PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.
For publications based on this study, see associated bibliography.

PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Zithromax® / Azithromycin

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert (USPI)

NATIONAL CLINICAL TRIAL NO.: NCT00809328

PROTOCOL NO.: A0661191

PROTOCOL TITLE: A Multicenter, Non-Randomized, Open-Label Study of Azithromycin Intravenous Followed by Oral Administration in Japanese Adult Subjects With Community Acquired Pneumonia (CAP) Requiring Initial Intravenous Therapy

Study Center(s): Thirty-five (35) centers in Japan

Study Initiation and Completion Dates: 4 February 2009 to 25 March 2010

Phase of Development: Phase 3

Study Objectives:

The primary objective was to evaluate the clinical response and safety of azithromycin switch therapy (switch from intravenous to oral) in patients with community acquired pneumonia requiring intravenous therapy.

The secondary objectives were the following:

To evaluate the bacteriological response of azithromycin

To measure the serum concentration of azithromycin following intravenous and/or oral administration and characterize the pharmacokinetics of azithromycin, and to explore the pharmacokinetics-pharmacodynamics (PK-PD) of intravenous azithromycin if minimum inhibitory concentrations (MICs) against causative pathogens were obtained

METHODS

Study Design: This is a Phase 3, multicenter, non-controlled, open-label study. Efficacy was measured on Day 3, at the end of treatment (EOT), on Day 15 and on Day 29.

Number of Subjects (Planned and Analyzed): A total of 100 subjects were targeted for treatment. A total of 102 subjects received treatment in this study.

Diagnosis and Main Criteria for Inclusion: Patients, 16 years old or older (less than 80 years old as a general rule) who were diagnosed as having CAP requiring intravenous therapy and the severity of which was moderate or severe according to the pneumonia patient seriousness evaluation method in the "Clinical evaluation methods for new antimicrobial agents to treat respiratory infections: Report (draft) of the Committee for the Respiratory System, Japan Society of Chemotherapy (June 1997)," were included in the study (as for patients evaluated as severe, only those diagnosed as none or mild in the severity of underlying diseases and complications and as severe in the severity of pneumonia infection were included).

Study Treatment: The subjects received 500 mg intravenous azithromycin QD for 2 to 5 days. The 500 mg intravenous azithromycin was administrated at concentrations of 1 mg/mL over 2 hours or more. Following intravenous administration, the subjects received 500 mg oral azithromycin (tablet formulation) QD to complete a total of 7 to 10 days therapy. The period of oral dosing was also judged by the investigator (subinvestigator) according to the patients' conditions.

The switch from intravenous to oral azithromycin was done at the discretion of the investigator (subinvestigator).

Efficacy Evaluations: The primary endpoint was clinical response assessed by the Data Review Committee at EOT, on Day 15 and Day 29.

The secondary endpoints were the following:

Clinical response at EOT, on Day 15 and on Day 29 and the tendency toward clinical improvement on Day 3 as assessed by the investigator (subinvestigator)

Bacteriological response on Day 3, at EOT, on Day 15 and Day 29 as assessed by both the Data Review Committee and the investigator (subinvestigator)

Reasons for switching from intravenous to oral therapy

Pharmacokinetic Evaluation: For pharmacokinetic analysis, blood samples were collected at the following time points: Just before the end of intravenous dosing, 0 to 2 hours after the end of intravenous dosing, between 4 hours after the end of intravenous dosing and the start of the next dosing, EOT, and Day 15. Serum samples were assayed using a validated high performance liquid chromatography/tandem mass spectrometry.

Safety Evaluations: Adverse events were recorded in the case report form from the time the subject received at least 1 dose of study treatment to the last subject visit. Serious adverse events were reported beginning from the time when the subject provided informed consent until 28 days after the last administration of the study treatment. Clinical laboratory tests were performed, and blood pressure, pulse rate and respiration rate were recorded on Day 1 (prior to dosing), Day 3, at the time of switching from intravenous to oral therapy, at EOT, at the time of discharge, on Day 15, and Day 29.

Statistical Methods: The Per Protocol Set (PPS) was the primary analysis set for the efficacy analyses. In this study the Clinical Per Protocol Set (CPPS) and the Bacteriologic Per Protocol Set (BPPS) were used as the PPS. The CPPS consisted of all subjects who received at least 1 dose of the study drug, have no significant violation of protocol, and underwent prescribed evaluations during the observation period as specified in the protocol. The BPPS consisted of all subjects in the CPPS in whom bacterial pathogens were identified at baseline. The Full Analysis Set (FAS) consisted of all subjects who received at least 1 dose of the study drug.

Regarding the primary analysis of the primary endpoints, the efficacy rate and 95% confidence interval (CI) in the clinical response in the CPPS on Day 15 as evaluated by the Data Review Committee were calculated. Regarding the secondary analysis of the clinical response evaluated by the Data Review Committee, the efficacy rate and 95% CI at EOT and on Day 29 in the CPPS and the efficacy rate and 95% CI on each evaluation day (EOT and Days 15 and 29) in the BPPS and the FAS were calculated. The frequency and proportion were calculated for the secondary endpoints, and further, the 95% CIs regarding the clinical and bacteriological efficacies were also calculated.

In the PK-PD analysis, population pharmacokinetic analysis in azithromycin intravenous therapy was to be performed using the data obtained in the present study and those obtained in Japanese and foreign Phase 1 studies as necessary, and PK-PD parameters such as AUC/MIC were to be evaluated from the AUC calculated and MICs of causative pathogens. Since the efficacy result in BPPS was limited, investigation of PK-PD parameters could not be performed. Results of the population PK analysis were described in the report prepared separately.

Safety was analyzed with all subjects who received at least 1 dose of the study drug. The safety analysis was performed mainly by descriptive statistics. Except the onset of adverse events, duration of adverse events, and vital signs, analyses were performed according to the algorithm and the format specified by Pfizer Data Standards (PDS).

RESULTS

Subject Disposition and Demography: A total of 102 subjects were assigned to treatment groups in this clinical study, and all of them received the study drug. Of those receiving the study drug, 29 subjects (28.4%) discontinued the study. The most common reasons for the discontinuation as judged by the investigator were insufficient efficacy in 18 subjects (17.6%) and adverse events in 6 subjects (5.9%). CPPS include 73 subjects. Most common reason for exclusion from CPPS was subjects were not the CAP of which criteria was specified in protocol. The subject disposition and the analysis sets are shown in Table 1.

Table 1. Subject Disposition and Subjects Analyzed

Number (%) of Subjects	Azithromycin
Assigned to Treatment	102
Treated	102
Completed	73 (71.6)
Discontinued	29 (28.4)
Lack of efficacy	18 (17.6)
Adverse event	6 (5.9)
Does not meet inclusion criteria	3 (2.9)
Subject no longer willing to participate in study	2 (2.0)
Analyzed for Efficacy	
Full Analysis Set	102 (100.0)
Clinical Per Protocol Set	73 (71.6)
Bacteriologic Per Protocol Set	33 (32.4)
Analyzed for Safety	
Adverse events	102 (100.0)
Laboratory data	101 (99.0)

The demographic characteristics are shown in Table 2. The FAS consisted of 63 male subjects (61.8%) and 39 female subjects (38.2%), with male subjects accounting for the higher percentage. The mean age of the subjects was 55.4 years, with 43 subjects (42.2%) being 65 years or older, and 16 subjects (15.7%) being 75 years or older. None of the parameters showed any major differences among the analysis sets.

Table 2. Demographic Characteristics

	Azithromycin		
	FAS (N=102)	CPPS (N=73)	BPPS (N=33)
Age (years) [n (%)]			
16-44	29 (28.4)	23 (31.5)	15 (45.5)
45-64	30 (29.4)	21 (28.8)	6 (18.2)
65-74	27 (26.5)	20 (27.4)	10 (30.3)
75-79	13 (12.7)	7 (9.6)	2 (6.1)
80<=	3 (2.9)	2 (2.7)	0
Mean±SD	55.4±18.6	54.0±18.8	49.2±19.6
Range	16-84	16-80	16-78
Sex [n (%)]			
Male	63 (61.8)	46 (63.0)	19 (57.6)
Female	39 (38.2)	27 (37.0)	14 (42.4)
Height (cm)			
Mean±SD	161.7±9.1	161.6±9.1	162.2±10.2
Range	140.0-184.0	140.0-184.0	140.0-184.0
Weight (kg)			
Mean±SD	57.2±10.8	57.0±10.2	57.5±10.3
Range	35.0-91.5	35.0-91.5	40.3-78.3
Body Mass Index[a] (kg/m^2)			
Mean±SD	21.9±3.8	21.8±3.7	21.9±3.6
Range	15.5-35.8	15.8-35.8	15.8-35.8
Smoking Classification [n (%)]			
Never smoke	45 (44.1)	35 (47.9)	18 (54.5)
Ex smoker	30 (29.4)	21 (28.8)	6 (18.2)
Smoker	27 (26.5)	17 (23.3)	9 (27.3)
Alcohol Classification [n (%)]			
Yes	43 (42.2)	28 (38.4)	14 (42.4)
No	59 (57.8)	45 (61.6)	19 (57.6)

SD = standard deviation, FAS = full analysis set, CPPS = clinical per protocol set, BPPS = bacteriologic per protocol set.
[a] Body Mass Index is calculated as Weight / (Height × 0.01) ^{2}.

Four different species of causative pathogens were identified from 33 of 73 subjects in the CPPS. A single causative pathogen was identified in 26 subjects and multiple causative pathogens were identified in 7 subjects. The major causative pathogens were *H. influenzae* (17 strains) and *S. pneumoniae* (14 strains).

Efficacy Results: As for the clinical response assessed by the Data Review Committee (primary efficacy endpoint), the efficacy rate in the CPPS was 84.5% on Day 15 (primary analysis), 86.3% at EOT, and 82.9% on Day 29. The efficacy rate exceeded 80% at all evaluation time points (Table 3).

Table 3. Clinical Response (Data Review Committee Assessment, CPPS)

	Total	Clinical Response			Efficacy Rate[a]	95%CI
		Effective (%)	Ineffective (%)	Indeterminate (%)		
End of Treatment	73	63 (86.3)	10 (13.7)	0	86.3	(76.2, 93.2)
Day 15	71	60 (84.5)	11 (15.5)	0	84.5	(74.0, 92.0)
Day 29	71	58 (81.7)	12 (16.9)	1 (1.4)	82.9	(72.0, 90.8)

CI = confidence interval.
[a] Response rate = effective / (total − indeterminate) × 100.

Major causative pathogens identified at baseline were *S. pneumoniae* and *H. influenzae*. Clinical response (efficacy rate) by causative pathogen on Day 15 in the BPPS as judged by the Data Review Committee was 85.7% (12/14) in subjects with *S. pneumoniae* at baseline and 88.2% (15/17) in subjects with *H. influenzae* at baseline (Table 4). Total 10 out of 11 subjects with azithromycin resistant strains (MIC: ≥2 μg/mL) of *S. pneumoniae*, were judged as effective. Only 2 subjects in whom *S. pneumoniae* was identified (azithromycin-resistant strain in 1 subject and a strain with unknown MIC in another subject) and 2 subjects in whom *H. influenzae* was isolated and identified (azithromycin-sensitive strains in both subjects) were judged ineffective at all evaluation time points.

Table 4. Clinical Response by Baseline Causative Pathogen (Data Review Committee Assessment, BPPS)

Pathogen[a]	Clinical Response					
	End of Treatment		Day 15		Day 29	
	n/N	Efficacy Rate [b]	n/N	Efficacy Rate[b]	n/N	Efficacy Rate[b]
S. pneumoniae	12/14	85.7	12/14	85.7	12/14	85.7
H. influenzae	15/17	88.2	15/17	88.2	15/17	88.2
M. catarrhalis	5/5	100	5/5	100	5/5	100
M. pneumoniae	5/5	100	4/4	100	4/4	100

n = number of subjects with effective, N = total subjects − number of subjects with indeterminate.
[a] A subject may have more than 1 pathogen isolated.
[b] Calculated as efficacy rate = n/N × 100.

Efficacy rate in the CPPS as judged by the investigator (subinvestigator) was 80.8% at EOT, 98.4% on Day 15, and 95.1% on Day 29.

As for the tendency toward clinical improvement on Day 3 in the CPPS as judged by the investigator (subinvestigator), 68 subjects (93.2%) continued the study.

Bacteriological response (eradication rate) by subject on Day 15 in the BPPS was 83.3% as judged by the Data Review Committee (Table 5) and 100% as judged by the investigator (subinvestigator).

Table 5. Bacteriological Response by Subject (Data Review Committee Assessment, BPPS)

	Total	N	n	Eradication Rate[a]	95%CI
Day 3	30	28	20	71.4	(51.3, 86.8)
End of Treatment	33	31	25	80.6	(62.5, 92.5)
Day 15	32	30	25	83.3	(65.3, 94.4)
Day 29	32	30	25	83.3	(65.3, 94.4)

N = number of subjects with total − indeterminate, n = total number of subjects with eradication, presumed eradication or microbial substitution, CI = confidence interval.
[a] Calculated as eradication rate = n/N × 100.

The eradication rate by causative pathogen identified at baseline on Day 15 as judged by the Data Review Committee was 85.7% (12/14 strains) for *S. pneumoniae* and 82.4% (14/17 strains) for *H. influenzae* (Table 6). Ten of the 11 resistant strains of *S. pneumoniae* were evaluated as eradication or presumed eradication. The total 2 strains of *S. pneumoniae* (azithromycin-resistant strain and a strain with unknown MIC) and 3 strains of *H. influenzae* (azithromycin-sensitive strains) were bacteriologically persistent on Day 15. The eradication rates by causative pathogen on Day 15 as assessed by the investigator (subinvestigator) were 100% (11/11 strains) for *S. pneumoniae* and 100% (14/14 strains) for *H. influenzae* as well.

Table 6. Bacteriological Response by Baseline Causative Pathogen (Data Review Committee Assessment, BPPS)

Pathogen[a]	Bacteriological Response							
	Day 3		End of Treatment		Day 15		Day 29	
	n/N	Eradication Rate[b]	n/N	Eradication Rate[b]	n/N	Eradication Rate[b]	n/N	Eradication Rate[b]
S. pneumoniae	6/13	46.2	9/14	64.3	12/14	85.7	12/14	85.7
H. influenzae	14/15	93.3	16/17	94.1	14/17	82.4	14/17	82.4
M. catarrhalis	5/5	100	5/5	100	5/5	100	5/5	100
M. pneumoniae	3/3	100	3/3	100	2/2	100	2/2	100
M. pneumoniae	3/3 (100)		3/3 (100)		3/3 (100)		2/2 (100)	

n = the number of pathogen with eradication or presumed eradication, N = total pathogens − number of pathogens with indeterminate.
[a] A subject may have more than 1 pathogen isolated.
[b] Calculated as eradication rate = n/N × 100.

Clinical signs and symptoms (cough, sputum volumes, nature of sputum, dyspnoea, consciousness disturbed, chest pain, chest rales, dehydration, pain pharyngeal) in subjects in the CPPS tended to improve from Day 3. Body temperature, white blood cell count, CRP, and SpO_2 improved in most of the subjects after switching to the oral preparation compared to the values observed on Day 1 (prior to dosing). The chest x-ray score improved from Day 3, and further improved over the therapeutic course. The reasons for switching from intravenous to oral therapy for subjects in the CPPS for whom clinical response on Day 15 was evaluated as effective by the Data Review Committee were improvement in clinical signs and symptoms (body temperature, white blood cell count, CRP) in 93.3% of subjects

(56/60) and improvement in clinical symptoms (other than body temperature, white blood cell count, CRP) in 6.7% of subjects (4/60).

Safety Results: Adverse events are summarized in Table 7. The number of subjects exhibiting all-causality adverse events among the 102 subjects was 55 (53.9%) during the entire period and in 42 (41.2%) during the intravenous therapy. Treatment-related adverse events were observed in 34 subjects (33.3%) during the entire period and 26 subjects (25.5%) during the intravenous therapy out of 102 subjects.

Table 7. Overall Summary of Adverse Events

	Azithromycin			
	All Causalities		Treatment Related	
	Entire Period	During IV Therapy	Entire Period	During IV Therapy
	N=102	N=102	N=102	N=102
Number of adverse events	116	63	44	32
Number (%) of subjects				
Adverse events	55 (53.9)	42 (41.2)	34 (33.3)	26 (25.5)
Serious adverse events	9 (8.8)[a]	2 (2.0)	1 (1.0)	1 (1.0)
Severe adverse events	2 (2.0)	0	0	0
Dose or study discontinuation due to adverse events	7 (6.9)[b]	3 (2.9)[b]	2 (2.0)	2 (2.0)
Dose reduced or temporary discontinuation due to adverse events	0	0	0	0

IV = intravenous.
[a] Includes 1 subject who experienced serious adverse event after study discontinuation.
[b] Includes 1 subject who discontinued the study drug, but continued the study.

The most common all-causality adverse events were diarrhoea (15 subjects, 14.7%), constipation (8 subjects, 7.8%), headache (8 subjects, 7.8%), injection site pain (6 subjects, 5.9%), and insomnia (6 subjects, 5.9%). Among these common adverse events, those that occurred during intravenous therapy were diarrhoea (11 subjects, 10.8%), constipation (3 subjects, 2.9%), headache (7 subjects, 6.9%), injection site pain (6 subjects, 5.9%), and insomnia (3 subjects, 2.9%); the adverse events observed during the entire study period and those observed during intravenous therapy were similar in type (Table 8).

Table 8. All-Causality Adverse Events Occurred in 2 Subjects or More During the Entire Period

System Organ Class and MedDRA (version 12.1) Preferred Term	Azithromycin	
	Entire Period	During IV Therapy
Number (%) of subjects	N=102	N=102
Gastrointestinal disorders		
Abdominal discomfort	2 (2.0)	1 (1.0)
Abdominal pain	2 (2.0)	1 (1.0)
Constipation	8 (7.8)	3 (2.9)
Diarrhoea	15 (14.7)	11 (10.8)
Nausea	2 (2.0)	2 (2.0)
General disorders and administration site conditions		
Injection site erythema	3 (2.9)	3 (2.9)
Injection site pain	6 (5.9)	6 (5.9)
Infections and infestations		
Pneumonia	3 (2.9)	1 (1.0)
Investigations		
Alanine aminotransferase increased	2 (2.0)	1 (1.0)
Musculoskeletal and connective tissue disorders		
Back pain	3 (2.9)	1 (1.0)
Myalgia	2 (2.0)	2 (2.0)
Nervous system disorders		
Headache	8 (7.8)	7 (6.9)
Psychiatric disorders		
Insomnia	6 (5.9)	3 (2.9)
Respiratory, thoracic and mediastinal disorders		
Asthma	2 (2.0)	0
Haemoptysis	3 (2.9)	1 (1.0)
Skin and subcutaneous tissue disorders		
Dermatitis contact	2 (2.0)	1 (1.0)
Eczema	2 (2.0)	1 (1.0)

IV = intravenous.

Severity of adverse events as summarized by preferred term was mild in 101 subjects, moderate in 13 subjects, and severe in 2 subjects. The 2 severe adverse events included pneumonia in 1 subject (investigator term, underlying disease aggravated) and lung neoplasm malignant in 1 subject. Causal relationship of these severe adverse events was ruled out.

Seven subjects (6.9%) discontinued the study or the administration of the study drug because of adverse events (Table 9). Of these adverse events, diarrhoea and abdominal pain in 1 subject each were judged to be treatment-related adverse events. The abdominal pain was confirmed to have resolved. Diarrhoea was not recovered at the time of study discontinuation, but was confirmed to have resolved at the follow-up monitoring.

Table 9. Adverse Events Leading to Dose or Study Discontinuation

System Organ Class and MedDRA (version 12.1) Preferred Term	Azithromycin
Number (%) of subjects	N=102
Gastrointestinal disorders	2 (2.0)
Abdominal pain	1 (1.0)
Diarrhoea	1 (1.0)
Infections and infestations	3 (2.9)
Pneumonia	3 (2.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.0)
Lung neoplasm malignant	1 (1.0)
Respiratory, thoracic and mediastinal disorders	1 (1.0)
Organising pneumonia	1 (1.0)

No subject died in this study. Ten serious adverse events were observed in 9 subjects (Table 10). Serious adverse events that resulted in discontinuation of the administration were pneumonia in 2 subjects (investigator term: pneumonia aggravated and underlying disease aggravated) and organising pneumonia in 1 subject. Other serious adverse events that resulted in study discontinuation were lung neoplasm malignant in 1 subject and pneumonia (investigator term: pneumonia aggravated) in 1 subject. The only serious adverse event judged by the investigator to be treatment-related adverse event was prothrombin time prolonged (mild) in 1 subject, which was confirmed to have resolved.

Table 10. Serious Adverse Events

System Organ Class and MedDRA (version 12.1) Preferred Term	Azithromycin N=102
Number (%) of subjects with serious adverse events	9 (8.8)
Cardiac disorders	1 (1.0)
Cardiac failure congestive	1 (1.0)
Infections and infestations	5 (4.9)
Bronchopulmonary aspergillosis[a]	1 (1.0)
Peritonsillar abscess	1 (1.0)
Pneumonia	3 (2.9)
Investigations	1 (1.0)
Prothrombin time prolonged	1 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.0)
Lung neoplasm malignant	1 (1.0)
Respiratory, thoracic and mediastinal disorders	2 (2.0)
Organising pneumonia	1 (1.0)
Pneumothorax	1 (1.0)

[a] The subject experienced serious adverse event after study discontinuation.

The most common laboratory abnormalities according to the PDS criteria were positive urinary occult blood, increased casual blood glucose level, and decreased lymphocyte count.

There were no cases of dose reduction, temporary discontinuation of administration, discontinuation of administration, or study discontinuation due to adverse events related to laboratory values. Most of the changes in systemic blood pressure, diastolic blood pressure, pulse rate, and respiratory rate from baseline were those associated with the recovery from the target disease of the study.

CONCLUSION(S):

The following conclusions were derived from the results of the multicenter, open-label, non-controlled study of azithromycin intravenous followed by oral administration in subjects with community acquired pneumonia requiring initial intravenous therapy.

As for the clinical response assessed by the Data Review Committee (primary endpoint), the efficacy rate was 84.5% on Day 15 (primary analysis), 86.3% at EOT, and 82.9% on Day 29. The efficacy rate exceeded 80% at all evaluation time points.

The bacteriological response (eradication rate) by subject on Day 15 in the BPPS as judged by the Data Review Committee was 83.3%. The eradication rate of the major causative pathogens *S. pneumoniae* and *H. influenzae* on Day 15 was 85.7% and 82.4%, respectively.

Most adverse events observed were mild to moderate in severity. Among adverse events that resulted in the discontinuation of the administration or study, diarrhoea and abdominal pain that occurred in 1 subject each and judged to be treatment-related were confirmed to have resolved during the study or at the follow-up after study discontinuation. Severe adverse events observed were pneumonia in 1 subject (investigator term, underlying disease aggravated) and lung neoplasm malignant in 1 subject, but causal relationship was ruled out for both of these adverse events. The treatment-related serious adverse event (prothrombin time prolonged) was mild in severity and confirmed to have resolved. The above results demonstrated that the study drug was well tolerated and posed no safety problem.