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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Zithromax® / Zmax® / Azithromycin / Azithromycin Extended Release

PROTOCOL NO.: A0661142

PROTOCOL TITLE: An Open-Label, Multi-Center Trial of Azithromycin Pharmacokinetics in Sinus Aspirate and Serum Following Oral Administration of Either a 500 mg Immediate-Release (IR) Once Daily 3 Day Regimen or a Single-Dose 2.0 g Azithromycin Microspheres Regimen in Subjects With Acute Bacterial Sinusitis

Study Centers: Three (3) centers took part in the study and randomized subjects: 1 each in Sweden, Finland and Germany.

Study Initiation Date and Final Completion Date: 07 December 2005 to 01 June 2006

Phase of Development: Phase 2

Study Objectives:

Primary Objective

- To characterize the pharmacokinetics (PK) of azithromycin (AZ) in maxillary sinus aspirate and in serum in adult subjects with acute bacterial sinusitis after treatment with AZ immediate-release (AZ-IR) 500 mg orally, once daily for 3 days, or a single 2.0 g oral dose of AZ microspheres (ie, AZ extended release [AZ-ER[a]]), for acute bacterial sinusitis.

Secondary Objectives

- To quantify the rate and extent of bacterial eradication (disappearance of original strains) during Day 1-5 visits for Cohort 1 and Day 1-3 for Cohort 2 visits for each formulation
- To assess clinical efficacy for each formulation
- To assess bacteriologic efficacy for each formulation
- To assess the safety and tolerability of each formulation

[a] Azithromycin microspheres (AZ-M) previously known as azithromycin-sustained release (AZ-SR) has now been approved in the US as azithromycin-extended release (AZ-ER, Zmax).

- To explore possible relationships between PK and bacteriologic/clinical responses
- To estimate the PK exposure (area under the concentration-time curve from time 0 to 24 hours [AUC_{24}]) of AZ-ER formulation compared to AZ-IR formulation in maxillary sinus aspirate

METHODS

Study Design: This was a 2-stage randomized, open-label, multi-center, Phase 2 study in adults (18 years of age or older) of either sex presenting with protocol-defined acute bacterial sinusitis suitable for treatment with oral antibiotics. The first 6 subjects were randomly allocated to Stage 1 (Cohort 1) and the remainder were allocated to Stage 2 (Cohort 2). All subjects were randomized within each stage to receive either AZ-IR 500 mg once daily for 3 days, or a single 2.0 g oral dose of AZ-ER.

All subjects were to have an indwelling sinus catheter placed in the maxillary sinus from which sinus aspirate was to be collected and assayed for AZ drug concentration on Days 1 through 6 for Cohort 1 and on Days 1 through 3 for Cohort 2. In addition to sinus aspirate, blood was to be collected simultaneously with aspirate and serum assayed for AZ drug concentration on Days 1 through 6 for Cohort 1 and on Days 1 through 3 for Cohort 2. Sinus aspirate was to be cultured for bacteriological evaluation on Days 1 through 5 for Cohort 1 and on Days 1 through 3 for Cohort 2. The sampling scheme for sinus aspirate and serum could be adjusted depending upon the results of PK analysis.

Clinical and bacteriological response rates were to be assessed at Visit 6 (Day 5) and the test-of-cure (TOC) visit (Days 8-15 for AZ-ER and Days 10-17 for AZ-IR), 7 to 14 days after starting study drug for each formulation.

Table 1 and Table 2 summarize the study assessments and procedures performed in the study for Cohorts 1 and 2, respectively.

Table 1. Schedule of Activities for Cohort 1

Visit	1 (Screening)	2	3	4	5	6	7	8 F/U[a]	8 F/U[b]
Study Day	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8-15**	**10-17**
Informed consent[c]	X								
Demography	X								
Medical history	X								
Physical examination	X								
Nasal examination	X								
Vital signs	X	X	X	X	X	X	X	X	X
Clinical signs/symptoms	X	X	X	X	X	X	X	X	X
Sinus radiography[d]	X								
Blood sample for chemistry/hematology[e]	X								
Urine for urinalysis and drug screen[e]	X								
Pregnancy test[e,f]	X								
Sinus puncture and catheter insertion		X[g]							
Sinus aspirate for bacteriology		X	X	X	X	X			
Sinus aspirate for AZ drug assay		X	X	X	X	X	X		
Blood sample for AZ drug assay		X	X	X	X	X	X		
Study medication[h]		X[i]	X	X					
Remove sinus catheter							X		
Determine clinical and bacterial response						X		X[j]	X[j]
Adverse event reporting	X	X	X	X	X	X	X	X	X
Prior/concomitant medication	X	X	X	X	X	X	X	X	X

AZ = azithromycin; CT = computed tomography; ER = extended release; F/U = follow-up; IR = immediate release; TOC = test of cure.

a. Days 8-15 (7-14 days post therapy) TOC visit (or Early Withdrawal) AZ-ER formulation.
b. Days 10-17 (7-14 days post therapy) TOC visit (or Early Withdrawal) AZ-IR formulation.
c. Informed consent was an ongoing dialogue between the subject and Investigator and not limited to the first visit only.
d. Waters' View sinus radiograph (X-ray) or CT scan (the latter where required by a local site). For Germany, sinus radiograph was performed independently of the study for clinical reasons (ie, to diagnose sinusitis).
e. Performed within 48 hours prior to dosing.
f. Females of childbearing potential had a urine pregnancy test. Subject was entered on the basis of a negative urine pregnancy test.
g. Sinus catheter inserted before administration of the first dose of study medication.
h. AZ-IR and AZ-ER formulations were to be administered at the study site at least 2-hours before or 2-hours after a meal.
i. Subjects randomized to AZ-ER received a single 2.0 g dose on Day 1 only.
j. If a subject withdrew from the study prior to Day 6, sinus aspirate was to be collected and the sinus catheter was to be removed at the Early Withdrawal visit.

Table 2. Schedule of Activities for Cohort 2

Visit	1 (Screening)	2	3	4	5	6 F/U[a]	6 F/U[b]
Study Day	**0**	**1**	**2**	**3**	**5**	**8-15**	**10-17**
Informed consent[c]	X						
Demography	X						
Medical history	X						
Physical examination	X						
Nasal examination	X						
Vital signs	X	X	X	X	X	X	X
Clinical signs/symptoms	X	X	X	X	X	X	X
Sinus radiography[d]	X						
Blood sample for chemistry/hematology[e]	X						
Urine for urinalysis and drug screen[e]	X						
Pregnancy test[e,f]	X						
Sinus puncture and catheter insertion		X[g]					
Sinus aspirate for bacteriology		X	X	X			
Sinus aspirate for AZ drug assay		X	X	X			
Blood sample for AZ drug assay		X	X	X			
Study medication[h]		X[i]	X	X			
Remove sinus catheter				X[j]			
Determine clinical and bacterial response					X	X[j]	X[j]
Adverse event reporting	X	X	X	X	X	X	X
Prior/concomitant medication	X	X	X	X	X	X	X

AZ = azithromycin; CT = computed tomography; ER = extended release; F/U = follow-up; IR = immediate release; TOC = test of cure.

a. Days 8-15 (7-14 days post therapy) TOC visit (or Early Withdrawal) AZ-ER formulation.
b. Days 10-17 (7-14 days post therapy) TOC visit (or Early Withdrawal) AZ-IR formulation.
c. Informed consent was an ongoing dialogue between the subject and Investigator and not limited to the first visit only.
d. Waters' View sinus radiograph (X-ray) or CT scan (the latter where required by a local site). For Germany, sinus radiograph was performed independently of the study for clinical reasons (ie, to diagnose sinusitis).
e. Performed within 48 hours prior to dosing.
f. Females of childbearing potential had a urine pregnancy test. Subject was entered on the basis of a negative urine pregnancy test.
g. Sinus catheter inserted before administration of the first dose of study medication.
h. AZ-IR and AZ-ER formulations were to be administered at the study site at least 2 hours before or 2 hours after a meal.
i. Subjects randomized to AZ-ER received a single 2.0 g dose on Day 1 only.
j. If a subject withdrew from the study prior to Day 3, sinus aspirate was to be collected and the sinus catheter was to be removed at the Early Withdrawal visit.

Number of Subjects (Planned and Analyzed): A total of 30 subjects were planned to be enrolled and randomized in the study. In total, 9 subjects (4 in Sweden, 4 in Finland and 1 in Germany) were randomized and treated. All of the 9 randomized (6 in Cohort 1 and 3 in Cohort 2) and treated subjects completed treatment and were analyzed for PK, efficacy, and safety.

Diagnosis and Main Criteria for Inclusion: Male or female subjects, at least 18 years of age, with a clinical diagnosis of acute bacterial sinusitis for a minimum duration of 7 days but not more than 28 days. Subjects had to have a positive sinus X-ray (Waters' View confirming sinusitis) and appropriate clinical signs/symptoms. Subjects had to be willing to undergo direct aspiration of the sinus cavity by puncture with the SinoJect.

Study Treatment: Subjects were randomized to receive either AZ-IR (500 mg oral tablet once daily for 3 days) or AZ-ER (single 2.0 g oral dose of AZ microspheres supplied as 2.0 g of powder for oral suspension) within each stage. Study drug was administered at the study site at scheduled times such that dosing times coordinated with PK sample collection times. Subjects were instructed to eat approximately 2 hours before study drug administration and were not allowed to eat for at least 2 hours after study drug administration.

Pharmacokinetic, Efficacy, and Safety Endpoints:

Primary Endpoint: Characterization of AZ PK in maxillary sinus aspirate and simultaneously collected serum after treatment with AZ-IR 500 mg orally, once daily for 3 days, or a single 2.0 g oral dose of AZ microspheres (ie, AZ-ER).

Secondary Endpoints:

- Rate of bacterial eradication from sinus aspirate (disappearance of original strains) during the Days 1 through 5 visits for Cohort 1 and Days 1 through 3 visits for Cohort 2
- Time to resolution of symptoms
- Clinical and bacteriologic response at the Day 5 (-0 to +2 days) visit and TOC visit (7-14 days post therapy)
- Investigator assessment of clinical response at the TOC visit (7-14 days post therapy)
- Quantification of bacteria in sinus aspirate
- Correlation of drug exposure, as measured from sinus aspirate and serum concentrations, with the rate and extent of bacterial eradication
- Safety was assessed for all subjects by treatment regimen
- Estimate the PK exposure (AUC_{24}) of AZ-ER formulation compared to AZ-IR formulation in maxillary sinus aspirate

Safety Evaluations: Safety and tolerability of both formulations of AZ were assessed by clinical monitoring after each dose and included vital signs, and monitoring of adverse events (AEs).

Statistical Methods: The population sets analyzed in the study included:

Pharmacokinetic Analysis Set: Subjects included in the statistical analysis of the PK parameters were those for whom at least 1 of the PK parameters were computed.

Safety Analysis Set: All subjects who received at least 1 dose of study medication were included in the safety analyses.

Efficacy Analysis Sets: The primary population of interest was the Clinical Per Protocol population.

Clinical Per Protocol Subjects: Subjects meeting the following criteria:

- Received all doses of study medication
- Received no concomitant systemic antibiotic potentially effective against rhinosinusitis pathogens
- Received an assessment in the appropriate visit window

PK analyses were carried out with WinNonlin (V.3.2, Pharsight®, Mountain View, CA) using standard non-compartmental methods. Maximum observed plasma concentration (C_{max}) for AZ was estimated directly from experimental data. T_{max} was defined as the time of the first occurrence of C_{max}; AUC_{72} and AUC_{120} were defined as the area under the plasma concentration time-curve from the dosing time until 72, and 120 hours, respectively, and were estimated using the linear-log trapezoidal method. For concentrations lower than the limit of quantification, a value of 0 was assigned for PK calculations. The individual PK parameters from Cohort 1 and Cohort 2 were combined for statistical analyses.

Mean and individual AZ concentration-time data and derived PK parameters were summarized using descriptive statistics (N, mean, standard deviation [SD], minimum, maximum, and median). All mean values reported were arithmetic means, unless otherwise indicated.

Analysis of Primary Endpoint: For each formulation, natural-log transformed parameters AUC from time 0 to 24 hours (AUC_{24}), and C_{max} were analyzed with a mixed-effects model, with matrix considered a fixed effect and subject considered a random effect. Estimates of adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals (CIs) were obtained from this model. The adjusted mean difference and 90% confidence limits for the difference were exponentiated to derive estimates of the ratios of the adjusted geometric means and the 90% CIs for these ratios. Each formulation's sinus aspirate matrix was the Test and each formulation's serum matrix was the Reference.

In addition, as a secondary analysis of this data, the AUC_{24} for the ER formulation was compared to the AUC_{24} for the IR formulation separately in maxillary sinus aspirate and plasma. The natural-log transformed AUC_{24} was analyzed with a mixed-effects model, with treatment considered a fixed effect and subject considered a random effect. Estimates of adjusted mean differences and the corresponding 90% CIs were obtained from this model. The adjusted mean differences and the 90% confidence limits for the differences were exponentiated to derive estimates of the ratios of the adjusted geometric means and the 90% CIs for these ratios. AZ-ERwas the Test and AZ-IR was the Reference.

Due to the low enrollment, a number of the planned secondary analyses were not performed. These included the analysis of the duration of time to the disappearance of the original strains from the sinus, the overall assessment of the symptoms, comparison of symptoms to the previous day, estimation of the median time to resolution of the symptoms, assessment of clinical response by Baseline pathogen, quantification of bacteria in sinus aspirate, and population PK and exposure-response analyses.

Safety data were summarized using descriptive statistics.

RESULTS

Subject Disposition and Demography: A total of 9 subjects were treated and all completed the study. All 9 subjects were evaluable for PK and safety. Table 3 summarizes subject disposition.

Table 3. Subject Disposition

Disposition		AZ-IR 500 mg	AZ-ER 2 g
Screened	N=9		
Assigned to study treatment		4	5
Treated		4	5
Completed		4	5
Discontinued		0	0
Analyzed for efficacy			
Pharmacokinetic		4	5
Analyzed for safety			
Adverse events		4	5

AZ-IR = azithromycin-immediate release; AZ-ER = azithromycin-extended release; N = number of subjects.

All subjects presented with a clinical diagnosis of acute bacterial sinusitis. Treatment groups were comparable with respect to demographic and baseline characteristics. All subjects were White and ranged in age from 20 to 55 years. Four (44%) subjects were male and 5 (56%) were female. Demographics are summarized in Table 4.

Table 4. Subject Demographics

Disposition	AZ-IR 500 mg			AZ-ER 2 g		
	Male	Female	Total	Male	Female	Total
Number of subjects	1	3	4	3	2	5
Age (years)						
Mean	22.0	46.3	40.3	43.3	28.5	37.4
SD	0.0	7.8	13.7	9.6	12.0	12.2
Range	22-22	40-55	22-55	33-52	20-37	20-52

AZ-IR = azithromycin-immediate release; AZ-ER = azithromycin-extended release; SD = standard deviation.

Pharmacokinetic and Efficacy Results:

Pharmacokinetic Results:

Calculation of Azithromycin PK in Serum: Individual and summary PK parameter results are shown in Table 5. AZ was absorbed following AZ-IR administration with T_{max} values ranging from 2 to 4 hours, and AZ-ER administration with T_{max} values ranging from 2 to 6 hours. Following peak concentrations, the disposition of AZ from the systemic circulation was also quick for both formulations. As indicated in Table 5, within the first 24 hours after dosing, the mean AUC_{24} and C_{max} values for AZ-ER were both approximately 4-fold higher compared to AZ-IR. Consistent with the higher dose for the AZ-ER of 2 g, the systemic exposure of AZ within the first 24 hours exhibited a dose-related increase relative to the 500 mg dose of AZ-IR, as judged by AUC_{24} and C_{max} values.

Table 5. Pharmacokinetic Parameters of Azithromycin in Serum

Azithromycin Formulation		C_{max} (µg/mL)	T_{max} (h)	AUC_{24} (h*µg/mL)	Sample Collection Time (h)	AUC_{72} (h*µg/mL)	AUC_{120} (h*µg/mL)
AZ-IR		0.40	3.0	1.89	120	N/A	N/A
AZ-IR		0.34	2.0	2.44	120	N/A	N/A
AZ-IR		0.31	2.0	1.67	120	N/A	N/A
AZ-IR		0.14	4.0	1.06	72.0	N/A	N/A
	Mean	0.30	2.75	1.77			
	Median	0.32	2.50	1.78			
	SD	0.11		0.57			
	CV%	37		32			
	Range		2.0-4.0				
AZ-ER		0.93	6.0	8.41	120	13.4	15.8
AZ-ER		1.52	4.0	7.26	120	9.74	10.9
AZ-ER		1.46	4.0	10.9	120	18.9	23.3
AZ-ER		1.23	4.0	7.29	72.0	9.88	
AZ-ER		0.60	2.0	2.85	72.0	3.79	
	Mean	1.15	4.00	7.35		11.1	16.7
	Median	1.23	4.00	7.29		9.88	15.8
	SD	0.38		2.93		5.54	6.20
	CV%	33		40		50	37
	Range		2.0-6.0				

AZ-IR = azithromycin-immediate release; AZ-ER = azithromycin-extended release; AUC_{24} = AUC from time 0 to 24 hours; AUC_{72} = AUC from time 0 to 72 hours; AUC_{120} = AUC from time 0 to 120 hours; C_{max} = maximum observed plasma concentration; CV% = percent coefficient of variation; N/A = not applicable; SD = standard deviation; T_{max} = time-to-first occurrence of C_{max}.

Estimation of Azithromycin Concentrations in Serum on Days 2 and 3 for AZ-IR: For the AZ-IR formulation, serum samples were only collected at the 24-hour interval following the first day of dosing; ie, full concentration-time profiles were not available for the second and third dose of AZ-IR. Therefore, the individual subject concentration-time profiles after the first dose were used to estimate the concentration-time curve after the second and third dose. This was done according to the principle of superposition using WinNonlin (V.3.2, Pharsight®, Mountain View, CA).

The individual subject AUC_{72} values derived from the simulated profiles and the summary statistics are shown in Table 6. The mean estimated AUC_{72} hour value for AZ-IR was 7.10 h∗µg/mL, which was approximately 64% of the AUC_{72} value for AZ-ER.

Table 6. Predicted Serum AUC_{72} Values Following Administration of AZ-IR

Serial No.	AUC_{72} (h*µg/mL)
1	7.06
2	10.4
3	6.54
4	4.37
Mean	7.10
Median	6.80
SD	2.51
CV%	35

AUC_{72} = area under curve from time 0 to 72 hours; AZ-IR = azithromycin-immediate release; CV% = percent coefficient of variation; SD = standard deviation.

Azithromycin PK in Sinus Fluid: There was considerable variability in the sinus AZ concentrations regardless of the formulation. For the AZ-ER group, 1 subject had a much higher concentration relative to the others, skewing the concentration-time curve.

Unlike the rapid disposition in serum, AZ concentration in sinus fluid was sustained over the sampling interval of 120 hours. Notably, the concentrations of AZ following administration of the ER formulation were higher within the first 24 hours compared to those obtained following administration of the IR formulation. At time points between 48 to 120 hours, mean sinus fluid concentrations of AZ were also higher for the ER formulation relative to the IR formulation. At 48, 72, 96, and 120 hour time points, the ratios of the AZ concentrations (ER to IR) were 2.7, 3.3, 1.5, and 2.0, respectively. Individual and mean sinus fluid PK parameters are shown in Table 7.

Table 7. Pharmacokinetic Parameters of Azithromycin in Sinus Fluid

Azithromycin Formulation		C_{max} (µg/mL)	T_{max} (h)	AUC_{24} (h*µg/mL)	Sample Collection Time (h)	AUC_{72} (h*µg/mL)	AUC_{120} (h*µg/mL)
AZ-IR		4.85	48.0	8.96	120	N/A	N/A
AZ-IR		2.97	96.0	7.06	120	N/A	N/A
AZ-IR		1.31	24.0	15.0	120	N/A	N/A
AZ-IR		1.20	48.0	4.14	72.0	N/A	N/A
	Mean	2.58	54.0	8.78			
	Median	2.14	48.0	8.01			
	SD	1.71		4.57			
	CV%	66		52			
	Range		24.0-96.0				
AZ-ER		25.4	72.0	37.0	120	895	1243
AZ-ER		6.63	96.0	25.9	120	99.3	248
AZ-ER		3.15	12.0	47.7	120	119	166
AZ-ER		0.87	24.0	14.0	72.0	36.6	N/A
AZ-ER		0.67	12.0	11.0	72.0	19.1	N/A
	Mean	7.34	43.2	27.1		234	552
	Median	3.15	24.0	25.9		99.3	248
	SD	10.4		15.5		372	599
	CV%	141		57		159	109
	Range		12.0-96.0				

AZ-IR = azithromycin-immediate release; AZ-ER = azithromycin-extended release; AUC_{24} = AUC from time 0 to 24 hours; AUC_{72} = AUC from time 0 to 72 hours; AUC_{120} = AUC from time 0 to 120 hours; C_{max} = maximum observed plasma concentration; CV% = percent coefficient of variation; NA = not applicable; SD = standard deviation; T_{max} = time-to-first occurrence of C_{max}.

As there were only 4 subjects in the IR group and 5 subjects in the ER group, there was considerable variability in the PK parameters regardless of formulation. Within the first 24 hours after dosing, the mean AUC_{24} and C_{max} values for AZ-ER were both approximately 3-fold higher compared to AZ-IR.

The results of the statistical analysis of the PK parameters comparing the AZ concentration from AZ-ER versus AZ-IR separately in sinus aspirate and plasma are shown in Table 8. For AUC_{24}, the ratio and 90% CI of ER to IR were 3.98 (2.26, 7.03) for serum and 2.96 (1.40, 6.24) for sinus aspirate. Thus the AZ concentrations were 3- to 4-times higher for AZ-ER compared to AZ-IR.

Table 8. Summary of Statistical Analysis of Pharmacokinetic Parameters (AUC_{24}) - AZ-ER vs AZ-IR, by Matrix

Parameter (units)		Adjusted Geometric Means			90% CI	
	Matrix	Test	Reference	Ratio (%)	Lower	Upper
AUC_{24} (ng•h/mL)	Serum	6.73	1.69	3.98	2.26	7.03
	Sinus	23.42	7.92	2.96	1.40	6.24

AZ-IR = azithromycin-immediate release; AZ-ER = azithromycin-extended release; AUC_{24} = AUC from time 0 to 24 hours; CI = confidence interval; Reference = AZ-IR; Test = AZ-ER.

Efficacy Results:

Clinical Response: At Baseline, subjects were required to have a clinical diagnosis of acute bacterial sinusitis as demonstrated by the presence of the following cardinal signs and symptoms for a minimum duration of 7 days but not more than 28 days: facial pain, pressure, and/or tightness over 1 or both maxillary sinuses, and/or pain in 1 or both maxillary areas that worsened with movement or percussion; and, presence of 1 or more of the following signs: purulent nasal discharge, purulent drainage in the posterior pharynx, or purulent discharge from the maxillary sinus orifice. Although the number of subjects assessed for clinical signs and symptoms was too low to draw any conclusions, improvement was observed in their signs and symptoms by Days 2 and 3, with resolution of symptoms occurring between Days 5 and 14. Table 9 summarizes the clinical response determined on Day 5 and at the time of the TOC visit. According to the investigator, all subjects had a clinical cure between Days 5 and 14.

Table 9. Summary of Clinical Response

Response	AZ-IR 500 mg	AZ-ER 2 g
Day 5	**N=4**	**N=4[a]**
Cure, n (%)	4 (100)	3 (75)
Failure, n (%)	0 (0)	1 (25)
Signs/symptoms persistent, n (%)	--	1 (100)[b]
TOC Visit	**N=4**	**N=5**
Cure, n (%)	4 (100)	5 (100)

a. One subject missed the Day 5 visit.
b. Represents the percentage of failure in this category.
AZ-IR = azithromycin-immediate release; AZ-ER = azithromycin-extended release; N = number of subjects; n = number of subjects in specified category; TOC = test of cure.

Bacteriological Response: There were no pathogens recovered at Baseline or on Days 1 to 5, therefore bacteriologic response could not be assessed.

Safety Results: The incidence of AEs was low between treatments and generally related to the disease under study or to the use of concomitant treatment with the SinoJect tube (ie, headaches, sinus headaches, sinus disorder, nasal congestion, facial pain, fatigue, postnasal drip). The Investigator considered a few gastrointestinal events (diarrhea, abdominal pain, and flatulence) to be related to the study medication. Table 10 summarizes the treatment-emergent AEs by severity and causality.

Table 10. Summary of Treatment-Emergent (All Causality and Treatment Related) Adverse Events

System Organ Class and MedDRA Preferred Term	AZ-IR 500 mg N=4		AZ-ER 2 g N=5	
	AC n	TR n	AC n	TR n
Total Number of AEs	**11**	**1**	**11**	**3**
Total Number of Subjects With AEs	**4**	**1**	**3**	**2**
Gastrointestinal disorders				
Abdominal pain upper	0	0	1	1
Diarrhea	1	1	0	0
Flatulence	0	0	1	1
General disorders and administration site conditions				
Facial pain	2	0	1	0
Fatigue	1	0	0	0
Infections and infestations				
Sinusitis	0	0	1	0
Tooth infection	1	0	0	0
Nervous system disorders				
Headache	2	0	0	0
Sinus headache	1	0	2	0
Respiratory, thoracic and mediastinal				
Epistaxis	1	0	0	0
Nasal congestion	0	0	1	0
Postnasal drip	1	0	1	0
Sinus disorder	1	0	2	0
Skin and subcutaneous tissue disorder				
Urticaria	0	0	1	1

AEs/SAEs are not separated out.
All AEs were mild in intensity unless otherwise noted.
Includes data up to 35 days after last dose.
AC = all causalities; AEs = adverse events; AZ-IR = azithromycin-immediate release; AZ-ER = azithromycin-extended release; MedDRA = Medical Dictionary for Regulatory Activities (Version 9.0); N = number of subjects; n = number of subjects with AE; SAE = serious adverse events; TR = treatment-related.

Discontinuations due to AEs: No subject discontinued the study due to an AE.

Serious Adverse Events (SAEs): No SAEs occurred during the study.

Deaths: No deaths occurred during the study.

None of the changes in vital signs were considered to be clinically significant.

CONCLUSIONS:

- Following administration of either AZ-IR or AZ-ER, the exposure of AZ in sinus fluid was markedly higher than that in serum for the first 24 hours, and concentrations remained relatively high in the sinus fluid for several days. Concentrations of AZ-ER were 3- to 4-fold higher than AZ-IR.

- Although the number of subjects investigated in the present study was small, the data suggested that a single dose of AZ-ER formulation given to subjects with acute maxillary sinusitis resulted in clinically significant higher drug concentrations in sinus fluid that persisted for at least 72 hours after oral administration.

- AZ-IR and AZ-ER were well tolerated and there were no safety concerns in this study.