Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer Healthcare Pharmaceuticals Inc.	
Study Number:	11980	NCT00656747
Study Phase:	IV Interventional	
Official Study Title:	A prospective, multinational, multicenter, randomized, double blind, double-dummy, controlled study comparing the efficacy and safety of moxifloxacin to that of amoxicillin-clavulanic acid for the treatment of subjects with acute exacerbations of chronic bronchitis MAESTRAL (**m**oxifloxacin in **AE**CB **s**uperiority **tri**a**l**).	
Therapeutic Area:	Anti-Infectives	
Test Product		
Name of Test Product:	Moxifloxacin (Avelox, BAY12-8039)	
Name of Active Ingredient:	Moxifloxacin	
Dose and Mode of Administration:	400 mg oral tablet; 1 tablet administered orally once daily (OD)	
Reference Therapy/Placebo		
Reference Therapy:	Amoxicillin-clavulanic acid	
Dose and Mode of Administration:	875/125 mg (BID), administered orally	
Duration of Treatment:	Test therapy: 5 days Reference therapy: 7 days	
Studied period:	Date of first subjects' first visit:	04 MAR 2008
	Date of last subjects' last visit:	15 DEC 2010
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	The original protocol, dated 18 DEC 2007 (Version 3.0), was amended 9 times during the study. Amendments 1 and 2 were applicable to France and were withdrawn as the country did not participate in the study. Amendment no. 3 (dated 27 APR 2008) was applicable to Ireland. This amended the exclusion criteria and warnings/precautions sections as required by the Clinical Trials Unit of the Irish Medicines Board. Additionally, the warnings/precautions section was expanded to align text in the protocol with the warnings/precautions sections of Summary of Product Characteristics which were available in Ireland. Amendment no. 4 (dated 19 AUG 2008), a global amendment, was applicable to all participating countries. This amendment further	

	clarified clinical failure and clarified Day 1 as baseline throughout the protocol. It gave additional details of the tests that were to be performed during the study and instructions on how to complete the different forms. Additionally, a few changes were made to the inclusion/exclusion criteria. Amendment no. 5 (dated 13 NOV 2008) was applicable to Colombia. This amendment required all Colombian investigators to perform hematology, liver function, and serum creatinine testing at the enrollment visit. These laboratory data were recorded in the subject's chart but not entered in the clinical study database. Amendment no. 6 (dated 17 MAR 2009), a global amendment, was applicable to all participating countries. This amendment changed the number of participating sites. It added clarifications to the rescreening of initial screen failure subjects, spirometry assessments, and corticosteroids dosing. Additional warnings/precautions on moxifloxacin were included. Amendment no. 7 (dated 18 SEP 2009) was applicable to Croatia and the Czech Republic. This amendment removed the requirement to complete the AECB-SS (Acute exacerbation of chronic bronchitis symptom scale) questionnaire due to the unavailability of a validated translation for these two countries. Amendment no. 8 (dated 01 DEC 2009), a global amendment, was non-substantial. Amendment no. 9 (dated 18 MAY 2010), a global amendment, was applicable to all participating countries. This amendment involved change in sample size estimations and addressed limitations regarding the collection of "first morning" sputum sample at enrollment and other visits for assessment.
Study Centre(s):	The subjects were enrolled at 153 centers in 30 countries in the following four geographic regions: • Asia Pacific (28 centers): Australia, China, Hong Kong, Indonesia, Pakistan, Philippines, and Thailand. • Europe 1 (37 centers): Belgium, Germany, Ireland, Latvia, Lithuania, the Netherlands, Switzerland, and the United Kingdom. • Europe 2 and South Africa (40 centers): Andorra, Croatia, Czech Republic, Greece, Italy, Portugal, Spain, and South Africa. • Latin America and Canada (48 centers): Argentina, Brazil, Chile, Colombia, Mexico, Peru, and Canada.
Methodology:	This was a multicenter, multinational, prospective, randomized, double-blind, double dummy, Phase IV clinical study in outpatients with AECB (acute exacerbation of chronic bronchitis), which was to determine the clinical non-inferiority at 8 weeks post-therapy of moxifloxacin versus amoxicillin-clavulanic acid in the per-protocol (PP) population. In the event that non-inferiority of moxifloxacin was demonstrated in the PP population, the study was powered to

	allow for the second analysis to test for clinical superiority of moxifloxacin in the intent-to-treat (ITT) population. Following stratification for the use of systemic corticosteroids, the subjects were randomized to treatment with either moxifloxacin 400 mg PO (per oral) OD or amoxicillin-clavulanic acid 875/125 mg PO BID. The study consisted of the following visits: • Enrollment/Randomization (Day 1 was the first day of study drug treatment) • During Therapy (Treatment Day 4 ± 1 day) • End of Therapy (Day 13 ± 1 day after start of study drug treatment) • 4 weeks post-therapy (Day 35 ± 3 days after start of study drug treatment) • 8 weeks post-therapy (Day 63 ± 3 days after start of study drug treatment) Sputum specimens for bacteriological examination were obtained for purulence and microscopic evaluations, and culture (done locally) at Enrollment, During Therapy, EOT (End of therapy/treatment), 4 weeks post-therapy, and 8 weeks post-therapy visits, as well as in subjects who met the criteria for clinical failure or discontinued prematurely from the trial. At every visit, the investigator assessed sputum purulence macroscopically by comparing the color of the sputum specimen with the provided color chart. Assessment for the clinical response was performed at every study visit following the enrollment visit. If the subject did not improve during therapy or experienced relapse, an unscheduled clinic visit (premature discontinuation) was booked and the subject underwent all 8 weeks post-therapy visit evaluations prior to initiation of an additional or alternative treatment. If the investigator assessed clinical failure, then the subject was prematurely terminated from the study and was not followed further. A chest X-ray or laboratory testing was not required for enrollment into the study. They were to be done at the discretion of the investigator. The chest X-ray results were recorded in the source documents and in the case report forms (CRFs). Laboratory testing (hematology, liver function, and serum creatinine) prior to study enrollment was required in Colombia. Post-bronchodilator spirometry was performed at each study visit according to the American Thoracic Society criteria, and the results were recorded in the CRF. The AECB-SS, a symptom assessment instrument for evaluating changes in subject reported AECB symptoms, was completed by the subject on a daily basis from the start of study drug treatment up to the EOT visit. As this study was not designed to document pre AECB reference values for symptom severity, a post AECB

	reference value was needed as a surrogate, hence the subjects completed the AECB-SS at the 4 weeks post-therapy and 8 weeks post-therapy visits. The subjects' self administered SGRQ (St. George's Hospital Respiratory Questionnaire) was completed at every study visit, except during Therapy visit for the healthrelated QoL (Quality of Life) data analysis. The SGRQ was a 76 item disease specific questionnaire that measured three dimensions: symptoms (associated with pulmonary disease), activities, and impacts (social and psychological functioning). In order to calculate the total health care costs related to CB (chronic bronchitis), all healthcare resource consumption related to CB from the first to last study visit were documented. Healthcare resource consumption information included concomitant medications, therapeutic adjuncts, diagnostic procedures, other medical care/medical staff requirements, hospitalizations (including ward and duration), work productivity, and activity impairment. Subject booklets were provided and completed up to the 8 weeks post-therapy visit. The booklets allowed the subject to document any changes in respiratory symptoms, medication and/or adverse events (AEs), and to help the subject remember healthcare resource consumption. The AECB SS was also included in the booklet. The relevant information was documented in the CRF at the subsequent study visits by either the investigator or the interviewer. Retrospective completion of the booklet was not permitted. The safety of study drug treatment was monitored by careful clinical observations at each visit following enrollment. All AEs were collected and recorded in the CRF up to 8 weeks post-therapy. Serious adverse events (SAEs) were reported within 24 hours of the investigator's awareness. SAEs continued to be monitored until event resolution or until any further change in the subject's condition was unlikely. To validate the investigator's assessment of clinical outcomes, an independent Data Review Committee (DRC) assessed the data for all clinical failures and indeterminate assessments prior to unblinding of the treatment assignments of datasets. The DRC evaluation was used in the efficacy analysis.
Indication/ Main Inclusion Criteria:	Indication: Bacterial infections (treatment of subjects with AECB). Main inclusion criteria: 1. Outpatients with chronic bronchitis. 2. Male or female subjects, ≥60 years old. 3. Subject who could be managed with oral antimicrobials. 4. Post-bronchodilator forced expiratory volume in one second (FEV_1- Forced expiratory volume in one second) less than or equal

	to 60% predicted, and FEV_1/forced vital capacity (FVC) less than 70% at enrollment. 5. Documented history of 2 or more AECB episodes, within 12 months of study enrollment, requiring a course of systemic antibiotics and/or systemic corticosteroids. 6. All symptoms/signs must have been present and confirmed by the Investigator: increase in dyspnea, purulent sputum, increase in sputum volume. 7. Subject must have provided a sputum sample. The sputum was to be assessed macroscopically by the investigator and should have been graded as either yellow or green or rust (according to the provided color chart). 8. Current or past cigarette smoker with ≥20 pack-year smoking history (pack-years were to be calculated by dividing the number of cigarettes smoked per day by 20 [number of cigarettes/pack] and multiplying by the number of years a person has smoked). 9. Subjects must have been exacerbation-free for at least 30 days prior to enrollment. 10. Subjects must have been willing and able to complete the questionnaires and the subject booklet without assistance. 11. Subjects with medical conditions and social status at the time of enrollment compatible with study protocol procedures. 12. Willing and able to provide written Informed Consent.
Study Objectives:	Primary: The primary objective of this study was to compare the efficacy of moxifloxacin 400 mg PO once daily for five days with the respective efficacy of amoxicillin-clavulanic acid 875/125 mg PO twice a day for 7 days in the treatment of subjects with AECB. The primary efficacy endpoint was the clinical failure rate at the 8 weeks post-therapy visit. Clinical failure was defined as the requirement for additional or alternate treatment (including increased dose or duration of treatment) for an exacerbation of respiratory symptoms, with systemic antibiotics and/or systemic corticosteroid administration within 8 weeks post-therapy. Secondary: The secondary objectives were to compare the following between the two treatment groups: • Clinical failure rates at the During Therapy, EOT, and at 4 weeks post-therapy visits. • Bacteriological eradication rates at the During Therapy, EOT, 4 weeks, and 8 weeks post-therapy visits. • Clinical failure rates (as of global amendment 4) (for subjects with positive sputum culture at enrollment) at the During Therapy, EOT, and 4 weeks post-therapy and 8 weeks post-therapy visits. • Weekly mean symptom scores measured by the AECB Symptom Scale (AECB-SS). • Rates and speed of symptom relief measured by the AECB-SS. • Need for any change in dosage or additional respiratory

	medication such as bronchodilators and inhaled steroids, excluding short acting bronchodilators. • Clinical failure rates for subjects with co-administration of systemic corticosteroids (Stratum 1). • Clinical failure rates for subjects without co-administration of systemic corticosteroids (Stratum 2). • Improvement in symptom burden measured by the AECB-SS • Improvement in health QoL measured by the SGRQ. • Spirometry tests were to be compared between treatment groups at each assessment visit. • Healthcare resource utilization/consumption related to CB management including rescue medications, concomitant medications, therapeutic adjuncts, diagnostic procedures, other medical care/medical staff requirements, hospitalizations, and work productivity and activity impairment. • Safety and tolerability of moxifloxacin versus amoxicillin clavulanic acid, with particular attention to rates of diarrhea.
Evaluation Criteria:	Efficacy (Primary): The primary efficacy variable was clinical failure at 8-weeks post-therapy. Efficacy (Secondary): The secondary efficacy variables were: • Clinical efficacy failure rates at the During Therapy, EOT, and 4-weeks post-therapy visits. • Bacteriological eradication rates at During Therapy, EOT, 4-weeks post-therapy, and 8-weeks post-therapy visits. • Clinical efficacy failure rates for subjects with positive sputum culture at enrollment at the During Therapy, EOT, 4-weeks post-therapy, and 8-weeks post-therapy visits. • Weekly mean symptom scores measured by the AECB-SS • Rates and speed of symptom relief measured by the AECB-SS. • Need for any change in dosage or additional respiratory medication such as bronchodilators and inhaled steroids, excluding short-acting bronchodilators. • Clinical failure rates for subjects with co-administration of systemic corticosteroids (Stratum 1). • Clinical failure rates for subjects without co-administration of systemic corticosteroids (Stratum 2). • Improvement in symptoms burden measured by the AECB-SS. • Improvement in health-related QoL measured by the SGRQ. • Spirometry tests were to be compared between treatment groups at each assessment visit. • Healthcare resource utilization related to chronic bronchitis management including rescue medications, concomitant medications, therapeutic adjuncts, diagnostic procedures, other medical care/medical staff requirement, hospitalizations (including ward and duration), work productivity, and activity impairment. • Safety and tolerability of moxifloxacin versus amoxicillin-clavulanic acid, with particular attention to rates of diarrhea.

	Safety: Subjects' safety was monitored through the incidence of AEs from enrollment up to the 8-week post-therapy visit.
Statistical Methods:	General considerations: All analyses were based on subjects "as treated". All statistical tests were two sided and performed at the 0.05 significant levels. All efficacy analyses and tabulation of efficacy data were performed for the PP population as well as for the valid for safety/ITT (intent-to-treat) population. For the non-inferiority analysis, the primary population was the PP population; for superiority analyses, the primary population was the ITT population. In both efficacy analyses, centers were clustered by geographic region (e.g., country). The ratio between the smallest and the largest region was not more than 1:2. Centers were pooled before unblinding. Statistical analyses were adjusted to these clusters of centers (geographic region) and strata (co-administration of systemic corticosteroid regimen for the current AECB: no/yes). Analysis sets: There were four analysis populations, and their validity criteria are defined below: PP subject population: Subjects were included in the PP analysis, if they met the following criteria: 1. Acute Exacerbation of chronic bronchitis (AECB) was confirmed at enrollment by the presence of signs and symptoms consistent with the definition in the study protocol. 2. The study drug must have been given for a minimum of 48 hours (in case of a clinical failure) or ≥80% of study medication delivered (in case of cure). 3. No random code was broken unless the subject was a clinical failure and the clinical assessment was made before unblinding. 4. Adequate compliance was documented with >80% of study drug administered. 5. The clinical evaluation at 8 weeks post-therapy must have been available and different from "indeterminate" or "missing" except for clinical failures prior to the 8 week Post-Therapy visit. 6. No protocol violations influencing the study treatment efficacy parameters must have been observed. 7. No other systemic antibiotic and/or systemic steroid was administered up to 8 weeks post-therapy unless the subject was a clinical failure. Microbiologically valid (MBV) subjects: MBV subjects were defined as all subjects valid per protocol, in whom at least one causative organism was cultured from the sputum sample provided prior to start of therapy and where at least one more bacteriological evaluation at appropriate time points was available and different from "indeterminate" or "missing".

	ITT subject population/valid for safety population: The valid for safety/ITT population included all subjects who were randomized and received at least one dose of study drug and with at least one safety observation post initiation of study treatment. ITT with causative organisms: All subjects valid for ITT and with at least one pre therapy causative organism were included in the ITT population with causative organisms. Populations used for analyses: Efficacy: For the primary non-inferiority analysis, the primary population was the PP population; for superiority analyses, the primary population was the ITT population. Safety: Safety analyses were performed for subjects in the valid for safety population (which was also the ITT population). All subjects who were randomized and received at least one dose of study drug and with one observation post initiation of study treatment were considered valid for the safety analysis. Efficacy variables Additional post-hoc analyses which were not pre-specified, but provided during the compilation of the clinical study report, compared the results for two additional analyses. One analysis compared all bacteriological responses at EOT versus the clinical response at Week 8 post-therapy. The other analysis compared only those bacteriological responses at EOT based on actual culture results (eradications and persistences/superinfections) versus the clinical response at Week 8 post-therapy. Efficacy (Primary): The primary goal of the study was to show non-inferiority of moxifloxacin as compared to the comparator, where non-inferiority was defined as a difference in failure rates of less than 6%. This corresponds to the following hypotheses: Ho: $pM \geq pC + 0.06$ H1: $pM < pC + 0.06$ (where pM = failure rate for moxifloxacin, pC = failure rate for amoxicillin clavulanic acid). For a successful study, this null hypothesis should be rejected at the 2.5% level (one-sided) (as of global amendment 4). To test the null hypothesis of moxifloxacin inferiority, a two-sided 95% confidence interval (CI) for the difference between the two clinical failure rates (treatment group "moxifloxacin" minus treatment group "amoxicillin clavulanic acid") was calculated using Mantel-Haenszel weights based on geographic region and the concomitant steroid use stratification variable. If, and only if, the

	upper limit of this CI was smaller than 6%, it was proven that treatment with moxifloxacin was clinically not less effective than treatment with amoxicillin/clavulanic acid, and noninferiority was demonstrated. If this first null hypothesis was rejected, i.e., non-inferiority was statistically proven, the second null hypothesis of treatment group equality was to be tested, this time using the ITT population. This corresponds to the usual superiority situation: Ho: pM ≥ pC. H1: pM < pC. (where pM = failure rate for moxifloxacin, pC = failure rate for amoxicillin clavulanic acid). To test this null hypothesis, again a two-sided 95% CI for the difference between the two clinical failure rates (treatment group "moxifloxacin" minus treatment group "amoxicillin-clavulanic acid" [co-amoxiclav]) was to be calculated using Mantel-Haenszel weights based on geographic region and the concomitant steroid use stratification variable. If, and only if, the upper limit of this CI was smaller than 0, superiority of treatment with moxifloxacin could be concluded. Determination of sample size: The primary aim of the study was to reject the Null hypothesis: A 5 day therapy with moxifloxacin, 400 mg OD is more than 6% less effective than a 7 day therapy with amoxicillin clavulanic acid 875/125 mg twice daily, based on failure rates up to 8 weeks post-therapy. Based on an assumed failure rate of 26% in the control group, and an assumed failure rate of 24% in the moxifloxacin group (i.e., an assumption of a 2% lower failure rate for moxifloxacin than control), a non-inferiority margin of 6%, alpha = 2.5 % (one-sided), and beta = 14% (power = 86%), the sample size estimation yields n = 540 subjects (as of global amendment 9) valid for the per protocol analysis in each treatment group. The sample size estimate was based on the formula provided by Farrington-Manning. With an assumed validity rate of approximately 80% for the primary efficacy parameter, 675 subjects in each treatment group needed to be randomized in the study, which meant a total of 1,350 subjects (as of global amendment 9). An important secondary endpoint was to prove superiority of moxifloxacin. For this comparison, the ITT population was the primary analysis population. With 675 subjects per group and an overall failure rate of 35% (in the ITT population), a statistically significant difference between the moxifloxacin and control groups could be tested with an

	observed difference between groups of at least 5% (as of global amendment 9). Primary test of non-inferiority in the PP population: For the primary test of non-inferiority in the PP population, failure rates were calculated by carrying forward the responses of failure and relapse occurring at the end of therapy and four weeks after the end of therapy, respectively, and adding these to the rates of relapse 8 weeks after the end of therapy. Failures or relapses which occurred outside of a regularly scheduled visit but any time between the end of therapy and the 8-week visit were also included. For the test of superiority in the ITT population, responses of indeterminate and missing were also included in the failure category. An independent DRC reviewed the primary efficacy variable, clinical response 8 weeks after the end of therapy. In order to keep the DRC blinded to country of origin, subjects were identified by their randomization number only. The subjects were selected for DRC review in all cases for which the investigator's clinical response assessment at the subject's last study visit was entered as "indeterminate" or "clinical failure/relapse". In addition, the DRC's review included all cases where the assessment of "clinical cure/continued clinical cure" was thrown into question (i.e., the subject met the protocol definition of clinical failure but was assessed by investigator as "clinical cure/continued clinical cure"). In the case that the DRC disagreed with the clinical response assessment made by the investigator for the primary efficacy variable, the clinical response assessment assigned by the DRC was used for the analysis instead. Efficacy (Secondary): Clinical response variables at the earlier timepoints were analyzed in the same manner as the primary efficacy variable, with two-sided 95% CI based on Mantel-Haenszel weights used to assess non-inferiority in the PP population. Then, if non-inferiority was proven, two-sided 95% CI were to be used to assess superiority in the ITT population. The non inferiority margin was to remain 6% for the earlier timepoints. This approach was also to be used for clinical response at 8 weeks post-therapy for subjects in the MBV and ITT with causative organisms populations. For clinical response variables at the earlier timepoints in the PP and the ITT populations, values of missing and indeterminate were treated as failures, and were combined with the other failure categories. For bacteriological response in the MBV population, a bacteriological failure was a subject with bacteriological responses of persistence, recurrence, presumed persistence, or eradication with re-infection or superinfection. For the ITT with causative

	organisms population, responses of indeterminate or missing were also considered bacteriological failures. For the bacteriological response by subject variable, the same hypothesis testing approach was used as for the clinical response variables; an initial test of non-inferiority in the MBV population, then, if non inferiority was proven, a test for superiority in the ITT with causative organism population. The non inferiority margin for bacteriological response was again 6%. The hypotheses was to be tested with the same approach as that used for clinical response, comparing the upper limits of the 95% CI based on Mantel-Haenszel weights to 6% (non inferiority) and 0% (superiority). Bacteriological eradication rates were summarized by causative organism and treatment group. Descriptive statistics only (frequency counts and percentages) were provided for this variable. Pre-therapy minimum inhibitory concentrations (MICs) by organism and drug for which susceptibility was tested was summarized in the ITT with causative organism population. Minimums, maximums, and the 25th, 50th, 75th, and 90th percentiles were provided for each organism/drug combination. Subjects from both treatment groups were combined for these summary tables since these were pre-therapy values and therefore unaffected by treatment. In addition, the displays were provided by treatment group to determine if any baseline imbalances existed in the susceptibility profiles. Descriptive statistics by timepoint for lung function tests and changes from pre therapy in lung function tests were provided for each treatment group. <u>Safety:</u> Safety parameters were analyzed by summary statistics for numerical data, and by frequency tables for categorical data. All safety tabulations were produced for the ITT population (which was equivalent to the valid for safety population). The safety analyses included tabulation of the type using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and primary term [PT]) and frequency of all AEs as well as events considered by the investigator to be drug-related. Vital sign values and change from pre-therapy values were analyzed descriptively by timepoint. AEs: Two sets of AE tables were provided. One set of AE tables included all AEs reported at any time during the study, starting on the first day of study drug treatment, through 8 weeks post-therapy (events occurring later than 8 weeks after the EOT visit were

	included if any such events were reported). Another set of summary tables was provided for those events occurring through 7 days after the EOT visit (or 30 days after end of therapy for serious events). The summaries described below are provided for each set of tables: Overviews of frequencies of subjects who died, experienced any AE, experienced any drug-related AE, experienced an SAE, experienced a drug-related SAE, or discontinued due to an AE are provided. Quality of life/resource use analysis All quality of life and resource use analyses were only to be performed for the valid for safety population. St. George's Hospital Respiratory Questionnaire, SGRQ: Changes in symptoms burden assessed by the AECB-SS questionnaires Means, standard deviations, medians, minimums and maximums were provided for the total score and change from baseline in total score at each visit, by treatment group. Distributions of the change in scores were also provided at each visit by treatment group. Work productivity and activity questions Incidence rates of healthcare resources utilization: An economic evaluation of the difference between treatment groups concentrated on the difference in the quantity of resources used (concomitant medications, therapeutic adjuncts, diagnosis procedures, and hospitalizations [including ward and duration] related to respiratory tract infections). The number of subjects with therapeutic adjuncts and concomitant medications was determined from the standard tables for these variables. The number of hospitalizations related to respiratory tract infections was calculated by counting the number of respiratory hospitalizations as taken from the hospitalization page of the CRF. Hospitalization frequencies were counted by using the respiratory related hospitalizations from the hospitalization page of the CRF. Each of these variables was summarized by using frequency counts. Additionally, 95% CIs were estimated for the treatment group difference in proportion of subjects with each resource use. The CI was again constructed using Mantel-Haenszel weights, adjusting for geographic region and stratum.

Number of Subjects:	Planned: 675 (Total 1350) Analyzed: 686 (Total 1372)

Study Results

Results Summary — Subject Disposition and Baseline

One thousand four-hundred ninety-two (1492) subjects were enrolled in the study; 1372 subjects completed screening and 686 each were randomized to moxifloxacin and co-amoxiclav treatment groups. Note: "co amoxiclav" as an abbreviated term is used with data presentation tables, representing amoxicillin-clavulanic acid in this synopsis.

Table 1: Disposition of study subjects

	Moxifloxacin	Co-amoxiclav	Total
Enrolled			1492
Screening failures / non randomized			120
Randomized	686 (100.0%)	686 (100.0%)	1372 (100.0%)
Study drug never administered	5 (0.7%)	6 (0.9%)	11 (0.8%)
Treated	681 (99.3%)	680 (99.1%)	1361 (99.2%)
Not completed study	177 (25.8%)	186 (27.1%)	363 (26.5%)
Completed study	509 (74.2%)	500 (72.9%)	1009 (73.5%)

The PP population was the primary efficacy analysis population that included 1056 subjects. Of these, 538 subjects received moxifloxacin (5 days followed by 2 days of placebo) and 518 subjects co-amoxiclav treatments for 7 days as defined in the protocol. The subject populations in both treatment groups were similar (lacking statistically significant difference), balanced for the standard demographic parameters and AECB characteristics.

Table 2: Valid subject populations for analysis (all randomized subjects)

	Moxifloxacin N=686 (100%)	Co-amoxiclav N=686 (100%)	Total N=1372 (100%)
Subjects randomized	**686 (100.0%)**	**686 (100.0%)**	**1372 (100.0%)**
Subjects valid for safety analysis / ITT	677 (98.7%)	675 (98.4%)	1352 (98.5%)
Subjects valid for per protocol analysis	538 (78.4%)	518 (75.5%)	1056 (77.0%)
Subjects valid for microbiological analysis	260 (37.9%)	261 (38.0%)	521 (38.0%)
Subjects valid for safety with causative organisms	327 (47.7%)	335 (48.8%)	662 (48.3%)

Abbreviation: ITT = intent to treat

Overall, the baseline characteristics of subjects for various demographic variables, medical history, concomitant medications, chronic bronchitis history, and signs and symptoms at baseline (exacerbation free status) and pre-therapy (enrollment) were similar and comparable in the two treatment groups.

The characteristics associated with the underlying disease in all enrolled subjects when assessed for the sputum sample characteristics and Gram stain results (with polymorphonuclear [PMN] leukocytes and squamous epithelial cell [SEC] counts) and the pattern of organisms at enrollment were also similar and comparable, lacking any significant difference. There were no major differences between the moxifloxacin and co-amoxiclav treatment groups with regard to the frequency or types of causative organisms

at enrollment isolated from the MBV subject population or the valid for safety/ITT with organisms population.

The majority of subjects in the safety population were White (816 subjects, 604%) and male (1079 subjects, 79.8%). Subjects had a mean age of 69.6 years (SD (standard deviation): 6.7) (range: 59.0 to 93.0 years), a mean height of 165.8 cm (SD: 9.0) (range: 133.0 to 195.0 cm), and a mean BMI (body mass index) of 24.8 kg/m^2 (SD: 5.3) (range: 13.3 to 48.9 kg/m^2).

Results Summary — Efficacy

The primary efficacy variable of clinical failure rates analysis is summarized as following:

- The protocol stated that if the upper limit of the 95% confidence interval for the difference in clinical failure rates in the primary analysis population (i.e., PP population) was less than 6%, then non inferiority would be concluded. Since the upper limit of the confidence interval (-5.89%, 3.83%) was less than 6%, noninferiority was demonstrated and the primary objective of the study was achieved.

- Since noninferiority was achieved in the PP population, superiority could be tested in the valid for safety/ITT population. In this population, although the failure rates were lower in the moxifloxacin group (20.4%) than the co-amoxiclav group (21.6%), this difference was not statistically significant (p = 0.571). Therefore, superiority was not demonstrated.

Table 3: Summary of clinical failure rates by timepoint and treatment – PP Population (N = 1,056)

Timepoint	Moxifloxacin (N=538)	Co-amoxiclav (N=518)
During therapy	2 (0.4%)	5 (1.0%)
End of therapy	36 (6.7%)	40 (7.7%)
4 Weeks post-therapy	74 (13.8%)	83 (16.0%)
8 Weeks post-therapy	111 (20.6%)	114 (22.0%)

Abbreviations: PP = per protocol, N = number, total.

Failures and relapses (at 4 and 8 weeks post-therapy) were included in the clinical failure rates.

- The pattern of increases in the failure rates over time in the PP population and in the valid for safety/ITT population were similar in the treatment groups.

- In the two populations of subjects with organisms, the clinical failure rates were lower for the moxifloxacin group than in the co-amoxiclav group at all timepoints. At 8 weeks post-therapy, failure rates were 19.2% and 26.1 % in the moxifloxacin and coamoxiclav groups of the MBV population, respectively. The rates in the valid for safety/ITT with causative organisms population were 19.0 % and 25.4% for moxifloxacin- and co-amoxiclav-treated subjects, respectively (p = 0.016). Although these populations were considered secondary, the differences between treatment groups were larger than the overall differences, and the comparisons had nominal p-values less than 0.05.

Table 4: Summary of comparisons of failure rates between moxifloxacin and co-amoxiclav at 8 weeks post-therapy by analysis population

Analysis Population	Moxifloxacin	Co-amoxiclav	95% confidence interval	p-valuea
Per Protocol	111/538 (20.6%)	114/518 (22.0%)	(-5.89%, 3.83%)	n/d[a]
Valid for safety / ITT	138/677 (20.4%)	146/675 (21.6%)	(-5.50%, 3.03%)	0.571
Microbiologically valid	50/260 (19.2%)	68/261 (26.1%)	(-15.00%, -0.75%)	n/d[a]
Valid for safety / ITT with organisms	62/327 (19.0%)	85/335 (25.4%)	(-13.90%, -1.44%)	0.016

Abbreviations: ITT = intent-to-treat, n/d = not done.

NOTE: Failures and relapses were included in the clinical failure rates.

a: p-values were not planned for the Per Protocol or Microbiologically Valid populations as the study was not designed to demonstrate superiority in these populations.

- Consistent with the by-timepoint results, time to clinical failure for the valid for safety/ITT population was very similar in the treatment groups, with the moxifloxacin group demonstrating a 1% - 2% lower failure rate starting at approximately Day 20. The p-value from the Log-rank test was 0.688.

- Failure rates were higher in the steroid stratum than in the non-steroid stratum for both treatment groups, and especially so in the co-amoxiclav group. In the PP population, failure rates at 8 weeks post-therapy in the steroid stratum were 26.4% in the moxifloxacin group, and 32.8% in the co-amoxiclav group. In the non-steroid stratum, the corresponding failure rates were 17.7% in the moxifloxacin group, and 15.8% in the co amoxiclav group. Thus, failure rates in the co amoxiclav group of the PP population as well as the valid for safety/ITT population were more than twice as high among subjects receiving steroids than those not receiving steroids.

Table 5: Summary of clinical failure rates by timepoint, steroid stratum, and treatment PP Population

Timepoint	Steroid Use		Non-steroid Use	
	Moxifloxacin (N = 182)	Co-amoxiclav (N = 189)	Moxifloxacin (N = 356)	Co-amoxiclav (N = 329)
During therapy	2 (1.1%)	0 (0.0%)	0 (0.0%)	5 (1.5%)
End of therapy	15 (8.2%)	16 (8.5%)	21 (5.9%)	24 (7.3%)
4 Weeks post-therapy	34 (18.6%)	41 (21.7%)	40 (11.3%)	42 (12.8%)
8 Weeks post-therapy	48 (26.3%)	62 (32.8%)	63 (17.7%)	52 (15.8%)

Abbreviations: PP = per protocol

NOTE: Failures and relapses (4 and 8 weeks post-therapy) were included in the clinical failure rates.

Table 6: Summary of clinical failure rates by timepoint, steroid stratum and treatment – valid for safety / ITT population

Timepoint	Steroid Use		Non-steroid Use	
	Moxifloxacin (N = 236)	Co-amoxiclav (N = 239)	Moxifloxacin (N = 441)	Co-amoxiclav (N = 436)
During therapy	3 (1.3%)	0 (0.0%)	3 (0.7%)	8 (1.8%)
End of therapy	23 (9.7%)	21 (8.8%)	28 (6.3%)	31 (7.1%)
4 Weeks post-therapy	49 (20.8%)	54 (22.6%)	51 (11.6%)	54 (12.4%)
8 Weeks post-therapy	65 (27.5%)	76 (31.8%)	73 (16.6%)	70 (16.1%)

Abbreviations: ITT = intent-to-treat, N = number, total.

NOTE: Failures and relapses (4 and 8 weeks post-therapy) were included in the clinical failure rates.

- This difference in response rates between the steroid stratum and the non-steroid stratum could suggest that the populations in the different strata were not similar with regard to the subject severity or risk factors for poor outcome. However, these are merely speculative assumptions since no comparisons between the two strata are available in the table set (these comparative analyses were not planned in the Statistical Analysis Plan).

- Failure rates varied across many of the subgroups, with higher failure rates seen in males, subjects <65 years old (especially in the moxifloxacin group), subjects with percent predicted FEV_1 <30%, subjects whose previous exacerbation was less than 63 days prior to entering the study, and subjects with four or more previous exacerbations. Treatment group comparisons showed the expected variation across the subgroups, with no meaningful differences from the overall population.

- Clinical cure rates at 8 weeks post-therapy in the MBV population ranged from 65% to 91% for the moxifloxacin group, and from 58% to 82% for the co-amoxiclav group against the major causative organisms. Against the predominant pathogens, *H. influenzae* and *P. aeruginosa*, the cure rates were 83.0% (moxifloxacin) and 71.4% (co-amoxiclav) for *H. influenezae*, and 76.6% (moxifloxacin) and 63.2% (co-amoxiclav) for *P. aeruginosa*. The same pattern was seen in the valid for safety/ITT with organisms population.

Bacteriological efficacy

- There was a relatively large difference in favor of moxifloxacin in the bacteriological failure rates at the during therapy visit (26.5% for the moxifloxacin group vs 40.6% for the co-amoxiclav group in the MBV population, and 26.0% for the moxifloxacin group vs 38.5% for the co-amoxiclav group in the valid for safety/ITT with organisms population). This difference declined somewhat over time as the moxifloxacin bacteriological failure rates gradually increased, while the co-amoxiclav bacteriological failure rates stayed relatively stable. The difference at 8 weeks post-therapy was still approximately 4 - 5% in favor of the moxifloxacin group. Formal statistical analysis of the bacteriological failure rates at 8 weeks post-therapy in the MBV population and in the valid for safety/ITT with organisms population was performed. Since the lower limit of the 95% confidence interval (-14.90%, 1.58%), was less than the noninferiority margin of 6%, consistent with the clinical response variable, noninferiority was demonstrated in the MBV population. Despite the adjusted treatment group difference of -5.35%, superiority was not demonstrated in the valid for safety/ITT with organisms population (p = 0.150).

- Conversely, bacteriological success rates in the MBV and valid for safety/ITT with organisms populations were consistently higher in the moxifloxacin group than in the co-amoxiclav group at all timepoints, but especially at during therapy and EOT timepoints. Indeed, the eradication rates (presumed + confirmed eradication) was approximately 16% higher in the moxifloxacin arm during therapy, and still 6% higher in the moxifloxacin-treated subjects (70.4%) than in the co-amoxiclav-treated subjects (64.4%) at EOT.

- Bacteriological failure rates at 8 weeks post-therapy were higher in subjects who were administered concurrent steroids (especially those in the co-amoxiclav group) than in subjects who were treated with study antibiotics alone. In subjects with steroids, bacteriological failure rates were 6 - 10% lower in moxifloxacin-treated

subjects than in co-amoxiclav-treated subjects. With regards to subjects who were not on steroids, bacteriological failure rates were 2 - 3% lower in the moxifloxacin group than in the coamoxiclav group.

- Bacteriological success rates at 8 weeks post-therapy ranged from 56% (against *E. coli*) to 82% (against *S. marcescens*) in moxifloxacin-treated subjects of the MBV population. They ranged from 53% (*P. aeruginosa*) to 83% (*S. pneumoniae*) in the co-amoxiclav group. Bacteriological success rates ranged from 52% (against *E. coli*) to 79% (against *S. marcescens*) in moxifloxacin-treated subjects of the valid for safety/ITT with organisms population. They ranged from 52% (*P. aeruginosa*) to 77% (*M. catarrhalis*) in the co-amoxiclav group. In both the MBV and valid for safety/ITT with organisms populations, eradication rates against *H. influenzae* and *P. aeruginosa* were higher for moxifloxacin-treated subjects. With regards to *M. catarrhalis*, there was a numerical difference in the eradication rates in favor of co-amoxiclav.

- The higher bacteriological success rates observed in the moxifloxacin-treated subjects who had an exacerbation caused by *H. influenzae* and/or *P. aeruginosa* mainly explain the overall higher eradication/presumed eradication rates in this group of subjects, compared with those in the co-amoxiclav group, at all timepoints, but especially at EOT.

- In all four analysis populations, superinfections were more common in the co-amoxiclav group than the moxifloxacin group, particularly at the During therapy visit. The most common superinfecting bacterial species were *S. aureus, K. pneumoniae, K. oxytoca, E. cloacae, S. marcescens, A. baumannii, P. aeruginosa, M. catarrhalis* and *H. influenzae. H. influenzae* was a more frequent superinfecting organism in the co-amoxiclav group than in the moxifloxacin group. At 4 weeks post-therapy, reinfection rates were very similar in the two treatment groups. At 8 weeks post-therapy, reinfection rates were slightly higher in the moxifloxacin group in all four analysis populations. *K. pneumoniae, P. aeruginosa, M. catarrhalis*, and *H. influenzae* were generally the most common reinfecting organisms.

- Clinical success rates at 8 weeks post-therapy by end of therapy bacteriological responses (i.e., bacteriological success [eradication/presumed eradication] vs bacteriological failure [persistence/presumed persistence/superinfection]) in the valid for safety/ITT with organisms population exhibited a very strong relationship between these endpoints, with cure rates of 79.7% for end of therapy bacteriological success and 54.7% for end of therapy bacteriological failure (P <0.0001). The corresponding rates for the two treatment groups were 84.3% vs 53.4% within the moxifloxacin subjects (P <0.0001), and 74.6% vs 55.7% within the co-amoxiclav subjects (p = 0.0007). Excluding presumed eradication and presumed persistence from the analysis, overall clinical success rates at 8 weeks post-therapy by end of therapy bacteriological eradication vs bacteriological persistence or superinfection also showed a very strong relationship between these endpoints, with cure rates of 76.8% for end of therapy bacteriological eradication and 62.1% for end of therapy bacteriological persistence or superinfection (p = 0.0014). The relationship was also observed for the moxifloxacin-treated subjects, but not for those in the co-amoxiclav group since the corresponding rates for the two treatment groups were 80.4% vs 61.1% within the moxifloxacin subjects (p = 0.0034), and 72.4% vs 63.0% within the co-amoxiclav subjects (p = 0.1492).

Lung function analyses

- Lung function analyses showed mean changes from pre-therapy to 8 weeks post-

therapy to be positive, indicating improvement for both FEV_1 and FVC.

- Mean increases in the FEV_1 values were somewhat higher for the moxifloxacin group than for the co-amoxiclav group at 8 weeks post-therapy, e.g., 0.207 L vs 0.177 L for absolute values, and 8.13% vs 7.07% for predicted values; no differences between groups were seen for the FVC values.

SGRQ Questionnaire

- Mean SGRQ scores improved from pretherapy to 8 weeks post-therapy by approximately 30% for the total score as well as each of the domain scores for the analysis using no imputation, and by approximately 25% using the last observation carried forward (LOCF) approach for missing values. Mean changes were very consistent across treatment groups using both approaches (p = 0.360 for total score using no imputation, p = 0.694 for total score using the LOCF approach).

- Responder analyses also demonstrated the improvement from pre-therapy to 8 weeks post-therapy in SGRQ total scores, with 77% of moxifloxacin subjects and 76% of co-amoxiclav subjects achieving decreases in SGRQ total score of 4 or more units (p = 0.520 for the between group comparison), and 70% of moxifloxacin subjects and 68% of co-amoxiclav subjects achieving decreases of 8 or more units (p = 0.528 for the between group comparison).

- The responder analyses using the LOCF approach showed 69% of moxifloxacin subjects and 67% of co-amoxiclav subjects achieving decreases in SGRQ total score of 4 or more units (p = 0.424 for the between group comparison), and 62% of moxifloxacin subjects and 60% of co-amoxiclav subjects achieving decreases of 8 or more units (p = 0.532 for the between group comparison).

AECB-SS Questionnaire

- As with the SGRQ, the AECB-SS demonstrated improvement in mean scores from pretherapy throughout the measuring period, with very consistent changes across treatment groups. Mean decreases in AECB-SS scores were seen already on Day 2, and scores continued to decline steadily through the Week 8 post-therapy visit, where the mean changes were -1.36 for the moxifloxacin group and -1.42 for the coamoxiclav group (p = 0.405). Mean changes in AECB-SS at 8 weeks post-therapy using the LOCF approach for missing values were -1.10 for the moxifloxacin group and -1.16 for the co-amoxiclav group (p = 0.235).

Other efficacy variables

- Consistent with a population experiencing clinical improvement, the frequency and intensity of signs and symptoms of AECB decreased steadily over the visits, and at very consistent rates in the two treatment groups.

- Change in respiratory medication with increases in the dose of respiratory medication were seen at some point of the study period for 4% of subjects in each treatment group. In the valid for safety/ITT population 36% of moxifloxacin subjects and 38% of co-amoxiclav subjects took at least one post-treatment medication. Antibacterial medications were taken post-study drug treatment in 20% of subjects in each treatment group, and corticosteroids for systemic use were taken by 15% of subjects in each treatment group.

- Among treatment failures, antibacterial medications were used in 79% of

moxifloxacin subjects and 73% of co-amoxiclav subjects, and corticosteroids for systemic use were taken by 54% of moxifloxacin subjects and 53% of co-amoxiclav subjects.

- Overall, no real differences were seen between the treatment groups with regard to the use of medications post-treatment or during or post-therapy adjunct.

- Hospitalization rates and durations were very consistent across the two treatment groups; in the valid for safety/ITT population, 6.1% of moxifloxacin subjects and 7.0% of co-amoxiclav subjects were hospitalized at some point during the study (p = 0.483). Mean hospital duration was 8.8 days for the moxifloxacin group and 9.3 days for the co-amoxiclav group; the median duration was 8 days in both treatment groups.

Results Summary — Safety

No new unexpected safety events were reported in this study. The overall safety profile of the two treatments was comparable and did not show any statistically significant differences. There were 1352 subjects (677 treated with moxifloxacin, and 675 with co-amoxiclav) in the valid for safety/ITT population. The exposure to study drug was similar in the treatment groups as was the compliance, which was high including in the valid for safety/ITT population.

Two sets of AE tables were provided in this study. (1) One set of AE tables ("Week 8") included all AEs reported at any time during the study, starting on the first day of study drug treatment, through 8 weeks post-therapy (events occurring later than 8 weeks after the end of therapy were included if any such events were reported). (2) Another set of summary tables ("Day 7") were prepared for those events occurring through 7 days after the end of therapy (or 30 days after end of therapy for serious events).

For subjects in the valid for safety/ITT population, the incidence rates of treatment-emergent adverse events (TEAEs) were 24.2% (164/677) in subjects of the moxifloxacin group and 22.1% (149/675) in subjects of the co amoxiclav group through Day 7. A slightly higher number of subjects in the moxifloxacin group (48 of 677 [7.1%]) than in the co amoxiclav group (39 of 675 [5.8%]) reported drug-related AEs through Day 7.

A total of 220 of 677 (32.5%) subjects in the moxifloxacin group and 218 of 675 (32.3%) subjects in the co amoxiclav group experienced at least 1 TEAE by Week 8. A slightly higher number of subjects in the moxifloxacin group (53 of 677 [7.8%]) than in the co amoxiclav group (41 of 675 [6.1%]) reported drug-related AEs through Week 8.

Similar to the observations through Day 7, a majority of the subjects in either of the treatment groups by Week 8 also reported TEAEs and drug-related AEs of mild intensity.

Three subjects in each group died in the course of the study through Week 8. For 5 subjects, death was the outcome of an AE (for the remaining subject, death was reported as the AE itself). Only one of these events occurred during the treatment period and all others were post-therapy.

A similar number of subjects in both treatment groups (38 [5.6%] in moxifloxacin and 40 [5.9%] in co amoxiclav groups) reported at least one SAE through Day 7. However, a slightly higher number of subjects who received moxifloxacin reported SAEs that were considered drug-related (4 in moxifloxacin versus 2 in co-amoxiclav treatments), and leading to discontinuation of the study drug due to SAE (7 in moxifloxacin versus 3 in co-

amoxiclav treatments).

A similar number of subjects in both treatment groups reported SAEs in the analysis by Week 8: (46 [6.8%] in moxifloxacin and 51 [7.6%] in co-amoxiclav groups).

Incidence rates of TEAEs reported through Day 7 or Week 8 did not differ by ≥1% between the treatment groups, with an exception that headache and nausea which were slightly more frequent in the moxifloxacin group when reported through Day 7, and back pain, nausea, which were slightly more frequent in the moxifloxacin group, whereas diarrhea was more frequent in the co-amoxiclav treated subjects for AEs reported through Week 8. All differences were less than 2%; there were no clear differences between the two treatment groups with regard to the frequency and nature of TEAEs, at either Day 7 or week 8 during the study. A similar pattern in comparable frequency of non-serious TEAE by primary SOC was observed for AEs reported through Day 7 and Week 8. There were no remarkable differences between the two treatment groups with regard to the frequency and nature of non-serious TEAEs reported through these timepoints.

Drug-related TEAEs were experienced by 48 (7.1%) subjects in moxifloxacin and 39 (5.8%) subjects in co-amoxiclav treatment groups by Day 7. A majority of drug-related TEAEs involved gastrointestinal disorders; 30 (4.4%) subjects in moxifloxacin and 24 (3.6%) subjects in co-amoxiclav treatment groups experienced drug-related gastrointestinal (GI) disorders through Day 7. More subjects in co-amoxiclav group experienced diarrhea (12 [1.8%] vs 6 [0.9%] in moxifloxacin group), whereas more subjects experienced nausea in moxifloxacin group (10 [1.5%] vs only 4 [0.6%] in co amoxiclav group) through Day 7. The same pattern was seen for events reported through Week 8. There were no other clear differences between the treatment groups with regard to the frequency and nature of drug-related TEAEs.

A total of 17 of 677 subjects (2.5%) in the moxifloxacin group and 12 of 675 subjects (1.8%) in the co amoxiclav group experienced AEs that resulted in premature discontinuation of the study medication through Day 7. These observations remained unchanged through Week 8 during the study. There were no clear differences between the treatment groups with regard to the frequency or profile of AEs that resulted in premature discontinuation of the study drug in this study.

A total of 12 of 677 subjects (1.8%) in the moxifloxacin group and 9 of 675 subjects (1.3%) in the co amoxiclav group experienced study drug-related AEs which resulted in premature discontinuation of study medication. The most frequently reported AEs by primary SOC were of the GI disorder type; 6 of 677 subjects (0.9%) in the moxifloxacin group and 7 of 675 subjects (1.0%) in the co amoxiclav group experienced study drug related AEs associated with GI disorders, of which diarrhea accounted for in 4 and 1 subjects of the co-amoxiclav and moxifloxacin groups, respectively. There were no clear or distinctive patterns of the study drug-related AEs leading to study drug discontinuation between the two treatment groups through Day 7 or Week 8.

A total of 38 subjects (5.6%) in the moxifloxacin group and 40 subjects (5.9%) in the co amoxiclav group experienced SAEs that were reported through Day 7. The most frequent SAEs by primary SOC were respiratory, thoracic and mediastinal disorders (21 subjects [3.1%] in the moxifloxacin group and 16 subjects [2.4%]) in the co amoxiclav group) and infections and infestations (12 subjects [1.8%] in the moxifloxacin group and 17 subjects [2.5%] in the co-amoxiclav group). The most frequent SAE by preferred term (PT) was COPD (Chronic obstructive pulmonary disease) in 17 subjects (2.5%) of the moxifloxacin group and 12 subjects (1.8%) in the co-amoxiclav group). During the period through Week 8, a total of 46 subjects (6.8%) in the moxifloxacin group and 51 subjects (7.6%) in

the co amoxiclav group experienced SAEs. The pattern of SAE frequency by primary SOC and PT recorded through Week 8 remained similar to that observed through Day 7, with COPD (21 in moxifloxacin group vs 16 in co amoxiclav group) and pneumonia (6 in moxifloxacin group vs 9 in co-amoxiclav group) being the predominant SAEs reported during this period.

A total of 6 subjects experienced study drug-related SAEs; 4 subjects (0.6%) in the moxifloxacin group and 2 subjects (0.3%) in the co amoxiclav group.

A total of 10 subjects experienced SAEs leading to discontinuation of the study drug. One of these SAEs was death, considered not related to the study drug by the investigator, and the other 9 SAEs were resolved. Of the 9 SAEs, 3 were considered related to the study drug by the investigator.

There were 3 deaths each in the two treatment groups of subjects valid for safety/ITT population through Week 8. None of these deaths reported through Day 7 or Week 8 in this study were considered by the investigators as related to the study medication.

AEs from the SOC "Cardiac disorders" were reported in 11 (1.6%) moxifloxacin and 3 (0.4%) co-amoxiclav-treated subjects through Week 8. Of these, 4 (0.6%) and 1 (0.1%) were considered to be related to the study drug by the investigator, i.e., palpitations (2 in the moxifloxacin group, 1 in the co-amoxiclav group), tachyarrhythmia and tachycardia (both in the moxifloxacin group). Three subjects in the moxifloxacin group (none in the co-amoxiclav group) experienced the SAE from the SOC "Cardiac disorders", and one was considered to be related to the study drug by the investigator, i.e., tachyarrythmia. Through Day 7, the incidence rates of AEs from the SOC "Cardiac disorders" were 1.5% (n = 10) and 0.3% (n = 2) in the moxifloxacin and co-amoxiclav groups, respectively. Other incidence rates were similar to those reported through Week 8.

One of the secondary objectives for safety analyses was to assess the safety and tolerability of moxifloxacin versus co-amoxiclav, with particular attention to the incidence rates of diarrhea. While the overall incidence of diarrhea remained low in both treatment groups, the rates in each study treatment remained comparable, with differences showing no statistical significance at both Day 7 and Week 8 timepoints.

No differences were seen between the treatment groups concerning the assessments of vital signs, which improved similarly during the course of the study.

The most commonly occurring drug-related AEs were gastrointestinal-related events, although reported individually in <2% of subjects in either arm. Diarrhea (through Week 8) was reported in 0.9% and 1.8% of subjects in the moxifloxacin and co-amoxiclav groups, respectively. Corresponding rates of nausea were 1.5% and 0.6%. In the co-amoxiclav arm there was one report of *Clostridium difficile*-related disease and one of *C. difficile*/pseudomembranous colitis.

All cause hospitalization rates were similar across arms (ITT population: moxifloxacin 41/677, 6.1%; co-amoxiclav 47/675, 7.0%; p = 0.48).

No new unexpected safety events were reported in this study. The overall safety profile of the two study treatments was comparable and did not show any statistically significant differences.

Conclusion(s)

In this study, a large number of chronic bronchitis subjects with underlying COPD and a Type 1 Anthonisen exacerbation were enrolled from 30 countries, evenly distributed across the Americas, Asia-Pacific, and Europe/South Africa. Demographic and disease characteristics were as expected in this population, and similar in the moxifloxacin and co-amoxiclav treatment groups. Pre-therapy post bronchodilator spirometry tests confirmed the severity of the underlying COPD. The sputum microbiological flora at baseline was consistent with the diagnosis of an exacerbation of moderate-to severe COPD showing *H. influenzae*, *P. aeruginosa*, *S. pneumoniae*, and *Enterobacteriaceae spp* as predominant pathogens.

In terms of clinical response, moxifloxacin was noninferior to co-amoxiclav at 8 weeks post-therapy in both the PP (primary) and ITT populations. Moxifloxacin was associated with a better clinical response in subjects with a proven bacterial exacerbation. In both treatment groups (but especially in the co-amoxiclav group), clinical failure rates were higher in steroid vs non-steroid-treated subjects.

Bacteriological failure rates were consistently lower in the moxifloxacin group at all timepoints (mainly driven by a higher response rate against *H. influenzae* and to a lesser extent against *P. aeruginosa*) but this difference was not statistically significant at 8 weeks post-therapy with moxifloxacin. There was a clear correlation between bacterial eradication (vs persistence/superinfection) rates at EOT and clinical cure rate at 8 weeks post-therapy, overall and in the moxifloxacin treatment group.

Both FEV_1 and FVC improved during the course of the study, to a similar extent in each treatment group. There was a small difference (for FEV_1) in favor of moxifloxacin.

An improvement in symptom burden measured by the AECB-SS and in health-related quality of life measured by the SGRQ, was observed up to Week 8, but no real differences were seen between the treatment groups. The analysis of healthcare resource consumption (hospitalization rates, concomitant medications including respiratory medications) showed no difference in the treatment groups.

The incidence rates of TEAEs, drug-related AEs, SAEs, premature discontinuation due to AEs, and AEs with fatal outcomes were similar in the 2 treatment groups. The nature and incidence of individual AEs was similar in the treatment groups. Both groups had a low level of AEs . The two events with a difference in the incidence rate ≥1% were diarrhea (more frequent in the co-amoxiclav group) and nausea (more frequent in the moxifloxacin group).

The acceptable efficacy and tolerability of both moxifloxacin and co-amoxiclav in this study confirmed their position as recommended treatment options for exacerbations in chronic bronchitis subjects with moderate-to-severe COPD. Moxifloxacin was considered as a better option in subjects with documented bacterial exacerbations due to its higher efficacy against *H. influenzae*.

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31	Scimed Research, Inc.	605 K.L.O. Road Suite 3a	V1Y 8E7	Kelowna	CANADA
32	University of Alberta	Walter McKenzie HSC 2E4.22 8440 112th Street	T6G 2B7	Edmonton	CANADA
33	University of Calgary	Calgary COPD & Asthma Program Faculty of Medicine HRIC 4C60 3280 Hospital Drive NW	T2N 4Z6	Calgary	CANADA
34	Winnipeg Clinic	425 St. Mary Avenue	R3C 0N2	Winnipeg	CANADA
35	Clinica Avansalud	Av. Salvador 130		Santiago	CHILE
36	Clínica Ciudad del Mar	Broncomed Calle 13 Norte 635		Viña del Mar	CHILE

37	Hospital Carlos van Buren	Unidad Broncopulmonar San Ignacio 727		Valparaíso	CHILE
38	Hospital Gustavo Fricke	Unidad de Cuidados Intensivos Coronarios Alvarez 1532		Viña del Mar	CHILE
39	Hospital Nacional del Tórax	Unidad Broncopulmonar José Miguel Infante 717 Providencia		Santiago	CHILE
40	1st Affiliated Hosp., Guangzhou Univ. TCM	Respiratory Dept. No.16 Jichang Road	510405	Guangzhou	CHINA
41	Beijing Friendship Hosp.	No.95 yong an Road, xuanwu district,	100050	Beijing	CHINA
42	first affiliated hospital of guangzhou medical college	Respiratory Dept. first affiliated hospital of guangzhou medical college/ guangzhou insitute of respiratory disease, No. 151,yanjiang Road,	510120	Guangzhou	CHINA
43	General Hospital, Tianjin Medical University	Anshan Road 154#, Heping Distirct	300052	Tianjin	CHINA
44	Respiratory Diseases Institute, Beijing Chaoyang Hospital	No.8 Bai jia zhuang Road, chaoyang district,	100020	Beijing	CHINA
45	Shanghai Changzheng Hospital	No.415, fengyang Road,	200003	Shanghai	CHINA

46	Shanghai Huadong Hospital	No.221, yanan xi Road,Shanghai	200040	Shanghai	CHINA
47	Shengjing Hosp. of China Medical Univ.	Respiratory Dept. No.36 Sanhao Rd. Heping District	110004	Shengyang	CHINA
48	The 6th People's Hospital of Shanghai Jiao Tong University	Respiratory Dept. No.600, yishan road,	200233	Shanghai	CHINA
49	The First hospital of China Medical University	No.155 North Nanjing street, heping district,	110001	Shenyang	CHINA
50	The Third Xiangya Hospital of Central South University	Respiratory Dept. No.138, Tongzipo Road,	410013	Changsha	CHINA
51	West China Hospital of Sichuan University	No.37, Guoxue Alley	610041	Chengdu	CHINA
52	Centro de Investigación Clínica FOQUS	Clinica Santa Bibiana Avenida Calle 127 No. 16A - 27 Consultorio 510		Bogotá	COLOMBIA
53	Centro Médico Imbanaco	Neumología Oficina 239 Carrera 38 A N°. 5 A - 100 Torre A		Cali	COLOMBIA
54	Clínica Medellín	Calle 54 No. 46 - 27 Piso 15 Consultorio 1505		Medellín	COLOMBIA
55	Clínica Soma	Calle 51 No. 45 - 93 Consultorio 217		Medellín	COLOMBIA

56	Hospital Militar Central	Depto. de Neumología Transversal 3 N°. 49 - 00. 7th floor		Santafe de Bogotá	COLOMBIA
57	Hospital San Vicente de Paul	Neumología Calle 64 No. 51D-34		Medellín	COLOMBIA
58	NeumoInvestigaciones	Calle 50 N0. 7-36 Piso 3ro. Edificio de Especialidades Marly 50		Bogotá	COLOMBIA
59	KBC Rijeka	Zavod za pulmologiju Tome Strizica 3	510 00	Rijeka	CROATIA
60	Klinicka bolnica Dubrava	Zavod za pulmologiju, Klinika za unutarnje bolesti Anenija G. Suska 6	10000	Zagreb	CROATIA
61	Klinika za plucne bolesti Jordanovac	Klinika za Pulmologiju Jordanovac 104	10000	Zagreb	CROATIA
62	OB dr. Ivo Pedisic	Specijalna bolnica za plucne i kronicne bolesti Perinja Vinogradi bb	44 250	Petrinja	CROATIA
63	Clinic of pulmonary diseases	Kojeticka 1021	227 11	Neratovice	CZECH REPUBLIC
64	Clinic of pulmonary diseases	Plananska 573/1	108 00	Praha - Malesice	CZECH REPUBLIC
65	Clinic of pulmonary diseases	Karla Sipka 282	530 09	Pardubice - Trnova	CZECH REPUBLIC
66	Clinic of pulmonary diseases and internal medicine	Terezinska 487/71	410 02	Lovosice	CZECH REPUBLIC

67	SPIiN	Department of tuberculosis Cimicka 446/37	182 00	Praha - Troja	CZECH REPUBLIC
68	Ambulantes Zentrum für Lungenkrankheiten	und Schlafmedizin Cottbus Thiemstr. 124	03050	Cottbus	GERMANY
69	Gemeinschaftspraxis Drs. Hartjen, Sostmann, Timmermann	für Allergologie, Lungen- und Bronchialheilkunde Collonaden 72	20354	Hamburg	GERMANY
70	Medizinisches AllergoPneumologisches Versorgungszentrum	Fetscherstr. 10	01307	Dresden	GERMANY
71	Medizinsches Versorgungszentrum Delitzsch	Facharztpraxis für Innere Medizin Pneumologie Lindenstr.3	04509	Delitzsch	GERMANY
72	Praxis Drs.Deckelmann/Eckhardt	Schönauer Str. 121a	04207	Leipzig	GERMANY
73	Praxis Drs. Laumen/Wiederhold	Gerloser Weg 23a	36039	Fulda	GERMANY
74	Praxis Drs. Westerhausen/Pettenkofer/Klüppelberg	Markgrafenstr. 20	10969	Berlin	GERMANY
75	Praxis Fr. Dr. K. Todoroff	Fritz-Kiehn-Str. 44	78073	Bad Dürrheim	GERMANY
76	Praxis fü Lungen- und Bronchialheilkunde,	Allergologie und Umweltschutz Hohenzollerndamm 2	10717	Berlin	GERMANY
77	Praxis Hr. Dr. A. Colberg	Kurhausstraße 14	23795	Bad Segeberg	GERMANY

78	Praxis Hr. Dr. A. de Roux	Pneumologische Praxis am Schloss Charlottenburg Spandauer Damm 3	14059	Berlin	GERMANY
79	Praxis Hr. Dr. A. Schwittay	Leipziger Str. 2	04564	Böhlen	GERMANY
80	Praxis Hr. Dr. C. Geßner	Facharztpraxis für Lungenkrankheiten Tauchaer Str. 12	04357	Leipzig	GERMANY
81	Praxis Hr. Dr. J. C. Becker	Pferdemarkt 6-8	23552	Lübeck	GERMANY
82	Praxis Hr. Dr. M. Huntemann	Rathausplatz 23	58515	Lüdenscheid	GERMANY
83	Praxis Hr. Dr. M. Raffenberg	Am Kietz 24	15806	Zossen	GERMANY
84	Praxis Hr. Dr. Th. Schultz	Mommsenstr. 2a	12203	Berlin	GERMANY
85	Evangelismos General Hospital of Athens	45-47, Ipsilantou Str.	106 76	Athens	GREECE
86	General University Hospital of Ioannina	University Hospital of Ioannina, Pneumonological Clinic Panepistimiou Avenue, Dorouti	45500	Ioannina	GREECE
87	Sotiria General State Hospital of Chest Diseases	152, Messogion Avenue	11527	Athens	GREECE
88	Sotiria General State Hospital of Chest Diseases	152, Messogion Avenue	11527	Athens	GREECE

89	University General Hospital of Larissa	Mezourlo	41110	Mezourlo	GREECE
90	University General Hospital of Patras	Department of Internal Medicine	265 04	Rio	GREECE
91	Princess Margaret Hospital	2-10 Princess Margaret Hospital Road Lai Chi Kok		Kowloon	HONG KONG
92	Tuen Mun Hospital	Medicine and Geriatrics Dept. Tsing Chung Koon Road, Tuen Mun, N. T.,		HongKong	HONG KONG
93	Dr Soetomo Hospital	Department of Pulmonology Airlangga University School of Medicine / Dr. Soetomo Hospital Jl. Mayjen Prof. Dr. Moestopo 7-8		Surabaya	INDONESIA
94	Immanuel Hospital	Immanuel Respiratory Center Jl. Kopo 161 Bandung		Bandung	INDONESIA
95	Persahabatan Hospital	Department of Respiratory Medicine Faculty of Medicine University of Indonesia Jl. Persahabatan Raya No. 1, Rawamangun	13230	Jakarta	INDONESIA

96	Farranfore Medical Centre	Farranfore		Killarney	IRELAND
97	Slaney Medical Centre	Templeshannon		Enniscorthy	IRELAND
98	A.O. Ospedale Circolo Busto Arsizio	Broncopneumologia Piazzale Solaro, 3	21052	Busto Arsizio	ITALY
99	ASL Salerno - Campania	Fisiopatologia Respiratoria Centro Medico Italo-Australiano ACISMOM P.O. S.Maria Incoronata dell'Olmo Via Sant'Oriello, 2	84013	Pregiato di Cava dei Tirreni	ITALY
100	ASUR Marche ZT13 Ascoli Piceno	Pneumologia Ospedale Generale Provinciale Mazzoni Via degli Iris, 6	63100	Ascoli Piceno	ITALY
101	AUSL 2 Lanciano-Vasto-Chieti - Abruzzo	Malattie Infettive Ospedale Clinicizzato SS. Annunziata Colle dell'Ara - Via dei Vestini	66100	Chieti	ITALY
102	Gimenes Arstu prakse	Gimenes Arstu prakse Dzirnavu str. 60-22	1050	Riga	LATVIA
103	Kraslavas hospital	Kraslavas hospital Rigas str. 159	5601	Kraslava	LATVIA
104	Ltd "BINI" (SIA "BINI")	SIA "BINI" Lielais prospekts 49	LV-3601	Ventspils	LATVIA

105	SIA Talsi veselibas centrer	SIA „Talsu veselibas centrs", V.Rugena str. 4, Talsu	3201	Talsu	LATVIA
106	Saules family medicine center	Birzelio 23-ios 4	LT-50425	Kaunas	LITHUANIA
107	Siauliai County Hospital	V.Kudirkos 99	76231	Siauliai	LITHUANIA
108	Silainiu family health center	Baltu str. 7A		Kaunas	LITHUANIA
109	UAB "Mano seimos gydytojas"	Taikos str. 119	LT-94231	Klaipeda	LITHUANIA
110	Vilnius region outpatient department	Laisves ave. 79	LT-06122	Vilnius	LITHUANIA
111	Antiguo Hospital Civil de Guadalajara "Fray Antonio Alcalde"	Calle del Hospital No. 278 Col. El Retiro Sector Hidalgo	44280	Guadalajara	MEXICO
112	Hospital Central Universitario	Rosales 3302 Col. Obrera	31350	Chihuahua	MEXICO
113	Hospital General O'Horán SS	Pneumology Department Av. Itzaes esq. Calle 57 A S/N Col. Centro	97001	Mérida	MEXICO
114	Hospital San Agustín Zacatecas	Neumología Av. García Salinas No. 19 Col. Guadalupe	98608	Zacatecas	MEXICO
115	Unidad de Investigación Clínica en Medicina	Av. La Clínica 2520 Col. Sertoma	64718	Monterrey	MEXICO
116	Atrium Medisch Centrum	Afdeling Longziekten, H.Dunantstraat 5	6419 PC	HEERLEN	NETHERLANDS

117	Catharina	Afd. Longgeneeskunde en Tuberculose Michelangelolaan 2	5623 EJ	EINDHOVEN	NETHERLANDS
118	Jinnah Postgraduate Medical Centre	Department of Chest Medicine Jinnah Postgraduate Medical Centre (JPMC) Rafiqui Shaheed Road	75500	Karachi	PAKISTAN
119	Clínica El Golf	Avenida Aurelio Miró Quesada 1030 4°piso	LIMA 27	Lima	PERU
120	Clínica Internacional	Av. Garcilazo de la Vega 1421		Lima	PERU
121	Clínica San Pablo	"Consultorio de Neumología" Av. El Polo 789	33	Lima	PERU
122	Hospital Central de la Fuerza Aerea del Perú	Avenida Aramburu cuadra 2 s/n Miraflores	LIMA 18	Lima	PERU
123	Hospital Nacional Cayetano Heredia	Av. Honorio Delgado 530	31	Lima	PERU
124	Lung Center of the Philippines	Quezon Avenue,		Quezon City	PHILIPPINES

125	Manila Doctors Hospital	Room 227 Doña Salustiana Building Manila Doctors Hospital, United Nations Avenue, Manila, Philippines		Manila	PHILIPPINES
126	Centro Hospitalar Coimbra	Serviço de Pneumologia Quinta dos Vales	3041-856	S. Martinho do Bispo	PORTUGAL
127	Clinresco Kempton Park	ARWYP Medical Suites 4th Floor 22 Pine Avenue	1610	Kempton Park	SOUTH AFRICA
128	Emmed Research	641 5th Avenue Eloffsdal	0084	Pretoria	SOUTH AFRICA
129	I. Engelbrecht Reseach (Pty) Ltd	174 Cradock Ave Lyttelton	0140	Centurion	SOUTH AFRICA
130	Intercare Medical & Dental Centre Glenfair	1st Floor Glenfair Shopping Centre c/o Daventry and Lynwood Road Lynwood		Pretoria	SOUTH AFRICA
131	Josha Research	Rubins Building 28 East Burger Street	9324	Bloemfontein	SOUTH AFRICA
132	Mercantile Hospital Centre	Cnr Durban and Kempston Roads Korsten	6014	Port Elizabeth	SOUTH AFRICA
133	Newkwa Medical Centre	909 - 913 Inanda Road Newlands	4037	Durban	SOUTH AFRICA

134	Paarl Research Centre	9A Verster Street	7647	Paarl	SOUTH AFRICA
135	Park Medical Centre	19 Rhodes Street	1035	Witbank	SOUTH AFRICA
136	Randles Road Medical Centre	468 Randles Road Syndenham	4091	Durban	SOUTH AFRICA
137	Tambotie Medical Centre	1536 Koedoe Street	0380	Thabazimbi	SOUTH AFRICA
138	University of Stellenbosch	Tygerberg Hospital Francie van Zijl Drive Parrow	7505	Cape Town	SOUTH AFRICA
139	Vergelegen Medi-Clinic	Main Road	7130	Somerset West	SOUTH AFRICA
140	Worthwhile Clinical Trials	1 Mowbray Avenue	1500	Benoni	SOUTH AFRICA
141	CAP Sarrià	c/Bonaplata, 54-58	08034	Barcelona	SPAIN
142	Consorci d'Atenció Primària de Salut de l'Eixample	C/ Rosselló 161	08036	Barcelona	SPAIN
143	Hospital General del Parc Sanitari de Sant Joan de Déu	Camí Vell de la Colònia, s/n	08830	Sant Boi de Llobregat	SPAIN
144	Hospital General de Requena	Servicio de Pneumología c/ Casablanca s/n	46340	Requena	SPAIN
145	Hospital Universitari Germans Trias i Pujol	Servicio de Neumología Ctra. del Canyet, s/n Planta 1	08916	Badalona	SPAIN
146	Hospital Universitari Son Espases	Servicio de Pneumología Ctra. de Valldemossa, 79	07010	Palma de Mallorca	SPAIN

147	Universitätsspital Basel	Departement Innere Medizin Pneumologische Abteilung Petersgraben 4	4031	Basel	SWITZERLAND
148	Chest Disease Institute	Department of COPD Clinic , Chest Disease Institute, Nonthaburi ,	11000	Nonthaburi	THAILAND
149	King Chulalongkorn Memorial Hospital	Division of Pulmonary and Critical Care Medicine, Department of Medicine, Faculty of medicine, King Chulalongkorn Memorial Hospital, Rama IV Road, Pathumwan	10330	Bangkok	THAILAND
150	Maharaj Nakorn Chiang Mai Hospital	Maharaj Nakorn Chiang Mai Hospital Chiang Mai University, Intawaroros Rd, Chiang Mai 50200,Thailand	50200	Chiang Mai	THAILAND
151	Baillieston Health Centre	20 Muirside Road Baillieston	G69 7AD	Glasgow	UNITED KINGDOM
152	Castlemilk Health Centre	71 Dougrie Drive	G45 9AW	Glasgow	UNITED KINGDOM
153	Thornliebank Health Centre	20 Kennishead Road	G46 8NY	Glasgow	UNITED KINGDOM

Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Avelox [*Oral formulation*]
Brand/Trade Name(s) ex-US	Avelon® Avelox® Avalox® Actira® Octegra® Izilox® Megaxin® Proflox® Promira®
Generic Name	Moxifloxacin
Main Product Company Code	BAY12-8039
Other Company Code(s)	n/a
Chemical Description	1-Cyclopropyl-6-fluoro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride.
Other Product Aliases	n/a

Date of last Update/Change: 19 Mar 2014