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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NCT NO.: NCT00254566

PROTOCOL NO.: A0661147

PROTOCOL TITLE: A Phase 3b Multicenter, Randomized, Double-Blind, Double-Dummy Comparative Trial to Evaluate the Efficacy and Safety of Azithromycin SR (Microspheres Formulation) versus Moxifloxacin for the Treatment of Acute Exacerbation of Chronic Bronchitis (AECB)

Study Centers: The study was conducted at 33 centers in Asia (15 centers in China, 2 centers in Malaysia, 4 centers in Philippines, 1 center in Singapore, 5 centers in Taiwan and 6 centers in Thailand); an additional 2 centers were shipped study drug but did not randomize any subjects.

Study Initiation and Completion Dates: 28 February 2006 to 01 August 2008.

Phase of Development: Phase 3b

Study Objectives:

Primary Objective

To confirm the hypothesis that a single, 2.0 g dose of azithromycin sustained release (SR) is clinically non-inferior to moxifloxacin 400 mg orally once a day for 5 days, in the treatment of AECB as measured by clinical response.

Secondary Objective

To compare the treatment regimens in terms of:

- bacteriologic response;
- time to first recurrence of AECB;
- improvement in health status;

- safety and tolerability.

METHODS

Study Design: This was a Phase 3b, multicenter, double-blind, double-dummy, placebo-controlled study in which subjects were randomized to 1 of 2 active treatment arms: azithromycin SR or moxifloxacin. Subjects were stratified at randomization based on steroid use.

The study was conducted in Asia and aimed to randomize approximately 416 subjects (208 subjects per arm) with evidence of AECB, to allow at least 352 subjects in the Clinical Per Protocol population. Subjects were required to attend the study center at Visit 1 (Baseline, Day 1), Visit 3 (test of cure [TOC], Day 12-19) and Visit 6 (AECB recurrence). At Visits 2 (on treatment, Day 3-5), 4 (first follow-up, Day 28-35) and 5 (monthly follow-up) subjects may have either received a telephone call or visited the study center. Total participation in the study for each subject was up to 9 months or until the last subject(s) that were enrolled reached their first follow-up visit (Visit 4), whichever occurred first.

Clinical response was assessed at Visit 3 (TOC). In subjects with isolated pathogens at baseline, bacteriologic response was assessed at the visit. All subjects who received at least 1 dose of study treatment were assessed for safety. Recurrence of AECB was evaluated by monthly telephone/clinic visits follow-up for 9 months during their participation in the study.

The subject reported health status was evaluated by the Clinical Chronic Obstructive Pulmonary Disease (COPD) Questionnaire (CCQ), which is comprised of 10 questions. The CCQ was administered daily from Days 1-7, at Visit 3 (TOC, Day 12-19) and at Visit 4 (first follow-up) using the daily version of the CCQ. The questionnaire was self-administered by the subject.

Number of Subjects (Planned and Analyzed): It was planned to randomize approximately 416 subjects (208 subjects per arm) with evidence of AECB, to allow at least 352 subjects in the Clinical Per Protocol population; 398 subjects were randomized and 378 subjects were included in the Clinical Per Protocol population.

Diagnosis and Main Criteria for Inclusion: Males or females, at least 50 years old, with a diagnosis of chronic bronchitis (chronic cough and sputum production on most days for 3 consecutive months for more than 2 consecutive years) and at least 2 exacerbations of AECB in the past 12 months, for whom oral antibiotic therapy was indicated. Subjects were to have a history of smoking of at least 20 pack-years and documented forced expiratory volume in 1 second (FEV_1) less than 80% of predicted. Subjects with a chest radiograph consistent with pneumonia, known or suspected hypersensitivity or intolerance to azithromycin, moxifloxacin, or other macrolides or quinolones and/or previously diagnosed disease of immune function were excluded.

Study Treatment: Azithromycin SR (2.0 g, microspheres formulation) or placebo were administered orally as single doses in the form of an oral suspension on Day 1. It was recommended that subjects consumed the medication on an empty stomach (at least 1 hour

before or 2 hours following a meal). Moxifloxacin (400 mg) or placebo were administered orally as capsules once daily for 5 days. Subjects were randomized to receive either (i) azithromycin SR with placebo to moxifloxacin, or (ii) placebo to azithromycin SR with moxifloxacin.

Efficacy Evaluations:

Primary Efficacy Endpoint

The primary efficacy endpoint was clinical response at Visit 3 (TOC, Day 12-19) for the Clinical Per Protocol set. The investigator assessed the subject's clinical response to therapy as either 'cure' or 'failure' according to the following criteria:

Cure (Success): Signs and symptoms related to the acute infection had returned to the subject's normal baseline level, or clinical improvement was such that no additional antibiotics were deemed necessary.

Failure: One or more of the following:

- Signs and symptoms related to the acute infection had persisted or worsened and additional antibiotics were necessary;
- New clinical signs and symptoms of acute infection had developed and additional antibiotics were necessary;
- Clinical/radiological evidence of pneumonia had developed during treatment and additional antibiotics were necessary.

Secondary Efficacy Endpoints

The secondary endpoints included the following:

- Clinical response at Visit 3 (TOC, Day 12-19).
- Bacteriological response was assessed on a per pathogen basis at Visit 3 (TOC, Day 12-19).
- Time to first recurrence of AECB.
- CCQ scores obtained during the course of the study.

Safety Evaluations: Adverse event (AE) monitoring, clinical laboratory evaluations (including serology and bacteriologic testing), vital signs, physical examinations and chest X-rays were performed.

Statistical Methods:

Five treatment populations were analyzed in this study.

- The Full Analysis Set (FAS) comprised all randomized subjects who received at least 1 dose of study medication.

- The Clinical Per Protocol set comprised subjects in the FAS who also met the following criteria:

1. Were clinically eligible (see definition below).

2. Received at least 80% of study medication, including active and placebo doses.

3. Received no concomitant systemic antibiotic with activity against AECB pathogens.

4. Received an assessment in the appropriate visit window.

- The All Randomized set comprised all subjects who received a randomization number from the central randomization system.

- The Clinically Eligible set comprised subjects from the FAS with a diagnosis of chronic bronchitis, clinical evidence of AECB based on signs and symptoms, and a negative chest radiograph for pneumonia based on the radiologist's opinion (if available).

- The Bacteriologic Per Protocol set comprised subjects from the Clinical Per Protocol set with a baseline bacterial pathogen.

Analysis of Efficacy Parameters

The primary efficacy analysis compared the clinical cure (success) rates of the azithromycin SR and moxifloxacin regimens at Visit 3 (TOC Visit, Day 12-19) in the Clinical Per Protocol set. A 95% confidence interval (CI) for the difference in cure (success) rates was constructed using a method of linear stratification that weighted according to the reciprocal of the variance. Stratification was by steroid use at the time of randomization. Azithromycin SR was considered non-inferior to moxifloxacin if the boundary of the 95% CI for the difference in cure (success) rates (azithromycin SR - moxifloxacin) was greater than -10%.

Secondary analyses comparing the 2 treatments on clinical cure (success) rates in the Bacteriological Per Protocol set, Clinically Eligible set, FAS and All Randomized set, as well as comparisons on bacteriologic response rates in the Bacteriologic Per Protocol set, employed the same methodology as that described above for the primary analysis.

Time to AECB recurrence was analyzed for the FAS using survival analysis methods to account for censored observations (ie, subjects who did not experience a recurrence). Subjects were censored at the date last known to have not experienced a recurrence. The median time to recurrence was estimated using the Kaplan-Meier method (if applicable). A log-rank test was performed to test for treatment differences. The ratio of the treatment groups' recurrence rate (ie, the hazard ratio) was estimated using a Cox proportional hazards model adjusting for steroid use, frequency of AECB in previous 12 months (<=4 versus >4), country and baseline FEV_1.

A 95% CI for the difference in least square (LS) mean change from baseline CCQ total score at Visit 3 (TOC, Day 12-19) was estimated for the FAS from an analysis of covariance (ANCOVA) with treatment, steroid use and country fitted as factors, and the baseline CCQ total score and FEV_1 fitted as covariates. CCQ total scores, and changes from baseline were summarized descriptively for the FAS by treatment group over time (Day 1 [for absolute values only], Days 2-7, TOC, and the first follow-up visit) using means, medians, standard deviations (SDs), minimum values, and maximum values. These descriptive analyses were repeated for the CCQ sub-scales.

A linear mixed model was used to relate the post-baseline CCQ scores (total and subscales) and independent (explanatory) variables taking into account the "repeated measures" element within subject. These analyses were performed on data from the FAS. The explanatory variables were treatment, FEV_1, baseline CCQ score, country, time point, and a treatment-by-time point interaction. Time point was fitted as a categorical variable; the treatment-by-time point interaction term allowed treatment effect to vary over time.

Safety Parameters

All AEs and medical history terms were coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system. Previous and concomitant medications were coded using the World Health Organization (WHO) Drug coding system. Standard summaries and listings of vital signs, AEs, treatment discontinuation, laboratory data, and concomitant medications were generated for the FAS. A listing of the chest X-ray data was generated.

RESULTS

Subject Disposition and Demography: A total of 486 subjects were screened; 398 of these subjects were assigned to study treatment, with 396 subjects treated (Table S1). There were an equal number of subjects (198) in the azithromycin and moxifloxacin treatment groups. Approximately 30% of subjects treated were categorized as steroid users.

Table S1. Summary of Subject Disposition

Number (%) of Subjects		Azithromycin	Moxifloxacin
Screened	486		
Assigned to Study Treatment	398		
Treated		198	198
Completed		167 (84.3)	172 (86.9)
Discontinued		31 (15.7)	26 (13.1)
Analyzed for Efficacy	396	198 (100.0)	198 (100.0)
Analyzed for Safety			
Adverse Events		198 (100.0)	198 (100.0)
Laboratory Data		123 (62.1)	130 (65.7)

The discontinuation rate was similar for the 2 treatment groups, 15.7% for azithromycin and 13.1% for moxifloxacin. The main reason for discontinuation was lack of efficacy, accounting for 21 of the 57 discontinuations (Table S2).

Table S2. Summary of Discontinuations

Number (%) of Subjects	Azithromycin (N=198)	Moxifloxacin (N=198)
Subject Died	1 (0.5)	0
Related to Study Drug	16 (8.1)	11 (5.6)
Adverse Event	4 (2.0)	2 (1.0)
Lack of Efficacy	12 (6.1)	9 (4.5)
Not Related to Study Drug	14 (7.1)	15 (7.6)
Adverse Event	1 (0.5)	2 (1.0)
Lost to Follow-Up	7 (3.5)	2 (1.0)
Other	1 (0.5)	5 (2.5)
Subject No Longer Willing to Participate in Study	5 (2.5)	6 (3.0)

All subjects were Asian, aged 50-89 years. Approximately 90% of subjects were male. Mean age, weight and height were similar for the 2 treatment groups. All subjects had a primary diagnosis of bronchitis, with a mean duration since first diagnosis of 8 days (range 1-50 days).

AECB exacerbations and FEV_1 were similar for the 2 treatment groups. All subjects were either current (approximately 25%) or past (75%) smokers, with 39-45 mean pack years. The most common baseline symptoms were cough, productive sputum, sputum purulence and dyspnea, all of which were present in at least 94% of subjects.

Efficacy Results: The clinical success rate at the TOC visit for the Clinical Per Protocol population was 93% for azithromycin and 94% for moxifloxacin. The pre-specified criteria for demonstrating the non-inferiority of azithromycin relative to moxifloxacin was met (Table S3). The lower bound of the CI was not greater than 0, so it could not be concluded that azithromycin was superior to moxifloxacin.

Table S3. Clinical Response at TOC Visit (Clinical Per Protocol Population)

	Azithromycin	Moxifloxacin	Difference in Cure Rate[a]	95% CI[a]
N	187	191		
Cure (%)	174 (93.0)	180 (94.2)	-0.9%	-5.8%, 3.9%
Failure (%)	13 (7.0)	11 (5.8)		

CI = confidence interval; TOC = test of cure
[a] Stratified by baseline steroid usage.

The bacterial eradication rate was similar for both treatments, with the lower limit of the associated 95% CI within the 10% non-inferiority margin specified for the primary endpoint (Table S4). Eradication rates were similar for both treatments for all pathogens. Of the pathogens that were tested for susceptibility, streptococci showed greater resistance to azithromycin (68%) compared to moxifloxacin (0%).

Table S4. Bacteriologic Eradication Rates (Bacteriologic Per Protocol)

	Azithromycin (N=121)	Moxifloxacin (N=128)	Difference in Eradication Rate[a]	95% CI[a]
N[b]	175	180		
Eradication (%)	168 (96.0)	174 (96.7)	-0.6%	-4.5%, 3.3%
Persistence (%)	7 (4.0)	6 (3.3)		

CI = confidence interval
[a] Stratified by baseline steroid usage
[b] Number of unique pathogens identified at baseline

There was no statistically significant treatment difference in the time taken to first occurrence of AECB (Table S5).

Table S5. Time to First AECB Recurrence (Full Analysis Set)

	Azithromycin (N=198)	Moxifloxacin (N=198)	Hazard Ratio[a]	95% CI[a]	p-value[a]
N	175	180			
First Quartile[b]	152	204	1.33	0.9, 2.0	0.159
Median[b]	NR	NR			

AECB = acute exacerbations of chronic bronchitis; CI = confidence interval; NR = Not reached
[a] Estimated from Cox's Proportional Hazards model with steroid use and country as factors and baseline FEV_1 fitted as a covariate
[b] Kaplan-Meier estimate of time taken for quartile to experience recurrence

For both treatments, mean CCQ total score decreased from approximately 3.0 at baseline to 2.3-2.4 at TOC and TOC/LOCF (Table S6). The difference at TOC/LOCF was -0.05 (95% CI: -0.21, 0.12; p=0.570). The CI did not include values that were suggestive of a clinically significant difference (i.e. 0.40) as presented in the protocol. Likewise, non-significant differences were observed for CCQ symptoms scores, functional state scores and mental state scores.

Table S6. Summary of CCQ Total Score Analyses (Full Analysis Set)

	Azithromycin (N=198)	Moxifloxacin (N=198)	Difference (95% CI [p-value])
Baseline Score			
Mean (SD)	3.02 (0.84)	3.04 (0.93)	
Min, Max	0.7, 5.9	0.7, 5.7	
N	189	196	
Change from Baseline to TOC			
Mean (SD)	-0.72 (0.92)	-0.66 (0.89)	
Min, Max	-4.1, 2.0	-3.1, 2.4	
N	169	177	
Change from Baseline to TOC/LOCF			
Mean (SD)	-0.66 (0.93)	-0.61 (0.90)	
Min, Max	-4.1, 2.5	-3.1, 2.4	
N	185	194	
Analysis of Covariance of Change from Baseline to TOC/LOCF[a]			
LS Mean (SE)	-0.76 (0.112)	-0.71 (0.106)	-0.05 (-0.21, 0.12 [p=0.57])
Repeated Measures Analysis of Change from Baseline Over Study Period			
Model with Interaction[b]			
LS Mean (SE)	-0.58 (0.078)	-0.56 (0.073)	-0.02 (-0.13, 0.10 [p=0.79])
Model without Interaction[c]			
LS Mean (SE)	-0.58 (0.078)	-0.56 (0.073)	-0.01 (-0.13, 0.10 [p=0.82])

CCQ = clinical chronic obstructive pulmonary disease questionnaire; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; SE = standard error; TOC = test of cure;

[a] Estimated from Analysis of Covariance with treatment, steroid use and country fitted as factors and baseline CCQ total score and FEV_1 fitted as covariates

[b] Estimated from a linear mixed model with treatment, steroid use, FEV_1, country, time point and treatment-by-time point interaction as factors and baseline CCQ score as a covariate

[c] Estimated from a linear mixed model with treatment, steroid use, FEV_1, country and time point as factors and baseline CCQ score as a covariate

Pharmacokinetic, Pharmacodynamic, and/or Other Results: No pharmacokinetic, pharmacodynamic or other analyses were performed.

Safety Results: The number of AEs and the number of subjects with AEs, both all causalities and treatment-related, were similar for both treatments (Table S7). The incidence of treatment-related AEs was low, being reported by 17% of subjects receiving azithromycin and 12% of subjects receiving moxifloxacin. Most AEs were mild or moderate in severity.

Table S7. Summary of Incidence of Adverse Events

	Azithromycin		Moxifloxacin	
Number (%) of Subjects	All Causalities	Treatment Related	All Causalities	Treatment Related
Subjects Evaluable for AEs	198	198	198	198
Number of AEs	71	42	71	35
Subjects with AEs	51 (25.8)	33 (16.7)	45 (22.7)	24 (12.1)
Subjects with SAEs	3 (1.5)	0	9 (4.5)	0
Subjects with Severe AEs	4 (2.0)	1 (0.5)	6 (3.0)	0
Subjects Discontinued with AEs[a]	9 (4.5)	4 (2.0)	4 (2.0)	2 (1.0)
Subjects with Dose Temporarily Discontinued Due to AEs	1 (0.5)	1 (0.5)	0	0

AE = adverse event; SAE = serious adverse event
[a] The AE was not necessarily the principal reason for discontinuation specified by the investigator

The most common AEs were gastrointestinal disorders, being reported by 14% of subjects receiving azithromycin and 8% of subjects receiving moxifloxacin. The most frequent AE was diarrhea: this was reported by 9% of subjects (8% treatment-related) receiving azithromycin but by only 2% of subjects receiving moxifloxacin (Table S8).

Table S8. Summary of Most Frequent Treatment-Emergent Adverse Events

	Azithromycin (N=198)		Moxifloxacin (N=198)	
Number (%) of Subjects	All Causalities	Treatment Related	All Causalities	Treatment Related
Diarrhea	18 (9.1)	16 (8.1)	4 (2.0)	4 (2.0)
Dizziness	1 (0.5)	1 (0.5)	6 (3.0)	6 (3.0)
Nasopharyngitis	1 (0.5)	0	6 (3.0)	0
Abdominal pain	4 (2.0)	3 (1.5)	1 (0.5)	1 (0.5)
Abdominal pain upper	4 (2.0)	4 (2.0)	1 (0.5)	1 (0.5)
ALT increased	4 (2.0)	4 (2.0)	1 (0.5)	1 (0.5)
Nausea	1 (0.5)	1 (0.5)	4 (2.0)	4 (2.0)
AST increased	4 (2.0)	3 (1.5)	0	0

ALT = alanine aminotransferase, AST = aspartate aminotransferase
Tables show AEs reported by at least 2% of subjects in 1 or both groups.

A total of 9 subjects discontinued due to AEs: 6 subjects due to treatment-related AEs and 3 subjects due to the disease under study. Diarrhea was the only AE that was the cause of discontinuation for more than 1 subject: 3 subjects receiving azithromycin discontinued due to diarrhea. Two subjects receiving moxifloxacin discontinued due to SAEs (dyspnea and bronchitis) that were due to the disease under study.

The incidence of SAEs was higher with moxifloxacin (4.5% of subjects) compared to azithromycin (1.5%). No SAEs were treatment-related but were typically due to the disease under study or to other illnesses.

There was 1 death: a 78-year old male, died approximately 3 months after the start of the study. On the day prior to the death the subject was reported as having a severe lung infection which was not treatment-related. The subject had been classed as having a clinical response of 'cure' at the TOC.

The most common abnormalities in clinical laboratory tests were eosinophils (%) >1.2 x upper limit of normal (ULN) (azithromycin, 18% of subjects; moxifloxacin, 16%), lymphocytes (%) <0.8 x lower limit of normal (LLN) (azithromycin, 9% of subjects; moxifloxacin, 12%) and basophils (%) >1.2 x ULN (azithromycin, 10% of subjects; moxifloxacin, 9%).

The median changes in vital signs from baseline to the last observation were negligible.

CONCLUSIONS:

- The clinical success rate at the TOC visit for the Clinical Per Protocol population was 93% for azithromycin and 94% for moxifloxacin. The pre-specified criteria for demonstrating the non-inferiority of a single, 2.0 g dose of azithromycin SR compared to moxifloxacin 400 mg orally once a day for 5 days was met.

- Bacterial eradication rate was similar for both treatments, approximately 96%, with the lower limit of the associated 95% confidence interval within the 10% non-inferiority margin specified for the primary endpoint. Eradication rates were similar for both treatments for all pathogens.

- There was no statistically significant treatment difference in the time taken to first occurrence of AECB.

- There were no significant differences between treatments for mean CCQ total score, symptoms scores, functional state scores and mental state scores. Furthermore the confidence interval for the difference between groups on the CCQ total score did not extend to values pre-specified in the protocol as indicative of clinical significance.

- The number of AEs and the number of subjects with AEs were similar for both treatments. The incidence of treatment-related AEs was low, with most AEs mild or moderate in severity. The most common AEs were gastrointestinal disorders, being reported by 14% of subjects receiving azithromycin and 8% of subjects receiving moxifloxacin. A total of 9 subjects discontinued due to AEs: 6 subjects due to treatment-related AEs and 3 subjects due to the disease under study.

- The incidence of SAEs was higher with moxifloxacin (4.5% of subjects) compared to azithromycin (1.5%). No SAEs were treatment-related but were typically due to the disease under study or to other illnesses.