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/INN: Zithromax®/Azithromycin Sustained Release

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms (see United States Package Insert for specific conditions).

PROTOCOL NO.: A0661145

PROTOCOL TITLE: A Randomized, Open Label, Clinical Trial of the Pharmacokinetics of Azithromycin in Serum, Bronchial Washings and Lung Tissue Following a Single Dose of Azithromycin Sustained Release (2 gram) or Commercial Azithromycin Tablet (500 mg) to Cancer Patients That Require Lung Resection

Study Center: 1 center, Italy

Study Initiation and Completion Dates: 08 November 2004 to 15 April 2005

Phase of Development: Phase 2.

Study Objective: The objective of this trial was to characterize the pharmacokinetics of the currently marketed azithromycin immediate release tablet formulation (AZ-IR) vs the azithromycin sustained release liquid formulation (AZ-SR) in lung tissue and bronchial washings, the latter consisting of the epithelial lining fluid (ELF) and cellular elements, mainly alveolar macrophages (AM).

METHODS

Study Design:

This was a randomized, open-label trial conducted in hospitalized subjects with lung cancer. Sixty-four subjects requiring open-chest surgery for lung resection were to be enrolled at a single site. One-half of the subjects (32) were to be randomized to receive either a single 500 mg dose of AZ-IR or a single 2-gram dose of AZ-SR. Subjects within each treatment arm were to be simultaneously randomized to one of 8 nominal postdose time points (4 subjects/time/treatment) for bronchoalveolar lavage (BAL) and lung tissue sampling.

Serial serum samples (10 mL each) were collected from all subjects up to 72 hours postdose. BAL and lung tissue samples were collected in the 4 subjects/time/treatment up to 72 hours postdose. BAL was performed just prior to surgery to obtain bronchial washings. At the time of surgery, lung tissue samples from a macroscopically normal segment of lung were obtained.

Number of Patients (planned and analyzed): The sample size was chosen empirically. A total of 66 subjects were enrolled and received treatment.

Diagnosis and Main Criteria for Inclusion: Subjects were men and women greater than 18 years of age with a diagnosis of lung cancer. Subjects were required to be hospitalized and had to consent to surgery requiring lung resection. Subjects had a life expectancy greater than 6 months.

Study Treatment: Subjects received a single oral dose of either 500 mg AZ-IR (tablet) or 2 g of AZ-SR (suspension). AZ-SR was reconstituted with 60 mL of water and administered within 10 minutes of reconstitution. Study drug was administered on an empty stomach in a manner such that each subject's BAL and lung surgery coincided with their pre-determined sampling time as per the randomization schedule (subjects fasted for 2 hours before dosing and continued to fast for 2 hours after dosing). Because subjects underwent a surgical procedure, additional fasting for up to 8 hours was required before surgery.

AZ-IR and AZ-SR were supplied by the sponsor. AZ-IR was supplied as the commercially available white, modified capsular-shaped, film-coated 500-mg tablet. Each tablet contained azithromycin dihydrate equivalent to 500 mg of azithromycin. AZ-SR was supplied as a 2 g white/off-white oral powder for constitution. This formulation was composed of azithromycin dihydrate microspheres, vehicle blend, sucrose, and common commercial excipients.

Efficacy Evaluations: No efficacy evaluations were done.

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations:
Serial serum samples (10 mL each) for analysis of azithromycin serum concentrations were collected from all subjects at the following times: predose, and at 2, 4, 8, 12, 16, 24, 48, and 72 hours postdose.

BAL and lung tissue samples were collected from 4 subjects per time point per treatment at the following sampling time interval: 2, 4, 8, 12, 16, 24, 48, and 72 hours postdose. BAL was done just prior to surgery to obtain bronchial washings. At the time of surgery, lung tissue samples from a macroscopically normal segment of the lung were obtained.

Serum, pooled BAL fractions, and lung tissue samples were assayed for azithromycin using validated methods. Concentration of azithromycin in ELF was determined based on the measured drug concentrations in each subject's pooled aspirate and an estimate of the volume of ELF in each subject's pooled aspirate based on the Urea Dilution Method as reported by Conte, et al.[1] Concentration of azithromycin in alveolar cells (AC) was determined based on the method reported by Conte, et al (1996).

[1] Conte JE, Golden J, Duncan S, McKenna E, Lin E, Zurlinden E. Single-dose intrapulmonary pharmacokinetics of azithromycin, clarithromycin, ciprofloxacin, and cefuroxime in volunteer subjects. Antimicrob Agents Chemother 1996;40(7):1617-22.

Since serial serum samples were collected from each subject, the serum concentration-time data from each subject were analyzed by non-compartmental methods. For the lung tissue, ELF, and AC, azithromycin concentrations were averaged for 4 subjects per time point for each treatment; the mean concentration-time profile for each matrix was then subjected to non-compartmental analyses. Pharmacokinetic parameters determined for serum, lung tissue, ELF, and AC included C_{max}, T_{max}, AUC_{72}, (or AUC_{last} for serum) and AUC_{24}. Pharmacokinetic parameters of azithromycin in serum, lung tissue, ELF, and AC were tabulated.

Safety Evaluations: Safety of azithromycin was assessed by clinical monitoring and included evaluations for adverse events (AEs), safety laboratory tests, vital signs, and 12-lead electrocardiograms (ECGs).

Data from all subjects who received at least 1 dose of study medication were included in the safety analyses. Adverse events, vital signs, ECGs, and safety laboratory data were summarized descriptively and presented in tabular format. Safety was also evaluated by the incidence, type, severity, and causality of individual AEs.

Statistical Methods: The Bailer-Satterthwaite method was utilized to construct the AUCs and 90% confidence intervals (CIs) around the differences of AUCs for this study (destructive sampling design).

RESULTS

Subject Disposition and Demography: A total of 66 subjects were enrolled and received treatment. Of these subjects, 64 (97%) completed the study. Two subjects discontinued the study due to reasons not attributed to the study medication (non-treatment related AE and not meeting the entrance criteria).

Pharmacokinetic, Pharmacodynamic, and/or Other Results:

Pharmacokinetics in Serum: Table S1 summarizes the mean pharmacokinetic parameters of azithromycin in serum.

Table S1. Mean (SD) Pharmacokinetic Parameters of Azithromycin in Serum

Treatment	AUC_{last}[a] (µg·h/mL)	AUC_{24} (µg·h/mL)	C_{max} (µg/mL)	T_{max}[b] (h)
AZ-IR (n=32)	5.0 (2.6)	3.1 (1.8)	0.39 (0.34)	4.0 [2.0, 16.0]
AZ-SR (n=32)	18.8 (6.9)	10.0 (3.5)	0.94 (0.54)	4.0 [2.0, 8.0]

AZ-IR = azithromycin-immediate release, AZ-SR = azithromycin sustained-release, SD = standard deviation.
[a] "Last" measurable time point ranged from 48 to 72 h for AZ-IR, and 72 h for AZ-SR.
[b] Median [range]

Consistent with the higher dose for the AZ-SR formulation, the systemic exposure of azithromycin (as judged by C_{max} and AUC values) exhibited a dose-related increase relative to AZ-IR. Within the first 24 hours after dosing, the mean AUC_{24} value for AZ-SR was about 3.2 fold higher compared to AZ-IR.

Pharmacokinetics in Lung Tissue: Table S2 summarizes the pharmacokinetic parameters of azithromycin in lung tissue.

Table S2. Pharmacokinetic Parameters of Azithromycin in Lung Tissue

Treatment	AUC_{72}[a] (µg·h/g)	AUC_{24}[a] (µg·h/g)	C_{max}[a] (µg/g)	T_{max}[a] (h)
AZ-IR	432	130	8.3	24
AZ-SR	1693	505	37.9	16

AZ-IR = azithromycin-immediate release, AZ-SR = azithromycin sustained-release.
[a] Determined based on composite profile (N=4 subjects/time point/formulation).

Following administration of AZ-IR or AZ-SR, detectable concentrations of AZ were seen in all 4 subjects/treatment randomized to the first sampling time point of 2 hours which is suggestive of rapid distribution to the lung tissue. However, peak concentration of azithromycin lagged behind the peak concentration observed in the serum. Within the first 24 hours after dosing, the AUC_{24} values were 3.9 fold higher for AZ-SR than AZ-IR.

Pharmacokinetics in Alveolar Cells (AC): The total number of cells recovered from the pooled BAL aspirate was generally similar between each treatment. The predominant cell types were macrophages followed by neutrophils. Overall, the differential cell count data appeared to be similar between treatments.

Table S3 summarizes the pharmacokinetic parameters of azithromycin in alveolar cells.

Table S3. Pharmacokinetic Parameters of Azithromycin in Alveolar Cells

Treatment	AUC_{72}[a] (µg·h/mL)	AUC_{24}[a] (µg·h/mL)	C_{max}[a] (µg/mL)	T_{max}[a] (h)
AZ-IR	5804	1674	194	16.0
AZ-SR	20403	7028	669	16.0

AZ-IR = azithromycin-immediate release, AZ-SR = azithromycin sustained-release.
[a] Determined based on composite profile (N=4 subjects/time/formulation).

Within the first 24 hours after dosing, the AUC_{24} values were 4.2-fold higher for AZ-SR than AZ-IR.

Pharmacokinetics in Epithelial Lining Fluid (ELF):

The pharmacokinetic parameters of azithromycin in ELF for both treatments are presented in Table S4.

Table S4. Pharmacokinetic Parameters of Azithromycin in ELF

Treatment	AUC_{72}[a] (µg·h/mL)	AUC_{24}[a] (µg·h/mL)	C_{max}[a] (µg/mL)	T_{max}[a] (h)
AZ-IR	33.5[b]	2.3	1.2	48.0
AZ-SR	131.0	17.6	3.2	48.0

AZ-IR = azithromycin-immediate release, AZ-SR = azithromycin-sustained release, ELF = epithelial lining fluid.
[a] Determined based on composite profile (N=4 subjects /time point /formulation).
[b] AUC_{all} used for AUC_{72}

Within the first 24 hours after dosing, the AUC_{24} values were 7.7-fold higher for AZ-SR than AZ-IR.

Bailer-Satterthwaite Statistical Analyses: Bioavailability estimates were similar to the aforementioned descriptive statistics of AZ-SR relative to AZ-IR when comparing mean AUC_{24} and AUC_{72}, respectively. Table S5 summarizes the statistical analysis of dose normalized AUC for all three matrices concentrations.

Table S5. Summary of Statistical Analysis of AUC_{24} (Dose Normalized) by Matrices

Parameter	Matrix	Means[a] Test	Means[a] Reference	Difference	90% CI
AUC_{24} (µg•h/mL)	AC	1756.87	1674.12	82.75	-1798.27, 1963.77
AUC_{24} (µg•h/mL)	ELF	4.40	2.33	2.08	0.06, 4.09
AUC_{24} (µg•h/g)	Lung	126.23	129.73	-3.50	-27.65, 20.65

AC = alveolar cells; AZ-IR = azithromycin-immediate release, AZ-SR = azithromycin sustained-release; CI = confidence interval; ELF = epithelial lining fluid.
[a]AZ-SR (Test) and AZ-IR (Reference).

After dose normalizing AUC_{24}, there was still approximately a 1.9-fold higher exposure in the ELF matrix when comparing mean AUC_{24} of AZ-SR relative to AZ-IR. However, there was no statistical difference in exposure for the alveolar cells and lung matrices as the 90% CIs encompassed zero.

Safety Results: No deaths occurred in the study. The most frequently occurring AE was pyrexia (14 cases), hypotension (7 cases), and atrial fibrillation (6 cases). The incidence of these events was generally similar between treatment groups. There were 10 cases of pyrexia reported in the AZ-IR group compared with 4 cases in the AZ-SR group. A total of 9 subjects experienced 1 or more serious adverse events (SAEs) and all SAEs were considered by the investigator to be unrelated to study treatment. One subject in the AZ-IR group discontinued the study due to a myocardial infarction that was considered by the investigator to be attributed to coronary artery disease. Table S6 summarizes the incidence of SAEs. A total of 6 severe AEs occurred in the study; all severe events were unrelated to study treatment. There were no clinically significant changes in safety laboratory tests, vital signs, or ECGs that were considered to be related to azithromycin.

Table S6. Incidence of Serious Adverse Events

Subject Number	SAE (Preferred Term)	Start Day	Stop Day	Outcome	Action Taken	Relationship to Study Drug	Most Likely Cause of SAE
AZ-SR							
10011045	Pneumothorax	12	36	Resolved	Treatment given	No	Post-surgical event
	Pneumothorax	1[a]	1[a]	Resolved	Treatment given	No	Post-surgical event
10011056	Pneumothorax	6	14	Resolved	Treatment given	No	Post-surgical complication
10011065	Pneumothorax	7	15	Resolved	Treatment given	No	Post-surgical event
10011066	Respiratory arrest	1	1	Resolved	Treatment given	No	Post-surgical event
AZ-IR							
10011008	Pyrexia	2	18	Resolved	Treatment given	No	Other[a]
	Postoperative wound infection	8	33	Resolved	Treatment given	No	Other[a]
	Bronchial fistula	11	33	Resolved	Treatment given	No	Other[a]
10011010	Myocardial infarction	1	21	Resolved	Discontinued	No	Other[a]
10011030	Respiratory arrest	3	36	Resolved	Intubated	No	Anesthesiological complication
	Respiratory arrest	1[b]	59[b]	Resolved	Intubated	No	Anesthesiological complication
10011044	Hemorrhage	2	14	Resolved	Blood transfusion	No	Post-surgical complication
10011048	Subcutaneous emphysema	5	18	Resolved	Treatment given	No	Post-surgical complication

AZ-IR = azithromycin-immediate release, AZ-SR = azithromycin-sustained release, SAE = serious adverse event.
[a]Other illness.
[b]Occurred post treatment phase.

CONCLUSION(S):

- A single dose of 2 g AZ-SR resulted in a dose-related increase in systemic exposure compared to a single dose of 500 mg AZ-IR.
- Increased systemic exposure translates into enhanced distribution of AZ in the lung, ELF, and AC.
- Following single dose administration, the exposure of azithromycin in lung tissue, ELF, and AC within the first 24 hours was markedly higher for AZ-SR relative to AZ-IR.
- Both formulations had similar safety profiles.