverse events, concomitant therapy included rifampin, isoniazid, pyrazinamide, ethambutol hydrochloride, vitamin B_6, erythromycin, cefotaxime sodium, acetaminophen, enalapril, glyburide, fosinopril, glipizide, and insulin. The investigator considered the diarrhea, myalgia, and nausea to be remotely related to study therapy, while the abnormal hepatic function was considered to be probably related to the study therapy. Additional follow-up information indicates that the subject died approximately five months after the completion of study therapy due to progression of tuberculosis.

MO Comment: Patient 25005 was taking a variety of medications at the time of her adverse event. In addition to the effect of these medications individually on her liver, one must also consider the potential effects of the drugs in combination, the potential for drug-drug interaction, and the patients underlying illness, pulmonary tuberculosis. The current product labeling for LEVAQUIN® includes abnormal hepatic function among the listed adverse reactions.

Subject 56009 (Allergic reaction): This 37-year-old Caucasian woman had no reported medical abnormalities. A single dose of levofloxacin p.o. 500mg was administered for the treatment of pneumonia. On Day 1, the subject presented with an allergic reaction. Additional information indicates that within 30 minutes of drug administration, the subject experienced trembling; diarrhea; vomiting; severe edema of the face, ears, and hands; itching in the throat; headache; cough; and trouble breathing. No concomitant medication was reported to have been administered at the time of the adverse event. The subject was prescribed diphenhydramine hydrochloride, lorazepam, codeine, and acetaminophen and was discontinued from study therapy. All symptoms resolved within 18 hours. The investigator considered the allergic reaction to be definitely related to the study therapy.

MO Comment: The current product labeling contraindicates LEVAQUIN® in patients with known hypersensitivity to levofloxacin or its components, or other quinolones. The labeling also includes a warning that serious and occasionally fatal hypersensitivity reactions have occurred in patients receiving therapy with quinolones, including levofloxacin.

From Table 42, of the 55 subjects who reported AEs (all causality) of marked severity, confusion, respiratory insufficiency, and arthralgia each occurred in 4 patients. Cardiac failure, chest pain, aggravation of condition, dyspnea, and diarrhea each occurred in 3 subjects. Angina, moniliasis, nausea, edema, abnormal hepatic function, myocardial infarction, and leg pain were each reported by two patients.

Deaths

Of the 650 subjects evaluable for safety, there were 16 deaths that occurred while on study or within 30 days of completion of therapy for a mortality rate of 2.5%. There were 3 additional deaths that occurred outside the 30-day window (Pt. No. 4038, respiratory insufficiency; Pt. No. 10004, myocardial infarction; Pt. No. 18007, renal failure). One additional patient died of pre-existing cancer on Day 26 (Pt. No. 1004, pancreatic cancer). (The Applicant noted that this case was not coded as an adverse event in the study database, but was captured upon review of the RWJPRI Global Safety and Pharmacovigilance Safety Database). Inclusion of these additional deaths results in an overall mortality rate of 3.1%. All of the deaths were considered by the investigators to be unrelated or remotely related to study therapy (Table 37). Patient narratives for selected patient deaths follow Table 37.

Table 37: Subjects Who Died[a]
(Protocol LOFBIV-PCAP-001)

Subject Number	Age	Sex	Serious Adverse Events	Study Day of Onset[b]	Duration of Therapy (Days)	Relationship to Study Drug[c]
1004	49	M	Pancreatic cancer[d]	2	2	None
1038[i]	81	M	Respiratory insufficiency[e,f]	2	2	None
1048	61	M	Cardiac arrest[g]	39	15	None
1056	46	F	Condition aggravated[e,f]	1	1	None
1059	71	F	Meningitis[g]	33	14	None
			Cardiac arrest[g]	36		None
1069	72	F	Dyspnea[f]	4	14	None
3038	41	M	Dyspnea[e,f]	2	1	None
			Emphysema[e,f]	2		None
4038	79	M	Syncope	12	14	Remote
			Respiratory insufficiency[h]	Unknown		None
8012[i]	63	M	Granulocytopenia[j,f]	22	9	None
10004	73	M	Myocardial infarction[h]	93	14	None
18007[i]	79	M	Renal failure[h]	62	13	None
28006[k,#]	72	M	Cardiac failure[e,f]	3	2	None
			Myocardial infarction[e,f]	3		None
28029[i]	64	M	GI hemorrhage[g]	16	1	None
28055[i]	42	F	Respiratory insufficiency[f]	14	14	None
51003	80	M	Myocardial infarction[e,f]	3	2	Remote
51012	47	M	Hepatic coma[g]	20	4	Remote
51019[i]	84	F	Intestinal obstruction[f,j]	29	2	None
55001[i]	68	F	Respiratory depression[f]	8	16	Remote
55004[k]	78	M	Exacerbation of COPD[h,l]	27	14	Remote
55028	37	F	Embolism pulmonary[f]	15	10	None

[a] Table based on data from the clinical database and the RWJPRI Global Safety and Pharmacovigilance serious adverse event reporting database.
[b] Relative to start of therapy (Day 1).
[c] Based on investigator's assessment.
[d] This death was not captured on the clinical study database because the subject's pre-existing pancreatic cancer was not coded as an adverse event. However, this event was captured by the RWJPRI Global Safety and Pharmacovigilance serious adverse event reporting database.
[e] Subject discontinued therapy due to this adverse event (see Table 39).
[f] This adverse event was of marked severity (see Table 36).
[g] This adverse event was reported after the Post-Therapy visit and therefore it does not appear on the case report form or in the clinical study database. However, this adverse event was collected as part of the RWJPRI Global Safety and Pharmacovigilance serious adverse event reporting database as having occurred within 30 days after the termination of therapy.
[h] Death occurred more than 30 days Post-Therapy and therefore this adverse event appears only in the RWJPRI Global Safety and Pharmacovigilance serious adverse event reporting database.
[i] Subject also had at least one treatment-emergent, markedly abnormal laboratory value (see Table 43).
[j] This death occurred after the Post-Therapy visit; however, it inadvertently was included in the clinical study database. This death also was reported by RWJPRI Global Safety and Pharmacovigilance serious adverse event reporting database.
[k] Subject experienced an adverse event(s) of marked severity (see Table 36).
[l] Exacerbation of COPD=Chronic Obstructive Pulmonary Disease, coded in the database as condition aggravated.

Adapted from Applicant's Table 36, NDA 20-634 SE1-008, Vol. 25.3, p. 212

Subject 1059 (Meningitis; Cardiac Arrest): This 71-year-old Caucasian woman had a history of hyperlipidemia, hypertension, hypothyroidism, coronary artery disease, gout, arthralgia, smoking, colostomy secondary to colon cancer, and a coronary artery bypass for peripheral vascular disease [Presumably this woman had coronary artery bypass surgery for coronary artery disease and/or arterial bypass surgery for peripheral vascular disease – MO]. She was admitted with pneumonia and had *S. pneumoniae* isolated from blood and respiratory cultures at the time of admission. After one dose of levofloxacin p.o. 500 mg q24h for pneumonia, levofloxacin therapy was reduced to p.o. 250 mg q24h due to renal insufficiency (admission creatinine: 2.1 mg/dL; normal range: 0.7-1.4 mg/dL) for an additional 13 days of therapy. She had follow-up blood cultures, 2 on Day 8 and 2 on Day 20, all of which were negative. Creatinine levels remained elevated at the Post-Therapy visit on Day 20 (1.8 mg/dL). The subject complained of headache at the Post-Study evaluation (Day 34), but was considered to be otherwise improved. Additional information indicates that on Day 34, the subject was hospitalized for severe headache, personality changes, and left-sided weakness, 21 days after the last dose of levofloxacin. Blood and cerebrospinal fluid cultures were positive for *S. pneumoniae*; PCR analysis of the organisms isolated from the cultures showed a different DNA fingerprint than that of the strain isolated during the study. White blood cells were elevated ($13.4x10^3/\mu L$; normal range: $4.0\text{-}10.5x10^3/\mu L$) from the Post-Therapy level ($5.67x10^3/\mu L$). Ceftriaxone therapy was initiated for pneumococcal meningitis. Her condition worsened: she required intubation and ventilatory support and experienced an episode of asystole. Although successfully resuscitated, she died a week and a half later, on Day 47. At the time of the adverse events, concomitant medications included allopurinol, thyroid, atenolol, pravastatin, gemfibrozil, and hydrochlorothiazide/triamterene. The investigator considered the adverse events unlikely to be related to the study therapy.

> **MO Comment:** While the occurrence of an episode of pneumococcal meningitis within a few weeks of an episode of bacteremic pneumococcal pneumonia raises the possibility of inadequately treated disease and persistence in the CNS, or extension to the CNS, the finding of a different DNA fingerprint for the pneumococcal strain causing meningitis does not lend support to such a conclusion.

Subject 51012 (Hepatic coma): This 47-year-old Caucasian man had a history of non-insulin-dependent diabetes mellitus, hepatitis A and C, depression, and anxiety attacks, and was HIV+. Levofloxacin i.v. 500mg q24h was administered for the treatment of pneumonia for three days after which the route of administration was changed to oral for an additional day of therapy before the subject left the hospital without the physician's approval (after a total of four days of therapy). Upon study admission, ALT (360 U/L; normal range:6-43 U/L), AST (333 U/L; normal range: 11-36 U/L), alkaline phosphatase (120 U/L; normal range: 31-110 U/L), glucose (378 mg/dL; normal range: 70-115 mg/dL), and LDH (313 U/L; normal range: 53-234 U/L) levels were elevated. BUN levels (16 mg/dL) were within normal range (4-24 mg/dL). Additional information indicates that on Day 20 the subject presented with a six day history of jaundice and abdominal pain and was hospitalized until he died three days later from hepatic encephalopathy and acute hepatic failure. At the time of the adverse events, concomitant medications included acetaminophen/codeine, diazepam, glyburide, human insulin, oxazepam, ibuprofen, sodium chloride, and potassium chloride. The investigator considered the adverse events to be remotely related to the study therapy.

> **MO Comment:** Following review of the CRFs, the role of levofloxacin in the hepatic decompensation observed in patient number 51012 is unclear due to

the multiple confounding factors. The patient entered the study with LFT abnormalities at the time of admission. In addition the patient is noted to have a history of hepatitis C and hepatitis A and is also noted to be HIV seropositive. He was also taking other medications including acetaminophen/codeine, ibuprofen, glyburide, insulin, diazepam, oxazepam sodium chloride, and potassium chloride. Hence, in this patient with pre-existing hepatic dysfunction, it is unclear whether or not levofloxacin contributed to the development of hepatic coma and the resulting death of the patient. The MO has requested additional clinical information on the development of hepatic coma in this patient.

MO Comment: A recent review of post-marketing data on hepatoxicity associated with use of fluoroquinolones done by the staff of the Office of Post-Marketing Drug Risk Assessment included some data on levofloxacin and liver-related adverse events. The available did not demonstrate an excess number of liver-related adverse events for levofloxacin when compared to other quinolones not typically associated serious liver-related adverse events.

The following cases present clinical scenarios in which arrhythmia is either present or a possibility. The case narratives for these three cases follow.

Subject 4038 (Syncope; Respiratory Insufficiency): This 79-year-old Caucasian man had a history of smoking, chronic obstructive pulmonary disease, right upper lobe pulmonary nodule, hypertension, right bundle branch block, chest pain, myocardial infarction, dizziness, headache; diarrhea, nausea, vomiting, and arthritis. Levofloxacin p.o. 500mg q24h was administered for the treatment of pneumonia for 14 days. On Day 12, the subject experienced a moderate syncopal episode, was treated with metoprolol, acetylsalicylic acid, and heparin, and was hospitalized for one week for observation and to rule out myocardial infarction. Additional information indicates that on Day 39 a chest x-ray revealed right lower lobe pneumonia, elevated WBC count, and "bandemia." The subject died on Day 82 of respiratory failure. At the time of the adverse events, concomitant medications included acetylsalicylic acid, furosemide, captopril, beclomethasone dipropionate, albuterol, ipratropium bromide, diphenhydramine, and acetaminophen. The investigator considered the syncope to be remotely related to study drug administration; the death was considered to be unrelated to study therapy.

Subject 28055 (Respiratory Insufficiency): This 42-year-old Caucasian woman had a history of hyperglycemia, mental retardation, and surgery for atrial septal defect and congestive heart failure. Upon admission, the subject was noted to have fever, chills, shortness of breath, cough, sputum production, purulent sputum, and bilateral infiltrates. Levofloxacin i.v. 500mg q24h was administered for 14 days. On Day 14, the subject developed moderate cardiac arrhythmia and marked respiratory failure subsequent to gross aspiration. She required mechanical ventilation. She was treated with lidocaine, theophylline, digoxin, diltiazem, dopamine, and potassium chloride and the arrhythmia resolved by Day 19. On Day 18, the subject's coagulation time was increased moderately.

The following day she developed a gastrointestinal hemorrhage, which was treated with ranitidine hydrochloride and vitamin K and persisted for two days. On Day 23, she had markedly elevated glucose (502 mg/dL; admission: 236 mg/dL; normal range: 70-115 mg/dL) and markedly decreased lymphocytes ($0.91x10^3/\mu L$; admission: $2.13x10^3/\mu L$; normal range: $0.91\text{-}4.28x10^3/\mu L$). Her condition continued to deteriorate and she died on Day 29 from respiratory failure. At the time of the adverse events, concomitant medications included albuterol, midazolam hydrochloride, lorazepam, potassium chloride, acetazolamide, acetaminophen, morphine sulfate, ipratropium bromide, and prednisone. The investigator considered the cardiac arrhythmia, increased coagulation time, and gastrointestinal hemorrhage to be remotely related to the study therapy, while the respiratory failure was considered to be unrelated to study therapy.

Subject 51003 (Myocardial Infarction): This 80-year-old Caucasian man had a history of hypertension, strokes, abnormal ECG, abdominal pain, enlarged prostate, and tuberculosis. He received one day of levofloxacin p.o. 500mg q24h for pneumonia as an outpatient, after which he received an additional day of levofloxacin therapy at the reduced dose of 250 mg q24h due to renal insufficiency (admission creatinine: 1.7 mg/dL; normal range: 0.8-1.6 mg/dL). At this time, the subject was discontinued from study therapy due to renal insufficiency (after a total of two days of levofloxacin therapy). On Day 3, the subject was found dead; the cause of death was considered to be a probable myocardial infarction. At the time of the adverse events, concomitant medications included captopril and acetylsalicylic acid. The investigator considered the adverse event to be remotely related to the study therapy.

MO Comment: The MO reviewed the case report forms for the 3 patients above in search of additional information that might further clarify causality of the observed events. Given the patients' medical histories, the clinical events encountered, the adverse events are reasonably attributed to causes other than levofloxacin induced QT prolongation or torsades de pointes. The CRFs for these three patients were reviewed to see if there was any apparent evidence of QT prolongation or torsade de pointes. No such association with QT prolongation was found in the limited information available in the CRFs that could be used to address this question. The MO also requested additional information from the Applicant regarding these cases in order to further investigate whether QT prolongation and/or torsades de pointes was a factor in the adverse events of these patients.

MO Comment: The Applicant provided the following additional information on the three patients mentioned above (submission dates January 4, 2000 and January 6, 2000).

Pt. No. 4038 – This 79-year-old male had a history of oxygen-dependent chronic obstructive pulmonary disease, prior myocardial infarction, hypertension, right bundle branch block (RBBB) on EKG, and episodes of dizziness. The patient reported that he "often came to the point of passing out" during the month prior to admission for his community-acquired pneumonia. His medications at baseline included furosemide 40 mg po BID and captopril 50 mg po BID for hypertension, aspirin for prophylaxis of

coronary artery disease, and inhaled beclomethasone, albuterol, and atrovent for COPD. The patient was admitted to the hospital on — for community-acquired pneumonia and began levofloxacin 500 mg daily on 11/2/97. He was discharged to home on — ' and remained on levofloxacin through 11/15/97.

On 11/13/97, while at home, the patient experienced a syncopal episode. He was admitted on — ' and evaluated for syncope. He had negative serial cardiac enzymes and EKG's. A 26-hour holter monitor that showed sinus rhythm with sinus arrhythmia and sinus bradycardia, occasional premature ventricular complexes (PVCs), frequent premature atrial complexes (PACS) with few couplets and triplets, occasional sinus pauses up to 2.0 seconds (blocked PACS and/or sinus arrest), eight bursts of paroxysmal supraventricular tachycardia from 4 to 17 beats at 110 to 150 beats per minute, no symptoms were recorded. He also had a carotid doppler study that showed no significant disease.

The patient had a series of EKGs from — through — An EKG from — (prior to levofloxacin therapy) showed sinus rhythm (SR) at 95 beats per minute, old inferior infarct cannot be ruled out, RBBB, and QT/QT_c interval of 320/400 msec. The day that the patient was admitted for syncope (—, he had 2 EKGs. The first showed SR with premature supraventricular complexes at 78 beats per minute, RBBB and a QT/QT_c interval of 378/428 msec. A second EKG done 25 minutes later showed sinus tachycardia at 105 beats per minute, RBBB, and a QT/QT_c interval of 326/476 msec. Subsequent EKGs were done on — – SR with sinus arrhythmia, rate of 64/minute, RBBB and a QT/QT_c interval of 428/435 msec; — ' – sinus bradycardia rate 56/minute, no evidence of RBBB and a QT/QT_c interval of 420/399 msec; — – (one month post-levofloxacin) atrial fibrillation, rate 128/minute, RBBB and a QT/QT_c interval of 308/446 msec.

On 11/14/97 furosemide was discontinued because of suspected orthostatic hypotension. While the patient was hospitalized on —, he experienced 2 episodes of lightheadedness and dizziness "almost to the point of passing out." Telemetry monitoring did not detect any associated arrhythmias. The patient was discharged on — in stable condition with the diagnosis of syncope due to hypotension and dehydration.

Given the patients orthostasis, lack of arrhythmia on telemetry at the time of symptoms, holter monitor results, negative carotid doppler study, and variable EKG findings, no conclusions regarding a causal role for levofloxacin in the above events can be made. The investigator's diagnosis of over diuresis resulting in dehydration and hypotension is reasonable.

Pt. No. 28055 – This 42-year-old female had an extensive cardiac history including previous surgical repair of an atrial septal defect. Review of her records revealed EKGs from 1982 with a QT_c interval of 480 msec and an EKG from 1997 with a QT_c interval of 410 msec (heart rate 108/min). She

received levofloxacin 500 mg QD 2/17/98 through 3/2/98. While on levofloxacin therapy she had daily rhythm strips on Day 2 through 5 with a QT_c greater the 440 msec. On Days 6 through 14 she had daily rhythm strips with an apparently QTc of less than 440 msec. On Day 14, she aspirated, developed hypoxia and required mechanical ventilation. Her rhythm strips showed a sinus rhythm of 100/minute with a QTc interval of about 430 msec. Later that same day she developed a supraventricular tachycardia with a rate of 206 to 240/minute with associated hypotension. She was treated with dopamine, carotid massage, lidocaine, digoxin, and diltiazem. The following day, —— she had a 12-lead EKG performed that showed a rate of 127/minute and a QTc interval of 387msec. The patient went on to develop persistent hypoxia and hypotension and experienced asystole and expired on —.

Given the patient's extensive underlying structural heart disease, pre-existing conduction abnormalities, and development of supraventricular arrhythmias while on levofloxacin therapy, the events that occurred do not appear to be attributable to levofloxacin induced QT prolongation and/or torsades de pointes.

Pt. No. 51003 – This 80 year-old male with a history of hypertension and cerebrovascular accident presented to the emergency room (ER) with complaints of epigastric pain. In the ER he was diagnosed with pneumonia and enrolled in the LOFBIV-PCAP-001 Study. As part of his ER evaluation he had an EKG which revealed left bundle branch block with a rate of 95 and a QTc interval of 518 msec (no baseline EKG available). He was discharged to home after completion of his ER evaluation. He received levofloxacin 500 mg on Day 1 and then 250 mg on Day 2. On Day 3 the patient was found at home dead with the suspected cause of death listed as myocardial infarction.

While this patient did have a prolonged QTc interval at baseline, which would put him at risk for the development of arrhythmia such as torsades de pointes, there is insufficient evidence to draw definitive conclusions regarding the cause of death. The investigator's conclusion of a suspected myocardial infarction is reasonable.

MO Comment: The current labeling includes arrhythmias, cardiac arrest, and syncope as events of potential medical importance that occurred at a rate of less than 0.5% regardless of drug relationship during the clinical trials. In addition, based on reporting of post-marketing adverse events, torsades de pointes and information from the postmarketing experience will be added to the label.

Other Serious Adverse Events

The serious adverse events reported for patients (other than death) are listed in Table 38. The most common serious adverse events reported for patients were, condition aggravated (progression of a previously existing condition during study drug treatment) (N=11), cardiac failure (N=6), and confusion (N=3). No other serious adverse event was reported for more than 2 patients.

Three patients reported serious adverse events that were considered drug-related (definitely or probably drug-related). Two patients (Pt. No. 56008 and Pt. No. 56009) reported a serious adverse event that was considered by the investigator to be definitely related to the study therapy. Both patients experienced an allergic reaction. One patient (Pt. No. 4024) reported a serious adverse event (aggravated condition) that was considered by the investigator to be probably related to the study therapy. This patient's pneumonia initially responded to levofloxacin therapy. His admission respiratory culture yielded levofloxacin-sensitive *P. aeruginosa, H. parahemolyticus* and levofloxacin-resistant *S. aureus*. On Day 35 the patient was re-admitted to the hospital and received treatment for a worsening pneumonia. His respiratory culture at the time of re-admission yielded levofloxacin-sensitive *P. aeruginosa* and levofloxacin-resistant *S. aureus*. The patient received 2 weeks of therapy and was discharged from the hospital. Further details are unavailable.

Table 38: Subjects Who Had Serious Adverse Events Other Than Death[a] (Protocol LOFBIV-PCAP-001)

Subject Number	Age	Sex	Adverse Event	Study Day of Onset[b]	Duration of Event (Days)	Relationship to Study Drug[c]	Duration of Therapy (Days)	Outcome of Adverse Event
1001	71	M	Cardiac failure[d]	20	9	Remote	14	Disappear
1016	69	F	Angina pectoris[e]	21	Unknown	None	14	Persisted
2003	74	F	Angioedema[d]	16	2	Remote	7	Disappear
3030	31	M	Cardiac failure[d]	19	3	None	10	Disappear
3047[f]	29	M	Diarrhea[e,g]	10	Unknown	None	9	Disappear
4002	50	M	Condition aggravated[e,g]	2	Unknown	None	2	Persisted
4009	82	M	Heart block[e]	10	2	Remote	11	Disappear
4016	66	M	Condition aggravated[d]	35	5	Remote	10	Disappear
4017	73	M	Fibrillation atrial	4	Unknown	Remote	12	Persisted
			Cardiac failure	15	5	Remote		Disappear
			Coagulation time increased[d]	27	6	Remote		Disappear
4019	56	M	Condition aggravated[d]	40	3	None	14	Disappear
4024	75	M	Condition aggravated[d]	35	16	Probable	17	Disappear
4030[f]	79	M	Aortic stenosis[e]	6	Unknown	None	14	Persisted
4031	55	M	Coagulation disorder	13	3	Remote	14	Disappear
4035	65	M	Angina pectoris	18	3	None	14	Disappear
4037	70	M	Coma hypoglycemic[e]	13	Unknown	Remote	13	Persisted
4039[f]	74	M	Respiratory disorder[d]	28	13	None	14	Disappear
4040	73	M	Pneumonia[d]	35	3	None	13	Disappear
4041	74	M	Bronchitis[d]	42	5	None	14	Disappear
4053[f]	71	M	Purpura thrombocytopenic[e]	21	Unknown	Possible	14	Persisted
4054	53	M	Abscess[d]	28	11	Remote	14	Disappear
4059	77	M	Rash	17	5	Remote	14	Disappear
4060[f]	63	M	Empyema	4	12	None	29	Disappear
7004	39	F	Delirium[d]	43	9	Remote	LTF	Disappear
			Asthma[d]	43	9	Remote		Disappear
7012[f]	53	M	Pancytopenia[d]	30	16	None	13	Disappear
			Renal failure acute[d]	30	16	None		Disappear
			Weight decrease[d]	30	16	None		Disappear
7020	37	M	Condition aggravated[g]	4	7	Remote	4	Disappear
8011	66	F	Cellulitis[e,g]	2	Unknown	None	5	Persisted
9002	86	M	Cardiac failure[d]	43	13	None	17	Disappear
9017	78	M	Cardiac failure[e]	6	5	None	15	Disappear
10002	60	F	Dehydration[e,h]	2	3	Remote	4	Disappear
			Diarrhea[h,e]	2	3	Possible		Disappear
13002	28	F	Bronchospasm[d]	14	6	Remote	12	Disappear
15002	42	F	Condition aggravated	2	6	Remote	14	Disappear
15003[i]	76	M	Shortness of breath[d]	10	2	Remote	3	Disappear
15010	21	M	Condition aggravated	6	4	Remote	14	Disappear

[a] Table based on data from the clinical study database and from the RWJPRI Global Safety and Pharmacovigilance database.
[b] Relative to start of therapy (Day 1).
[c] Based on investigator's assessment.
[d] This adverse event was reported after the Post-Therapy visit and therefore it does not appear on the case report form or in the clinical study database. However, this adverse event was collected as part of the RWJPRI Global Safety and Pharmacovigilance database as having occurred within 30 days after termination of therapy.
[e] This adverse event was of marked severity (see Table 36).
[f] Subject also had at least one treatment-emergent, markedly abnormal laboratory value (see Table 43).
[g] Subject discontinued therapy due to this adverse event (see Table 39).
[h] Subject discontinued therapy due to this adverse event, among others (see Table 39).
[i] Subject discontinued therapy due to another adverse event (see Table 39).
LTF= Lost to follow-up.

Adapted from Applicant's Table 37, NDA 20-634 SE1-008, Vol. 3, p. 221

Table 38: Subjects Who Had Serious Adverse Events Other Than Death[a] (Continued)
(Protocol LOFBIV-PCAP-001)

Subject Number	Age	Sex	Adverse Event	Study Day of Onset[b]	Duration of Event (Days)	Relationship to Study Drug[c]	Duration of Therapy (Days)	Outcome of Adverse Event
16001[d]	86	F	Infection TBC	14	9	None	10	Disappear
			Infection TBC[e]	36	8	Remote		Disappear
19004	72	M	Pneumonia[f]	26	3	None	4	Disappear
19008	78	F	Condition aggravated[g]	19	Unknown	Remote	10	Persisted
19019	53	M	Diabetes mellitus aggravated[f]	38	10	None	14	Disappear
			Gangrene[f]	38	10	None		Disappear
			Peripheral ischemia[f]	38	10	None		Disappear
20004	38	F	Cardiac failure[g,h]	2	16	None	1	Disappear
			Respiratory insufficiency[g,h]	2	16	None		Disappear
21002[i]	79	M	Somnolence[g]	5	3	None	14	Disappear
22001	76	M	Myelomatosis multiple[g]	3	Unknown	None	14	Persisted
23014[j]	22	M	Condition aggravated[h]	5	11	Remote	4	Disappear
28013	77	M	Convulsions[k]	9	1	Possible	9	Disappear
28027	57	F	Nausea[g]	3	5	Possible	14	Disappear
			Vomiting	3	5	Possible		Disappear
28050	62	M	Pulmonary carcinoma[g]	19	Unknown	None	14	Persisted
28056	84	F	Diverticulitis[f]	22	14	None	10	Disappear
28063	76	M	Respiratory insufficiency[f]	26	7	None	14	Disappear
51017	23	F	Asthma[g]	2	3	None	3	Disappear
51023	82	M	Ataxia[g,h]	1	1	Possible	1	Disappear
			Confusion[g,h]	1	1	Possible		Disappear
52005[l]	64	F	Condition aggravated	9	Unknown	None	10	Persisted
55002	24	F	Agitation	12	4	Possible	8	Disappear
			Confusion[g,h]	12	4	Possible		Disappear
55005	72	M	Convulsions[g,h]	2	1	Possible	1	Disappear
55010	37	M	Confusion[g,h]	1	3	Possible	2	Disappear
			Convulsions grand mal[g,h]	1	3	Remote		Disappear
55025	78	M	Condition aggravated[f]	35	4	Remote	8	Disappear
55026	48	M	Infection bacterial[f]	24	8	Remote	15	Disappear
56008	49	M	Allergic reaction[h]	1	1	Definite	1	Disappear
56009	37	F	Allergic reaction[g,h]	1	3	Definite	1	Disappear
59001[l]	79	M	SIADH[f]	6	7	None	4	Disappear

[a] Table based on data from the clinical study database and from the RWJRPI Global Safety and Pharmacovigilance database.
[b] Relative to start of therapy (Day 1).
[c] Based on investigator's assessment.
[d] Subject had positive skin test (20 mm induration) on study Day 14; possible diagnosis of tuberculosis on study Day 36.
[e] This event occurred after the Post-Therapy visit; however, it inadvertently was included in the clinical study data base.
[f] This adverse event was reported after the Post-Therapy visit and therefore it does not appear on the case report form or in the clinical study database. However, this adverse event was collected as part of the RWJPRI Global Safety and Pharmacovigilance database as having occurred within 30 days after termination of therapy.
[g] This adverse event was of marked severity (see Table 36).
[h] Subject discontinued therapy due to this adverse event (see Table 39).
[i] Subject also had at least one treatment-emergent, markedly abnormal laboratory value (see Table 43).
[j] This subject received only 250 mg of levofloxacin on Days 2-4 due to a prescription error.
[k] Subject discontinued therapy due to this adverse event, among others (see Table 39).
[l] Subject discontinued therapy due to another adverse event (see Table 39).

COPD=Chronic Obstructive Pulmonary Disease; SIADH=Syndrome of inappropriate ADH secretion.

Adapted from Applicant's Table 37, NDA 20-634 SE1-008, Vol. 3, p. 222

MO Comment: The MO reviewed the patient narratives for all patients for whom serious adverse events were reported. The current levofloxacin product labeling addresses the serious adverse events that were reported in Study LOFBIV-PCAP-001.

Discontinuations due to Adverse Events

Of the 655 patients enrolled in the study, 25 were lost to follow-up. Of the 630 patients who provided information at follow-up visits, 37 (6%) discontinued study therapy prematurely due to treatment-emergent adverse events (Table 39). The two most commonly reported adverse events in patients discontinuing therapy were nausea, reported in 6 patients (Pt. Nos. 9008, 15003, 15012, 27010, 28013, and 28022) and aggravated condition, reported in 4 patients (Pt. Nos. 1056, 4002, 7020, and 23014).

MO Comment: Note that patients discontinuing therapy because of an adverse event often had more than one adverse event reported.

Of the 37 patients discontinuing study therapy due to an AE, 19 experienced AEs that were considered serious. Sixteen of the 37 patients had an AE of marked severity that led to discontinuation of therapy, 15 of which were considered to be serious. Three patients experienced AEs that were considered by the investigator as having a definite relationship to study therapy (Pt. No.15003 – nausea, Pt. No. 56008 – allergic reaction, Pt. No. 56009 – allergic reaction). Five patients had AEs that were considered by the investigator as having a probable relationship with the study therapy (Pt. No. 9014 – dysphagia, Pt. No. 25005 - abnormal hepatic function, Pt. No. 27010 – nausea, Pt. No. 52001 – dizziness, and Pt. No. 52011 – bacterial infection – *C. difficile* colitis). Eight patients discontinued after the first day of therapy.

Table 39: Subjects Who Discontinued Therapy due to Adverse Events (Protocol LOFBIV-PCAP-001)

Subject Number	Age	Sex	Adverse Event	Study Day of Onset[a]	Duration of Event (Days)	Severity[b]	Relationship to Study Drug[b]	Duration of Therapy (Days)	Outcome
1038	81	M	Respiratory insufficiency[d,e]	2	2	Marked	None	2	Death
1049	41	M	Rash	8	6	Mild	Possible	8	Disappear
1056	46	F	Condition aggravated[d,e]	1	2	Marked	None	1	Death
3008	43	M	Anxiety	3	4	Moderate	Remote	5	Disappear
3038	41	M	Agitation	1	2	Moderate	None	1	Death
			Dyspnea[d,e]	2	1	Marked	None		Death
			Emphysema[d,e]	2	1	Marked	None		Death
3047[f]	29	M	Diarrhea[c,e]	10	Unknown	Marked	None	9	Disappear
4002	50	M	Condition aggravated[c,e]	2		Marked	None	2	Persisted
7020	37	M	Condition aggravated[e]	4	7	Moderate	Remote	4	Disappear
7032	47	F	Vision abnormal	3	2	Moderate	Possible	3	Disappear
8011	66	F	Cellulitis[c,e]	2		Marked	None	5	Persisted
9008[f]	78	M	Anorexia	5	15	Moderate	Possible	9	Disappear
			Nausea	8	12	Moderate	Possible		Disappear
			Dizziness	11	9	Moderate	Possible		Disappear
9014	76	F	Dysphagia	6	3	Moderate	Probable	8	Disappear
10002	60	F	Abdominal pain	2	3	Moderate	Possible	4	Disappear
			Dehydration[c,e]	2	3	Marked	Remote		Disappear
			Diarrhea[c,e]	2	3	Marked	Possible		Disappear
			Headache	2	3	Moderate	Remote		Disappear
			Hypertension	2	3	Mild	Remote		Disappear
			Vomiting[e]	2	3	Marked	Remote		Disappear
15003	76	M	Nausea	4	7	Mild	Definite	3	Disappear
15012	41	F	Nausea	1	2	Moderate	Possible		Disappear
			Vomiting	1	2	Moderate	Possible		Disappear
17008	70	F	Rash erythematous	7	5	Mild	None	8	Disappear
20002	61	M	Cardiac failure	3		Moderate	None	3	Persisted
20004	38	F	Cardiac failure[c,e]	2	16	Marked	None	1	Disappear
			Respiratory insufficiency[c,e]	2	16	Marked	None		Disappear
20006	82	F	Blindness	4	1	Mild	None	4	Disappear
23014	22	M	Condition aggravated[e]	5	11	Moderate	Remote	4	Disappear
25005[f]	56	F	Hepatic function abnormal[e]	3	21	Marked	Probable	3	Disappear
27010[f]	37	M	Nausea	11	4	Moderate	Probable	13	Disappear
28006	72	M	Cardiac failure[d,e]	3	2	Marked	None	2	Death
			Myocardial infarction[d,e]	3	2	Marked	None		Death
28013	77	M	Nausea	8	4	Moderate	Possible	9	Disappear
			Vomiting	8	4	Moderate	Possible		Disappear
			Convulsions[e]	9	1	Mild	Possible		Disappear
			Dehydration	9	3	Moderate	Possible		Disappear
			Headache	10	2	Moderate	Possible		Disappear
28022	22	M	Diarrhea	6		Moderate	Possible	10	Unknown
			Nausea	9	2	Moderate	Possible		Disappear
			Vomiting	9	2	Moderate	Possible		Disappear
51003	80	M	Myocardial infarction[d,e]	3	1	Marked	Remote	2	Death
51023	82	M	Ataxia[c,e]	1	1	Marked	Possible	1	Disappear
			Confusion[c,e]	1	1	Marked	Possible		Disappear
52001	29	F	Dizziness	1		Moderate	Probable	1	Unknown
52011	80	F	Infection bacterial	3	3	Mild	Probable	4	Disappear
53010	61	M	Insomnia	1	13	Moderate	Possible	2	Disappear
55002	24	F	Confusion[e,e]	8	2	Marked	Possible	8	Disappear
55005	72	M	Convulsions[c,e]	2	1	Marked	Possible	1	Disappear

[a] Relative to start of therapy (Day 1).
[b] Based on investigator's assessment.
[c] Serious adverse event other than death (see Table 38).
[d] Subject died as a result of the adverse event (see Table 37).
[e] This adverse event was of marked severity (see Table 36).
[f] Subject also had at least one treatment-emergent, markedly abnormal laboratory value (see Table 43).

Applicant's Table 38. From NDA 20-634, SE1-008, vol. 3, p. 239

Table 39: Subjects Who Discontinued Therapy due to Adverse Events (Continued)
(Protocol LOFBIV-PCAP-001)

Subject Number	Age	Sex	Adverse Event	Study Day of Onset[a]	Duration of Event (Days)	Severity[b]	Relationship to Study Drug[b]	Duration of Therapy (Days)	Outcome
55010	37	M	Confusion[c,d]	1	3	Marked	Possible	2	Disappear
			Convulsions grand mal[c,d]	1	3	Marked	Remote		Disappear
55027	40	F	Headache	4		Moderate	None	4	Unknown
			Insomnia	4		Moderate	None		Unknown
			Paroniria	4		Moderate	None		Unknown
56008	49	M	Allergic reaction[c]	1	1	Mild	Definite	1	Disappear
56009	37	F	Allergic reaction[c,d]	1	3	Marked	Definite	1	Disappear
59001	79	M	Rash	4		Mild	Possible	4	Unknown
			Tongue disorder	4	1	Mild	Possible		Disappear

[a] Relative to start of therapy (Day 1).
[b] Based on investigator's assessment.
[c] Serious adverse event other than death (see Table 38).
[d] This adverse event was of marked severity (see Table 36).

Applicant's Table 38. From NDA 20-634, SE1-008, vol. 3, p. 239

Concomitant Therapy for Treatment-Emergent Adverse Events

Ten patients experienced drug-related adverse events of mild or moderate severity, remained on therapy, and received concomitant therapy to counteract their AE (Table 40).

Table 40: Subjects Who Required Concomitant Therapy due to Drug-Related[a] Adverse Events
(Protocol LOFBIV-PCAP-001)

Subject Number	Age	Sex	Adverse Event (Preferred Term)	Day of Onset[b]	Severity	Relationship
1032	65	M	Moniliasis	2	Mild	Probable
8009	49	F	Moniliasis	8	Moderate	Probable
19023	67	F	Gastritis	8	Mild	Probable
			Esophagitis	8	Mild	Probable
27001	67	M	Abdominal pain	1	Moderate	Definite
			Nausea	1	Moderate	Definite
			Pruritus	8	Moderate	Probable
27004	70	F	Diarrhea	2	Moderate	Probable
27011	72	M	Rash erythematous	6	Moderate	Probable
27014	61	F	Pruritus genital	13	Moderate	Probable
51007	46	M	Nausea	3	Mild	Probable
			Vomiting	3	Mild	Probable
55003	33	F	Nausea	4	Moderate	Probable
57003	72	M	Abdominal pain	1	Moderate	Probable
			Insomnia	1	Moderate	Probable

[a] Includes treatment-emergent adverse events considered by the investigator to be probably or definitely related to study drug except for those resulting in study drug discontinuation or those considered serious.
[b] Relative to start of therapy (Day 1).

Applicant's Table 39, NDA 20-634 SE1-008, vol. 3, p. 241

MO Comment: The mild and moderate drug-related AEs listed in Table 40 are well represented in the current levofloxacin product labeling.

Clinical Laboratory Evaluations

Laboratory Values Over Time

The Applicant summarized the population means for selected laboratory values from the Admission and Post-Therapy visit. These values and their differences are listed in Table 41.

Table 41: Means and Mean Changes from Admission to Post-Therapy for Laboratory Analytes: All Subjects Evaluable for Safety with Data Available at Admission and Post-Therapy (Protocol LOFBIV-PCAP-001)

		Levofloxacin					
		Admission		Post-Therapy		Change	
Laboratory Test	N[a]	Mean	(SD)	Mean	(SD)	Mean	(SD)
Blood chemistry							
Glucose (mg/dL)	537	134.8	(78.31)	118.9	(60.64)	-15.9	(80.66)
Blood urea nitrogen (mg/dL)	570	16.3	(9.55)	15.3	(7.27)	-1.0	(7.72)
Total bilirubin (mg/dL)	523	0.7	(0.63)	0.5	(0.35)	-0.2	(0.52)
Lactic dehydrogenase (U/L)	561	212.4	(101.19)	177.7	(69.09)	-34.7	(92.28)
Alkaline phosphatase (U/L)	563	80.5	(43.19)	79.8	(39.02)	-0.7	(25.36)
AST (SGOT) (U/L)	537	32.0	(57.34)	27.3	(28.23)	-4.7	(57.94)
ALT (SGPT) (U/L)	537	29.4	(55.20)	27.1	(41.09)	-2.3	(60.27)
Creatinine (mg/dL)	570	1.2	(0.41)	1.2	(0.33)	-0.0	(0.29)
Hematology							
Hemoglobin (g/dL)	508	13.2	(1.94)	13.2	(1.72)	0.1	(1.16)
Hematocrit (%)	467	40.6	(5.76)	40.8	(5.01)	0.2	(3.96)
RBC ($x10^6/\mu L$)	508	4.4	(0.62)	4.4	(0.56)	0.0	(0.39)
WBC ($x10^3/\mu L$)	508	13.4	(7.65)	8.0	(5.22)	-5.4	(6.55)
Neutrophils ($x10^3/\mu L$)	508	10.6	(5.89)	5.1	(3.07)	-5.5	(5.96)
Bands ($x10^3/\mu L$)	508	0.2	(0.86)	0.0	(0.02)	-0.2	(0.86)
Lymphocytes ($x10^3/\mu L$)	508	1.7	(3.72)	2.2	(3.98)	0.4	(1.08)
Monocytes ($x10^3/\mu L$)	508	0.7	(0.46)	0.5	(0.20)	-0.2	(0.46)
Eosinophils ($x10^3/\mu L$)	508	0.1	(0.13)	0.2	(0.17)	0.1	(0.18)
Basophils ($x10^3/\mu L$)	508	0.1	(0.10)	0.1	(0.10)	0.0	(0.08)
Platelet count ($x10^3/\mu L$)	489	250.9	(101.37)	313.4	(115.27)	62.4	(109.09)

[a] N=Number of subjects with Admission and Post-Therapy results

Applicant's Table 40, NDA 20-634 SE1-008, Vol. 3, p. 242

MO Comment: The population means for laboratory values do not suggest any particular problems with laboratory parameters. The few values that exhibit changes from the Admission to Post-Therapy visit are consistent with changes that would be expected in the setting of successful treatment of infection.

Individual Subject Changes

Individual Clinically Significant Abnormalities

The treatment-emergent markedly abnormal laboratory values reported for patients with admission laboratory data are listed in Table 42. The marked abnormalities noted most frequently were elevated glucose and decreased lymphocytes, both of which occurred in fewer than 3% of subjects.

Table 42: Incidence of Treatment-Emergent Markedly Abnormal Laboratory Values: Subjects Evaluable for Safety (Protocol LOFBIV-PCAP-001)

Laboratory Test	Levofloxacin Proportion[a]	Levofloxacin (%)
Blood chemistry		
Elevated glucose	15/538	(2.8%)
Decreased glucose	11/538	(2.0%)
Elevated BUN	2/572	(0.3%)
Elevated bilirubin	1/526	(0.2%)
Elevated LDH	1/562	(0.2%)
Elevated alkaline phosphatase	1/564	(0.2%)
Elevated AST (SGOT)	11/538	(2.0%)
Elevated ALT (SGPT)	12/538	(2.2%)
Elevated creatinine	1/572	(0.2%)
Hematology		
Decreased hemoglobin	5/509	(1.0%)
Decreased neutrophils	7/509	(1.4%)
Decreased lymphocytes	13/509	(2.6%)
Decreased platelet count	1/490	(0.2%)

[a] Numerator=number of subjects with a treatment-emergent markedly abnormal test value and denominator=number of subjects evaluable (i.e., admission and post-admission [≤30 days after therapy stop] data available) for that analyte.

Applicant's Table 41, NDA 20-634 SE1-008, Vol. 3, p. 244

MO Comment: The **ADVERSE REACTIONS** section in the approved product labeling includes the abnormalities noted in Table 42.

Table 43 provides a listing of the individual patients that experienced treatment emergent markedly abnormal laboratory values.

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Table 43: Subjects Who Had Treatment-Emergent Markedly Abnormal Laboratory Values: Subjects Evaluable for Safety (Protocol LOFBIV-PCAP-001)

Laboratory Test[a] Subject	Age	Sex	Admission Value	Abnormal Value	Study Day[b]	Duration of Therapy (Days)	Comments
Blood Chemistry							
Elevated Glucose (>200 mg/dL)							
1015	50	M	147.00	390.00	19	14	
1051	75	M	135.00	237.00	20	14	See lymphocytes
10014	64	M	91.00	211.00	16	10	
17012	56	M	99.00	241.00	17	12	Hx of diabetes mellitus
21008	81	M	117.00	218.00	15	10	
27001	67	M	212.00	373.00	19	12	Hx of diabetes mellitus
28017	53	F	136.00	245.00	19	14	Repeat value of 182.00 on Day 26; Hx of diabetes mellitus
28032	76	F	197.00	476.00	21	14	Hx of insulin-dependent diabetes mellitus
28035	79	M	53.00	275.00	18	13	Hx of diabetes mellitus
28039	52	M	152.00	314.00	14	8	Hx of hyperglycemia
28055[c,d]	42	F	236.00	502.00	23	14	See lymphocytes; Hx of hyperglycemia
52005[e]	64	F	119.00	252.00	16	10	
55001[c,d,e]	68	F	238.00	472.00	15	16	Hx of diabetes mellitus
55024	50	M	71.00	213.00	20	10	See lymphocytes
57003	72	M	139.00	376.00	15	10	Repeat value of 212.00 on Day 33; Hx of diabetes mellitus
Decreased Glucose (<70.00 mg/dL)							
1029	71	M	108.00	62.00	20	14	
3034	36	M	153.00	67.00	21	14	
4044	61	M	145.00	68.00	20	14	
7029	72	F	125.00	62.00	16	14	
17006	34	M	114.00	60.00	25	15	Hx of alcohol abuse
19016	58	F	102.00	66.00	17	10	
23008	22	M	100.00	66.00	21	14	
27007	27	F	119.00	64.00	21	13	
28024	79	F	109.00	69.00	36	14	
55012	41	F	101.00	58.00	15	9	
55013[d]	74	M	146.00	68.00	19	14	
Elevated BUN (>40 mg/dL)							
7012[c]	53	M	14.00	41.00	19	13	
28029[c]	64	M	24.00	44.00	2	1	See LDH, AST, ALT
Elevated Total Bilirubin (>1.5 mg/dL)							
9006	22	M	1.00	2.30	23	14	Repeat value of 1.10 on Day 35
Elevated LDH (>600 U/L)							
28029	64	M	242.00	1008.00	2	1	See BUN, AST, ALT
Elevated Alkaline phosphatase (>250 U/L)							
18007[c]	79	M	131.00	330.00	25	13	Hx of chronic renal insufficiency
Elevated AST (SGOT) (>75 U/L)							
3007	43	F	19.00	177.00	18	13	See ALT; Hx of hepatitis
4036	67	M	62.00	317.00	39	14	See ALT; Hx of elevated liver enzymes
7013	49	M	53.00	121.00	12	8	Hx of hepatitis
7023	40	F	50.00	105.00	15	10	See neutrophils

[a] Only markedly abnormal range given in table.
[b] Relative to start of therapy (Day 1).
[c] Subject died as a result of an adverse event(s) (see Table 37).
[d] Subject experienced an adverse event(s) of marked severity (see Table 36).
[e] Subject experienced a serious adverse event(s) other than death (see Table 39).
Hx=History

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Table 43: Subjects Who Had Treatment-Emergent Markedly Abnormal Laboratory Values: Subjects Evaluable for Safety (Continued)
(Protocol LOFBIV-PCAP-001)

Laboratory Test[a] Subject	Age	Sex	Admission Value	Abnormal Value	Study Day[b]	Duration of Therapy (Days)	Comments
Blood chemistry (continued)							
Elevated AST (SGOT) (continued) (>75 U/L)							
9008[c]	78	M	37.00	91.00	15	9	See creatinine
19011	20	F	20.00	88.00	12	7	See ALT; Hx of irritable bowel syndrome
21011	39	M	21.00	132.00	19	14	
25005[c,d]	56	F	32.00	160.00	7	3	See ALT; Hx of right nephrectomy and NIDDM
27004	70	F	30.00	91.00	22	14	
27010[c]	37	M	21.00	82.00	22	13	See ALT
28029[e]	64	M	51.00	352.00	2	1	See BUN, LDH, ALT
Elevated ALT (SGPT) (>75 U/L)							
3007	43	F	18.00	193.00	18	13	See AST; Hx of hepatitis
3048	61	M	39.00	82.00	15	14	
4010	47	M	41.00	150.00	22	17	Hx of Crohn's disease
4036	67	M	52.00	205.00	39	14	See AST; Hx of elevated liver enzymes
19011	20	F	31.00	80.00	12	7	See AST; Hx of irritable bowel syndrome
21011	39	M	22.00	217.00	19	14	
25005[c,d]	56	F	28.00	692.00	7	3	See AST; Hx of right nephrectomy and non-insulin dependent diabetes mellitus
27010[c]	37	M	19.00	142.00	22	13	See AST
28029[e]	64	M	42.00	145.00	2	1	See BUN, LDH, AST
28052	24	F	59.00	174.00	16	10	See neutrophils
51019[d,e]	84	F	39.00	82.00	5	2	
53011	23	M	12.00	105.00	16	10	
				77.00	37		
Elevated Creatinine (>1.5 mg/dL)							
9008[c]	78	M	2.00	3.70	15	9	See AST
Hematology							
Decreased Hemoglobin (<12 g/dL)							
4060[f]	63	M	11.70	8.20	19	29	
8012[d,e]	63	M	15.00	11.70	18	9	
21017	60	F	15.00	11.80	20	14	
28049	62	F	15.10	10.60	27	14	
28051	78	F	15.10	11.60	21	11	
Decreased Neutrophils (<1.0 x $10^3/\mu L$)							
1005	66	M	19.86	0.96	19	14	
3044	42	M	15.09	0.66	24	14	
3047[c,d,f]	29	M	4.47	0.99	11	9	
4039[f]	74	M	3.55	0.00	28	14	Hx of chronic lymphocytic leukemia
7023	40	F	3.89	0.99	15	10	See AST
28052	24	F	15.44	0.92	16	10	See ALT
28058	43	M	8.79	0.77	19	14	

[a] Only markedly abnormal range given in table.
[b] Relative to start of therapy (Day 1).
[c] Subject discontinued therapy due to an adverse event(s) (see Table 39).
[d] Subject experienced an adverse event(s) of marked severity (see Table 36).
[e] Subject died as a result of an adverse event(s) (see Table 37).
[f] Subject experienced a serious adverse event(s) other than death (see Table 38).
Hx=History

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Table 43: Subjects Who Had Treatment-Emergent Markedly Abnormal Laboratory Values: Subjects Evaluable for Safety (Continued)
(Protocol LOFBIV-PCAP-001)

Laboratory Test / Subject	Age	Sex	Admission Value	Abnormal Value	Study Day[b]	Duration of Therapy (Days)	Comments
Hematology (continued)							
Decreased Lymphocytes (<1.0x10³/μL)							
1051	75	M	0.90	0.46	20	14	See elevated glucose
1057	78	F	1.60	0.39	17	14	
4030[c,d]	79	M	0.90	0.42	16	14	Hx of chronic myelogenous leukemia and systemic lupus erythematosus
16007	77	F	0.91	0.58	14	9	
21002[c,d]	79	M	1.31	0.70	19	14	
28001	90	M	1.38	0.66	20	15	
28055[c,e]	42	F	2.13	0.91	23	14	See elevated glucose
28066	64	F	0.72	0.47	18	13	
51008	34	M	1.33	0.83	16	18	
51014	33	F	2.35	0.85	21	14	
53003	61	M	1.53	0.72	16	7	
55024	50	M	3.95	0.55	20	10	See elevated glucose
59005	62	M	1.52	0.66	11	11	Repeat value of 3.69 on Day 18
Decreased Platelet Count (75x10³/μL)							
4053[c,d]	71	M	309.00	19.00	21	14	

[a] Only markedly abnormal range given in table.
[b] Relative to start of therapy (Day 1).
[c] Subject experienced an adverse event(s) of marked severity (see Table 36).
[d] Subject experienced a serious adverse event(s) other than death (see Table 38).
[e] Subject died as a result of an adverse event(s) (see Table 37).
Hx=History

Applicant's Table 42, NDA 20-634 SE1-008, Vol. 3, p. 247

MO Comment: The case narratives for the patients experiencing markedly abnormal laboratory values were reviewed. The events that occurred are consistent with the adverse events described in the current labeling. The ability to infer association with study therapy is limited because the study was non-comparative and patients were frequently receiving multiple medications in addition to study therapy.

Other Safety Observations

Vital Signs

The Applicant analyzed population changes in vital signs that occurred from the Admission Visit to the Post-Therapy Visit. The changes noted, in general, reflect changes that would be expected with the successful treatment of an infection.

Safety Conclusions

In general, the adverse events that were reported in Study LOFBIV-PVCAP-001 are consistent with the adverse event profile of levofloxacin as described in the current product labeling. The most common adverse events observed were nausea, headache, insomnia, and diarrhea. Fifty-five patients experienced adverse events of marked severity; however, of these 55 patients, only 2 had adverse events that were considered drug-related (probably or definitely related to study therapy). The events experienced by these 2 subjects were an allergic reaction in one patient and liver function abnormalities in the other patient. Of the 37 patients who discontinued levofloxacin prematurely due to a treatment-emergent adverse event, only 8 of the patients had adverse events that were considered probably or definitely related to study therapy. Of the 8 drug-related adverse events leading to discontinuation, 2 events were of marked severity (the allergic reaction and abnormal liver functions discussed previously). The remainder of the drug-related adverse events were considered either mild or moderate in severity.

In Study LOFBIV-PCAP-001, the observed mortality rate was approximately 3%. This rate is consistent with other trials of levofloxacin in the treatment of CAP. Of the serious adverse events reported for the 20 patients who died, 5 were scored by the investigator as remotely related to Study Drug. The other 15 were considered by the investigator to have no relationship to study therapy. The laboratory abnormalities that were observed were consistent with what is described in the current product labeling. Study LOFBIV-PCAP-001 was a non-comparative trial and therefore, it is not possible to compare rates of abnormalities between treatment arms as a means of inferring association of AEs with study drug. However, the observed rates of abnormalities are within the range of what would be expected in this population and are consistent with the current product labeling.

Overall Study Conclusions

The results from the Study LOFBIV-PCAP-001 (a non-comparative study of levofloxacin to treat community-acquired pneumonia with an emphasis on studying patients with CAP due to PRSP) corroborates the results that were observed in the original NDA studies of levofloxacin in the treatment of CAP. Unfortunately, Study LOFBIV-PCAP-001 did not manage to enroll as many patients with CAP due to PRSP as was expected (before initiating the study), despite exceeding the planned enrollment of 600 patients. The efficacy results for patients with CAP due to *S. pneumoniae* was similar to the results observed in patients with CAP of all causes. This is similar to what was observed in the original NDA studies.

The 5 cases of CAP due to PRSP from Study LOFBIV-PCAP-001 are presented in the section of this documented titled Integrated Summary of Efficacy for LEVAQUIN for the Treatment of Community-Acquired Pneumonia due to PRSP. The 5 cases are discussed along with the other cases of CAP due to PRSP or PISP.

The Safety results from this non-comparative study of patients with pneumonia are similar to what was described for the original NDA studies. Similarly, the current product labeling adequately represents the adverse events that were observed in Study LOFBIV-PCAP-001.