CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-634/S-008, S-009
20-635/S-007, S-008

MEDICAL REVIEW

HFD590
TKITSCH
FEB 16 2000

Clinical and Statistical Review
NDA 20-634 SE1-008 and NDA 20-635 SE1-007

LEVAQUIN® (levofloxacin tablets and injection) for the Treatment of Community-Acquired Pneumonia due to Penicillin-Resistant *Streptococcus pneumoniae*

General Information
NDA 20-634 SE1-008 (tablet) and 20-635 SE1-007 (injection)

Applicant identification
The R.W. Johnson Pharmaceutical Research Institute
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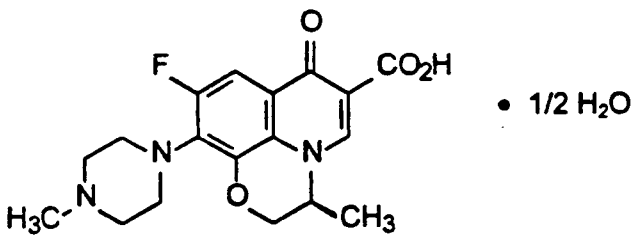
Submission/review dates
Date of submission: March 31,1999
CDER stamp date: April 1, 1999
Date review begun: August 30, 1999
Date review completed: February 1, 2000
User fee #: 3671

Drug identification
Generic name: levofloxacin
Trade name: LEVAQUIN® Tablets and Injection
Chemical name: (-)- (S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H- pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate
Chemical structure



Molecular formula: $C_{18}H_{20}FN_3O_4 \bullet ½ H_2O$
Molecular weight: 370.38

Pharmacologic category: Fluorinated carboxyquinolone
Dosage form: tablet or injection
Route of administration: oral (tablet) or intravenous (injection)

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MO Comment: With the Applicant's proposed elevation of PRSP to the first Microbiology list as shown above, the listing of PRSP in the second Microbiology list would be removed.

INDICATIONS AND USAGE

LEVAQUIN Tablets/Injection are indicated for the treatment of adults (≥ 18 years of age) with mild, moderate, and severe infections caused by susceptible strains of the designated microorganisms in the conditions listed below...

Community-acquired pneumonia due to *Staphylococcus aureus*, *Streptococcus pneumoniae* (including penicillin-resistant strains), *Haemophilus influenzae*, etc.

CLINICAL STUDIES

Community-Acquired Bacterial Pneumonia

Adult inpatients and outpatients with a diagnosis of community-acquired bacterial pneumonia were evaluated in two pivotal clinical studies. In the first study, 590 patients were enrolled in a prospective, multi-center, unblinded randomized trial comparing levofloxacin 500 mg once daily orally or intravenously for 7 to 14 days to ceftriaxone 1 to 2 grams intravenously once or in equally divided doses twice daily followed by cefuroxime axetil 500 mg orally twice daily for a total of 7 to 14 days. Patients assigned to treatment with the control regimen were allowed to receive erythromycin (or doxycycline if intolerant of erythromycin) if an infection due to atypical pathogens was suspected or proven. Clinical and microbiologic evaluations were performed during treatment, 5 to 7 days posttherapy, and 3 to 4 weeks posttherapy. Clinical success (cure plus improvement) with levofloxacin at 5 to 7 days posttherapy, the primary efficacy variable in this study, was superior (95%) to the control group (83%) [95% CI of -19,-6]. In the second study, 264 patients were enrolled in a prospective, multi-center, noncomparative trial of 500 mg levofloxacin administered orally or intravenously once daily for 7 to 14 days. Clinical success for clinically evaluable patients was 93%. For both studies, the clinical success rate in patients with atypical pneumonia due to *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila* were 96%, 96%, and 70%, respectively. Microbiologic eradication rates across both studies were as follows:

Pathogen	No. Pathogens	Microbiologic Eradication Rate (%)
H. influenzae	55	98
S. pneumoniae	83	95
S. aureus	17	88
M. catarrhalis	18	94
H. parainfluenzae	19	95
K. pneumoniae	10	100.0

Additional studies were initiated to evaluate the utility of LEVAQUIN in community-acquired pneumonia due to *S. pneumoniae*, with particular interest in penicillin-resistant strains. In addition to the studies previously discuss, inpatients and outpatients with mild to severe community-acquired pneumonia were evaluated in six additional clinical studies; two open labeled randomized studies, one double blind study, and three open label non-comparative studies.

Across these studies, 250 clinical and microbiologically evaluable patients had documented infections due to *S. pneumoniae*. Of these 250 infections due to *S. pneumonia*, 99 patients had severe* community-acquired pneumonia. Of these 99 severe cases, 55 were bacteremic.

The overall clinical success (cure plus improved) and microbiologic eradication with levofloxacin for infections due to *S. pneumoniae* was as follows:

Penicillin Susceptibility of *S. pneumoniae*	No. Patients	Clinical Success	Microbiologic Eradication
Penicillin-resistant (Penicillin MIC —2 µg/ml)			
All patients	15	15/15 (100%)	15/15 (100%)
Severe	6	6/6 (100%)	6/6 (100%)
Bacteremic	6	6/6 (100%)	6/6 (100%)
Penicillin-intermediate and –susceptible (Penicillin MIC < 2 µg/ml)			
All patients	201	196/201 (98%)	196/201 (98%)
Severe	79	76/79 (96%)	76/79 (96%)
Bacteremic	35	35/35 (100%)	35/35 (100%)
Unknown penicillin susceptibility			
All patients	34	34/34 (100%)	34/34 (100%)
Severe	14	14/14 (100%)	14/14 (100%)
Bacteremic	14	14/14 (100%)	14/14 (100%)
Total			
All patients	250	245/250 (98%)	245/250 (98%)
Severe	99	96/99 (97%)	96/98 (97%)
Bacteremic	55	55/55 (100%)	55/55 (100%)

* Severe included at least one of the following: bacteremia, diastolic hypotension, use of vasopressors, altered mental status, intubation, mechanical ventilation or baseline respiratory rate greater than 28/min.

Regulatory Background

NDAs 20-634 (LEVAQUIN® Tablets) and 20-635 (LEVAQUIN® Injection) were approved on December 20, 1996. Included among the approved indications was community-acquired pneumonia (CAP) caused by LEVAQUIN® susceptible strains of *Streptococcus pneumoniae*. In the clinical studies submitted in the original NDA, there was insufficient experience with CAP due to PRSP to warrant the inclusion of PRSP among the indicated pathogens in the CAP indication. Currently there is no available therapy specifically approved for the treatment of CAP due to PRSP. In the current submission (NDA 20-634 SE1-008 and NDA 20-635 SE1-007), the Applicant presents data in support of the efficacy and safety of LEVAQUIN® in the treatment of patients with CAP caused by PRSP.

On several occasions, RWJPRI has discussed with the Agency their plan to provide additional data on the activity of LEVAQUIN® in the treatment of CAP due to [redacted] As part of these discussions the Agency conveyed the following recommendations to the sponsor regarding the type of data and an estimate of the

quantity of data that would likely be needed to support a claim for efficacy and safety in the treatment of CAP due to PRSP:

- The need to demonstrate clinical (as opposed to *in vitro)* data of efficacy in the treatment of PRSP
- 15-20 clinical cases of CAP caused by PRSP
- If the sponsor chose to submit only their 13 cases of CAP due to PRSP, the sNDA would likely be the subject of an Advisory Committee Meeting
- Isolates from others serious infections (e.g. meningitis, nosocomial pneumonia, or bacteremia) would also be acceptable
- A penicillin MIC of 2 mcg/mL or greater would be used to identify PRSP
- Supportive data from intermediately resistant, and susceptible organisms would also be needed

The Applicant's proposed filing strategy was to use one non-comparative phase 3 study, LOFBIV-PCAP-001 "A Noncomparative, Multicenter Study to Evaluate the Safety and Efficacy of Levofloxacin 500mg Once-Daily in the Treatment of Community-Acquired Pneumonia in Adults," as the primary study in support of the claim for PRSP in CAP. This study included 5 documented cases of CAP due to PRSP. The Applicant proposed pooling this data with the efficacy data for other patients with CAP due to PRSP identified from 7 other clinical studies of patients with CAP. The 8 studies from which the patients with CAP due to PRSP or PISP were drawn are enumerated in Table 1.

> **MO Comment:** During the review of NDA 20-634 SE1-008, the Applicant identified additional patients with CAP due to PRSP and PISP from their on-going clinical studies. These additional patients were submitted in an amendment to the sNDA (dated September 20, 1999). Table 1 below provides the number of patients with CAP due to PRSP or PISP from each of the studies, including the additional patients that were submitted in the amendment of September 20, 1999.

Table 1. Source of Patients with Community-Acquired Pneumonia due to Penicillin-Resistant *S. pneumoniae* (PRSP) or Penicillin-Intermediate *S. pneumoniae* (PISP)

Study No. (Location)	Design	Regimen (Duration)	Number of CAP Patients with PRSP	Number of CAP Patients with PISP
Original NDA Studies				
K90-071 (USA)	open label, randomized, comparative	Levo IV or PO vs Ceftriaxone IV or Cefuroxime PO +/- Erythromycin or Doxycycline (7-14 days)	1 (levo) 0 (cef)	4 (levo) 4 (cef)
M92-075 (USA)	open label, non-comparative	Levo IV or PO (7-14 days)	2 (levo)	3 (levo)
LOFBIV-MULT-001 (USA)	open label, non-comparative	Levo IV or PO (7-14 days)	1 (levo)	0 (levo)
Additional Studies				
LOFBIV-PCAP-001[a] (USA & Canada)	open label, non-comparative	Levo IV or PO (7-14 days)	5 (levo)	26 (levo)
CAPSS-018 (USA)	open label, randomized, comparative (non-IND)	Levo IV or PO vs Ceftriaxone and Erythromycin (IV) to Amoxicillin/Clav and Clarithromycin (7-14 days)	0 (levo) 3 (cef)	1 (levo) 4 (cef)
CAPSS-043 (USA)	open label, non-comparative (non-IND)	Levo IV or PO (7-14 days)	6 (levo)	14 (levo)
CAPSS-056 (USA)	open label, randomized, comparative (non-IND)	Levo IV or PO vs Ceftriaxone/ Azithromycin(PO) (10 days)	2 (levo) 1 (cef/az)	1 (levo) 1 (cef/az)
FF/93/355/02 (Europe, South Africa, Argentina)	double-blind, randomized, comparative	Levo PO vs Amox/Clav (7-10 days)	1 (levo) 0 (am/cl)	0 (levo) 0 (am/cl)
TOTALS			18 (levo) 4 (comp)	49 (levo) 9 (comp)

[a] Study initiated specifically to study resistant pneumococci in CAP

The 18 cases of levofloxacin-treated patients with CAP due to PRSP and 49 patients with CAP due to PISP represent the total number of cases of CAP due to penicillin non-susceptible *S. pneumoniae* (PNSSP) in this application. These cases are reviewed as a group in the Integrated Summary of Efficacy for LEVAQUIN® for the Treatment of CAP due to PRSP (p. 95 of this document).

Scientific Background

Since the original descriptions of penicillin-resistant *Streptococcus pneumoniae* in the 1960s, the prevalence and geographic distribution of PRSP has been increasing.[1,2] While there is considerable variation in rates of resistance in different at-risk-populations and geographic

locations, rates of isolation of PNSSP above 20% and penicillin-resistance (penicillin MIC ≥ 2 mcg/mL) above 3% are not infrequently reported in the literature.[1, 3, 4] These studies have also shown significant degrees of cross-resistance of PNSSP to other antimicrobials including cephalosporins, macrolides, trimethoprim-sulfamethoxazole, and tetracycline.[4] However, an association between penicillin-resistance and significant rates of fluoroquinolone resistance in *S. pneumoniae* has typically not been demonstrated.

More recently, a publication from the Canadian Bacterial Surveillance Network reported on the prevalence of pneumococci with reduced susceptibility to fluoroquinolones in Canada. They examined the first 20 consecutive clinical isolates and all isolates from sterile sites from each of their member institutions during each reporting period. The authors report the prevalence of pneumococci with reduced susceptibility to fluoroquinolones as 1.7% (2.9% in the adult population) for the years 1997 and 1998 combined (fluoroquinolone resistance was defined as an MIC ≥ 4 mcg/mL for ciprofloxacin).[5] This level of resistance represents an increase from the 0% rate of fluoroquinolone resistance observed during the years 1988 and 1993. The report also found that pneumococci with reduced susceptibility to fluoroquinolones were more likely to be resistant to other antimicrobial agents including the following: penicillin, relative risk (RR) of 5 (95% CI 2.5 to 10); trimethoprim-sulfamethoxazole, RR = 3.9 (95% CI 2.2 to 7.0); tetracycline, RR = 2.7 (95% CI 1.2 to 5.8).[5]

MO Comment: Continuing studies of the evolving resistance profile of DRSP will help to track trends in the rates of resistance to penicillin, fluoroquinolones, other antimicrobials, and patterns of cross-resistance.

Regulatory Guidance for the Indication of Community Acquired Pneumonia

The information provided by the IDSA/FDA guidelines (1992), the Points-to-Consider Document, and the recent Agency Draft Guidance for CAP are briefly summarized below.

IDSA/FDA Guidelines

The IDSA/FDA guidelines recommend that the patients included in clinical trials of antimicrobial agents for the treatment of CAP should meet the following minimal diagnostic criteria. Patients must have clinical signs and symptoms of bacterial pneumonia and radiographic or other laboratory evidence that supports the diagnosis of CAP. Suitable specimens from the respiratory tract should be obtained for microbiological analysis. In addition, blood cultures should be obtained on all patients. The guidelines state that a microbiologic diagnosis should be based upon the identification of a pathogen from an

appropriate microbiologic specimen. For some microbes, diagnosis by non-culture techniques is acceptable.

The IDSA/FDA Guidelines state in part the following regarding the conduct of the clinical study. Patients should be monitored while on study for signs of response to therapy. An assessment within 5-7 days after completion of therapy is recommended. In order to be evaluable, patients should have received at least 5 days of therapy and must have taken at least 80% or more of the prescribed medication. The recommended categories for clinical response are clinical cure, clinical failure, or indeterminate. The recommended microbiological response categories include eradication, presumed eradication, persistence, presumed persistence, relapse, colonization, superinfection, and indeterminate.

Points-to-Consider

The Points to Consider (PTC) document recommends one statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product and one open trial corroborating the findings of the controlled trial. Preferably the trials should be conducted in the United States. The study design should incorporate rigid case definitions and specific entry criteria. The primary effectiveness endpoints should be clinical and radiographic endpoints. Microbiological evaluations should also be performed. The data analysis should evaluate outcomes in the clinically evaluable population and also in the clinically and microbiologically evaluable population. The analysis of the data should also generally confirm (by means of comparing the direction of the independent 95% confidence intervals) the successful outcome rates for the clinically evaluable and clinically and microbiologically evaluable population. The analysis should also establish a correlation between clinical cure and bacterial eradication in both of the aforementioned evaluable populations.

The PTC document also recommends that the open trial should have at least 2 investigators. It should also be similar to the adequate and well-controlled multicenter trial with regards to patient demographics, disease severity, exclusion/inclusion criteria, evaluability criteria, and the effectiveness parameters that are evaluated. The results from the second study should corroborate the results of the adequate and well-controlled trial.

Agency Draft Guidance on CAP

More recently CDER has produced a Draft Guidance Document describing the design of studies intended to evaluate the safety and efficacy of antimicrobials for the treatment of

community-acquired pneumonia (CAP). This Draft Guidance Document states that in order to be eligible for study, patients should have a combination of clinical signs and symptoms and radiographic findings of pneumonia. A thorough microbiological evaluation should be performed on all patients in search of the microbial etiology for their pneumonia. In general, studies should exclude patients with medical or pulmonary conditions that would impair their ability to respond to antimicrobial therapy for their pneumonia.

Regarding evaluability, the Draft Guidance Document recommends that patients be required to receive at least 48-72 hours of therapy before the clinical assessment for failure can be made and at least 5 days of therapy with a minimum of 80% compliance before an assessment of a favorable outcome can be assigned. Patient evaluations at the following time points are described: pre-therapy, on-therapy, end-of-therapy, early post-therapy, and test-of-cure (TOC) visits. The Draft Guidance Document recommends that the TOC visit occur between 7 days and 3 weeks after the completion of treatment. The half-life of the drug under study should also be considered when specifying the timing of the TOC visit.

The Draft Guidance Document specifies that clinical outcome should be the primary efficacy variable for the indication of CAP and classifies clinical outcome as clinical cure or clinical failure. The categories of microbiological response that are described are the following: eradication, presumed eradication, persistence, presumed persistence, superinfection, recurrence, new infection, and colonization.

MO Comment: The study that was undertaken specifically to gather additional clinical data on CAP due to PRSP (Study LOFBIV-PCAP-001) was performed under the levofloxacin INDs. This study, in general, agrees with the aforementioned documents that provide guidance on the conduct of studies to evaluate antimicrobial products for the treatment of CAP. As noted in Table 1, several of the studies from which patients with CAP due to PRSP or PISP were drawn from were non-IND studies. In some of these studies, the timing of the test-of-cure visit differed from the above guidelines. Therefore, specific criteria for evaluating the patients that were derived from these studies were developed for the analysis of patients with CAP due to PRSP or PISP. These criteria and analyses are further described in the section of this document titled Integrated Summary of Efficacy for LEVAQUIN® for the Treatment of CAP due to PRSP.

CLINICAL STUDIES

The Applicant identified all patients with CAP due to PRSP or PISP from all clinical efficacy trials of levofloxacin for the treatment of CAP performed by RWJPRI, Ortho McNeil Pharmaceutical, Inc (an RWJPRI affiliate), Hoescht Marion Roussel (HMR, now Aventis, an RWJPRI partner), and Daiichi Pharmaceuticals (an RWJPRI partner). Primary data was provided for all patients with CAP due to PRSP or PISP for review. The company did not knowingly exclude any CAP trials or any patients with CAP due to PRSP or PISP. These 8 trials include the following:

- three previously submitted CAP studies (the original NDA studies supporting the CAP indication) K90-071, M92-075, and LOFBIV-MULT-001
- one non-comparative study specifically designed to gather clinical data on the safety and efficacy of levofloxacin for the treatment of penicillin-resistant and ——— *S. pneumoniae* (Study LOFBIV-PCAP-001)
- three on-going non-IND studies of adult patients with CAP (CAPSS-018, CAPSS-043, and CAPSS-056)
- one double-blind, randomized, comparative international CAP study conducted by Hoescht Marion Roussel

MO Comment: The trials that comprised the basis for this application were discussed with the Division in several teleconferences that took place during the year prior to the submission of this sNDA. Prior to the submission of this sNDA, most of the PRSP and PISP cases were presented at the 65th meeting of the Anti-Infective Drug Products Advisory Committee, October 15th and 16th, 1998.

The review of Study LOFBIV-PCAP-001, the study designed specifically to evaluate the safety and efficacy of levofloxacin in the treatment of CAP due to PRSP, will be described first. Then an Integrated Summary of Efficacy for levofloxacin for all of the patients with PRSP or PISP will be presented.

MO Comment: Note that the results presented for the original NDA clinical studies (K90-071, M92-075, and LOFBIV-MULT-001) are based upon Dr. Karen Frank's Medical Officer's Review of the Original NDA, dated December 20, 19[redacted].

MO Comment: Note that the number of patients with CAP due to PRSP or PISP contributed by each of the studies varies across the 8 studies. One study contributed only one patient to the group of patients with CAP due to either PRSP or PISP.

MO Comment: Because patients with CAP due to PRSP or PISP were drawn from across 8 studies and there were some variations in study design, all of the cases were reviewed at the level of the case report forms. Further descriptions of the analysis methods are provided in the section of this document entitled Integrated Summary of Efficacy for LEVAQUIN® for the Treatment of CAP due to PRSP.

REVIEW OF STUDY LOFBIV-PCAP-001

Background to Study

This study was originally designed to gain additional experience with levofloxacin in the treatment of CAP due to *L. pneumophila* and penicillin- and ———resistant *S. pneumoniae*. The Study was initiated in October 1996. Levofloxacin was approved in December of 1996 and included among its indications was CAP, including CAP due to *L. pneumophila*. Therefore, the focus of the study shifted to gathering additional clinical data on CAP due to penicillin- and r ———esistant *S. pneumoniae*.

Objective/Rationale

The objective of the study was to gain additional clinical experience with levofloxacin in the treatment of CAP due to penicillin- and ———resistant strains of *S. pneumoniae*.

MO Comment: The MO reviewed a randomly selected sample of 10% of the study population prepared by the Agency's Statistical Reviewer to determine whether the Applicant's assessment's of evaluability and outcomes could be accepted for Study LOFBIV-PCAP-001. The MO reviewed study eligibility; assessments at Admission, On-Therapy, Post-Therapy, and Post-Study; concurrent medications used; reasons for study discontinuation/withdrawal; determination of evaluability; and timing of the Post-Therapy and Post-Study assessments. The MO disagreed with some of the assessments for two patients. Pt. No. 6004 was scored by the Applicant as clinical relapse and Microbiologically unknown at Post-Study. The MO scored this patient as clinical relapse and microbiologic relapse based on the clinical response of relapse in the absence of an available culture. Pt. No. 52013 was scored by the Applicant as clinically and microbiologically unevaluable at the Post-Study assessment. The MO scored the patient as clinical relapse and microbiological presumed relapse (no culture performed) because the patient received ofloxacin between the Post-Therapy and Post-Study visits for "continuing symptoms." The results of the review of the 10% random sample were discussed with the Statistical Reviewer. The small number of changes to the response classifications limited to the Post-Study assessment were unlikely to influence the overall conclusions from the Applicant's Efficacy analysis regarding outcomes.

An additional concern that the MO addressed is the evaluability criteria regarding the timing of Post-Therapy assessments. In the Applicant's protocol-specified evaluability criteria, a patient's Post-Therapy assessment 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 the MOs concerns regarding the timing of the Post-Therapy and Post-Study assessments, the MO requested that the Applicant re-analyze the efficacy data using the strict protocol-specified windows of 5-7 days for the Post-Therapy assessment and 21-28 days for the Post-Study assessment. This re-analysis forms the basis of the MO Efficacy analysis. In addition to the strict windows for Post-Therapy and Post-Study evaluability, any specific patients for whom the MO disagreed with the Applicant's evaluability or response assignments are reclassified and included in the MO Efficacy analysis. These patients are identified within the following portion of the review examining the Applicant's Efficacy analysis. Within this review the Applicant's Efficacy analysis will be presented first, then the MO Efficacy Analysis results will follow.

Design

LOFBIV-PCAP-001 was a non-comparative, multicenter study of levofloxacin for the treatment of CAP in adults. The study involved 33 study centers located in the United States (n=25) and Canada (n=8). The planned enrollment for the study was approximately 600 patients (inpatients and outpatients) who were at least 18 years of age and who had CAP. Patients were assigned to receive 500 mg of levofloxacin, either intravenously or orally once daily for 7 to 14 days. The decision as to whether a subject was to be started on either intravenous or oral levofloxacin was made by the investigator. Subjects started on intravenous levofloxacin could be switched to oral levofloxacin at any time during the study when deemed appropriate by the investigator.

The efficacy analyses for the study included the following:

- clinical response (assessed as cured, improved, failure, or unable to evaluate) at Post-Therapy
- microbiologic response by patient at Post-Therapy (assessed as eradicated, persisted, or unknown)
- microbiologic response by pathogen at Post-Therapy (assessed as eradicated, presumed eradicated, persisted, presumed persisted, persisted with acquisition of resistance, and unknown)

Clinical response at Post-Therapy and microbiologic response at Post-Therapy in the group of subjects evaluable for microbiologic efficacy represented the Applicant's protocol defined primary efficacy variables for Study LOFBIV-PCAP-001.

Safety was evaluated by examining the incidence and severity (mild, moderate, or marked) of treatment-emergent adverse events; review of laboratory tests of hematology, blood chemistry, and urinalysis; and evaluation of vital sign measurements.

Study Overview

Patients were eligible for study enrollment if they met the following inclusion and exclusion criteria.

Note: The Arial font is used to represent text copied from the Applicant's NDA

Inclusion Criteria

Male and female subjects were eligible for enrollment into the study if they:

- were at least age 18 years of age;
- had a clinical picture consistent with pneumonia, including:
  - clinical signs and symptoms of pneumonia, including at least 2 of the following:
    - fever (oral temperature ≥38°C/100.4°F or rectal temperature ≥39°C/102.2°F);
    - cough;
    - chest pain;
    - shortness of breath;
    - evidence of pulmonary consolidation on physical examination (rales on auscultation, dullness to percussion, or egophony);
  - radiographic evidence of infiltrate compatible with acute infection;
  - production of sputum;
    Note: sputum production was not an absolute requirement for a subject to be enrolled in this study. [The Applicant notes] that not all subjects with community acquired pneumonia are capable of generating a "good" sputum for purposes of gram stain and culture (that is, specimens showing >25 PMNs and <10 squamous epithelial cells per low power field). All reasonable attempts to obtain a reliable sputum specimen must be made by the investigator and study staff. At a minimum, ultrasonic saline-induced specimens should be attempted for all subjects. Procedures such as bronchoscopy with bronchoalveolar lavage or brushings should be considered for subjects requiring hospitalization.

- had received previous antimicrobial therapy as long as the previous therapy duration was 24 hours or less.
- were female and:
  - were postmenopausal for at least one year, surgically sterile; or using an acceptable method of contraception and agreed to continue with the same method during the study;
  - if of childbearing potential, had maintained a normal menstrual pattern within one month prior to study entry and had a negative pregnancy test immediately prior to study entry;
- provided written informed consent after the nature of the study had been fully explained.

Exclusion Criteria

Subjects were not to be enrolled into the study if it was determined upon pre-study examination that they:

- had an infection due to organisms known to be resistant to levofloxacin prior to study entry;
- had a previous allergic or serious adverse reaction to any member of the quinolone class of antimicrobials;
- had a diagnosis of cystic fibrosis or pulmonary infection due to a fungus, parasite, virus, or mycobacteria;
- had renal insufficiency (calculated creatinine clearance <20 mL/min);
- were neutropenic (<500 PMNs/mm^3);
- had a high probability of death during the course of the study;
- had an infection acquired in a hospital (>48 hours after hospital admission and <7 days after hospital discharge);
- required any nonstudy systemic antimicrobial regimen (subjects who contracted bacterial pneumonia while on antifungals or antivirals were eligible for enrollment);
- had a history of seizure disorder or were at significant risk for seizures (recent severe head trauma, alcohol withdrawal, etc.);
- had the presence of an unstable psychiatric disorder;
- had empyema;
- were pregnant or nursing;
- were exposed to any investigational agent within 30 days of entry;
- were treated previously under this protocol;

- were known to be HIV positive with CD4 counts <200 cells/mm^3.

MO Comment: The exclusion of patients with isolates known to be resistant to levofloxacin prior to study entry might result in selective underestimation of the proportion of isolates that are resistant to levofloxacin or that exhibit cross-resistance to both levofloxacin and penicillin.

Drug Dosage

Participants were given levofloxacin 500 mg daily either as a single oral tablet or as a one-hour intravenous infusion. The route of administration was determined by the investigator. Patients on intravenous therapy could be switched to oral therapy at any time. The specified duration of therapy was 7-14 days. Permission could be sought by the investigator to extend therapy beyond 14 days if medically necessary. In patients with a creatinine clearance of 20-49 mL/min, a 500 mg loading dose was given followed by 250 mg q24h. Patients with a creatinine clearance <20 mL/min were excluded.

Treatment compliance was monitored by recording the start and stop dates for all doses of study drug and the total number of doses received. For patients receiving oral therapy, compliance was measured by counting unused study drug in the medication containers returned by subjects to the investigators.

Administration of non-study antibacterials was prohibited during study. The use of other concomitant medications during the study was to be kept to a minimum. Use of antacids containing magnesium and aluminum hydroxide and use of other vitamins and mineral supplements was strongly discouraged because these compounds may decrease the bioavailability of quinolones. If antacids were necessary, calcium carbonate antacids were preferred and were not to be administered within 2 hours of oral levofloxacin administration.

MO comment: Patients who received non-protocol antibacterials were considered treatment failures if the antibacterial was used to treat disease related to the patient's community-acquired pneumonia. Patients who received non-protocol antimicrobials for documented alternative conditions unrelated to the patient's underlying CAP, were considered non-evaluable.

Study Evaluations

The protocol specified study evaluations included a total of 4 visits (including the Admission visit). Patients were to be evaluated at the time of study admission. The next visit was an On-Therapy assessment scheduled for Study Days 2-4. Following the completion of therapy, a Post-Therapy evaluation was scheduled for 5-7 days after completion of therapy and a Post-Study evaluation was scheduled for 21-28 days after the completion of therapy. The study procedures scheduled for each of these visits are illustrated in Table 2.

Table 2. Schedule of Study Procedures for Protocol LOFBIV-PCAP-001

Procedures	Admission	On-Therapy Evaluation (Study Day 2-4)	Post-Therapy Evaluation (5-7 Days After Completion of Therapy)[a]	Post-Study Evaluation (21-28 Days After Completion of Therapy)
Pertinent medical history	X			
Pertinent physical including vital signs	X		X	X[b]
Evaluation of signs and symptoms	X	X	X	X[b]
Chest X-ray (PA & lateral)	X		X	X[c]
Hematology	X		X	
Serum chemistry	X		X	
Serology for atypical pathogens	X		X	X
Urinalysis	X		X	
Sputum culture and gram stain	X		X[d]	X[e]
Nasopharyngeal swab for *Chlamydia* culture	X		X	X[b]
Blood cultures	X[f]	X[g]	X[g]	
Sputum culture for *L. pneumophila*	X		X[i]	X[e]
Pregnancy test[h]	X		X	
Urinary antigen test for *L. pneumophila*	X			
Assess adverse events		X	X	

[a] Or upon early withdrawal.
[b] For subjects with a successful clinical outcome (cured or improved) at the Post-Therapy visit or for subjects who withdraw prior to the Post-Therapy visit due to any reason other than clinical failure.
[c] Required of those subjects with a significant persistent infiltrate at the Post-Therapy evaluation or relapse
[d] If subject continues to produce sputum.
[e] If relapse or re-infection is suspected.
[f] For subjects ill enough to be hospitalized.
[g] If initially positive.
[h] If of childbearing potential.
[i] If initially positive. If Admission results not known, repeat at Post-Therapy.
(Adapted from Applicant's Table 1, NDA 20-634 SE-008, Vol. 25.3, p. 129)

The following additional details regarding the study procedures scheduled at each of the study assessments were also stated. The Admission microbiological specimens were to be obtained within 48 hours prior to initiation of study drug. At the On-Therapy visit, patients who had not yet recovered or had resistant organisms were allowed to continue on the study drug provided there was no clinical deterioration. At the Post-Therapy visit, clinical and radiologic findings were compared to those on Admission. At the Post-Study visit, a

patient's clinical and radiologic findings were compared to those at the Post-Therapy visit. Any antimicrobial therapy received between the Post-Therapy and Post-Study visits was to be noted and the reason(s) for therapy were to be documented.

MO Comment: Up to 24 hours of appropriate antibiotic therapy was permitted prior to study enrollment. To assess the extent to which patients with CAP due to PRSP or PISP were exposed to antibiotics for up to 24 hours before study enrollment, the number of patients meeting this criteria is enumerated in the Integrated Summary of Efficacy for LEVAQUIN for the Treatment of CAP due to PRSP (p. 95 of this document).

Susceptibility testing to levofloxacin, penicillin, and ——— was to be performed for all organisms isolated. NCCLS methods were to be used in the performance of these procedures. Levofloxacin susceptibility using diffusion techniques was interpreted as follows (Table 3.).

Table 3. Interpretation of susceptibility testing for levofloxacin and ———

Inhibition Zone Diameter (mm)	
Interpretation	Levofloxacin
Susceptible	≥17 mm
Intermediate	14-16 mm
Resistant	≤13 mm

Minimum inhibitory concentrations (MICs) for levofloxacin, penicillin, and ——— were determined by a reference laboratory for all typical aerobic pathogens. The protocol specified MIC breakpoints were used in determining susceptibility (Table 4).

Table 4. Interpretation of MIC testing for Levofloxacin ——— and Penicillin

MIC (µg/mL)		
Interpretation	Levofloxacin	Penicillin
Susceptible	≤2	≤0.06
Intermediate	4	0.1-1
Resistant	≥8	≥2

MO Comment: The levofloxacin susceptibility breakpoints used in the protocol are consistent with the breakpoints listed in the approved product labeling. The MIC criteria used to identify PSSP, PISP, and PRSP are consistent with the NCCLS specified criteria.

The following case definitions for atypical pathogens causing pneumonia were specified in the protocol. Testing for atypical pathogens was performed at the VA Medical Center, Pittsburgh, PA and State University of New York at Brooklyn.

- **Legionella case definition:** Clinical and radiologic evidence of pneumonia in association with one or more of the following: (1) IgM Elisa- a four-fold increase in titer between the acute (admission) and convalescent (posttherapy or poststudy) serology to ≥1:256; (2) IgG Elisa- a four-fold increase in titer between the acute and convalescent serology to ≥1:256; (3) a positive culture for *L. pneumophila* or other Legionella species from sputum or other respiratory fluid or material; (4) positive urine antigen; (5) a positive direct fluorescence antibody (DFA) test on sputum, bronchial lavage or tracheal aspirate.
- ***C. pneumoniae* case definition:** Clinical and radiologic evidence of pneumonia in association with one or more of the following: (1) a single microimmunofluorescence IgM titer ≥1:32 or a four-fold increase in IgM titer between the acute and convalescent serology; (2) a single microimmunofluorescence IgG titer >1:512 between the acute and convalescent serology.
- **Mycoplasma case definition:** Clinical and radiologic evidence of pneumonia in association with one or more of the following: (1) a single IgM Elisa ≥1:16 or a four-fold increase or decrease in titer between the acute and convalescent serology; (2) a single IgG Elisa ≥1:128 or a four-fold increase or decrease in titer between the acute and convalescent serology.

Clinical Evaluations

At each of the 4 scheduled assessment visits, clinical symptoms of community-acquired pneumonia including fever, chills, pleuritic chest pain, shortness of breath, cough, sputum production, and purulent sputum were to be noted by the investigator as present or absent. Clinical signs of pneumonia demonstrated on clinical examination of the chest (diminished breath sounds, rales, egophony, dullness to percussion, rhonchi, and wheezing) were to be graded by the investigator as none, mild, moderate, or severe at each of the 4 visits. Findings on chest X-rays performed at Admission and Post-Therapy were to be recorded.

Clinical response was evaluated at the Post-Therapy visit by the investigator using a rating scale of cured, improved, failure, or unable to evaluate. These assessments were made by comparing the clinical assessment of the patient at the Post-Therapy visit to the assessment at

the Admission visit. A second assessment of clinical response was also performed at the Post-Study visit. Clinical status at the Post-Study visit was compared to the patient's clinical status at the Post-Therapy assessment. At the Post-Study visit, patients previously determined to be cured or improved could be judged as cured, improved, clinical relapse, or unable to evaluate.

Efficacy Criteria

Clinical Response, Post-Therapy

Clinical response was assessed by the investigator as cured, improved, failure, or unable to evaluate at the Post-Therapy visit (5 to 7 days after the completion of therapy). The assessments of clinical response were defined as follows:

- **Cure:** Resolution of signs and symptoms associated with active infection along with improvement or stabilization in chest X-ray findings.
- **Improved:** Partial resolution of clinical signs and symptoms so that no further antibiotic therapy was required along with improvement or stabilization in chest X-ray findings.

  [For subjects who completed the study, an evaluation of "improved" indicated that, although the subject's clinical status had not completely returned to pre-infection baseline, the infectious process had been controlled and no further antibiotics were required.

  For subjects who discontinued prematurely from the study for reasons other than clinical failure (such as death, adverse event, personal preference, etc.), an evaluation of "improved" indicated that the subject's infectious process was resolving and that, if the subject had continued for the duration of the study, there was every expectation a successful outcome would have been achieved.]
- **Failure:** Inadequate response to therapy so that additional antibiotic therapy for treatment of the original infection was required.
- **Unable to Evaluate:** Unable to determine a response because the subject was not evaluated after study Day 1 (i.e. lost to follow-up).

Clinical Response, Post-Study

A Post-Study clinical response was to be assigned for all subjects who were cured or improved at the Post-Therapy visit. The investigator was to determine the Post-Study clinical response of these subjects as follows:

- **Cure:** Resolution of signs and symptoms associated with an active infection, along with improvement or stabilization in chest X-ray findings.

- **Improved:** Continued incomplete resolution of signs and symptoms with no deterioration or relapse during the follow-up period and no requirement for additional antimicrobial therapy.

- **Clinical Relapse:** Resolution or improvement of signs and symptoms at the Post-Therapy evaluation with the reappearance or deterioration of signs and symptoms of the infection.

- **Unable to Evaluate:** Unable to determine response because the subject was not evaluated after the Post-Therapy visit. In addition, subjects who had not relapsed but who received an effective antimicrobial therapy for an unrelated infection between the Post-Therapy and Post-Study visits also were categorized as unable to evaluate (definition developed subsequent to the protocol).

Microbiologic Response

Microbiologic response to treatment at the Post-Therapy assessment was evaluated in terms of both by patient and by pathogen eradication rates. Each organism isolated was assigned a pathogenic classification according to the following criteria:

- **Original Pathogen:** Organism(s) identified from appropriately obtained specimens responsible for admission diagnosis of pneumonia.

- **Superinfector:** Organism(s) other than that (those) identified at Admission, identified from any site while on-therapy through to, and including, the Post-Therapy specimens, associated with emergence or worsening of clinical signs and symptoms and laboratory evidence of active infection that required antimicrobial therapy.

- **Colonizer:** Organism, identified at any visit from any site, not considered pathogenic, not associated with signs or symptoms of active infection, and not requiring antimicrobial therapy.

- **New Infector:** Organism(s), other than that (those) identified at Admission, obtained after the Post-Therapy visit and associated with emergence or worsening of clinical signs and symptoms and/or laboratory evidence of active infection, and requiring antimicrobial therapy.

Microbiologic Response for Respiratory Pathogens, Post-Therapy

The microbiologic response at Post-Therapy for respiratory pathogens isolated at Admission was assigned to one of the microbiologic response categories based on the Post-Therapy culture results according to the following criteria:

- **Eradicated:** Absence of the admission pathogen in the Post-Therapy culture.

- **Presumed Eradicated:** Presumed absence of the admission pathogen due to substantial improvement of infection so that no material for culture was available.
- **Persisted:** Continued presence of the admission pathogen in the Post-Therapy culture.
- **Presumed Persisted:** Presumed presence of the admission pathogen at Post-Therapy for subjects with clinical failure for whom no test-of-cure culture was taken or for whom the culture was taken while the subject was on antibiotics.
- **Persisted with acquisition of resistance:** Continued presence of the admission pathogen in the Post-Therapy respiratory culture with documented acquisition of resistance.
- **Unknown:** No test-of-cure culture available because the subject was either lost to follow-up or the culture was obtained while the subject was on antibiotics (except as noted above under presumed persisted).

Microbiologic Response for Respiratory Pathogens, Post-Study

Patients who 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 microbiologic response for each admission pathogen was based on Post-Study microbiologic culture data and was assessed according to the following criteria:

- **Eradicated:** A continued absence of the admission pathogen at the Post-Study evaluation.
- **Presumed eradicated:** Presumed absence of the admission pathogen due to substantial improvement of infection so that no material for culture was available (definition developed subsequent to the protocol).
- **Microbiologic Relapse:** Reappearance of an organism identical to that isolated at admission, isolated from the site of the admission infection at the Post-Study visit following eradication or presumed eradication of the original pathogen at the Post-Therapy evaluation. As a working definition, this classification also includes subjects who were considered a clinical relapse but for whom no culture results were available (presumed microbiologic relapse).
- **Unknown:** No Post-Study culture results were available for subjects who were lost to follow-up. As a working definition, this classification also includes pathogens considered as eradicated or presumed eradicated from subjects who had taken a course of potentially effective antibiotics between the Post-Therapy and Post-Study visits.

MO Comment: Patients with negative cultures given antimicrobial therapy between the Post-Therapy and the Post-Study visit for the treatment of a condition related to inadequate treatment of the patient's underlying pneumonia should be scored as presumed microbiological relapse unless the indication for the antibiotic is unrelated to the pneumonia.

Microbiologic Response for Blood Pathogens, Post-Therapy

The microbiologic response for blood pathogens was based on Post-Therapy blood culture results for subjects with confirmed bacteremia at admission. Bacteremia was defined as at least one positive blood culture obtained at Admission. Microbiologic response for each admission pathogen was determined for subjects with blood culture results available Post-Therapy as follows:

Post-Therapy Blood Culture 1	Post-Therapy Blood Culture 2	Clinical Response[a]	Microbiologic Response
Negative	Negative	All	Eradicated
Negative	Unknown	Cure/Improved	Eradicated
Negative	Unknown	Failure	Presumed Persisted[b]
Positive	Positive	All	Persisted
Positive	Negative	All	Persisted
Positive	Unknown	All	Persisted

[a] "All" includes cured, improved, failure, and unable to evaluate.
[b] Listed as persisted in the protocol.

Microbiologic response for subjects with no blood culture results available Post-Therapy was determined as follows:

Post-Therapy Blood Culture 1	Post-Therapy Blood Culture 2	Clinical Response	Microbiologic Response
Unknown	Unknown	Cure/Improved	Presumed Eradicated
Unknown	Unknown	Failure	Presumed Persisted
Unknown	Unknown	Unable to Evaluate	Unknown

Microbiologic Response for Blood Pathogens, Post-Study

Post-Study blood cultures were not required by the protocol. However, the following criteria were developed subsequent to the protocol such that a Post-Study microbiologic response was assigned based on the clinical response and whether or not the subject had taken an antibiotic between Post-Therapy and Post-Study.

Post-Study Clinical Response	Antibiotic Use Between Post-Therapy and Post-Study[a]	Microbiologic Response
Cure or Improved	Yes	Unknown
	No	Eradicated or Presumed eradicated
Failure	Yes or No	Microbiologic relapse
Unable to evaluate	Yes or No	Unknown

[a] Criteria developed subsequent to the protocol.

MO Comment: Patients with negative cultures who require antimicrobial therapy between the Post-Therapy and the Post-Study visit for the treatment of

a condition related to inadequate treatment of the underlying pneumonia should be scored as microbiological relapse unless the indication for the antibiotic is unrelated to the pneumonia.

Microbiologic Response for Atypical Pathogens (Non-Culture Method), Post-Therapy

Serologic studies for *C. pneumoniae, M. pneumoniae,* and *L. pneumophila* were to be performed on all study subjects. The microbiologic response for *M. pneumoniae, L. pneumophila*, or *C. pneumoniae* was based on clinical response at Post-Therapy and antibiotic use at the Post-Therapy visit. Microbiologic response was determined as follows:

Post-Therapy Clinical Response	Antibiotic Use at Post-Therapy Visit[a]	Post-Therapy Microbiologic Response
Cured or Improved	Yes	Unknown
	No	Presumed Eradicated
Failure	Yes or No	Presumed Persisted
Unable to Evaluate	Yes or No	Unknown

[a] Criteria developed subsequent to the protocol.

MO Comment: Only antibiotic use for conditions other than pneumonia should apply in the table above. Patients who receive a non-study antimicrobial for the treatment of pneumonia should be regarded as failures (presumed persistence) unless the indication for the antibiotic is unrelated to the pneumonia.

Microbiologic Response for Atypical Pathogens (Non-Culture Method), Post-Study

The microbiologic response for *M. pneumoniae, L pneumophila,* or *C. pneumoniae* was based on clinical response at Post-Study and was determined as follows:

Post-Study Clinical Response	Antibiotic Use Between Post-Therapy and Post-Study[a]	Post-Study Microbiologic Response
Cured or Improved	Yes	Unknown
	No	Presumed Eradicated[b]
Failure	Yes or No	Microbiologic Relapse
Unable to Evaluate	Yes or No	Unknown

[a] Criteria developed subsequent to the protocol.
[b] Definition developed subsequent to the protocol.

MO Comment: As noted previously, patients with a microbiologic diagnosis for his/her pneumonia established by non-cultures methods, who are given antimicrobial therapy between the Post-Therapy and the Post-Study visit for the treatment of a condition related to inadequate treatment of the patient's

underlying pneumonia should be scored as presumed microbiological relapse unless the indication for the antibiotic is unrelated to the pneumonia.

Microbiologic Response by Patient, Post-Therapy

The microbiologic response at Post-Therapy by patient was assigned based on the following criteria:

- **Eradication:** All admission pathogens eradicated or presumed eradicated.
- **Persisted:** Persistence, presumed persistence, or persistence with acquisition of resistance for at least one pathogen isolated at admission.
- **Unknown**: Unknown microbiologic response for at least one pathogen with no other pathogen(s) persisting (definition developed subsequent to the protocol).

Microbiologic response was based only on the fate of the original pathogen(s). Organisms classified as superinfectors were not considered in determining microbiologic response, but are addressed separately. Organisms classified as colonizers were not addressed.

Microbiologic Response by Patient, Post-Study

The microbiologic response at the Post-Study follow-up visit by patient was based on the following criteria:

- **Eradication:** All admission pathogens eradicated or presumed eradicated.
- **Relapse:** Microbiologic relapse of at least one admission pathogen.
- **Unknown:** No microbiologic relapse for any pathogen and at least one pathogen with a Post-Study microbiologic response of unknown (definition developed subsequent to the protocol).

Study Withdrawal/ Discontinuation

The protocol-specified reasons for study withdrawal included the occurrence of an adverse event, clinical failure, subject choice, or "other reasons." In the event that a subject was withdrawn from study, the protocol specifies that the evaluations planned for the Post-Therapy visit should be completed at the time of study withdrawal.

Evaluability Criteria

Clinically Evaluable Population at Post-Therapy

In order for a patient to be clinically evaluable at Post-Therapy, the patient must not be classified in any of the following categories:

- unevaluable for safety (did not take at least one dose of study drug or had no post-Admission safety data available);
- clinical diagnosis unconfirmed (a subject must have been diagnosed as having community-acquired pneumonia as described by the protocol);
- insufficient course of therapy (a subject must have taken study drug for at least five days; however, a subject judged as a clinical failure after receiving study drug for at least 48 hours was to be considered evaluable);
- effective systemic antimicrobial therapy taken at any time between the time of study enrollment through the Post-Therapy (test of cure) culture, unless judged to be a clinical failure, in which case the pathogen(s) was (were) assumed to have persisted;
- Post-Therapy clinical evaluation did not occur between 2 to 10 days Post-Therapy; however, if a subject discontinued due to clinical failure or was considered a clinical failure upon the completion of therapy and the Post-Therapy (test-of-cure) evaluation was obtained outside of the 2- to 10-day window, the subject was considered evaluable provided all other evaluability criteria were met;
- lost to follow-up but provided safety information;
- other significant protocol violation.

MO Comment: The above criteria are verbatim from the Applicant's Study Report.

Microbiologically Evaluable Population at Post-Therapy

In order for a patient to be microbiologically evaluable at Post-Therapy, the patient must not be classified in any of the following categories:

- unevaluable for safety (did not take at least one dose of study drug or had no post-Admission safety data available);
- infection not bacteriologically proven (i.e., no admission pathogen was identified);
- clinical diagnosis unconfirmed (a subject must have been diagnosed as having community-acquired pneumonia as described by the protocol);
- insufficient course of therapy (a subject must have taken study drug for at least five days; however, a subject judged as a clinical failure after receiving study drug for at least 48 hours was to be considered evaluable);

- effective systemic antimicrobial therapy taken at any time between the time of study enrollment through the Post-Therapy (test-of-cure) culture, unless judged to be a clinical failure, in which case the pathogen(s) was (were) assumed to have persisted;
- inappropriate bacteriologic culture (admission culture >48 hours prior to the start of therapy or any time following initiation of therapy; Post-Therapy microbiologic culture/evaluation not between 2 to 10 days post-therapy; adequate microbiologic data not available). A subject who discontinued due to clinical failure, or who was considered a clinical failure upon the completion of therapy, and for whom a Post-Therapy culture was either not obtained or was obtained while on therapy or one day after therapy, was considered evaluable);
- lost to follow-up but relayed safety information;
- other significant protocol violation(s).

MO Comment: The above criteria are verbatim from the Applicant's Study Report.

MO Comment: The protocol specified evaluability criteria (both clinical and microbiological evaluability) allowed patients to be evaluated at a Post-Therapy visit that could occur as soon as 2 days post-therapy or up to 10 days post-therapy. A Post-Therapy assessment that occurred only 2 days after completing study drug may not allow sufficient time for drug to clear and for clinical manifestations of inadequately treated disease to recrudesce. The Efficacy results presented in the MO Efficacy Analysis section address this concern by requiring that Post-Therapy assessments and Post-Study assessments occur within the protocol specified windows.

Evaluability Criteria for Safety

In order for a patient to be considered evaluable for safety, the patient had to take at least one dose of study medication and relay post-Admission safety information.

Endpoints Defined

Efficacy

The primary efficacy endpoints, as defined in the protocol, were clinical and microbiological response in the microbiologicallly evaluable population at the Post-Therapy assessment. The protocol also notes that the efficacy parameteres will also be summarized by disease severity. In addition, the protocol also notes that clinical response at Post-study would also be summarized.

Safety

Safety evaluations were based on the incidence, severity (mild, moderate, and marked), relationship to therapy (none, remote, possible, probable, and definite), and type of treatment-emergent adverse events (i.e., those adverse events that newly appeared or increased in severity or frequency following therapy initiation) reported during the study period (through the Post-Therapy visit), and on changes in physical findings, vital signs, and clinical laboratory results from Admission to Post-Therapy.

Statistical Considerations

The protocol specified a planned enrollment of 600 patients to yield approximately 15 microbiologically evaluable subjects with each of the targeted pathogens (i.e., [redacted] penicillin-resistant *S. pneumoniae*, and [redacted] *S. pneumoniae*). However, difficulty was encountered enrolling patients with PRSP. Therefore, the study enrollment was continued until a total of 655 subjects had been enrolled in the study, at which time only 5 patients with PRSP had been enrolled.

The analyses planned included determination of the microbiological and clinical response rates for adults with CAP due to penicillin-resistant or [redacted] *S. pneumoniae* or [redacted] The Applicant's primary population for the efficacy analysis was the microbiologically evaluable population. The response variables to be analyzed for this population were the microbiological eradication rate (eradicated and presumed eradicated) by patient and by pathogen at the Post-Therapy assessment and the clinical success rate (cured and improved) based on the Post-Therapy reduction of signs and symptoms, along with improvement or stabilization of the infiltrate on chest radiography. The clinical response rates Post-Study were also to be analyzed.

The efficacy parameters were also summarized by severity of infection with severe infection defined as patients satisfying any of the following criteria:

- bacteremia
- diastolic hypotension (diastolic blood pressure <60 mmHg) in the absence of volume depletion
- use of vasopressors
- altered mental status (altered from pre-infection baseline)
- requiring intubation, mechanical ventilation, or baseline respiration rate >28 beats/min.

The Applicant's analyses focus on the microbiologically evaluable population (the protocol specified primary efficacy analysis group). The Applicant also performed analyses on the

intent-to-treat population (all subjects enrolled), the evaluable for clinical efficacy population, and the evaluable for safety population. These additional analyses were not specified in the study protocol but are described in the study report as providing supportive information.

RESULTS

The analyses the Applicant performed on each of the analysis populations are summarized in Table 5. A total of 655 subjects were enrolled in the study. Of these patients, 155 had *S. pneumoniae* isolates at Admission. One hundred forty of the patients with *S. pneumoniae* were evaluable for clinical efficacy. The same 140 patients with *S. pneumoniae* were also evaluable for microbiologic efficacy, making the subject populations for these analysis groups identical.

Table 5: Number of Subjects and Summaries for Each Analysis Population (Protocol LOFBIV-PCAP-001)

	Primary Efficacy Analyses	Secondary Efficacy Analyses		Safety Analyses
	Microbiologically Evaluable	Clinically Evaluable	Intent-to-Treat	Subjects Evaluable for Safety
Overall population	398	532	655	650
Subjects with *S. pneumoniae*	140	140	155	N/A
Analyses and/or summaries performed				
Demographics	X	X	X	X
Extent of therapy	X	X	X	
Microbiologic response	X	X	X	
Clinical response	X	X	X	
Signs/symptoms	X	X	X	
Adverse events				X
Laboratory results				X
Vital signs				X

Adapted from Applicant's Table 2, NDA 20-634 SE-008, Vol. 25.3, p. 149

Demographic and Baseline Characteristics

The demographic and baseline (admission) characteristics of the intent-to-treat population are summarized in Table 6. The ITT population had a mean age of 55 years and was 59% male. The distribution of race in the ITT population was 69% Caucasian, 26% Black and 2% Hispanic. At the time of enrollment 56% of the patients were inpatients and 27% had disease at baseline classified as severe. The Applicant also tabulated the demographic and baseline characteristics for each of the 4 analysis populations. The distribution of baseline characteristics was similar in each of the 4 analysis populations.

Table 6: Demographic and Baseline Characteristics: Intent-to-Treat Subjects (Protocol LOFBIV-PCAP-001)

	Levofloxacin (N=655)	
	N[a]	(%)[a]
Sex		
Men	384	(58.6)
Women	271	(41.4)
Race		
Caucasian	453	(69.2)
Black	171	(26.1)
Oriental	5	(0.8)
Hispanic	15	(2.3)
Other	11	(1.7)
Age (yrs)		
<65	427	(65.2)
≥65	228	(34.8)
N	655	
Mean±SD	54.8±18.5	
Range	18-96	
Weight (lbs)		
N	631	(96.3)
Mean±SD	167.0±42.8	
Range	80-326	
Missing	24	(3.7)
Height (in)		
N	612	(93.4)
Mean±SD	67.1±3.9	
Range	52-82	
Missing	43	(6.6)
Severity of Infection		
Severe	176	(26.9)
Mild/moderate	479	(73.1)
Status		
Inpatient	364	(55.6)
Outpatient	291	(44.4)

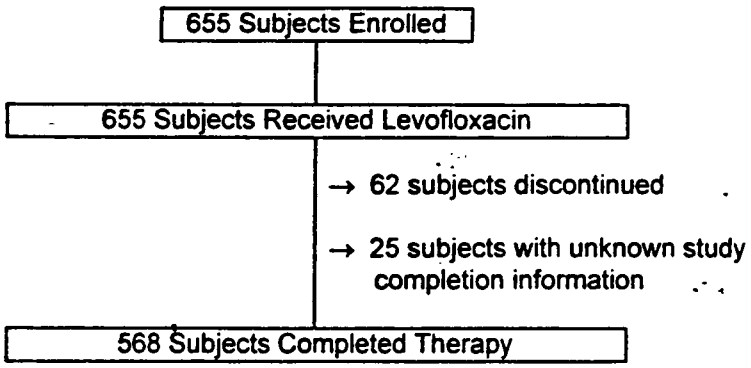
[a] Values represent number (%) of subjects except as otherwise indicated.

Adapted from the Applicant's Table 3, NDA 20-634 SE1-008, Vol. 25.3, p. 151

Study Completion/Withdrawal Information

A total of 655 subjects were enrolled in the study and all received levofloxacin treatment. Study completion information is unknown for 25 subjects. These 25 subjects were lost to follow-up (did not return for the Post-Therapy or Post-Study evaluations). Twenty of these 25 subjects did however, contribute limited safety information. Of the 630 subjects with known study completion information, 62 (10%) subjects discontinued therapy prematurely, while 568 (90%) subjects completed therapy according to the regimen prescribed by the investigator (Figure 1).

Figure 1: Study Completion Information: Intent-to-Treat Subjects (Protocol LOFBIV-PCAP-001)



Adapted from the Applicant's Figure 1 , NDA 20-634 SE1-008, Vol. 25.3, p. 152

The reasons that levofloxacin was prematurely discontinued are summarized in Table 7. The occurrence of a treatment-emergent adverse event was the most common reason for premature study drug discontinuation.

Table 7: Reasons for Discontinuation: Intent-to-Treat Subjects (Protocol LOFBIV-PCAP-001)

Reason for Premature Discontinuation/Withdrawal	Levofloxacin (N=655) N (%)
Adverse event	37 (5.9)[a]
Clinical failure	7 (1.1)[a]
Personal reason	6 (1.0)[a]
Other[b]	12 (1.9)[a]
Total discontinued	62 (9.8)[a]
Total with discontinuation/completion information	630 (96.2)
Total with unknown discontinuation/completion information[c]	25 (3.8)

[a] Percentages are based on total number of subjects with discontinuation/completion information.
[b] Other reasons for discontinuation included error in initial diagnosis of pneumonia, miscommunication between physician and staff regarding the subject's vital signs and response to therapy, use of non-study antibiotic, and concurrent illness.
[c] These subjects were lost to follow-up; therefore their extent of exposure to study drug is unknown.

Adapted from the Applicant's Table 4, NDA 20-634 SE1-008, Vol. 25.3, p. 152

MO Comment: As noted in footnote b in Table 7, one of the reasons that patients in the "other" category were discontinued from study was the use of

non-study antimicrobials. Information on the 5 patients who received a non-study antimicrobial and were discontinued from study under the category of "other" follows.

- Pt. No. 15008 – The patient's physician did not want the patient to be treated with study drug and therefore the patient was discontinued from study on Day 1. The patient's physician changed the antimicrobial therapy to ampicillin/sulbactam.
- Pt. No. 3058 – On Day 3, the patient's private physician (not the study investigator) changed the patient's antimicrobial therapy to azithromycin because of "inexperience with levofloxacin." On Day 3, the patients on therapy assessment revealed symptomatic improvement and a chest examination with resolved rhonchi with other chest findings unchanged from admission.
- Pt. No. 28028 – On Day 3 the patient was discontinued from study drug because he was unable to swallow a tablet (the patient had a feeding tube). On Day 3 the patient was scored as clinically improved. He was switched to trimethoprim/sulfamethoxazole.
- Pt. No. 8001 – The patient did not have an admission chest x-ray and hence did not meet the eligibility criteria. He was also noted to have received a non-study antibiotic (trimethoprim/sulfamethoxazole) starting on Day 5. At the patient's on-therapy assessment on Day 4 the patient was symptomatically improved.
- Pt. No. 8007 – On Day 2 the patient was discharged from the hospital on a non-study oral antibiotic (cefuroxime axetil), prior to 48 hours of study therapy. The patient's condition was scored as clinically improved on Day 2. Review of the patient's concomitant medications, other antimicrobials reported, treatment emergent adverse events, and investigator comments does not shed any light on the reason why the patient was discharged on a non-study oral antibiotic.

In summary, the patients who were discontinued from study because they received non-study antimicrobial therapy are small in number. These discontinuations do not appear to be selectively removing patients who are either clinically deteriorating or failing to respond to therapy. These discontinuation events are unlikely to invalidate the study results.

Treatment Compliance

Eighty-three percent of patients received between 7 to 14 days of therapy. The mean duration of therapy was 11.7 days. The remaining 17 % of patients received therapy beyond 14 days (6%), less than 7 days of therapy (7%), or an unknown amount of therapy (4%).

Concomitant Therapies

The study protocol prohibited the administration of any non-study systemic antibacterial agent. The most commonly used concomitant therapies were analgesics and agents used for respiratory, cardiovascular, and gastrointestinal indications. Ten subjects received concomitant therapy to counteract a drug-related adverse event.

Protocol Deviations

Most of the protocol deviations that occurred were related to patients who had received previous antimicrobial therapy and had failed to respond. The RWJPRI study monitor granted 32 protocol exceptions to patients who had received more than 24 hours of antimicrobial therapy and were not responding. In general, the failure to respond to previous antimicrobial therapy was considered as a possible indicator of CAP secondary to a resistant pathogen (e.g. PRSP). Two patients (Pt. No. 1039 and 1057) who had received more than 24 hours of prior antimicrobial therapy were admitted to the study by their investigator without permission from RWJPRI medical monitor. Three patients (Pt. No. 4059, 55028, and 59007) received an unknown amount of previous antimicrobial therapy and also were enrolled without permission from the RWJPRI medical monitor. One patient (Pt. No. 28021) who was receiving concurrent antimicrobial therapy for an alternative condition (suspected meningitis) was enrolled.

> **MO Comment:** Given that the objective of this clinical trial was to study levofloxacin in the treatment of CAP due to PRSP, inclusion of patients who are clinical failures to prior antimicrobial therapy is a reasonable strategy to enrich the population for patients with resistant pathogens. Ideally such a strategy would be prospectively defined in the study protocol. Further details of patients who received prior antimicrobial therapy and had PRSP or PISP as their admission pathogen are described in the Integrated Summary of Efficacy for LEVAQUIN for the Treatment of CAP due to PRSP.

Other protocol deviations that occurred were incorrect drug dosage administration (n=4) and inadvertent enrollment of a subject who met an exclusion criterion [tuberculosis (n=3), AIDS and pneumonia due to *Pneumocystis carinii* (n=1), and empyema (n=1)].

Evaluability

Evaluability by study center is shown in Table 8. Of the 655 subjects enrolled in the study, 532 (81%) were evaluable for clinical efficacy and 398 (61%) subjects were evaluable for microbiologic efficacy. One study center (Fogarty) enrolled 24% (156/655) of the patients.

Table 8: Number of Subjects Evaluable by Analysis Group and Study Center (Protocol LOFBIV-PCAP-001) per Applicant

	Levofloxacin		
Investigator	Intent-to-Treat	Clinical Efficacy[a]	Microbiologic Efficacy[a]
	11	9 (81.8)	2 (18.2)
	17	13 (76.5)	11 (64.7)
	4	4 (100.0)	2 (50.0)
	25	15 (60.0)	11 (44.0)
	11	5 (45.5)	4 (36.4)
	1	0 (0.0)	0 (0.0)
	59	45 (76.3)	38 (64.4)
	10	10 (100.0)	5 (50.0)
	156	143 (91.7)	122 (78.2)
	16	13 (81.3)	10 (62.5)
	18	14 (77.8)	7 (38.9)
	13	11 (84.6)	7 (53.8)
	60	53 (88.3)	47 (78.3)
	7	4 (57.1)	2 (28.6)
	15	12 (80.0)	9 (60.0)
	8	5 (62.5)	3 (37.5)
	6	5 (83.3)	2 (33.3)
	7	6 (85.7)	3 (42.9)
	33	21 (63.6)	13 (39.4)
	2	2 (100.0)	0 (0.0)
	23	22 (95.7)	19 (82.6)
	21	20 (95.2)	7 (33.3)
	13	10 (76.9)	8 (61.5)
	24	24 (100.0)	19 (79.2)
	35	21 (60.0)	14 (40.0)
	15	12 (80.0)	8 (53.3)
	7	4 (57.1)	2 (28.6)
	4	3 (75.0)	3 (75.0)
	4	4 (100.0)	3 (75.0)
	4	3 (75.0)	3 (75.0)
	13	8 (61.5)	5 (38.5)
	7	6 (85.7)	5 (71.4)
	6	5 (83.3)	4 (66.7)
Total	**655**	**532 (81.2)**	**398 (60.8)**

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

Adapted from Applicant's Table 5, NDA 20-634 SE1-008, Vol. 25.3, p. 155

The primary reasons that patients were excluded from either the clinical or microbiologic analyses of efficacy are summarized in Table 9. The most common reasons that patients were excluded from the clinically evaluable population were, insufficient course of therapy (36 patients), lost to follow-up (25 patients), and inappropriate bacteriologic culture (24 patients). The most common reason that patients were excluded from the microbiologically evaluable population was, the absence of a bacteriologically proven infection (184 patients).

Table 9: Primary[a] Reasons for Clinical and Microbiological Non-Evaluability: Intent-to-Treat Subjects (Protocol LOFBIV-PCAP-001) per Applicant

Reasons	Levofloxacin N=655
Clinical efficacy	
Insufficient course of therapy	36
Lost to follow-up, but provided safety information	25
Inappropriate bacteriologic culture	24
Other protocol violation	16
Effective concomitant therapy	11
Clinical diagnosis unconfirmed	6
Non-Evaluable for safety	5
Total Non-Evaluable for clinical efficacy	123 (18.8%)
Microbiological efficacy	
Infection not bacteriologically proven	184
Insufficient course of therapy	19
Inappropriate bacteriologic culture	16
Lost to follow-up, but provided safety information	14
Other protocol violation	11
Effective concomitant therapy	5
Non-Evaluable for safety	5
Clinical diagnosis unconfirmed	3
Total Non-Evaluable for microbiologic efficacy	257 (39.2%)

[a] The Primary Reasons for Non-Evaluability, subjects were counted only once.

Adapted from Applicant's Table 6, NDA 20-634 SE1-008, Vol. 25.3; p. 156

MO Comment: The MO reviewed the patients that were non-evaluable because of effective concomitant therapy. The MO disagreed with the evaluability status of two of the patients who were non-evaluable for clinical efficacy (one of whom was also non-evaluable for microbiological efficacy). Pt. No. 13002 began a course of azithromycin for the indication of pneumonia on the day of the Post-Therapy assessment and therefore should be scored as a clinical failure at the Post-Therapy assessment. Pt. No. 55033 was non-evaluable because she received oral vancomycin for *C. difficile* colitis. Because the protocol states that non-study systemic antibiotics are prohibited and oral vancomycin is not absorbed (i.e. not a systemic antibiotic when given orally), the MO considered this patient as clinically and microbiologically evaluable. In the MO Efficacy analysis that follows, these two patients are included in the analysis with the above changes to their evaluability status and/or clinical response as noted.

Applicant's Efficacy Analysis

Clinical Response for All Subjects with Community-Acquired Pneumonia

Post-Therapy Clinical Response

The Applicant analyzed clinical response rates for the intent-to-treat, the clinically evaluable, and the microbiologically evaluable populations at the Post-Therapy assessment. The clinical response rates for these three populations are summarized in Table 10. Following Table 10, analyses of clinical success rates by study center, disease severity; and age are presented for the clinically evaluable population.

Table 10: Post-Therapy Clinical Response: All Subjects with Community-Acquired Pneumonia by Population Type
(Protocol LOFBIV-PCAP-001) (per Applicant)

Population	N	Clinical Success [a,b]	
		n/N	(%)
Intent-to-Treat Subjects	655	605/655	(92.4)
Clinically Evaluable Subjects	532	511/532	(96.1)
Microbiologically Evaluable Subjects	398	384/398	(96.5)

[a] Numbers shown in parentheses are percentages for that category.
[b] Clinical success = cured + improved; Clinical failure = failed + unable to evaluate.
Adapted from Applicant's Table 31b, NDA 20-634 SE1-008 Vol. 25.3, p. 202

Of the 655 subjects enrolled in the study, 532 met the Applicant's clinical evaluability criteria. The response rates among these 532 patients at the post-therapy visit was 348 (65%) cure, 163 (31%) improved, and 21 (4%) failure. The clinical success rate (cure + improvement) was 511 of 532 patients (96%). The clinical response rate in the microbiologically evaluable population was 96.5% (384/398).

The clinical response rate for the Post-Therapy visit and response rates stratified by study center are summarized in Table 11. One study center (Investigator Fogarty) enrolled 27% of the clinically evaluable population.

Table 11: Clinical Response Rate Five to Seven Days Post-Therapy for Each Study Center: Subjects Evaluable for Clinical Efficacy (Protocol LOFBIV-PCAP-001) (per Applicant)

	Levofloxacin						
In[illegible]	N	Cured[a]		Improved[a]		Failed[a]	
	9	7	(77.8%)	1	(11.1%)	1	(11.1%)
	13	4	(30.8%)	8	(61.5%)	1	(7.7%)
	4	3	(75.0%)	1	(25.0%)	0	(0.0%)
	15	11	(73.3%)	4	(26.7%)	0	(0.0%)
	5	2	(40.0%)	3	(60.0%)	0	(0.0%)
	45	40	(88.9%)	4	(8.9%)	1	(2.2%)
	10	8	(80.0%)	2	(20.0%)	0	(0.0%)
	143	93	(65.0%)	46	(32.2%)	4	(2.8%)
	13	6	(46.2%)	7	(53.8%)	0	(0.0%)
	14	11	(78.6%)	3	(21.4%)	0	(0.0%)
	11	9	(81.8%)	1	(9.1%)	1	(9.1%)
	53	26	(49.1%)	26	(49.1%)	1	(1.9%)
	4	0	(0.0%)	4	(100.0%)	0	(0.0%)
	12	4	(33.3%)	8	(66.7%)	0	(0.0%)
	5	2	(40.0%)	3	(60.0%)	0	(0.0%)
	5	4	(80.0%)	0	(0.0%)	1	(20.0%)
	6	4	(66.7%)	2	(33.3%)	0	(0.0%)
	21	11	(52.4%)	9	(42.9%)	1	(4.8%)
	2	0	(0.0%)	2	(100.0%)	0	(0.0%)
	22	10	(45.5%)	8	(36.4%)	4	(18.2%)
	20	18	(90.0%)	0	(0.0%)	2	(10.0%)
	10	3	(30.0%)	7	(70.0%)	0	(0.0%)
	24	20	(83.3%)	2	(8.3%)	2	(8.3%)
	21	19	(90.5%)	1	(4.8%)	1	(4.8%)
	12	12	(100.0%)	0	(0.0%)	0	(0.0%)
	4	2	(50.0%)	2	(50.0%)	0	(0.0%)
	3	3	(100.0%)	0	(0.0%)	0	(0.0%)
	4	2	(50.0%)	2	(50.0%)	0	(0.0%)
	3	3	(100.0%)	0	(0.0%)	0	(0.0%)
	8	4	(50.0%)	4	(50.0%)	0	(0.0%)
	6	3	(50.0%)	3	(50.0%)	0	(0.0%)
	5	4	(80.0%)	0	(0.0%)	1	(20.0%)
Total	**532**	**348**	**(65.4%)**	**163**	**(30.6%)**	**21**	**(3.9%)**

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

Adapted from Applicant's Table 23, NDA 20-634 SE1-008, Vol. 25.3, p. 190

The Applicant also analyzed the clinical response rates by age (<65 years vs. ≥ 65 years), sex, and race (white, black, or other). The clinical response rates observed were comparable across these groups.

Post-Therapy Clinical Response by Pathogen

The Applicant summarized the Post-Therapy clinical response rates by pathogen for those pathogens isolated 5 or more times (Table 12). Clinical success rates (cure + improved) for *S. pneumoniae* were 97% (126/130). The clinical success rates for [redacted] were 92% (34/37).

Table 12: Clinical Response Five to Seven Days Post-Therapy Summarized by Pathogen Category for Prevalent Pathogens[a]: Subjects Evaluable for Clinical Efficacy (Protocol LOFBIV-PCAP-001) (per Applicant)

Pathogen Category	Levofloxacin						
Pathogen(s)[a]	N[b]	Cured[c]		Improved[c]		Failed[c]	
Respiratory cultures							
Streptococcus pneumoniae	130	85	(65.4%)	41	(31.5%)	4	(3.1%)
Haemophilus influenzae	58	36	(62.1%)	21	(36.2%)	1	(1.7%)
Staphylococcus aureus	18	12	(66.7%)	5	(27.8%)	1	(5.6%)
Moraxella (Branhamella) catarrhalis	15	6	(40.0%)	9	(60.0%)	0	(0.0%)
Haemophilus parainfluenzae	14	10	(71.4%)	4	(28.6%)	0	(0.0%)
Klebsiella pneumoniae	12	5	(41.7%)	7	(58.3%)	0	(0.0%)
Escherichia coli	11	7	(63.6%)	4	(36.4%)	0	(0.0%)
Pseudomonas aeruginosa	10	6	(60.0%)	4	(40.0%)	0	(0.0%)
Enterobacter cloacae	6	3	(50.0%)	3	(50.0%)	0	(0.0%)
Streptococcus pyogenes	6	4	(66.7%)	1	(16.7%)	1	(16.7%)
Haemophilus parahemolyticus	5	3	(60.0%)	2	(40.0%)	0	(0.0%)
Blood cultures							
Streptococcus pneumoniae	25	11	(44.0%)	14	(56.0%)	0	(0.0%)
Atypical pathogens							
Mycoplasma pneumoniae	182	128	(70.3%)	51	(28.0%)	3	(1.6%)
Chlamydia pneumoniae	84	54	(64.3%)	28	(33.3%)	2	(2.4%)
Legionella pneumophila	37	25	(67.6%)	9	(24.3%)	3	(8.1%)

[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.

Adapted from Applicant's Table 25, NDA 20-634 SE1-008, Vol. 25.3, p. 192.

Post-Therapy Clinical Response by Severity of Infection

The Applicant also analyzed the clinical response rates by severity of infection at baseline (severe vs. mild/moderate). Of the 532 patients in the clinically evaluable population, 144 (27%) were considered to have severe disease at baseline, 388 (73%) had disease graded as mild/moderate at baseline. The cure rates at Post-Therapy were slightly higher in the patients with disease graded as mild/moderate, 69% vs. 56% for patients with severe disease at baseline (Table 13). The clinical success rates were similar for patients with mild/moderate disease 96% vs. patients with severe disease 97%.

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Table 13: Clinical Response Five to Seven Days Post-Therapy Summarized by Severity of Infection: Subjects Evaluable for Clinical Efficacy (Protocol LOFBIV-PCAP-001) (per Applicant)

	Levofloxacin						
Severity of Infection	N	Cured[a]		Improved[a]		Failed[a]	
Severe	144	80	(55.6%)	59	(41.0%)	5	(3.5%)
Mild/moderate	388	268	(69.1%)	104	(26.8%)	16	(4.1%)
Total	532	348	(65.4%)	163	(30.6%)	21	(3.9%)

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

Adapted from Applicant's Table 26, NDA 20-634 SE1-008, Vol. 25.3, p. 193.

Post-Study Clinical Response

Patients who were evaluable for clinical efficacy and were not scored as clinical failures at the Post-Therapy evaluation were to return for a Post-Study assessment 21 to 28 days after completing therapy. Of the 461 patients who underwent a Post-Study clinical response assessment, 404 (88%) were cured, 38 (8%) were improved, and 19 (4%) relapsed at the Post-Study visit (Table 14). The clinical response of 50 subjects evaluable for clinical efficacy at Post-Therapy was unable to be evaluated because these subjects either did not return for the Post-Study visit or received effective antimicrobial therapy between the Post-Therapy and Post-Study visits.

MO Comment: The MO reviewed the 29 patients who were classified as unevaluable because they received effective antimicrobial therapy between Post-Therapy and Post-Study. The purpose of the review was to investigate the reasons for which these patients were given antibacterial therapy. If a patient is given an antibacterial agent to treat inadequately treated or recrudescent CAP, that patient should be scored as a clinical relapse between the Post-Therapy and Post-Study assessment.

Review of the 29 cases revealed 3 groups of patients. Those patients who received antimicrobial therapy for unrelated conditions, patients who received antimicrobial therapy for other conditions involving the respiratory tract that were judged by the investigator to be unrelated to pneumonia, and a third group of patients (n=5) in whom the reasons that the investigator initiated antimicrobial therapy was, suspected pneumonia or inadequate response. The patient numbers for these five patients were 4018, 4052, 28063, 52013, and 56006. The MO considered patients in this third group as clinically evaluable at the Post-Study visit and they were scored as clinical relapse and presumed microbiologic relapse (clinical relapse in the absence of a microbiologic specimen) at the Post-Study assessment in the MO Efficacy Analysis that follows.

Table 14: Clinical Response Post-Study (21 to 28 days post-therapy) for Each Study Center: Subjects[a] Evaluable for Clinical and Microbiologic Efficacy (Protocol LOFBIV-PCAP-001) (per Applicant)

		Clinically Evaluable Subjects: Post-Study Clinical Response					Microbiologically Evaluable Subjects: Post-Study Clinical Response				
Investigator	Post-therapy	N	Cured	Improved	Relapse	Unable to Evaluate	N	Cured	Improved	Relapse	Unable to Evaluate
	Cured	7	5	0	0	2	2	1	0	0	1
	Improved	1	0	0	0	1	0	0	0	0	0
	Cured	4	3	0	0	1	4	3	0	0	1
	Improved	8	3	1	3	1	6	1	1	3	1
	Cured	3	3	0	0	0	1	1	0	0	0
	Improved	1	0	0	1	0	1	0	0	1	0
	Cured	11	8	0	1	2	7	6	0	0	1
	Improved	4	2	0	0	2	4	2	0	0	2
	Cured	2	1	0	0	1	2	1	0	0	1
	Improved	3	1	1	0	1	2	1	1	0	0
	Cured	40	37	0	0	3	33	30	0	0	3
	Improved	4	1	2	0	1	4	1	2	0	1
	Cured	8	8	0	0	0	3	3	0	0	0
	Improved	2	2	0	0	0	2	2	0	0	0
	Cured	93	87	0	0	6	80	75	0	0	5
	Improved	46	32	10	2	2	38	26	9	2	1
	Cured	6	5	0	0	1	4	4	0	0	0
	Improved	7	6	1	0	0	6	5	1	0	0
	Cured	11	10	0	0	1	6	5	0	0	1
	Improved	3	1	0	0	2	1	1	0	0	0
	Cured	9	9	0	0	0	5	5	0	0	0
	Improved	1	1	0	0	0	1	1	0	0	0
	Cured	26[b]	20	0	3	3[b]	21[b]	16	0	3	2[b]
	Improved	26	14	6	3	3	25	13	6	3	3
	Improved	4	1	1	2	0	2	0	1	1	0
	Cured	4	4	0	0	0	2	2	0	0	0
	Improved	8	3	3	0	2	7	3	3	0	1
	Cured	2	2	0	0	0	1	1	0	0	0
	Improved	3	3	0	0	0	2	2	0	0	0
	Cured	4	3	0	0	1	2	1	0	0	1
	Cured	4	4	0	0	0	2	2	0	0	0
	Improved	2	2	0	0	0	1	1	0	0	0
	Cured	11	10	0	0	1	6	5	0	0	1
	Improved	9	4	3	0	2	7	3	3	0	1
	Improved	2	2	0	0	0	0	0	0	0	0
	Cured	10	10	0	0	0	9	9	0	0	0
	Improved	8	4	1	2	1	7	4	0	2	1
	Cured	18	17	0	0	1	6	6	0	0	0
	Cured	3	3	0	0	0	3	3	0	0	0
	Improved	7	4	3	0	0	5	2	3	0	0
	Cured	20	14	3	0	3	16	11	2	0	3
	Improved	2	1	0	1	0	2	1	0	1	0
	Cured	19	16	0	0	3	14	13	0	0	1
	Improved	1	1	0	0	0	0	0	0	0	0
	Cured	12	12	0	0	0	8	8	0	0	0
	Cured	2	2	0	0	0	1	1	0	0	0
	Improved	2	0	0	0	2	1	0	0	0	1
	Cured	3	2	0	0	1	3	2	0	0	1

[a] Clinical response is presented as cured, improved, or relapse for subjects who were evaluable for efficacy, had a Post-Therapy clinical response of cured or improved, and had their clinical response evaluated at the Post-Study visit.

[b] Subject 4060 had a clinical response of cured at the Post-Therapy evaluation and is included in this table as unable to evaluate for the Post-Study clinical response. However, in the clinical study data base this subject erroneously was considered to be not applicable (N/A) for the Post-Study clinical evaluation.

Adapted from Applicant's Table 29, NDA 20-634 SE1-008, pp. 197, 198

(Continued)

Table 14: Clinical Response Post-Study (21 to 28 days post-therapy) for Each Study Center: Subjects[a] Evaluable for Microbiologic and Clinical Efficacy (Continued) (Protocol LOFBIV-PCAP-001) (per Applicant)

		Clinically Evaluable Subjects: Post-Study Clinical Response					Microbiologically Evaluable Subjects: Post-Study Clinical Response				
Investigator	Post-therapy	N	Cured	Improved	Relapse	Unable to Evaluate	N	Cured	Improved	Relapse	Unable to Evaluate
	Cured	2	2	0	0	0	1	1	0	0	0
	Improved	2	1	1	0	0	2	1	1	0	0
	Cured	3	3	0	0	0	3	3	0	0	0
	Cured	4	3	0	1	0	2	2	0	0	0
	Improved	4	2	2	0	0	3	2	1	0	0
	Cured	3	3	0	0	0	2	2	0	0	0
	Improved	3	3	0	0	0	3	3	0	0	0
	Cured	4	4	0	0	0	3	3	0	0	0
Total	Cured	348[b]	310	3	5	30[b]	252[b]	225	2	3	22[b]
	Improved	163	94	35	14	20	132	75	32	13	12

[a] Clinical response is presented as cured, improved, or relapse for subjects who were evaluable for efficacy, had a Post-Therapy clinical response of cured or improved, and had their clinical response evaluated at the Post-Study visit.
[b] Subject 4060 had a clinical response of cured at the Post-Therapy evaluation and is included in this table as unable to evaluate for the Post-Study clinical response. However, in the clinical study database this subject erroneously was considered to be not applicable (N/A) for the Post-Study clinical evaluation.

Adapted from Applicant's Table 29, NDA 20-634 SE1-008, Vol. 25.3, pp. 197, 198

Nineteen patients from the clinically evaluable population and one additional patient from the intent-to-treat population were scored as clinical relapse at the Post-Study assessment. Eleven of these 20 patients with clinical relapse had an atypical pathogen at Admission. Three subjects with *S. pneumoniae* isolates (subjects 4041, 4054, and 27006) experienced clinical relapse.

MO Comment: Pt. No. 4041 had PSSP, H. influenza, and S. aureus in his admission respiratory culture, all sensitive to levofloxacin. This patient was judged a clinical relapse at Post-Study and microbiologic status at Post-Study was unknown.

Pt. No. 4054 had *S. pneumoniae* of unknown sensitivity from blood cultures. He was a clinical and microbiological relapse at the Post-Study visit.

Pt. No. 27006 had PSSP from a respiratory culture that was sensitive to levofloxacin. He was a clinical and microbiological relapse at the Post-Study visit.

Of the 20 patients with clinical relapse, 16 were microbiologically evaluable. Of these 16, 13 patients were considered to have microbiological relapse (presumed or documented). Among these 13 patients, the most common admission pathogens were *M. pneumoniae* (7 patients), *S. aureus* (4 patients), and *P. aeruginosa* (4 patients). None of the subjects with relapse developed a new infection.

Microbiological Efficacy

In Vitro Susceptibility for All Admission Pathogens

Levofloxacin susceptibility results were available for 362 of the 407 pathogens obtained from admission cultures (respiratory and blood). Ninety-eight percent (355/362) of the pathogens were susceptible to levofloxacin, 1% (3/362) were resistant to levofloxacin, and 1% (4/362) were intermediate to levofloxacin (Table 15). One of the 3 resistant isolates was a *S. pneumoniae* (PISP), 2 were *S. aureus*, one of which was methicillin-resistant.

> **MO Comment:** Pt. No. 3026 from this study (LOFBIV-PCAP-001) is the patient with CAP and levofloxacin resistant PISP from his sputum culture. The clinical details of his case are discussed in the section of this document entitled, Integrated Summary of Efficacy for LEVAQUIN for the Treatment of CAP due to PRSP. The patient was scored as a clinical cure and microbiological eradication at both the Post-Therapy and Post-Study assessments.

Table 15: In Vitro Susceptibility to Levofloxacin of All Respiratory and Blood Pathogens Isolated at Admission: Intent-to-Treat Subjects (Protocol LOFBIV-PCAP-001)

Susceptibility of Pathogens	Levofloxacin[a] (N=407)	
Susceptible	355	(98.1%)
Intermediate	4	(1.1%)
Resistant	3	(0.8%)
Unknown	45	

[a] Percentages are based on numbers of pathogens with known susceptibilities. Pathogens were isolated from 307 subjects.

Adapted from the Applicant's Table 18 , NDA 20-634 SE1-008, Vol. 25.3, p. 181

Post-Therapy Microbiologic Response for All Subjects with Community-Acquired Pneumonia

The Applicant's protocol specified primary efficacy variable was microbiologic response at the Post-Therapy visit.

The Applicant analyzed microbiological response rates for the intent-to-treat and the microbiologically evaluable populations (Table 16). Following Table 16, analyses of microbiological response rates by study center, by pathogen, and by disease severity, will be presented for the microbiologically evaluable population. Then the microbiological response results for the Post-Study visit will be presented