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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: N/A

NCT NO.: NCT 00392223

PROTOCOL NO.: A0661150

PROTOCOL TITLE: A Phase 3, Multicenter, Randomized, Double Blind-Double Dummy Study, to Evaluate Efficacy and Safety of Treatment with Azithromycin, Microspheres, Oral Powder for Suspension, 2 g, in One Administration a Week, for 8 Weeks, Compared with Treatment with Minocycline Capsules, 100 mg Daily for 8 Weeks, in Outpatients with Moderate to Severe Inflammatory Acne

Study Center: The study was conducted at 19 sites in Italy, of which 17 recruited subjects

Study Initiation and Completion Dates: 03 Oct 2007 to 11 Jun 2008

Phase of Development: Phase 3

Study Objectives: The primary objective of this study was to evaluate the clinical efficacy of azithromycin microspheres treatment in outpatients with moderate to severe inflammatory acne (papulopustular), compared with the first-line treatment minocycline, after 8 weeks of therapy, confirming the hypothesis of noninferiority of azithromycin treatment.

Secondary objectives of this study were:

- To evaluate the safety and tolerability of cyclical courses of azithromycin microspheres administrations in outpatients with papulopustular acne.
- To measure the impact on quality of life (QoL) of the treatment in patients with moderate to severe inflammatory acne.

METHODS

Study Design: This was a Phase 3, multicenter, randomized, double-blind, double-dummy study with 2 parallel groups of treatment in subjects with moderate to severe inflammatory acne. It was planned to enroll 212 ambulatory subjects (>16 years of age) with inflammatory

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acne, graded as moderate to severe, in 19 dermatology clinics in Italy. The study was terminated due to recruitment delays; as such, 118 subjects were randomized into the study.

Subjects were randomized in a 1:1 ratio into 1 of the following 2 parallel treatment groups:

- Treatment Group A: azithromycin microspheres, powder for oral suspension, 2 gm per week administered PO for 8 weeks; and minocycline placebo capsules PO QD for 8 weeks

- Treatment Group B: minocycline capsules, 100 mg administered PO QD for 8 weeks; and azithromycin microspheres-placebo PO once per week for 8 weeks

Treatment was administered for 8 weeks in each treatment group. Subjects were assessed at baseline, after 4 weeks of treatment, at the end of treatment, and 8 weeks after completing treatment.

Number of Subjects (Planned and Analyzed): A total of 212 subjects were planned to be recruited into this study. The study was terminated due to recruitment delays; as such, 118 subjects were randomized into the study.

Diagnosis and Main Criteria for Inclusion: Male and female subjects ≥16 years of age with a diagnosis of moderate (Global Acne Grading System [GAGS] score: 19 to 30) to severe (GAGS score: 31 to 33) papulopustular or pustular acne, who were willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures, and had evidence of a personally signed and dated informed consent document indicating that the subject had been informed of all pertinent aspects of the study were included in the study. Exclusion criteria included pregnancy, gastrointestinal disease, endocrine disease, and specific systemic diseases or other medical conditions that would have interfered with the evaluation of the therapeutic response or safety of the study drug.

Study Treatment: The study treatments were administered in a double-blind, double-dummy fashion that required subjects to take the dose of slurry (azithromycin microspheres or matching placebo) 1 day per week for 8 weeks and 1 rigid capsule (minocycline capsules [active or placebo]) QD for a total of 8 weeks.

Efficacy Evaluations: Clinical efficacy was assessed at the end of treatment visit and 8 weeks after completing treatment. Clinical efficacy was based on the GAGS and the Leeds technique. QoL was assessed with a disease specific Acne QoL scale.

GAGS was used to assess 6 locations on the face and chest/upper back, with a factor for each location based roughly on surface area, and distribution and density of pilosebaceous units. Each of the 6 locations was graded separately on a 0 to 4 scale, with the most severe lesion within that location determining the local score. The global score was factored based on a summing of all the local scores.

The Leeds technique was used to assess each subject's skin by visualization of and feeling the skin. A subjective grading scale was used for this assessment, as follows:

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0 = no acne to 10 = most severe acne

Three body sites were assessed and graded with the Leeds technique: face, back, and chest. Lesions were divided into inflamed and noninflamed lesions as follow:

- Noninflamed: blackheads and whiteheads

- Inflamed lesions: superficial (papules and pustules) or deep (nodules, cysts, and deep pustules). Superficial papules and pustules varied in size from 0.1 cm (with minimal erythema) to 0.5 cm (with a marked macular flare). Deep lesions were predominantly considered to be nodules, which were ≥0.5 cm.

Pharmacokinetic Evaluations: No pharmacokinetic evaluations were performed during this study.

Safety Evaluations: Evaluation of subjects for safety and tolerability were assessed through physical examination, adverse event (AE)/concomitant medication assessment, safety laboratory tests (including pregnancy testing for women of childbearing potential), vital sign measurements (blood pressure [BP], axillary temperature, and pulse rate), and by 12-lead electrocardiogram (ECG).

Statistical Methods: Sample size was based on the difference in change from baseline to endpoint of the GAGS global score. Based on a mean change of 8.3 and a standard deviation (SD) of 6 (The BEST Study) and a noninferiority margin of 3 (the largest difference judged as being clinically acceptable), it was calculated that 85 subjects per treatment group were estimated for rejecting the null hypothesis (at alpha = 5% and power = 90%) that minocycline was better than azithromycin. Being a noninferiority study, analysis was also performed on a per-protocol (PP) set of subjects. For this reason, and considering a potential 15% rate of subject withdrawal and a 10% rate of subjects with major protocol violations, a total of 212 subjects were planned to be recruited. The initial sample size of 212 subjects was not achieved; as such, the study was potentially underpowered. A total of 118 subjects were enrolled into the study.

The following populations were defined for the analysis:

- Safety analysis set: The safety analysis set included all enrolled subjects who received at least 1 dose of study drug. In cases where all dispensed study drug was returned, the subject was considered as nontreated and was to be excluded from the safety group.

- Full analysis set (FAS): The FAS included all enrolled subjects who received at least 1 dose of study drug and who had at least 1 postbaseline assessment of the primary variable.

- PP analysis set: The PP analysis set included all enrolled subjects belonging to the FAS group who met the protocol inclusion/exclusion criteria, who had a dosing compliance ≥80%, who did not take restricted medications, and who didn't deviate from the protocol in a way that could have affected efficacy assessments.

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The primary analysis was based on the FAS and the primary endpoint was the change from baseline to the end of treatment in the GAGS global score. To support the interpretation of the primary analysis, an identical analysis based on the PP set was conducted. If any component of the GAGS global score was missing, the GAGS global score was considered as missing. If subjects had missing GAGS scores at Week 8, but the GAGS score was present at Week 4, the Week 8 GAGS score was replaced using the last observation carried forward (LOCF).

Mean changes from baseline and 95% confidence intervals (CIs) were calculated. Comparison between treatment groups was performed using an analysis of covariance (ANCOVA) method, with treatment, center, and baseline value GAGS global score included as covariates.

The analysis to assess the noninferiority between the 2 study treatments was performed by computing the 95% CI for the difference in the change from baseline in GAGS global score. To show noninferiority of azithromycin compared to minocycline, the two-sided 95% CI for the difference in the GAGS global score at the end of treatment was required to lie entirely to the right of the noninferiority margin.

The treatment difference was calculated as 'minocycline – azithromycin'. As a lower GAGS score is a more optimal result, noninferiority was concluded if the 95% CI was entirely above the noninferiority margin of -3.

Summary statistics were presented separately for each of the anatomic locations making up the GAGS global score.

The number and percentage of subjects with mild, moderate, severe and very severe acne graded according to the GAGS score were to be assessed at each visit for the FAS. No inferential statistical analyses were performed on this assessment.

The change from baseline to the end of treatment in the GAGS score was also assessed separately in the subgroup of subjects graded as moderate according to the GAGS score at baseline, and the subgroup of subjects graded as severe or very severe according to the GAGS score at baseline. Summary statistics only were presented.

The number of lesions at each visit was summarized separately based on predetermined lesion types.

The grade of lesions was summarized separately for the face, back, and chest. Comparison between groups was assessed using an ANCOVA, assessing the change from baseline.

The improvement in GAGS score was categorized and summarized for each visit for the FAS. No formal statistical analyses were performed. This was repeated separately in the subgroup of subjects graded as moderate according to the GAGS score at baseline, and the subgroup of subjects graded as severe or very severe according to the GAGS score at baseline.

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The improvement of GAGS score during the study, defined as follows, was calculated for each subject and summarized by means of descriptive statistics:

- Best improvement: reduction of GAGS score >75% pre-post evaluation
- Good improvement: reduction of GAGS score >50% to 75% pre-post evaluation
- Moderate improvement: reduction of GAGS score >25% to 50% pre-post evaluation
- Light improvement: reduction of GAGS score <25% pre-post evaluation
- No change: reduction of GAGS score = 0% (pre-post evaluation)
- Worsening: increase of GAGS score >0 % (pre-post evaluation)

The secondary endpoint assessing QoL and Leeds technique was expected to show noninferiority of azithromycin compared to minocycline; however, no noninferiority bounds were specified for these endpoints. For the Leeds technique, 95% CIs comparing the 2 treatments, calculated from ANCOVA, were presented. No formal assessment of noninferiority was planned or performed.

For analyses that required complete subject data, missing values were replaced, for all secondary variables, with the LOCF technique. If a subject had only baseline secondary variable values, no replacement was done and the subject was to be excluded from the LOCF analysis for that particular secondary efficacy variable.

The acne QoL score for individual items and the overall score are presented by means of descriptive statistics. P-values were computed for the comparison between baseline and end-of-treatment values.

Safety analyses were performed on the safety population, which included all enrolled subjects. AEs were tabulated using the treatment-emergent algorithm. The standard grouping of AE preferred terms to body system was used. The frequencies of treatment-emergent AEs (all causalities and treatment related) were summarized by body system and preferred term. Summary tables of the severity of treatment-emergent AEs were provided.

The median change from baseline (the measurement collected at screening) to the end of treatment was calculated by treatment group for the hematology, chemistry, and urinalysis parameters. For each laboratory test performed, the number of subjects tested and the incidence of clinically significant laboratory test abnormalities were descriptively summarized. The percentage of subjects with a laboratory test abnormality was based on only those subjects undergoing that specific laboratory test. Subject listings of all clinical laboratory measurements include flags for laboratory values above or below the normal range; a separate table was prepared for all laboratory abnormalities.

The change in vital sign parameters from baseline to each visit was summarized using means, medians, minimum, maximum, and number of subjects. All vital signs data were listed.

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The number of subjects with an abnormal physical examination finding at baseline was summarized by body system using number of subjects and percentages. The number of subjects with a significant change in their physical examination was also presented. Physical examination findings at baseline and changes from baseline were listed for each subject.

RESULTS

Subject Disposition and Demography: Of the 118 subjects assigned to study treatment, 58 subjects were treated with azithromycin and 60 with minocycline (Table S1). Among subjects randomized to azithromycin, 84.5% completed the study compared with 78.3% of those randomized to minocycline. AEs were analyzed for all subjects randomized to azithromycin and minocycline (Table S1).

Table S1. Subject Evaluation Groups, Overall

Number (%) of Subjects	Azithromycin 2 gm	Minocycline 100 mg
Screened: 118		
Assigned to study treatment	58	60
Treated	58	60
Completed	49 (84.5)	47 (78.3)
Discontinued	9 (15.5)	13 (21.7)
Analyzed for efficacy		
Moderate acne analysis set	49 (84.5)	52 (86.7)
Severe acne analysis set[a]	4 (6.9)	6 (10.0)
Per protocol analysis set	48 (82.8)	48 (80.0)
Full analysis set	53 (91.4)	59 (98.3)
Analyzed for safety		
Adverse events	58 (100.0)	60 (100.0)
Laboratory data	49 (84.5)	51 (85.0)
Safety analysis set	58 (100.0)	60 (100.0)

[a] The severe acne analysis set also included subjects with very severe acne at baseline.
Discontinuations occurring outside the lag period were attributed to the last study treatment received.

Discontinuations from the study are summarized in Table S2. Among subjects randomized to azithromycin, 5 (8.6%) subjects discontinued for reasons related to study drug and 4 (6.9%) subjects discontinued for reasons not related to study drug. Among subjects randomized to minocycline, 3 (5.0%) subjects discontinued for reasons related to study drug and 10 (16.7%) subjects discontinued for reasons not related to study drug.

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Table S2. Discontinuations from Study

Number (%) of Subjects	Azithromycin 2 gm N=58	Minocycline 100 mg N=60
Discontinuations		
Related to study drug	5 (8.6)	3 (5.0)
Adverse event	5 (8.6)	3 (5.0)
Not related to study drug	4 (6.9)	10 (16.7)
Adverse event	0	1 (1.7)
Lost to follow-up	1 (1.7)	4 (6.7)
Other	0	4 (6.7)
Subject no longer willing to participate in study	3 (5.2)	1 (1.7)
Total	**9 (15.5)**	**13 (21.7)**

Discontinuations occurring outside the lag period were attributed to the last study treatment received.

The mean age was 22.0 years (range 16 to 35 years) and 21.6 years (range 15 to 35 years) for subjects in the azithromycin and minocycline treatment groups, respectively (Table S3). There were more females than males in each treatment group; the majority of subjects within each treatment group were white. The 2 treatment groups were similar with respect to overall demographic characteristics. A summary of demographic characteristics is presented in Table S3.

Table S3. Demographic Characteristics, Overall

Demographic Characteristic	Azithromycin 2 gm			Minocycline 100 mg		
	Male	Female	Total	Male	Female	Total
Number of subjects	23	35	58	24	36	60
Age (years)						
<18	6 (26.1)	4 (11.4)	10 (17.2)	11 (45.8)	6 (16.7)	17 (28.3)
18-44	17 (73.9)	31 (88.6)	48 (82.8)	13 (54.2)	30 (83.3)	43 (71.7)
Mean	19.5	23.7	22.0	18.8	23.4	21.6
SD	3.1	5.5	5.1	3.2	4.9	4.8
Range	16-28	16-35	16-35	15-27	16-35	15-35
Race						
White	21 (91.3)	35 (100.0)	56 (96.6)	24 (100.0)	32 (88.9)	56 (93.3)
Black	2 (8.7)	0	2 (3.4)	0	2 (5.6)	2 (3.3)
Asian	0	0	0	0	1 (2.8)	1 (1.7)
Other	0	0	0	0	1 (2.8)	1 (1.7)
Weight (kg)						
Mean	71.0	58.4	63.4	70.4	58.1	63.0
SD	9.2	10.3	11.6	9.4	12.3	12.7
Range	50.0-88.0	45.0-85.0	45.0-88.0	48.0-90.0	42.0-100.0	42.0-100.0
Height (cm)						
Mean	178.7	165.7	170.8	178.0	163.2	169.1
SD	6.2	6.2	8.9	7.3	6.4	9.9
Range	166.0-189.0	150.0-180.0	150.0-189.0	156.0-188.0	150.0-176.0	150.0-188.0

Abbreviation: SD = standard deviation

All subjects had a diagnosis of acne on admission to the study. The mean duration since first diagnosis was 6.1 years (range 0.0 to 25.8 years) and 4.6 years (range 0.1 to 20.8 years) for subjects in the azithromycin and minocycline treatment groups, respectively.

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Subjects were to take their assigned treatment QD for 8 weeks (ie, 56 days). The median number of days of treatment administrations among subjects randomized to azithromycin was 56.0 days (range of 1 to 73 days), and 56.5 days (range of 5 to 70 days) among subjects randomized to minocycline.

Efficacy Results: The primary efficacy assessment, GAGS global score, showed trends of improved scores with azithromycin and minocycline (Table S4). Based on results from this study, treatment of acne with azithromycin 2 gm/week is noninferior to treatment of acne with minocycline 100 mg QD; similar results were obtained for the FAS and PP populations.

Table S4. Summary of Global Acne Grading System Score; Full Analysis Set

Visit Week	Baseline Week 0, Day 1	Interim Visit Week 4	End of Treatment Week 8	End of Treatment Week 8 (LOCF)	Follow-Up 8 Weeks after EOT
Azithromycin 2 gm; N=53					
n	53	50	52	53	49
Mean (SD)	24.9 (3.66)	17.8 (5.55)	15.1 (6.97)	15.3 (7.07)	13.6 (7.85)
Median (Min, Max)	25.0 (19, 34)	18.0 (4, 31)	14.0 (0, 32)	14.0 (0, 32)	14.0 (0, 32)
Mean change (SD)	NA	-7.0 (4.83)	-9.7 (6.99)	-9.5 (7.05)	-11.1 (8.01)
95% CI on mean change	NA	-8.33, -5.59	-11.66, -7.77	-11.47, -7.59	-13.42, -8.82
Minocycline 100 mg; N=59					
n	59	56	56	59	49
Mean (SD)	25.7 (4.13)	19.3 (6.03)	15.3 (5.96)	15.9 (6.53)	12.5 (5.79)
Median (Min, Max)	26.0 (18, 35)	20.0 (0, 35)	14.5 (0, 27)	15.0 (0, 35)	12.0 (0, 23)
Mean change (SD)	NA	-6.5 (4.87)	-10.2 (6.13)	-9.8 (6.45)	-12.9 (6.58)
95% CI on mean change	NA	-7.77, -5.16	-11.86, -8.57	-11.48, -8.12	-14.79, -11.01

Abbreviations: CI = confidence interval, EOT = end of treatment, LOCF = last observation carried forward, Max = maximum, Min = minimum, N = number of subjects belonging to the population, n = number of subjects belonging to the population and considered for this analysis, NA = not applicable, SD = standard deviation

Table S5 provides a summary of analysis of change from baseline to end of treatment for GAGS scores for the FAS. The azithromycin treatment was to be declared noninferior to minocycline if the two-sided CI for the difference in GAGS global score at the end of treatment was entirely to the right of the noninferiority margin. The interval from -2.48 to 1.54 does lie entirely to the right of the value of -3; hence, the treatment difference (minocycline minus azithromycin) shows that azithromycin is noninferior to minocycline; results from the FAS and PP populations were similar.

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Table S5. Analysis of Change from Baseline to End of Treatment in Global Acne Grading System Score

Parameter	Full Analysis Set Value	Per Protocol Set Value
P-value for effect from ANCOVA model		
Center	<0.0001	<0.0001
Covariate (baseline)	0.2122	0.0715
LS mean (95% confidence interval)		
Azithromycin	-8.69 (-10.33, -7.05)	-9.35 (-10.75, -7.94)
Minocycline	-9.16 (-10.62, -7.71)	-10.22 (-11.54, -8.90)
Treatment difference (minocycline-azithromycin)		
Estimated difference	-0.47	-0.87
95% confidence interval	-2.48, 1.54	-2.58, 0.84

Abbreviations: ANCOVA = analysis of covariance, LS = least squares

The number and percent of subjects with mild acne increased (ie, improved from moderate, severe, or very severe) in both treatment groups beginning with the Week 4 visit, with a higher decrease at Week 8 (and Week 8 LOCF), and continuing through the follow-up visit. This increase continued through the follow-up visit for subjects in the azithromycin treatment group. A slightly higher number and percentage of subjects in the minocycline group had mild acne at end of treatment (Week 8) and end of treatment (Week 8, LOCF) compared to the azithromycin treatment group. By 8 weeks after the end of treatment, a higher percentage of subjects in the azithromycin treatment group had mild acne.

The summary of acne scores for the face graded by Leeds technique showed improvement (ie, decreased) in both treatment groups, beginning with the Week 4 visit, with a higher decrease at Week 8 (and Week 8 LOCF), and continuing through the follow-up visit. The mean change (SD) at Week 8 LOCF for the azithromycin treatment group was -2.5 (1.90) (95% CI: -3.01, -1.97) compared with -2.3 (1.59) (95% CI: -2.74, -1.91) for the minocycline treatment group. The mean acne score for the face was nearly identical at the follow-up visit for both treatment groups. The treatment difference (minocycline minus azithromycin) shows that azithromycin and minocycline for treatment of acne of the face provide similar results.

The summary of acne scores for the back graded by Leeds technique showed improvement (ie, decreased) in both treatment groups, beginning with the Week 4 visit, with a higher decrease at Week 8 (and Week 8 LOCF), and continuing through the follow-up visit. The mean change (SD) at Week 8 LOCF for the azithromycin treatment group was -1.5 (1.69) (95% CI: -1.96, -1.02) compared with -1.4 (1.47) (95% CI: -1.76, -0.99) for the minocycline treatment group. The mean acne score for the back was slightly better at the follow-up visit for the minocycline treatment group compared with the azithromycin treatment group. The treatment difference (minocycline minus azithromycin) shows that azithromycin and minocycline for treatment of acne of the back provide similar results.

The summary of acne scores for the chest graded by Leeds technique showed improvement (ie, decreased) in both treatment groups, beginning with the Week 4 visit, with a higher decrease at Week 8 (and Week 8 LOCF), and continuing through the follow-up visit. The mean change (±) at Week 8 LOCF for the azithromycin treatment group was -1.5 (2.00)

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(95% CI: -2.00, -0.90) compared with -1.1 (1.51) (95% CI: -1.51, -0.73) for the minocycline treatment group. The mean acne score for the chest was nearly identical at the follow-up visit for both treatment groups. The treatment difference (minocycline minus azithromycin) shows that azithromycin and minocycline for treatment of acne of the chest provide similar results.

A summary of GAGS scores for the FAS showed improvement (ie, decreased) in both treatment groups, beginning with the Week 4 visit, with a higher decrease at Week 8 (and Week 8 LOCF), and continuing through the follow-up visit for each of the following locations: forehead, right cheek, left cheek, nose, chin, and chest and upper back. A summary of the total GAGS scores showed improvement (ie, decreased) in both treatment groups, beginning with the Week 4 visit, with a higher decrease at Week 8 (and Week 8 LOCF), and continuing through the follow-up visit for subjects with moderate acne at baseline and subjects with severe or very severe acne at baseline.

A summary of the number of lesions based on the Leeds technique for the FAS showed improvement (ie, decreased) in both treatment groups, with a trend towards a higher decrease for subjects in the azithromycin treatment group beginning with the Week 4 visit and continuing through the Week 8 (and Week 8 LOCF) visit for the face, back, and chest; similar improvement (ie, decrease) was noted between treatment groups at the follow-up visit for the face, back, and chest.

Overall improvement of GAGS scores was noted for the FAS in both treatment groups, for subjects with moderate acne at baseline, and subjects with severe or very severe acne at baseline. However, the number of subjects with severe or very severe acne at baseline was small (azithromycin = 4 subjects; minocycline = 6 subjects).

Among subjects randomized to azithromycin, 20 (40.0%) subjects showed improvement in acne based on the acne QoL scale score from baseline to end of treatment compared with 28 (50.9%) subjects randomized to minocycline.

A higher proportion of subjects randomized to minocycline were classified as ‘improved’ relative to baseline than those subjects randomized to azithromycin; however, the difference was not statistically significant. Similar proportions of subjects in both treatment groups were classified as ‘improved or same’ relative to baseline.

Among subjects randomized to treatment with minocycline, 17 (30.4%) subjects reported improvement in relations (ie, Item 2 [relations with others decreased], full analysis set, ‘improved’ [and ‘improved or remained the same’]) with others compared with 3 (6.0%) subjects randomized to treatment with azithromycin. The percent of subjects who reported improvement in the individual items in the QoL scale were similar between treatment groups for the remainder of the items (ie, Item 1 and Items 3 through 9).

Pharmacokinetic Results: No pharmacokinetic evaluations were performed during this study.

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Safety Results: There were no deaths or serious adverse events (SAEs) reported in this study. Among subjects randomized to azithromycin, 29 (50.0%) subjects reported AEs, 1 (1.7%) subject had a severe AE, 6 (10.3%) subjects permanently discontinued at least 1 of the 2 study medications due to an AE, and 1 (1.7%) subject had a dose reduction or temporary discontinuation due to AEs. Among subjects randomized to minocycline, 21 (35.0%) subjects reported AEs, no subject had a severe AE, 5 (8.3%) subjects permanently discontinued at least 1 of the 2 study medications due to an AE, and 2 (3.3%) subjects had dose reductions or temporary discontinuations due to AEs.

Overall, 28 (48.3%) of 58 subjects in the azithromycin group had treatment-related AEs, compared with 10 (16.7%) of 60 subjects in the minocycline group. Among subjects randomized to azithromycin, 26 (44.8%) of 58 subjects reported a gastrointestinal disorder AE, of which all were considered by the investigator to be treatment related, compared to 9 (15.0%) of 60 subjects in the minocycline treatment group, of which 4 (6.7%) subjects were considered by the investigator to have treatment-related gastrointestinal AEs.

Overall, 29 (50.0%) of 58 subjects in the azithromycin treatment group and 21 (35.0%) of 60 subjects in the minocycline treatment group reported at least 1 treatment-emergent AE (all causalities). Treatment-related AEs were reported by 28 (48.3%) and 10 (16.7%) subjects in the azithromycin and minocycline treatment groups, respectively (Table S6).

The most frequently reported AEs (all causalities) overall (by Medical Dictionary for Regulatory Activities [MedDRA; Version 11.1] system organ class [SOC]) were gastrointestinal disorders, general disorders and administration site conditions, and infections and infestations, reported by 26 (44.8%), 5 (8.6%), and 5 (8.6%) subjects and 9 (15.0%), 4 (6.7%), and 8 (13.3%) subjects in the azithromycin and minocycline treatment groups, respectively. The most frequently reported treatment-related AEs (by MedDRA SOC) were also gastrointestinal disorders, general disorders and administration site conditions, and nervous system disorders, reported by 26 (44.8%), 3 (5.2%), and 2 (3.4%) subjects and 4 (6.7%), 3 (5.0%), and 2 (3.3%) subjects in the azithromycin and minocycline treatment groups, respectively (Table S7).

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Table S6. Summary of Treatment-Emergent Adverse Events

Number of Subjects, N (%)	Azithromycin 2 gm N = 58		Minocycline 100 mg N = 60	
	All Causality	Treatment Related	All Causality	Treatment Related
Subjects evaluable for adverse events	58	58	60	60
Number of adverse events[a, b, c]	49	42	34	15
Subjects with adverse events[c]	29 (50.0)	28 (48.3)	21 (35.0)	10 (16.7)
Subjects with serious adverse events[c, d]	0	0	0	0
Subjects with severe adverse events	1 (1.7)	0	0	0
Subjects discontinued due to adverse events	6 (10.3)	6 (10.3)	5 (8.3)	3 (5.0)
Subjects with dose reduced or temporary discontinuations due to adverse events	1 (1.7)	0	2 (3.3)	0

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities
[a] MedDRA (V11.1) coding dictionary was applied.
[b] Includes data up to 35 days after the last dose of study drug.
[c] Except for the number of adverse events, subjects were counted only once per treatment in each row.
[d] Serious adverse event according to investigator assessment.

Table S7. Treatment-Emergent Adverse Events by Body System

Number (%) of Subjects	Azithromycin 2 gm n (%)		Minocycline 100 mg n (%)	
	All Causality	Treatment Related	All Causality	Treatment Related
Evaluable for adverse events	58	58	60	60
With adverse events	29 (50.0)	28 (48.3)	21 (35.0)	10 (16.7)
Discontinued due to adverse events	6 (10.3)	6 (10.3)	5 (8.3)	3 (5.0)
Number (%) of Subjects with Adverse Events by System Organ Class[a, b]				
Eye disorders	0	0	1 (1.7)	0
Gastrointestinal disorders	26 (44.8)	26 (44.8)	9 (15.0)	4 (6.7)
General disorders and administration site conditions	5 (8.6)	3 (5.2)	4 (6.7)	3 (5.0)
Immune system disorders	0	0	2 (3.3)	1 (1.7)
Infections and infestations	5 (8.6)	0	8 (13.3)	1 (1.7)
Injury, poisonings, and procedural complications	0	0	1 (1.7)	0
Investigations	0	0	2 (3.3)	2 (3.3)
Metabolism and nutrition disorders	1 (1.7)	1 (1.7)	0	0
Nervous system disorders	2 (3.4)	2 (3.4)	4 (6.7)	2 (3.3)
Reproductive system and breast disorders	0	0	1 (1.7)	0
Skin and subcutaneous tissue disorders	0	0	1 (1.7)	1 (1.7)

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities
[a] MedDRA (V11.1) coding dictionary was applied
[b] If the same subject in a given treatment had more than 1 occurrence in the same preferred term event category, only the most severe occurrence was taken. Subjects were counted only once per treatment in each row. Any missing severities were imputed as severe, unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity was summarized. Missing baseline severities were imputed as mild.

Overall, 5 subjects treated with azithromycin discontinued the study due to treatment-emergent AEs, compared with 4 subjects treated with minocycline; all discontinuations in the azithromycin treatment group were attributed to gastrointestinal disorders. Two subjects (1 each in the azithromycin treatment group and minocycline treatment group) discontinued study drug, but were not permanently discontinued from the

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study. One subject (minocycline treatment group) reported mild localized finger infection; the other subject (azithromycin treatment group) reported diarrhea and nausea (both moderate in intensity).

The baseline medians and changes from baseline for laboratory test results were similar between treatment groups; none of the values or changes was considered to be clinically meaningful. The treatment groups were similar with respect to median laboratory test changes from baseline. Relatively few laboratory abnormalities were noted during this study.

Two subjects each had increased alanine aminotransferase (ALT) reported as an AE; both subjects were in the minocycline treatment group. Other laboratory value changes from baseline were similar between treatment groups.

The changes from baseline for vital sign measurements were similar between treatment groups; none of the values or changes was considered to be clinically meaningful. Among subjects randomized to azithromycin, 3 subjects had AEs of pyrexia reported (1 of which was reported during the posttreatment period) compared with 4 subjects randomized to minocycline.

Physical examination findings at baseline were similar between the treatment groups. One subject (minocycline treatment group) had a physical examination change from baseline reported (ie, edema of eyelid). This subject had an AE related to this physical examination finding, which was considered to be related to an allergic reaction, and not related to treatment with study drug. There were no other physical examination changes from baseline reported during this study.

CONCLUSIONS:

- The primary efficacy assessment, GAGS scores, showed trends of improved scores with azithromycin and minocycline. Based on results from this study, treatment of acne with azithromycin 2 gm/week is noninferior to treatment of acne with minocycline 100 mg QD; similar results were obtained for the FAS and PP populations.

- There were no SAEs or deaths reported during this study. Among subjects randomized to treatment with azithromycin, gastrointestinal disorders were reported for 26 (44.8%) of 58 subjects compared with 9 (15.0%) of 60 subjects randomized to treatment with minocycline.

- Overall, azithromycin 2 gm/week administered PO to male and female subjects with a diagnosis of moderate to severe papulopustular or pustular acne was well tolerated. No new safety concerns emerged from this study.

- Overall, secondary efficacy endpoints showed that the number and percent of subjects with improvement in acne symptoms or QoL was similar in both treatment groups beginning with the Week 4 visit, and continuing both through the end of treatment (Week 8 and Week 8 [LOCF]) and the follow-up visit at 8 weeks after the end of treatment.

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