Medical Officer Review of Pediatric sNDAs

Submission Number	20-634/S-043, 21-635/S-046, 21-721/S-011
Applicant	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Letter Date	December 20, 2006
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Reviewer Name	Kassa Ayalew, M.D.
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Review Completion Date	Tuesday, June 19, 2007
Established Name	LEVOFLOXACIN
Trade Name	LEVAQUIN®
Therapeutic Class	FLUOROQUNOLONE
Formulation	Tablets, IV and Solution
[redacted] (b) (4)	
Indication	Not applicable
Intended Population	Pediatrics 6 months to 16 years of age
Subject	Requesting six months of pediatric exclusivity for products, labeling change

Table of Contents

Page

1 Recommendations on Approvability

Levofloxacin, the L-isomer of ofloxacin, is a synthetic broad-spectrum fluoroquinolone antibacterial agent. The tablet, intravenous (i.v.), and oral solution formulations have been approved by the United States Food and Drug Administration (FDA) for the treatment of: complicated and uncomplicated urinary tract infections, acute pyelonephritis, chronic prostatitis, complicated and uncomplicated skin and skin structure infections, community-acquired pneumonia (CAP, including that due to multi-drugresistant Streptococcus pneumoniae), nosocomial pneumonia, acute bacterial sinusitis, and acute bacterial exacerbation of chronic bronchitis and as postexposure prophylaxis against Bacillus anthracis in adults (18 years of age and older).

The data reviewed in this supplemental New Drug Application support the approval of a labeling change. This recommendation is based on a review of safety and efficacy information on pediatric patients between 6 month and 16 years of age treated with levofloxacin for 10 to 14 days.

It is recommended that this labeling supplement be approved provided that the sponsor agrees with the labeling revisions proposed by the agency to addresses the musculoskeletal safety findings observed in children.

2 Background

This supplemental NDA was submitted by Johnson & Johnson Pharmaceutical Research & Development, L.L.C. on December 20, 2006. The Applicant submitted this supplemental NDA as response to the pediatric Written Request for Pediatric Studies that was issued originally on 20 December 2001 and issued in its final, amended form on 16 June 2006 . Prior to the submission of the sNDA the applicant had a Written Request for Pediatric Studies that was issued originally on 20 December 2001 and issued in its final, amended form on 16 June 2006.

The applicant Johnson & Johnson Pharmaceutical Research & Development, L.L.C was asked to provide the safety profile of levofloxacin to assess the potential for levofloxacin therapy to be associated with abnormalities in cartilage affecting normal joint function in children, antibacterial activity in pediatric patients with community acquired pneumonia including due to penicillin-resistant *S. pneumoniae and* pharmacokinetic of levofloxacin in pediatric subjects ($\geq$ 6 months to 17 years of age) with bacterial infections. The submissions in this review consist of safety and efficacy data from the Phase 3 studies during which study drug was administered in both active-controlled and uncontrolled manner.

The table below summarizes the studies performed in response to a Written Request and safety data from the two AOM studies.

Table 1: Summary of Phase 3 Pediatric Levofloxacin Studies (Studies LOFBIV-PCAP-003, LOFBO-OTMD-001, LOFBO-OTMD-002 and LOFBO-LTSS-001)

Disease & Study ID	Study Design	No. of Subjects (Levofloxacin/ Comparator)	Comparator(s) /Levofloxacin by Group	Duration of Treatment (days) Mean (Range)
Community-acquired pneumonia (LOFBIV-PCAP-003_	Open-label, randomized, active-comparator, non-inferiority, multicenter study in subjects >6 months to 16 years	728 (546/182)	Ceftriaxone, amoxicillin/ clavulnate, clarithromycin Group I (≥ 6 months to < 5 years) : 10 mg/kg oral suspension b.i.d. (up to 500 mg/day) Group II (≥ 5 to 16 years, inclusive): 10 mg/kg q.d	10.5 (1 - 32)
Acute otitis media (bacteriologic outcome)(LOFBO-OTMD-001)	Open-label, multicenter study in subjects > 6 months to < 5 years	204 (204/0)	10 mg/kg oral suspension b.i.d. (up to 500 mg/day)	9.9 (1 -21)
Acute otitis media (clinical outcome) (LOFBO-OTMD-002)	Evaluator-blinded, randomized, active-comparator, non-inferiority, multicenter study in subjects > 6 months to < 5 years	1650 (827/823)	Amoxicillin /clavulanate 10 mg/kg oral suspension b.i.d. (up to 500 mg/day)	10.2 (1 - 19)
LOFBO-LTSS-001)	phase 3, prospective, long-term, comparative, multicenter, observational study in subjects > 6 months to < 16 years	2233 1340/893	See LOFBO-OTMD-001 & LOFBO-OTMD-002	10.5 (1-30)

In addition to the above clinical studies the sponsor also submitted three pharmacokinetic studies (LOFBIV-PHI-057, LOFBIV-PHI-058, and LOFBO-PHI-115) that were initially submitted to NDA 20-634/S-035 on 25 May 2004, as a partial response. For the review details of the pharmacokinetic studies, please see Dr Seong H Jang.

3 Summary of the Study Results

A. Safety

A total of 1,534 subjects were exposed to levofloxacin and 989 were exposed to a comparator treatment in both active controlled and non comparative Phase 3 studies (CAP /AOM). The average duration of therapy for both the levofloxacin and comparator groups overall was 10.3 days. A total of 1,429 (93%) levofloxacin-treated subjects and 928 (94%) comparator-treated subjects completed the study procedures.The subjects ranged in age from 0.5 to 16.7 years; 49% were < 2 years of age. The majority of subjects were male (55%) and white (67%).

Demographic data and baseline characteristics (age, gender, country) for the PCAP and AOM studies are shown below:

Table 2: Demographics and Baseline Characteristics: Pooled Phase 3 Studies (StudiesLOFBIV-PCAP-003, LOFBO-OTMD-001, and LOFBO-OTMD-002: Safety Analysis Set)

	PCAP		**AOM**	
	Levofloxacin (N=533)	Comparator (N=179)	Levofloxacin (N=1,001)	Comparator (N=810)
Age(year)				
N	533	179	1001	810
Mean	5.49	5.39	1.99	2.10
SD	4.017	4.050	1.191	1.224
Median	4.90	4.60	1.60	1.70
Range	0.5-16.7	0.5-15.5	0.5-5.0	0.5-5.3
Age group, n (%)				
N	533	179	1001	810
<2 years	128 (24)	50 (28)	596 (60)	452 (56)
2-<6 years	188 (35)	59 (33)	405 (40)	358 (44)
6-<12 years	168 (32)	55 (31)	0	0
12-<17 years	49 (9)	15 (8)	0	0
Sex, n (%)				
N	533	179	1001	810
Male	269 (50)	91 (51)	560 (56)	464 (57)
Female	264 (50)	88 (49)	441 (44)	346 (43)
Race, n (%)				
N	533	179	1000	810
White	268 (50)	97 (54)	740 (74)	584 (72)
Black	54 (10)	17 (9)	57 (6)	41 (5)

Asian	2 (<1)	0	11 (1)	6 (1)
Othera	209 (39)	65 (36)	192 (19)	179 (22)
Baseline weight(kg)				
N	533	179	1001	810
Mean	21.4	21.3	12.3	12.6
SD	14.27	15.50	3.56	3.45
Median	17.2	17.0	11.5	12.0
Range	4-97	4-137	6-38	6-29
Baseline height(cm)				
N	524	176	981	798
Mean	106.7	106.6	84.3	85.5
SD	27.00	27.76	11.88	11.74
Median	106.0	104.0	82.0	83.8
Range	56-179	55-182	60-130	60-120
Country, n (%)				
N	533	179	1001	810
Argentina	26 (5)	9 (5)	133 (13)	108 (13)
Brazil	78 (15)	27 (15)	45 (4)	45 (6)
Chile	11 (2)	4 (2)	67 (7)	67 (8)
Costa Rica	146 (27)	50 (28)	261 (26)	218 (27)
Israel	0	0	82 (8)	0
Mexico	118 (22)	40 (22)	0	0
Panama	51 (10)	15 (8)	29 (3)	27 (3)
United States	103 (19)	34 (19)	384 (38)	345 (43)

Source: sponsors submission

The most frequently reported adverse events involved the System Organ Class of Infections and Infestations (30% levofloxacin, 33% comparator. Diarrhea was the most frequent adverse event (11% levofloxacin, 18% comparator).Most adverse events were mild to moderate in severity and evaluated by the investigators as having no relationship or an unlikely relationship to study therapy. The incidence of serious adverse events was low in both treatment groups: 3% levofloxacin group, 2% comparator group. Musculoskeletal adverse events were reported in 3% of subjects in both treatment groups. The most common MS adverse events, arthralgia and myalgia, were reported in 1% of subjects in each treatment group. All other MS adverse events were reported in <1% of subjects. Musculoskeletal disorders (as classified by the DSMC) were reported in 32 subjects (25 [1.6%] in levofloxacin-treated, 7 [<1%] in comparator-treated subjects). There were more MS disorders reported in the weight-bearing joints (23 [1.5%] levofloxacin, 6 [0.6%] comparator) than in the non-weight bearing joints (1 [0.1%] both treatment groups.

Table 3 shows the summary of treatment-emergent adverse events occurring in ≥3% of subjects by indication.

Table 3. Incidence of Treatment-Emergent Adverse Events Occurring in ≥3% of Subjects in any Treatment Group by indication, System Organ Class, and Preferred Term: Pooled Phase 3 Studies (Studies LOFBIV-PCAP-003, LOFBO-OTMD-001, and LOFBO-OTMD-002)

Indication	**PCAP**		**AOM**		**Total**	
System Organ Class	Levofloxacin	Comparator	Levofloxacin	Comparator	Levofloxacin	Comparator
Preferred Term	(N=533)	(N=179)	(N=1,001)	(N=810)	(N=1,534)	(N=989)
Total no. subjects with adverse events	304 (57)	103 (58)	642 (64)	533 (66)	946 (62)	636 (64)
Infections and infestations	120 (23)	43 (24)	334 (33)	279 (34)	454 (30)	322 (33)
Upper respiratory tract infection	31 (6)	14 (8)	72 (7)	67 (8)	103 (7)	81 (8)
Otitis media	6 (1)	1 (1)	99 (10)	57 (7)	105 (7)	58 (6)
Nasopharyngitis	9 (2)	2 (1)	37 (4)	37 (5)	46 (3)	39 (4)
Acute otitis media	1 (<1)	0	43 (4)	14 (2)	44 (3)	14 (1)
Pneumonia	15 (3)	4 (2)	4 (<1)	8 (1)	19 (1)	12 (1)
Gastrointestinal disorders	108 (20)	41 (23)	252 (25)	219 (27)	360 (23)	260 (26)
Diarrhoea	38 (7)	19 (11)	138 (14)	162 (20)	176 (11)	181 (18)
Vomiting	36 (7)	16 (9)	110 (11)	70 (9)	146 (10)	86 (9)
Abdominal pain	21 (4)	6 (3)	19 (2)	12 (1)	40 (3)	18 (2)
Skin and subcutaneous tissue	61 (11)	15 (8)	171 (17)	166 (20)	232 (15)	181 (18)
disorders						
Dermatitis diaper	15 (3)	3 (2)	62 (6)	81 (10)	77 (5)	84 (8)
Rash	9 (2)	1 (1)	37 (4)	24 (3)	46 (3)	25 (3)
Dermatitis	6 (1)	1 (1)	34 (3)	26 (3)	40 (3)	27 (3)
Respiratory, thoracic and mediastinal	80 (15)	32 (18)	122 (12)	104 (13)	202 (13)	136 (14)
disorders						
Cough	11 (2)	5 (3)	49 (5)	40 (5)	60 (4)	45 (5)
Rhinorrhoea	12 (2)	4 (2)	39 (4)	27 (3)	51 (3)	31 (3)
Bronchospasm	16 (3)	9 (5)	8 (1)	11 (1)	24 (2)	20 (2)
Asthma	17 (3)	4 (2)	5 (<1)	6 (1)	22 (1)	10 (1)
General disorders and administration	29 (5)	15 (8)	122 (12)	94 (12)	151 (10)	109 (11)
site conditions						
Pyrexia	17 (3)	13 (7)	93 (9)	77 (10)	110 (7)	90 (9)
Irritability	3 (1)	0	27 (3)	19 (2)	30 (2)	19 (2)
Nervous system disorders	29 (5)	11 (6)	18 (2)	18 (2)	47 (3)	29 (3)
Headache	19 (4)	6 (3)	5 (<1)	5 (1)	24 (2)	11 (1)

Note: Percentages in 'Total' column for each group calculated with the number of subjects in each group as denominator. Percentages of treatment group sub-groups calculated with number of subjects per sub-group as denominator.

1,340 (87%) of the 1,534 levofloxacin-treated subjects and 893 (90%) of the 989 comparator-treated subjects continued to and were evaluable for the safety analyses in the long-term follow-up study LOFBO-LTSS-001. Of these subjects, 1,199 (89%) levofloxacin-treated subjects and 804 (90%) comparator-treated subjects completed the study. The primary reason for discontinuation was "Lost to follow-up" (9% in each group).

Musculoskeletal adverse events were reported in 8% of levofloxacin-treated subjects compared to 6% of comparator-treated subjects. This difference was not statistically significant (p-value: 0.060). The most common MS adverse events in both treatment groups were arthralgia (36 [3%] levofloxacin subjects, and 15 [2%] comparator subjects) and Myalgia (26 [2%] levofloxacin subjects, and 13 [1%] comparator subjects).

Pediatric subjects treated for an acute bacterial infection with levofloxacin showed a significantly higher incidence of MS disorders (defined in the protocol as tendinopathy, arthritis, arthralgia, or gait abnormality) compared to 'standard' non-fluoroquinolone therapy (comparator) (p-value: 0.038) at the 60-day period after the first dose. Arthralgia was the most frequently occurring MS disorder occurring at the 30-day, 60-day, and 1-year period after the first dose for both treatment groups (please see the table below):

Table 4: The incidences of musculoskeletal disorders in the 60-day and 1 year period after the first dose study drugs are summarized below:

Follow-up Period	Levofloxacin	*Non-Fluoroquinolone	P-value[a]
60 days	n=1340 (%)	n=883 (%)	p=0.038
	28 (2.1%)	8 (0.9%)	
1 year	n=1199 (%)	n=804 (%)	p=0.024
	46 (3.8%)	16 (2.0%)	

[a] Pairwise comparison: 2-sided Fisher's exact test, *Non-Fluoroquinolone: Ceftriaxone, amoxicillin/ clavulnate, clarithromycin

Most of the musculoskeletal disorders reported in the weight-bearing joints at 1-year (39 [3.2 %] levofloxacin, 14 [1.7%] comparator) than in the non-weight bearing joints (6 [0.5 %] levofloxacin, 3 [0.4 %] comparator) . The incidence of musculoskeletal disorders that occurred at weight-bearing joints was significantly higher in the levofloxacin-treated compared to the non-fluoroquinolone treated group at 60-day (p-value: 0.025), and 1-year (p-value: 0.047) periods after the first dose.

The majority of musculoskeletal disorders resolved within 10 days (56% and 59%, respectively) and was self limited.

(b) (4)

The Applicant is not requesting approval for CAP or AOM indication for pediatric use. (b) (4) The AOM studies which are submitted primarily for safety reasons were not a part of Pediatric Written Request.

Participants in the CAP study ranged in age from 6 months to 16 years. Participants in the otitis media studies ranged in age from 6 months to 5 years. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

C. Brief Statement of Conclusions

The most important safety finding was the results of the reviewed prospective, long term, surveillance study where 1340 pediatric patients (6 months to 16 years of age) received 10 mg/kg of levofloxacin twice a day (6 month to 5 years of age) days and children 10 mg/kg to a maximum of 500 mg of levofloxacin once a day or non fluoroquinolone therapy for approximately 10 days in the CAP and AOM trials demonstrated the higher incidence rate of protocol-defined musculoskeletal disorders (arthralgia, arthritis, tendinopathy or gait abnormality) in the levofloxacin treated patients occurring within 60 days and 1 year of exposure to the drug.

At the present time, the Applicant is not requesting approval for any indication for pediatric use and has determined that the risks associated with use of levofloxacin in pediatric subjects for treatment of community acquired pneumonia outweighs the benefits observed in the clinical trials submitted with this supplemental NDA (the long-term safety surveillance study). As recognized by the applicant, based on the above findings from the clinical trials reviewed (based on the exposure of 1534 pediatric patients to levofloxacin across 3 active controlled or single arm open-label Phase 3 clinical trials), it is determined that the risks associated with use of levofloxacin in pediatric subjects for treatment of community acquired pneumonia and acute otitis media may outweighs the benefits observed in the clinical trials. The company included the summary of musculoskeletal safety findings in the labeling. The submission consists a proposed labeling that complies with the Physician Labeling Rule based on a review of Levofloxacin activity, safety, pharmacokinetic, and dosing information in pediatric patients above 6 months of age.

Based on the review of the data submitted in the NDA, it is recommended that the application for levofloxacin (LEVAQUIN®) be approved dependant upon the label negotiation.

4 DRUG ESTABLISHED AND PROPOSED TRADE NAME, DRUG CLASS, SPONSOR'S PROPOSED INDICATION(S), (b) (4) AGE GROUPS

Established Name	LEVOFLOXACIN
Trade Name	LEVAQUIN®
Therapeutic Class	FLUOROQUNOLONE
Priority Designation	6 Month Review
Formulation	Tablets, IV and Solution
(b) (4)	
Indication	Not applicable
Intended Population	Pediatrics 6 months to 16 years of age
Subject	Requesting six months of pediatric exclusivity for products, labeling change

5 Clinical Study by Indication

5.1 LONG TERM ACTIVE SURVEILLANCE STUDY OF MUSCULOSKELETAL DISORDERS (LOFBO-LTSS-001)

The study was a prospective, long-term, comparative, multicenter, observational study conducted in the United States, Argentina, Brazil, Chile, Costa Rica, Israel, Mexico, and Panama.

5.1.1 Objectives /Endpoints

The primary objective and endpoint of this study was to evaluate and compare the overall incidence of musculoskeletal (MS) disorders (tendinopathy, arthritis, arthralgia, and gait abnormality) in pediatric subjects that occurred during the 60-day period after the first dose of levofloxacin with that of 'standard' non-fluoroquinolone therapy (comparator) for an acute bacterial infection. Secondary objectives included assessment of 1) overall incidence of MS disorders including impaired growth in the 1-year period after the first dose, 2) incidence of MS disorders that occurred at weight- and non-weight-bearing joints in the 30-day, 60-day and 1-year periods after the first dose, and 3) incidence of each MS disorder including impaired growth (1-year only) in the 30-35 days, and from the 35-day visit through the 1-year follow-up visit and 1-year periods after the first dose. Safety was also to be evaluated by monitoring MS and serious adverse events (SAE) and changes in physical examination findings.

5.1.2 Inclusion Criteria

Male and female subjects aged 6 months to 16 years who took at least 1 dose of levofloxacin or comparator as part of a Phase 3 levofloxacin study to treat an acute bacterial infection.

Received at least 1 dose of levofloxacin or comparator as part of the studies in the community acquired pneumonia and two controlled and uncontrolled studies in acute otitis media

Subject's parent(s) or legal guardian(s) read and signed the informed consent

5.1.3 Exclusion Criteria

There were no exclusion criteria for this study

5.1.4 Treatment

Levofloxacin oral suspension 10 mg/kg b.i.d. (up to 500 mg/day) for children (≥ 6 months to < 5 years) and 10 mg/kg oral suspension q.d up to 500 mg/day (≥ 5 to 16 years) were administered for 10 to 14 days (see table 1 for the study details). Comparator patients received ceftriaxone or amoxicillin/ clavulanate or clarithromycin.

Children participating in clinical trials aimed at assessing the safety and efficacy of levofloxacin as treatment for community acquired pneumonia (LOFBIV-PCAP-003) or acute otitis media (LOFBO-OTMD-001, -002) were eligible to participate in LOFBOLTSS- 001 with the goal of extending observations related to the MS system in these children beyond the treatment phase of these efficacy trials.

One of these trials LOFBO-OTMD-001 was an open-label non-comparative trial involving treatment of children with acute otitis media. The other trials were randomized comparative trials. LOFBO-OTMD-002 was a large trial in which investigators, but not parents or children were blinded to study drug assignment. LOFBIV-PCAP-003, was an open-labeled trial in which both investigators and subjects were not blinded to study drug assignment. All subjects completed this long-term, surveillance study.

5.1.5 Study Evaluation Procedures

Safety was evaluated by monitoring MS disorders (including impaired growth), MS and serious adverse events, and changes from baseline in physical examination findings and measurement of height. Any MS or serious adverse events persisting at the end of the study were to be followed until resolution, or until they reached a clinically stable endpoint. Safety evaluations for MS adverse events were to be performed throughout the study as a means of active surveillance for MS disorders. The objective of this study is the incidence of musculoskeletal adverse events; therefore only musculoskeletal adverse events were to be reported. Non-musculoskeletal adverse events were not to be collected as part of this study other than spontaneously reported non-musculoskeletal serious adverse events.

5.1.6 Study Evaluation Procedures

Table 6: Time and Events Schedule (Study LOFBO-LTSS-001)

	Screening		Telephone Contact	Surveillance Telephone Contacts				Musculoskeletal Disorder Follow-up[b]
	Visit 1			Visit 2	Visit 3	Visit 4	Visit 5 (or early withdrawal)	Visit 6, 7, 8, 9
Visit Study Day	Predoising	10-17 days after last dose	25-35 days after last dose	54-64 days after first dose	80-90 days after first dose	170-180 days after first dose	350-375 days after first dose	Yearly
Screening Procedures								
Informed consent/assent[c]		X						
Inclusion/exclusion		X						
Medical history	X							
Physical examination (including MS examination with evaluation of joints)	X							
Height								
Growth curve[d]		X						
Surveillance Procedures								
Interval history interview[e]			X	X	X	X	X	X
Physical examination (including MS examination with evaluation of joints)		X					X	X
Height		X					X	X
Decision of need for follow-up							X	
MS adverse event monitoring[f]	X	X	X	X	X	X	X	X
MS data sheet							X[g]	X[g]

a Shading indicates procedures performed as part of a previous Phase 3 protocol. All data required by the current protocol and collected as part of the Phase 3 studies from predosing through the 25 to 35 days after last dose was copied (by the Sponsor) to the database for Visit 1 of this study. NOTE: Subjects who withdrew from a Phase 3 study before the visit at 10 to 17 days after last dose had these procedures and evaluations performed at a visit 10 to 17 days after the last dose as part of procedures for this study. The telephone contact 25 to 35 days after last dose was performed only as part of the Phase 3 study.

B For subjects who experienced a MS disorder during the 1-year Surveillance Phase and required follow-up beyond 1 year, as determined by an expert advisory group (DSMC). Visits were performed yearly within ± 30 days of the 1-year anniversary of Visit 5 and continued for 5 years after the first dose of antimicrobial therapy in the preceding Phase 3 study.

C Assent was typically obtained for subjects 6 years of age and older, depending on the individual child's ability to understand the study and the institutional policies. Subjects could have been consented/assented for participation in this study at any time after the first dose of study drug (levofloxacin or comparator) and before the last scheduled visit in the Phase 3 study. Consent/assent must have been obtained before procedures specific to this study were performed (i.e., collection of historical height measurements for construction of a growth curve).

D Growth curve was to be constructed for subjects who had at least 3 height measurements (collected at least 1 month apart) recorded before the first dose of study drug (levofloxacin or comparator).

E Focused on assessing the occurrence of MS adverse events.
F Subjects with signs or symptoms of a MS disorder were evaluated within 72 hours of presentation by an investigator trained in evaluation of joint pathology or in consultation with aspecialist (e.g., orthopedist, rheumatologist [preferably a pediatric rheumatologist]).The appropriateness of additional examinations (e.g., MRI, ultrasound, x-ray) of the involved joint was assessed by the trained investigator or in consultation with the specialist. All MS adverse events were to be evaluated according to the procedures listed on the MS Data Sheet. The specialist evaluating the MS adverse event must have remained blinded to study therapy for subjects who entered from randomized studies.
G Only completed for subjects who had a MS adverse event during the 1-year Surveillance Phase.
Source: Sponsors Submission

Screening
The screening phase for this study (predosing to 10-17 days after the last dose in the previous study) included evaluations performed as part of both the previous Phase 3 pediatric study and the current study, and included: review of inclusion criteria, medical history, physical examination (with MS examination with evaluation of the joints), and height.

A growth curve was constructed for subjects who had at least 3 predosing documented height measurements (collected at least 1 month apart). In addition to the informed consent/assent obtained in the previous Phase 3 pediatric study, a separate written informed consent was required for this study from a parent or guardian and assent from subjects > 6 years of age, depending on the child's ability to understand the study and institutional policies.

Surveillance
Eligible subjects were evaluated up to 375 days after the first dose of study drug in the previous Phase 3 study.

The surveillance procedures (interval history interview [focused on occurrence of MS adverse events], physical examination including MS examination with evaluation of joints, height measurement, and MS adverse event monitoring) conducted as part of Visit 1 were performed as part of the previous Phase 3 study. Telephone contacts were performed, 25 to 35 days (Visit 1), 54 to 64 days (Visit 2), 80 to 90 days (Visit 3), and 170 to 180 days (Visit 4) after the first dose of study drug, using a standardized questionnaire that focused on assessing the occurrence of MS adverse events. At Visit 5 (350 to 375 days after the first dose of study drug) or at the time of early withdrawal, the interval history interview, physical examination (including MS examination with evaluation of joints), height measurement, and MS adverse event monitoring were repeated. The MS Data Sheet was required to be completed at this visit for all subjects who had MS adverse events during the 1-year Surveillance Phase. At that time, the DSMC reviewed all MS adverse events and classified them into categories based on the cause of the adverse event, joint involvement, and on the results of physical examinations, laboratory findings, or imaging, and determined the relationship to study drug (regardless of whether treatment included levofloxacin or comparator). The DSMC also determined whether a subject needed further follow-up. All available data as of the 04 October 2006 data cutoff are included for the review.

Musculoskeletal Disorder Follow-up
All subjects who had 1 or more adverse events that could be classified to 1 of the specific MS disorders (tendinopathy, arthritis, arthralgia or gait abnormality) during the Surveillance Phase were to have their data evaluated by the responsible investigator, and the DSMC to determine the need for further follow-up. All follow-up visits were to be completed yearly within ± 30 days of the anniversary of Visit 5 for 5 years after their first dose of therapy. At each follow-up visit, an interval history interview was to be performed using the same standardized questionnaire that focused on assessing the occurrence of MS adverse events, the MS Data Sheet was to be completed, a physical examination (including MS examination with evaluation of joints) was to be performed, and height was to be measured.

Unscheduled Visit
Any subject who presented with arthralgia or clinical evidence of joint disease from the first dose of study drug (levofloxacin or comparator) through the final visit day (other than those who presented at a defined study visit) was to be evaluated at an unscheduled visit. This evaluation was to be performed according to procedures listed on the MS Data Sheet and included an examination by an investigator trained in evaluation of joint pathology or in consultation with a specialist (e.g., orthopedist, rheumatologist [preferably a pediatric rheumatologist]) within 72 hours of the subject's presentation. The appropriateness of additional examinations (e.g., magnetic resonance imaging [MRI], ultrasound, x-ray) of the involved joint was to be assessed by the trained investigator or in consultation with the specialist. The specialist evaluating the MS event was blinded to previous study therapy, and confirmation of this blinding was indicated on the MS Data Sheet.

Planned Analysis
The primary aim of the planned analysis was to determine: the overall incidence of MS disorders (tendinopathy, arthritis, arthralgia, and gait abnormality as defined in the protocol) during the 60-day period after the first dose of study drug (levofloxacin or comparator).

Secondary aims included determining:

- the overall incidence of MS disorders (including impaired growth) during the 1-year period after the first dose,
- incidence of each MS disorder at weight- and nonweight-bearing joints at 30-day (Days 1-34 from the start of study medication)
- incidence of each MS disorder at weight- and nonweight-bearing joints at 60-day (Days 1-64 from the start of study medication),
- incidence of each MS disorder at weight- and nonweight-bearing joints at 1-year (Days 1-375 from the start of study medication).
- incidence of tendinopathy, arthritis, arthralgia, and gait abnormality (30-day, 60-day)
- Incidence of tendinopathy, arthritis, arthralgia, and gait abnormality including impaired growth (1-year)
- Safety, by monitoring MS and serious adverse events (SAE) and changes in physical examination findings.
- Duration of musculoskeletal disorders in the 1-year period after the first dose

Musculoskeletal and serious adverse events were to be summarized by system organ class (SOC) using a MedDRA dictionary maintained by the Sponsor. The preferred term is the description most closely related to the investigator's terminology and the SOC is a broad category that includes related preferred terms. The severity (mild, moderate, marked) and relationship (not related, doubtfully, possibly, probably, or very likely) of MS adverse events to study drug were to be summarized by treatment for all events.

The incidence of MS adverse events were also to be summarized by treatment, age group, sex, those that occurred in the US vs. Non-US, and by race. Two-sided 95% exact confidence intervals (C.I.) were to be constructed for the incidence of serious adverse events, MS adverse

events, and MS disorders for each treatment group. The 2 treatment groups were also to be compared with respect to their incidence of MS adverse events and MS disorders using Fisher's exact test.

Deaths were to be listed and summarized. Descriptive narratives were to be provided for all subjects who had serious adverse event or MS adverse events and for those who entered the MS Disorder Follow-up Phase.

Definitions of MS disorders:

Tendinopathy: inflammation or rupture of a tendon as determined by physical examination, MRI or ultrasound;
Arthritis: inflammation of a joint as evidenced by redness or swelling of the joint;
Arthralgia: pain in the joint as evidenced by complaint or decreased or abnormal movement of the joint as determined by physical examination;
Gait abnormality: limping or refusal to walk.
Impaired growth (only subjects with at least 3 predosing height measurements): height measured approximately 1 year after enrollment that is >20% less than the expected height increase as determined by the growth curve constructed at study entry.

Growth curves on subjects with sufficient data (3 or more predose height easurements) using the Center for Disease Control (CDC) length-for-age (for children less than 36 months of age) and stature-for-age (for children 2-20 years of age) charts.

5.1.7 Statistical Methods

The single analysis population included subjects who took at least 1 dose of the study drug in the preceding Phase 3 studies, provided safety information after the first dose, and who enrolled in the current study. Subjects were assigned to the same treatment that they were assigned to in the preceding Phase 3 studies.

All subjects who participated in one of the Phase 3 levofloxacin clinical studies were eligible to enroll in this study. Based on this, the sample size was expected to be approximately 2200 to 2500 subjects depending on the number that consented to the long-term surveillance. It was anticipated that out of the 2200 to 2500 subjects enrolled in the study, there would be approximately 1100 levofloxacin-exposed subjects who would stay in the study for at least 1 year. This sample size was sufficient to exclude an incidence rate of >0.3% with 95% confidence if there were no serious adverse events in the population.

5.1.8 RESULTS AND ANALYSIS

5.1.9 Population

There were 2233 subjects (1340 levofloxacin, 893 comparator) who consented to participate in this study. A total of 1620 (73%) of these came from 2 otitis media studies and 613 (27%) of the subjects were enrolled in the community-acquired pneumonia study (Table 7).

Table 7: Number of Subjects in Previous Phase 3 Studies (Study LOFBO-LTSS-001: All Subjects Analysis Set)

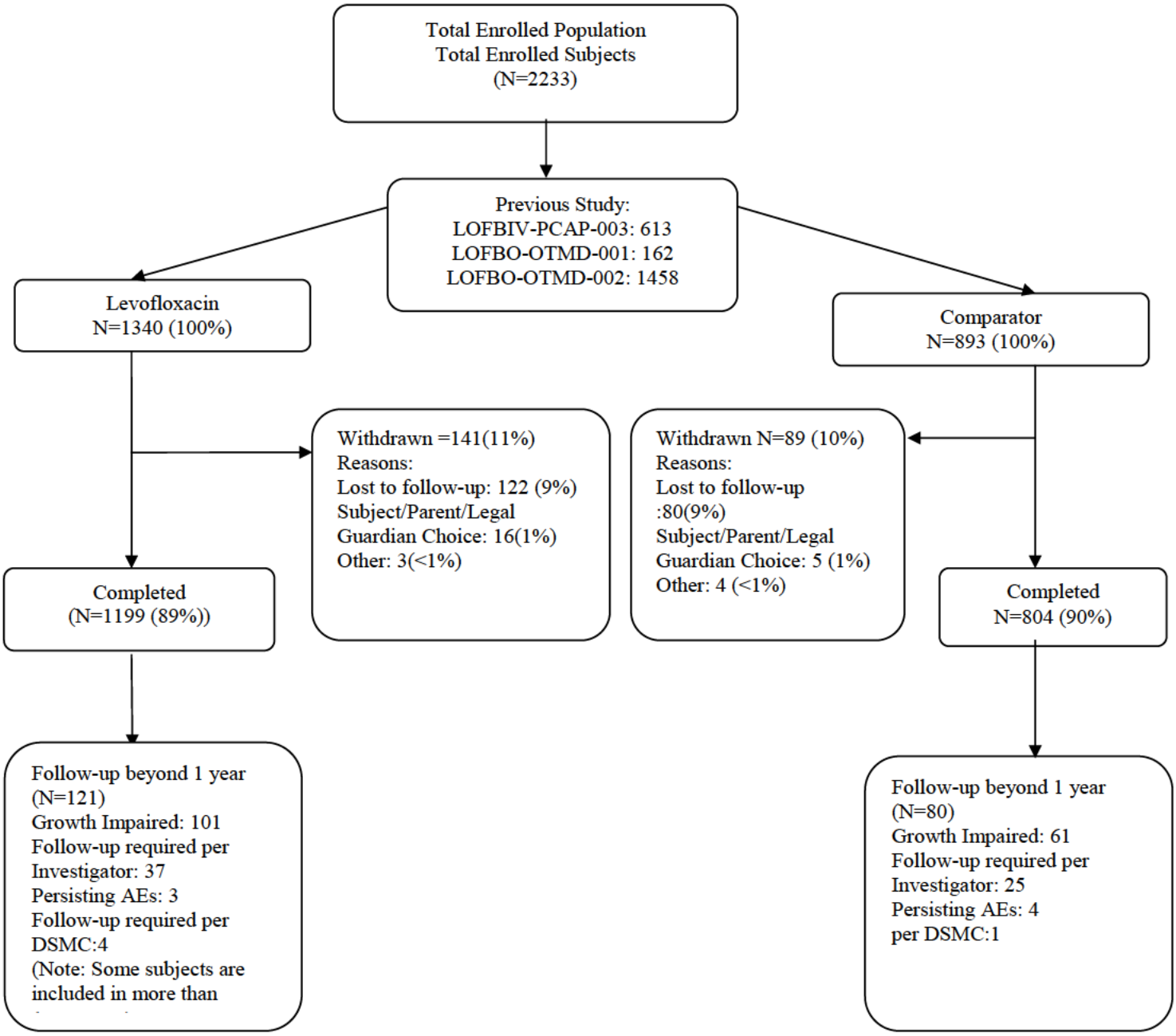
Previous Phase 3 Study	Levofloxacin n (%)	Comparator n (%)	Total n (%)
Community Acquired Pneumonia (CAP)	466 (35)	147 (16)	613 (27)
Acute Otitis Media (uncontrolled)	162 (12)	*0	162 (8)
Acute Otitis Media (Controlled)	712 (53)	746 (84)	1458 (65)
Total	1340	893	2233

*Comparator treatment not administered during the conduct of study LOFBO-OTMD-001
Source: Sponsors Submission

Medical Reviewer Comment: study LOFBO-OTMD-001 (uncontrolled) had no comparator arm and only 8% (162) of the patients were enrolled from the uncontrolled acute otitis media study.

Subject Enrollment and Disposition
Subject enrollment and disposition for the study is shown in figure 1.

Figure 1: Subject enrollment and disposition



Reviewer Comment: As shown in figure, there were about 10 % of patients who lost to follow and prematurely discontinued the study. There were no important differences between the two treatment groups in any of reasons for premature discontinuation.

5.1.10 Demographics

Demographic and baseline characteristic for the study are shown in Table 8. A total of 2,233 male and female subjects, 6 months to 16 years of age, who took at least 1 dose of levofloxacin or comparator as part of a Phase 3 clinical study were eligible to be enrolled in this trial. A total of 2003 (90%) subjects (89% levofloxacin and 90% comparator) completed the study. 141 (11%) of patients in levofloxacin and 89(10%)patients in the comparator group withdrawn from the study.

Table 8: Demographic and Baseline Characteristics (Study LOFBO-LTSS-001: Safety Analysis Set)

	Levofloxacin (N=1340)	Comparator (N=893)
Age (years)[a]		
N	1340	893
Mean (SD)	3.23 (3.099)	2.70 (2.392)
Median	2.10	1.90
Range	(0.5-16.7)	(0.5-15.0)
Age group[a]		
N	1340	893
<2 years	631 (47)	452 (51)
2-<6 years	516 (39)	379 (42)
6-<12 years	148 (11)	48 (5)
12-<17 years	45 (3)	14 (2)
Sex, n (%)		
N	1340	893
Male	726 (54)	507 (57)
Female	614 (46)	386 (43)
Race, n (%)		
N	1339	893
White	904 (68)	634 (71)
Black	83 (6)	40 (4)
Asian	13 (1)	6 (1)
Other[b]	339 (25)	213 (24)
Baseline weight (kg)		
N	1340	893
Mean (SD)	15.6 (10.08)	14.2 (7.87)
Median	12.5	12.5
Range	(4-97)	(4-137)
Height (cm)		
N	1330	884
Mean (SD)	92.3 (21.73)	89.4 (17.65)
Median	86.4	85.5
Range	(56-179)	(55-182)
Country, n (%)		
N	1340	893
Argentina	142 (11)	111 (12)
Brazil	113 (8)	65 (7)
Chile	75 (6)	69 (8)
Costa Rica	384 (29)	254 (28)
Israel	58 (4)	0
Mexico	112 (8)	35 (4)
Panama	47 (4)	31 (3)

United States	409 (31)	328 (37)
Pubescence stage, n (%)		
N	1340	893
Prepubescent	1264 (94)	865 (97)
Pubescent	63 (5)	28 (3)
Postpubescent	13 (1)	0

[a] At time of entry in the previous Phase 3 pediatric studies [b] "Other" includes Hispanic and mixed-race subjects.
Source: Sponsors Submission

Medical Reviewer Comment: The mean age of enrolled patients in the study was 2 years. Approximately 48% of patients were younger than 2 years of age. The mean weight of patients was 12.5 kg. The majority of patients in this study were males, Caucasian and were enrolled from US and Costa Rica.

There were no clinical important differences in any of the baseline demographic characteristics between the two treatments. Based on a review of literature, fluoroquninolone induced tendonopathy appears to occur in patients with concomitant use of corticosteroid, chronic renal failure, advanced age.

5.1.11 Extent of Exposure

Exposure to study drug was summarized using duration of therapy and summarized below.

Table 9: Duration of Therapy by Time Intervals in the Previous Phase 3 Studies
(Study LOFBO-LTSS-001: Safety Analysis Set)

Duration of therapy (days) n (%)	Levofloxacin (N=1340)	Comparator (N=893)
<7	44 (3)	25 (3)
7-11	1166 (87)	811 (91)
12-15	120 (9)	54 (6)
>15	10 (1)	3 (<1)
Mean (SD)	10.5 (1.86)	10.5 (1.62)
Median	11.0	11.0
Range	(1 - 30)	(1 - 32)

Source: Sponsors Submission

Medical Reviewer Comment: The average duration of therapy for both the levofloxacin and comparator groups overall was 10.5 days which is consistent with the protocol specified durations of therapy of 10 days. Most subjects completed at least 7 days of their assigned treatment in both treatment groups. This is similar and consistent across the three studies.

5.1.12 Concomitant Therapies

No study drug was administered in this surveillance study. Subjects requiring additional antimicrobial therapy after completion of the course of therapy in the previous Phase 3 study were to have a non-fluoroquinolone prescribed, if possible. Treatment with quinolones, chronic corticosteroids (prednisone [or its equivalent] >2 mg/kg or > 20mg/day >14 days) or nonsteroidal anti-inflammatory drugs (NSAIDs, >14 days) taken at any time during the study were to be documented on the CRF.

The concomitant fluoroquinolones, corticosteroids, and NSAIDS us during the Phase 3 long-term safety surveillance study is shown below:

(b) (4)

Medical Reviewer Comment: (b) (4)

5.1.13 Discontinuations of Study Drug

A total of 2003 (90%) subjects (89% levofloxacin and 90% comparator) completed the study. Because there was no administration of drugs there was no discontinuation of the study drugs due to adverse events. Musculoskeletal adverse events were evaluated because they were known to be of clinical concern among patients treated with levofloxacin.

5.1.14 Incidence of Musculoskeletal Adverse Events

The musculoskeletal adverse events in the 1 year period have been summarized below:

Table 11: Incidence of Musculoskeletal Adverse Events by Preferred Term (Study LOFBO-LTSS-001: Safety Analysis Set) in the 1 year period.

System organ class Preferred Term	Levofloxacin (N=1340)		Comparator (N=893)		P-value[b]
	n (%)	95%CI[a]	n (%)	95%CI[a]	
Total no. subjects with MSD adverse event	103 (8)	(6.3; 9.2)	50 (6)	(4.2; 7.3)	0.060
Arthralgia	36 (3)	(1.9; 3.7)	15 (2)	(0.9; 2.8)	0.148
Myalgia	26 (2)	(1.3; 2.8)	13 (1)	(0.8; 2.5)	0.416
Pain in extremity	14 (1)	(0.6; 1.7)	10 (1)	(0.5; 2.0)	>0.999
Pathological fracture	9 (1)	(0.3; 1.3)	6 (1)	(0.2; 1.5)	>0.999
Arthropathy	8 (1)	(0.3; 1.2)	6 (1)	(0.2; 1.5)	>0.999
Back pain	6 (<1)	(0.2; 1.0)	0	(0.0; 0.4)	0.087
Bone disorder	2 (<1)	(0.0; 0.5)	1 (<1)	(0.0; 0.6)	>0.999
Myopathy	2 (<1)	(0.0; 0.5)	0	(0.0; 0.4)	0.520
Synovitis	2 (<1)	(0.0; 0.5)	0	(0.0; 0.4)	0.520
Bone development abnormal	1 (<1)	(0.0; 0.4)	0	(0.0; 0.4)	>0.999
Hemarthrosis	1 (<1)	(0.0; 0.4)	0	(0.0; 0.4)	>0.999
Joint swelling	1 (<1)	(0.0; 0.4)	0	(0.0; 0.4)	>0.999
Muscle disorder	1 (<1)	(0.0; 0.4)	0	(0.0; 0.4)	>0.999
Musculoskeletal pain	1 (<1)	(0.0; 0.4)	1 (<1)	(0.0; 0.6)	>0.999
Myositis	1 (<1)	(0.0; 0.4)	0	(0.0; 0.4)	>0.999
Polymyalgia	1 (<1)	(0.0; 0.4)	0	(0.0; 0.4)	>0.999
Synovial cyst	1 (<1)	(0.0; 0.4)	0	(0.0; 0.4)	>0.999
Tendonitis	1 (<1)	(0.0; 0.4)	0	(0.0; 0.4)	>0.999
Arthritis reactive	0	(0.0; 0.3)	1 (<1)	(0.0; 0.6)	0.400
Muscular weakness	0	(0.0; 0.3)	1 (<1)	(0.0; 0.6)	0.400
Scoliosis	0	(0.0; 0.3)	1 (<1)	(0.0; 0.6)	0.400
Shoulder pain	0	(0.0; 0.3)	1 (<1)	(0.0; 0.6)	0.400
Tendon disorder	0	(0.0; 0.3)	1 (<1)	(0.0; 0.6)	0.400

Note: Percentages calculated with the number of subjects in each group as denominator.
Musculoskeletal and serious adverse events were summarized by system organ class (SOC) using a MedDRA dictionary maintained by the Sponsor. In this dictionary, the preferred term is the description most closely related to the investigator's terminology and the SOC is a broad category that includes related preferred terms.
[a] Exact interval for binomial parameter. Numbers represent percentages
[b] Pairwise comparison: 2-sided Fisher's exact test
Source: Sponsors Submission

Medical Reviewer Comments: A total of 103 out of 1340 (8%) subjects in the levofloxacin group and 50 out of 893 (6%) subjects in the comparator group reported at least 1 MS adverse event

during the 1-year period. The difference in the incidence of these events between the treatment groups was numerically small and not statistically significant (p-value: 0.060). The most common MS adverse events in both treatment groups were arthralgia (36 [3%] levofloxacin subjects, and 15 [2%] comparator subjects) and myalgia (26 [2%] levofloxacin subjects, and 13 [1%] comparator subjects). No other event occurred at a rate >1% in either group.

In addition to reviewing the overall MS adverse events during the 1-year period we also evaluated the incidence of musculoskeletal adverse events up to the 35-Day Visit and from the 35-day visit through the 1-year follow-up visit. At both time points, the difference in the incidence of Musculoskeletal Adverse Events by preferred term was higher in levofloxacin treated subjects.

5.1.15 Incidence of Musculoskeletal Adverse Events in the 1 year period by Severity

The musculoskeletal adverse events divided into defined severity categories (mild, moderate, severe) are presented below

Table 12: Incidence of Musculoskeletal Adverse Events by Severity in the 1 year period

Category	Levofloxacin (N=1340)	Comparator (N=893)
Total n (%)	103 (8)	50 (6)
Mild	76 (74)	38 (76)
Moderate	24(23)	10 (20)
Marked	3 (3)	2(4)

Source: Sponsors Submission

Medical Reviewer Comment: Five subjects had events that were marked in severity. These included one event each of arthralgia, pathological fracture, and myositis (left gluteus myositis) in subjects administered levofloxacin, and 1 event each of pathological fracture and arthropathy in comparator-treated subjects. Most patients experienced musculoskeletal adverse events that were mild in severity.

5.1.16 Incidence of Musculoskeletal Adverse Events by Relationship to Study Drug

Table 13 :Incidence of Musculoskeletal Adverse Events by Relationship to Study Drug

Category	Levofloxacin (N=1340)	Comparator (N=893)
Total n (%)	103 (8)	50 (6)
Not Related	74 (71.8)	47 (94)
Doubtfully Related	14 (13.6)	2 (4)
Possibly Related	8 (7.7%)	1 (2)
Probably Related	4 (3.8)	0
Very likely Related	0	0

Source: Sponsors Submission

Medical Reviewer Comment: Four events were determined to be probably related to study drug. These included 2 subjects with arthralgia and 1 each with myalgia and pain in extremity. All four of these subjects received levofloxacin.

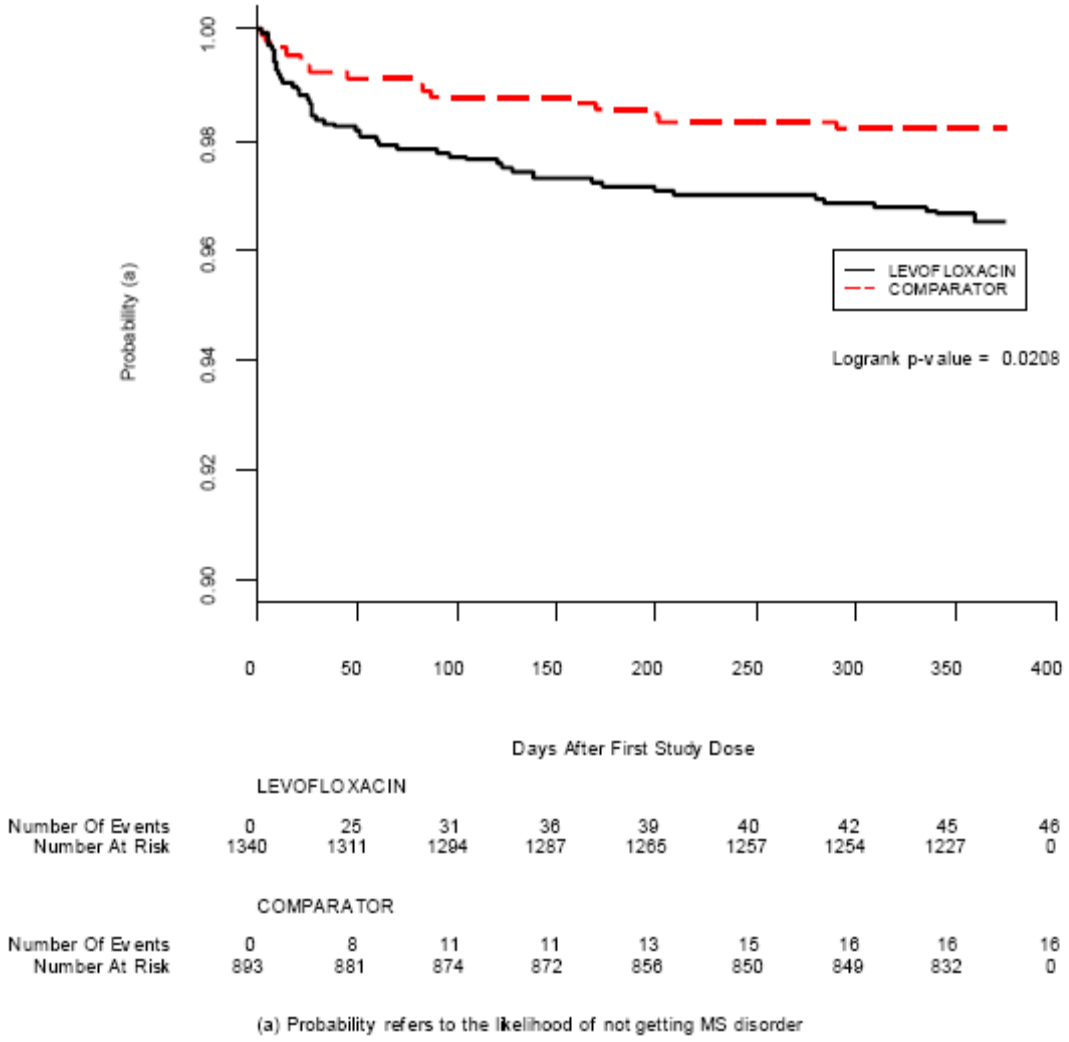
5.1.17 Incidence of Musculoskeletal Disorders as Defined by the Protocol

Incidence of musculoskeletal disorder over the 1 year of follow-up

The primary aim of the study was the analysis of the overall incidence of MS disorders (tendinopathy, arthritis, arthralgia, and gait abnormality) within 60 days after the first dose of study medication.

Figure 2 shows the Kaplan-Meier incidence of musculoskeletal disorder curves for levofloxacin and comparator over the 1 year of follow-up.

Figure 2: Kaplan-Meier mortality curve –Time to Onset of Musculoskeletal Disorders in the 1 year Period after First Study Dose



(a) Probability refers to the likelihood of not getting MS disorder. Note: Number of events refers to the cumulative number of subjects who had a musculoskeletal disorder at each of the time points given on the x-axis. Number at risk refers to the number of subjects who have not had a musculoskeletal disorder at the time points given on the x-axis .Subjects who did not have a musculoskeletal disorder at 375 days were censored at 375 days
Source: Sponsors Submission

The Kapalan Meier curve demonstrated that patients in the in the levofloxacin group had higher incidence rate of musculoskeletal disorder as defined by protocol compared with the comparator antibiotics over the entire duration of follow-up.

Medical Reviewer Comment: as shown in Figure 2, the divergence in the incidence rate of musculoskeletal disorder between the two treatment groups (curves) occurred very early and remained significantly higher (p-value: 0.0208) in levofloxacin group than the comparator

treated patients during the entire 1 year follow-up period. The overall incidence rate of musculoskeletal disorders in levofloxacin treated patients was also significantly higher (2.1% vs. 0.9%, p-value: 0.038) during the 60 days follow-up period. The above result (the higher incidence of MS disorders in levofloxacin treated patients) implies that a risk benefit assessment is needed in determining the use of levofloxacin in children for the indications where there will be alternative product/s.

The incidence of musculoskeletal disorders as defined in the protocol in the 1-year period after the first dose of the study drugs are summarized in Table 14.

Table 14: Incidence of Musculoskeletal Disorders in the 1-Year Period after the First Dose (Study LOFBO-LTSS-001: Safety Analysis Set)

MS disorder	Levofloxacin (N=1340)		Comparator (N=893)		Total (N=2233)	P-value[b]
	n (%)	95%CI[a]	n (%)	95%CI[a]	n (%)	
In the 1-Year Period						
Any MS disorder	46 (3.8)	(2.5; 4.6)	16 (2.08)	(1.0; 2.9)	62 (2.8)	0.024
Tendinopathy	1 (0.1)	(0.0; 0.4)	1 (0.1)	(0.0; 0.6)	2 (0.1)	>0.999
Arthritis	9 (0.7)	(0.3; 1.3)	2 (0.2)	(0.0; 0.8)	11 (0.5)	0.217
Arthralgia	35 (2.6)	(1.8; 3.6)	14 (1.6)	(0.9; 2.6)	49 (2.2)	0.106
Gait abnormality	3 (0.2)	(0.0; 0.7)	0	(0.0; 0.4)	3 (0.1)	0.280
Impaired growth[c]	1 (0.1)	(0.0; 0.4)	0	(0.0; 0.4)	1 (<0.1)	>0.999

A total of 62 subjects reported MS disorders in the 1-year period following the first dose of the study drug. The result showed that an increase in the incidence rate of MS disorders in both treatment arms over time.Similar to the incidences MS disorders in the 60 days period, the analysis of the 1-year follow up demonstrates that patients who were treated with levofloxacin developed a higher rate of MS disorder than patient in the comparator arm (3.8% vs. 2.0%; p-value: 0.024).

5.1.18 Duration of Musculoskeletal Disorders in the 1-Year Period

The duration of musculoskeletal disorders was assessed and compared across both treatment groups. The results are shown in Table 15.

Table 15: Duration of Musculoskeletal Disorders (Study LOFBO-LTSS-001: Safety Analysis Set) -Year Period after the First Dose

Duration (days)	Levofloxacin 45 n(%)	Comparator 16 n(%)
10	27 (56)	10 (59)
11-34	8 (17)	2 (12)
35-64	6 (13)	3 (18)
65-100	4 (8)	0
>100	3 (6)	2 (12)
Mean (SD)	39.95 (84.08)	30.12(68.5)
Median	7.0	4.5
Range	(1 - 474)	(1 - 277)

Source: Sponsors Submission

Medical Reviewer Comment: As shown in table, the median duration musculoskeletal disorders in patients who were treated with levofloxacin was 2.5 days shorter than patients who were treated with comparator. There were 5 patients (3 levofloxacin, 2 comparator) who had musculoskeletal disorders for >100 days.

The reviewer examined the CRF of 5 patients. Other than some use of NSAIDs, those patients did not require any medical intervention such as surgery or hospital admission .

5.1.19 Patients with Musculoskeletal Disorders in the 1-Year Period after the First Dose

There musculoskeletal adverse events that were observed in the 1- year period are presented in Table 16 and summarized in Table 17.

Table 16: summarizes patients who developed musculoskeletal disorders in the one year period.

Pt #	Study	Age	Sex	Affected MS System	Presentation	Relative day of symptom onset	Severity	Duration of the MS disorder
Levofloxacin								
111109	CAP	7	M	Knee	Arthritis	90	moderate	1
112004	CAP	1.7	M	Non Specific	Polyarthralgia	27	mild	4
115025	CAP	1	F	Knee	Arthritis	60	mild	76
115041	CAP	4.7	F	Knees	Polyarthralgia	10	mild	4
115117	CAP	6.4	M	Poly	Polyarthralgia	5	mild	1
115142	CAP	11.5	F	leg/feet	Polyarthralgia	21	mild	3
118015	CAP	1.9	M	Ankle, wrist	Polyarthralgia	5	mild	18
118020	CAP	1	M	Achilles	Gait abnormality	139	moderate	unknown
118028	CAP	2	F	Leg, back	Arthralgia	97	mild	474
118048	CAP	3.6	F	Ankle	Arthralgia	13	marked	2
118389	CAP	13.5	F	MP thumbs	Polyarthralgia	9	mild	7
118424	CAP	15.4	F	Ankle Lt	Arthralgia	341	moderate	1
118439	CAP	5.7	M	Knee/ankle	Polyarthralgia	11	mild	1
125111	CAP	14.4	M	Knee	Arthralgia	51	mild	36
211207	OMD1	4.9	F	ankles	Polyarthralgia	26	mild	5
212117	OMD1	3.2	M	ankles	Polyarthralgia	284	mild	275
212119	OMD1	2.3	M	Knee	Arthralgia	25	mild	54
212147	OMD1	3.3	F	Knee	Arthritis	359	mild	36
213175	OMD1	1.5	M	Leg Lt	Gait abnormality	2	mild	64
215257	OMD1	3.1	F	Knee	Polyarthralgia	208	mild	31
215258	OMD1	1	M	growth	Impaired growth	173	N/A	33
310205	OMD2	3.8	F	Leg	Arthralgia	12	mild	1
310212	OMD2	3.3	F	Knee/leg	Polyarthralgia	5	mild	1
310620	OMD2	1.2	M	Hip Lt	Arthritis	105	mild	2
310829	OMD2	3.7	F	Knee/elbow	Polyarthralgia	122	mild	1
311304	OMD2	2.2	F	Knee Lt	Arthralgia	19	mild	4
311327	OMD2	2.3	M	Knee/elbow	Polyarthralgia	9	mild	1
312103	OMD2	1.3	M	Leg Rt	Arthralgia	10	moderate	12
312106	OMD2	2.2	M	Knee Lt	Arthritis	59	moderate	169
124105	OMD2	11.6	F	Non Specific	Polyarthralgia	11	Polyarthralgia	33
312123	OMD2	1.5	M	hip/knee	Arthritis	27	moderate	7
312148	OMD2	4.5	F	hip/knee	Poly arthritis	17	mild	1
312302	OMD2	2.2	M	Wrist/arms	Polyarthralgia	199	mild	1

312357	OMD2	4	M	Ankles	Polyarthralgia	70	moderate	88
312404	OMD2	3.1	F	Hip Rt	Gait Abnormality	27	mild	3
315631	OMD2	1.3	F	Gait	Arthralgia	8	mild	8
318904	OMD2	1.4	F	Leg Rt	Arthralgia	335	N/Assessed	6
322010	OMD2	1.5	M	Knee	Arthralgia	280	mild	
323603	OMD2	2.6	M	Knee	Arthralgia	128	mild	73
325102	OMD2	1.9	M	Poly	Arthritis	34	mild	7
325107	OMD2	0.8	F	Knee Rt	arthralgia	49	mild	3
325134	OMD2	1.3	F	Non Specific	Arthralgia	120	mild	57
325275	OMD2	2	M	Knee/elbow	Polyarthralgia	309	mild	61
326988	OMD2	4.6	F	All body	Polyarthralgia	30	mild	76
325124	OMD2	3	M	Ankle Lt	Arthritis	38/326	moderate	14
327031	OMD2	4.9	F	Wrist Lt	Arthralgia	167	mild	3
Comparator								
112013	CAP	2.7	F	Foot/Leg	Polyarthralgia	2	mild	2
112129	CAP	6.3	F	Ankle Rt	Arthritis	82	mild	1
118428	CAP	7.4	F	Ankle	Arthralgia	15/138	moderate	13
311329	OMD2	1.6	M	Foot Rt	Arthralgia	4	mild	4
312377	OMD2	0.9	F	Knee Rt	Arthritis	290	moderate	54
314201	OMD2	4.3	M	Hip Rt	Arthralgia	6	mild	9
315333	OMD2	1.5	M	Leg Rt	Arthralgia	202	moderate	3
318601	OMD2	2	M	Knee	Arthralgia	87	mild	277
323304	OMD2	3.1	m	Knee pain	Arthralgia	65/343	mild	4
325101	OMD2	2	m	Knee Lt	Arthralgia	26/7	mild	31
325108	OMD2	4.1	f	Non Specific	Arthralgia	170/364	mild	11
325118	OMD2	4.8	f	Ankle/knee/hip	Poly arthralgia	22	mild	2
325119	OMD2	2.6	M	Arthralgia	Arthralgia	368	Mild	3
325132	OMD2	4.9	M	Non Specific	Poly arthralgia	23	mild	5
326941	OMD2	1.3	M	Wrists	Arthralgia	80	Mild	1
326987	OMD2	1.7	M	Arms/leg	Polyarthralgia	45	Mild	62

5.1.20 Musculoskeletal disorders that occurred during the one year are summarized below:

Table 17 Summary of musculoskeletal disorders that occurred during the one year period

	Levofloxacin N=46 (%)	Comparator N=16 (%)
Study		
CAP (Community Acquired Pneumonia)	14 (30.4)	3 (18.7)
AOM (Uncontrolled)	7 (15.2)	0
AOM (Controlled)	25 (54.3)	13(81.2)
Age (years)		
Mean (SD)	3.94 (3.6)	3.2% (1.9)
Range	(0.8-15.4)	(0.9-7.4)
Sex, n (%)		
Female	23 (50)	6 (37.5)
Male	23 (50%)	10 (62.5)
Race		
White	34 (73.9)	14 (87.7)
Black	8 (17.3)	0
Asian	0	0
Other	4 (8.6)	2 (12.5)
# of MS Disorders	49	17
Tendinopathy	1 (2)	1(5.9)
Arthritis	9 (18.4)	2 (11.8)
Arthralgia	35 (71.4)	14 (82.3)
Gait abnormality	3 (6.1)	0
Impaired Growth	1(2)	0
# of Patients > 1 Disorder	2	1
Arthritis, tendinopathy	1	0
Arthrits, Arthralgia	1	0
Arthralgia, tendinopathy	0	1
Presentation by Joint Type		
Knee	12 (26.7)	4 (25.0)
Knee/Elbow	3(6.5)	0
Knee/Ankle	1(2.2)	
Knee/ Ankle/ /hip	0	1 (6.2)
Knee/Hip/	2(4.3)	0
Knee/Leg	1(2.2)	0
Leg	4(8.7)	1(6.2)
Leg/Feet	1(2.2)	1(6.2)
Leg/ Arms		1 (6.2)
Leg/ Back	1(2.2)	0
Achilles	1(2.2)	

Ankle	6(13.0)	2(12.5)
Ankle/ Wrist	1(2.2)	0
Wrist	1(2.2)	1(6.2)
Wrist/Arms	1(2.2)	0
Foot	0	1(6.2)
Hip	2.(4.3)	1(6.2)
Mercaptophalengeal Joint/s	1(2.2)	0
Growth	1(2.2)	0
Gait	1(2.2)	
Non Specific	6(13.1)	3(18.7)
Severity ,n (%)		
Severe	0	0
Moderate	7 (15.21%)	3 (18.7)
Mild	36 (78.1%)	13 (81.3)
Not assessed	3(6.5%)	0
Duration of MS disorders (days), n (%)		
N	48	17
≤10	27 (56)	10 (59)
11-34	8 (17)	2 (12)
35-64	6 (13)	3 (18)
65-100	4 (8)	0
>100	3 (6)	2 (12)
Mean (SD)	39.9 (84.1)	30.1 (68.5)
Median	7.0	4.5
Range	(1 - 474)	(1 - 277)
Days of Onset of MS Disorders		
N	46	16
0-50	25 (54.3)	8 (50)
>50-100	6 (13.0)	4 (25)
>100-150	5 (10.9)	0
>150-200	3 (6.5)	1 (6.2)
>200-250	1 (2.2)	1(6.2)
>250-300	33 (6.5)	1(6.2)
>300-350	33 (6.5)	0
>350-400	11 (2.2)	1(6.2)
Mean (SD)	90 (105.2)	93.0 (109.5)
Median	36	55
Range	(2-359)	(1 - 368)
Number of Patients > 1 Disorder	2	1
Arthritis, tendinopathy	1	0
Arthrits, Arthralgia	1	0
Arthralgia, tendinopathy	0	1
More than 1X MSD event, n (%)	1 (2.2%)	3 (17.6%)

Medical Reviewer's Comments: A total of 62 (46 levofloxacin and 16 comparator) subjects developed protocol defined MS disorders *during the one year follow up period. The mean age of study subjects was 3.94 yrs (range 0.8 to 15.4 years) in the levofloxacin treated subjects and 3.2yrs (range 0.9 to 7.4 years) in the comparator group. The majority of patients with MS disorders were white [34 (73.9%) in the levofloxacin arm and 14 (87.7%) in the comparator]. The total numbers of the MS disorders occurrences in the levofloxacin and comparator arms were 49 and 17 respectively. In both treatment arms arthralgia was the most frequent MS disorder. Arthritis, gait abnormality and impaired growth more often occurred in the levofloxacin arm than the comparator group. The mean duration of MS disorders was 40 days (range 1 to 474 days) in the levofloxacin group and 30 days (range 1 to 277 days) in the comparator group. Overall, most of the MS disorders in both arms were mild in nature. The mean days to the onset of symptoms for both treatment groups were similar (* 90 *days (range 2 to 359) days in the levofloxacin arm and 93 days (range 1 to 368 days) in the comparator group). Most patients developed MS disorders during the first 50 days.*

5.1.21 Musculoskeletal Disorders in the 60-Day Period

The primary aim of the study was determining the overall incidence of MS disorders as per protocol defined criteria (tendinopathy, arthritis, arthralgia, or gait abnormality) within 60 days after the first dose of study medication.

Table 18 below shows the Incidence of Musculoskeletal Disorders in the 60-Day Period After the First Dose:

Table 18: Incidence of Musculoskeletal Disorders in the 60-Day Period after the First Dose

MS disorder	Levofloxacin (N=1340)		Comparator (N=893)		P-value
	n (%)	95%CI[a]	n (%)	95%CI[a]	
60-Day Period					
Any MS disorder	28 (2.1)	(1.4; 3.0)	8 (0.9)	(0.4; 1.8)	0.038
Tendinopathy	1 (0.1)	(0.0; 0.4)	1 (0.1)	(0.0; 0.6)	>0.999
Arthritis	5 (0.4)	(0.1; 0.9)	0	(0.0; 0.4)	0.164
Arthralgia	22 (1.6)	(1.0; 2.5)	7 (0.8)	(0.3; 1.6)	0.088
Gait abnormality	2 (0.1)	(0.0; 0.5)	0	(0.0; 0.4)	0.520

*More than one event/subject counted only once
Source: Sponsors Submission

Medical Reviewer Comment: The overall incidence rate of musculoskeletal disorders in levofloxacin treated patients was significantly higher (2.1% vs. 0.9%, p-value: 0.038 when compared with the comparator group. The most frequently occurring MS disorder in both groups was Arthralgia. There was no significant difference in the in the type of the MS disorders that occurred during among the treatment arms during the 60 days.

5.1.22 Severity of Musculoskeletal Disorders by Study Drug over the first 60 days

We evaluated severity of the MS disorders in the two treatments. The results are presented in Table 19.

Table 19: Relationship to study drug to severity MS disorder over the first 60 days of evaluation,

MS disorders	Levofloxacin	Comparator
Total number of Patients	28 (100%)	8(100%)
Serious	0	0
Moderate	3(10.7)	1(12.5)
Mild	24(85.7)	7(87.5)
Not assessed	1(3.6)	0

The severity of the MS disorder was numerically similar between levofloxacin treated -and comparator treated patients during the 60 days of evaluation. Most patients had MS disorders that were mild in nature. There were no patients with severe MS disorder during the 60 days of evaluation.

5.1.23 Incidence of Musculoskeletal Disorders at weight-bearing and non-weight-bearing joints in 60-day

The incidences of musculoskeletal disorders at weight-bearing and on weight-bearing joints in 60-day, after the first dose of study drug are presented in Table 20.

Table 20 Incidence of Musculoskeletal Disorders at weight-bearing and nonweight-bearing joints in 60-day, after the first dose of study drug

Joints	Levofloxacin (N=1340) n (%)	Comparator (N=893) n (%)	Total (N=2233) n (%)	P-value
Weight-bearing	25 (1.9)	6 (0.7)	31 (1.4)	0.025
Nonweight-bearing	2 (0.1)	2 (0.2)	4 (0.2)	>0.999

**Joint status not classified in one patient.,*

Medical Reviewer Comments: there was statistically significant higher incidence rate of MS disorder at the weight-bearing joints of patients treated who were treated with levofloxacin when compared with the incidence rate of patients who were treated with non-fluoroquinolone antibiotic agents (comparator). The difference in the rate of MS disorder at non weight-bearing joints was not significantly different across the two treatment groups.

5.1.24 Incidence of Musculoskeletal Disorders in the 60-Day Period by Subgroups

The incidence of MS disorders (tendinopathy, arthritis, arthralgia, and gait abnormality) within 60 days after the first dose of study medication across different subgroups by age, sex, pubescence stage, and country group (US vs non-US) is presented in Table 21.

Table 21: Incidence of Musculoskeletal Disorders in the 60-Day Period after the First Dose by Different Subgroups (Study LOFBO-LTSS-001: Safety Analysis Set)

Any MS disorder	Total n	Levofloxacin (N=1340) Disorders, n (%)	Total n	Comparator (N=893) Disorders, n (%)	P-value[a]
Any MS disorder	1340	28 (2.1)	893	8 (0.9)	0.038
Age					
<2 years	631	9 (1.4)	452	2 (0.4)	0.1339
2-<6 years	516	14 (2.7)	379	5 (1.3)	0.1680
6-<12 years	148	3 (2.0)	48	1 (2.1)	>0.9999
12-<17 years	45	2 (4.4)	14	0	>0.9999
Sex					
Male	726	13 (1.8)	507	5 (1.0)	0.3359
Female	614	15 (2.4)	386	3 (0.8)	0.0841
Pubescence stage					
Prepubescent	1264	24 (1.9)	865	8 (0.9)	0.0725
Pubescent	63	4 (6.3)	28	0	0.3078
Postpubescent	13	0	0	0	
Country					
US	409	5 (1.2)	328	1 (0.3)	0.2338
NON-US	931	23 (2.5)	565	7 (1.2)	0.1275

[a] Pairwise comparison: 2-sided Fisher's exact test.
Note: Other disorders (tendinopathy, arthritis, gait abnormality) are not presented since most of the incidence rates are <0.7%.
Source: Sponsors Submission

Medical Reviewer Comment: The results from this study shows a higher incidence of musculoskeletal disorders in levofloxacin treated patients was observed almost across all subgroups during the 60-day period after the first dose.

5.1.25 Magnetic Resonance Imaging (MRI)/ CT scan Reports

There were only 5 levofloxacin-treated children who underwent MRI or CT as part of the evaluation of their disorders. There were no abnormal MRI or CT findings identified.

Medical Reviewer Comment: The MRI/CT evaluation was done only in 5 patients. The fact that there was not identified abnormalities in the joints of those children would not be adequate enough to make a generalized statement or conclusion about the effect of levofloxacin in cartilages.

5.1.26 Impaired Growth

Growth impairment was defined as a change in height measured approximately 1 year after enrollment that was >20% less than the expected height increase as determined by the growth curve constructed at study enrollment.

A total of 1948 subjects (1165 levofloxacin, 783 comparator) completed the height evaluation at the 1-year visit. One hundred sixty-seven (101/1165 levofloxacin, 66/783 comparator) subjects were assessed as being growth-impaired by this protocol definition.

Table 22: Incidence of Protocol-Defined Impaired Growth(Study LOFBO-LTSS-001: Safety Analysis Set)

Disorder	Levofloxacin (N=1165) n (%) 95%CI		Comparator (N=783) n (%) 95%CI		Total (N=1948) n (%)	P-value
Protocol-defined impaired growth	101 (8.7)	(7.1; 10.4)	66 (8.4)	(6.6; 10.6)	167 (8.6)	0.869

Note: Percentages calculated with the number of subjects in each group as denominator.
* Only those subjects who completed their 1-year height evaluation are included in the assessment of incidence of protocol-defined impaired growth. The following formula was used:
(1-Year Expected height – Screening Height)- (1-Year Actual height – Screening Height) X 100
(1-Year Expected Height – Screening Height)

Source: Sponsors Submission

Medical Reviewers Comment: The overall difference in the linear growth impairment (8.7% levofloxacin vs. 8.4% comparator) was not statistically significant (p-value: 0.869) (Table 22). The reviewer evaluated the Incidence of Protocol-Defined Growth Impairment between the two treatments by age group, sex and country. There were no important clinical differences.

5.1.27 General Review of Safety

This general review of safety includes safety information for 2233 subjects who enrolled in a previous Phase 3 levofloxacin study and continued in this long-term safety study. This group included 1340 subjects who received levofloxacin and 893 subjects who received a comparator in a previous study. The safety review compares serious and MS adverse events across the two treatment groups as the study did not require the reporting of other adverse events. The safety data was presented by System Organ Class and Preferred Term.

5.1.28 Deaths

There were no deaths reported in this study.

5.1.29 Serious Adverse Events

According to the protocol, serious adverse events were defined as any untoward medical occurrence that was fatal, life-threatening, required or prolonged inpatient hospitalization (except for drug administration, protocol-required testing, social reasons in absence of an adverse event, or surgery/procedure planned before study entry), resulted in persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

The reviewer used the case report forms and serious adverse events narrative and tabular summaries provided by the sponsor for this review. A total of 134 (6%) of subjects 90 (7%) levofloxacin; 44 (5%) comparator) reported serious adverse events. Serious adverse events by system organ class and preferred term are displayed in the table below:

Table 23: Incidence of Serious Adverse Events by System Organ Class and Preferred Term (Study LOFBO-LTSS-001: Safety Analysis Set) (> 1 patient)

System organ class/ Preferred Term	Levofloxacin		Comparator	
	(N=1340)		(N=893)	
	n (%)	95%CI(a)	n (%)	95%CI(a)
Total no. subjects with serious adverse event	90 (7)	(5.4; 8.2)	44 (5)	(3.6; 6.6)
Infections and infestations	46 (3)	(2.5; 4.6)	26 (3)	(1.9; 4.2)
Pneumonia	20 (1)	(0.9; 2.3)	11 (1)	(0.6; 2.2)
Bronchiolitis	5 (<1)	(0.1; 0.9)	2 (<1)	(0.0; 0.8)
Bronchopneumonia	5 (<1)	(0.1; 0.9)	1 (<1)	(0.0; 0.6)
Otitis media	3 (<1)	(0.0; 0.7)	3 (<1)	(0.1; 1.0)
Gastroenteritis	2 (<1)	(0.0; 0.5)	3 (<1)	(0.1; 1.0)
Otitis media acute	2 (<1)	(0.0; 0.5)	1 (<1)	(0.0; 0.6)
Viral infection	2 (<1)	(0.0; 0.5)	2 (<1)	(0.0; 0.8)
Respiratory, thoracic & mediastinal	21 (2)	(1.0; 2.4)	7 (1)	(0.3; 1.6)
disorders				
Asthma	8 (1)	(0.3; 1.2)	1 (<1)	(0.0; 0.6)

Respiratory distress	5 (<1)	(0.1; 0.9)	1 (<1)	(0.0; 0.6)
Bronchial disorder	2 (<1)	(0.0; 0.5)	0	(0.0; 0.4)
Bronchial hyperactivity	2 (<1)	(0.0; 0.5)	0	(0.0; 0.4)
Bronchospasm	2 (<1)	(0.0; 0.5)	3 (<1)	(0.1; 1.0)
Wheezing	0	(0.0; 0.3)	1 (<1)	(0.0; 0.6)
Gastrointestinal disorders	10 (1)	(0.4; 1.4)	5 (1)	(0.2; 1.3)
Diarrhoea	6 (<1)	(0.2; 1.0)	2 (<1)	(0.0; 0.8)
Vomiting	5 (<1)	(0.1; 0.9)	2 (<1)	(0.0; 0.8)
Surgical and medical procedures	8 (1)	(0.3; 1.2)	6 (1)	(0.2; 1.5)
Surgery	7 (1)	(0.2; 1.1)	5 (1)	(0.2; 1.3)
Metabolism and nutrition disorders	6 (<1)	(0.2; 1.0)	5 (1)	(0.2; 1.3)
Dehydration	4 (<1)	(0.1; 0.8)	5 (1)	(0.2; 1.3)
Injury, poisoning and procedural complications	5 (<1)	(0.1; 0.9)	3 (<1)	(0.1; 1.0)
Injury	3 (<1)	(0.0; 0.7)	0	(0.0; 0.4)
Cardiac disorders	4 (<1)	(0.1; 0.8)	0	(0.0; 0.4)
Pericarditis	2 (<1)	(0.0; 0.5)	0	(0.0; 0.4)
Blood and lymphatic system disorders	3 (<1)	(0.0; 0.7)	1 (<1)	(0.0; 0.6)
Anaemia	1 (<1)	(0.0; 0.4)	0	(0.0; 0.4)
Febrile neutropenia	1 (<1)	(0.0; 0.4)	0	(0.0; 0.4)
Thrombocytopenic purpura	1 (<1)	(0.0; 0.4)	0	(0.0; 0.4)
Musculoskeletal and connective tissue disorders	3 (<1)	(0.0; 0.7)	2 (<1)	(0.0; 0.8)
Arthralgia	1 (<1)	(0.0; 0.4)	0	(0.0; 0.4)
Bone disorder	1 (<1)	(0.0; 0.4)	0	(0.0; 0.4)
Myositis	1 (<1)	(0.0; 0.4)	0	(0.0; 0.4)
Arthropathy	0	(0.0; 0.3)	1 (<1)	(0.0; 0.6)
Pathological fracture	0	(0.0; 0.3)	1 (<1)	(0.0; 0.6)

Source: Sponsors Submission

Medical Reviewer Comments: The overall serious adverse event profile was similar between the two arms. There were 5 (<1%) subjects (3 levofloxacin [arthralgia, myositis, bone disorder]; 2 comparator drug [arthropathy and pathological fracture]) who experienced serious MS adverse events. The SAEs in all 5 patients in both treatment groups were considered not related to the study drug. The most common frequently-reported serious adverse events were infections and infestations (3% in each treatment group).

5.1.30 Conclusion

The results from the reviewed prospective, long term, surveillance study where 1340 pediatric patients (6 months to 16 years of age) received 10 mg/kg of levofloxacin twice a day (6 month to 5 years of age) days and children 10 mg/kg to a maximum of 500 mg of levofloxacin once a day or non fluoroquinolone therapy for approximately 10 days demonstrated the higher incidence rate of protocol-defined musculoskeletal disorders (arthralgia, arthritis, tendinopathy or gait abnormality) in the levofloxacin treated patients occurring within 60 days and 1 year of exposure to the drug.

Arthralgia was the most frequently occurring MS disorder for both treatment groups. The majority of MS disorders reported in levofloxacin- and non-fluoroquinolone-treated children resolved within 10 days (56% and 59%, respectively). The Study also showed the levofloxacin treated patients had a longer duration of MS disorder than patients treated with the non fluoroquinolones. The mean duration of MS disorders was 40 days in the levofloxacin group and 30 days in the non-fluoroquinolone group. The findings of a higher incidence of MS disorders in the levofloxacin treated subjects were not associated with severity of the symptoms or permanent damage to the joints or tendons.

5.2 COMMUNITY-ACQUIRED PNEUMONIA

5.2.1 Study design

The study was a randomized, open-label, randomized, active-comparator, multicenter, noninferiority, Phase 3 study consisting of 4 phases: Screening, Treatment, Pos-treatment and Follow-up. The study was conducted in the United States, Mexico, and various Latin American countries (Argentina, Brazil, Chile, Costa Rica, and Panama).

A total of 650 in- or outpatients with suspected community-acquired pneumonia were to be enrolled to achieve 380 clinically evaluable levofloxacin subjects and 127 clinically evaluable comparator subjects. The randomization was to be stratified by age group (Group I: ≥ 6 months to < 5 years; Group II: ≥ 5 to 16 years) and country and that subjects be randomized to levofloxacin and comparator in a 3:1 ratio within each age group in each country.

Subjects were to be assigned to treatment groups based on a computer-generated randomization schedule using randomly permuted blocks and were to be stratified by age group (Group I: ≥ months to < 5 years; Group II: ≥ to 16 years, inclusive) and country. Due to the differences in the microbiological etiology for pneumonia and differences in drug clearance in children, the comparators and the dose and dosing schedule for the study drugs would to differ by age group. Similar dosing regimens would to be used for levofloxacin and the active comparators (Group I: ceftriaxone or amoxicillin/clavulanate (7:1); Group II: ceftriaxone plus erythromycin lactobionate or clarithromycin).

Study eligibility was to be determined at the Screening Visit (Day 1) based on signs and symptoms of pneumonia (e.g., fever, cough, chest pain, shortness of breath, rales, dullness to percussion) and radiographic evidence of pulmonary infiltrate compatible with acute infection. A combination of clinical assessment, serology, and bacterial culturing was to be used to evaluate efficacy. Blood samples were to be collected from levofloxacin-treated subjects at specified visits for the determination of steady-state exposures of levofloxacin. Safety was to be evaluated throughout the study by assessment of adverse events and changes in physical examinations (including musculoskeletal examination with evaluation of joints), vital signs, and clinical laboratory findings. Safety evaluation for musculoskeletal adverse events was to be performed throughout the study. All subjects who enroll in this study and take at least 1 dose of levofloxacin or comparator(s) were to be eligible to rollover into a long-term surveillance study primarily focused on the musculoskeletal system. A separate informed consent was to be required for participation in the long-term surveillance study.

5.2.2 Objectives

The primary objective of this study was to establish the efficacy (in terms of clinical response [cured versus not cured] at the test-of-cure visit) of levofloxacin to be non-inferior to "standard of care" antibiotic therapy in the treatment of community-acquired pneumonia in children aged 6 months to 16 years.

Secondary objectives include evaluation of clinical response of levofloxacin and comparator agents at the post therapy visit, evaluation of microbiological responses of levofloxacin and comparator agents, evaluation of clinical and microbiological responses of levofloxacin and comparator agents in 2 age groups (Group I: ≥ 6 months to <5 years; Group II: ≥ to 16 years, inclusive), and determination of steady-state exposure of levofloxacin in each age group. Safety will also be assessed.

5.2.3 Endpoints

The primary endpoint was clinical response (cured versus not cured) at Visit 4 (test-of-cure visit). This response will be based on resolution of signs and symptoms of pneumonia reported at admission. The clinical response rate in the levofloxacin treatment arm was to be compared to the clinical response rate in the standard therapy arm. This endpoint was to be assessed for the entire clinically evaluable population (6 months to 16 years). Secondary endpoints were to be the post therapy clinical response at Visit 3, microbiologic response at Visits 3 and 4, and clinical and microbiological response within each age group (Group I: ≥ 6 months to < 5 years; Group II: ≥ 5 to 16 years, inclusive) at Visits 3 and 4. The microbiologic responses were to be summarized overall and by pathogen for levofloxacin and comparators for the microbiologically evaluable population. The steady-state exposure of levofloxacin in each age group was also to be assessed.

Inclusion Criteria

Patients were to be included if they were Age 6 months to 16 years, inclusive; has clinical signs and symptoms of pneumonia, including at least 2 of the following: fever (rectal or oral temperature ≥ 38^{o}C (100.4^{o}F) for children > 2 years; rectal or oral temperature ≥ 38.3^{o}C (101^{o}F) for children 6 months to ≤ 2 years); cough; chest pain; shortness of breath; evidence of pulmonary consolidation on physical examination (e.g. rales on auscultation, dullness to percussion, egophony); white blood cell (WBC) count >15,000/µL or <5000/µL in addition to radiographic evidence of pulmonary infiltrate compatible with acute bacterial, mycoplasma, or chlamydial infection .If female, the subject must be premenarchal, or have had a hysterectomy or tubal ligation or otherwise be incapable of pregnancy, or have practiced 1 of the following methods of contraception for at least 1 month prior to study entry and agree to continue the same method during the study: hormonal contraceptives, intrauterine device, spermicide and barrier, spousal/partner sterility, or abstinence. If a female subject is capable of becoming pregnant and is practicing an acceptable method of birth control, she must have a negative urine/serum β-hCG pregnancy test before study drug administration. Subject's parent(s) or legal guardian(s) must read and sign the informed consent form. Subjects must not have participated in an experimental drug or experimental medical device trial within 30 days prior to the planned start of treatment.

5.2.4 Exclusion Criteria

Patients were to be excluded from participation in the study if they use of systemic antibiotics for more than 24 hours immediately prior to enrollment; requires use of systemic antibiotic therapy other than study drug(s); suspected infection with microorganisms (virus, fungi, parasites or bacteria) known to be resistant to levofloxacin, amoxicillin/clavulanate, ceftriaxone, clarithromycin, or erythromycin lactobionate; signs and symptoms of a bacterial infection of the central nervous system; history of a previous hypersensitivity or serious adverse reaction against any quinolone, macrolide, beta-lactam, cephalosporin, or clavulanic acid; history of cystic fibrosis; abnormal renal function defined as serum creatinine >0.5 mg/dL in infants ≥ 6 months and < 1 year of age, >0.8 mg/dL in children ≥ 1 and ≤ 12 years of age, and >1.2 mg/dL in children >12 years of age; history or presence of arthropathy or periarticular disease or any other musculoskeletal signs or symptoms that in the opinion of the investigator may confound a future safety evaluation of musculoskeletal complaints; high probability of death during the study; hospitalization or residence in a long-term care facility for 14 or more days before the onset of symptoms; infection acquired in a hospital (>48 hours after hospital admission and <7 days after hospital discharge); previous participation in this protocol or another levofloxacin clinical study; seizure disorder that is poorly controlled (e.g., a seizure in the past 6 months or more than 2 seizures in the past year) or at significant risk for seizures (e.g., recent serious head trauma); unstable psychiatric disorder; known or highly suspected to have infection with Mycobacterium tuberculosis; known HIV infection requiring pneumocystis carinii pneumonia (PCP) prophylaxis; chronic use of corticosteroids (Prednisone [or its equivalent] ≥ 2 mg/kg or ≥ 20mg/day > 14 days); pregnant or nursing females; employees of the investigator or study center with direct involvement in the proposed study or other studies under the direction of that investigator or study center, family members are also excluded.

5.2.5 Completion &Treatment Discontinuation & Withdrawal

A subject was to be considered as having completed the study if he/she has completed study procedures according to the protocol through Visit 4. Subjects may have discontinued study drug before completion of treatment for the following reasons:

- Lack of efficacy
- Subject/Parent or guardian choice
- Lost to follow-up
- Adverse Event
- Other causes

Subjects who discontinue study treatment (except those lost to follow-up) were to have Visit 4/treatment discontinuation procedures performed and then were to be contacted at 25 to 35 days following the last dose of study drug and have Visit 5 procedures performed. Subject participation was to be terminated (e.g., subject/parent or guardian choice, lost to follow-up) before completing Visit 4 procedures. When a subject withdraws prior to completing the study, the reason for withdrawal is was to be documented on the CRFs and in the source document. Study drug assigned to the withdrawn subject was not to be assigned to another subject. Subjects who withdraw were not to be replaced.

5.2.6 Treatment

Subjects aged 6 months to 16 years with 2 or more clinical signs and symptoms of pneumonia as defined in the protocol (fever, shortness of breath, cough, chest pain, abnormal white blood cell (WBC) count, and pulmonary consolidation on physical examination) and radiographic evidence of pulmonary infiltrate compatible with acute infection requiring antibiotic therapy were to be randomized to receive either levofloxacin or a comparator antimicrobial therapy (amoxicillin + clavulanic acid, ceftriaxone with and without erythromycin lactobionate, or clarithromycin) for 10 days (minimum of 7 to a maximum of 14 days) followed by post treatment assessment. The randomization was to be stratified by age group (Group I: ≥ 6 months to < 5 years; Group II: ≥ 5 to 16 years) and country to ensure balance between treatment groups. Subjects were to be randomized to treatment groups in a 3:1 levofloxacin: comparator ratio within each stratum.

5.2.7 Dosing

Table 24: Study Drug Dosage Regimens

	Study Drug	Oral Suspension Dose	Tablet Dose	Intravenous Dose	Infusion Rate	Maximum Dose
Group I (≥ 6 months to < 5 years)						
Levofloxacin	Levofloxacin or	10 mg/kg b.i.d.				500 mg/day
	Levofloxacin			10 mg/kg b.i.d.	60 min	500 mg/day
Comparator	Ceftriaxone			25 mg/kg b.i.d.	30 min	4 grams/day
	or					
	Amoxicillin/clavulanate	22.5 mg/kg b.i.d				875 mg b.i.d.
Group II (≥ 5 to 16 years, inclusive)						
Levofloxacin	Levofloxacin or	10 mg/kg q.d.				500 mg/day
	Levofloxacin or			10 mg/kg q.d.	60 min	500 mg/day
	Levofloxacin or		250 mg q.d.[a, b]			250 mg/day
	Levofloxacin		500 mg q.d.[a,c,d]			500 mg/day
Comparator	Ceftriaxone and			25 mg/kg b.i.d. [a, b]	30 min	4 grams/day
	Erythromycin lactobionatee			10 mg/kg q6hr [a, c, d]	45–60 min	4 grams/24 hr
	or					
	Clarithromycin	7.5 mg/kg b.i.d.	250 mg b.i.d.			250 mg b.i.d.

a Those subjects weighing ,< 22.5 kg, or > 27.5 and < 45.5 kg must use oral suspension or i.v. formulations (10 mg/kg) for dosing.
b Subjects weighing ≥ 22.5 kg and ≤ 27.5 kg.
c Subjects weighing ≥ 45.5 kg.
d The 500 mg dose consists of 2 levofloxacin 250 mg tablets.
e Subjects capable of taking oral medication may substitute oral clarithromycin (7.5 mg/kg b.i.d. to a maximum of 250 mg b.i.d.) for i.v. erythromycin.
Source: Sponsors Clinical Protocol LOFBIV-PCAP-003

The duration of study drug treatment for all children was to be a target of 10 days. If, in the investigator's opinion, a subject requires more or less than 10 days of study therapy, the duration of therapy could have been extended (up to a maximum of 14 days) or shortened (down to a minimum of 7 days) by the investigator. The investigator was to inform the medical monitor when there is a change in the target duration of treatment for any subject. The route of administration of study drugs was to depend on clinical circumstances, the ability of the subject to take oral medication, and the investigator's discretion. Investigators could switch a subject's route of administration at any time during the 10-day course of therapy.

5.2.8 Study Evaluation Procedures

The time and events schedule consisting of 4 phases: screening, treatment, post treatment and follow-up is summarized the various pharmacokinetic, efficacy, and safety measurements in Table 25.

Table 25: shows the study flowchart for subjects completing 12 months of treatment.

Phase	Screening [a,b]	Treatment,[a]		Posttreatment[a]		Follow-Up Telephone Contact
				Posttherapy	Test-of-Cure	
Visit	1	1	2	3	4	5
Study Day	1	1	3-5	1-3 days after last dose	10-17 days after last dose	25-35 days after last dose
Screening /Informed consent/	X					
Medical history	X					
Inclusion/exclusion	X					
Chest X-Ray	X				X	
Administration of Study Drug[e]						
Randomization		X				
Dispense study drug		X	X			
Collect study drug				X	X[f]	
Check compliance			X	X	X[f]	
Efficacy Procedures						
Signs and symptoms of pneumonia	X		X	X	X	
Chest x-ray[g],	X		X[i]	X	X	
Sputum culture[h]	X		X[i]	X[j]	X[i]	
Blood culture	X				X[i]	
Serology[k]	X				X	
Clinical response				X	X	
PK Procedures						
PK blood			X	Xm	X[g, m]	
Pleural fluid		X[n]	X[n]			
Serum protein blood sample[l]		X[n]	X[n]			
Safety Procedures						
Hematology, chemistry, U/A	X			X	X[g, o]	
Serum pregnancy test[p]	X			X	X[g]	
Urine pregnancy test[p]	X					
PPD test[q]	X			X		
Physical examination	X	Xr	Xr	Xr		
Vital signs	X		X	X	X	
Height	X				X	
Interval history [r,s]			X	X	X	X
Adverse events[t]	X	X	X	X	X	X

a Study procedures were the same regardless of study drug route of administration.
b Within 24 hours before first dose of study drug.
c At time of treatment discontinuation or discontinuation after completion of study drug.
d Assent obtained from subjects ≥ 6 years of age, depending on the child's ability to understand the study and the institutional policies.
e Route of administration (i.v. or oral) was based on investigator's discretion. The duration of study drug treatment was 10 days. If, in the investigator's opinion, a subject required more or less than 10 days of study drug, the duration of therapy was extended (to a maximum of 14 days) or shortened (to a minimum of 7 days).
f ONLY at time of discontinuation before the Posttherapy Visit.
g PA and lateral views. Results of chest x-ray were required before dosing. Test-of-Cure Visit chest x-ray read by an observer blinded to study drug.
h Sputum was collected, if possible, for gram stain and culture. Not all subjects were capable of generating an adequate sputum specimen.

i Only if pathogen was isolated from most recent culture or if there was recurrence of symptoms suggestive of pneumonia. At the
Test-of-Cure Visit, sputum (if available) was cultured regardless of presence of pathogen at the Posttherapy Visit.
j If blood culture was negative at screening, it was not necessary to repeat culture.
k Serum was tested for acute and convalescent antibody titer to *Mycoplasma pneumoniae* and *Chlamydia pneumoniae.*
l Subjects randomized to levofloxacin.
m A blood sample was only collected if the last dose of levofloxacin was taken within approximately 24 hours before the visit.
n In subjects randomized to levofloxacin, if pleural fluid (i.e., effusion or empyema) was obtained by thoracentesis as part of the subjects clinical care at anytime after the first dose of levofloxacin, a sample of the fluid was collected for determination of levofloxacin concentration. At the time of a pleural fluid collection, a blood sample was also collected to determine the corresponding plasma levofloxacin concentration and for serum protein concentration. A portion of the pleural fluid sample was sent to the local laboratory for cell count, biochemical analysis (glucose, protein, and LDH), and culture.
o If clinically indicated.
p Females of childbearing potential were enrolled on the basis of a negative urine pregnancy test pending the results of a serum β-HCG pregnancy test. If the serum test was positive, subjects were discontinued and followed appropriately.
q 5 tuberculin units PPD placed on study entry and read 48 to 72 hours later. Subjects were discontinued if tuberculosis was confirmed.
r Subjects with arthralgia or clinical evidence of arthropathy were evaluated by an investigator trained in joint pathology or in consultation with a specialist within 72 hours of presentation. Additional examinations (e.g., MRI, ultrasound, x-ray) were determined by the trained investigator or in consultation with the specialist. All MS adverse events were evaluated per the MS Data Sheet. The investigator or specialist evaluating the MS event remained blinded to study drug.
s Focused on assessing the occurrence of adverse events
t Included MS adverse event monitoring.
Source: Sponsors Table 4: Time and Events Schedule

5.2.9 Outcome Parameters

Clinical Response

Visit 3 (post therapy) 1-3 days after last dose
The clinical response was to be determined by the investigator at Visit 3 (1-3 days after last dose) by comparing a subject's signs and symptoms at Visit 3 to those recorded at admission.

- Visit 3 (post therapy) clinical response was to be assessed as follows:
- Cured: Resolution of signs and symptoms associated with active infection;
- Improved: Incomplete resolution of signs and symptoms associated with infection but no need for further antimicrobial therapy;
- Failure: No response to therapy (can also be designated if subject discontinued study drug due to treatment failure after 48 hours of therapy);
- Unable to Evaluate: Due to administration of antimicrobial on day of assessment, insufficient course of therapy (48 hours or less), subject not returning for evaluations, etc.

Visit 4 (Test-of-cure) : 10-17 days after last dose

The investigator was to determine the clinical response at Visit 4 (10-17 days after last dose) by comparing a subject's signs and symptoms and chest x-ray at Visit 4 to those recorded at admission and the clinical response recorded at Visit 3.

- Cured: Resolution of signs and symptoms associated with active infection along with an improvement or lack of progression of abnormal chest x-ray findings;

- Improved: Continued incomplete resolution of signs and symptoms with no deterioration or relapse after Visit 3 and no requirement for additional antimicrobial therapy;

- Clinical Relapse: Resolution or improvement of signs and symptoms at Visit 3 evaluation with reappearance or deterioration of signs and symptoms of infection;
- Failure: Subject was considered a clinical failure at Visit 3, response will be carried forward to Visit 4;

- Unable to Evaluate: Unable to determine response because subject was not evaluated after the Visit 3 evaluation, i.e., lost to follow-up after Visit 3; Response carried forward to Visit 4 for subjects considered "unable to evaluate" at Visit 3 due to administration of antimicrobial, insufficient course of therapy (48 hours or less), etc.

Microbiological Response

Respiratory Pathogens by Culture

Visit 3 (post therapy): 1-3 days after last dose

At Visit 3 (1-3 days after last dose) microbiological response was to be assigned as follows:

- Eradicated: Absence of admission pathogen in the Visit 3 culture;
- Presumed Eradicated: Presumed absence of admission pathogen due to substantial improvement of infection so that no material for culture is available;
- Persisted: Continued presence of the admission pathogen in the Visit 3 culture;
- Presumed Persisted: Presumed presence of the admission pathogen at Visit 3 for subjects with clinical failure for whom no culture was taken or for whom the culture was taken while the subject was on antibiotics;
- Persisted with acquisition of resistance: Continued presence of admission pathogen in the Visit 3 culture with documented acquisition of resistance;
- Unknown: No 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").

Visit 4 (Test-of-cure): 10-17 days after last dose

At visit 4 (10-17 days after last dose) microbiological response was to be assigned as follows:

- Eradicated: Absence of the admission pathogen at the Visit 4 evaluation;
- Presumed Eradicated: Presumed absence of admission pathogen due to substantial improvement of infection so that no material for culture is available;
- Persisted: Presence of the admission pathogen in the Visit 4 culture;
- Presumed Persisted: Presumed presence of the admission pathogen at Visit 4 for subjects with clinical failure for whom no culture was taken or for whom the culture was taken while the subject was on antibiotics;
- Persisted with acquisition of resistance: Presence of admission pathogen in the Visit 4 culture with documented acquisition of resistance;
- Microbiological Relapse: Reappearance of an organism identical to that isolated at admission, isolated from the site of the admission infection at Visit 4 following eradication or presumed eradication of the original pathogen at Visit 3;
- Unknown: No Visit 4 culture results available due to subject lost to follow-up.

Blood Pathogens

The microbiologic response for each admission blood pathogen was to be based on Visit 3 (post therapy) and Visit 4 (test-of-cure) blood culture results for subjects with confirmed bacteremia (positive blood culture) at admission. The Visit 3 microbiological response was to be carried forward to Visit 4 when a blood culture was done at Visit 3 and not done at Visit 4.

Microbiologic response for each admission pathogen was to be determined for blood culture results available at Visit 3 and/or Visit 4 as follows:

Table 26: Microbiologic and Clinical Response of Blood pathogen

Blood Culture	Clinical Response*	Microbiologic Response
Negative	All	Eradicated
Unknown	Cure/Improved	Presumed Eradicated
Unknown	Failure/Clinical Relapse	Presumed Persisted
Unknown	Unable to evaluate	Unknown
Positive	All	Persisted

* "All" includes cured, improved, failure, clinical relapse, and unable to evaluate.

Atypical Pathogens by Non-Culture Methods

The microbiological response was to be assigned at Visit 3 (posttherapy) and Visit 4 (test-of-cure) for *M.pneumoniae* or *C. pneumoniae* and was to be based on clinical response as follows:

Table 27 Microbiological and Clinical Response for *M. pneumoniae* or *C. pneumoniae*

Clinical Response	Microbiologic Response
Cured/Improved	Presumed Eradicated
Failure/Clinical Relapse	Presumed Persisted
Unable to Evaluate	Unknown

By Subject's Infection

Each subject's respiratory infection due to 1 or more pathogens was to be assigned a microbiological response by the sponsor. Microbiologic response was to be based only on the fate of the original pathogen(s).

Microbes isolated from blood and sputum cultures at Visits 1 through 4 were to be classified by the sponsor using data provided on the CRF according to the following definitions:

- 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 Visit 3 specimens associated with emergence or worsening of clinical signs and symptoms and/or laboratory evidence of active infection which required antimicrobial therapy;
- Colonizer: Organism, identified at any visit from any site, not considered pathogenic and 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 Visit 3, associated with emergence or worsening of clinical signs and symptoms and/or laboratory evidence of active infection, and requiring antimicrobial therapy.

- Atypical pathogens, *M. pneumoniae* and *C. pneumoniae,* diagnosed via serology were to be classified as original pathogens. Organisms classified as superinfectors or new infectors were not to be considered in determining microbiologic response, but were to be addressed separately. Organisms classified as colonizers were not to be addressed.

5.2.10 Safety Evaluations

Safety evaluations were to be based on changes in physical examinations (including musculoskeletal examination with evaluation of joints), vital signs, and clinical laboratory findings from pretherapy to Visit 4 and the observation or report of any adverse events from screening through Visit 5.

Safety evaluations were to include a listing of all adverse events, summaries of treatment-emergent adverse events (i.e., those events occurring after first dose of study drug through Visit 5), and summaries of the change from baseline in clinical laboratory parameters (chemistry, hematology, and urinalysis) and vital signs. To be evaluable for the safety analysis a subject must take at least 1 dose of study drug and must relay safety information.

Subjects were supposed to report any adverse events voluntarily or in response to general, non-directed questioning. For each adverse event reported by the subject, the investigator should obtain all the information required to complete the adverse event page of the CRF.

All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, were to be recorded using medical terminology in the source document and on the CRF. All measures required for adverse event management were to be recorded in the source document and reported according to sponsor instructions.

The study was to include the following evaluations of safety and tolerability:

Adverse Events: Adverse events were to be reported by the subject (or where appropriate by the subject's legally authorized representative) or by the investigator if discovered on examination from the time of first study related procedure through completion of Visit 5.

Musculoskeletal Adverse Events: Musculoskeletal adverse events were to be reported by the subject (or where appropriate by the subject's legally authorized representative) or from musculoskeletal evaluations by the investigator or specialist from the time of first study related procedure through completion of Visit 5.

All musculoskeletal events were to be recorded on the adverse event CRF page. Scheduled examinations and an interval history focused on the occurrence of musculoskeletal adverse events were to be used. The occurrence of tendinopathy, arthritis, and gait abnormality was to be determined by physical examination (including musculoskeletal examination with evaluation of joints) and additional evaluations as needed to define the abnormality. The occurrence of arthralgia was to be determined by subject complaint or signs consistent with arthralgia. Subjects were to be instructed to be evaluated within 72 hours of onset of symptoms or signs of a musculoskeletal disorder. Subjects were to be evaluated by an investigator trained in evaluation of joint pathology or in consultation with a specialist (e.g., orthopedist, rheumatologist [preferably a pediatric rheumatologist]) within 72 hours of the subject's presentation. The

appropriateness of additional examinations (e.g., MRI, ultrasound, x-ray) of the involved joint was to be assessed by the trained investigator or in consultation with the specialist. The investigator or specialist evaluating the musculoskeletal event was to remain blinded to study therapy. It is anticipated that nearly all musculoskeletal disorders were to be defined on unscheduled visits. The purpose of this evaluation was to define any joint related disease that may have occurred as a result of cartilage-related abnormalities similar to that which has been described in animals given quinolones or tendon abnormalities that have been reported in adults taking fluoroquinolones. All treatment-emergent musculoskeletal adverse events were to be evaluated according to procedures listed on the Musculoskeletal Data Sheet provided as part of the CRF. Musculoskeletal adverse events were to be followed.

Definitions of musculoskeletal disorders:

- Tendinopathy: inflammation or rupture of a tendon as determined by physical examination and/or MRI or ultrasound;
- Arthritis: inflammation of a joint as evidenced by redness and/or swelling of the joint;
- Arthralgia: pain in the joint as evidenced by complaint or decreased or abnormal movement of the joint as determined by physical examination;
- Gait abnormality: limping or refusal to walk.

5.2.11 Statistical Methods

Primary analysis of efficacy was to be based on clinical response at Visit 4 or Test of Cure (10 to 17 days after last dose). According to the protocol the analysis was to be performed for the entire population (6 months to 16 years) of clinically evaluable subjects.

A 2-sided 95% confidence interval for the difference in clinical cure rates (comparator minus levofloxacin) between the 2 treatment groups was to be provided to assess therapeutic non-inferiority.

The response rate of children with bacterial pneumonia who are not treated with antibiotics has not been established. The sponsor presented supporting literature on clinical trials involving children with community-acquired pneumonia that have reported response rates which generally exceed 80-90% to justify the noninferiority margin. Assuming that response rate in this trial would approximate 90%, based on results of a recent registration trial involving children with pneumonia, and that the worse estimate of a response rate would exceed 80%, a rate that approximates response rates in children with the most severe disease, a noninferiority margin of 10% was deemed a minimal clinically relevant difference between levofloxacin and comparator for the current study).In order to claim non-inferiority, the upper bound of the 95% confidence interval must remain below a non-inferiority margin of 10%. To demonstrate consistency of results, 2-sided 95% descriptive confidence intervals was to be provided for each of the age groups (Group I: $\geq$ 6 months to < 5 years; Group II: $\geq$ 5 to 16 years, inclusive) and severity groups.

Secondary analyses of efficacy were to include assessment of:

- clinical response at Visit 3 for the clinically evaluable population;

- clinical response within each age group at Visits 3 and 4 for the clinically evaluable population;
- microbiologic response, overall and by pathogen, for entire group and within each age group at Visits 3 and 4, for the microbiologically evaluable population.
- In order to allow for a dichotomous analysis, the clinical response categories (cured, improved, clinical relapse, failure, unable to evaluate) were to be grouped together as follows:
- For Visit 3, "cured" and "improved" will be combined into 1 category of "clinical success" versus the other 2 categories (failure, unable to evaluate).
- For Visit 4, "cured" will be 1 category and the other 4 categories (improved, clinical relapse, failure, unable to evaluate) will be grouped together as "not cured".

The microbiologic eradication rates were to be summarized overall and by pathogen. The overall infection eradication rates (eradicated versus persisted) was to be analyzed in a similar fashion to the clinical response rates, first for the entire population of microbiologically evaluable subjects using a 95% confidence interval and then within each age group.

Similarly, in order to allow for a dichotomous analysis, the microbiologic response categories of "eradicated" and "presumed eradicated" was to be combined into 1 category of "eradicated" and the categories "persisted", "presumed persisted", "persisted with acquisition of resistance", "microbiological relapse", and "unknown" was to be combined into 1 category of "persisted". Test-of-cure microbiologic determination for bacteremic subjects was to be based on the Visit 3 blood culture if a blood culture was not performed at Visit 4.

Medical Reviewer's Comment: This review will consider findings from the intent-to-treat and modified intent-to-treat study populations in addition to results in the clinically evaluable population.

5.2.12 Sample Size Determination

The sample size was calculated to show levofloxacin is at least as effective as standard of care therapy. (b) (4)

5.2.13 Evaluability Criteria

Clinical Evaluability

A subject will be evaluable for clinical efficacy unless categorized into 1 of the following groups:

- Not evaluable for safety ;
- Clinical diagnosis unconfirmed
- Insufficient course of therapy. Subject does not take the study drug for at least 5 days. However, subjects who take study drug for greater than 48 hours but for less than 5 days because they are judged a clinical failure by the investigator are evaluable. The pathogen(s) is (are) presumed to persist in these situations;

Effective concomitant therapy. Subject takes an effective systemic antimicrobial between time of study enrollment through test-of-cure culture (Visit 4). However, if the subject takes an effective systemic antimicrobial therapy because the subject has been judged a clinical failure by the investigator, the subject is evaluable and the pathogen(s) is (are) presumed to persist;
Test-of-cure clinical evaluation is not completed 7 to 21 days following the last dose of study drug. However, if a subject is discontinued due to clinical failure or is considered a clinical failure upon the completion of therapy and the test-of-cure evaluation is obtained before 7 days after therapy, the subject is not considered unevaluable for this reason;
Lost to follow-up but relays safety information (no test-of-cure evaluation);
Other protocol violation.

Medical Reviewers Comment: patients receiving effective concomitant treatment during the study or not completed 7-21 days of Test-of-cure clinical evaluation should remain evaluable for the clinical efficacy assessment and be considered treatment failures in the analysis.

Microbiologic Evaluability

A subject is evaluable for microbiologic efficacy if all criteria for clinical efficacy are met and the subject is not classified by any of the following:

- Infection not bacteriologically proven;
- Inappropriate bacteriologic culture: Admission culture is greater than 24 hours prior to start of therapy or any time following initiation of therapy.
- Test-of-cure evaluation including microbiologic culture is not completed 7 to 21 days following the last dose of study drug (or if a blood culture, carried forward from Visit 3). However, if the subject is discontinued due to clinical failure or considered a clinical

failure upon the completion of therapy and the test-of-cure culture is either not done or is obtained while on therapy, the subject is not considered unevaluable.

Subjects who are determined by serology to have infection due to *M. pneumoniae* or *C. pneumoniae* are evaluable for microbiologic efficacy unless any of the following criteria are met:

- Subject is not evaluable for safety;
- insufficient course of therapy;
- Effective concomitant therapy;
- Test-of-cure clinical evaluation is not completed 7 to 21 days following the last dose of study drug;
- Lost to follow-up but relayed safety information;
- Other significant protocol violation.

The microbiologic response of these atypical pathogens is based on the clinical response of the subject.

Medical Reviewers Comment: Subjects who are determined by serology to have infection due to M. pneumoniae or C. pneumoniae who received effective concomitant treatment during the study or not completed 7-21 days of Test-of-cure clinical evaluation should remain evaluable for microbiologic efficacy assessment; and be considered treatment failures in the analysis.

5.2.14 RESULTS AND ANALYSIS

5.2.15 Disposition

Figure 3 graphically represent subject enrollment and disposition for the study respectively. A total of 728 patients, 546 in the levofloxacin group and 182 in the comparator group underwent randomization. 529 in the levofloxacin group and 180 in the comparator group constituted the M ITT population for the primary analysis.

Disposition Table Test of Cure

Figure 3: graphically represents subject enrollment and Disposition

(b) (4)

[redacted]

.

(b) (4)

[redacted]

Medical Reviewer's Comment: (b) (4)

5.2.16 Demographics

A total of 709 male and female subjects, 6 months to 16 years of age, who took at least 1 dose of levofloxacin or comparator as part of a Phase 3 clinical study were eligible to be enrolled in this trial.

The demographic and baseline characteristics for the MITT Analysis Set are summarized in Table 28.

Table 28: Demographic and Baseline Characteristics (MITT)

	Levofloxacin (N=529)	Comparator (N=180)
Age (year)		
N	529	180
Mean (SD)	5.52 (4.014)	5.47 (4.118)
Median	5.00	4.65
Range	0.5 - 16.7	0.5 - 16.1
Age group, n (%)		
N	529	180
<5 years	264 (50)	92 (51)
5 years	265 (50)	88 (49)
Sex, n (%)		
N	529	180
Male	266 (50)	92 (51)
Female	263 (50)	88 (49)
Race, n (%)		
N	529	180
White	265 (50)	96 (53)
Black	53 (10)	19 (11)
Asian	2 (<1)	0
Other[a]	209 (40)	65 (36)
Baseline weight (kg)		
N	529	180
Mean (SD)	21.4 (14.29)	21.6 (15.88)
Median	17.2	17.0
Range	4 - 97	4 - 137
Baseline height (cm)		
N	521	177
Mean (SD)	106.9 (26.98)	107.1 (28.35)
Median	106.0	106.0
Range	56 - 179	55 - 185
Risk assessment[b]		
N	518	175
At risk	266 (51)	89 (51)
Low risk	252 (49)	86 (49)
Initial status		
N	529	180
Inpatient	277 (52)	98 (54)
Outpatient	252 (48)	82 (46)
Country, n (%)		
N	529	180

Argentina	26 (5)	9 (5)
Brazil	76 (14)	26 (14)
Chile	11 (2)	4 (2)
Costa Rica	146 (28)	50 (28)
Mexico	117 (22)	40 (22)
Panama	52 (10)	17 (9)
United States	101 (19)	34 (19)

[a]Other includes primarily Hispanic and Latino subjects. [b]Risk for severe disease at baseline was based on age, concomitant severe disease, altered mental status, and abnormal age-adjusted vital signs
Source: Sponsors Clinical Protocol LOFBIV-PCAP-003

Reviewer comment: the two treatment groups were generally balanced with respect to baseline demographic characteristics. Most of the patients were enrolled from South and Central America.

The demographic and baseline characteristics by country (U.S. versus Non-U.S.) for the MITT Analysis Set are summarized in Table 29.

Table 29: Demographic and Baseline Characteristics by Country - U.S. vs. Non-U.S. (MITT Analysis Set)

	Levofloxacin		Comparator	
	U.S. (N=101)	Non-U.S. (N=428)	U.S. (N=34)	Non-U.S. (N=146)
Age (year)				
N	101	428	34	146
Mean (SD)	6.41 (4.25)	5.30 (3.92)	6.58 (4.41)	5.21 (4.02)
Median	5.70	4.60	5.30	4.45
Range	0.5 - 16.7	0.5 - 16.5	0.5 - 16.1	0.5 - 14.4
Age group, n (%)				
N	101	428	34	146
<5 years	43 (43)	221 (52)	15 (44)	77 (53)
>= 5 years	58 (57)	207 (48)	19 (56)	69 (47)
Sex, n (%)				
N	101	428	34	146
Male	54 (53)	212 (50)	20 (59)	72 (49)
Female	47 (47)	216 (50)	14 (41)	74 (51)
Race, n (%)				
N	101	428	34	146
White	47 (47)	218 (51)	17 (50)	79 (54)
Black	28 (28)	25 (6)	10 (29)	9 (6)
Asian	2 (2)	0	0	0
Other [a]	24 (24)	185 (43)	7 (21)	58 (40)
Baseline weight (kg)				
N	101	428	34	146
Mean (SD)	26.2 (17.0)	20.3 (13.3)	29.5 (26.4)	19.7 (11.6)
Median	20.6	16.3	18.9	16.8
Range	7 - 97	4 - 96	8 - 137	4 - 60
Baseline height (cm)				
N	96	425	31	146
Mean (SD)	116.5 (28.5)	104.7 (26.18)	119.3 (30.3)	104.5 (27.3)
Median	112.0	103.0	109.0	103.3
Range	66 - 179	56 - 175	79 - 185	55 - 165
Risk assessment[b]				
N	98	420	33	142
At risk	41 (42)	225 (54)	15 (45)	74 (52)
Low risk	57 (58)	195 (46)	18 (55)	68 (48)
Initial status				
N	101	428	34	146
Inpatient	56 (55)	221 (52)	21 (62)	77 (53)
Outpatient	45 (45)	207 (48)	13 (38)	69 (47)

[a]Other includes primarily Hispanic and Latino subjects. [b]Risk for severe disease at baseline was based on age, concomitant severe disease, altered mental status,and abnormal age-adjusted vital signs.Source: Sponsors Clinical Protocol LOFBIV-PCAP-003

A greater proportion of Non-U.S. subjects were at risk for severe disease (54% levofloxacin group and 52% comparator group) vs (42% levofloxacin group and 45%) comparator group. The Non-U.S. subjects were also 1 year younger than the U.S. subjects. Black patients were enrolled at the U.S (28%) centers compared to the Non-U.S. centers (6%). A lower percentage of subjects at the U.S. centers were of 'other' races (23%) compared to the Non-U.S. centers (42%). These differences probably reflect the population compositions in these geographic regions.

The demographic and baseline characteristics by country (U.S. versus Non-U.S.) for the Clinically Evaluable Analysis Set are summarized in Table 30.

Table 30: Demographic and Baseline Characteristics by Country - U.S. vs. Non-U.S. (Clinically Evaluable Analysis Set)

	Levofloxacin		Comparator	
	U.S.	Non-U.S.	U.S.	Non-U.S.
	(N=79)	(N=326)	(N=20)	(N=114)
Age (year)				
N	79	326	20	114
Mean (SD)	6.59 (4.19)	5.20 (3.83)	6.13 (3.75)	5.52 (4.10)
Median	5.90	4.35	5.20	5.15
Range	0.6 - 16.7	0.5 - 15.8	0.5 - 15.0	0.5 - 14.4
Age group, n (%)				
N	79	326	20	114
<5 years	31 (39)	174 (53)	9 (45)	56 (49)
5 years	48 (61)	152 (47)	11 (55)	58 (51)
Sex, n (%)				
N	79	326	20	114
Male	42 (53)	163 (50)	12 (60)	59 (52)
Female	37 (47)	163 (50)	8 (40)	55 (48)
Race, n (%)				
N	79	326	20	114
White	35 (44)	195 (60)	10 (50)	69 (61)
Black	22 (28)	20 (6)	7 (35)	7 (6)
Asian	2 (3)	0	0	0
Other [a]	20 (25)	111 (34)	3 (15)	38 (33)
Baseline weight (kg)				
N	79	326	20	114
Mean (SD)	26.3 (16.4)	20.1 (13.4)	28.3 (28.5)	20.7 (12.0)
Median	21.1	15.9	17.2	17.8
Range	7 - 97	4 - 96	8 - 137	4 - 60
Baseline height (cm)				
N	76	323	17	114
Mean (SD)	116.7 (27.2)	103.9 (25.6)	119.0 (27.9)	106.7 (27.7)
Median	113.9	101.0	108.0	107.0
Range	66 - 172	56 - 175	84 - 182	55 - 165
Risk assessment[b]				
N	76	321	20	111
At risk	30 (39)	164 (51)	10 (50)	57 (51)
Low risk	46 (61)	157 (49)	10 (50)	54 (49)
Initial status				
N	79	326	20	114
Inpatient	43 (54)	148 (45)	12 (60)	56 (49)
Outpatient	36 (46)	178 (55)	8 (40)	58 (51)

[a] Other includes primarily Hispanic and Latino subjects. [b] Risk for severe disease at baseline was based on age, concomitant severe disease, altered mental status, and abnormal age-adjusted vital signs .Source: Sponsors Clinical Protocol LOFBIV-PCAP-003

Medical Reviewer's Comments: the demographic and baseline characteristic profile by-country was similar to the profile for clinically evaluable (Test-of-Cure Visit) Analysis Set. There were no clinically relevant baseline imbalances between the treatment groups.

5.2.17 Extent of Exposure

The numbers of patients exposed to the study drugs are summarized in the table 31 by duration of exposure. The Safety Analysis Set consisted of 712 subjects (533 levofloxacin;179 comparator).

Table 31: Duration of Therapy by Time Intervals (Study LOFBIV-PCAP-003: Modified Intent-to-Treat Analysis Set)

Duration of therapy (days)	Levofloxacin (N=529) n (%)	Comparator (N=180) n (%)
<7	23 (4)	11(6)
7-9	57(11)	19(11)
10-11	355 (67)	120 (67)
12-14	74(14)	24 (13)
>14	20 (4)	6(3)
Mean (SD)	10.5 (2.56)	10.4 (2.94)
Median	10.0	11.0
Range	(1-30)	(1-32)

Source: Sponsors Clinical Protocol LOFBIV-PCAP-003

Most subjects completed at least 10-11 days of their assigned treatment . The average duration of therapy for both the levofloxacin and comparator groups overall was 10.0 days. These durations are consistent with the protocol specified durations of therapy of 10 days.

5.2.18 Protocol Exceptions and Violations

Summary of protocol exceptions and violations identified during the conduct of the study are summarized below:

Table 32: Significant Protocol Deviations (All Randomized Subjects)

Deviation	Levofloxacin (N=546) n (%)	Comparator (N=182) n (%)
Received incorrect dose*	67 (12.3)	20 (11.0)
>15 days of study drug therapy	12 (2.2)	3 (1.6)
Inclusion/Exclusion criteria not met	14 (2.6)	1 (0.5)
Height not measured at screening	12 (2.2)	3 (1.6)
Effective concomitant therapy	13 (2.4)	1 (0.5)
MS evaluation performed > 72 hours of event onset	6 (1.1)	4 (2.2)
Posttreatment chest x-ray not performed	8 (1.5)	2 (1.1)
Clinical diagnosis unconfirmed	5 (0.9)	2 (1.1)
Received inappropriate study drug based on age	0	4 (2.2)

Cross-reference: Other Documentation, Protocol Deviations (available upon request)

*These subjects were prescribed the incorrect dose of study medication. This occurred at study sites in Mexico (67 subjects) and Brazil (9), and involved b.i.d. dosing whereas the protocol required q.d. dosing. Six subjects in the U.S. and 1 subject each in Argentina and Costa Rica were also dosed incorrectly. These errors were identified during the course of the study. Three additional subjects who were also dosed incorrectly discontinued study drug treatment due to adverse events

Source: Sponsors Clinical Protocol LOFBIV-PCAP-003

Reviewer comment: The majority of exceptions and violations did not appear to differ between groups. However, over 22% of the patients in this study were treated with effective concomitant therapy. Effective concomitant therapy was more frequently administered to patients in levofloxacin arm than the comparator.

5.2.19 Concomitant Therapy

Prestudy Systemic Antimicrobial Therapy

Prestudy (within 24 hours before first dose of study drug) systemic antimicrobial therapy is summarized in Table 33.

(b) (4)

Medical Reviewer's Comment: (b) (4)

(b) (4)

Antimicrobials Taken During the Study (Up to the Test-of-Cure Visit [25-35 days after the last dose])

(b) (4)

Reviewer Comment: (b) (4)

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5.2.20 Discontinuations of Study Drug

The following table below shows a summary of treatment completion and discontinuation information for the MITT Analysis.

Table 35: Treatment Completion and Discontinuation Information (Modified Intent-to-Treat Analysis Set)

Treatment Completion Status	Levofloxacin, n (%)	Comparator, n (%)	Total, n (%)
Total no. of subjects	529 (100)	180 (100)	709 (100)
Completed[a]	443 (84)	147 (82)	590 (83)
Discontinued	86 (16)	33 (18)	119 (17)
Adverse event	12 (2)	2 (1)	14 (2)
Lost to follow-up	3 (1)	5 (3)	8 (1)
Subject or legal guardian choice	5 (1)	3 (2)	8 (1)
Misdosed [b]	63 (12)	21 (12)	84 (12)
Other	3 (1)	2 (1)	5 (1)

[a] Subjects who completed the treatment regimen as described in the protocol were considered to have completed study treatment. One subject in the comparator group (112029) was incorrectly dosed, but in error, was considered to have completed treatment. [b] These subjects were prescribed the incorrect dose of study medication . *This occurred primarily at study sites in Mexico (67 subjects) and Brazil (9), and involved b.i.d. dosing whereas the protocol required q.d. dosing*. Six subjects in the U.S. and 1 subject each in Argentina and Costa Rica were also dosed incorrectly. These errors were identified during the course of the study. Three additional subjects who were also dosed incorrectly discontinued study drug treatment due to adverse events (Subjects 116103, 116110, and 116114).

Source: Sponsors Clinical Protocol LOFBIV-PCAP-003

Reviewer Comment: Dosing errors were the leading reported cause of study drug discontinuation in both treatment groups. In general, there were only small numerical differences between the two treatment groups in any of the causes for discontinuations. Discontinuation due to adverse events occurred in less than 2% of the patients in both arms.

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5.2.23 REVIEW OF SAFETY

The safety data were reviewed with particular reference to the occurrence of musculoskeletal adverse events. Safety evaluations for this study included assessments of duration of study drug exposure, serious adverse events, and adverse events (serious and nonserious) that were considered by the investigator to be related to study drug. The analyses of safety included all randomly assigned patients who received any amount of study drug.

Safety was evaluated by monitoring treatment-emergent adverse events and changes from baseline in clinical laboratory values (serum chemistry, hematology, and urinalysis), vital sign measurements temperature, pulse, blood pressure, respiration rate and physical examination findings. Safety evaluations for MS adverse events were also performed
throughout the study.

In general, the types of adverse events were similar to those observed in both treatment arms. The incidence of MSAE was not higher in levofloxacin arm.

A. Adverse Events

Adverse event (AE) data were collected for all subjects at various time points. Incidence rates of adverse events were summarized by body system and preferred term. Adverse events were reported by the subject (or the subject's legally authorized representative) or by the investigator if discovered on examination from the time of the first study related procedure through completion of the follow-up telephone contact. An adverse event was defined as any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of the investigational product, whether or not the event was related to the investigational product.

All adverse events were recorded regardless of seriousness, severity, or presumed relationship to study drug, in the source document along with all measures required for adverse event management and the ultimate outcome (resolved, persisted, unknown). the severity of the adverse event (mild, moderate, or marked), action taken (none, dose reduced, drug stopped temporarily, drug stopped permanently), and the relationship of the adverse event to the study drug (not related, doubtful, possible, probable, very likely) were also recorded. All serious adverse events that were not resolved by the end of the study were followed until they resolved or stabilized, or could be attributed to something other than the study drug or procedures.

B. Deaths

There were two deaths during the study. The narratives describing both deaths are summarized in the table below.

Table 51 shows an overview of deaths that occurred during the study by, subject number, age, study days at the time of death, days of study therapy, and relation to the study drug.

Table 51: Subjects Who Died (Study LOFBIV-PCAP-003: Safety Analysis Set)

Treatment / Subject No.	Age in Years/ Sex	Preferred Term	Day of Death Based on day of first dose	Last Dosage Before Death	Action Taken	Relationship to Drug	Days on Therapy
Levofloxacin 116114	13.7 Female	Heart Rate & Rhythm disorders (Cardiac arrest) Death secondary to bronchoscopic procedure, vagal effect possible	3	250 mg	Drug stopped permanently	Not Related	3
Levofloxacin 117021	2.2 Male	Respiratory System disorders (Pneumothorax) Bronchospasm	30	121 mg	None	Not Related	10

The narratives describing both deaths are summarized below:

Subject 116114: This 13.7-year old, 38.0 kg, Latino female from Mexico was randomly assigned to the levofloxacin group. She did not have any significant medical history. Concomitant medications included ranitidine for abdominal pain and gastritis, Ambroxyl as a mucolytic, and metamizole for fever. The subject was hospitalized on Day 1 due to the severity of her respiratory symptoms (signs and symptoms: fever, shortness of breath, cough, abnormal WBC count; chest examination: severe rales; chest x-ray: multiple foci pneumonia with pneumatocele, sputum). Pathogens were not isolated at screening. Levofloxacin i.v. treatment was initiated on Day 1. The subject received 250 mg b.i.d. instead of the recommended dose of 10 mg/kg/day (e.g., 380 mg q.d.). On Day 3, a bronchoscopy was performed as tuberculosis was

suspected. Pre-operative medications included halothane, sevoflurane, propofol, nitrous oxide, midazolam, tramadol, and metoclopramide. Five minutes after the procedure was completed, the subject went into cardiorespiratory arrest and died despite resuscitation attempts. Treatment included atracurium (muscle relaxation), atropine and epinephrine (asystole), and sodium bicarbonate (acidosis). The cause of death was listed as hypoxia. An autopsy was not performed. The investigator considered this event marked in severity, related to the bronchoscopy procedure, and not related to levofloxacin therapy.

Subject 117021: This 2.2-year old, 12.1 kg, Hispanic male was randomly assigned to the levofloxacin group. He did not have any significant medical history, and did not receive any concomitant medications. The subject was hospitalized on Day 1 due to the severity of his respiratory symptoms (signs and symptoms: fever, shortness of breath, cough, chest pain, abnormal WBC count; chest examination: mild rales, mild egophony; chest x-ray: left pneumonia, bilateral pleural effusion). Pathogens were not isolated at screening. The subject's plasma levofloxacin concentration was 0.246µg/mL on Day 4 (sample taken 2 to < 4 hours postdose). Levofloxacin treatment (121 mg oral suspension b.i.d.) was completed on Day 10. The subject was considered clinically cured at the Posttherapy Visit (Day 11). The subject's plasma levofloxacin concentration was below the quantifiable level (0.0500µg/mL) on Day 11 (sample taken 12 to < 24 hours postdose).

At an unscheduled visit on Day 23, the subject was diagnosed with pharyngitis and parasitosis. Treatment included acetaminophen, amoxicillin, and piperazine. At the Test-of-Cure Visit (Day 25), all clinical signs and symptoms associated with active infection (except fever) were resolved. This was confirmed by improvement of abnormal screening chest x-ray findings (performed on Day 23). The clinical response was 'unable to evaluate' as the subject had received effective concomitant therapy (amoxicillin). On Day 30, the subject was evaluated in the Emergency Room (ER) for a febrile illness and diagnosed with purulent pharyngitis and leukocytosis. A chest x-ray showed airway trapping. Additionally, the subject had a markedly high serum glucose level (345 mg/dL). The subject was discharged from the ER for ambulatory care the same day. Thirty minutes after discharge, he developed severe bronchospasm followed by cardiorespiratory arrest. The subject returned to the hospital; intubation and mechanical ventilation were required. His intubation tube was incorrectly placed, and the subject experienced a second cardiorespiratory arrest. He died despite resuscitation attempts. The subject completed study drug on Day 10 and completed the study on Day 25. The investigator considered this event marked in severity and not related to levofloxacin therapy.

Reviewer comment: The reviewer agrees that neither death appear to be related to the study drug. However, in the case of subject 117021 the relationship of the markedly high serum glucose level (345 mg/dL) to her death is unclear. The investigator did not comment on the relationship between this laboratory abnormality and study drug or relationship to the death. Baseline and Day 10 values for this subject were 100 mg/dL and 107 mg/dL, respectively. Treatment-emergent markedly abnormal glucose value other than this case was not observed in this study.

C. Serious Adverse Events

The serious adverse events data were examined and presented below.

In general, the types of serious adverse events were similar between the two treatment groups and were known adverse events.

Thirty-three (6%) levofloxacin-treated subjects and 8 (4%) comparator-treated subjects had 1 or more serious adverse event. Two of these events resulted in fatal outcomes that were unrelated to the study drug. Table 52 presents a summary of SAEs by treatment group

Table 52: Incidence of Serious Adverse Events by Body System and Preferred Term (Study LOFBIV-PCAP-003: Safety Analysis Set)

Body System Preferred Term	Levofloxacin (N=533) n (%)	Comparator (N=179) n (%)
Total no. of subjects with serious adverse events	33 (6)	8 (4)
Respiratory system disorders	13 (2)	4 (2)
Asthma	3 (1)	2 (1)
Pneumonia	3 (1)	2 (1)
Bronchospasm	2 (<1)	0
Dyspnea	2 (<1)	1 (1)
Pleural effusion	2 (<1)	0
Pneumothorax	2 (<1)	0
Hypoxia	2 (<1)	1 (1)
Laryngitis	0	1 (1)
Body as a whole - general disorders	11 (2)	3 (2)
Condition aggravated	9 (2)	2 (1)
Fever	1 (<1)	1 (1)
Infection (tuberculosis)	1 (<1)	0
Liver and biliary system disorders	2 (<1)	1 (1)
Hepatitis	2 (<1)	0
Hepatomegaly	0	1 (1)
Myo endo pericardial & valve disorders	2 (<1)	0
Pericarditis	2 (<1)	0
Cardiovascular disorders, general	1 (<1)	0
Cardiac failure	1 (<1)	0
Gastrointestinal system disorders	1 (<1)	0
Gastroenteritis	1 (<1)	0
Heart rate and rhythm disorders	1 (<1)	0
Cardiac arrest	1 (<1)	0
Musculoskeletal system disorders	1 (<1)	0
Myositis	1 (<1)	0
Red blood cell disorders	1 (<1)	0
Anemia	1 (<1)	0
Resistance mechanism disorders	1 (<1)	0
Infection	1 (<1)	0
Skin and appendages disorders	1 (<1)	0
Rash	1 (<1)	0

Note: Incidence was based on the number of subjects, not the number of events. Percentages were calculated with the total no. of subjects as the denominator.
Source: Sponsors Clinical Protocol LOFBIV-PCAP-003

Reviewer comments: even though the numbers are too small, the incidence of cardiovascular Serious Adverse Events by Body System and Preferred Term were higher in levofloxacin treated patients.

Incidence of Treatment-Limiting Adverse Events

Table 53 contains summaries of incidence of treatment-limiting adverse events that occurred by treatment group. Twelve (2%) levofloxacin-treated subjects and 2 (1%) comparator-treated subjects discontinued study drug due to 1 or more adverse event. All treatment-limiting adverse events occurred in <1% of subjects.

Table 53: Incidence of Treatment-Limiting Adverse Events by Body System and Preferred Term (Study LOFBIV-PCAP-003: Safety Analysis Set)

Body System Preferred Term	Levofloxacin (N=533) n (%)	Comparator (N=179) n (%)
Total no. of subjects with treatment-limiting adverse events	12 (2)	2 (1)
Gastrointestinal system disorders	4 (1)	0
Vomiting	2 (<1)	0
Abdominal pain	1 (<1)	0
Gastritis	1 (<1)	0
Stomatitis ulcerative	1 (<1)	0
Myo endo pericardial & valve	2 (<1)	0
disorders		
Pericarditis	2 (<1)	0
Skin and appendages disorders	2 (<1)	1 (1)
Rash	1 (<1)	0
Rash erythematous	1 (<1)	0
Urticaria	0	1 (1)
Body as a whole - general disorders	1 (<1)	1 (1)
Condition aggravated	1 (<1)	1 (1)
Central and peripheral nervous	1 (<1)	0
system disorders		
Dizziness	1 (<1)	0
Headache	1 (<1)	0
Fetal disorders	1 (<1)	0
Pulmonic stenosis congenital	1 (<1)	0
Heart rate and rhythm disorders	1 (<1)	0
Cardiac arrest	1 (<1)	0
Musculoskeletal system disorders	1 (<1)	0
Myositis	1 (<1)	0
Respiratory system disorders	1 (<1)	0
Asthma	1 (<1)	0

Note: Incidence was based on the number of subjects, not the number of events.
Percentages were calculated with the total no. of subjects as the denominator. Source: Sponsors Clinical Protocol LOFBIV-PCAP-003

D. Adverse Events of Special Interest

To assess the effect of treatment on Musculoskeletal Adverse Events comparison of MS disorders and adverse events were made between treatment groups. The incidence of musculoskeletal adverse events and disorders are provided in Table 54 and 55.

The incidence of musculoskeletal adverse events is provided in Table 54.

Table 54: Incidence of Musculoskeletal Adverse Events by Preferred Term (Study LOFBIV-PCAP-003: Safety Analysis Set)

Preferred Term	Levofloxacin (N=533)	Comparator (N=179)	p-value[a]
Total number of subjects with any MS adverse event	19 (4)	6 (3)	>0.999
Myalgia	10 (2)	4 (2)	0.759
Arthralgia	9 (2)	1 (1)	0.465
Skeletal pain	0	2 (1)	>0.063
Arthropathy	1 (<1)	0	>0.999
Muscle hypertrophy	1 (<1)	0	>0.999
Myositis	1 (<1)	0	>0.999
Tendinitis	1 (<1)	0	>0.999

a 2-sided p-value using Fisher's Exact test Note: Percentages were calculated with the no. of subjects in each group as the denominator. Source: Sponsors Clinical Protocol LOFBIV-PCAP-003

Reviewer comment: The overall incidence of musculoskeletal adverse events in this study was < 4%. Most of the musculoskeletal adverse events were myalgia and arthralgia . Overall, there were no apparent differences across the treatment groups .

Table 55: Incidence of Musculoskeletal Disorders (Study LOFBIV-PCAP-003: Safety Analysis Set)

Preferred Term	Levofloxacin (N=533)	Comparator (N=179)	p-value[a]
Total number of subjects with any MS disorder	10 (2)	2 (1)	0.740
Arthralgia	9 (2)	1 (1)	0.465
Arthritis	1 (<1)	0	>0.999
Tendinopathy	1 (<1)	1 (1)	0.440

2-sided p-value using Fisher's Exact test
Note: Percentages were calculated with the no. of subjects in each group as the denominator.
Source: Sponsors Clinical Protocol LOFBIV-PCAP-003

Reviewer comment: The overall incidence of MS disorders in this study was ≤ 2 %. There were no apparent differences in the incidence of MS disorders across the groups.

E. Most Common Adverse Events

The following two tables (Table 56 and Table 57) show summary of adverse events occurring in at least 5% of subjects up to the Test-of-Cure Visit and the incidence of treatment-emergent adverse events up to the Test-of-Cure Visit by severity and by relationship to study drug for the Safety Analysis, respectively.

Table 56: Incidence of Treatment-Emergent Adverse Events Occurring in ≥ 5% of Subjects in Any Treatment Group up to the Test-of-Cure and Follow-up Visit by Body System and Preferred Term (Study LOFBIV-PCAP-003: Safety Analysis Set)

Body System Preferred Term	Levofloxacin (N=533) n (%)	Comparator (N=179) n (%)
Test-of-Cure Visit		
Total no. of subjects with adverse events	275 (52)	94 (53)
Body as a whole - general disorders	40 (8)	16 (9)
Fever	12 (2)	11 (6)
Gastrointestinal System disorders	102 (19)	42 (23)
Diarrhea	37 (7)	19 (11)
Vomiting	34 (6)	15 (8)
Abdominal pain	24 (5)	12 (7)
Respiratory System disorders	92 (17)	36 (20)
Upper respiratory tract infection	26 (5)	9 (5)
Rhinitis	19 (4)	10 (6)
Bronchospasm	16 (3)	10 (6)
Post Therapy		
Total no. of subjects with adverse events	304 (57)	103 (58)
Body as a Whole - General Disorders	48 (9)	20 (11)
Fever	18 (3)	13 (7)
Gastrointestinal System Disorders	113 (21)	43 (24)
Diarrhea	40 (8)	19 (11)
Vomiting	36 (7)	16 (9)
Abdominal pain	27 (5)	12 (7)
Respiratory System Disorders	125 (23)	49 (27)
Upper respiratory tract infection	43 (8)	16 (9)
Bronchospasm	24 (5)	12 (7)
Rhinitis	23 (4)	11 (6)

Note: Incidence was based on the number of subjects, not the number of events. Percentages were calculated with the total no. of subjects as the denominator.
Source: Sponsors Clinical Protocol LOFBIV-PCAP-003

Medical Reviewer's Comment: The overall incidence of treatment-emergent adverse events occurring in ≥ 5% in this study was similar in both treatment groups. Overall, there were no apparent differences across the treatment groups. Diarrhea and upper respiratory tract infection were the most frequent adverse events.

Table 57: Incidence of Treatment-Emergent Adverse Events up to the Test-of-Cure Visit That Were Marked in Severity by Body System and Preferred Term (Study LOFBIV-PCAP-003: Safety Analysis Set)

Body System Preferred Term	Levofloxacin (N=533) n (%)	Comparator (N=179) n (%)
Total no. of subjects with adverse events that were marked in severity	14 (3)	3 (2)
Body as a whole - General Disorders	6 (1)	0
Chest pain	1 (<1)	0
Condition aggravated	4 (1)	0
Fever	1 (<1)	0
Gastrointestinal System Disorders	1 (<1)	0
Gastrointestinal hemorrhage	1 (<1)	0
Liver and Biliary System Disorders	0	1 (1)
Hepatomegaly	0	1 (1)
Metabolic and Nutritional Disorders	1 (<1)	0
Phosphatase alkaline increased	1 (<1)	0
Musculoskeletal System Disorders	1 (<1)	0
Myositis	1 (<1)	0
Myo endo pericardial & valve Disorders	2 (<1)	0
Pericarditis	2 (<1)	0
Red blood cell Disorders	1 (<1)	0
Anemia	1 (<1)	0
Resistance mechanism Disorders	1 (<1)	0
Moniliasis	1 (<1)	0
Respiratory System Disorders	3 (1)	2 (1)
Asthma	1 (<1)	0
Bronchospasm	0	1 (1)
Dyspnea	2 (<1)	1 (1)
Hypoxia	1 (<1)	1 (1)
Pneumonia	1 (<1)	1 (1)

Note: Incidence was based on the number of subjects, not the number of events. Percentages were calculated with the total no. of subjects as the denominator.
Source: Sponsors Clinical Protocol LOFBIV-PCAP-003

Medical Reviewer's Comment: *The overall incidence of Treatment-Emergent Adverse Events up to the test of cure visit in this study was similar in both treatment groups. Overall, there were no apparent differences across the treatment groups.*

F. Clinical Laboratory Evaluations

Clinical laboratory measurements were obtained from all the patients and laboratory assessment values that were potentially affected by study treatments or were of particular interest were compared between treatment groups (see Table 59 to 61). To identify clinically relevant laboratory abnormalities, markedly abnormal limits were defined for hematology, serum chemistry, and urinalysis analysis. Laboratory values were considered markedly abnormal for this study if they met all of the following criteria:

- were treatment-emergent
- exceeded the markedly abnormal limit
- represented at least a 10% change from pretreatment values.

G. Hematology

Table 58: Mean (SD) Change From Admission to the Posttherapy Visit (or Early Withdrawal) for Select Hematology Laboratory Evaluation (Study LOFBIV-PCAP-003: Safety Analysis Set)

	Levofloxacin (N=533)	Comparator (N=179)
Differential (absolute) -bands (x109/L)		
N	398	133
Mean baseline	0.3	0.3
Mean change (SD)	-0.3 (0.84)	-0.3 (0.82)
Differential (absolute) -eosinophils (x109/L)		
N	429	139
Mean baseline	0.2	0.2
Mean change (SD)	0.1 (0.68)	0.1 (0.39)
Differential (absolute) -neutrophils (x109/L)		
N	429	140
Mean baseline	8.4	9.0
Mean change (SD)	-4.6 (6.07)	-5.3 (6.81)
Hematocrit (%)		
N	411	130
Mean baseline	37.2	37.4
Mean change (SD)	2.1 (4.02)	1.7 (3.58)
Hemoglobin (g/dL)		
N	432	140
Mean baseline	12.3	12.2
Mean change (SD)	0.4 (1.08)	0.4 (0.89)
Platelet count (x109/L)		
N	384	125
Mean baseline	350.5	343.6
Mean change (SD)	95.5 (187.18)	94.0 (168.59)
WBC, total (x109/L)		
N	429	140
Mean baseline	13.0	13.4
Mean change (SD)	-3.9 (7.20)	-4.5 (7.64)

N = numbers of subjects with evaluable admission and Posttherapy Visit results (or results at early withdrawal).
Source: Sponsors Clinical Protocol LOFBIV-PCAP-003

Reviewer comment: There were no clinically notable changes in mean changes from admission to the Posttherapy Visit (or early withdrawal) for select hematology assessments. The mean decreases in WBCs and neutrophils and the mean increases in platelet counts observed are expected in this population of sick children. This observation needs to be interpreted with caution since patients had a short duration of exposure to both treatments.

H. Chemistry

Table 59: Mean (SD) Change From Admission to Posttherapy Visit (or Early Withdrawal) for Selected Chemistry Values (Study LOFBIV-PCAP-003: Safety Analysis Set)

	Levofloxacin (N=533)	Comparator (N=179)
Chloride (mmol/L)		
N	464	150
Mean baseline	105.7	105.2
Mean change (SD)	1.4 (4.55)	1.8 (4.74)
Creatinine (mg/dL)		
N	477	158
Mean baseline	0.4	0.4
Mean change (SD)	-0.0 (0.16)	-0.0 (0.17)
G-glutamyl transferase (U/L)		
N	429	138
Mean baseline	18.6	16.0
Mean change (SD)	0.2 (21.15)	1.0 (15.17)
Glucose (mg/dL)		
N	472	154
Mean baseline	102.6	102.5
Mean change (SD)	-16.0 (35.52)	-16.1 (34.85)
Magnesium (mg/dL)		
N	434	144
Mean baseline	2.1	2.1
Mean change (SD)	-0.0 (0.26)	-0.1 (0.26)
Phosphorus, inorganic (mg/dL)		
N	442	146
Mean baseline	4.5	4.4
Mean change (SD)	0.8 (1.62)	0.9 (1.23)
Potassium (mmol/L)		
N	453	143
Mean baseline	4.1	4.2
Mean change (SD)	0.2 (0.61)	0.2 (0.61)
Sodium (mmol/L)		
N	464	150
Mean baseline	139.5	139.3
Mean change (SD)	0.4 (4.05)	0.7 (3.87)
Total protein (g/dL)		
N	461	154
Mean baseline	7.2	7.1
Mean change (SD)	0.1 (0.84)	0.0 (0.82)

N = numbers of subjects with evaluable admission and Posttherapy Visit results (or results at early withdrawal).
Source: Sponsors Clinical Protocol LOFBIV-PCAP-003

Reviewer comment: the data indicate that there were no clinically notable Mean changes from admission to the post therapy visit (or early withdrawal) for select chemistry evaluation. The change in serum glucose in both treatment groups was similar (16mg/dl from baseline) and was not clinically relevant or associated with clinical symptoms of hypoglycemia.

I. Creatinine

Table 60: Mean (SD) Change From Admission to the Posttherapy Visit (or Early Withdrawal)for Creatinine Values by Age Group (Study LOFBIV-PCAP-003: Safety Analysis Set)

Creatinine (mg/dL)	Levofloxacin (N=533)	Comparator (N=179)
< 5 years		
N	235	82
Mean baseline	0.3	0.3
Mean change (SD)	-0.0 (0.16)	-0.0 (0.16)
≥ 5 years		
N	242	76
Mean baseline	0.5	0.5
Mean change (SD)	-0.0 (0.15)	-0.1 (0.17)

N = numbers of subjects with evaluable admission and Posttherapy results (or results at early withdrawal).
Source: Sponsors Clinical Protocol LOFBIV-PCAP-003

Reviewer comment: There were no important differences between the two treatment groups in mean laboratory values for creatinine at baseline and the mean changes at the post baseline visit in all subjects who also had normal renal function. No differences were observed between age groups.

J. Treatment-Emergent Markedly Abnormal Clinical Laboratory Values

The incidences of treatment-emergent markedly abnormal clinical laboratory values (Chemistry and Hematology) are summarized in Table 61. Forty subjects had 1 or more markedly abnormal laboratory value (levofloxacin: 34 subjects; comparator: 6 subjects).

Table 61: Incidence of Treatment-Emergent Markedly Abnormal Clinical Laboratory Values (Study LOFBIV-PCAP-003: Safety Analysis Set)

Chemistry	Levofloxacin, N=507	Comparator, N=167
Alanine amino transferase (U/L)	476	158
Increase	1 (<1)	1 (1)
Alkaline phosphatase (U/L)	490	161
Increase	2 (<1)	0
Aspartate amino transferase (U/L)	450	143
Increase	0	1 (1)
Blood urea nitrogen (mg/dL)	472	158
Increase	1 (<1)	1 (1)
Calcium (mg/dL)	482	157
Decrease	3 (1)	0
Chloride (mmol/L)	491	159
Increase	2 (<1)	2 (1)
Creatinine (mg/dL)	505	164
Increase	1 (<1)	1 (1)
Glucose (mg/dL)	499	161
Increase	1 (<1)	0
Potassium (mmol/L)	482	152
Decrease	1 (<1)	0
Increase	2 (<1)	0
Sodium (mmol/L)	491	159
Increase	2 (<1)	1 (1)
Uric acid (mg/dL)	472	152
Increase	1 (<1)	0
Hematology	470	149
Differential -eosinophils (x109/L)	467	148
Increase	13 (3)	1 (1)
Differential -neutrophils (x109/L)	467	149
Decrease	2 (<1)	0
Hematocrit (%)	451	138
Decrease	1 (<1)	0
Hemoglobin (g/dL)	470	149
Decrease	2 (<1)	0
Platelet count (x109/L)	428	134
Decrease	1 (<1)	0
Increase	2 (<1)	0
RBC, total (x1012/L)	470	149
Decrease	1 (<1)	0
WBC, total (x109/L)	467	149
Decrease	2 (<1)	0
Increase	2 (<1)	1 (1)

a Analytes for which no subject met criteria are not presented n = Number of subjects with admission and posttherapy data available for that analyte. Source: Sponsors Clinical Protocol LOFBIV-PCAP-003

K. Vital Signs and Physical Findings

Vital signs were measured in all of the patients. Mean values and changes from baseline in vital signs by age group at the Posttherapy is shown in Table 62. Subjects who were not included in the vital sign analyses) did not have both baseline and postbaseline values (not done or performed outside the analysis window). In general, there were no clinically relevant findings.

Table 62: Vital Signs - Mean Values and Changes From Baseline by Age Group at the Posttherapy Visit (Study LOFBIV-PCAP-003: Safety Analysis Set)

Variable **Age Group**	Levofloxacin (N=533)	Comparator (N=179)
Systolic BP (mmHg)		
0.5 - <5 years		
N	248	85
Mean baseline	91.73	89.86
Mean change (SD)	-2.46 (11.466)	-1.48 (11.124)
≥5 -≤10 years		
N	176	51
Mean baseline	96.45	99.12
Mean change (SD)	-1.72 (12.946)	-4.55 (14.632)
> 10 years		
N	75	31
Mean baseline	106.15	101.97
Mean change (SD)	-3.20 (13.510)	-3.58 (12.680)
Diastolic BP (mmHg)		
0.5 - <5 years		
N	247	85
Mean baseline	56.95	54.34
Mean change (SD)	0.27 (9.606)	0.65 (9.896)
≥5 -≤10 years		
N	176	51
Mean baseline	60.07	60.67
Mean change (SD)	-0.07 (10.051)	0.02 (11.680)
> 10 years		
N	75	31
Mean baseline	66.21	64.00
Mean change (SD)	-2.09 (12.135)	0.35 (12.478)

Pulse Rate (bpm)		
0.5 - <5 years		
N	257	89
Mean baseline	123.74	128.93
Mean change (SD)	-16.02 (21.273)	-19.64 (22.280)
≥5 -≤10 years		
N	177	52
Mean baseline	107.21	112.58
Mean change (SD)	-15.24 (20.752)	-21.83 (27.708)
> 10 years		
N	76	31
Mean baseline	99.84	98.03
Mean change (SD)	-16.28 (19.434)	-15.45 (19.816)
Respiration Rate (bm)		
0.5 - <5 years		
N	256	88
Mean baseline	41.07	41.38
Mean change (SD)	-12.54 (11.828)	-12.48 (12.180)
≥5 -≤10 years		
N	177	52
Mean baseline	28.06	28.04
Mean change (SD)	-6.98 (8.820)	-6.62 (10.897)
> 10 years		
N	76	31
Mean baseline	26.62	25.94
Mean change (SD)	-6.25 (9.392)	-6.45 (6.913)
Temperature (°C)		
0.5 - <5 years		
N	255	89
Mean baseline	37.61	37.37
Mean change (SD)	-1.08 (1.040)	-0.83 (1.045)
≥5 -≤10 years		
N	177	52
Mean baseline	37.26	37.27
Mean change (SD)	-0.83 (0.988)	-0.84 (0.918)
> 10 years		
N	76	31
Mean baseline	37.37	37.18
Mean change (SD)	-0.96 (1.089)	-0.80 (1.015)

N = number of subjects with evaluable admission and Posttherapy Visit data for that vital sign. bpm = beats per minute
bm = breaths per minute
Source: Sponsors Clinical Protocol LOFBIV-PCAP-003

Table 63 shows treatment-emergent markedly abnormal systolic and diastolic blood pressure and temperature values based on age-specific criteria in both treatment groups .

Table 63: Incidence of Treatment-Emergent Markedly Abnormal Vital Sign Values Based on Age-Specific Criteria (Study LOFBIV-PCAP-003: Safety Analysis Set)

Vital Sign[a]	Levofloxacin (N=533)	Comparator (N=179)
Markedly Abnormal Change	n (%)	n (%)
Temperature	503	171
Low	18 (4)	5 (3)
Systolic BP	495	165
Low	6 (1)	2 (1)
Diastolic BP	493	164
Low	6 (1)	2 (1)

a Vital sign parameters for which no subject met criteria are not presented.
n = number of subjects with admission and posttherapy data available for that vital sign There were no significant findings in physical examination abnormalities.

Fifteen subjects experienced 1 or more markedly abnormal changes in blood pressure. Twenty-three subjects had markedly abnormal changes in temperature. None of the markedly abnormal vital sign changes were reported as adverse events.

5.2.24 Safety Conclusions

The data of safety was obtained from a total of 712 (533 levofloxacin;179 comparator, MITT) patients that were evaluable for safety.

Two-hundred seventy-five (52%) levofloxacin-treated subjects and 94 (53%) comparator-treated subjects reported at least 1 adverse event up to the Test-of-Cure Visit. Adverse events leading to treatment discontinuation occurred in 12 (2%) levofloxacin-treated and 2 (1%) comparator-treated subjects. Two levofloxacin-treated subjects with serious adverse events (levofloxacin group) had fatal outcomes that do not appear to be due to levofloxacin. (One death occurred 3 weeks after completion of levofloxacin treatment; the other death occurred after 3 days of levofloxacin treatment during a bronchoscopy procedure). In general, the safety profile defined in children in this study is similar to that defined in clinical trials involving adults.

Serious adverse events were reported in 33 (6%) levofloxacin-treated subjects and 8 (4%) comparator-treated subjects. Most serious adverse events were considered by the investigators to be doubtfully related or not related to study drug.

Diarrhea was the most frequent adverse event (7% and 11% for levofloxacin and comparator, respectively). Twenty-five subjects (4%) experienced MS adverse events. The frequency of MS disorders was comparable in levofloxacin- and comparator-treated subjects (2% vs. 1%) in this short term study. Reports of adverse events related to the musculoskeletal system were similar in the two treatment arms.

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5.3 ACUTE OTITIS MEDIA (CLINICAL OUTCOME) (LOFBO-OTMD-002

5.3.1 Study Protocol

This was a randomized, evaluator-blinded, active-comparator, non-inferiority, multicenter, Phase 3 study conducted in the United States and several Latin American countries (Argentina, Brazil, Chile, Costa Rica, and Panama).

The primary objective of this study was to demonstrate non-inferiority of levofloxacin compared with amoxicillin + clavulanic acid with respect to the clinical response (cured versus not cured) at the end of therapy (Visit 3, 2 to 5 days after last dose) in infants and children who had recurrent and/or persistent acute otitis media (AOM). Secondary objectives were to assess the efficacy of levofloxacin based on the clinical cure rate at Visit 4 (10 to 17 days after the last dose), the clinical success rate (cured or improved versus failed) at Visit 3 and Visit 4, the clinical failure rate at Visit 2 (4 to 6 days after the first dose), and persistence of middle ear effusion at Visit 3. Safety was also assessed.

Clinical response (defined as: cured, improved, failure, or unable to evaluate) was determined at Visits 3 and 4. *The primary endpoint was the clinical cure rate (cured versus not cured) at Visit 3 (2 to 5 days after the last dose of study drug)* based on resolution of the clinical signs and symptoms of acute otitis media. Secondary efficacy endpoints included clinical cure at Visit 4 (10 to 17 days after the last dose), clinical success (cured or improved response categories) at Visit 3 and Visit 4, clinical failure at Visit 2 (4 to 6 days after the first dose), and persistence of middle ear effusion at Visit 3.

Safety was evaluated by monitoring treatment-emergent adverse events (with special emphasis on MS adverse events) and changes in clinical laboratory tests, vital signs, and physical examination findings.

The primary efficacy endpoint, clinical cure rate (cured versus not cured) at Visit 3, was summarized overall and by age group (¡Ü2 years, >2 years), sex, race, and for US versus Non-US subjects. Secondary endpoints were summarized overall, by age group, and for US versus Non-US subjects. A 2-sided 95% confidence interval (CI) for the difference in clinical cure and clinical success rates between the 2 treatments (comparator minus levofloxacin) was performed to assess therapeutic non-inferiority. To claim noninferiority, the upper bound of the 95% CI must have remained below a non-inferiority margin of 10%.

The incidence of treatment-emergent adverse events was summarized by treatment, severity, relationship to study drug, age group, sex, and race using a standard adverse event dictionary based on the World Health Organization Adverse Reaction Terminology (WHOART). Musculoskeletal adverse events were summarized by
treatment and diagnosis and classified as 1 of the following MS disorders: tendinopathy, arthritis, arthralgia, or gait abnormality. Changes in clinical laboratory tests and vital signs were assessed

by descriptive statistics and summarized by treatment. Physical examination abnormalities were listed.

5.3.2 Study Procedure

Outpatient pediatric subjects (aged ≥ 6 months to <5 years) who had recurrent and/or persistent acute otitis media and met the prestudy eligibility criteria were randomized to receive either levofloxacin (10mg/kg oral suspension b.i.d. (up to 500 mg/day)) or Amoxicillin + clavulanic acid (14:1) 45 mg/kg (amoxicillin) oral suspension (up to 3,600 mg/day twice daily (b.i.d.) for 10 days followed by posttreatment assessment. The randomization was stratified by study center to ensure balance between treatment groups. Subjects were randomized to the treatment groups in a 1:1 levofloxacin: comparator ratio.

Male and female subjects aged ¡Ý6 months to <5 years who had clinical signs and symptoms of recurrent and/or persistent acute otitis media (defined as: middle ear effusion and 1 or more indicators of acute inflammation [defined as ear pain within 24 hours, including unaccustomed tugging or rubbing of ear; marked redness of the tympanic membrane; distinct fullness or bulging of the tympanic membrane; or acute purulent otorrhea of less than 48 hours duration not due to otitis externa]).

Efficacy was based on the comparison of the clinical cure rate in levofloxacin-treated subjects with the cure rate in comparator treated subjects. Safety was based on the incidence, relationship to therapy, and severity of treatment-emergent adverse events, and on changes in clinical laboratory values (hematology, chemistry, and urinalysis), vital signs, and physical examination findings. Supplementary safety evaluations for musculoskeletal (MS) adverse events were performed throughout the study. A Data Safety Monitoring Committee (DSMC) reviewed serious and MS adverse events on an ongoing basis.

The time and events schedule for this study is presented in Table 65.

Table 65: Time and Events Schedule

Phase	Screening[a]	Treatment		Posttreatment		Follow-Up Telephone Contact
Visit	1	1	2	3	4[c]	5
Study Day	1	1	4-6	2-5 days after last dose	10-17 days after last dose	25-35 days after last dose
Screening Procedures						
Informed consent/assent [b]	X					
Medical history	X					
Inclusion/exclusion	X					
Administration of Study Drug [d]						
Randomization		X				
Dispense study drug		X				
Collect study drug				X	X[e]	
Check compliance			X	X	X[e]	
Efficacy Procedures						
Signs and symptoms of acute otitis media	X		X	X	X	
Blood culture	X[f]		X[g]	X[g]	X[g]	
Clinical response				X	X	
Safety Procedures						
Hematology, chemistry, urinalysis	X			X	X[h]	
Physical examination (including MS examination)	X		X[i]	X[i]	X[i]	
Vital signs including weight	X		X	X	X	
Height	X				X	
Interval history [i,j]			X	X	X	X
Adverse events [k]	X	X	X	X	X	X

[a] Within 24 hours before first dose of study drug. [b] Assent to be obtained depending on the ability of an individual child to understand the study and the institutional policies. [c] At time of study completion or premature discontinuation. [d] Study drug to be administered twice daily for 10 days. [e] Performed only at the time of treatment discontinuation (or at the time of study discontinuation if discontinuation occurred after completion of study therapy before Visit 3). [f] Only subjects who were identified as being at risk for bacteremia. [g] Blood culture to be repeated only if a pathogen was isolated from the most recent blood culture or if bacteremia was suspected. [h] Only if clinically indicated, or at time of treatment discontinuation or discontinuation after completion of study therapy before Visit 3. [i] Subjects with arthralgia or clinical evidence of arthropathy were to be evaluated by an investigator trained in evaluation of joint pathology or in consultation with a specialist (e.g., orthopedist, rheumatologist [preferably a pediatric rheumatologist]) within 72 hours of the subject's presentation. The appropriateness of additional examinations (e.g., magnetic resonance imagining [MRI], ultrasound, x-ray) of the involved joint was to be assessed by the trained investigator or in consultation with the specialist. The investigator or specialist evaluating the musculoskeletal event was to remain blinded to study therapy. All musculoskeletal adverse events were to be evaluated according to procedures listed on the Musculoskeletal Data Sheet (Appendix 1.1, Attachment 3) [j] Focused on assessing the occurrence of adverse events and musculoskeletal adverse events since the

previous visit. [k] Included musculoskeletal adverse event monitoring. Source: Sponsors submission, Results and Analysis, Disposition and Study Population

1,650 planned (to achieve 660 clinically evaluable levofloxacin subjects and 660 clinically evaluable comparator subjects); 1,678 screened; 1,650 randomized (827 levofloxacin, 823 comparator); (b) (4)
1,607 evaluable for safety (797 levofloxacin, 810 comparator).

Table 66: Number of Subjects for Each Analysis Set (Study LOFBO-OTMD-002: All Randomized Subjects Analysis Set)

.

Analysis Set Visit	Levofloxacin n (%)	Comparator n (%)	Total n (%)
Total Randomized	827 (100)	823 (100)	1,650 (100)
Modified Intent-to-Treat [a]	786 (95)	800 (97)	1,586 (96)
(b) (4)			
Safety [b]	797 (96)	810 (98)	1,607 (97)

[a] Sixty-four subjects were not included in the MITT Analysis Set as they either did not take the study medication (28 subjects randomized to levofloxacin, 10 randomized to comparator) or they did not have a confirmed clinical diagnosis of recurrent and/or persistent AOM (13 levofloxacin and 13 comparator subjects). [b] In error, 2 subjects (310333, 315620) randomized to amoxicillin + clavulanic acid received levofloxacin, and 1 subject (323110) randomized to levofloxacin received amoxicillin + clavulanic acid. These 3 subjects were (b) (4) placed in the treatment group of the study drug they actually took for the safety analyses. None of these subjects had a serious adverse event or adverse event leading to treatment discontinuation. (b) (4) (b) (4) *Source: sponsors submission*

(b) (4)

(b) (4)

5.3.3 Treatment and Study Completion/Withdrawal Information

Treatment completion and discontinuation information for the MITT Analysis Set is summarized in Table 68.

Table 68: Treatment Completion and Discontinuation Information (Study LOFBO-OTMD-002: Modified Intent-to-Treat Analysis Set)

Treatment Completion Status Reason for Discontinuation	Levofloxacin (N=786) n (%)	Comparator (N=800) n (%)
Completed[a]	715 (91)	738 (92)
Discontinued	71 (9)	62 (8)
Adverse event	31 (4)	22 (3)
Subject/parent or legal guardian choice	19 (2)	13 (2)
Lost to follow-up	12 (2)	11 (1)
Other	7 (1)	8 (1)
[redacted]		(b) (4)

[a] Subjects who completed the treatment regimen as described in the protocol were considered to have completed study treatment.
Source: sponsors submission

Overall 8-9% of patients discontinued their treatments during the study. *The primary reason for discontinuation regardless of treatment group was 'adverse event'.. Thirty-one (4%) levofloxacin-treated subjects and 22 (3%) comparator-treated subjects discontinued study drug treatment due to adverse event.*

5.3.4 Study completion and withdrawal information

Study completion and withdrawal information for the MITT Analysis Set is summarized in Table 69.

Table 69: Study Completion and Withdrawal Information (Study LOFBO-OTMD-002: Modified Intent-to-Treat Analysis Set)

Study Completion Status Continuation Information	Levofloxacin (N=786) n (%)	Comparator (N=800) n (%)
Total no. subjects	786 (100)	800 (100)
Completed [a]	736 (94)	748 (94)
Continued to the Follow-up Visit [b]	733 (93)	743 (93)
Withdrawn	50 (6)	52 (7)

[a]Subjects who received at least 1 dose of study drug and who either 1) completed the study procedures through Visit 4, 2) prematurely discontinued the study and completed the Visit 4 discontinuation procedures, or 3) prematurely discontinued study drug and completed the Visit 4

discontinuation procedures were considered to have completed the study. [b] The Follow-up Visit (Visit 5) occurred 25 to 35 days after the last dose of study drug. Source Sponsors submission

Medical Reviewer's Comment: In both treatment arms, 94% of subjects completed the study and 93% of the patients had a follow up visit (Visit 5) that occurred 25 to 35 days after the last dose of study drug. Fifty (6%) from levofloxacin and 52 (7%) patients from the comparator arm withdrawn from the study.

5.3.5 Demography

Demographic and baseline characteristics were obtained for 1586 patients. Demographic data and baseline characteristics (age, gender, race, country and severity of disease) for the study are shown in Table 70.

Table 70: Demographic and Baseline Characteristics (Study LOFBO-OTMD-002: Modified Intent-to-Treat Analysis Set)

	Levofloxacin (N=786)	Comparator (N=800)
Age (year)		
N	786	800
Mean (SD)	2.10 (1.219)	2.10 (1.222)
Median	1.70	1.70
Range	(0.5 - 5.0)	(0.5 - 5.3)
Age group, n (%)		
N	786	800
2 years	453 (58)	477 (60)
>2 years	333 (42)	323 (40)
Sex, n (%)		
N	786	800
Male	444 (56)	458 (57)
Female	342 (44)	342 (43)
Race, n (%)		
N	786	800
White	552 (70)	579 (72)
Black	51 (6)	42 (5)
Asian	10 (1)	6 (1)
Other [a]	173 (22)	173 (22)
Extent of disease, n (%)		
N	786	800
Bilateral	407 (52)	417 (52)
Unilateral	379 (48)	383 (48)
Baseline weight (kg)		
N	786	800
Mean (SD)	12.7 (3.62)	12.6 (3.44)
Median	12.0	12.0
Range	(6 - 38)	(6 - 29)
Baseline height (cm)		
N	779	789
Mean (SD)	85.6 (12.10)	85.4 (11.68)
Median	83.8	83.8
Range	(60 - 130)	(60 - 120)

Disease characteristic, n (%)		
N	786	800
Recurrent	572 (73)	618 (77)
Persistent	104 (13)	90 (11)
Recurrent and persistent	110 (14)	92 (12)
Country, n (%)		
N	786	800
Argentina	109 (14)	109 (14)
Brazil	44 (6)	44 (6)
Chile	66 (8)	66 (8)
Costa Rica	211 (27)	218 (27)
Panama	29 (4)	26 (3)
United States	327 (42)	337 (42)

[a] Other includes primarily Hispanic subjects., Source: sponsor submission

Subjects ranged in age from 0.5 to 5.3 years of age (mean age 2.10 years). Fifty-seven percent of subjects were male and 43% were female. Fifty-nine percent of subjects were 2 years of age and 41% were >2 years. The majority of subjects were white, most enrolled from the US and Costa Rica.

Eight-hundred and twenty-four (52%) subjects had bilateral AOM and 762 (48%) had unilateral AOM at study entry. Eleven-hundred and ninety (75%) subjects had recurrent disease, 194 (12%) had persistent disease, and 202 (13%) had both recurrent and persistent disease.

Overall there were no clinically relevant differences between treatment groups in any demographic or baseline characteristic.

The demographic and baseline characteristics for US versus Non-US subjects in the MITT Analysis Set are summarized in Table 71.

Table 71: Demographic and Baseline Characteristics: US versus Non-US Subjects (MITT)
(Study LOFBO-OTMD-002: Modified Intent-to-Treat Analysis Set)

	Levofloxacin		Comparator	
	US (N=327)	Non-US (N=459)	US (N=337)	Non-US (N=463)
Age (year)				
N	327	459	337	463
Mean (SD)	1.81 (1.072)	2.31 (1.274)	1.71 (0.973)	2.38 (1.307)
Median	1.50	2.10	1.40	2.00
Range	(0.5 - 5.0)	(0.5 - 4.9)	(0.5 - 5.0)	(0.5 - 5.3)
Age group, n (%)				
N	327	459	337	463
2 years	227 (69)	226 (49)	245 (73)	232 (50)
>2 years	100 (31)	233 (51)	92 (27)	231 (50)
Sex, n (%)				
N	327	459	337	463
Male	187 (57)	257 (56)	202 (60)	256 (55)
Female	140 (43)	202 (44)	135 (40)	207 (45)
Race, n (%)				
N	327	459	337	463
White	128 (39)	424 (92)	148 (44)	431 (93)
Black	34 (10)	17 (4)	26 (8)	16 (3)
Asian	9 (3)	1 (<1)	5 (1)	1 (<1)
Other [a]	156 (48)	17 (4)	158 (47)	15 (3)
Extent of disease, n (%)				
N	327	459	337	463
Bilateral	195 (60)	212 (46)	193 (57)	224 (48)
Unilateral	132 (40)	247 (54)	144 (43)	239 (52)
Baseline weight (kg)				
N	327	459	337	463
Mean (SD)	12.5 (3.75)	12.8 (3.53)	12.1 (3.18)	13.0 (3.57)
Median	11.6	12.2	11.6	12.5
Range	(6 - 38)	(6 - 29)	(6 - 26)	(6 - 29)
Baseline height (cm)				
N	323	456	327	462
Mean (SD)	83.7 (11.52)	86.9 (12.33)	82.8 (10.43)	87.3 (12.16)
Median	81.3	86.0	80.5	87.0

Range	(60 - 130)	(64 - 117)	(60 - 118)	(62 - 120)
Disease characteristic, n (%)				
N	327	459	337	463
Persistent	34 (10)	70 (15)	26 (8)	64 (14)
Recurrent	239 (73)	333 (73)	269 (80)	349 (75)
Recurrent and persistent	54 (17)	56 (12)	42 (12)	50 (11)

there were no clinically meaningful differences between treatment groups for any demographic or baseline characteristic. Within each treatment group, a greater percentage of US subjects were 2 years of age (69% levofloxacin group and 73% comparator group) compared to Non-US subjects (49% levofloxacin group and 50% comparator group). A greater percentage of Non-US subjects were white (93%) compared to US subjects (42%). A greater percentage of US subjects had more serious (bilateral) disease (58%) compared to Non-US subjects (47%).

The demographic and baseline characteristics that were summarized for US versus Non-US subjects in the Clinically Evaluable Analysis Set (at Visit 3) were similar to the results of the MITT Analysis Set..

5.3.6 Extend of Exposure

Most subjects completed at least 8 days of their assigned treatment (92% in the levofloxacin group and 93% in the comparator group). In the MITT Analysis Set, the mean duration of therapy for both treatment groups was 10.2 days (Table 72).

Table 72:Duration of Therapy by Time Intervals (Study LOFBO-OTMD-002: Modified Intent-to-Treat Analysis Set)

	Levofloxacin (N=786) n (%)	Comparator (N=800) n (%)	Total (N=1,586) n (%)
Duration of therapy (days)			
<8	61 (8)	57 (7)	118 (7)
8-12	699 (89)	730 (91)	1,429 (90)
>12	26 (3)	13 (2)	39 (2)
Mean (SD)	10.2 (2.33)	10.2 (1.99)	10.2 (2.16)
Median	11.0	11.0	11.0
Range	(1 - 19)	(1 - 16)	(1 - 19)

Source: sponsors submission

5.3.7 Concomitant Therapy

A. Prestudy Systemic Antimicrobial Therapy

Prestudy (received within 24 hours before the start of study drug) systemic antimicrobial therapy is summarized in Table 73.

(b) (4)

Comment: (b) (4)

B. Systemic Antimicrobials Taken During the Study

Systemic antimicrobials taken during the study are summarized in Table 74.

(b) (4)

Medical Reviewer's Comment: (b) (4)

C. Systemic Antimicrobials Taken During Study Drug Therapy

Systemic antimicrobials taken or given during study drug therapy are summarized in Table 75.

5.3.8 Protocol Deviations

Protocol deviations data for the study are shown in Table 76..

Table 76: Significant Protocol Deviations (Study LOFBO-TMD-002: All Randomized Subjects)

Deviation	Levofloxacin (N=827) n (%)	Comparator (N=823) n (%)
Received <17 doses	60 (7.3)	59 (7.2)
>11 days of study drug therapy	51 (6.2)	34 (4.1)
Inclusion/Exclusion criteria not met	26 (3.1)	22 (2.7)
Effective concomitant therapy [a]	21 (2.5)	21 (2.6)
Clinical diagnosis unconfirmed	13 (1.6)	13 (1.6)
Height not measured at screening	10 (1.2)	12 (1.5)
MS evaluation performed >72 hours after event onset	11 (1.3)	8 (1.0)
Received 20% ± from the calculated dose	6 (<1)	9 (1.1)
Received incorrect dose regimen	4 (<1)	10 (1.2)
Received >27 doses in 11 days	0	5 (<1)
Received incorrect study drug	1 (<1)	2 (<1)

[a] Effective concomitant therapy includes any nonstudy systemic antibacterial use taken during the time of study enrollment and the final study evaluation.
Source: sponsors submission

There were several protocol deviations identified. The majority of protocol deviations that occurred during the conduct of the study were due to dosing and dosing regimen errors. 2.5 - 26% % of patients received effective concomitant nonstudy systemic antibacterial therapy during the time of study enrollment and the final study evaluation.

(b) (4)

(b) (4)

Medical Reviewer's Comment: (b) (4)

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4. Safety

The safety data were reviewed with particular reference to the occurrence of unexpected adverse events. Safety evaluations for this study included assessments of duration of study drug exposure, serious adverse events, and adverse events (serious and nonserious) that were considered by the investigator to be related to study drug. The analyses of safety included all patients who received any amount of study drug.

Safety was evaluated by monitoring treatment-emergent adverse events and changes from baseline in clinical laboratory values (serum chemistry, hematology, and urinalysis), vital sign measurements temperature, pulse, blood pressure, respiration rate and physical examination findings. Safety evaluations for MS adverse events were also performed throughout the study.

The DSMC did not identify any safety concerns during the current study or any other levofloxacin Phase 3 pediatric study that would have precluded study continuation. All safety analyses were based on the actual treatment received rather than the randomized treatment assignment.

The Safety Analysis Set consisted of 1,607 subjects (797 levofloxacin; 810 comparator)

5. Adverse Events

a) Deaths

There were no deaths during the conduct of this study.

b) Serious Adverse Events

A summary of serious adverse events is provided in Table 84.

Table 84: Incidence of Serious Adverse Events by Body System and Preferred Term
(Study LOFBO-OTMD-002: Safety Analysis Set)

Body System Preferred Term	Levofloxacin (N=797) n (%)	Comparator (N=810) n (%)	Total (N=1,607) n (%)
Total no. Subjects With Serious Adverse Events	10 (1)	13 (2)	23 (1)
Gastrointestinal System Disorders	4 (1)	5 (1)	9 (1)
Diarrhea	2 (<1)	2 (<1)	4 (<1)
Vomiting	2 (<1)	1 (<1)	3 (<1)
Gastroenteritis	1 (<1)	2 (<1)	3 (<1)
Stomatitis	1 (<1)	0	1 (<1)
Respiratory System Disorders	3 (<1)	5 (1)	8 (<1)
Bronchospasm	2 (<1)	1 (<1)	3 (<1)
Pneumonia	1 (<1)	2 (<1)	3 (<1)
Bronchitis	0	2 (<1)	2 (<1)
Body as a Whole - General Disorders	2 (<1)	1 (<1)	3 (<1)
Allergic reaction	1 (<1)	0	1 (<1)
Injury	1 (<1)	0	1 (<1)
Fever	0	1 (<1)	1 (<1)
Fetal Disorders	1 (<1)	0	1 (<1)
Hernia congenital	1 (<1)	0	1 (<1)
Metabolic and Nutritional Disorders	1 (<1)	3 (<1)	4 (<1)
Dehydration	1 (<1)	3 (<1)	4 (<1)
Red Blood Cell Disorders	1 (<1)	0	1 (<1)
Anemia	1 (<1)	0	1 (<1)
Urinary System Disorders	1 (<1)	0	1 (<1)
Urinary tract infection	1 (<1)	0	1 (<1)
White Cell and RES Disorders	1 (<1)	0	1 (<1)
Agranulocytosis	1 (<1)	0	1 (<1)
Cardiovascular Disorders, General	0	1 (<1)	1 (<1)
Circulatory failure	0	1 (<1)	1 (<1)
Resistance Mechanism Disorders	0	4 (<1)	4 (<1)
Infection viral	0	2 (<1)	2 (<1)
Otitis media	0	2 (<1)	2 (<1)
Secondary Terms	0	1 (<1)	1 (<1)
Burn	0	1 (<1)	1 (<1)
Skin and Appendages Disorders	0	1 (<1)	1 (<1)
Dermatitis	0	1 (<1)	1 (<1)

Note: Incidence was based on the number of subjects, not the number of events. Percentages calculated with the total no. of subjects as the denominator.

Medical Reviewer's Comment:Ten (1%) levofloxacin-treated subjects and 13 (2%) comparator-treated subjects had 1 or more serious adverse event.

c) Treatment-Limiting Adverse Events

The incidence of treatment-limiting adverse events is summarized in Table 85.

Table 85: Incidence of Treatment-Limiting Adverse Events by Body System and Preferred Term(Study LOFBO-OTMD-002: Safety Analysis Set)

Body System Preferred Term	Levofloxacin (N=797) n (%)	Comparator (N=810) n (%)	Total (N=1,607) n (%)
Total no. subjects with treatment- limiting adverse events	31 (4)	22 (3)	53 (3)
Gastrointestinal System Disorders	21 (3)	14 (2)	35 (2)
Vomiting	12 (2)	7 (1)	19 (1)
Diarrhea	7 (1)	13 (2)	20 (1)
Abdominal pain	2 (<1)	1 (<1)	3 (<1)
Nausea	2 (<1)	2 (<1)	4 (<1)
Psychiatric Disorders	6 (1)	4 (<1)	10 (1)
Nervousness	5 (1)	2 (<1)	7 (<1)
Sleep disorder	2 (<1)	1 (<1)	3 (<1)
Insomnia	1 (<1)	1 (<1)	2 (<1)
Anorexia	0	1 (<1)	1 (<1)
Skin and Appendages Disorders	4 (1)	9 (1)	13 (1)
Dermatitis	4 (1)	6 (1)	10 (1)
Rash erythematous	0	2 (<1)	2 (<1)
Urticaria	0	1 (<1)	1 (<1)
Respiratory System Disorders	2 (<1)	0	2 (<1)
Bronchospasm	1 (<1)	0	1 (<1)
Pharyngitis	1 (<1)	0	1 (<1)
Application Site Disorders	1 (<1)	0	1 (<1)
Cellulitis	1 (<1)	0	1 (<1)
Body as a Whole - General Disorders	1 (<1)	2 (<1)	3 (<1)
Fever	1 (<1)	0	1 (<1)
Allergic reaction	0	2 (<1)	2 (<1)
Cardiovascular Disorders, General	0	1 (<1)	1 (<1)
Circulatory failure	0	1 (<1)	1 (<1)
Hearing and Vestibular Disorders	0	1 (<1)	1 (<1)
Ear ache	0	1 (<1)	1 (<1)

Note: Incidence was based on the number of subjects who experienced at least 1 treatment-limiting adverse event, not the number of events.
Percentages calculated with the total no of subjects as the denominator.

Medical Reviewer's Comment: Thirty-one (4%) levofloxacin-treated subjects and 22 (3%) comparator-treated subjects discontinued study drug due to 1 or more adverse event. All treatment-limiting adverse events occurred in 1% of subjects overall. The most frequent treatment-limiting events occurred in the gastrointestinal system (2%).

d) Summary of Common Adverse Events

A summary of adverse events occurring in at least 5% of subjects in any treatment group and marked in severity up to Visit 4 is provided in Table 86 and 87 respectively. A summary of the incidence of treatment-emergent adverse events occurring in 5% of Subjects in any treatment group up to Visit 5 is provided in Table 86.

Table 86: Incidence of Treatment-Emergent Adverse Events Occurring in 5% of Subjects in Any Treatment Group up to Visit 4 by Body System and Preferred Term(Study LOFBO-OTMD-002: Safety Analysis Set)

Body System Preferred Term	Levofloxacin (N=797) n (%)	Comparator (N=810) n (%)	Total (N=1,607) n (%)
Total no. subjects with adverse events	448 (56)	475 (59)	923 (57)
Gastrointestinal System Disorders	201 (25)	218 (27)	419 (26)
Diarrhea	108 (14)	161 (20)	269 (17)
Vomiting	81 (10)	61 (8)	142 (9)
Respiratory System Disorders	157 (20)	188 (23)	345 (21)
Upper respiratory tract infection	53 (7)	78 (10)	131 (8)
Rhinitis	43 (5)	39 (5)	82 (5)
Skin and Appendages Disorders	134 (17)	165 (20)	299 (19)
Dermatitis	108 (14)	129 (16)	237 (15)
Body as a Whole - General Disorders	82 (10)	96 (12)	178 (11)
Fever	60 (8)	64 (8)	124 (8)
Resistance Mechanism Disorders	66 (8)	78 (10)	144 (9)
Otitis media	45 (6)	34 (4)	79 (5)

Note: Incidence was based on the number of subjects, not the number of events.
Percentages calculated with the total no. of subjects as the denominator.
Cross-reference: Attachment 4.1.1

Medical Reviewer's Comment: Four-hundred forty-eight (56%) levofloxacin-treated subjects and 475 (59%) comparator-treated subjects reported at least 1 adverse event up to Visit 4 (10 to 17 days after the last dose of study drug).

Adverse events related to the gastrointestinal system occurred more frequently than in other body systems for both levofloxacin and comparator subjects (25% and 27%, respectively). Diarrhea was the most frequent adverse event, and occurred in 14% and 20% of levofloxacin-exposed and comparator-exposed subjects, respectively.

Table 87: Incidence of Treatment-Emergent Adverse Events up to Visit 4 Visit That Were Marked in Severity by Body System and Preferred Term (Study LOFBO-OTMD-002: Safety Analysis Set)

Body System Preferred Term	Levofloxacin (N=797) n (%)	Comparator (N=810) n (%)	Total (N=1,607) n (%)
Total no. subjects with adverse events that were marked in severity	25 (3)	26 (3)	51 (3)
Gastrointestinal System Disorders	12 (2)	13 (2)	25 (2)
Vomiting	6 (1)	5 (1)	11 (1)
Diarrhea	4 (1)	6 (1)	10 (1)
Nausea	2 (<1)	1 (<1)	3 (<1)
Abdominal pain	1 (<1)	1 (<1)	2 (<1)
Gastroenteritis	1 (<1)	3 (<1)	4 (<1)
Stomatitis	1 (<1)	0	1 (<1)
Psychiatric Disorders	3 (<1)	2 (<1)	5 (<1)
Nervousness	2 (<1)	1 (<1)	3 (<1)
Anorexia	1 (<1)	0	1 (<1)
Sleep disorder	1 (<1)	0	1 (<1)
Insomnia	0	1 (<1)	1 (<1)
Skin and Appendages Disorders	3 (<1)	9 (1)	12 (1)
Dermatitis	3 (<1)	9 (1)	12 (1)
Body as a Whole - General Disorders	2 (<1)	1 (<1)	3 (<1)
Allergic reaction	1 (<1)	0	1 (<1)
Fever	1 (<1)	1 (<1)	2 (<1)
Central & Peripheral Nervous System Disorders	1 (<1)	1 (<1)	2 (<1)
Hyperkinesia	1 (<1)	0	1 (<1)
Hypokinesia	0	1 (<1)	1 (<1)
Fetal Disorders	1 (<1)	0	1 (<1)
Hernia congenital	1 (<1)	0	1 (<1)
Metabolic and Nutritional Disorders	1 (<1)	1 (<1)	2 (<1)
Dehydration	1 (<1)	1 (<1)	2 (<1)
Resistance Mechanism Disorders	1 (<1)	6 (1)	7 (<1)
Otitis media	1 (<1)	2 (<1)	3 (<1)
Infection viral	0	2 (<1)	2 (<1)
Moniliasis	0	1 (<1)	1 (<1)
Moniliasis genital	0	1 (<1)	1 (<1)
Respiratory System Disorders	1 (<1)	2 (<1)	3 (<1)
Coughing	1 (<1)	0	1 (<1)
Bronchitis	0	1 (<1)	1 (<1)
Pneumonia	0	1 (<1)	1 (<1)
White Cell and RES Disorders	1 (<1)	0	1 (<1)
Agranulocytosis	1 (<1)	0	1 (<1)
Musculoskeletal System Disorders	0	1 (<1)	1 (<1)
Fracture pathological	0	1 (<1)	1 (<1)

Note: Incidence was based on the number of subjects, not the number of events. Percentages calculated with the total number of subjects as the denominator.

Medical Reviewer's Comment: Most adverse events were mild or moderate in severity (levofloxacin: 97% [894/924]; comparator: 96% [945/984]. Fifty-one subjects had 69 adverse events of marked severity.

Table 88: Incidence of Treatment-Emergent Adverse Events Occurring in 5% of Subjects in Any Treatment Group up to Visit 5 by Body System and Preferred Term (Study LOFBO-OTMD-002: Safety Analysis Set)

Body System Preferred Term	Levofloxacin (N=797) n (%)	Comparator (N=810) n (%)	Total (N=1,607) n (%)
Total no. subjects with adverse events	497 (62)	533 (66)	1,030 (64)
Gastrointestinal System Disorders	219 (27)	234 (29)	453 (28)
Diarrhea	117 (15)	165 (20)	282 (18)
Vomiting	84 (11)	70 (9)	154 (10)
Respiratory System Disorders	218 (27)	257 (32)	475 (30)
Upper respiratory tract infection	93 (12)	112 (14)	205 (13)
Rhinitis	50 (6)	45 (6)	95 (6)
Coughing	38 (5)	40 (5)	78 (5)
Pharyngitis	28 (4)	37 (5)	65 (4)
Skin and Appendages Disorders	146 (18)	173 (21)	319 (20)
Dermatitis	117 (15)	133 (16)	250 (16)
Resistance Mechanism Disorders	113 (14)	115 (14)	228 (14)
Otitis media	87 (11)	70 (9)	157 (10)
Body as a Whole - General Disorders	101 (13)	111 (14)	212 (13)
Fever	74 (9)	78 (10)	152 (9)

Note: Incidence was based on the number of subjects, not the number of events. Percentages calculated with the total no. of subjects as the denominator.

5.3.12 Musculoskeletal Adverse Events

There were 42 (23 levofloxacin, 19 comparator subjects with MS adverse events. Twenty-three MS adverse events were reported by the investigators and auto encoded to preferred terms that map to the MS Systems Disorder Body System. After database lock and analysis, 19 additional MS adverse events were identified that auto encoded to 'preferred terms' that mapped to other body systems. The incidence of muskuloskeltal adverse events are shown in Table 89.

Table 89: Incidence of Musculoskeletal Adverse Events by Preferred Term (Study LOFBO-OTMD-002: Safety Analysis Set)

Preferred Term	Levofloxacin (N=797) n (%)	Comparator (N=810) n (%)	p value[a]
Total No. Subjects With Any MS Adverse Event	23 (3)	19 (2)	0.5341
Arthralgia	12 (2)	6 (1)	0.162
Arthropathy	0	2 (<1)	0.500
Fracture pathological	0	4 (<1)	0.125
Muscle weakness	0	1 (<1)	>0.999
Myalgia	11 (1)	7 (1)	0.353
Synovitis	1 (<1)	0	0.496

[a]2-sided p value using Fisher's Exact test
Note: Percentages calculated with the number of subjects in each group as the denominator.

Medical Reviewer's Comment: The Incidences of musculoskeletal adverse events in the levofloxacin group and the comparator group were 23(3%) and 19(2%) respectively. The difference in the incidence of subjects with MS adverse events in the levofloxacin- and comparator-treated groups (3% versus 2%, respectively ;) was not statistically significant (p=0.534).

The DSMC reviewed all MS adverse events and classified 17 of the 44 events (12 in levofloxacin-treated and 5 in comparator-treated subjects) as MS disorders (defined in the protocol as arthralgia, arthritis, tendinopathy, or gait abnormality). The difference in the number of subjects with MS disorders in the levofloxacin- and comparator-treated groups (2% versus <1%, respectively) was not statistically significant (p = 0.0921).

5.4 ACUTE OTITIS MEDIA (BACTERIOLOGIC OUTCOME) (LOFBO-OTMD-001)

5.4.1 Study Protocol

The study was a multicenter, nonrandomized, open-label study conducted in the United States, Argentina, Costa Rica, and Israel. Pediatric subjects (>6 months to <5 years of age) with clinical signs and symptoms of AOM who were at high risk for difficult-to-treat AOM, and who met the prestudy eligibility criteria were enrolled and received levofloxacin 10 mg/kg oral suspension twice daily for 10 days followed by posttreatment assessment.

The primary objective of this study was to assess the rate of eradication of bacteria from the middle ear fluid (MEF) at Visit 2 (Study Days 4 to 6) in infants and children who had acute otitis media (AOM) and were at high risk for difficult-to-treat infections caused by *Streptococcus pneumoniae* or *Haemophilus influenzae.*

Secondary objectives were to assess the efficacy of levofloxacin based on clinical cure rate, clinical success (cured plus improved) rate, and microbiologic responses at 2 to 5 and 10 to 17 days after the last dose; and the clinical failure rate at Visit 2.

The primary objective of this study was to assess the rate of eradication of bacteria from the middle ear fluid (MEF) at Visit 2 (Study Days 4 to 6) in infants and children who had acute otitis media (AOM) and were at high risk for difficult-to-treat infections caused by *Streptococcus pneumoniae* or *Haemophilus influenzae.* Secondary objectives were to assess the efficacy of levofloxacin based on clinical cure rate, clinical success (cured plus improved) rate, and microbiologic responses at 2 to 5 and 10 to 17 days after the last dose; and the clinical failure rate at Visit 2..

The eradication rates were expressed as the percent of the Microbiologically Evaluable Analysis Set at Visit 2 showing documented or presumed eradication of the admission pathogens. Eradication rates were also summarized by age group (<= years, >2 years), race, sex, country, and study center (primary analysis only).

Descriptive statistics were used to summarize clinical cure and clinical success rates at Visits 3 and 4 and clinical failure rate at Visit 2. The clinical cure, success, and failure rates were expressed as percentages and analyzed by age group. The clinical response rates at Visits 2, 3, and 4 were summarized. Ninety-five percent CIs were constructed for the clinical and microbiologic response rates. The relationship between microbiologic and clinical responses was also assessed, but without formal statistical analysis.

Safety was evaluated by monitoring treatment-emergent adverse events (with special emphasis on MS adverse events) and changes in clinical laboratories, vital signs, and physical examination findings and steady-state levofloxacin exposure (Css) was estimated from plasma and MEF.

The incidence of treatment-emergent adverse events was summarized by severity, relationship to study drug, and age group (<=2 years, >2 years) using a standard adverse event dictionary based on WHOART. MS adverse events were described and classified as 1 of the following MS disorders: tendinopathy, arthritis, arthralgia, or gait abnormality. Changes in clinical laboratory tests and vital signs were summarized using descriptive statistics.Physical examination abnormalities were listed.

Determination of the sample size for this study was based on historical data provided in the Augmentin ES Advisory Committee Briefing Document dated 30 January 2001 (BRL-025000/RSD-101GJ5/2) and a recent publication of the results of an Augmentin ES clinical trial involving children. Based on this experience, it was approximated that 75% of the subjects 6 months to 5 years with difficult-to-treat AOM undergoing tympanocentesis would have bacteria isolated at baseline and, of those, 60% would have a second tympanocentesis. Of the subjects so identified, approximately 40% would have infection due to *S. pneumoniae* and 30% would have infection due to *H. influenzae*. Therefore, it was estimated that 186 subjects would provide at least 25 subjects with S. pneumoniae and 25 subjects with *H. influenzae.*

5.4.2 Study Procedure

Pediatric subjects (6 months to <5 years of age) with clinical signs and symptoms of AOM who were at high risk for difficult-to-treat AOM, and who met the prestudy eligibility criteria were enrolled and received levofloxacin 10 mg/kg oral suspension twice daily for 10 days followed by posttreatment assessment.

A combination of clinical assessment and microbiologic assessment of MEF and blood was used to evaluate efficacy. MEF samples were collected at screening for determination of levofloxacin susceptibility. Safety was based on the incidence, relationship to therapy, and severity of treatment-emergent adverse events, and on changes in clinical laboratory values (hematology, chemistry, and urinalysis), vital signs, and physical examination findings. Supplementary safety evaluations for musculoskeletal (MS) adverse events were performed throughout the study, as needed. An independent expert advisory group, Data Safety Monitoring Committee (DSMC), evaluated the safety data on an ongoing basis with emphasis on serious and MS adverse events. The time and schedule of the procedures for the study are shown in Table 90.

Table 90: Time and Events Schedule

		Screening[a]	Treatment			Completion/ Discontinuation	Telephone Contact
	Phase						
	Visit	1	1	2	3	4	5
	Study Day	1	1	4-6	2–5 days after last dose	10–17 days after last dose	25-35 after last dose
Screening Procedures							
Informed consent/assent[b]		X					
Medical history		X					
Inclusion/exclusion		X					
Administration of Study Treatment[c]							
Dispense study drug			X				
Collect study drug					X	X[d]	
Check compliance				X	X	X[d]	
Pharmacokinetic Procedures[e]							
MEF sample[f]				X			
Blood sample[g]				X			
Efficacy Procedures							
Assess signs and symptoms of AOM		X		X	X	X	
Blood culture		X[h]		X[i]	X[i]	X[i]	
Tympanocentesis[j]		X		X[k]	X[l]	X[l]	
MEF culture		X		X[k]	X[l]	X[l]	
Clinical response				X	X	X	
Safety Procedures							
Hematology, serum chemistry, U/A		X			X	X[m]	
Vitals signs (blood pressure, pulse		X		X	X	X	
rate, respiratory rate) and weight							
Height		X				X	
Physical examination (including MS		X		X[n]	X[n]	X[n]	
examination with evaluation of joints)							
Interval history [n,o]				X	X	X	X
Adverse events[p]		X	X	X	X	X	X

aWithin 24 hours before first dose of study drug.
b Assent to be obtained depending on the ability of an individual child to understand the study and the institutional policies.
c Study drug to be administered for 10 days.

d Only at time of treatment discontinuation or discontinuation after completion of study therapy before Visit 3.
e PK procedures were performed only at the Israeli center.
f In subjects who had an adequate amount of MEF for both microbiologic and PK evaluations, as determined by the investigator, a sample of MEF was taken for determination of the levofloxacin concentration.
g Subjects who had a sample of MEF collected for determination of the levofloxacin concentration also had a blood sample drawn immediately afterward for determination of the levofloxacin concentration in plasma.
h Only subjects who were identified as being at risk for bacteremia.
i Blood culture to be repeated only if a pathogen was isolated from the most recent blood culture or if bacteremia was suspected. j Tympanocentesis or sampling of spontaneously draining fluid (if MEF started to drain within 48 hours before the time of sampling) from the middle ear.
k Repeat culture of MEF if either *S. pneumoniae* or *H. influenzae* were isolated from screening culture of MEF and the subject had signs or symptoms of middle ear disease, OR the subject was assessed to be failing therapy, as evidenced by persistence of middle ear disease requiring alternative therapy as determined by the investigator.
l At Visits 3 and 4, if tympanocentesis was clinically indicated and performed, or new onset spontaneous drainage of less than 48 hours duration was present, a sample of the MEF was to be collected for culture.
m Only if clinically indicated, or at time of treatment discontinuation, or discontinuation after completion of study therapy before Visit 3.
n Subjects with arthralgia or clinical evidence of arthropathy were to be evaluated by an investigator trained in evaluation of joint pathology or in consultation with a specialist (e.g., orthopedist, rheumatologist [preferably a pediatric rheumatologist])
within 72 hours of the subject's presentation. The appropriateness of additional examinations (e.g., MRI, ultrasound, x-ray) of the involved joint were to be assessed by the trained investigator or in consultation with the specialist. All MS adverse events were to be evaluated according to procedures listed on the MS Data Sheet. The specialist evaluating the MS event was kept blinded to study therapy.
o Focused on assessing the occurrence of adverse events and MS adverse events since the previous visit.
p Including MS adverse event monitoring.

5.4.3 RESULTS AND ANALYSIS

A. Analysis Set

Table 91 shows the number of subjects for each analysis set.

Table 91: Number of Subjects for Each Analysis Set (Study LOFBO-OTMD-001: All Subjects Analysis Set)

Analysis Set Visit Total Enrolled	Levofloxacin n (%) 205 (100)
Modified Intent-to-Treat[a]	204 (>99)
(b) (4)	
Safety[c]	204 (>99)

(b) (4)

B) Demographics

A total of 205 patients were studied. 204 (99%) constituted the M ITT population for the primary analysis. (b) (4)

Demographic and baseline characteristic for the study are shown in Table 92.

Table 92: Demographic and Baseline Characteristics: Modified Intent-to-Treat Analysis Set)

	Total (N=204)
Age (year)	
N	204
Mean (SD)	1.52 (0.948)
Median	1.20
Range	0.5 - 4.9
Age group, n (%)	
N	204
2 years	163 (80)
>2 years	41 (20)
Sex, n (%)	
N	204
Male	110 (54)
Female	94 (46)
Race, n (%)	
N	203
White	187 (92)
Black	4 (2)
Other[a]	12 (6)
Extent of disease, n (%)	
N	204
Bilateral	94 (46)
Unilateral	110 (54)
Baseline weight (kg)	
N	204
Mean (SD)	10.6 (2.86)
Median	10.0
Range	6 - 20
Baseline height (cm)	
N	191
Mean (SD)	79.2 (9.60)
Median	77.5
Range	61 - 105

[a]Other includes Hispanic and mixed-race subjects; Source sponsors submission .

Medical Reviewer's Comment: subjects enrolled in this study ranged from (6 months to 5 years of age with the median age of 1.2 years. 163 (80%) patients were ,>=2 years. 110 (54%) of the patients were males and 197 (92%) were white.94 (46%) patients had AOM of both ears.
The demographic and baseline characteristics of patients in microbiologically evaluable [at Visit 2] analysis set was similar to demographic characteristics that was observed in the MITT analysis.

5.4.4 Extent of Exposure

In this study children age 6 months and <5 years of age with AOM received levofloxacin 10 mg/kg twice daily for 10 days. The duration of exposure in the study is summarized in the table below:

Table 93: Duration of Therapy by Time Intervals (Study LOFBO-OTMD-001: Modified Intent-to-Treat Analysis Set)

Duration of therapy (days), n (%)	Levofloxacin (N=204)
<7	22 (11)
7-9	3 (1)
10-11	171 (84)
>11	8 (4)
Mean (SD)	9.9 (2.75)
Median	11.0
Range	1 - 21

Source: sponsors submission

5.4.5 Discontinuations of Study Drug

The following table shows a summary of treatment completion and discontinuation information for the MITT Analysis.

Table 94: Treatment Completion and Discontinuation Information (Modified Intent-to-Treat Analysis Set)

Treatment Completion Status Reason for Discontinuation	Levofloxacin (N=204) n (%)
Total no. subjects	204 (100)
Completed[a]	155 (76)
Discontinued	49 (24)
[redacted]	(b) (4)
Lost to follow-up	4 (2)
Adverse event	12 (6)
Subject choice/parent or legal guardian choice	6 (3)
Other[b]	26 (13)

[a]Subjects who completed 10 days of levofloxacin treatment were considered to have completed study treatment.,[b]22 subjects were prescribed half the recommended dose of study drug.

One hundred fifty-five (76%) subjects completed study treatment; 49 (24%) discontinued study treatment. The primary reason for treatment discontinuation was 'other' (13%). Twenty-two subjects in this category (22/26; 85%) were prescribed half of the recommended dose of levofloxacin. This occurred at 2 sites in Argentina.

The treatment completion and discontinuation status for 3 additional subjects who were prescribed half of the recommended dose of levofloxacin were captured in the following categories: discontinued due to an adverse event (1), and lost to follow-up (2). Twelve (6%) subjects discontinued treatment due to an adverse event. See Section 6.2.2.3, Other Significant Adverse Events, for details of these subjects. (b) (4)

Study completion and withdrawal information for the MITT Analysis Set is summarized in Table 95.

Table 95: Study Completion and Withdrawal Information (Study LOFBO-OTMD-001: Modified Intent-to-Treat Analysis Set)

Study Completion Status Continuation Information	Levofloxacin (N=204) n (%)
Total no. subjects	204 (100)
Completed[a]	171 (84)
Continued to Visit 5	165 (81)
Withdrawn	33 (16)

[a]Subjects who received at least 1 dose of levofloxacin and who either completed the study procedures through Visit 4, prematurely discontinuedthe study and completed the Visit 4 discontinuation procedures, or who prematurely discontinued levofloxacin and completed the Visit 4 discontinuation procedures were considered to have completed the study.

One hundred seventy-one (84%) subjects completed the study procedures according to the protocol. One hundred sixty-five (81%) subjects continued to Visit 5 (25 to 35 days after the last dose of study drug).

Medical Reviewer's Comment: Dosing errors were the leading reported cause of study drug discontinuation in both treatment groups. In general, there were only small numerical differences between the two treatment groups in any of the causes for discontinuations. Discontinuation due to adverse events occurred in less than 2% of the patients in both arms.

5.4.6 Protocol Exceptions and Violations

Prtocol exceptions and violations data for the study are shown in Table 96.

Table 96: Significant Protocol Deviations (Study LOFBO-OTMD-001: Modified Intent-to-Treat Analysis Set)

Deviation	Levofloxacin (N=204)
Inclusion/Exclusion criteria not met	2 (1)
Enrolled as inpatient	1 (<1)
Height not done at Visit 1	13 (6)
Dosed incorrectly with levofloxacin	1 (<1)
Prescribed half of the recommended dose of levofloxacin	25 (12)
>11 days of levofloxacin therapy	8 (4)

Source sponsors submission

Subject 212115 had 2 seizures in 1 year and Subject 215109 participated in an experimental taste study within 30 days of study entry. A third subject who was entered into the study without a confirmed clinical diagnosis of AOM (Subject 215255) was not discussed with or approved by the sponsor.

Medical Reviewer's Comment: Of the 37 patients with the protocol violation 13 who had no height measurement at visit 1 may not affect the generalizbility of the outcome of the study.

5.4.7 Prestudy Systemic Antimicrobial Therapy

Prestudy antimicrobial therapy is summarized in Table 97.

(b) (4)

Medical Reviewer's Comment: (b) (4)

Antimicrobials taken during the study are summarized in table below:

(b) (4)

Baseline Microbiologic In Vitro Susceptibility

The in vitro susceptibility of pathogens of interest, *H. influenzae* and *S. pneumoniae,* isolated from MEF at admission are summarized for the MITT Analysis Set in Table 99.

(b) (4)

Medical Reviewer's Comment: (b) (4)

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5.4.9 Safety Analysis

The safety data were reviewed with particular reference to the occurrence of unexpected adverse events. Safety evaluations for this study included assessments of duration of study drug exposure, serious adverse events, and adverse events (serious and nonserious) that were considered by the investigator to be related to study drug. The analyses of safety included all patients who received any amount of study drug.

Safety was evaluated by monitoring treatment-emergent adverse events and changes from baseline in clinical laboratory values (serum chemistry, hematology, and urinalysis), vital sign measurements temperature, pulse, blood pressure, respiration rate and physical examination findings. Safety evaluations for MS adverse events were also performed throughout the study.

A. Deaths

No deaths occurred in any subject enrolled in the clinical trial .

B. Serious Adverse Events

The serious adverse events data was examined and the data is summarized and presented in the Table 112.

Table 112: Incidence of Serious Adverse Events by Body System and Preferred Term
(Study LOFBO-OTMD-001: Safety Analysis Set)

Body System Preferred Term	Levofloxacin (N=204) n (%)
Total no. subjects with serious adverse events	7 (3)
Gastro-intestinal system disorders	2 (1)
Diarrhoea bloody	1 (<1)
Vomiting	1 (<1)
Respiratory system disorders	2 (1)
Asthma	1 (<1)
Pneumonia	1 (<1)
Body as a whole - general disorders	1 (<1)
Hernia nos	1 (<1)
Centr & periph nervous system disorders	1 (<1)
Fever convulsions	1 (<1)
Metabolic and nutritional disorders	1 (<1)
Dehydration	1 (<1)
Skin and appendages disorders	1 (<1)
Rash maculo-papular	1 (<1)

Note: Incidence was based on the number of subjects, not the number of events.
Percentages calculated with the total no. of subjects as the denominator., Source: sponsors submission

A listing of subjects with treatment-emergent serious adverse events is provided in Table 113.

Seven subjects (3%) experienced 8 serious adverse events.

Table 113: Patients Who Discontinued Therapy Due to Adverse Events (Study LOFBO-OTMD-001: Safety Analysis Set)

Body System Preferred Term	Levofloxacin (N=204) n (%)
Total no. subjects with treatment-limiting adverse events	12 (6)
Gastro-intestinal system disorders	10 (5)
Vomiting	8 (4)
Abdominal pain	1 (<1)
Diarrhoea	1 (<1)
Diarrhoea bloody	1 (<1)
Gastroenteritis	1 (<1)
Body as a whole - general disorders	3 (1)
Fever	2 (1)
Hernia nos	1 (<1)
Psychiatric disorders	1 (<1)
Nervousness	1 (<1)
Resistance mechanism disorders	1 (<1)
Otitis media	1 (<1)
Respiratory system disorders	1 (<1)
Upper respiratory tract infection	1 (<1)
Skin and appendages disorders	1 (<1)
Rash maculo-papular	1 (<1)

Note: Incidence was based on the number of subjects who experienced at least 1 treatment-limiting adverse event, not the number of events. Percentages calculated with the total no. of subjects as the denominator.
Source: sponsors submission

C. Incidence of Treatment-Emergent Adverse Events

One hundred twenty-two subjects (60%) reported at least 1 adverse event up to Visit 4 (6 to 21 days after the stop of the study drug.

A summary of adverse events that occurred in at least 5% of subjects up to Visit 4 is provided in Table 114.

Table 114: Incidence of Treatment-Emergent Adverse Events Occurring in 5% of Subjects up to Visit 4 by Body System and Preferred Term (Study LOFBO-OTMD-001: Safety Analysis Set)

Body System Preferred Term	Levofloxacin (N=204) n (%)
Total no. subjects with adverse events	122 (60)
Gastro-intestinal system disorders	51 (25)
Vomiting	24 (12)
Diarrhoea	19 (9)
Respiratory system disorders	38 (19)
Upper respiratory tract infection	16 (8)
Resistance mechanism disorders	35 (17)
Otitis media[a]	30 (15)[a]
Skin and appendages disorders	29 (14)
Rash	14 (7)
Body as a whole - general disorders	19 (9)
Fever	13 (6)

[a]Bilateral otitis media was reported for Subject 215114 without an onset date. This event is, however, included in this table for completeness.
Note: Incidence was based on the number of subjects, not the number of events. Percentages calculated with the total no. of subjects as the
denominator.
Source: sponsors submission

The most common adverse event was AOM (15%, episode of AOM distinct from that which was diagnosed upon study entry) followed by vomiting (12%), diarrhea (9%), upper respiratory tract infection (8%), rash (7%), and fever (6%). Adverse events occurred most frequently in the gastrointestinal body system (25%).

Most adverse events (95%) reported up to Visit 4 were mild to moderate in severity. Eleven were marked in severity: vomiting (2 events), otitis media (1), abdominal pain (1), fever (1), palmar-plantar erythrodysaesthia (1), rash (1), heat rash (1), anorexia (1), increased alkaline phosphatase (1), varicella (1). Two additional adverse events (maculo-papular rash and acute otitis media) were also considered marked in severity, but occurred after the last study visit. The majority of marked events (10/13; 77%) were considered by the investigators to be doubtfully related or not related to study drug. The 2 cases of vomiting were considered probably related, and 1 case of maculo-papular rash was considered possibly related.

A summary of adverse events occurring in at least 5% of subjects up to Visit 5 is provided in Table 115.

Table 115: Incidence of Treatment-Emergent Adverse Events Occurring in 5% of Subjects up to Visit 5 by Body System and Preferred Term (Study LOFBO-OTMD-001: Safety Analysis Set)

Body System Preferred Term	Levofloxacin (N=204) n (%)
Total no. subjects with adverse events	145 (71)
Resistance mechanism disorders	62 (30)
Otitis media [a]	56 (27)
Gastro-intestinal system disorders	58 (28)
Vomiting	27 (13)
Diarrhoea	24 (12)
Respiratory system disorders	55 (27)
Upper resp tract infection	28 (14)
Skin and appendages disorders	31 (15)
Rash	14 (7)
Body as a whole - general disorders	28 (14)
Fever	21 (10)
Psychiatric disorders	17 (8)
Nervousness	10 (5)

[a] Bilateral otitis media was reported for Subject 215114 without an onset date. This event is, however, included in this table for completeness.
Note: Incidence was based on the number of subjects, not the number of events. Percentages calculated with the total no. of subjects as the denominator.
Source: sponsors submission

One hundred forty-five subjects (71%) reported at least 1 adverse event up to Visit 5 (25 to 35 days after the last dose of study drug). The most common adverse event was AOM (27%, episodes of AOM distinct from that which was diagnosed upon entry to the study) followed by upper respiratory tract infection (14%), vomiting (13%), diarrhea (12%), fever (10%), rash (7%), and nervousness (5%). Adverse events related to the gastrointestinal system occurred in 58 (28%) subjects and those related to the respiratory system occurred in 55 (27%) subjects.

D. Musculoskeletal Adverse Events

The investigators identified 6 MS adverse events during the conduct of the study. A listing of subjects whose adverse events were recoded is summarized in Table 116.

Table 116: Adverse Event Preferred Terms That Were Recoded to Map to the Musculoskeletal Body System by Subject (Study LOFBO-OTMD-001: Safety Analysis Set)

Subject No.	Investigator Reported Term	Original Coding Preferred Term (Body System)	New Coding Preferred Term (Body System)
211207	Pain in both ankles	Pain (Body as a Whole-General Disorders)	Arthralgia (MS Systems Disorders)
212144	Left leg pain	Leg pain (Body as a Whole-General Disorders)	Arthralgia (MS Systems Disorders)
213175	Limping left leg	Leg pain (Body as a Whole-General Disorders)	Myalgia (MS Systems Disorders)
215118	Dislocated left elbow	Joint dislocation (Body as a Whole-General Disorders)	Arthropathy (MS Systems Disorders)
215261	Broken wrist (right)	Injury (Secondary Terms)	Fracture pathological (MS Systems Disorders)

Source: sponsors submission

These 6 subjects are enrolled in the long-term safety surveillance study (LOFBO-LTSS-001). Of the 6 musculoskeletal adverse events, musculoskeletal disorders (arthralgia, arthritis, tendinopathy, or gait abnormality, as defined in the protocol) were identified by the DSMC in 3 subjects (1.47% of the total population); 2 arthralgia and 1 gait abnormality (each <1% of total population)

A listing of subjects who had muskuloskeltal disorders are summarized in Table 117.

Table 117: Subjects with Musculoskeletal Adverse Events (Study LOFBO-OTMD-001: Safety Analysis Set)

Subject No. Age[a]/ Sex	Body System (Preferred term) Included Term	Day of Onset[b] (Day of Resolution)	Dosage at Onset	Action Taken	Severity of Event	Relationship to Study Drug [c]	Outcome (Duration) Total Days on Therapy
211207 4.9 Female	Musculo-skeletal System disorders (Arthralgia) [d,f] Arthralgia	26 (30)	None	None	Mild	Doubtful [e]	Resolved (5 days) 10
212119 2.3 Male	Musculo-skeletal System disorders (Arthralgia) [d] Joint pain	25 (78)	None	None	Mild	Not related [e]	Resolved (54 days) 12
212144 4.6 Female	Musculo-skeletal System disorders (Arthralgia) [f] Arthralgia	16 (35)	None	None	Mild	Not related	Resolved (20 days) 11
213175 1.5 Male	Musculo-skeletal System disorders (Myalgia) [d, f] Myalgia	2 (65)	105 mg	None	Mild	Doubtful	Resolved (64 days) 11
215118 1.9 Female	Musculo-skeletal System disorders (Arthropathy) [f] Arthropathy	21 (21)	None	None	Moderate	Not related	Resolved (1 day) 11
215261 1.3 Female	Musculo-skeletal System disorders (Fracture pathological) [f] Fracture pathological	38 (54)	None	None	Moderate	Not related	Resolved (17 days) 11

[a] Years unless otherwise specified
[b] Based on day of first dose
[c] Investigator assessment.
[d] Considered a musculoskeletal disorder by DSMC
[e] Relationship considered possible by DSMC.
[f] Event recoded to map to the Musculoskeletal Disorder Body System
MS = musculoskeletal
NA = Not applicable

E. Clinical Laboratory and Vital Sign Evaluation

There were no clinical significant changes observed in the laboratory evaluation conducted and the changes in vital sign values during this study. There were no clinically meaningful differences between treatment groups.

1. Individual Subject Changes

The incidences of treatment-emergent markedly abnormal clinical laboratory values are summarized in Table 118.

Table 118: Incidence of Treatment-Emergent Markedly Abnormal Clinical Laboratory Values (Study LOFBO-OTMD-002: Safety Analysis Set)

Profile	Levofloxacin	Comparator
Analyte [a]	(N=797)	(N=810)
Markedly Abnormal Change	n (%)	n (%)
Chemistry	644	659
Alanine amino transferase (U/L)	605	627
Increase	1 (<1)	2 (<1)
Alkaline phosphatase (U/L)	622	642
Increase	1 (<1)	2 (<1)
Calcium (mg/dL)	635	651
Decrease	2 (<1)	2 (<1)
Increase	1 (<1)	1 (<1)
Phosphorus, inorganic (mg/dL)	628	645
Increase	2 (<1)	0
Potassium (mmol/L)	592	619
Decrease	0	1 (<1)
Increase	2 (<1)	0
Hematology	557	581
Differential (absolute) -eosinophils ($x10^9$/L)	556	580
Increase	3 (1)	10 (2)
Differential (absolute) -neutrophils ($x10^9$/L)	557	581
Decrease	3 (1)	1 (<1)
Platelet count ($x10^9$/L)	487	528
Decrease	2 (<1)	3 (1)
Increase	0	1 (<1)
WBC, total ($x10^9$/L)	557	581
Decrease	1 (<1)	1 (<1)
Increase	1 (<1)	0

[a] Analytes for which no subject met criteria are not presented.
n = Number of subjects with admission and posttherapy data available for that analyte.

The most common markedly abnormal clinical laboratory abnormality was eosinophilia (levofloxacin: 3 [1%] subjects; comparator: 10 [2%] subjects). Between 0 and 3 subjects in each treatment group had markedly abnormal changes in alanine amino transferase, alkaline phosphatase, calcium, inorganic phosphorous, potassium, neutrophils, platelets, and WBCs.

2. Vital Signs and Physical Findings

Mean values and changes from baseline in vital signs by age group (2 years, >2 years) at Visit 3 (or early withdrawal) and incidence of treatment-emergent markedly abnormal vital sign values based on age-specific criteria were compared .

There were no clinically relevant vital sign findings in either treatment group or between treatment groups. There were no clinically meaningful findings in physical examination abnormalities.

5.4.9.1 Conclusion of the AOM study (LOFBO-OTMD-001)

This study was designed to establish the efficacy (clinical cure rate at Visit 3, 2 to 5 days after the last dose of study drug) of levofloxacin to be non-inferior to "standard of care" antibiotic therapy in the treatment of recurrent and/or persistent AOM in children aged 6 months to 5 years.

A total of 1,650 subjects were randomized in this study. Six-hundred and thirty (76%) levofloxacin-treated and (b) (4) 1,607 (97%) were evaluable for safety. (b) (4) The safety profile defined in children in this study is similar across the treatment arms.

Four-hundred forty-eight (56%) levofloxacin-treated subjects and 475 (59%) comparator-treated subjects reported at least 1 adverse event up to Visit 4 (10 to 17 days after the last dose of study drug). Diarrhea was the most frequently reported adverse event (14% and 20% for levofloxacin and comparator, respectively). Most adverse events were mild to moderate in severity. Forty-two subjects (3%) experienced MS adverse events. The difference in the incidence of subjects with MS adverse events in the levofloxacin- and comparator-treated groups (3% versus 2%, respectively;) was not statistically significant (p=0.534). The DSMC reviewed all MS adverse events and classified 17 of the 44 events (12 in levofloxacin-treated and 5 in comparator-treated subjects) as MS disorders (defined in the protocol as either arthralgia, arthritis, tendinopathy, or gait abnormality). The difference in the number of subjects with MS disorders in the levofloxacin- and comparator-treated groups (2% versus <1%, respectively) was not statistically significant (p = 0.0921).

Serious adverse events were reported in 10 (1%) levofloxacin-treated subjects and 13 (2%) comparator-treated subjects. There were no deaths. Adverse events leading to treatment discontinuation occurred in 31 (4%) levofloxacin-treated and 22 (3%) comparator-treated subjects.

7 Overall Conclusion

Safety and efficacy data are available from Phase 3 studies where levofloxacin was administered as the study drug in active controlled trials of community acquired pneumonia (CAP-003) and acute otitis media (AOM: clinical outcome). (b) (4)

(b) (4)

In fact patients who received levofloxacin had a slightly higher incidence rate of musculoskeletal disorders (arthralgia, arthritis, gait abnormality or tendinopathy) (2.1% vs. 0.9%, p-value: 0.038 when compared with the non fluoroquinolones). Arthralgia was the most frequently occurring MS disorder occurring at the 30-day, 60-day, and 1-year period after the first dose for both treatment groups

8. Recommendation

The overall incidence rate of musculoskeletal disorders in pediatric subjects treated for an acute bacterial infection with levofloxacin showed a significantly higher incidence of MS disorders (defined in the protocol as tendinopathy, arthritis, arthralgia, or gait abnormality) compared to 'standard' non-fluoroquinolone therapy at the 60-day and 1 year period after the first dose. Even though the musculoskeletal disorders that were observed were reversible, less serious, self limited and resolved within short period musculoskeletal disorder findings were consistent with what has been observed previous studies both in humans and animals .

Therefore, it is very important to reflect the safety findings from the studies reviewed in to the current labeling.

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