# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**50-797**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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|---|---|
| NDA# | 50-797 (N-000) |
| PRODUCT | Azithromycin ER (Zmax™) |
| FORMULATION | Extended-release powder for oral suspension |
| SUBMISSION DATES | 8/12/04, 12/1/04, 2/4/05, 2/22/05, 3/3/05, 5/4/05 |
| SUBMISSION TYPE | Original New Drug Application |
| SPONSOR | Pfizer, Inc., New London, CT 06320 |
| OCPB DIVISION | Division of Pharmaceutical Evaluation III |
| MEDICAL DIVISION | Division of Anti-Infective Drug Products |
| REVIEWER | Charles R. Bonapace, Pharm.D. |
| TEAM LEADER | Venkat R. Jarugula, Ph.D. |

## CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

## TABLE OF CONTENTS

## 1. EXECUTIVE SUMMARY

Pfizer, Inc. submitted a New Drug Application (NDA) to market azithromycin extended-release powder for oral suspension (azithromycin ER) for the treatment of [redacted] acute bacterial sinusitis (ABS) due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*, and community-acquired pneumonia (CAP) due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, [redacted] *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*. The proposed dosage of azithromycin ER for adults is 2 g [redacted] administered orally as a single dose on an empty stomach (at least 1 hr before or 2 hrs following a meal).

In support of the NDA, the sponsor performed ten Phase 1 studies to assess the relative bioavailability, bioequivalence, food effect, drug-drug interactions, GI tolerability, and pharmacokinetics of azithromycin ER in adults and pediatrics. Four Phase 3 clinical studies were performed to evaluate the safety and efficacy of azithromycin ER for the treatment of [redacted] ABS (Study A0661078), and CAP (Studies A0661075 and A0661103). The most commonly observed adverse events in clinical studies were usually related to the gastrointestinal tract and consisted of diarrhea/loose stools, nausea, abdominal pain, headache, and vomiting. The selection of the dosage regimen is based on PK/PD relationships identified from animal models of infection that suggest a relationship between azithromycin efficacy and the ratio of the area under the serum concentration-time curve to the minimal inhibitory concentration (AUC/MIC) as well as observations that higher initial concentrations of the drug at the infection site may help prevent selection of less susceptible sub-populations of the pathogen(s).

The sponsor has not evaluated the impact of age, gender, renal impairment, and hepatic impairment on the pharmacokinetics of azithromycin following administration of azithromycin ER. However, the impact of age, gender, and renal impairment on the pharmacokinetics of azithromycin has been evaluated following the administration of azithromycin immediate release capsules and tablets. The sponsor has not evaluated the impact of hepatic impairment with any formulation of azithromycin. No dosage adjustments are recommended following the administration of other azithromycin dosage forms based on age, gender, and $CL_{CR}$ >10 mL/min. No dosage adjustment with azithromycin ER is recommended based on age, gender, and $CL_{CR}$ >10 mL/min.

Since the proposed regimen is a single dose, the impact of vomiting and the necessity for a second dose or an alternate therapy if vomiting occurs are potential concerns. In the Phase 3 clinical trials, the study protocols stated that any patient who vomited within 5 min of dosing would receive a second 2 g dose of azithromycin ER and remain in the clinic for an additional 2 hrs after re-dosing for collection of a blood sample. If a patient vomited any time after 5 min, a second dose would not be administered and a blood sample obtained if the patient vomited between 5 and 30 min following administration. Overall, no patients vomited within 30 min after dosing in the four Phase 3 clinical trials and no blood samples were obtained to assess the impact of vomiting on the absorption of azithromycin ER. However, the sponsor recommends administration of a second dose of azithromycin ER if a patient vomits within 5 min and offers no recommendation if vomiting occurs after 5 min.

Thirty-three subjects vomited after receiving azithromycin ER in Phase 1 studies. Concentration-time data collected from 12 of the 33 subjects that vomited support that a second dose of azithromycin ER is not necessary for adult patients that vomit ≥1 hr following dosing. Insufficient data are available to make a recommendation of re-dosing for adult patients that vomit between 5 min and 1 hr after dosing.

## 1.1 RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation III (OCPB/DPE-III) has reviewed NDA 50-797 and it is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

The proposed labeling comments in Section 4.1 should be communicated to the sponsor as appropriate.

## 1.2 PHASE IV COMMITMENTS:

No Phase IV commitments are recommended.

## 1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

**Single dose pharmacokinetics:**

Following the administration of a single 2 g dose of azithromycin ER and azithromycin commercial sachets (2 × 1 g sachets) to 16 healthy subjects, the mean $C_{max}$ and $AUC_{0-t}$ were 0.85 µg/mL and 16.8 µg*hr/mL, respectively for azithromycin ER and 2.10 µg/mL and 19.5 µg*hr/mL, respectively for azithromycin sachets. The mean $T_{max}$ was 4.13 hrs for azithromycin ER and 1.56 hrs for azithromycin sachets. Following the administration of 2 g azithromycin ER, the mean $C_{max}$ and $AUC_{0-t}$ were 60% and 14% lower, respectively compared to administration of 2 g azithromycin immediate-release sachets.

**Bioequivalence:**

The sponsor performed a two-way crossover study to demonstrate bioequivalence between the to-be-marketed product (primary ICH stability supplies) and the Phase 3 study supplies (supportive stability supplies). The main difference between these two batches was the annealing time necessary to recrystallize any azithromycin that dissolved in the matrix during extrusion of microspheres (10 days for the to-be-marketed formulation vs. 21 days for the Phase 3 supplies) and not a change in formulation. The geometric mean ratios and 90% confidence intervals were 0.99 (0.90 - 1.08) for $AUC_{0-72}$ and 0.97 (0.90 - 1.05) for $C_{max}$ and demonstrated bioequivalence between the to-be-marked product and Phase 3 study supplies.

**Effect of food:**

Following the administration of azithromycin ER with a standard high-fat breakfast (150 kcal from protein, 250 kcal from carbohydrate, and 500-600 kcal from fat), the mean $C_{max}$ increased by 111% and the mean $AUC_{0-t}$ increased by 23%. The mean $T_{max}$ was reduced from 4.93 hrs to 2.67 hrs. Administration of azithromycin ER following a standard meal consisting of 1 blueberry muffin, 3/4 cup cereal, 2 tsp of margarine, 6 ounces of orange juice, and 1 cup of 2% milk (56 kcal from proteins, 316 kcal from carbohydrates and 207 kcal from fats) altered the pharmacokinetics similar to a high-fat meal. The mean $C_{max}$ increased 120% and the mean $AUC_{0-24}$ and $AUC_{0-72}$ increased 19% and 11%, respectively following administration of a standard meal. The mean $T_{max}$ decreased from 4.67 hrs to 2.83 hrs. Azithromycin ER should be administered on an empty stomach (at least 1 hr before or 2 hrs following a meal).

**Drug-Drug interactions:**

The sponsor assessed the impact of co-administration of 2 g azithromycin ER and 20 mL of Regular Strength Maalox® (magnesium and aluminum hydroxide) on the pharmacokinetics of azithromycin. When azithromycin ER was administered with Maalox®, the mean $AUC_{0-24}$ increased 7%, the mean $AUC_{0-t}$ increased 10%, and the mean $C_{max}$ was not altered. The mean $T_{max}$ increased from 4.67 hrs to 5.33 hrs. The geometric mean ratios and 90% confidence intervals were 1.078 (0.996 - 1.168) for $AUC_{0-t}$ and 1.013 (0.947 - 1.084) for $C_{max}$ and were within the 0.80 to 1.25 no effect boundaries. Azithromycin ER may be administered without regard to concomitant administration of magnesium and aluminum hydroxide products such as Maalox®.

**Dissolution:**
The proposed *in vitro* dissolution method and specification are USP Apparatus 2 (paddle) at 50 rpm, 900 mL phosphate buffer pH 6.0 at 37°C. The proposed specification is [redacted] of label claim at 30 min and NLT [redacted] of label claim at 180 min. The sponsor claims that a two-point specification is adequate for the dissolution testing of azithromycin ER because the dissolution of azithromycin from the microspheres in the drug product exceeds [redacted] within three hrs.

Based on data from primary and supportive stability batches, the mean percentage of azithromycin dissolved at 30 min ranged from [redacted] at time zero and [redacted] after 12 months at 30°C/60-65% RH. The reviewer proposes narrowing the dissolution specification at 30 min from [redacted] The mean percentage of azithromycin dissolved at 180 min ranged from [redacted] at time zero and [redacted] after 12 months at 30°C/60-65% RH. The reviewer also proposes narrowing the dissolution specification at 180 min from [redacted] dissolved to [redacted] dissolved. None of the individual units from the seven batches at time zero and six batches at 12 months were outside of the proposed specification ranges.

Charles R. Bonapace, Pharm.D.
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Venkat R. Jarugula, Ph.D.,
Team Leader

cc:
Division File: NDA 50-797
HFD-520 (CSO/Milstein)
HFD-520 (MO/Alexander, Cooper, Moledina, Imoisili)
HFD-880 (Division File, Lazor, Selen, Jarugula, Bonapace)
CDR (Clin. Pharm./Biopharm.)

## 2. QUESTION-BASED REVIEW

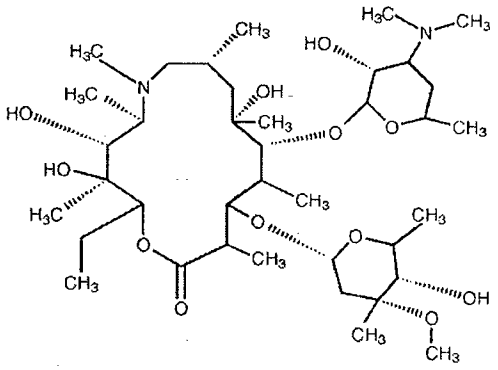
### 2.1 General attributes of the drug

**What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?**

Azithromycin was originally approved in November of 1991 and is currently available in immediate-release formulations administered orally by tablet (250 mg, 500 mg, and 600 mg), sachet (1 gram), powder for oral suspension (100 mg/5 mL and 200 mg/5 mL), and in an intravenous formulation (500 mg/vial). The recommended duration of treatment for respiratory tract infections in adults (acute bacterial sinusitis, community-acquired pneumonia, acute bacterial exacerbations of chronic obstructive pulmonary disease, and pharyngitis/tonsillitis) ranges from 3-5 days, but all of the regimens deliver the same total cumulative dose (1500 mg). The recommended duration of treatment for respiratory tract infections in pediatrics (acute otitis media, acute bacterial sinusitis, community-acquired pneumonia, and pharyngitis/tonsillitis) ranges from 1-5 days and delivers a cumulative dose of 30 mg/kg for all indications except for pharyngitis/tonsillitis (60 mg/kg).

**2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?**

Azithromycin is the first of a subclass of macrolide antibiotics designated chemically as azalides. A derivative of erythromycin, azithromycin differs chemically from this compound by virtue of a methyl-substituted nitrogen atom in the lactone ring. Azithromycin possesses amphiphilic cationic properties that distinguish its activity from erythromycin, facilitate penetration into phagocytic cells, and impart increased stability in gastric acid. The amphiphilic cationic properties of azithromycin permit penetration into macrophages, fibroblasts, and polymorphonuclear cells (neutrophils) such that intracellular azithromycin concentrations exceed serum or plasma azithromycin concentrations by up to several hundred-fold and intracellular concentrations remain greater than serum concentrations for prolonged periods of time. It is hypothesized that azithromycin concentrations are increased at the site of infection due to the migration of white blood cells by chemotaxis and release of drug into the interstitial space.



Azithromycin extended-release powder for oral suspension (azithromycin ER) is provided as a single-dose oral powder for suspension. The formulation is composed of azithromycin dihydrate microspheres, vehicle blend, and sucrose. Please refer to section 2.5 General Biopharmaceutics for specifics on the drug product.

The most common adverse events associated with azithromycin are gastrointestinal (e.g., diarrhea, nausea, abdominal pain, vomiting) and it is believed that such adverse events are of local origin. It is thought that macrolides (including azithromycin) interact with the motilin receptors present on the smooth muscle cells and nerve endings in the upper gastrointestinal tract. The azithromycin ER drug product is formulated to release azithromycin at a slower rate and lower in the gastrointestinal tract than immediate-release azithromycin formulations. This allows a higher single-dose of azithromycin ER to be administered while achieving similar gastrointestinal tolerability compared with a lower dose of immediate-release azithromycin formulations.

**2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?**

[redacted]

The proposed therapeutic indications of azithromycin ER are [redacted], acute bacterial sinusitis (ABS) due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*, and community-acquired pneumonia (CAP) due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, [redacted] *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*.

**2.1.3 What are the proposed dosage(s) and route(s) of administration?**

The proposed dosage of azithromycin ER for adults is 2 g administered as a single dose for the treatment of acute bacterial sinusitis, community-acquired pneumonia [redacted] via oral administration. For adults, 60 mL of water is added to the bottle of azithromycin ER to form a suspension. The entire bottle of suspension is administered orally as a single dose.

**2.2 General Clinical Pharmacology**

**2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?**

The sponsor performed 10 Phase 1 studies to assess the relative bioavailability, bioequivalence, effect of food, effect of co-administration with aluminum and magnesium hydroxide, GI tolerability, and pharmacokinetics in pediatrics. Four additional Phase 1 studies were performed to assess the impact of a p-glycoprotein inhibitor (vitamin E, poloxamer 407, and poloxamer 124) on the bioavailability of an experimental formulation of azithromycin ER and were not reviewed.

The sponsor performed four Phase 3 clinical studies evaluating the safety and efficacy of azithromycin ER for the treatment of [redacted] ABS (Study A0661078), and CAP (Studies A0661075 and A0661103).

[redacted]

**A0661078:** This study was a randomized, double-blind, double-dummy, active-controlled, multicenter trial in which patients were randomized to receive a single dose of azithromycin ER 2 g (n=271) or levofloxacin 500 mg (2 × 250 mg tablets) QD for 10 days (n=270) for the treatment of ABS in adults. Clinical efficacy was assessed at the TOC visit 17-24 days after the first dose of study drug.

**A0661075:** This study was a randomized, double-blind, double-dummy, active-controlled, multicenter trial in which patients were randomized to receive a single dose of azithromycin ER 2 g (n=247) or clarithromycin extended-release 1000 mg (2 × 500 mg tablets) QD for 7 days (n=254) for the treatment of CAP in adults. Clinical efficacy was assessed at the TOC visit 14-21 days after the first dose of study drug.

**A0661103:** This study was a randomized, double-blind, double-dummy, active-controlled, multicenter trial in which patients were randomized to receive a single dose of azithromycin ER 2 g (n=213) or levofloxacin 500 mg (2 × 250 mg tablets) QD for 7 days (n=214) for the treatment of CAP in adults. Clinical efficacy was assessed at the TOC visit 14-21 days after the first dose of study drug.

**2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?**

The primary efficacy assessment in the Phase 3 studies was the clinical response for the Clinical Per Protocol population at the test of cure (TOC) visit. The secondary efficacy assessment was the bacteriological eradication rate per pathogen in the Bacteriologic Per protocol population at the TOC visit.

[redacted]

ABS

Clinical response was defined as cure (signs and symptoms related to the acute infection had resolved, or clinical improvement was such that no additional antibiotics were deemed necessary) or failure. Failure was defined as one or more of the following: 1) Signs and symptoms related to the acute infection persisted or worsened and additional antibiotics were necessary; and 2) new clinical signs and/or symptoms of acute infection appeared and additional antibiotics were necessary.

CAP

The primary efficacy endpoint was the assessment of clinical response at the test of cure (TOC) visit. Clinical response was defined as cure (signs and symptoms related to the acute infection had resolved, or clinical improvement was such that no additional antibiotics were deemed necessary AND the chest X-ray

performed at the TOC visit had either improved or did not progress) or failure. Failure was defined as one or more of the following: 1) Signs and symptoms related to the acute infection persisted or worsened and additional antibiotics were necessary; 2) new clinical signs and/or symptoms of acute infection appeared and additional antibiotics were necessary; 3) radiological evidence of pneumonia progression during treatment; and 4) death due to pneumonia.

**2.2.3 Are the active moieties in plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

Azithromycin, the active moiety following the administration of azithromycin dihydrate, was appropriately determined in plasma and urine using high performance liquid chromatography with [redacted] (LC[redacted]). Please refer to section 2.6 Analytical Section for further information.

**2.2.4 Exposure-response**

**2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to onset and offset of the desirable pharmacological response or clinical endpoint.**

The antimicrobial activity of azithromycin appears to correlate best with the ratio of area under the concentration-time curve to minimum inhibitory concentration (AUC/MIC) for certain pathogens (*S. pneumoniae* and *S. aureus*). Studies comparing azithromycin with other macrolides using a neutropenic mouse thigh infection model demonstrated that the dose required to produce a net bacteriostatic effect of azithromycin was independent of the dosing interval used within a 24-hr period (6, 12, and 24 hrs). Prolonged in vivo postantibiotic effects (determined in the mouse model) likely account for the minimal impact of the dosing interval on the in vivo efficacy. For the respiratory pathogen *S. pneumoniae*, a direct correlation was demonstrated between azithromycin efficacy and the AUC/MIC ratio. Within a 100-fold range of AUC/MIC ratios tested (10 to 1,000), the greatest efficacy was observed at the highest AUC/MIC ratio tested. In addition, the concentration of azithromycin inside white blood cells contribute to the efficacy of this drug. Using the mouse thigh infection model with immunocompetent and neutropenic mice, the static dose required to produce a net bacteriostatic effect (no net growth or killing) over 24 hrs was 3.4-fold to 3.6-fold greater in neutropenic mice than immunocompetent mice.

There is evidence that the maximum plasma concentration to MIC ratio ($C_{max}$/MIC) may also be important. Data from gerbil otitis media studies were used in a preclinical PK/PD model to further discriminate between the single dose and multiple dose regimens of azithromycin. This mechanism-based mathematical model described the relationship between exposure to azithromycin and the time course of bacterial killing. The model used two *H. influenzae* strains (MICs of 0.5 and 2 μg/mL) and a first-order rate constant of bacterial death (Kd) based on changes in $\log_{10}$ CFU over time. Results for the single dose regimen showed that bacterial burden fell below the limit of detection by approximately 10 hrs and Kd increased four-fold for about 16 hours, rapidly reaching the maximum Kd. In contrast, when the same total dose was given over 3 days, bacterial burden fell below the limit of detection at approximately 30 hrs and Kd was maximized for only 5 hrs of a 24-hr dosing interval. The front-loaded exposure from the single dose regimen occurred early in the treatment and caused a faster reduction in bacterial burden. It is anticipated that front-loading may optimize the probability of a successful clinical outcome.

**2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to onset and offset of the desirable pharmacological response or clinical endpoint.**

The sponsor has not assessed the characteristics of the exposure-response relationships for safety. However, it appears that the gastrointestinal adverse events are likely the result of azithromycin interacting with the motilin receptors at a local level and not related to systemic concentrations. Exploratory gastrointestinal intubation studies in healthy adult subjects demonstrated that dosing 2 g of azithromycin directly to the ileocecal region of the gastrointestinal tract results in comparable systemic exposure but a lower incidence of gastrointestinal adverse events than when the same amount of drug is dosed directly to the duodenum. This is supported by the observation that subjects receiving 500 mg/day of intravenous azithromycin do not have a higher rate of gastrointestinal-related adverse events than is seen with oral administration despite greater serum concentrations (mean $C_{max}$ values 3.63 µg/mL following administration of 500 mg IV to CAP patients vs. 0.41 µg/mL following administration of 500 mg [2 × 250 mg tablets] to healthy subjects).

**2.2.4.3 Does this drug prolong the QT or QTc interval?**

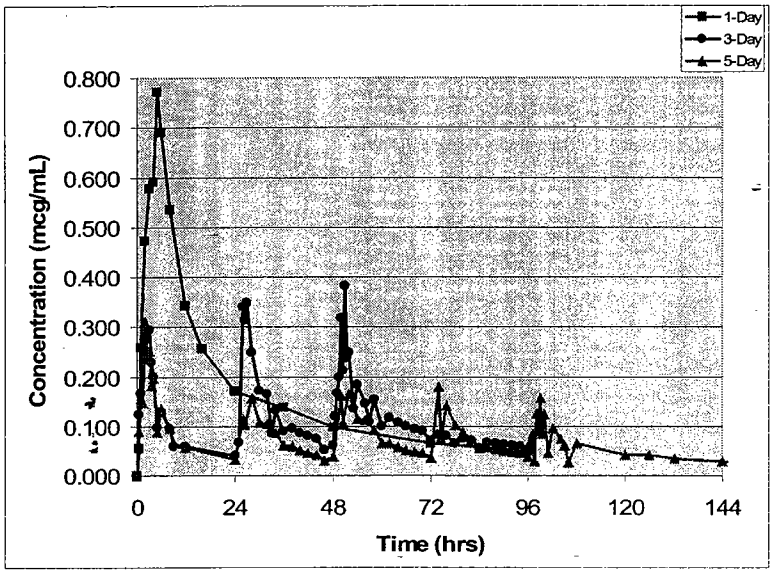
The sponsor did not assess the potential of azithromycin to prolong the QT or QTc interval. However, azithromycin has been on the market in the U.S. since 1991 and other currently available formulations result in plasma concentrations that exceed those anticipated following administration of 2 g of azithromycin ER.

**2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?**

The dose and dosing regimen selected by the sponsor is consistent with the known relationship between dose-concentration-response. The approved dosage regimens of azithromycin immediate-release tablets (250 mg and 500 mg tablets) for the treatment of respiratory tract infections ([redacted]ABS, and CAP) deliver a cumulative dose of 1500 mg of azithromycin over 3 to 5 days. The relative bioavailability of azithromycin ER compared to azithromycin immediate-release tablets has not been evaluated. However, four azithromycin 250 mg tablets are bioequivalent to 1 g azithromycin immediate-release sachet. The relative bioavailability of azithromycin ER compared to azithromycin immediate-release sachet is 85.8%. Thus, the relative bioavailability of azithromycin ER compared to immediate-release tablets is likely to be similar. The known PK/PD data for azithromycin support administration of a single 2 g dose of azithromycin ER (refer to Section 2.2.4.1).

A comparison of the mean serum concentration-time profiles of azithromycin when administered as a single dose of azithromycin ER 2 g compared to the 3-day regimen of azithromycin 500 mg immediate-release tablets (500 mg/day × 3 days) and the 5-day regimen of azithromycin 250 mg immediate-release tablets (2 × 250 mg on day 1, then 250 mg/day × 4 days) is shown in Figure 1.

**Figure 1. Mean serum azithromycin concentration-time profiles following administration of 2 g azithromycin ER (1-day) vs. azithromycin 500 mg/day × 3 days (3-day) and azithromycin 500 mg on day 1, then 250 mg/day × 4 days (5-day)**




The front-loading of azithromycin is apparent from the concentration-time profiles following administration of 2 g azithromycin ER compared to administration of a similar total cumulative dose of azithromycin administered over 3 days (azithromycin 500 mg tablets) and 5 days (azithromycin 250 mg tablets). Assuming a relative bioavailability of 85.8% for azithromycin ER compared to immediate-release tablets, the relative dose of azithromycin is approximately 1700 mg from azithromycin ER and 1500 mg from azithromycin immediate-release tablets (3-day and 5-day regimens).

NOTE: The data from the 3-day and 5-day regimens were obtained from studies 066-087, AZM-NY-90-011, AZM-F-93-004, GA2000 submitted with NDA 50-710 (SE2-009, 2/16/01).

An unresolved dosing or administration issue is the necessity of re-dosing in patients who vomit after administration of azithromycin ER. With single dose therapy, a potential concern is whether patients who vomit immediately following administration received an adequate dose to treat their infections. In all of the Phase 3 studies, no patient vomited within 30 min of dosing. Because re-dosing was to occur only if vomiting occurred within 5 min of dosing, and because serum azithromycin concentrations were to be obtained from patients only if vomiting occurred within 30 min of dosing, no adult patients were re-dosed and no adult patients had serum concentrations obtained.

In the Phase 1 studies, 33 subjects vomited after receiving azithromycin ER (Table 1). Individual concentration data were available from 12 of the 33 subjects. Based on the data from Studies A0661084 and A0661114, the individual AUC values from subjects who vomited ≥1 hr following administration of azithromycin ER commonly exceeded the mean AUC value reported in the study and was associated with the lowest AUC value only once among subjects who received azithromycin ER (see Figure 2). The individual and mean AUC values from subjects who received azithromycin immediate release sachets in Study A0661084 are also shown. Insufficient data are available to make a recommendation of re-dosing

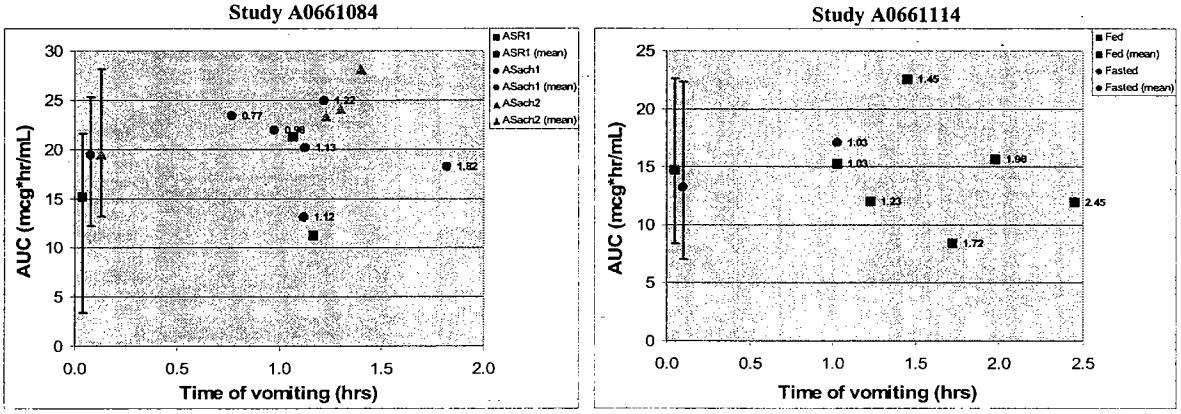
for adult patients that vomit between 5 min and 1 hr after dosing. Based upon the data available, no re-dosing of azithromycin ER is necessary for patients that vomit ≥1 hr following administration.

**Table 1. Subjects from Phase 1 studies that vomited after receiving azithromycin ER**

| Study | N (received azithromycin ER) | N (vomited) | Time of vomiting (range) | N (Conc data available) |
|---|---|---|---|---|
| A0661084 | 32 | 2[a] | 1.07-1.17 hrs | 2 |
| A0661124 | 41 | 2[b] | 0.88-1.03 hrs | 2 |
| A0661107 | 16 | 2[c] | 1.55-1.85 hrs | 2 |
| A0661114 | 88 | 7[d] | 1.03-2.53 hrs | 6 |
| A0661054 | 240 | 12[e] | 0.50-2.83 hrs | 0 |
| A0661086 | 212 | 8[f] | 0.03-11.52 hrs | 0 |

a-azithromycin ER w/o magnesium hydroxide in the fasted state
b-azithromycin ER Phase 3 study supplies in the fasted state
c-azithromycin ER in the fed state (n=1) and fed and fasted state (n=1)
d- azithromycin ER in the fed state (n=6) and fed and fasted state (n=1)
e-5 subjects received azithromycin ER 2 g and 7 subjects received azithromycin ER 3 g in the fasted state
f-4 subjects received azithromycin ER w/o magnesium hydroxide and 4 subjects received azithromycin ER with magnesium hydroxide

**Figure 2. Mean and individual azithromycin ER and sachet AUC values from Study A0661084 (left) and A0661114 (right) and the time at which vomiting occurred**




NOTE: The mean AUC value for each regimen is shown on the left and the error bar represents the range of AUC values. ASR1=azithromycin ER w/o magnesium hydroxide 2 g; ASach1=azithromycin sachet 2 g; ASach2=azithromycin sachet 2 g.

### 2.2.5 What are the PK characteristics of the drug and its major metabolite?

#### 2.2.5.1 What are the single dose and multiple dose PK parameters

The proposed dosage regimen of azithromycin ER is administration of a 2 g single dose. Since the sponsor does not propose multiple dose administration, the multiple dose pharmacokinetics of azithromycin ER have not been established.

The serum concentration-time profiles of azithromycin following administration of 2 g azithromycin ER (with and without magnesium hydroxide) and 2 g azithromycin immediate-release sachet (2 × 1 gram sachets) are shown in Figure 3. The mean (CV%) pharmacokinetic parameters are shown in Table 2.

**Figure 3. Mean serum azithromycin concentration-time profiles following administration of 2 g azithromycin ER with (ASR2) and without (ASR1) magnesium hydroxide or commercial sachets to healthy subjects (n=32)**

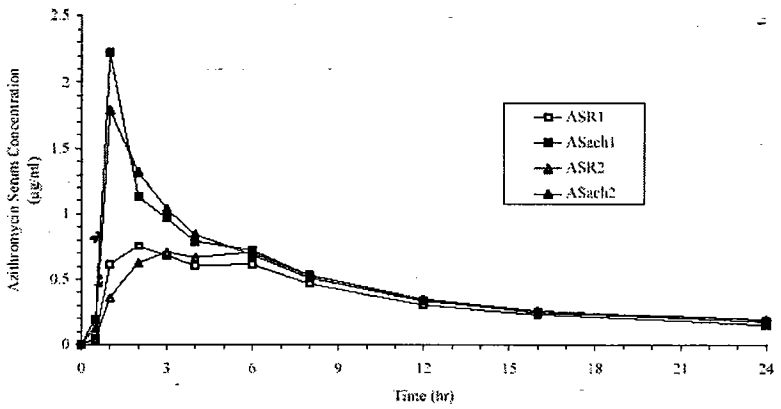



**Table 2. Mean (CV%) azithromycin pharmacokinetics following administration of azithromycin ER with and without $Mg(OH)_2$ and azithromycin commercial sachets**

| Parameter | Azithromycin ER without $Mg(OH)_2$ | Azithromycin ER with $Mg(OH)_2$ | Azithromycin Sachet (Asach1) | Azithromycin sachet (ASach2) |
|---|---|---|---|---|
| $AUC_{0-t}$ (µg*hr/mL) | 15.1 (35%) | 16.8 (40%) | 19.4 (22%) | 19.5 (24%) |
| $C_{max}$ (µg/mL) | 0.97 (36%) | 0.85 (26%) | 2.23 (36%) | 2.10 (49%) |
| $T_{max}$ (hrs) | 2.94 (59%) | 4.13 (50%) | 1.13 (30%) | 1.56 (47%) |
| F (%) | 77.4% | 85.8% | --- | --- |

NOTE: The relative bioavailability (F) of azithromycin ER without $Mg(OH)_2$ was compared to the azithromycin sachet (ASach1), whereas azithromycin ER with $Mg(OH)_2$ was compared to the azithromycin sachet (Asach2).

Administration of azithromycin ER with magnesium hydroxide increased the mean $AUC_{0-t}$ by 11.3% and is reflected in the greater relative bioavailability of azithromycin ER administered with magnesium hydroxide compared to azithromycin ER without magnesium hydroxide. In addition, administration of magnesium hydroxide decreased the mean $C_{max}$ by 13.1% and increased the mean $T_{max}$ by 40%. The gastrointestinal adverse events (nausea, vomiting, abdominal pain, and diarrhea) were lower among subjects who received azithromycin ER with magnesium hydroxide compared to those who received azithromycin ER without magnesium hydroxide. Thus, the sponsor made a decision to add magnesium hydroxide to the azithromycin ER formulation based on the pharmacokinetic and tolerability results from this study.

**2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?**

The pharmacokinetics of azithromycin ER have not been assessed in patients from Phase 2 or Phase 3 clinical trials. Based on the modest impact of renal impairment and age on the pharmacokinetics of

azithromycin, clinically relevant differences in the pharmacokinetics between healthy volunteers and patients are not anticipated.

**2.2.5.3 What are the characteristics of drug absorption?**

The rate and extent of the absorption of azithromycin following administration of azithromycin ER is dependent upon the presence of magnesium hydroxide in the formulation, concentration of poloxamer 407 in the formulation, and presence of food. The impact of magnesium hydroxide added to the formulation has been discussed in Section 2.2.5.1, Single Dose Pharmacokinetics. The effect of food on the bioavailability of azithromycin is discussed in Section 2.5.3 General Biopharmaceutics, Effect of Food.

Poloxamer 407, azithromycin from the microspheres in the drug product.

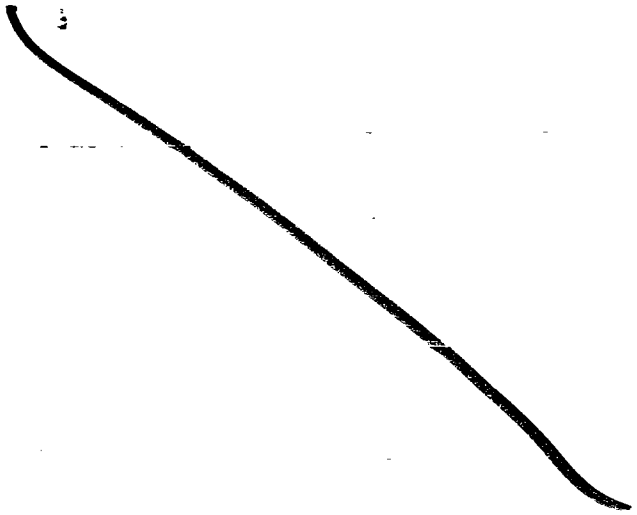


**Table 3. Mean (CV%) azithromycin pharmacokinetic parameters following administration of 2 g azithromycin ER with and without $Mg(OH)_2$ and 2 g azithromycin sachet under fasted conditions**

| | Study A0661090- [redacted] | | Study A0661084- [redacted] | |
|---|---|---|---|---|
| **Parameter** | **Azithromycin ER with $Mg(OH)_2$** | **Azithromycin sachet** | **Azithromycin ER with $Mg(OH)_2$** | **Azithromycin sachet** |
| $AUC_{0-48}$ (µg*hr/mL) | 14.0 (25%) | 15.7 (24%) | | |
| $AUC_{0-96}$ (µg*hr/mL) | | | 16.8 (40%) | 19.5 (24%) |
| $C_{max}$ (µg/mL) | 0.89 (26%) | 2.27 (42%) | 0.85 (26%) | 2.10 (49%) |
| $T_{max}$ (hrs) | 4.88 (38%) | 1.25 (46%) | 4.13 (50%) | 1.56 (47%) |
| F (%) | 89.1% | --- | 85.8% | --- |

Phase 1 clinical studies A0661054 (n=359) and A0661086 (n=320) evaluated the gastrointestinal tolerability of azithromycin ER formulations containing [redacted] All subjects received 2 g azithromycin ER. Serum samples were obtained at pre-dose, 2, and 3 hrs post-dose in Study A0661054 and pre-dose, 1, 2, 3, and 4 hrs in Study 0661086 (Table 4). The mean serum concentrations at 2 and 3 hrs were modestly greater in Study A0661054 [redacted]

**Table 4. Mean (SD) azithromycin serum concentrations following administration of 2 g azithromycin ER with [redacted]**

| Study # | Group | Serum concentration (µg/mL) | | | |
|---|---|---|---|---|---|
| | | 1 hr | 2 hrs | 3 hrs | 4 hrs |
| A0661054 | [redacted] | --- | 1.04 (0.38) | 0.93 (0.32) | --- |
| A0661086 | [redacted] | 0.59 (0.51) | 0.79 (0.19) | 0.79 (0.12) | 0.74 (0.17) |

The concentration of [redacted] in the Phase 3 clinical trial formulation and the to-be-marketed formulation is [redacted]

**2.2.5.4 What are the characteristics of drug distribution?**

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 µg/mL to 7% at 2 µg/mL. Azithromycin has an apparent steady-state volume of distribution of 31.1 L/kg.

**2.2.5.6 What are the characteristics of drug metabolism?**

*In vitro* studies to assess the metabolism of azithromycin have not been performed. However, azithromycin is known to be a weak inhibitor of cytochrome P450 isozymes based on the results of 17 clinical drug-drug interaction studies previously submitted and reviewed that assessed the interaction between azithromycin and various co-administered drugs (refer to Section 4.1 Proposed Label).

**2.2.5.7 What are the characteristics of drug excretion?**

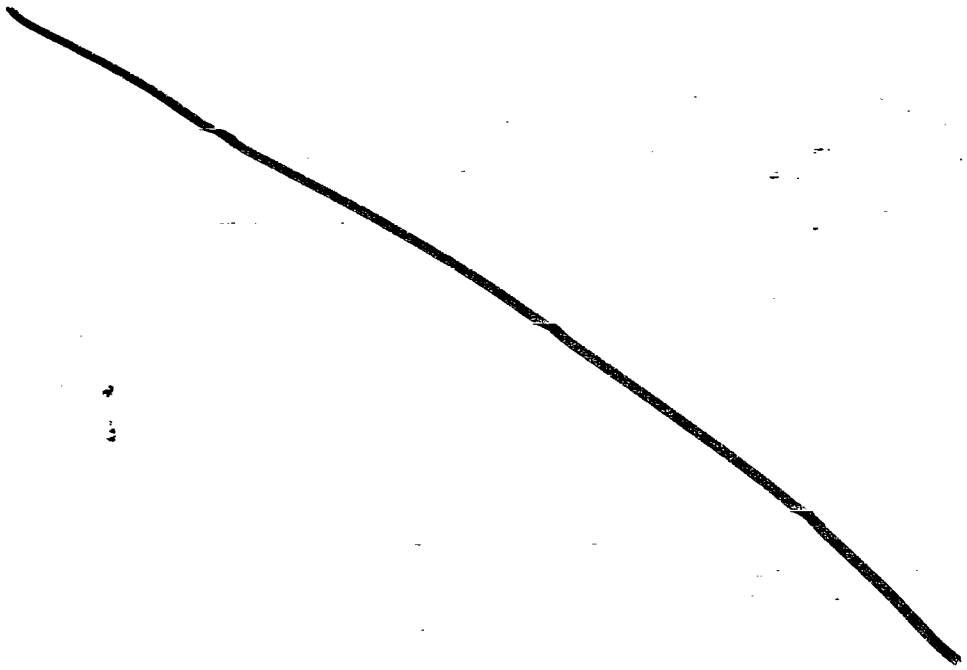
The major route of elimination of azithromycin is biliary excretion, predominantly as unchanged drug. Over the course of a week, approximately 6% of the administered dose is excreted as unchanged drug in urine.

**2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?**

The inter-subject variability in the azithromycin $C_{max}$ and $AUC_{0-t}$ is 26% and 40%, respectively in normal volunteers. The high degree of variability observed in the current NDA is consistent with previous estimates of azithromycin and may be related to the large apparent volume of distribution (31.1 L/kg) and the disposition pharmacokinetics of azithromycin (3-compartment model).

**2.3 Intrinsic factors**

**2.3.2.2 Pediatric patients. What is the status of pediatric studies and/or any pediatric plan for study?**

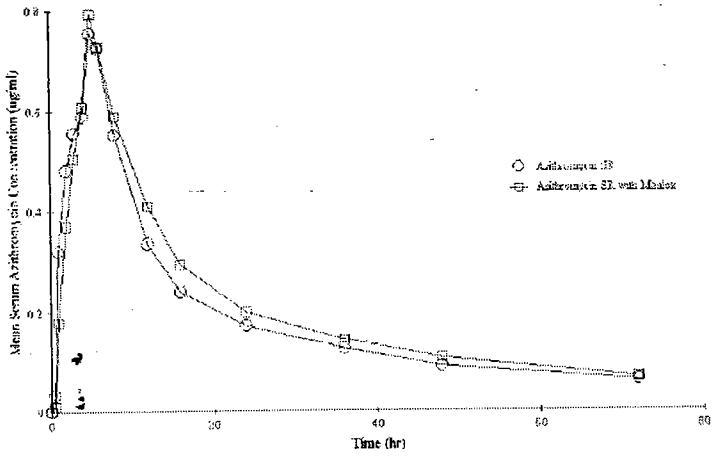


**2.4 Extrinsic Factors**

**2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?**

The sponsor assessed the impact of co-administration of 2 g azithromycin ER (containing 250 mg magnesium hydroxide) and 20 mL of Regular Strength Maalox® on the pharmacokinetics of azithromycin. The mean serum azithromycin concentration-time profiles following administration of 2 g azithromycin ER with and without 20 mL of Regular Strength Maalox® are shown in Figure 7. The mean serum concentration-time profiles of azithromycin were similar and co-administration with Maalox® did not appear to alter the rate and extent of absorption of azithromycin ER.

**Figure 7. Mean serum azithromycin concentration-time profiles following administration of 2 g azithromycin ER with and without concomitant administration of 20 mL Regular Strength Maalox®**




The mean azithromycin pharmacokinetic parameters following the administration of 2 g azithromycin ER with and without Regular Strength Maalox® are shown in Table 5. When azithromycin ER was administered with Maalox®, the mean $AUC_{0-24}$ increased 7%, the mean $AUC_{0-t}$ increased 10%, and the mean $C_{max}$ was not altered. The mean $T_{max}$ increased 14% from 4.67 hrs to 5.33 hrs.

**Table 5. Mean (CV%) azithromycin pharmacokinetic following administration azithromycin ER with and without 20 mL Regular Strength Maalox®**

| Parameter | Azithromycin ER alone | Azithromycin ER + Maalox | Point estimate | 90% CI |
|---|---|---|---|---|
| $AUC_{0-24}$ (µg*hr/mL) | 8.75 (28%) | 9.39 (34%) | 1.057 | 0.977 - 1.144 |
| $AUC_{0-t}$ (µg*hr/mL) | 13.53 (28%) | 14.93 (37%) | 1.078 | 0.996 - 1.168 |
| $C_{max}$ (µg/mL) | 0.85 (31%) | 0.85 (30%) | 1.013 | 0.947 - 1.084 |
| $T_{max}$ (hrs) | 4.67 (34%) | 5.33 (19S%) | --- | --- |

The 90% confidence intervals of the geometric mean ratio for $AUC_{0-24}$, $AUC_{0-t}$, and $C_{max}$ were within the predetermined no-effect boundary of 0.80 to 1.25. Co-administration of azithromycin ER and Regular Strength Maalox does not effect the pharmacokinetics of azithromycin.

### 2.5 General Biopharmaceutics

Azithromycin extended-release powder for oral suspension (Azithromycin ER) is provided as a single-dose oral powder for suspension. The formulation is composed of azithromycin dihydrate microspheres, vehicle blend, and sucrose. The composition of azithromycin ER is shown in Table 6.

**Table 6. Composition of azithromycin extended-release powder for oral suspension**
Dosage Strength [Label Claim (g/bottle)]

| Component | Grade | Function | Amount of composition (g/bottle) | %_(w/w) |
|---|---|---|---|---|
| | | | 4.193[a] | |
| Azithromycin Dihydrate | Pfizer | Drug substance | | |
| Glyceryl Behenate | NF | | | |
| Poloxamer 407 | NF | | | |
| Purified Water, USP | USP/Ph. Eur. | | | |
| Sucrose | NF | | | |
| Sodium Phosphate Tribasic Anhydrous | FCC | | | |
| Magnesium Hydroxide | USP | | | |
| Hydroxypropyl Cellulose | NF | | | |
| Xanthan Gum | NF | | | |
| Colloidal Silicon Dioxide | NF | | | |
| Titanium Dioxide | USP | | | |
| Artificial Cherry | Food | | | |
| Artificial Banana | Food | | | |
| Sucrose | NF | | | |
| **Total** | | | | |

a-Based on a theoretical potency for azithromycin in microspheres for Azithromycin ER. Fill weight will be adjusted based on the actual potency of the azithromycin drug substance.
b-The active ingredient based on a potency of for azithromycin in azithromycin dihydrate.

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**2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?**

The sponsor performed an open label, randomized, two-way crossover study to demonstrate bioequivalence between the to-be-marketed formulation (primary ICH stability supplies) and the Phase 3 formulation (supportive stability supplies). The main difference between these two batches was the [redacted] for the manufacturing of microspheres [redacted] : for the to-be-marketed formulation vs. [redacted] for the Phase 3 supplies) and not a change in formulation.

[redacted]

The mean serum azithromycin concentration-time profiles following administration of 2 g azithromycin ER (ICH supplies) and 2 g azithromycin ER (Phase 3 supplies) are shown in Figure 8. Azithromycin serum concentrations were similar from both regimens. The mean azithromycin pharmacokinetic parameters are shown in Table 7.

**Figure 8. Mean serum azithromycin concentration-time profiles following administration of 2 g azithromycin ER (ICH or Phase 3 supplies)**

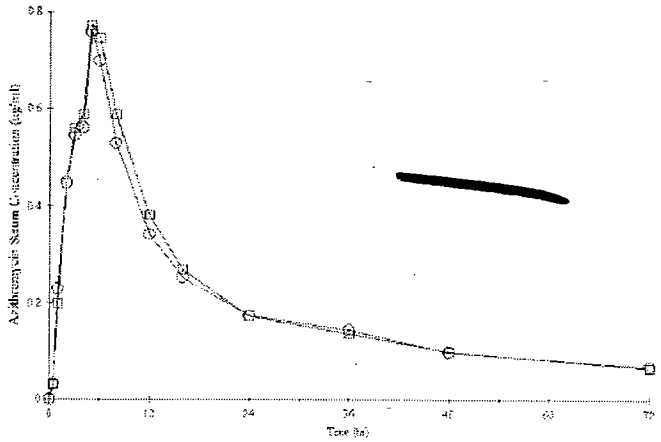


**Table 7. Mean (CV%) azithromycin pharmacokinetic following administration of 2 g azithromycin ER (ICH and Phase 3 supplies)**

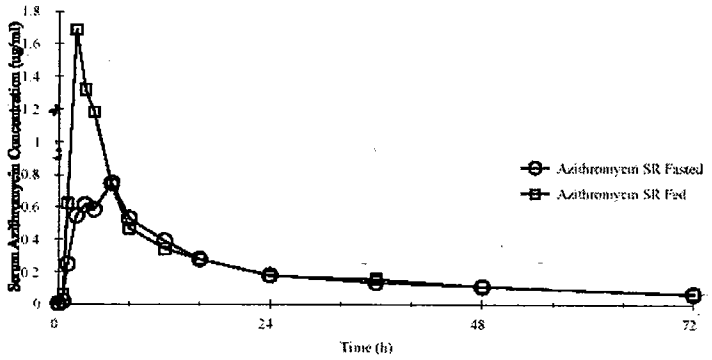
| Parameter | ICH supplies (n=41) | Phase 3 supplies (n=41) | Point estimate | 90% CI |
|---|---|---|---|---|
| $AUC_{0-72}$ (µg*hr/mL) | 13.9 (29%) | 14.3 (34%) | 0.989 | 0.904 - 1.082 |
| $AUC_{0-t}$ (µg*hr/mL) | 16.1 (35%) | 14.3 (34%) | --- | --- |
| $C_{max}$ (µg/mL) | 0.82 (34%) | 0.85 (33%) | 0.973 | 0.901 - 1.050 |
| $T_{max}$ (hrs) | 4.98 (26%) | 5.24 (22%) | --- | --- |
| [redacted] $t_{1/2}$ (hrs) | [redacted] | [redacted] | --- | --- |

The 90% confidence intervals of the geometric mean ratio for $AUC_{0-72}$ and $C_{max}$ were within the 0.80 to 1.25 boundary for establishing bioequivalence. The to-be-marketed formulation of azithromycin ER is bioequivalent to the formulation used in the Phase 3 studies.

**2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?**

Administration of azithromycin ER with a standard FDA high-fat breakfast (150 kcal from protein, 250 kcal from carbohydrate, and 500-600 kcal from fat) increased the mean $C_{max}$ by 111% and mean $AUC_{0-t}$ by 23%. The mean $T_{max}$ was reduced from 4.93 hrs to 2.67 hrs. The mean serum concentration-time profiles of azithromycin ER administered under fasted and following a high-fat meal are shown in Figure 9.

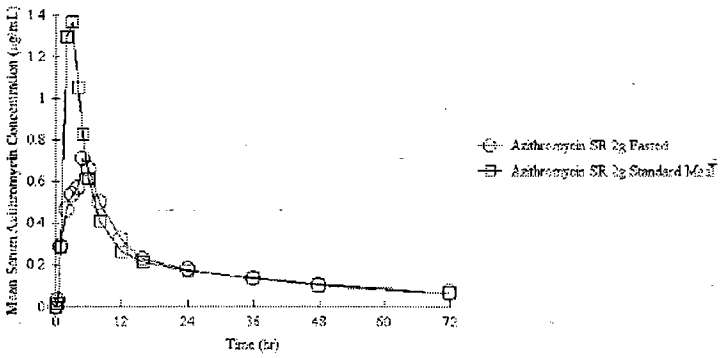
**Figure 9. Mean azithromycin concentration-time profiles following administration of 2 g azithromycin ER under fasting conditions and following a high-fat breakfast**




The mean $C_{max}$ observed with administration of 2 g azithromycin ER following a high-fat meal was only modestly lower than what was observed following the administration of 2 g azithromycin sachets in study A0661084 (1.82 µg/mL vs. 2.10 µg/mL, respectively) and occurred at a similar time (mean $T_{max}$ 2.0 vs. 1.6 hrs). Since previous studies have shown that patients receiving azithromycin immediate release sachets experience a high percentage of gastrointestinal adverse events and azithromycin plasma concentrations following administration of azithromycin ER with food are similar to concentrations following administration of azithromycin sachets, all Phase 3 protocols were amended to restrict azithromycin ER dosing to 1 hour before or 2 hours after a meal. Less than 10% (range 0% to 9.7%) of patients had been enrolled in a Phase 3 clinical trial before the amendment was instituted.

Administration of azithromycin ER following a standard meal consisting of 1 blueberry muffin, 3/4 cup cereal, 2 tsp of margarine, 6 ounces of orange juice, and 1 cup of 2% milk (56 kcal from proteins, 316 kcal from carbohydrates and 207 kcal from fats) altered the pharmacokinetics similar to a high-fat meal. The mean $C_{max}$ increased 120% and the mean $AUC_{0-24}$ and $AUC_{0-72}$ increased 19% and 11%, respectively. The mean $T_{max}$ decreased from 4.67 hrs to 2.83 hrs. The mean serum concentration-time profiles of azithromycin ER administered under fasted and following a standard meal are shown in Figure 10.

**Figure 10. Mean azithromycin concentration-time profiles following administration of 2 g azithromycin ER under fasting conditions and following a standard breakfast**




Based on the results of the two studies, food appears to have a greater effect on the rate than on the extent of azithromycin ER absorption. Since the exposure increased, the observed food effect is unlikely to have a negative impact on efficacy. The faster release of azithromycin observed when azithromycin ER was administered with food negates the improved gastrointestinal tolerability of the extended-release formulation. Thus, azithromycin ER should be taken on an empty stomach.

**2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?**

The proposed *in vitro* dissolution method and specification are USP Apparatus 2 (paddle) at 50 rpm, 900 mL phosphate buffer pH 6.0 at 37°C. The proposed specification is [redacted] of label claim at 30 min and NLT [redacted] of label claim at 180 min.

The sponsor claims that a two-point specification is adequate for the dissolution testing of azithromycin ER because the dissolution of azithromycin from microspheres in the drug product exceeds [redacted] within three hrs. Azithromycin ER behaves more like a modified immediate-release dosage form than a extended-release dosage form. The acceptance limits at the 30-min time point ensures dose dumping does not occur and the intended release profile is achieved, while the limit at the 180-min time point ensures that most of the labeled drug content is released within three hours. The acceptance criteria of [redacted] azithromycin dissolved at 30 min [redacted] the acceptable bioavailability of azithromycin and the improved gastrointestinal toleration, respectively, for the drug product. The relationship between the in vivo $AUC_{0-4}$ and the *in vitro* percentage released at 30 min is shown in Figure 11.

[redacted]

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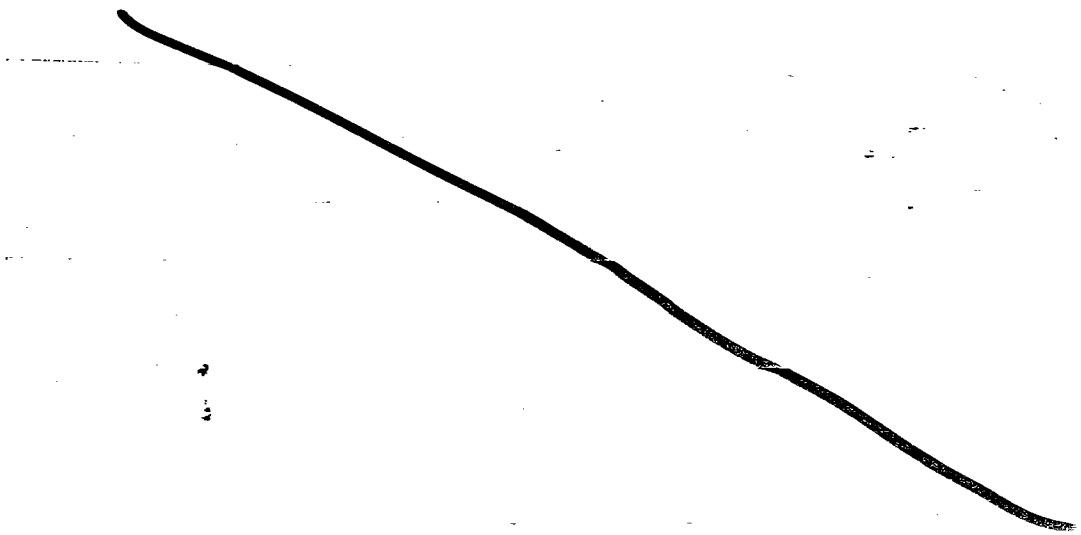

in vivo performance of the formulations are anticipated.

## 2.6 ANALYTICAL SECTION

**2.6.1 How are the active moieties identified and measured in plasma in the clinical pharmacology and biopharmaceutics studies?**

The sponsor used a reverse phase high performance liquid chromatography with [redacted] (LC/[redacted] to quantitate azithromycin concentrations from serum in all Phase 1 studies except Study A0661113 (pediatric patients). [redacted]

**2.6.2 Which metabolites have been selected for analysis and why?**

No metabolites of azithromycin have been selected for analysis. Since metabolites of azithromycin have not been identified, it is appropriate to assess only the parent compound.

**2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?**

The reported concentrations of azithromycin in serum represent total concentrations. The protein binding of azithromycin in serum is non-linear and ranges from 51% at 0.02 µg/mL to 7% at 2 µg/mL.

**2.6.4 What bioanalytical methods are used to assess concentrations?**

See the response for 2.6.1 stated above.

**2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?**

The azithromycin standard curve in serum ranged from [redacted] with LC, [redacted] and [redacted] with LC/MS/MS. Following the administration of 2 g azithromycin ER, the mean $C_{max}$ of azithromycin is usually ≤1 µg/mL in adults. However, following a standard or high-fat meal, the mean $C_{max}$ of azithromycin approached 2 µg/mL. Thus, serum concentrations that exceeded the range of the standard curve were diluted into the validated range with blank serum.

**2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?**

The lower and upper limits of quantification were [redacted] with LC [redacted] and [redacted] with LC/MS/MS.

**2.6.4.3 What is the accuracy, precision, and selectivity at these limits?**

The accuracy of azithromycin was 100 ± 15% and the precision was within -15% to +15%. Selectivity for azithromycin was based on the absence of peaks in serum not containing drug.

**2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?**

The stability of azithromycin in plasma was assessed in extracted samples (0.05, 0.2, and 0.5 µg/mL) at room temperature for 120 hrs, after 3 freeze/thaw cycles, in serum at room temperature for 144 hrs, and for long-term stability at -60°C for up to 4.5 yrs. The results of the sample stability assessment were acceptable.

**2.6.4.5 What is the QC sample plan?**

The sponsor's quality control sample plan consisted of four QC samples at [redacted] for serum.

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## 3. DETAILED LABELING RECOMMENDATIONS

See Section 4.1. Proposed Package Insert



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### 4.2 Clinical Pharmacology and Biopharmaceutics Individual Study Reviews

Since different formulations of azithromycin ER were used in the Phase 1 clinical studies, a comparison of the differences in the formulation is shown in Table 11. Components are only listed if their composition varied between studies. For a complete listing of azithromycin ER components, refer to Section 2.5. General Biopharmaceutics.

**Table 11. Composition of formulations used in Phase 1 and Phase 3 clinical studies (g/dose)**

| Component | | | | | |
|---|---|---|---|---|---|
| Phase | Phase 1 | Phase 1 | Phase 1 | Phase 1 | Phase 1 and 3 |
| Microspheres formulation identification and batch No. | G02295AA<br>ED-O-432-Z00 | G02295AA<br>ED-O-432-Z00 | G02474AA<br>ED-G-346-801 | G02394AA<br>ED-G-409-X01 | G02660AA<br>T0582G and<br>T0213G |
| Studies | A0661058 | A0661054 | A0661084<br>A0661086 | A0661090 | A0661107<br>A0661124<br>A0661113<br>A0661114<br>A0661115<br>Phase 3 studies |
| Azithromycin dihydrate | | | | | |
| Glyceryl behenate | | | | | |
| Poloxamer 407 | | | | | |
| Sucrose | | | | | |
| Magnesium hydroxide | | | | | |
| Colloidal silicon dioxide | | | | | |
| Magnesium hydroxide | | | | | |
| **Total** | | | | | |

**4.2.1 An open-label, randomized, crossover pilot study evaluating the pharmacokinetics and tolerability of a single 2 gram dose of a [redacted]-release formulation of azithromycin with and without magnesium hydroxide compared to a single 2 gram dose of the commercial formulation under fasted conditions in healthy adult volunteers (Study A0661084)**

Dates: November 12, 2001 to December 19, 2001
Clinical site: [redacted]
Analytical site: [redacted]

**OBJECTIVES:**
The primary objective of this study was to evaluate the pharmacokinetic profile of a single 2 g oral dose of azithromycin [redacted] with and without magnesium hydroxide compared to the commercially available sachets, each under fasted conditions in healthy adult volunteers.

A secondary objective of this study was to evaluate the tolerability of a single 2 g oral dose of azithromycin [redacted] with and without magnesium hydroxide compared to a single 2 gram dose of the commercially available sachets, each under fasted conditions in healthy adult volunteers.

**FORMULATIONS:**
Azithromycin powder for oral suspension (Sachet), 1 g (Pfizer, Lot No. 1HP033A-G1)
Azithromycin microspheres [redacted] poloxamer 407, 2 g (Pfizer, Lot No. ED-G-377-901, FID No. G02493AA)
Magnesium hydroxide powder, 250 mg (Pfizer, Lot No. ED-G-376-901, FID No. G02435AA)

**STUDY DESIGN:**
This study was a randomized, open-label, two-way crossover design, single-dose study of azithromycin in fasted healthy adult subjects. Thirty-two subjects 18 to 55 yrs of age were sequentially allocated to two cohort groups of 16 subjects each (as shown in the table below). On day 1, half of the subjects in group 1 were randomly assigned to receive ASR1 (azithromycin [redacted] formulation without magnesium hydroxide) and the other half received ASach1 (azithromycin sachet formulation for group 1), while in group 2, half of the subjects were randomly assigned to receive ASR2 (azithromycin [redacted] formulation with magnesium hydroxide) and the other half received ASach2 (azithromycin sachet formulation for group 2). On day 15, subjects in each group were crossed over to receive the formulation not received on day 1.

| Day | Group 1 (N=16) | | | Group 2 (N=16) | |
|---|---|---|---|---|---|
| 1 | ASR1[a] under fasted conditions (N=8) | ASach1[c] under fasted conditions (N=8) | | ASR2[b] under fasted conditions (N=8) | ASach2[d] under fasted conditions (N=8) |
| 2-14 | Washout Treatment-Free | Washout Treatment-Free | | Washout Treatment-Free | Washout Treatment-Free |
| 15 | ASach1 under fasted conditions (N=8) | ASR1 under fasted conditions (N=8) | | ASach2 under fasted conditions (N=8) | ASR2 under fasted conditions (N=8) |

ASR1 = Azithromycin [redacted] 2 g without magnesium hydroxide
ASR2 = Azithromycin [redacted] 2 g with magnesium hydroxide
ASach 1 = Azithromycin sachets 2 g administered to Group 1
ASach 2 = Azithromycin sachets 2 g administered to Group 2

In order to standardize conditions, all subjects were required to refrain from lying down, eating and drinking beverages other than water during the first 4 hours after dosing. Azithromycin formulations (azithromycin [redacted] and azithromycin sachets) were reconstituted such that the total volume of each formulation to be ingested was 240 mL. Subjects were dosed between 0700 and 0833 hrs following an 8-hr fast. There was at least a 14-day washout period between the two dosing days.

Blood samples for determination of serum azithromycin concentrations were obtained at the following times relative to each of days 1 and days 15: 0 (predose), 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hrs after administration.

**AZITHROMYCIN ASSAY METHODOLOGY:**
High performance liquid chromatography [redacted] (LC/ [redacted]

| Criterion | Serum | Comments |
|---|---|---|
| Concentration range | [redacted] | Satisfactory |
| LLOQ | | Satisfactory |
| Linearity | | Satisfactory |
| Accuracy | | Satisfactory |
| Precision | | Satisfactory |
| Specificity | | Satisfactory |
| Stability | | Satisfactory |

RT = room temperature

**PHARMACOKINETIC ANALYSIS:**
Maximum observed serum concentrations ($C_{max}$) of azithromycin were estimated directly from the experimental data. $T_{max}$ was defined as the time of the first occurrence of $C_{max}$. The area under the plasma concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration ($AUC_{0-t}$) was estimated using the linear-trapezoidal rule. The half-life ($t_{1/2}$) and AUC extrapolated to infinity ($AUC_{0-\infty}$) could not be estimated due to the long half-life of azithromycin and the limited sampling in this study. Because the majority of the dose is eliminated during the 96-hr collection interval and because no differences were anticipated in clearance between azithromycin SR w/o magnesium hydroxide, azithromycin [redacted] with magnesium hydroxide, and azithromycin sachets, $AUC_{0-t}$ was used to estimate relative bioavailability (F):

$$F = \frac{(AUC_{0-last})_{SR}}{Dose_{SR}} * \frac{Dose_{Sach}}{(AUC_{0-last})_{Sach}}$$

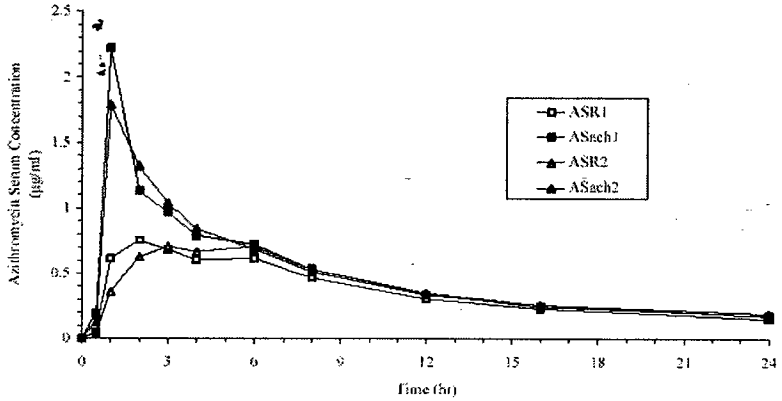
**STATISTICAL ANALYSIS:**
Comparisons between the experimental azithromycin [redacted] formulation and the commercial sachet formulation were performed on the natural log-transformed azithromycin $AUC_{0-t}$, $C_{max}$ and untransformed $T_{max}$ parameters using a mixed effects model containing fixed effects for sequence, period, and treatment with random effects for subject (within sequence). Estimates of the adjusted mean differences between treatments (LS Means) and 90% confidence intervals around the differences were calculated. For $AUC_{0-t}$ and $C_{max}$, the anti-log was calculated individually for the differences and corresponding confidence limits and these values were used to estimate the ratios between treatments and the confidence intervals of the ratios. For $T_{max}$ the confidence intervals on the mean differences were calculated. Geometric means were provided for $AUC_{0-t}$ and $C_{max}$ while arithmetic means were supplied for $T_{max}$.

**RESULTS:**

Thirty-two subjects entered and completed the study. The mean (SD) age, weight, and height of the 32 subjects were 30.8 (10.5) yrs, 70.9 (10.0) kg, and 169.2 (7.5) cm, respectively.

The mean serum azithromycin concentration-time profiles following administration of 2 g azithromycin [redacted] with (ASR2) and without (ASR1) magnesium hydroxide and 2 g azithromycin commercial sachets (ASach1 and ASach2) are shown in Figure 1. Compared to azithromycin sachets (ASach1 and ASach2), the absorption was slower and the peak concentrations were lower for both ASR1 and ASR2. The mean relative bioavailability compared to the sachet was 77.4% for ASR1 and 85.8% for ASR2. The mean $T_{max}$ was delayed by 1.81 hours for ASR1 and 2.56 hours for ASR2 compared with the commercial sachet (ASach1 and ASach2, respectively).

**Figure 1. Mean serum azithromycin concentration-time profiles following administration of 2 g azithromycin [redacted] or azithromycin sachets to healthy subjects (n=32)**




The mean azithromycin $AUC_{0-t}$, $C_{max}$, and $T_{max}$ values following the administration of 2 g azithromycin [redacted] without (ASR1) and with (ASR2) magnesium hydroxide and commercial sachets (ASach1 and ASach2) in the fasted state are shown in Table 1. Administration of azithromycin [redacted] with magnesium hydroxide increased the mean $AUC_{0-t}$ by 11.3% and is reflected in the greater relative bioavailability of ASR2 compared to ASR1. In addition, administration of magnesium hydroxide decreased the mean $C_{max}$ by 13.1% and increased the mean $T_{max}$ by 40%.

**Table 1. Mean (CV%) azithromycin pharmacokinetics following administration of azithromycin SR (ASR1 and ASR2) and azithromycin sachets (ASach1 and ASach2)**

| Parameter | ASR1 | ASach1 | ASR2 | Asach2 |
|---|---|---|---|---|
| $AUC_{0-t}$ (µg*hr/mL) | 15.1 (35%) | 19.4 (22%) | 16.8 (40%) | 19.5 (24%) |
| $C_{max}$ (µg/mL) | 0.97 (36%) | 2.23 (36%) | 0.85 (26%) | 2.10 (49%) |
| $T_{max}$ (hrs) | 2.94 (59%) | 1.13 (30%) | 4.13 (50%) | 1.56 (47%) |
| F (%) | 77.4% | --- | 85.8% | --- |

The geometric mean ratios and 90% confidence intervals for azithromycin [redacted] with and without magnesium hydroxide compared to azithromycin sachet are shown in Table 2. The 90% confidence interval of the geometric mean ratio for $AUC_{0-72}$ and $C_{max}$ were both outside of the 0.80 to 1.25 no-effect boundary and statistically significantly decreased.

**Table 2. Geometric mean ratios (ASR/ASach) and 90% confidence intervals comparing azithromycin with and without magnesium hydroxide to azithromycin sachet**

| | Group 1 (ASR1/ASach1) | | Group 2 (ASR2/ASach2) | |
|---|---|---|---|---|
| **Parameter** | **Point estimate** | **90% CI** | **Point estimate** | **90% CI** |
| $AUC_{0-t}$ | 0.728 | 0.589 - 0.900 | 0.827 | 0.708 - 0.968 |
| $C_{max}$ | 0.437 | 0.369 - 0.517 | 0.432 | 0.342 - 0.546 |

Vomiting of moderate intensity was observed among two subjects following administration of ASR1 (1.07 to 1.17 hrs), six subjects following administration of ASach1 (0.77 to 1.82 hrs), and three subjects following administration of ASach2 (1.23 to 1.30 hrs). No subjects vomited after administration of ASR2. The impact of vomiting was assessed by comparing the pharmacokinetic parameters among subjects who vomited with those who did not vomit. The results are shown in Table 3. Although the number of subjects are small, the mean $AUC_{0-t}$ was not reduced among subjects who vomited approximately 1 hr or more following administration of all three azithromycin regimens.

**Table 3. Mean (CV%) azithromycin pharmacokinetics among subjects with and without vomiting**

| **Parameter** | **ASR1** | | **ASach1** | | **Asach2** | |
|---|---|---|---|---|---|---|
| | Vomiting (n=2) | Without vomiting (n=14) | Vomiting (n=6) | Without vomiting (n=10) | Vomiting (n=3) | Without vomiting (n=13) |
| $AUC_{0-t}$ (µg*hr/mL) | 16.3 (44%) | 14.9 (36%) | 20.3 (21%) | 19.0 (23%) | 25.2 (10%) | 18.2 (22%) |
| $C_{max}$ (µg/mL) | 0.76 (32%) | 1.00 (36%) | 2.36 (42%) | 2.15 (34%) | 1.55 (12%) | 2.23 (50%) |
| $T_{max}$ (hrs) | 3.50 (20%) | 2.86 (64%) | 1.17 (35%) | 1.10 (29%) | 2.00 (0%) | 1.46 (53%) |

**SAFETY:**

No deaths, serious adverse events, or withdrawals due to adverse events were reported in this study. Most of the adverse events reported were treatment related. There were 25 adverse events (AEs) reported by 9 subjects receiving ASR1, 11 AEs reported by 6 subjects receiving ASR2, 36 AEs reported by 11 subjects receiving ASach1, and 22 AEs reported by 11 subjects receiving ASach2. Most of the adverse events in this study were of mild intensity but 6/21 of nausea (2 subjects each from ASR1, ASach1, and ASach2) and 11/11 of vomiting (2 subjects from ASR1, 6 subjects from ASach1, and 3 subjects from ASach2) were of moderate intensity. All adverse events following treatment with ASR2 were of mild intensity. There were no adverse events of severe intensity.

The most frequent adverse events reported were related to the gastrointestinal system, particularly nausea, abdominal pain, diarrhea and vomiting (Table 4). All of the gastrointestinal adverse events were considered treatment related. Although tolerability was assessed only on an exploratory basis, subjects reported fewer gastrointestinal adverse events (nausea and vomiting) following administration of ASR2 than when they received commercial sachets.

**Table 4. Number (%) of gastrointestinal adverse events by group**

| **Adverse Event** | **Group 1** | | **Group 2** | |
|---|---|---|---|---|
| | **ASR1 (n=16)** | **ASach1 (n=16)** | **ASR2 (n=16)** | **ASach2 (n=16)** |
| Nausea | 6 (38%) | 7 (44%) | 1 (6%) | 7 (44%) |
| Vomiting | 2 (13%) | 6 (38%) | 0 (0%) | 3 (19%) |
| Abdominal pain | 6 (38%) | 6 (38%) | 4 (25%) | 4 (25%) |
| Diarrhea | 4 (25%) | 3 (19%) | 2 (13%) | 4 (25%) |

**CONCLUSIONS:**
The addition of magnesium hydroxide in ASR2 was able to slow the rate of absorption of azithromycin and increase the relative bioavailability compared to the commercial sachet.

Without the addition of magnesium hydroxide, azithromycin [redacted] (ASR1) slowed the rate of absorption but was unable to maintain at least 80% relative bioavailability compared to the commercial sachet.

The addition of magnesium hydroxide improved the tolerability of azithromycin [redacted] (ASR2) as illustrated by the reduction in gastrointestinal adverse events, including nausea, vomiting, abdominal pain, and diarrhea.

**4.2.2 An open-label, randomized, 2-way crossover study to evaluate the bioequivalence of a single 2-gram dose of azithromycin sustained-release oral powder for suspension between the ICH supplies and the Phase 3 study drug supplies in healthy adult subjects (Study A0661124)**

Dates: August 19, 2003 to October 7, 2003
Clinical site: [redacted]
Analytical site: [redacted]

**OBJECTIVES:**
The primary objective of this study was to evaluate the bioequivalence of single 2 gram doses of azithromycin [redacted] (ICH supplies) and azithromycin [redacted] (Phase 3 supplies) in healthy adult subjects. The secondary objective was to assess the safety and tolerability of azithromycin [redacted].

**FORMULATIONS:**
Azithromycin [redacted] microspheres [redacted] poloxamer 407, ICH supplies 2 g (Pfizer, Lot No. ED-O-195-703, FID No. G02701AA)
Azithromycin [redacted] microspheres [redacted] poloxamer 407, Phase 3 supplies 2 g (Pfizer, Lot No. TO582V-G1, FID No. G02701AA)

**STUDY DESIGN:**
This study was a randomized, open-label, two-way crossover design, single-dose study of azithromycin in fasted healthy adult subjects. Forty-six subjects 18 to 65 yrs of age were assigned to receive a single 2-g oral dose of azithromycin [redacted] (Phase 3 study supplies) and a single 2-g oral dose of azithromycin [redacted] (ICH study supplies). Subjects were randomly assigned to one of two treatment sequences:

Sequence 1 - Phase 3 study supplies, followed by ICH study supplies
Sequence 2 - ICH study supplies, followed by Phase 3 study supplies

Subjects abstained from all food and drink (except water) at least 8 hrs prior to administration of study medication. Water was permitted until 1 hour prior to administration of study medication. Subjects remained fasting through 4 hrs following administration of study medication. Water (240 mL) was administrated immediately following the study medication dose. There was at least a 16-day washout period between the two dosing days.

Blood samples for determination of serum azithromycin concentrations were obtained at 0 (predose), 0.5, 1, 2, 3, 4, 5, 6, 8 12, 16, 24, 36, 48, and 72, hrs following dosing with study drug on Day 1 of Periods 1 and 2. An additional sample (7 mL) was collected at 96, 144, and 192 hours following administration on day 1 from the subjects treated with azithromycin [redacted] (ICH supplies) in Period 1 for determination of the terminal elimination phase half-life.

**AZITHROMYCIN ASSAY METHODOLOGY:**
High performance liquid chromatography with [redacted] (LC/[redacted]

| Criterion | Serum | Comments |
|---|---|---|
| Concentration range | [redacted] | Satisfactory |
| LLOQ | | Satisfactory |
| Linearity | | Satisfactory |
| Accuracy | | Satisfactory |
| Precision | | Satisfactory |
| Specificity | | Satisfactory |
| Stability | | Satisfactory |

**PHARMACOKINETIC ANALYSIS:**
Maximum observed serum concentrations ($C_{max}$) of azithromycin were estimated directly from the experimental data. $T_{max}$ was defined as the time of the first occurrence of $C_{max}$. The area under the plasma concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration ($AUC_{0-t}$) and the AUC from time 0 to 72 hrs post-dose ($AUC_{0-72}$) was estimated using the linear/log trapezoidal rule. The terminal elimination phase rate constant (Ke) was estimated using least-squares regression analysis of the plasma concentration-time data obtained during the terminal log-linear phase. The terminal elimination phase half-life ($t_{1/2}$) was calculated as ln(2) divided by Ke and was only calculated for subjects who received the azithromycin [redacted] ICH supplies in Period 1.

**STATISTICAL ANALYSIS:**
The natural log-transformed $AUC_{0-72}$ and log-transformed $C_{max}$ were analyzed using a mixed effects model, with sequence, treatment, and period effects considered fixed and subject (within sequence) considered random. Least-squares means (LSMeans) and their associated standard errors were calculated to obtain estimates for adjusted treatment mean differences and their associated standard errors (log-transformed). After the 90% confidence intervals for these differences were calculated, the anti-log was taken on the confidence limits to obtain the corresponding confidence limits for the ratio of the test and reference averages.

**RESULTS:**
Forty-six subjects were assigned to treatment and 41 subjects completed the study. Three subjects received azithromycin [redacted] (Phase 3 supplies) only and two subjects received azithromycin [redacted] (ICH supplies) only. Subjects 10011006 and 10011035 were discontinued due to mild vomiting after receiving a 2 g dose of azithromycin [redacted] (Phase 3 supplies) on day 1 of Period 1 at 0.88 hrs and 1.03 hrs, respectively. Another subject (Subject 10011042) vomited at 12.02 hrs after receiving azithromycin [redacted] (ICH supplies) and withdrew from the study after the 12 hr post-dose blood draw. Two additional subjects chose not to continue to participate in the study after receiving only one of the randomized treatments. Subject 10011041 received a 2g dose of azithromycin [redacted] ICH supplies) on day 1 of Period 1 and withdrew from the study after the 2 hr post-dose blood draw. Subject 10011074 received a 2g dose of azithromycin [redacted] Phase 3 supplies) on day 1 of Period 1 and withdrew from the study after the 72 hr post-dose blood draw.

The mean (SD) age, weight, and height of the 46 subjects enrolled were 24.8 (8.8) yrs, 66.2 (10.8) kg, and 165.6 (7.8) cm, respectively. The mean serum azithromycin concentration-time profiles following administration of 2 g azithromycin [redacted] ICH supplies) and 2 g azithromycin [redacted] Phase 3 supplies) are shown in Figure 1. Azithromycin serum concentrations were similar from both regimens and appeared to peak at approximately the same time and to the same extent for both treatments.

The mean azithromycin $AUC_{0-72}$, $AUC_{0-t}$, $C_{max}$, and $T_{max}$ values following the administration of 2 g azithromycin [redacted] ICH supplies) and 2 g azithromycin [redacted] Phase 3 supplies) are shown in Table 1. The mean $AUC_{0-72}$ and $C_{max}$ decreased 2.7% and 3.2%, respectively following administration of azithromycin [redacted] ICH supplies) compared azithromycin [redacted] (Phase 3 supplies). In addition, the mean $T_{max}$ was similar between the two regimens (5.1% lower with the ICH supplies compared to Phase 3 supplies).

The sponsor has only reported pharmacokinetic parameters for subjects who completed both the azithromycin [redacted] ICH supplies) and azithromycin [redacted] (Phase 3 supplies) regimens. Subject 10011006 vomited 0.88 hrs and Subject 10011035 vomited 1.03 hrs after administration of azithromycin [redacted] (Phase 3 supplies). Thus, no data are available to assess the impact of vomiting on the $AUC_{0-72}$ and $C_{max}$ for the two subjects that vomited.

**Figure 1. Mean serum azithromycin concentration-time profiles following administration of 2 g azithromycin [redacted] (ICH or Phase 3 supplies) to healthy subjects (n=41)**

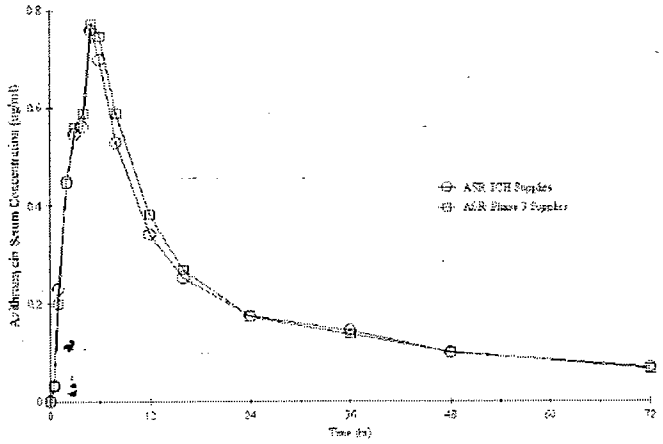


**Table 1. Mean (CV%) azithromycin pharmacokinetic following administration of 2 g azithromycin [redacted] (ICH and Phase 3 supplies)**

| Parameter | ICH supplies (n=41) | Phase 3 supplies (n=41) |
|---|---|---|
| $AUC_{0-72}$ (µg*hr/mL) | 13.9 (29%) | 14.3 (34%) |
| $AUC_{0-t}$ (µg*hr/mL) | 16.1 (35%) | 14.3 (34%) |
| $C_{max}$ (µg/mL) | 0.82 (34%) | 0.85 (33%) |
| $T_{max}$ (hrs) | 4.98 (26%) | 5.24 (22%) |
| $t_{1/2}$ (hrs) | 58.8 (12%) | NA |

The geometric mean ratios and 90% confidence intervals for azithromycin [redacted] (ICH supplies) and azithromycin [redacted] (Phase 3 supplies) are shown in Table 2. The 90% confidence interval of the geometric mean ratio for $AUC_{0-72}$ and $C_{max}$ were within the 0.80 to 1.25 boundary for establishing bioequivalence. Thus, the results confirm that 2 g of the to-be-marketed formulation of azithromycin [redacted] (ICH supplies) was bioequivalent to 2 g of azithromycin [redacted] Phase 3 clinical study supplies.

**Table 2. Geometric mean ratios (ICH/Phase 3 supplies) and 90% confidence intervals for 2 g azithromycin [redacted] (n=41)**

| | ICH/Phase 3 supplies | |
|---|---|---|
| Parameter | Point estimate | 90% CI |
| $AUC_{0-72}$ | 0.989 | 0.904 - 1.082 |
| $C_{max}$ | 0.973 | 0.901 - 1.050 |

**SAFETY:**
No deaths or serious adverse events (AEs) were reported in this study. Twenty-one of 44 subjects (47.7%) experienced a total of 38 AEs following a single 2g dose of azithromycin (Phase 3 supplies), and 24 of 43 subjects (55.8%) experienced a total of 40 AEs following a single 2g dose of azithromycin (ICH supplies). The majority of the AEs were related to the gastrointestinal system. The most frequently reported AE was abdominal pain in 19 subjects (5 subjects following Phase 3 supplies; 8 subjects following ICH supplies; 6 subjects following both treatments). Four subjects vomited after receiving azithromycin three subjects following administration of Phase 3 study supplies and one subject after administration of the ICH stability supplies.

**Table 3. Treatment-emergent signs and symptoms - All causalities (number of subjects [%])**

| Adverse Event | Phase 3 Supplies (n=44) | ICH Supplies (n=43) |
|---|---|---|
| **Body as a whole** | | |
| Headache | 6 (14%) | 8 (19%) |
| **Digestive system** | | |
| Diarrhea | 5 (11%) | 4 (9%) |
| Dyspepsia | 2 (5%) | 0 (0%) |
| Nausea | 3 (7%) | 2 (5%) |
| Vomiting | 3 (7%) | 1 (2%) |
| **Nervous system** | | |
| Dizziness | 3 (7%) | 4 (9%) |

Two subjects vomited after receiving azithromycin Phase 3 supplies) at 0.88 and 1.03 hrs following administration. One subject vomited after receiving azithromycin (ICH supplies) at 12.02 hrs after administration. Pharmacokinetic parameters were reported only for subjects 10011006 and 10011035 following administration of azithromycin Phase 3 supplies). Although the sponsor stated that four subjects vomited, only three subjects vomited based on the case report forms.

**CONCLUSIONS:**
The 90% confidence intervals for the geometric mean ratios of $AUC_{0-72}$ and $C_{max}$ values were within the 80-125% range of bioequivalence.

$T_{max}$ was similar after administration of the ICH supplies and Phase 3 supplies.

Azithromycin (ICH supplies) and azithromycin Phase 3 supplies) are bioequivalent to one another.

**4.2.3 An open-label, randomized, crossover study to evaluate the relative bioavailability of a single 2-gram oral dose of an experimental azithromycin dihydrate microspheres [redacted] release formulation (Zithromax ER) under fasting and fed conditions in healthy volunteers (Study A0661107)**

Dates: November 25, 2002 to January 14, 2002
Clinical site:
Analytical site.

**OBJECTIVES:**
The primary objective of this study was to evaluate the effect of a high-fat meal on the pharmacokinetics of a single 2 g oral dose of azithromycin [redacted] A secondary objective was to evaluate the safety and tolerability of a single 2 g oral dose of azithromycin [redacted] in healthy volunteers under fasting and fed conditions.

**FORMULATIONS:**
Azithromycin dihydrate microspheres [redacted] poloxamer 407, 2 g (Pfizer, Lot No. T0582V-G1, FID#G02701AA)

**STUDY DESIGN:**
This study was an open-label, randomized, 2 period crossover study of azithromycin in fed and fasted healthy adult subjects. Sixteen subjects 18 to 55 yrs of age received a single 2 g oral dose of azithromycin [redacted] in either the fasting (Treatment A) or fed (Treatment B) states in each dosing period. Subjects were randomly assigned to one of the following treatment sequences:

Sequence 1: Period 1 followed by Period 2
Sequence 2: Period 2 followed by Period 1

Subjects receiving the fasted regimen (Treatment A) fasted from all food and drink (except water, which was permitted until 1 hour prior to dosing) for at least 8 hrs prior to dosing through 4 hrs post-dose. Subjects receiving the fed regimen (Treatment B) fasted from all food and drink (except water, as described above) for at least 8 hours prior to receiving the test meal. Approximately 20 minutes prior to dosing on Day 1, subjects on Treatment B were served a standard FDA high-fat breakfast composed of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with 2 pats of butter, 4 ounces of hash browns and 8 ounces of whole milk (150 kcal from protein, 250 kcal from carbohydrate, and 500-600 kcal from fat). Subjects were encouraged to eat the entire breakfast within 20 min and were dosed immediately thereafter. There was at least a 16-day washout period between the 2 dosing days.

Blood samples for determination of azithromycin concentrations were obtained at time 0 (predose), 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hrs after administration.

**AZITHROMYCIN ASSAY METHODOLOGY:**
High Performance Liquid Chromatography [redacted] (LC/[redacted]

| Criterion | Serum | Comments |
|---|---|---|
| Concentration range | | Satisfactory |
| LLOQ | | Satisfactory |
| Linearity | | Satisfactory |
| Accuracy | | Satisfactory |
| Precision | | Satisfactory |
| Specificity | | Satisfactory |
| Stability | | Satisfactory |

**PHARMACOKINETIC ANALYSIS:**
The maximum observed serum concentrations ($C_{max}$) of azithromycin were estimated directly from the experimental data. $T_{max}$ was defined as the time of the first occurrence of $C_{max}$. The lag time ($T_{lag}$) was defined as the time prior to the time corresponding to the first measurable (non-zero) concentration. The area under the plasma concentration-time curve from time 0 to the time of last quantifiable concentration ($AUC_{0-t}$) and from time 0 to 24 hours post-dose ($AUC_{0-24}$) were estimated using the log-linear trapezoidal rule. The ratios of $C_{max}$ and $AUC_{0-t}$ values were calculated for each subject by dividing the result from the fed treatment by the result from the fasting treatment.

**STATISTICAL ANALYSIS:**
Natural log-transformed $AUC_{0-t}$ and log-transformed $C_{max}$ were analyzed using a mixed effects model with sequence, treatment, and period effects considered fixed and subject (within sequence) considered random. Estimates of the adjusted mean differences between treatments and 90% confidence intervals around the differences were calculated.

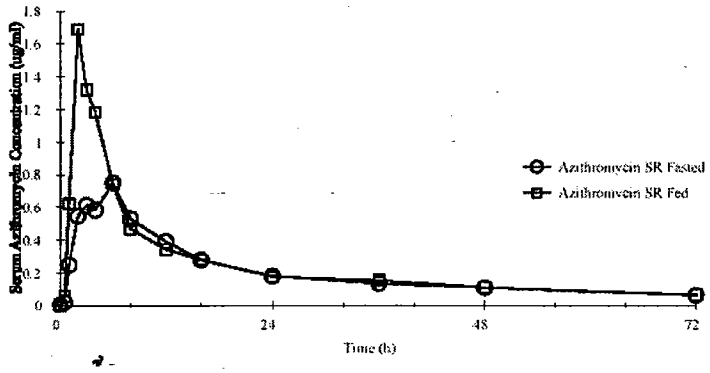
Estimates of the adjusted mean differences between treatments, and 90% confidence intervals around the differences were calculated. For $AUC_{0-t}$ and $C_{max}$, the anti-log (exponent) of the differences and confidence limits were taken to estimate the ratios between treatments and the confidence intervals of the ratios. Geometric means were provided for $AUC_{0-t}$ and $C_{max}$. The fasted treatment served as the reference.

**RESULTS:**
Sixteen subjects (3 male and 13 female) were randomized into the two dosing sequences. All 16 subjects received azithromycin [redacted] in the fasted state whereas 15 subjects received azithromycin [redacted] in the fed state. Subject 10011003 was withdrawn after administration of azithromycin [redacted] in the fasted state because study personnel was unable to draw blood beyond the predose sample. The mean (SD) age, weight, and height of the 16 subjects randomized were 32.1 (12.9) yrs, 65.9 (12.5) kg, and 166 (11) cm, respectively.

Two subjects vomited within 2 hrs of dosing of administration. Subject 10011053 vomited 1.85 hrs after receiving azithromycin [redacted] in the fed state and 1.10 hrs in the fasted state. Subject 100111045 vomited 1.55 hrs after receiving azithromycin [redacted] in the fed state.

The mean serum azithromycin concentration-time profiles following administration of 2 g azithromycin [redacted] in the fasted state and following a high-fat breakfast for all subjects are shown in Figure 1. As shown in the plot, the mean serum concentrations of azithromycin in the fed state exceeded the mean azithromycin concentrations in the fasted state over the first six hrs.

**Figure 1. Mean azithromycin concentration-time profiles following administration of 2 g azithromycin ▬ under fasting conditions and following a high-fat breakfast (n=15)**




The mean azithromycin $C_{max}$, $AUC_{0-t}$, and $T_{max}$ values following the administration of 2 g azithromycin ▬ in the fasted or fed states are shown in Table 1. When azithromycin ▬ was administered with a high-fat breakfast, the mean $AUC_{0-t}$ increased 19% and the mean $C_{max}$ increased 111%. Since the serum concentrations in the fed state were greater than the fasted state primarily for the first 6 hrs, the mean $AUC_{0-24}$ increased 28%. The mean $T_{max}$ decreased 46% from 4.93 hrs to 2.67 hrs. Thus, administration of azithromycin with a high-fat meal increased the rate and extent of absorption.

**Table 1. Mean (CV%) azithromycin pharmacokinetic following administration under fasting and fed conditions for subjects with and without vomiting**

| | All subjects (n=15) | | Subjects w/o vomiting (n=13) | |
|---|---|---|---|---|
| **Parameter** | **High-fat breakfast** | **Fasted** | **High-fat breakfast** | **Fasted** |
| $AUC_{0-t}$ (μg*hr/mL) | 17.2 (30%) | 14.4 (35%) | 16.7 (32%) | 14.9 (34%) |
| $C_{max}$ (μg/mL) | 1.82 (30%) | 0.86 (33%) | 1.78 (33%) | 0.89 (31%) |
| $T_{max}$ (hrs)* | 2.0 (2 to 4) | 6.0 (2 to 6) | 3.0 (2 to 4) | 6.0 (2 to 6) |

* Median (range)

Although subject 100111045 vomited 1.55 hrs after receiving azithromycin ▬ in the fed state, the $AUC_{0-t}$ and $C_{max}$ values for this subject were 26% and 20% greater than the mean values, respectively. Subject 10011053 vomited 1.85 hrs after receiving azithromycin ▬ in the fed and 1.10 hrs in the fasted state. Although the $AUC_{0-t}$ and $C_{max}$ values were 16% and 8% greater than the mean values in the fed state, respectively, the $AUC_{0-t}$ and $C_{max}$ values for this subject in the fasted state were approximately half the mean values (7.48 vs. 14.43 μg*hr/mL for $AUC_{0-t}$; 0.44 vs. 0.86 μg/mL for $C_{max}$) and were the lowest values among the 15 subjects. The time between administration on the onset of vomiting was the shortest for subject 100111053 in the fasted state (1.10 hrs).

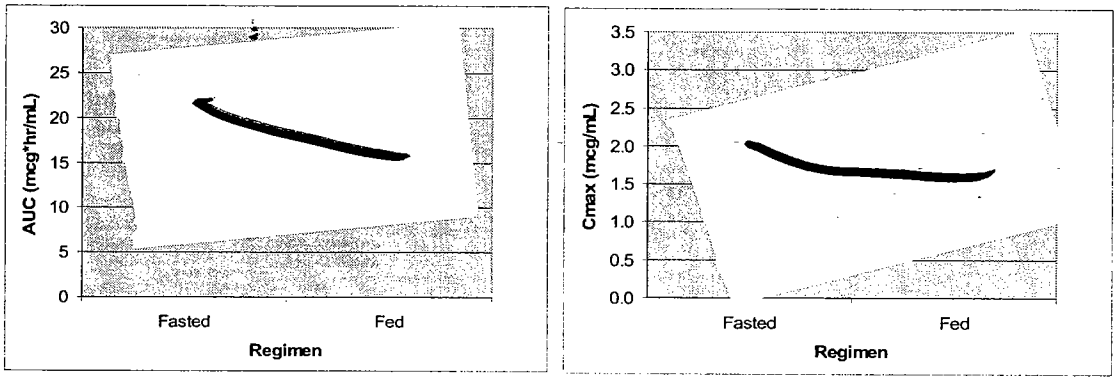
The geometric mean ratios and 90% confidence intervals for azithromycin (fed/fasted) are shown in Table 2. The 90% confidence intervals of the geometric mean ratios for $AUC_{0-t}$ and $C_{max}$ were outside of the boundaries of 0.80-to 1.25. Thus, a food effect was observed when azithromycin was administered with a high-fat meal based on $AUC_{0-t}$ and $C_{max}$.

**Table 2. Geometric mean ratios (fed/fasted) and 90% confidence intervals for azithromycin administered under fasted and fed conditions**

| | All subjects (n=15) | | Subjects w/o vomiting (n=13) | |
|---|---|---|---|---|
| **Parameter** | **Point estimate** | **90% CI** | **Point estimate** | **90% CI** |
| $AUC_{0-t}$ | 1.23 | 1.01 - 1.49 | 1.17 | 0.94 - 1.45 |
| $C_{max}$ | 2.15 | 1.83 - 2.53 | 2.08 | 1.74 - 2.49 |

Stick plots showing the individual $AUC_{0-\infty}$ and $C_{max}$ values for azithromycin administered under fasted and fed conditions are shown in Figure 2. Subjects without emesis are represented with blue circles, subjects with emesis as green triangles, and the geometric mean as red squares. It is apparent that the fasted $AUC_{0-t}$ and $C_{max}$ values for Subject 10011053 in the fasted state (vomited 1.10 hrs following administration) are lower than the values from all other subjects.

**Figure 2. Stick plots demonstrating the individual $AUC_{0-t}$ (left) and $C_{max}$ (right) of azithromycin administered under fasted and fed conditions**




**SAFETY:**

No deaths, serious adverse events (SAEs) or withdrawals due to an adverse event were reported in the study. There were 19 adverse events (AEs) reported by 10 subjects receiving azithromycin SR in the fasted state and 17 AEs reported by eight subjects receiving azithromycin in the fed state. Three of four moderate AEs (two instances of vomiting and one instance of nausea) were experienced following treatment with azithromycin [redacted] in the fed state. The treatment emergent adverse events are shown in Table 3.

**Table 3. Treatment emergent adverse events**

| Gastrointestinal System | Azithromycin [redacted] Fasted | Azithromycin [redacted] Fed |
|---|---|---|
| Abdominal pain | 4 (25%) | 3 (20%) |
| Diarrhea | 4 (25%) | 4 (27%) |
| Flatulence | 1 (6%) | 2 (13%) |
| Nausea | 3 (19%) | 4 (27%) |
| Vomiting | 1 (6%) | 2 (13%) |

**CONCLUSIONS:**
A high-fat meal dramatically increases the rate and extent of absorption of azithromycin [redacted]

Although the study was not powered to assess the tolerability of azithromycin in the fasted vs. fed state, three of four moderate adverse events occurred in the fed state.



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**4.2.4 An open-label, randomized, 2-way crossover study to evaluate the effect of a standard meal on the pharmacokinetics of azithromycin [redacted] release oral powder for suspension in healthy volunteers (Study A0661114)**

Dates: October 7, 2003 to December 9, 2003
Clinical site: [redacted]
Analytical site

**OBJECTIVES:**
The primary objective of this study was to assess the pharmacokinetic equivalence, safety, and tolerability of azithromycin [redacted] powder for oral suspension under fasted conditions and after a standard meal in healthy adult subjects.

**FORMULATIONS:**
Azithromycin dihydrate microspheres [redacted] poloxamer 407, 2 g (Pfizer, Lot No. ED-O-195-703, FID No. G02701AA)

**STUDY DESIGN:**
This study was an open-label, randomized, 2 period crossover study of azithromycin in fed and fasted healthy adult subjects. Ninety-two male and female subjects 18 to 65 yrs of age received a single 2 g oral dose of azithromycin [redacted] in either the fasted or fed states in each dosing period with 240 ml of ambient temperature water. Subjects were randomly assigned to one of the following treatment sequences:

Sequence 1: Fasted followed by fed
Sequence 2: Fed followed by fasted

Subjects abstained from alcohol consumption for 24 hours prior to the start of dosing until collection of the last pharmacokinetic sample of each study session. Subjects were not allowed to take grapefruit-containing products from seven days prior to the first dose of study medication until collection of the last pharmacokinetic sample.

Subjects abstained from all food and drink (except water, which could be consumed ad libitum beginning 2 hrs following dosing) and at least 10 hrs prior to administration of study medication (fasted conditions) or a standard breakfast (fed conditions). Subjects who were treated under fed conditions were served a standard breakfast 30 min prior to dosing with study medication and were to consume the entire breakfast within 30 min. The standard breakfast consisted of 1 blueberry muffin, 3/4 cup cereal, 2 tsp of margarine, 6 ounces of orange juice, and 1 cup of 2% milk (56 kcal from protein, 316 kcal from carbohydrate, and 207 kcal from fat). There was at least a 16-day washout period between the two dosing sequences.

Blood samples for determination of serum azithromycin concentrations were obtained at time 0 (predose), 0.5, 1, 2, 3, 4, 6, 8 12, 16, 24, 36, 48, and 72 hrs after administration.

**AZITHROMYCIN ASSAY METHODOLOGY:**
High performance liquid chromatography [redacted] (LC/ [redacted]

| Criterion | Serum | Comments |
|---|---|---|
| Concentration range | | Satisfactory |
| LLOQ | | Satisfactory |
| Linearity | | atisfactory |
| Accuracy | | atisfactory |
| Precision | | atisfactory |
| Specificity | | Satisfactory |
| Stability | | Satisfactory |

RT = room temperature

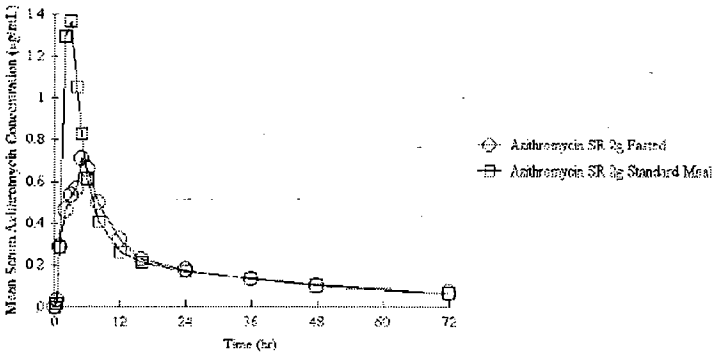
**PHARMACOKINETIC ANALYSIS:**
The maximum observed serum concentrations ($C_{max}$) of azithromycin were estimated directly from the experimental data. $T_{max}$ was defined as the time of the first occurrence of $C_{max}$. The lag time ($T_{lag}$) was defined as the time elapsed before the first measurable concentration. The area under the serum concentration-time curve (AUC) from time 0 to 24 hrs post-dose ($AUC_{0-24}$) and from time 0 to 72 hours post-dose ($AUC_{0-72}$) were estimated using the log-linear trapezoidal rule.

**STATISTICAL ANALYSIS:**
Natural log-transformed $AUC_{0-72}$ and log-transformed $C_{max}$ were analyzed using a mixed effects model with sequence, treatment, and period effects considered fixed and subject (within sequence) considered random. Estimates of the adjusted mean differences between treatments and 90% confidence intervals around the differences were calculated. For $AUC_{0-72}$ and $C_{max}$, the anti-log of the differences and confidence limits were taken to estimate the ratios between treatments and the confidence intervals of the ratios. The fasted condition served as the reference.

**RESULTS:**
Ninety-two subjects were enrolled in the study. Of these, 88 subjects received both treatments (two subjects were dosed under fasted conditions only and two subjects were dosed under fed conditions only). Four subjects were excluded from pharmacokinetic analysis due to incomplete data because the subjects discontinued from the study (Subjects 10011045, 10011096, 10011111, and 10011124). Nine subjects did not have $AUC_{0-72}$ estimations; eight subjects (Subjects 10011011, 10011025, 10011030, 10011035, 10011047, 10011053, 10011086, and 10011123) did not have blood drawn at 72 hr sampling time and one subject (Subject 10011118) had insufficient blood volume collected at the 72 hr sampling time and the $AUC_{0-72}$ could not be calculated.

The mean (SD) age, weight, and height of the 92 subjects randomized were 24.8 (9.6) yrs, 68.7 (10.9) kg, and 168.5 (8.3) cm, respectively. Twenty-eight subjects were male and 64 subjects were female. The mean serum azithromycin concentration-time profiles following administration of 2 g azithromycin SR in the fasted state and following a standard breakfast for 88 subjects are shown in Figure 1. As shown in the figure, the mean serum concentrations of azithromycin in the fed state initially exceeded the mean azithromycin concentrations in the fasted state and the mean concentration peaked earlier in the fed-state.

**Figure 1. Mean serum azithromycin concentration-time profiles following administration of 2 g azithromycin ● under fasted and fed conditions (n=88)**




The mean azithromycin $C_{max}$, $AUC_{0-t}$, and $T_{max}$ values following the administration of 2 g azithromycin ● in the fasted and fed states are shown in Table 1. When azithromycin ● was administered with a standard breakfast, the mean $AUC_{0-24}$ increased 19% (n=88), mean $AUC_{0-72}$ increased 11% (n=79), and the mean $C_{max}$ increased 120% (n=88). The mean $T_{max}$ decreased 39% from 4.67 hrs to 2.83 hrs (n=88). Considering only subjects with an AUC $_{0-72}$ estimate (n=79), the mean $AUC_{0-24}$ increased 17% and the mean $C_{max}$ increased 113%. Thus, administration of azithromycin ● with a standard breakfast increased the mean $C_{max}$ and $AUC_{0-72}$ similar to administration of azithromycin ● with a high-fat breakfast.

**Table 1. Mean (CV%) azithromycin pharmacokinetic parameters following administration of azithromycin ● under fasted and fed conditions for subjects**

| Parameter | N | Fed | Fasted |
|---|---|---|---|
| $AUC_{0-24}$ (µg*hr/mL) | 88 | 9.77 (24%) | 8.22 (26%) |
| $AUC_{0-72}$ (µg*hr/mL) | 79 | 14.67 (23%) | 13.23 (28%) |
| $C_{max}$ (µg/mL) | 88 | 1.69 (30%) | 0.77 (28%) |
| $T_{max}$ (hrs) | 88 | 2.83 (30%) | 4.67 (38%) |

The geometric mean ratios and 90% confidence intervals for azithromycin (fed/fasted) are shown in Table 2. Although the 90% confidence interval of the geometric mean ratio for $AUC_{0-72}$ was within the 0.80 to 1.25 boundaries, there was a statistically significant increase in $AUC_{0-72}$. The 90% confidence interval of the geometric mean ratio for $C_{max}$ was outside of the boundary of 0.80 to 1.25 and was also statistically significantly increased.

**Table 2. Geometric mean ratios (fed/fasted) and 90% confidence intervals for azithromycin administered under fasted and fed conditions for subjects that received both treatments**

| Parameter | N | Point estimate | 90% CI |
|---|---|---|---|
| $AUC_{0-72}$ | 79 | 1.12 | 1.08 - 1.17 |
| $C_{max}$ | 88 | 2.19 | 2.05 - 2.35 |

The individual $AUC_{0-72}$ and $C_{max}$ values are shown in Figures 2 and 3, respectively. As shown in Figure 2, the range of $AUC_{0-72}$ values from subjects in the fed state is within the range of $AUC_{0-72}$ values in the fasted state. However, the range of $C_{max}$ values from subjects in the fed state exceeds the range of $C_{max}$

values in the fasted state and illustrates that administration of azithromycin [redacted] with food primarily impacts the rate of absorption and has only a modest impact on the extent of absorption.

**Figure 2. Individual $AUC_{0-72}$ values of azithromycin following administration of 2 g azithromycin [redacted] under fasted and fed conditions (n=79)**

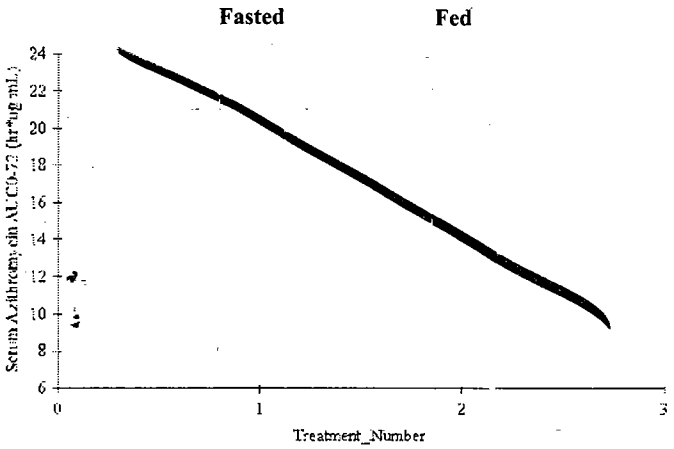
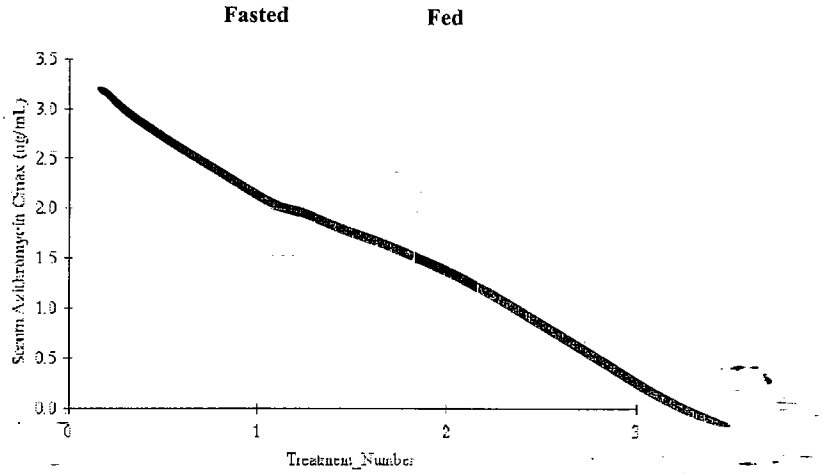



**Figure 3. Individual $C_{max}$ values of azithromycin following administration of 2 g azithromycin [redacted] under fasted and fed conditions (n=88)**



Seven subjects vomited after administration of azithromycin [redacted] in the fed state and one subject vomited after administration of azithromycin [redacted] in the fasted state. PK data were not reported for one subject (Subject 10011096) who received azithromycin [redacted] in the fed state. Subjects in the fed state vomited 1.03 to 2.53 hrs after drug administration and the one subject in the fasted state vomited 1.03 hrs after drug administration. Among the six subjects who vomited (and PK data were available), the mean $AUC_{0-24}$, $AUC_{0-72}$, and $C_{max}$ decreased 7%, 3%, and 9%, respectively compared to subjects who didn't vomit.

**Table 3. Mean azithromycin pharmacokinetic parameters among subjects with and without vomiting**

| Parameter | N | Subjects without vomiting | N | Subjects with vomiting | Mean Ratio (with/without vomiting) |
|---|---|---|---|---|---|
| $AUC_{0-24}$ (µg*hr/mL) | 82 | 9.81 | 6 | 9.14 | 0.93 |
| $AUC_{0-72}$ (µg*hr/mL) | 73 | 14.70 | 6 | 14.24 | 0.97 |
| $C_{max}$ (µg/mL) | 82 | 1.70 | 6 | 1.54 | 0.91 |
| $T_{max}$ (hrs) | 82 | 2.84 | 6 | 2.67 | 0.94 |

**SAFETY:**

No deaths, serious adverse events (SAEs) or withdrawals due to an adverse event were reported in the study. Twenty-six of 90 subjects (28.9%) analyzed for safety and received a single 2g dose of azithromycin [redacted] under fasted conditions experienced a total of 41 adverse events (AEs) (34 were considered treatment-related). Forty-four of 90 subjects (48.9%) who received a single 2g dose of azithromycin [redacted] following a meal experienced a total of 79 AEs (65 were considered to be treatment-related). The majority of the reported AEs were related to the GI system.

The most frequently reported adverse events are shown in Table 3. Approximately 1% of subjects (n=1) vomited when administered in the fasted state and 8% of subjects (n=7) vomited in the fed state. Pharmacokinetic parameters were not reported for subject 10011096 as this subject discontinued from the study after receiving azithromycin [redacted] in the fed state.

**Table 3. Number (%) of the most frequently reported (>1% of subjects in a treatment group) adverse events - all causalities**

| Body System | AEs - All causalities | |
|---|---|---|
| | Fasted (n=90) | Fed (n=90) |
| **Body as a whole** | | |
| Abdominal pain | 16 (17.8%) | 21 (23.3%) |
| Headache | 6 (6.7%) | 4 (4.4%) |
| Pain | | |
| **Digestive system** | | |
| Diarrhea | 2 (2.2%) | 8 (8.9%) |
| Flatulence | 1 (1.1%) | 3 (3.3%) |
| Nausea | 3 (3.3%) | 13 (14.4%) |
| Vomiting | 1 (1.1%) | 7 (7.8%) |
| **Nervous system** | | |
| Dizziness | 4 (4.4%) | 9 (10.0%) |

**CONCLUSIONS:**
Administration of azithromycin [redacted] with a standard breakfast increased the mean $C_{max}$ by 120% and reduced the mean $T_{max}$ by nearly 2 hrs compared to fasted conditions.

Although the increase in the extent of azithromycin [redacted] absorption in the fed state was statistically significant, the 90% confidence of the $AUC_{0-72}$ geometric mean ratio was within the predetermined no-effect boundaries and is not likely to be clinically significant.

While the study was not statistically powered to compare the incidence of adverse events in fed and fasted states, the incidence of GI events, especially nausea, diarrhea, and vomiting, was lower in the fasted state.

**4.2.5 An open-label, randomized, 2-way crossover study to evaluate the effect of Maalox on the pharmacokinetics of azithromycin [redacted] release oral powder for suspension in healthy volunteers (Study A0661115)**

Dates: May 5, 2003 to June 24, 2003
Clinical site:
Analytical site [redacted]

**OBJECTIVES:**
The primary objective of this study was to evaluate the effect of Maalox® on the pharmacokinetics of azithromycin [redacted] in healthy subjects. The secondary objective was to assess the safety and tolerability of co-administration of Maalox® and azithromycin [redacted] in healthy subjects.

**FORMULATIONS:**
Azithromycin [redacted] poloxamer 407, 2 g (Pfizer, Lot No. T0582V-G1, FID No. G02701AA)
Regular Strength Maalox®, 20 mL (Novartis, Lot No. 31725)

**STUDY DESIGN:**
This study was an open-label, randomized, 2 period crossover study. Thirty-nine healthy male and female subjects 18 to 65 yrs of age received a single 2 g oral dose of azithromycin [redacted] and a single 2 g oral dose of azithromycin [redacted] plus a single 20 mL oral dose of Regular Strength Maalox® on separate treatment periods. When the treatments were administered concomitantly, azithromycin [redacted] was administered immediately after Maalox®, followed by 240 mL of water.

Sequence 1: Azithromycin [redacted] followed by azithromycin [redacted] + Maalox®
Sequence 2: Azithromycin [redacted] + Maalox® followed by azithromycin [redacted]

Subjects abstained from all food and drink (except water) at least 8 hrs prior to administration of study medication and fasted through 4 hrs following dosing. Water was permitted until 1 hr prior to administration of study medication. Following administration of study medication, 240 mL of water was administered and water could also be consumed ad libitum beginning 2 hrs post dose. Non-caffeinated drinks (except grapefruit juice) or caffeinated drinks could be consumed with meals and the evening snack. Subjects were not allowed to take grapefruit-containing products from 7 days prior to the first dose of study medication until collection of the last pharmacokinetic sample. There was a washout period of at least 16 days between the treatment periods.

Blood samples for determination of serum azithromycin concentrations were obtained at time 0 (predose), 0.5, 1, 2, 3, 4, 6, 8 12, 16, 24, 36, 48, and 72 hrs after administration.

**AZITHROMYCIN ASSAY METHODOLOGY:**
High performance liquid chromatography [redacted] (LC/[redacted]

| Criterion | Serum | Comments |
|---|---|---|
| Concentration range | [redacted] | Satisfactory |
| LLOQ | | Satisfactory |
| Linearity | | Satisfactory |
| Accuracy | | Satisfactory |
| Precision | | Satisfactory |
| Specificity | | Satisfactory |
| Stability | | Satisfactory |

RT = room temperature

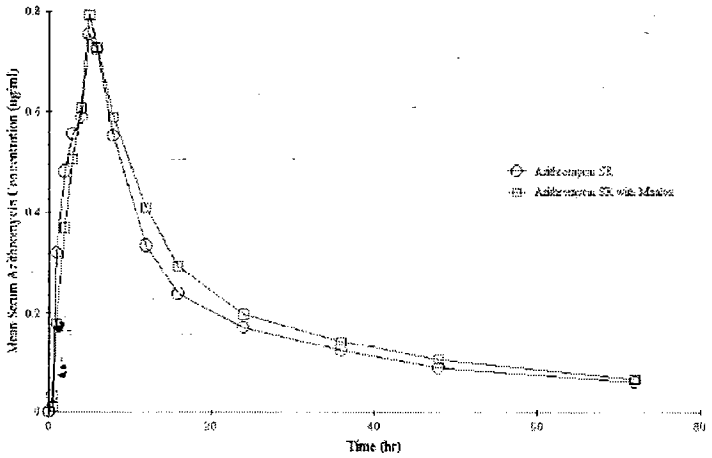
**PHARMACOKINETIC ANALYSIS:**
Maximum observed serum concentrations ($C_{max}$) of azithromycin were estimated directly from the experimental data. $T_{max}$ was defined as the time of the first occurrence of $C_{max}$. Area under the plasma concentration-time curve (AUC) was estimated using the log-linear trapezoidal rule from time zero to the last quantifiable concentration ($AUC_{0-t}$) and from time zero to 24 hrs post-dose ($AUC_{0-24}$).

**STATISTICAL ANALYSIS:**
Natural log-transformed $AUC_{0-t}$ and $C_{max}$ of azithromycin were analyzed using a mixed effects model containing fixed effects for sequence, period, and treatment and a random effect for subjects (within sequence). Least-squares means (LS Means) and their associated standard errors were calculated to obtain estimates for adjusted treatment mean differences and their associated standard errors (log-transformed). After the 90% confidence intervals for these differences were calculated, the anti-log was taken on the confidence limits to obtain the corresponding confidence limits for the ratio of the test and reference averages. Azithromycin [redacted]alone served as the reference.

**RESULTS:**
Thirty-nine subjects were enrolled into and completed the study. The mean (SD) age, weight, and height of the 39 subjects randomized were 34.3 (12.3) yrs, 70.5 (10.6) kg, and 166.6 (9.5) cm, respectively.

The mean serum azithromycin concentration-time profiles following administration of 2 g azithromycin [redacted] with and without 20 mL of Regular Strength Maalox® are shown in Figure 1. The mean serum concentration-time profiles of azithromycin were similar and co-administration of Regular Strength Maalox® did not appear to alter the rate and extent of absorption of azithromycin [redacted]

**Figure 1. Mean serum azithromycin concentration-time profiles following administration of 2 g azithromycin [redacted] with and without concomitant administration of 20 mL Regular Strength Maalox® (n=39)**




The mean azithromycin $AUC_{0-24}$, $AUC_{0-t}$, $C_{max}$, and $T_{max}$ values following the administration of 2 g azithromycin [redacted] with and without Regular Strength Maalox® are shown in Table 1. When azithromycin [redacted] was administered with Maalox®, the mean $AUC_{0-24}$ increased 7%, the mean $AUC_{0-t}$ increased 10%, and the mean $C_{max}$ was not altered. The mean $T_{max}$ increased 14% from 4.67 hrs to 5.33 hrs. Thus, administration of azithromycin with Regular Strength Maalox® modestly increased the extent but not the rate of azithromycin [redacted] absorption.

**Table 1. Mean (CV%) azithromycin pharmacokinetic following administration azithromycin [redacted] with and without 20 mL Regular Strength Maalox®**

| Parameter | Azithromycin [redacted] alone | Azithromycin [redacted] Maalox |
|---|---|---|
| $AUC_{0-24}$ (µg*hr/mL) | 8.75 (28%) | 9.39 (34%) |
| $AUC_{0-t}$ (µg*hr/mL) | 13.53 (28%) | 14.93 (37%) |
| $C_{max}$ (µg/mL) | 0.85 (31%) | 0.85 (30%) |
| $T_{max}$ (hrs) | 4.67 (34%) | 5.33 (19S%) |

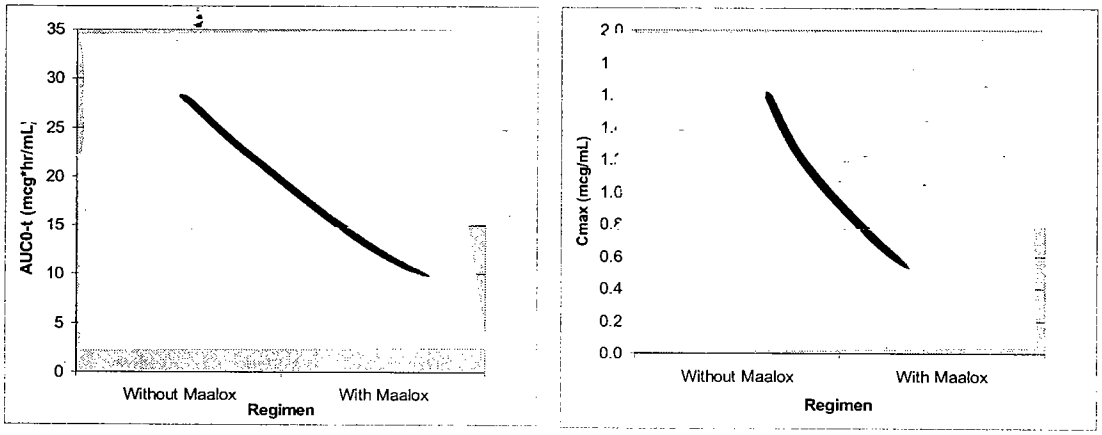
The geometric mean ratios and 90% confidence intervals for azithromycin (fed/fasted) are shown in Table 2. The 90% confidence intervals of the geometric mean ratio for $AUC_{0-t}$ and $C_{max}$ were within the predetermined no-effect boundary of 0.80 to 1.25.

**Table 2. Geometric mean ratios (with/without) and 90% confidence intervals for azithromycin administered with and without Regular Strength Maalox®**

| Parameter | Point estimate | 90% CI |
|---|---|---|
| $AUC_{0-24}$ | 1.057 | 0.977 - 1.144 |
| $AUC_{0-t}$ | 1.078 | 0.996 - 1.168 |
| $C_{max}$ | 1.013 | 0.947 - 1.084 |

The individual $AUC_{0-72}$ and $C_{max}$ values are shown in Figure 2. Except for one subject, the range of $AUC_{0-t}$ and Cmax values from subjects administered azithromycin with Regular Strength Maalox® is within the range of values from subjects administered azithromycin without Regular Strength Maalox®.

**Figure 2. Individual $AUC_{0-t}$ (left) and $C_{max}$ (right) values of azithromycin following administration of 2 g azithromycin with and without Regular Strength Maalox® (bold red line represents the geometric mean)**




**SAFETY:**

No deaths, serious adverse events (SAEs), or withdrawals due to adverse events (AEs) were reported in the study. Following a single 2 g dose of azithromycin alone, 17 subjects (43.6%) experienced a total of 24 AEs (18 of which were GI-related). Following a single 2-g dose of azithromycin + Regular Strength Maalox®, 14 subjects (35.9%) experienced a total of 28 AEs (18 GI-related). The most frequently reported AEs were abdominal pain and diarrhea. No subjects vomited during the study. The treatment emergent AEs are summarized in Table 3.

**Table 3. Treatment emergent signs and symptoms (Number of subjects)**

| Body System | Azithromycin [redacted] alone (n=39) | Azithromycin [redacted] + Regular Strength Maalox (n=39) |
|---|---|---|
| **Body as a whole** | | |
| Abdominal pain | 9 (23.1%) | 4 (10.3%) |
| **Digestive system** | | |
| Diarrhea | 6 (15.4%) | 7 (17.9%) |
| Nausea | 1 (2.6%) | 3 (7.7%) |
| Vomiting | 0 (0.0%) | 0 (0.0%) |
| Flatulence | 2 (5.1%) | 3 (7.7%) |
| Increased appetite | 0 (0.0%) | 1 (2.6%) |

**CONCLUSIONS:**
Administration of azithromycin [redacted] with Regular Strength Maalox® modestly increased the $AUC_{0-t}$ and $C_{max}$ of azithromycin.

Although not statistically significant, administration of azithromycin [redacted] with Regular Strength Maalox® was associated with a mild increase in adverse events associated with the digestive system.

**COMMENTS:**
Plasma samples for azithromycin serum concentration determination were obtained for up to 72 hrs. The concentration of azithromycin was above the LLOQ ( [redacted] at 72 hrs in the azithromycin alone and azithromycin + Maalox® samples from all 39 subjects. Even though the sponsor stated that the $C_{max}$ and $AUC_{0-t}$ were analyzed as the pharmacokinetic endpoints, the $AUC_{0-t}$ should be reported as the $AUC_{0-72}$.

**4.2.6 An open-label study of the pharmacokinetics, safety, tolerability, and clinical response of a 60 mg/kg single oral dose of an experimental azithromycin dihydrate microspheres [redacted] -release formulation in pediatric subjects (Study A0661113)**

Dates: June 24, 2003 to August 28, 2003
Clinical sites: [redacted]

Analytical site: [redacted]

**OBJECTIVES:**
The primary objective of the study is to evaluate the pharmacokinetics, safety, tolerability, and clinical response in the fasted and fed states of a single oral dose of azithromycin in pediatric patients with non-life-threatening respiratory tract infections or with uncomplicated skin or soft tissue infections for which azithromycin, alone or in combination, could be beneficial.

**FORMULATIONS:**
Azithromycin [redacted] poloxamer 407, 2 g (Pfizer, Lot No. T0582V-G1, FID No. G02701AA)

**STUDY DESIGN:**
This study was an open-label, non-randomized, single-dose study. Forty-four pediatric patients (27 male, 17 female) between 3 months and 16 yrs received a single oral dose of azithromycin [redacted] Six patients were enrolled into each of the following age groups:

| | |
|---|---|
| Group I: | 3 months to 18 months, dosed on an empty stomach |
| Group II: | >18 months to 36 months, dosed on an empty stomach |
| Group III: | >36 months to 48 months, dosed on an empty stomach |
| Group IV: | >48 months to 8 yrs, dosed on an empty stomach |
| Group V: | >8 yrs to 12 yrs, dosed on an empty stomach |
| Group VI: | >12 yrs to 16 yrs, dosed on an empty stomach |
| Group VII: | 18 months to 8 yrs, dosed following a high-fat meal |

Each subject in Groups I through VI received a single oral dose of azithromycin [redacted]60 mg/kg (total dose not to exceed 2g) on an empty stomach (at least 1 hour before or 2 hours after a meal.) At one study site, an additional cohort of 8 patients (Group VII), ages 18 months to 8 years (inclusive) was dosed with azithromycin [redacted]60 mg/kg within 5 min of consuming an age-appropriate, high-fat breakfast. The investigator assigned patients to be dosed on an empty stomach or under fed conditions based on subject (and/or parent) preference until the fed cohort was filled. Thereafter, patients only had the option of receiving the study drug on an empty stomach. Administration of aluminum- or magnesium-containing antacids was prohibited within 2 hrs before and 4 hours after study drug dosing.

NOTE: The contents of the high-fat breakfast were not reported in the study report and it is unknown if the high-fat meal evaluated in the study met the criteria of an FDA high-fat meal.

Pharmacokinetic data from patients who vomited within 2 hrs following dosing with azithromycin [redacted] were analyzed separately. The time of vomiting in relationship to the dose of azithromycin [redacted] and the approximate volume of emesis were recorded in the CRF. A subject who vomited within 5 min of azithromycin [redacted] administration received alternative therapy. Azithromycin was not re-administered to any subject who vomited.

Blood samples for determination of serum azithromycin concentrations were obtained at time 0 (predose), 1.5, 3, 6, 12-24, 48-72, 96, and 144-168 hrs after administration.

**AZITHROMYCIN ASSAY METHODOLOGY:**
High performance liquid chromatography with mass spectrometry detection (LC/MS/MS)

| Criterion | Serum | Comments |
|---|---|---|
| Concentration range | | Satisfactory |
| LLOQ | | Satisfactory |
| Linearity | | Satisfactory |
| Accuracy | | Satisfactory |
| Precision | | Satisfactory |
| Specificity | | Satisfactory |
| Stability | | Satisfactory |

RT = room temperature

**PHARMACOKINETIC ANALYSIS:**
Maximum observed serum concentrations ($C_{max}$) of azithromycin were estimated directly from the experimental data. $T_{max}$ was defined as the time of the first occurrence of $C_{max}$. Area under the plasma concentration-time curve (AUC) from time zero to the last quantifiable concentration ($AUC_{0-t}$) and when data permitted, from time 0 to 24 hrs post-dose ($AUC_{0-24}$), from time 0 to 72 hrs post-dose ($AUC_{0-72}$), and from time 0 to 96 hrs post-dose ($AUC_{0-96}$). When data permitted, the terminal phase elimination rate constant (Kel) was estimated using least-squares regression analysis of the serum concentration-time data obtained during the terminal log-linear phase. The terminal phase half-life ($t_{1/2}$) was calculated as ln(2)/Kel. The AUC extrapolated to infinity ($AUC_{0-\infty}$) was estimated as the sum of $AUC_{0-t}$ plus $C_{last}$/Kel.

**STATISTICAL ANALYSIS:**
The arithmetic means were reported for all pharmacokinetic parameters except $T_{max}$, for which the median was reported. All pharmacokinetic parameters were summarized and tabulated using descriptive statistics. Exploratory plots of $C_{max}$, $AUC_{0-t}$ and/or $AUC_{0-72}$ versus age and sex were evaluated to determine any trends.

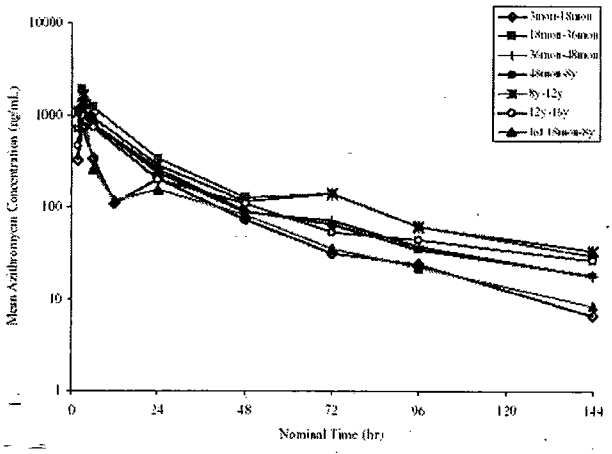
**RESULTS:**
Forty-four patients were enrolled into and 43 patients completed the study. One subject (Subject 10011007) in the fed state cohort discontinued due to an adverse event (patients vomited immediately after dosing and discontinued without completing the protocol). The mean (SD) age, weight, and height of the 44 patients randomized are shown in Table 1.

**Table 1. Demographic characteristics by cohort**

| Demographic | Group I | Group II | Group III | Group IV | Group V | Group VI | Group VII |
|---|---|---|---|---|---|---|---|
| **Sex** | | | | | | | |
| Male | 3 | 2 | 1 | 4 | 4 | 6 | 7 |
| Female | 3 | 4 | 5 | 2 | 2 | 0 | 1 |
| **Age** | | | | | | | |
| >1 month - 2 yrs | 6 | 6 | 0 | 0 | 0 | 0 | 2 |
| >2 yrs - 12 yrs | 0 | 0 | 6 | 6 | 6 | 4 | 6 |
| >12 yrs - 18 yrs | 0 | 0 | 0 | 0 | 0 | 2 | 0 |
| **Weight (kg)** | 9.3 (1.9) | 14.5 (1.2) | 17.5 (1.9) | 24.3 (4.6) | 39.3 (7.8) | 59.3 (19.5) | 17.7 (3.8) |
| **Height (cm)** | 71.6 (4.2) | 90.2 (6.0) | 103.2 (7.3) | 117.7 (6.9) | 141.2 (4.0) | 162.0 (12.2) | 106.0 (12.1) |

The mean serum azithromycin concentration vs. time profiles following administration of 60 mg/kg (maximum 2 g) azithromycin [redacted] an empty stomach or following a high-fat meal in different age groups are shown in Figure 1. The mean azithromycin serum concentrations appear comparable across the different age groups. Among all of the profiles, the mean azithromycin concentration-time profiles of the youngest age group (Group I, 3 to 18 months) and the fed group (Group VII, 18 months to 8 years) were at the lower end, while the mean azithromycin concentration-time profile of the second youngest group (Group II, 18 to 36 months) was at the upper end. With the exceptions of two patients in Group I and one subject in Group VII, all patients had quantifiable serum concentrations of azithromycin 96 hrs after dosing.

**Figure 1. Mean serum azithromycin concentration-time profiles following administration of 60 mg/kg azithromycin [redacted] (maximum 2 g) on an empty stomach (n=36) and under fed conditions (n=7)**




The mean azithromycin pharmacokinetic parameters following administration of 60 mg/kg azithromycin [redacted] are shown in Table 2. The mean azithromycin exposure ($AUC_{0-96}$ and $C_{max}$) were comparable in pediatric patients aged 3 months to 16 years given large inter-individual variability. However, patients in group I (3 months to 18 months) had the lowest mean $C_{max}$ and $AUC_{0-96}$ whereas patients in group II (18 to 36 months) had the highest mean $C_{max}$ and $AUC_{0-96}$. The individual $C_{max}$ and $AUC_{0-96}$ values among

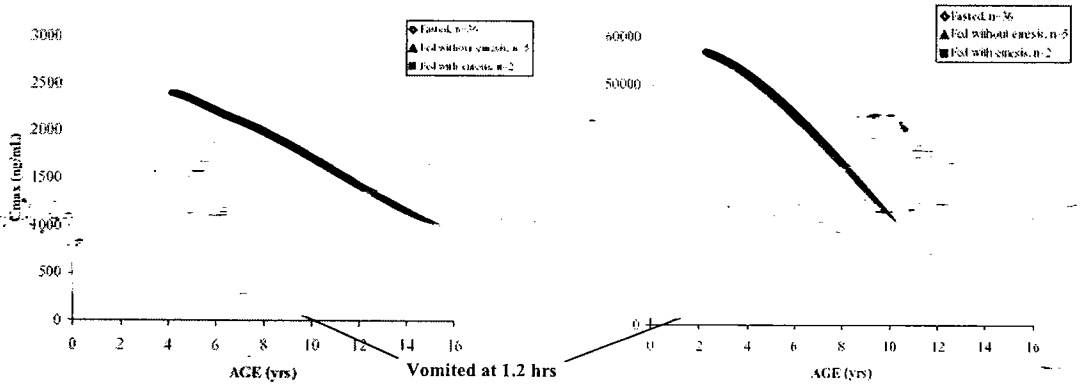
patients in group I were consistently low whereas two patients in group II (Patients 10031037 and 10031046) were associated with unexpectedly high $C_{max}$ values (2,590 and 2,340 ng/mL, respectively) and $AUC_{0-96}$ values (50,100 and 38,600 ng*hr/mL, respectively). Without these two patients, the adjusted mean $C_{max}$ and $AUC_{0-96}$ values were 1,593 ng/mL and 25,250 ng*hr/mL, respectively. Since the pH of the GI tract affects the extent of the absorption of azithromycin [redacted] variable GI physiological conditions in the younger age groups might explain the large variability of the exposure.

**Table 2. Mean (SD) azithromycin pharmacokinetic parameters following administration of 60 mg/kg (maximum 2 g) azithromycin [redacted] to pediatric patients aged 3 months to 16 yrs**

| Group | Dose (mg) | $C_{max}$ (ng/mL) | $T_{max}$ (hrs) | $AUC_{0-t}$ (ng*hr/mL) | $AUC_{0-24}$ (ng*hr/mL) | $AUC_{0-72}$ (ng*hr/mL) | $AUC_{0-96}$ (ng*hr/mL) |
|---|---|---|---|---|---|---|---|
| **Group I (n=6)** | 550 (110) | 736 (200) | 3.0 (3-3) | 11,317 (2,676) | 6,293 (1,170) | 10,682 (1,727) | 11,658 (2,066) |
| **Group II (n=6)** | 860 (62) | 1,883 (501) | 3.0 (3-3) | 33,750 (11,766) | 19,750 (5,329) | 29,517 (9,658) | 31,617 (10,704) |
| **Group III (n=6)** | 1,040 (124) | 1,231 (416) | 3.5 (3-6) | 21,417 (5,637) | 12,872 (3,794) | 18,967 (4,868) | 20,167 (5,228) |
| **Group IV (n=6)** | 1,460 (278) | 1,128 (344) | 3.5 (3-6) | 21,150 (6,596) | 12,973 (4,219) | 18,800 (5,944) | 19,900 (6,256) |
| **Group V (n=6)** | 1,957 (106) | 1,647 (377) | 3.5 (3-6) | 27,933 (9,900) | 16,000 (4,998) | 23,850 (8,035) | 25,733 (8,948) |
| **Group VI (n=6)** | 2,000 (0.0) | 983 (346) | 4.0 (3-6) | 19,410 (8,375) | 10,962 (4,773) | 16,447 (6,896) | 17,728 (7,514) |
| **Group VII (n=8)** | 1,020 (240) | 1,407 (616) | 2.4 (1.5-3) | 12,283 (5,541) | 7,437 (3,019) | 11,021 (4,499) | 12,548 (4,770) |

Individual $C_{max}$ and $AUC_{0-t}$ values were randomly distributed across pediatric patients aged 3 months to 16 years (Figure 2). The large degree of inter-subject variability, especially with the younger age groups, is demonstrated in the plots and the two patients in Group II with higher than average $C_{max}$ and AUC values are noticeable. In the fed group (solid symbols), $AUC_{0-t}$ values in 4 out of 7 patients resided at the lower bound of the distribution whereas individual $C_{max}$ values were randomly distributed among the others. Thus, administration of azithromycin [redacted] with food appeared to have no effect on the exposure of azithromycin.

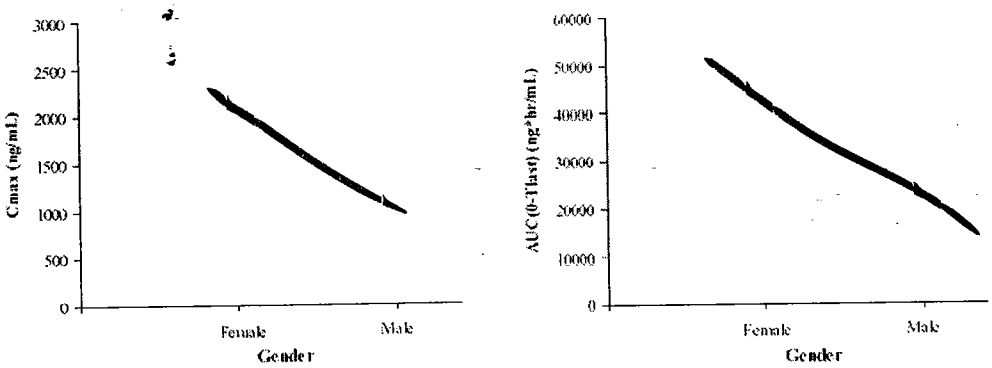
**Figure 2. Individual $C_{max}$ (left) and $AUC_{0-t}$ (right) values of azithromycin following administration of 60 mg/kg (max 2 g) azithromycin [redacted]**



No patients who were dosed on an empty stomach vomited while three patients who were dosed after a high-fat meal vomited (1 subject vomited approximately 11 minutes after dosing and was withdrawn from the study, and 2 patients vomited at 1.2 and 2.25 hours after dosing). The patients who vomited are designated as solid red square in Figure 2. Vomiting at 2.25 hrs appears to have no impact on the $C_{max}$ and $AUC_{0-t}$ values of azithromycin. However, the patient who vomited 1.20 hrs after administration was associated with the lowest $AUC_{0-72}$ and $AUC_{0-t}$ values compared to all other patients. Although the low $AUC_{0-t}$ value may be the result of vomiting, insufficient data are available to determine the impact of vomiting at approximately 1 hr following administration.

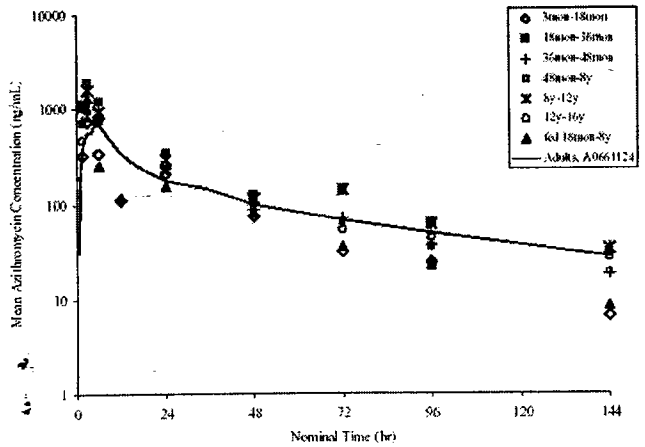
There appeared to be no effect of on the individual $C_{max}$ and $AUC_{0-t}$ values azithromycin based on visual inspection of the data (Figure 3). The range of values were similar for females and males.

**Figure 3. Individual azithromycin $C_{max}$ (left) and $AUC_{0-t}$ (right) values in females and males following administration of 60 mg/kg (max 2 g) azithromycin in the fasted state**




The mean pharmacokinetic profile in pediatric patients given 60 mg/kg (max 2g) azithromycin on an empty stomach was comparable to that observed in adults given 2g azithromycin under fasted conditions in Study A0661124 (Figure 4). Study A0661124 compared to bioequivalence of 2 g azithromycin from the ICH supplies and Phase 3 study supplies under fasted conditions. The mean $T_{max}$ in adults was approximately 5 hrs and the mean $T_{max}$ in pediatric patients was 3-4 hrs. The mean $AUC_{0-72}$ and $C_{max}$ in pediatric patients ranged from 10.7 to 29.5 µg*hr/mL and 0.74 to 1.88 µg/mL, respectively and encompassed the mean $AUC_{0-72}$ and $C_{max}$ values in fasted adult subjects with the ICH supplies (13.9 µg*hr/mL and 0.82 µg/mL).

**Figure 4. Mean azithromycin serum concentrations following administration of 60 mg/kg (max 2 g) azithromycin [redacted] in pediatric patients aged 3 month to 16 yrs and healthy adults**




In the adult food effect study with 2g azithromycin [redacted] (Study A0661107), ingestion of a high-fat meal prior to dosing increased the $C_{max}$ and $AUC_{0-t}$ by 111% and 19%, respectively. In this study, however, the azithromycin $AUC_{0-t}$ and $C_{max}$ in the fed pediatric patients appeared to be randomly distributed among that of patients who were dosed on an empty stomach, which may indicate that food had less of an effect on the azithromycin exposure in pediatric patients. However, the small sample size and parallel design limit the ability to make such conclusions in this study.

**SAFETY:**
No deaths or serious adverse events were reported in the study. One subject in the fed cohort discontinued from the study due to an adverse event (vomiting). A total of 27 AEs were reported, of which 17 were considered to be related to the study medication. All AEs were mild in severity.

Among patients who were dosed on an empty stomach (6 patients in each age group), AEs were reported for 4 patients in Group I, 2 patients in Group II, 1 patient in Group III, 2 patients in Group IV, 4 patients in Group V, and 1 subject in Group VI. Among the eight patients dosed under fed conditions (Group VII), 6 patients had AEs (Table 3).

**Table 3. Digestive system treatment-emergent signs and symptoms, N (%)**

| Body System | Group I (n=6) | Group II (n=6) | Group III (n=6) | Group IV (n=6) | Group V (n=6) | Group VI (n=6) | Group VII (n=8) |
|---|---|---|---|---|---|---|---|
| **Digestive system** | | | | | | | |
| Abdominal pain | 0 | 0 | 0 | 0 | 1 (17%) | 1 (17%) | 2 (25%) |
| Diarrhea | 3 (50%) | 1 (17%) | 0 | 0 | 0 | 0 | 3 (38%) |
| Nausea | 0 | 0 | 0 | 1 (17%) | 0 | 0 | 1 (13%) |
| Vomiting | 0 | 0 | 0 | 0 | 0 | 0 | 3 (38%) |

The most frequently reported AEs were related to the GI system and consisted of diarrhea and abdominal pain. Vomiting was reported by three patients in Group VII only. One patient vomited approximately 11 min post-dose and was discontinued from the study. No post-dose blood samples were collected for

pharmacokinetic analysis from this patient. Two patients (Patients 11001 and 11009) vomited 2.25 and 1.20 hrs after administration and remained in the study.

**CONCLUSIONS:**
In pediatric patients with non-life-threatening respiratory tract or uncomplicated skin or soft tissue infections, serum azithromycin exposure was similar among patients aged 3 months to 16 years following a single oral dose of 60 mg/kg (maximum 2g) of azithromycin [redacted]

Pediatric patients aged 3 months to 18 months had the lowest $C_{max}$ and $AUC_{0-t}$ values among pediatric patients. Compared to adults in the fasted state, the $C_{max}$ and $AUC_{0-t}$ values in pediatric patients aged 3 months to 18 months were 86% and 78% of adult values. Thus, pediatric patients aged 3 month to 18 months may require greater than 60 mg/kg of azithromycin [redacted] to obtain an exposure comparable to older pediatric patients and adults.

Although azithromycin [redacted] was well tolerated by all age groups when dosed on an empty stomach, the incidence of gastrointestinal adverse events were increased following administration of a high-fat meal. The only patients that vomited after administered of azithromycin [redacted] did so in the fed state.

**4.2.7 Phase 1, observer-blind, randomized, parallel study to evaluate the gastrointestinal tolerability of 2 g doses of two different [redacted]-release formulations of azithromycin compared to a single 2 g dose of the commercial formulation in healthy adult volunteers (Study A0661086)**

Dates: November 28, 2001 to December 17, 2001
Clinical sites. [redacted]
Analytical site

**OBJECTIVES:**
The primary objective of this study was to evaluate the gastrointestinal (GI) tolerability of single 2-g oral doses of two different sustained-release formulations of azithromycin compared to a single 2-g dose of the commercially available sachets in healthy adult volunteers. The secondary objective of this study was to evaluate the pharmacokinetic profile of each formulation in a subset of these volunteers.

**FORMULATIONS:**
Azithromycin [redacted] poloxamer 407, 2 g (Pfizer, Lot No. ED-G-377-901, FID No. G02493AA)
Magnesium hydroxide powder, 250 mg (Pfizer, Lot No. ED-G-376-901, FID No. G02435AA)
Azithromycin commercial sachet, 1 g (Pfizer, Lot No. 1HP033A-G1)

**STUDY DESIGN:**
This study was a randomized, observer-bind, parallel group, single dose study. Three hundred twenty subjects 18 to 65 yrs of age were stratified by gender and randomly assigned with equal probability to one of the following three treatment groups:

ASR1 - 2 g azithromycin [redacted] microspheres
ASR2 - 2 g azithromycin [redacted] microspheres with 250 mg magnesium hydroxide
ASach - 2 g azithromycin commercial sachet (2 × 1 g sachet)

Following an overnight fast of at least 8 hours, randomized subjects received a single dose of azithromycin [redacted] 2 g without magnesium hydroxide (ASR1), azithromycin [redacted] 2 g plus magnesium hydroxide (ASR2), or azithromycin sachets 2 g (ASach). All preparations were constituted in sterile water (for injection or irrigation) and consumed in a total volume of 8 ounces (240 mL). Water was added directly to the individual powders for ASR1 and ASach prior to mixing. For ASR2, the formulation of azithromycin dihydrate microspheres and the magnesium hydroxide powders were combined prior to mixing with water. Subjects were dosed after an overnight fast of at least 8 hrs.

The first 6 subjects at each site (24 subjects total) were assessed for azithromycin pharmacokinetics. On Day 1, blood samples were collected at the following times: 0 (just prior to dosing), 1, 2, 3, and 4 hrs after drug administration.

**AZITHROMYCIN ASSAY METHODOLOGY:**
High performance liquid chromatography [redacted] (LC, [redacted]

| Criterion | Serum | Comments |
|---|---|---|
| Concentration range | [redacted] | Satisfactory |
| LLOQ | | Satisfactory |
| Linearity | | Satisfactory |
| Accuracy | | Satisfactory |
| Precision | | Satisfactory |
| Specificity | | Satisfactory |
| Stability | | Satisfactory |

**PHARMACOKINETIC ANALYSIS:**
Maximum observed serum concentrations ($C_{max}$) of azithromycin were estimated directly from experimental data. $T_{max}$ was defined as the time of the first occurrence of $C_{max}$. Individual azithromycin serum concentrations, $C_{max}$, and $T_{max}$ were summarized using descriptive statistics and tabulated. Mean and individual serum concentrations were plotted.

**GASTROINTESTINAL TOLERABILITY:**
The rates and severity of GI adverse events (nausea, vomiting, diarrhea, abdominal pain) were tabulated for each treatment. The difference in the proportion of subjects receiving ASR1 or ASR2 experiencing one or more GI adverse events and the proportion of subjects receiving ASach experiencing the same GI adverse events was estimated. Inferential statistics and 95% confidence intervals on the differences in these proportions were calculated (ASR1 vs. ASach and ASR2 vs. ASach) using the normal approximation to the binomial distribution with continuity correction.

**RESULTS:**
Three hundred twenty subjects were enrolled and completed the study. One hundred six subjects received ASR1, 106 subjects received ASR2, and 108 subjects received ASach. Pharmacokinetic samples were obtained from 24 subjects, eight subjects for each formulation. The mean (SD) age, weight, and height of the 320 subjects by treatment group are shown in Table 1.

**Table 1. Mean (SD) demographic parameters**

| | ASR1 | | ASR2 | | ASach | |
|---|---|---|---|---|---|---|
| **Demographic** | **Male** | **Female** | **Male** | **Female** | **Male** | **Female** |
| Age (yrs) | 33.4 (11.8) | 34.5 (13.8) | 30.4 (11.4) | 32.8 (13.3) | 27.0 (9.2) | 32.4 (12.2) |
| Weight (kg) | 80.6 (7.7) | 65.5 (9.0) | 80.7 (9.9) | 65.7 (9.9) | 79.4 (10.2) | 63.7 (7.9) |
| Height (cm) | 177.5 (6.2) | 164.3 (6.4) | 178.4 (7.6) | 164.7 (6.7) | 178.4 (5.8) | 163.9 (6.3) |

ASR1 = 2 g azithromycin without magnesium hydroxide
ASR2 = 2 g azithromycin plus magnesium hydroxide
ASach = 2 g azithromycin sachets (2 × 1 g sachet)

The mean azithromycin serum concentration-time profiles following administration of 2 g azithromycin without (ASR1) and with (ASR2) magnesium hydroxide and 2 g azithromycin commercial sachets are shown in Figure 1. The mean azithromycin serum concentrations at each sampling time are shown in Table 2.

**Table 2. Mean (SD) azithromycin serum concentration following administration of 2 g azithromycin without (ASR1) and with (ASR2) magnesium hydroxide compared to 2 g azithromycin sachets (ASach)**

| Treatment group | Time (hrs) | | | |
|---|---|---|---|---|
| | **1** | **2** | **3** | **4** |
| ASR1 | 0.591 (0.514) | 0.788 (0.186) | 0.791 (0.118) | 0.739 (0.165) |
| ASR2 | 0.572 (0.390) | 0.537 (0.214) | 0.602 (0.284) | 0.638 (0.216) |
| ASach | 2.00 (1.39) | 1.00 (0.49) | 0.916 (0.313) | 0.703 (0.165) |

ASR1 - 2 g azithromycin microspheres without magnesium hydroxide
ASR2 - 2 g azithromycin microspheres plus 250 mg magnesium hydroxide
ASach - 2 g azithromycin sachets (2 × 1 g sachet)

Administration of 2 g azithromycin without (SR1) and with magnesium hydroxide (ASR2) resulted in lower azithromycin serum concentrations for the first 3 hrs and similar concentrations at 4 hrs compared

to administration of 2 g azithromycin sachet (Table 3). In addition, administration of ASR2 resulted in lower mean serum concentrations at 2-4 hrs compared to ASR1.

**Figure 1. Mean azithromycin serum concentrations following administration of 2 g azithromycin [redacted] (with and without magnesium hydroxide) and 2 g azithromycin sachets to healthy subjects**

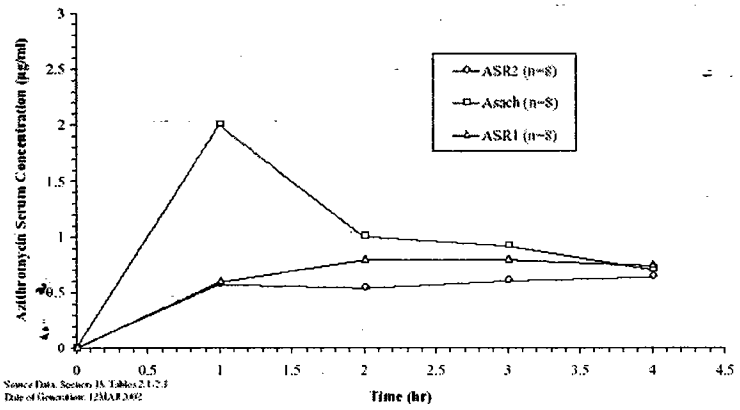



**Table 3. Ratios of mean azithromycin serum concentrations for ASR1/ASach, ASR2/Asach, and ASR2/ASR1**

| Treatment group | Time (hrs) | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| ASR1/ASach | 0.29 | 0.79 | 0.86 | 1.05 |
| ASR2/ASach | 0.29 | 0.54 | 0.66 | 0.91 |
| ASR2/ASR1 | 0.97 | 0.68 | 0.76 | 0.86 |

Blood samples for azithromycin concentration determination were obtained from a single subject (Subject 602) who vomited 1.17 hrs after administration of ASach. Blood samples were not obtained from any subject who received ASR1 or ASR2 and vomited. The serum concentrations of azithromycin from Subject 602 and the mean and range of the eight subjects that received ASach are shown in Table 4. Azithromycin concentrations from Subject 602 were below the mean (n=8) for all four samples and was the minimum reported concentration for the 3-hr and 4-hr time points.

**Table 4. Mean and range of azithromycin concentrations (µg/mL) from all subjects who received ASach compared to Subject 602**

| Data source | Time (hrs) | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Subject 602 | 1.070 | 0.523 | 0.435 | 0.459 |
| ASach (mean) | 2.004 | 1.001 | 0.916 | 0.703 |
| ASach (range) | 0.349-3.990 | 0.311-1.890 | 0.435-1.450 | 0.459-0.897 |

**SAFETY:**

For ASR1 a total of 124 adverse events were reported or observed in 75 subjects (71%) as shown in Table 5. Most were mild in intensity (94%) and 7 of the 124 events (6%) were moderate. All moderate events were GI related (abdominal pain, nausea and vomiting). For ASR2, a total of 123 adverse events were

reported or observed in 68 subjects (64%). Most were mild in intensity (98%) and 2 of the 123 events (2%) were moderate. One subject experienced a GI related event, and the other subject experienced back pain. For ASach, a total of 190 adverse events were reported in 88 subjects (81%). Most were mild in intensity (92%), 15 were moderate and 1 was severe. Of the moderate events 13 of the 15 subjects experienced a GI related event. Two subjects experienced dizziness and syncope, both treatment related. One subject had a severe event of nausea.

**Table 5. Treatment-emergent signs and symptoms - All causalities (number of subjects [%])**

| Adverse Event | ASR1 (n=106) | ASR2 (n=106) | ASach (n=108) |
|---|---|---|---|
| Total number of AEs | 124 | 123 | 190 |
| Number of subjects with AEs | 75 (71%) | 68 (64%) | 88 (81%) |
| Severity of AEs | | | |
| **Mild** | **117** | **121** | **174** |
| **Moderate** | **7** | **2** | **15** |
| Abdominal pain | 1 (0.9%) | 0 | 2 (1.9%) |
| Syncope | 0 | 0 | 1 (0.9%) |
| Nausea | 3 (2.8%) | 0 | 6 (5.6%) |
| Vomiting | 3 (2.8%) | 1 (0.9%) | 5 (4.6%) |
| Back pain | 0 | 1 (0.9%) | 0 |
| Dizziness | 0 | 0 | 1 (0.9%) |
| **Severe** | **0** | **0** | **1** |
| Nausea | 0 | 0 | 1 (0.9%) |

Administration of a 2 g dose of both azithromycin [redacted] formulations (ASR1 and ASR2) was associated with significantly lower incidences of nausea and/or vomiting compared to a 2 g dose of ASach (2 × 1 g sachet). Subjects administered ASR2 also reported a significantly lower incidence of diarrhea compared to ASach. The proportions of subjects who had single or combined GI events of nausea, vomiting, and diarrhea were lower for ASR1 and ASR2 compared to those for ASach.

NOTE: Although the sponsor reported that three, one, and five subjects vomited after administration of ASR1, ASR2, and ASach, respectively, the number of subjects that vomited based on the case report forms is four, four, and 28, respectively. Thus, the percentage of subjects that vomited following administration of ASR1, ASR2, and ASach was 3.8%, 3.8%, and 25.9%, respectively.

**CONCLUSIONS:**

Azithromycin [redacted] without (ASR1) and with (ASR2) magnesium hydroxide increased the gastrointestinal tolerability by decreasing incidences of subjects who had single or combined GI events of nausea, vomiting, and diarrhea compared with the azithromycin sachet. The two azithromycin [redacted] formulations significantly decreased the relevant events of nausea and/or vomiting.

The sparse pharmacokinetic data demonstrated that 2 g of azithromycin [redacted] with and without magnesium hydroxide reduced the initial azithromycin serum concentrations compared with 2 g dose of azithromycin sachet.

Mean azithromycin concentrations were consistently lower following administration of azithromycin [redacted] with magnesium hydroxide compared to azithromycin [redacted] without magnesium hydroxide.

**4.2.8 An open-label, randomized, crossover pilot study evaluating the pharmacokinetics and tolerability of a single 2 gram oral dose of an experimental azithromycin dihydrate microspheres [redacted] release formulation administered with magnesium hydroxide compared to a single 2 gram oral dose of the commercial azithromycin formulation under fasted conditions in healthy subjects (Study A0661090)**

Dates: May 15, 2002 to June 24, 2002
Clinical site:
Analytical site [redacted]

**OBJECTIVES:**
The primary objective of this study was to evaluate the relative bioavailability and pharmacokinetic profile of a single 2 g oral dose of an experimental azithromycin dihydrate microspheres [redacted] release (ER) formulation administered with magnesium hydroxide compared to that of a single 2 g oral dose of the commercially available sachets, each under fasted conditions in healthy subjects.

A secondary objective of this study was to evaluate the tolerability of a single 2 g oral dose of an experimental azithromycin dihydrate microspheres ER formulation administered with magnesium hydroxide compared to that of a single 2 g oral dose of the commercially available sachets, each under fasted conditions in healthy subjects.

**FORMULATIONS:**
Azithromycin microspheres [redacted] poloxamer 407, 2 g (Pfizer, Lot No. ED-0-453-Y01, FID No. G02413AA)
Magnesium hydroxide powder, 250 mg (Pfizer, Lot No. ED-G-376-901, FID No. G02435AA)
Azithromycin powder for oral suspension (Sachet), 1 g (Pfizer, Lot No. 1HP033A-G2)

**STUDY DESIGN:**
This study was a randomized, open-label, two-way crossover, single-dose study of azithromycin in fasted healthy adult subjects. Sixteen male and female subjects 18 to 55 yrs of age (randomly assigned to one of the two treatment sequences) received either a single 2 g dose of azithromycin dihydrate microspheres ER with magnesium hydroxide (ASR) or a single 2 g (2 × 1 g sachet) dose of the commercial azithromycin IR sachets (ASach) in a fasted state on Day 1 (first dosing day). Following at least a 14-day washout period, subjects in each treatment sequence were crossed over to receive the formulation not received during period 1.

The azithromycin formulations were reconstituted per separately provided written dosing instructions (ASR) or product label instructions (ASach) such that the total volume of each formulation to be ingested was 240 mL. Subjects were dosed at approximately 0800 hours following an 8-hour fast. In order to standardize conditions, all subjects were required to refrain from lying down, eating, or drinking beverages other than water during the first 4 hours after dosing.

Blood samples for determination of serum azithromycin concentrations were obtained at the following times relative to administration of each dose: 0 (predose), 0.5, 1, 2, 3, 4, 6, 8 12, 16, 24, 36, and 48 hrs after administration.

**AZITHROMYCIN ASSAY METHODOLOGY:**
High performance liquid chromatography [redacted] (LC/ [redacted]

| Criterion | Serum | Comments |
|---|---|---|
| Concentration range | | Satisfactory |
| LLOQ | | Satisfactory |
| Linearity | | Satisfactory |
| Accuracy | | Satisfactory |
| Precision | | Satisfactory |
| Specificity | | Satisfactory |
| Stability | | Satisfactory |

RT = room temperature

**PHARMACOKINETIC ANALYSIS:**
Maximum observed serum concentrations ($C_{max}$) of azithromycin were estimated directly from the experimental data. $T_{max}$ was defined as the time of the first occurrence of $C_{max}$. The area under the plasma concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration ($AUC_{0-t}$) was estimated using the log-linear trapezoidal rule.

The AUC0-tlast was used to estimate relative bioavailability (F) for both preparations:

$$F = \frac{(AUC_{0-last})_{SR}}{Dose_{SR}} * \frac{Dose_{Sach}}{(AUC_{0-last})_{Sach}}$$

**STATISTICAL ANALYSIS:**
For the comparison of treatment mean differences, log-transformed $AUC_{0-t}$ and $C_{max}$ and untransformed (or raw) $T_{max}$ were analyzed using a mixed effects model containing fixed effects for sequence, period and treatment and random effects for subject (within sequence). Estimates of the adjusted treatment mean differences (LSMeans), as well as their associated standard errors, were calculated, followed by the construction of the 90% confidence intervals around the differences. For $AUC_{0-t}$ and $C_{max}$ the anti-log (exponent) of the differences and confidence limits were taken to estimate the ratios between treatments and the confidence intervals of the ratios. The lower bound of the 90% confidence intervals for the ratio of mean $AUC_{0-t}$ (ASR vs. ASach) was used to determine the minimum relative bioavailability of the azithromycin [redacted] formulation.

**RESULTS:**
Sixteen subjects entered and completed the study. The mean (SD) age, weight, and height of the 16 subjects were 28.1 (7.3) yrs, 70.4 (10.7) kg, and 170.1 (11.7) cm, respectively.

The mean serum azithromycin concentration-time profiles following administration of 2 g azithromycin [redacted] with magnesium hydroxide (ASR) and 2 g azithromycin sachet (ASach) are shown in Figure 1. The mean (CV%) azithromycin $AUC_{0-t}$, $C_{max}$, and $T_{max}$ values following the administration of 2 g azithromycin [redacted] and azithromycin sachets in the fasted state are shown in Table 1. The mean $AUC_{0-t}$ and $C_{max}$ of azithromycin [redacted] were 10.7% and 60.9% lower, respectively compared to azithromycin sachets. The mean $T_{max}$ was delayed by 3.63 hours for azithromycin [redacted] compared to azithromycin sachets. The mean relative bioavailability of azithromycin [redacted] compared to the sachet was 89.1%. These data suggest that the sustained-release formulation had a greater impact on the rate than on the extent of azithromycin absorption.

**Figure 1. Mean serum azithromycin concentration-time profiles following administration of 2 g azithromycin [redacted] or 2 g commercial sachets to healthy subjects under fasted conditions (n=16)**

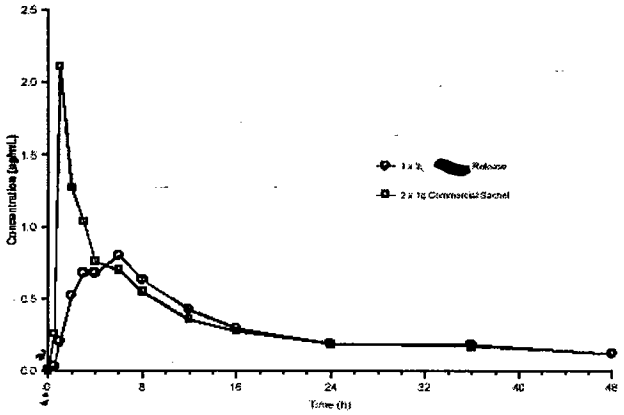



**Table 1. Mean (CV%) azithromycin pharmacokinetic parameters following administration of 2 g azithromycin [redacted] and 2 g azithromycin sachet under fasted conditions**

| Parameter | Azithromycin [redacted] | Azithromycin sachet |
|---|---|---|
| $AUC_{0-t}$ (µg*hr/mL) | 14.0 (25%) | 15.7 (24%) |
| $C_{max}$ (µg/mL) | 0.89 (26%) | 2.27 (42%) |
| $T_{max}$ (hrs) | 4.88 (38%) | 1.25 (46%) |
| F (%) | 89.1% | --- |

The geometric mean ratios and 90% confidence intervals for azithromycin [redacted] compared to azithromycin sachet are shown in Table 2. The 90% confidence interval of the geometric mean ratio for $AUC_{0-t}$ and $C_{max}$ were both outside of the 0.80 to 1.25 range and both were statistically significantly decreased.

**Table 2. Geometric mean ratios and 90% confidence intervals comparing azithromycin [redacted] (test) to azithromycin sachet (reference) under fasted conditions**

| Parameter | Point estimate | 90% CI |
|---|---|---|
| $AUC_{0-t}$ | 0.891 | 0.813 - 0.976 |
| $C_{max}$ | 0.411 | 0.348 - 0.486 |

**SAFETY:**

No deaths, serious adverse events, or withdrawals due to adverse events (AEs) were reported in this study. There were 16 AEs reported by 9 subjects receiving azithromycin [redacted] and 21 AEs reported by 11 subjects receiving azithromycin sachet. Most of the AEs in this study were of mild intensity. The AEs of moderate intensity were one incidence of abdominal pain, 3 incidences of nausea, and 1 incidence of vomiting. One subject (Subject 8) vomited in the ASach group 0.93 hrs following administration. All AEs of moderate intensity were experienced following treatment with ASach. There were no AEs of severe intensity.

The most frequent AEs reported were related to the gastrointestinal system, particularly nausea, abdominal pain, and diarrhea. All of the incidences of abdominal pain, diarrhea, flatulence, vomiting, and the majority of the incidences of nausea were considered treatment-related.

The incidence of nausea was lower following administration of azithromycin [redacted] than following administration of azithromycin sachet (Table 3) and only 2 of the 3 cases observed during azithromycin treatment were considered to be related to study medication.

**Table 3. Incidence (number of subjects) of gastrointestinal adverse events by treatment**

| | ASR (n=16) | ASach (n=16) |
|---|---|---|
| Nausea | 3 (19%) | 8 (50%) |
| Abdominal pain | 7 (44%) | 5 (31%) |
| Diarrhea | 3 (19%) | 3 (19%) |
| Flatulence | 0 | 1 (6%) |
| Vomiting | 0 | 1 (6%) |

**CONCLUSIONS:**

The data from this study suggest that the azithromycin [redacted] formulation [redacted] (magnesium hydroxide) slowed the rate of absorption of azithromycin and maintained at least an 80% systemic exposure relative to the azithromycin sachet.

The azithromycin [redacted] formulation had a greater impact on the rate of absorption compared to the extent of azithromycin absorption.

Although not statistically significant, azithromycin [redacted] was associated with a lower incidence of nausea and a decrease in the severity of gastrointestinal adverse events.

**4.2.9 Phase 1, randomized, parallel study to evaluate the toleration profile of 2 g and 3 g doses of a [redacted]-release formulation of azithromycin in healthy volunteers (Study A0661054)**

Dates: February 7, 2001 to March 25, 2001
Clinical sites: [redacted]
Analytical site

**OBJECTIVES:**
The purpose of the study was to evaluate the toleration profile of 2 g and 3 g doses of the azithromycin [redacted] formulation in healthy subjects.

**FORMULATIONS:**
Azithromycin [redacted] poloxamer 407, 2 g and 3 g (Pfizer, Lot No. ED-O-432-Z00, FID No. G02295AA)
Azithromycin commercial tablet, 250 mg (Pfizer, Lot No. N9056-G1, FID No. QC3261)
Vehicle (Pfizer, Lot No. ED-G-033-101, FID No. G02297AC)

**STUDY DESIGN:**
This study was a randomized, observer-bind, parallel group, single dose study. Three hundred fifty-nine subjects 18 to 65 yrs of age were randomly assigned to receive a single dose of either 2 g azithromycin [redacted] 3 g azithromycin [redacted] or 2 g of azithromycin commercial tablets (8 × 250 mg).

Subjects were dosed at approximately 0800 hours following an overnight fast of at least 8 hrs. The powder for the 2 g and 3 g azithromycin [redacted] formulations was reconstituted in 60 mL of water and administered. A rinse of 60 mL of water and an additional 120 mL of water was given to reach the total volume of 240 mL. The commercial 2 g dose of tablets (8 × 250 mg) was administered with 240 mL of water.

The first 6 subjects at each of the four sites (24 subjects total) were assessed for azithromycin pharmacokinetics. On Day 1, blood samples were collected at the following times: 0 (just prior to dosing), 2, and 3 hrs after drug administration.

**AZITHROMYCIN ASSAY METHODOLOGY:**
High performance liquid chromatography [redacted] (LC/ [redacted]

| Criterion | Serum | Comments |
|---|---|---|
| Concentration range | [redacted] | Satisfactory |
| LLOQ | | Satisfactory |
| Linearity | | Satisfactory |
| Accuracy | | Satisfactory |
| Precision | | Satisfactory |
| Specificity | | Satisfactory |
| Stability | | Satisfactory |

RT = room temperature

**PHARMACOKINETIC ANALYSIS:**
Pharmacokinetic data were summarized using descriptive statistics.

**GASTROINTESTINAL TOLERABILITY:**
The gastrointestinal (GI) adverse events (AEs) were the events of primary interest and data from the analysis of specific GI events (abdominal pain, diarrhea, dyspepsia, nausea, and vomiting) provided the toleration profile of each treatment. The proportion of subjects in each treatment group who experienced GI AEs was tabulated for nausea, vomiting, diarrhea, abdominal pain, and any other GI AE. The difference in proportion of subjects on the tablet formulation who had GI AEs and the proportion of subjects on each of the azithromycin [redacted] treatments with GI AEs was estimated. A 95% confidence interval on the difference in these proportions was calculated for 2 g azithromycin SR vs. 2 g of tablets and 3 g azithromycin [redacted] vs. 2 g of tablets using the normal approximation to the binomial with continuity correction.

**RESULTS:**
Three hundred fifty-nine subjects were enrolled into the study. One subject was discontinued due to withdrawn consent. The remaining 358 subjects completed the study. Pharmacokinetic samples were obtained from 24 subjects, eight subjects for each formulation. The mean age of the 359 subjects were 30.8 yrs and ranged from 18-65 yrs. The mean weight for males and females were 75.7 kg and 62.9 kg, respectively.

The mean azithromycin serum concentrations at 2 hrs and 3 hrs following administration of 2 g are shown in Table 1. The mean azithromycin serum concentrations following administration of 2 g azithromycin [redacted] and 2 g azithromycin tablets were similar at 2 hrs and 3 hrs. Azithromycin serum concentrations were approximately 1.51 times and 1.35 times greater following administration of 3 g azithromycin [redacted] compared to 2 g azithromycin [redacted] at 2 hrs and 3 hrs, respectively.

**Table 1. Mean (SD) azithromycin serum concentration at 2 hrs and 3 hrs following administration of 2 g azithromycin [redacted] 3 g azithromycin [redacted] and g azithromycin commercial tablets (8 × 250 mg)**

| Group | Serum concentration (μg/mL) | |
|---|---|---|
| | 2 hrs | 3 hrs |
| 2 g azithromycin [redacted] | 1.04 (0.38) | 0.93 (0.32) |
| 3 g azithromycin [redacted] | 1.57 (0.74) | 1.26 (0.32) |
| 2 g azithromycin tablets | 1.08 (0.40) | 0.96 (0.31) |

Although blood samples were obtained from the first 6 subjects at each of the four sites (24 subjects total), no blood samples were obtained from subjects who vomited. Thus, no data are available to compare azithromycin serum concentrations at the 2-hr and 3-hr sampling times among subjects who received 2 g azithromycin [redacted] and vomited from those who did not vomit.

**TOLERABILITY:**
No statistically significant differences were found in rates or severity of gastrointestinal (GI) adverse events (AEs) for the 2 g azithromycin [redacted] treated subjects compared to subjects treated with 2 g of azithromycin tablets (8 × 250 mg). Subjects treated with 3 g azithromycin [redacted] had a higher incidence of diarrhea and nausea than those treated with 2 g azithromycin tablets. However, there was no statistically significant difference in mean severity of the events for either the 2 g or 3 g azithromycin [redacted] treatment compared to 2 g of azithromycin commercial tablets.

**Table 3. Incidence of treatment-emergent gastrointestinal adverse events (Number [%])**

| Adverse Event | 2 g azithromycin [redacted] (n=120) | 3 g azithromycin [redacted] (n=120) | 2 g azithromycin tablets (n=119) |
|---|---|---|---|
| Abdominal pain | 50 (42%) | 61 (51%) | 52 (44%) |
| Diarrhea | 44 (37%) | 59 (49%) | 39 (33%) |
| Nausea | 28 (23%) | 51 (43%) | 30 (25%) |
| Vomiting | 6 (5%) | 9 (8%) | 7 (6%) |
| Dyspepsia | 4 (3%) | 7 (6%) | 11 (9%) |

Seventy-two percent of subjects who received 2 g azithromycin [redacted] treatment experienced at least one type of GI adverse event compared to 74 % of subjects who received 2 g commercial azithromycin tablets. The difference was not statistically significant. However, 85% of subjects on the 3 g azithromycin [redacted] treatment had at least one type of GI adverse event compared to 74% of subjects who received 2 g dose of commercial azithromycin tablets, a statistically significant difference.

According to the sponsor's incidence of treatment-emergent gastrointestinal adverse events, six, nine, and seven subjects vomited after administration of 2 g azithromycin [redacted] 3 g azithromycin [redacted] and 2 g azithromycin sachets, respectively. When requested, the sponsor provided vomiting information for each of the three regimens and reported that only five, seven, and two subjects vomited after administration of 2 g azithromycin [redacted] 3 g azithromycin [redacted] and 2 g azithromycin sachets, respectively. The rationale for the discrepancy is unknown.

**CONCLUSIONS:**

Mean serum azithromycin concentrations for the 2 g azithromycin [redacted] and 2 g of commercial tablets were similar at 2 and 3 hours and may suggest a similar exposure of azithromycin immediately following administration.

The serum azithromycin concentrations at 2 and 3 hours for 3 g azithromycin [redacted] were higher compared to 2 g azithromycin [redacted] and 2 g azithromycin commercial tablets. The higher concentrations were accompanied by a greater incidence of GI adverse events.

The safety profiles of the two azithromycin SR formulations were similar to those of the already approved comparator, commercial azithromycin tablets. Thus, the results of the present study did not confirm the superiority of azithromycin [redacted] 2 g and 3 g single dose formulations.

The toleration profiles of neither the 2 g nor 3 g azithromycin [redacted] formulations evaluated in this study can be recommended for further development.

### 4.3 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics
***New Drug Application Filing and Review Form***

General Information About the Submission

| | Information | | Information |
|---|---|---|---|
| **NDA Number** | NDA 50-797 | **Brand Name** | Zmax [redacted] |
| **OCPB Division (I, II, III)** | DPE III | **Generic Name** | Azithromycin |
| **Medical Division** | DAIDP, HFD-520 | **Drug Class** | Azalide antibiotic |
| **OCPB Reviewer** | Charles R. Bonapace, Pharm.D. | **Indication(s)** | CAP, [redacted] ABS |
| **OCPB Team Leader** | Venkat R. Jarugula, Ph.D. | **Dosage Form** | Azithromycin microspheres for oral suspension |
| | | **Dosing Regimen** | 2 g single dose adults, 60 mg/kg single dose pediatrics |
| **Date of Submission** | August 12, 2004 | **Route of Administration** | Oral |
| **Estimated Due Date of OCPB Review** | January 15, 2005 | **Sponsor** | Pfizer, Inc. |
| **PDUFA Due Date** | June 12, 2005 | **Priority Classification** | Standard |
| **Division Due Date** | May 12, 2005 | | |

***1.2.1.1.1.1.1 Clin. Pharm. and Biopharm. Information***

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | X | | | |
| **Tabular Listing of All Human Studies** | X | | | |
| **HPK Summary** | X | | | |
| **Labeling** | X | | | |
| **Reference Bioanalytical and Analytical Methods** | X | | | |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | | | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| *Healthy Volunteers-* | | | | |
| single dose: | X | 14 | 10 | |
| multiple dose: | | | | |
| **Patients-** | | | | |
| single dose: | X | 1 | 1 | A0661113 |
| multiple dose: | | | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | X | 5 | 1 | A0661115 |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | X | 1 | 1 | A0661113 |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| Obesity: | | | | |
| Cardiac repolarization: | | | | |
| Tissue penetration: | | | | |
| **PD:** | | | | |
| Phase 2: | | | | |

| | | | | |
|---|---|---|---|---|
| Phase 3: | | | | |
| **PK/PD:** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability:** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | X | 1 | 1 | A0661124 |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies:** | X | 3 | 2 | A0661107, A0661114 |
| **Dissolution:** | X | 1 | 1 | |
| **(IVIVC):** | | | | |
| **Bio-wavier request based on BCS** | | | | |
| **BCS class** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies:** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | X | | | |
| **Total Number of Studies** | | 14 | 10 | |

**Filability and QBR comments**

| | "X" if yes | *1.2.1.1.1.1.1.1.1 Comments* |
|---|---|---|
| **Application filable?** | X | |
| **Comments sent to firm?** | | |
| **QBR questions (key issues to be considered)** | 1) What PK/PD data support a single 2 gram dose of azithromycin [redacted] for the treatment ( [redacted] ABS, and CAP?<br>2) Is administration of a single dose necessary for patients who vomit following administration of azithromycin SR.<br>3) What is the impact of food on the bioavailability of azithromyci. [redacted] | |
| **Other comments or information not included above** | | |
| **Primary reviewer Signature and Date** | | |
| **Secondary reviewer Signature and Date** | | |

CC: NDA 21-572, HFD-520 (Milstein), HFD-880 (Lazor, Selen, Jarugula, Bonapace), CDR (B. Murphy)

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/

Charles Bonapace
6/10/05 03:21:37 PM
BIOPHARMACEUTICS

Venkateswar Jarugula
6/10/05 03:39:44 PM
BIOPHARMACEUTICS