

1.0 TITLE PAGE

Protocol Title	A Phase II, Randomized, Double-Blind, Multicenter, Comparative Study to Determine the Safety, Tolerability, Pharmacokinetics and Efficacy of Oral Nafithromycin Versus Oral Moxifloxacin in the Treatment of Community-Acquired Bacterial Pneumonia (CABP) in Adults	
Short Title	Phase II study of oral nafithromycin in CABP	
Protocol Number	W-4873-201	
Study Drug	Nafithromycin	
Original Protocol Date	10 May 2016	
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3.0 SYNOPSIS AND SCHEDULE OF ASSESSMENTS

Study Number	W-4873-201
Title of Study	A Phase II, Randomized, Double-Blind, Multicenter, Comparative Study to Determine the Safety, Tolerability, pharmacokinetics and Efficacy of Oral Nafithromycin Versus Oral Moxifloxacin in the Treatment of Community-Acquired Bacterial Pneumonia (CABP) in Adults
Study Centers (Planned)	Approximately 40 to 50 study centers in the US, Europe and South Africa
Development Phase	II
Background and Rationale	<p>Lower respiratory tract infection, including CABP, remains the second largest cause of death and years of life lost worldwide; its associated age-standardized death rate was 41.7 per 100,000 population in 2013. The global incidence of pneumonia is estimated to be between 1.5 and 14.0 cases per 1000 person-years, varying by region, season, and patient characteristics. Short-term mortality (in-hospital and 30-day mortality) for hospitalized patients with CABP ranges from 4.0% to 18.0%. Costs related to CABP are high, and few approaches (such as reducing the length-of-stay, adequate use of antibiotics, and the introduction of vaccines) have reduced these costs to date. <i>Streptococcus pneumoniae</i> remains the most common pathogen of CABP worldwide, independent of age. Other frequent causes of CABP include <i>Haemophilus influenzae</i>, <i>Moraxella catarrhalis</i>, <i>Staphylococcus aureus</i>, and atypical bacteria (including <i>Mycoplasma</i>, <i>Chlamydia</i> and <i>Legionella</i> spp.).</p> <p>A major therapeutic challenge impacting the treatment of CABP is the widespread resistance of <i>S. pneumoniae</i> to β-lactam (especially penicillins and cephalosporins) and macrolide antibiotics. For example, the prevalence of <i>S. pneumoniae</i> macrolide resistance on a global scale is estimated to be 25% to 40%, varying by region. The prevalence of multidrug-resistant (MDR) <i>S. pneumoniae</i> is also worrisome. For example, in the US, a recent analysis of 1498 clinical pneumococci strains collected between 2012 and 2013 found that 21.0% were MDR. Community-acquired MDR <i>S. pneumoniae</i> poses treatment challenges for outpatient CABP—most notably the lack of effective oral antibacterial options—because of resistance to the most commonly-used oral penicillins, cephalosporins, and/or macrolides. Failure of therapy due to resistance will continue to contribute to the morbidity and mortality of CABP, and treatment failures of mild disease will result in increased hospitalizations and contribute to increased healthcare costs.</p> <p>Nafithromycin (previously known as WCK 4873) is an intravenous (IV) and oral antibacterial agent of the ketolide class that is structurally related to the macrolide class. Diverse in vitro, in vivo, preclinical pharmacokinetic (PK) and safety studies have provided strong scientific evidence of the therapeutic potential of nafithromycin for difficult-to-treat respiratory tract infections caused by multidrug-resistant (MDR) pathogens, including CABP. Preclinical studies have shown that nafithromycin has potent activity against macrolide- and ketolide-resistant strains of <i>S. pneumoniae</i> and Group A streptococci. Additionally, nafithromycin is active against other important CABP pathogens such as <i>Haemophilus influenzae</i>, <i>Moraxella catarrhalis</i>, and atypical pathogens.</p> <p>The ketolide class of antibiotics provides a convenient orally-administered and effective therapeutic option for pneumococci, streptococci, and multiple Gram-negative respiratory pathogens. Innovative structural modifications among newer ketolides provide them with several distinguishing features such as high-affinity binding to domain V and domain II of the 23S ribosomal ribonucleic acid (rRNA) target, in contrast to macrolides that bind only to domain V. Such dual-target binding by ketolides overcomes multiple macrolide resistance mechanisms such as (1) <i>erm</i> gene-encoded methylases (macrolide, lincosamide and streptogramin B [MLS_B]-type resistance, involving methylation of the 23 rRNA target), (2) point mutations within rRNA domain V and (3) diverse mutations in ribosomal proteins L-4 and L-22. Additionally, newer ketolides such as nafithromycin are not susceptible to mef efflux pump-mediated resistance that impacts the activity of macrolides against <i>S. pneumoniae</i> and <i>S. pyogenes</i>. Thus, these newer ketolides possess several features that not only confer activity</p>

	<p>against various resistotypes, irrespective of β-lactam and macrolide susceptibility, but also minimize the risk of resistance emergence or induction of cross-resistance to other agents. A new ketolide antibiotic with improved coverage of MDR pathogens—especially respiratory pathogens that are resistant to the older macrolides —would help address this unmet need.</p> <p>In all, nafithromycin is expected to have the following advantages over older, available macrolides based on data from in vivo, in vitro and preclinical studies conducted to date:</p> <ol style="list-style-type: none"> 1. Mechanism-based activity potential against macrolide- and ketolide-resistant pneumococci and Group A streptococci 2. Excellent target-organ-tissue concentration leading to: <ol style="list-style-type: none"> a. Enabling potent activity vs. MDR pathogens in vivo b. Once-a-day dosing convenience c. Potential for shorter duration of therapy 3. Minimal CYP inhibition leading to ease of co-administration of other drugs 4. Favorable hepatic safety potential owing to favorable drug disposition resulting from lower accumulation in liver 5. Comprehensive coverage of all key CABP pathogens, including atypical pathogens
<p>Objectives</p>	<p>Primary Objectives:</p> <ul style="list-style-type: none"> • To assess the overall safety and tolerability of oral nafithromycin • To assess the clinical response in the Intent-to-Treat (ITT) population at Day 4 <p>Secondary Objectives:</p> <ul style="list-style-type: none"> • To assess the clinical response in the Microbiological Intent-to-Treat (micro-ITT) population at Day 4 • To assess the clinical outcome in the ITT and Clinically Evaluable (CE) populations at End-of-Treatment (EOT) and Test-of-Cure (TOC) (Day 15 \pm 3 days) • To assess early improvement in clinical symptoms and normalization of vital signs in the ITT population at Day 4 • To assess clinical outcome in micro-ITT population at TOC • To assess by-subject and by-pathogen microbiological response in micro-ITT and microbiologically evaluable (ME) populations at TOC • To assess readmission to the hospital (or admission to the hospital if not previously hospitalized) for any reason prior to Follow-Up (FU)
<p>Study Endpoints</p>	<p>Primary efficacy endpoint: Clinical Response at Day 4 in the ITT population</p> <ul style="list-style-type: none"> • Clinical Response: Alive and programmatically-determined improvement of at least 1 level (e.g., severe to moderate, moderate to mild, mild to absent) in at least 2 CABP symptoms (dyspnea, cough, production of purulent sputum, and pleuritic chest pain) compared to Screening, without worsening in any other symptom. Severity of symptoms is based on a 4-point scale (absent, mild, moderate, or severe) (Appendix III). • Clinical Non-Response: No programmatically-determined improvement of at least 1 level in at least 2 CABP symptoms compared to Screening; or worsening in any of the 4 CABP symptoms compared to Screening; or requires alternative rescue antibacterial therapy for CABP prior to Day 4; or death from any cause prior to Day 4. • Indeterminate: Study data are missing for evaluation of efficacy at Day 4 for any reason, including lost to follow-up. <p>Secondary efficacy endpoints:</p> <ul style="list-style-type: none"> • Clinical Response at Day 4, as described above, in the micro-ITT population • Clinical Outcome at EOT (ITT and CE populations) and TOC (ITT, CE, and micro-ITT populations): <ul style="list-style-type: none"> ○ Clinical Cure: Alive and CABP is sufficiently resolved such that further antibacterial therapy is not needed. These subjects may have some residual

	<p>findings related to infection (i.e., cough) requiring non-antibiotic ancillary treatment (e.g., expectorant).</p> <ul style="list-style-type: none"> ○ Clinical Failure: Requires alternative rescue antibacterial treatment for CABP prior to the assessment (EOT or TOC) related to progression or worsening of CABP symptoms, development of infectious complications of CABP (e.g., empyema, lung abscess), or development of a treatment-emergent adverse event (TEAE) that required discontinuation of study therapy; or death from any cause prior to the assessment. ○ Indeterminate: Study data are missing for evaluation of efficacy at the assessment visit for any reason, including lost to follow-up. <ul style="list-style-type: none"> ● Improvement in CABP Symptoms and Normalization in Vital Signs at Study Day 4 (ITT population): Programmatically-determined improvement of at least 1 level in at least 2 CABP symptoms (dyspnea, cough, production of purulent sputum, and pleuritic chest pain) compared to Screening, without worsening in any other symptom (Appendix III), plus normalization of vital signs (temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation within predefined normal ranges [Section 13.2.3]), ability to maintain oral intake and normal mental status ● By-subject and by-pathogen Microbiological Response at TOC (micro-ITT and ME populations): <ul style="list-style-type: none"> ○ Favorable Microbiological Response: Meet criteria for eradication or presumed eradication (defined in Section 13.3) ○ Unfavorable Microbiological Response: Meets criteria for persistence or presumed persistence (defined in Section 13.3) ○ Indeterminate: Post-baseline respiratory specimen culture or blood culture was not available and the subject’s clinical response was assessed as indeterminate ● Hospitalization Prior to FU (ITT population): Hospital readmission for any reason between Day 1 and FU Visit, if previously hospitalized and discharged, or initial hospital admission for any reason between Day 2 and FU Visit, if not previously hospitalized on Day 1 (Section 13.2.4) <p>Safety Endpoints:</p> <p>Safety evaluation is based on TEAEs, clinical laboratory evaluation, vital signs, physical examination findings and electrocardiograms (ECGs) collected during the study.</p>
<p>Study Design</p>	<p>This is a Phase II prospective, multicenter, multinational, randomized (1:1:1), double-blind, comparative efficacy, safety, tolerability, and PK study of oral nafithromycin versus oral moxifloxacin for treatment of male and female adults with CABP. Study drug is defined as oral nafithromycin or oral moxifloxacin.</p> <p>Subjects providing informed consent and meeting all study eligibility criteria will be enrolled in the study and randomized into the study in a 1:1:1 ratio to either of the following 3 treatment arms:</p> <ul style="list-style-type: none"> ● Arm A: Nafithromycin 800 mg (two 400 mg tablets) PO q24h for 3 days; subjects will receive matching placebo (two nafithromycin placebo tablets PO q24h) on Days 4 through Day 7, and one moxifloxacin placebo capsule PO q24h on Days 1 through 7, to maintain the blind ● Arm B: Nafithromycin 800 mg (two 400 mg tablets) PO q24h for 5 days; subjects will receive matching placebo (two nafithromycin placebo tablets PO q24h) on Day 6 and Day 7, and one moxifloxacin placebo capsule PO q24h on Days 1 through 7, to maintain the blind ● Arm C: Moxifloxacin 400 mg (one 400 mg capsule) PO q24h for 7 days; subjects will also receive two nafithromycin placebo tablets PO q24h on Days 1 through Day 7 to maintain the blind <p>Baseline assessments for study eligibility will occur during the Screening visit, within 24 h prior to administration of the first dose of the study drug. Block randomization using an</p>

interactive voice/web response system (IXRS), stratified by region (US vs. ex-US) and Pneumonia Outcomes Research Team (PORT) Risk Class (II vs. III/IV), will be used to assign subjects (1:1:1) to Arm A, Arm B, or Arm C. Enrolment of PORT Risk Class II will be capped at 50% and enrolment of subjects with allowed prior systemic antibiotic use will be capped initially at 25% (subject to change during study conduct). Study Day 1 is defined as the day that the study drug is first administered, and subsequent study days are defined by the number of consecutive calendar days thereafter.

Subjects may be treated in the study as inpatients or outpatients based on their clinical condition, at the discretion of the Investigator; however, only oral study drug will be administered (i.e., parental moxifloxacin will not be administered). Subjects will be assessed daily by the Investigator between Day 1 and Day 5, whether being treated for CABP in the inpatient or outpatient setting. Investigators will assess for clinical outcome at Day 7 (EOT), and TOC (Day 15 ± 3 days). Vital signs, physical exam, assessment of CABP symptom severity, and other study procedures are detailed in [Table 3-1](#). A FU visit will be conducted on Day 31 ± 3 days from the start of treatment. The FU visit may be conducted via telephone contact or by another interactive technology for subjects who were considered to be clinical successes and had no AEs or clinically significant laboratory or ECG abnormalities noted at or after the TOC visit; otherwise, the visit must be conducted in person.

Rationale for moxifloxacin as a comparator:

Moxifloxacin is a member of the fluoroquinolone class of antibiotics. It is active against most CABP pathogens including macrolide- and penicillin-resistant *S. pneumoniae*, Gram-negative bacteria, and atypical pathogens. Empiric treatment of CABP with moxifloxacin, especially in subjects admitted to the hospital, is consistent with current US (Infectious Diseases Society of America [IDSA]/American Thoracic Society [ATS]) and European (The Task Force of the European Respiratory Society in collaboration with the European Society for Clinical Microbiology and Infectious Diseases [ESCMID]) therapeutic guidelines. The recommended dose (IDSA/ATS) is 400 mg once daily for 7-14 days, and in this study, a 7-day regimen will be used.

Rationale for 800 mg of nafithromycin once daily:

Preclinical PK conducted in rodent and non-rodent species and Phase I clinical studies have shown optimal PK profile commensurate to the once-a-day dosing potential of nafithromycin. Administration of multiple-ascending oral doses (600 mg, 800 mg, and 1000 mg) of nafithromycin to humans was well tolerated. No serious adverse events have been reported for any dose in clinical studies conducted to date. On average, steady state of plasma concentrations was achieved at Day 3-4 of multiple dosing.

Rationale of therapeutic treatment duration with nafithromycin of 3 days and 5 days:

Nafithromycin attained a geometric mean $T_{1/2}$ of approximately 11 h in steady state at 800 mg/day in healthy human subjects (steady state was achieved on average within 3-4 days over the 600 to 1000 mg/d dose range). In addition, significant accumulation of nafithromycin in polymorphonuclear cells (PMNs) was observed.

Furthermore, superior tissue penetration observed in rodents — particularly in the target organ (lung) — is expected to drive superior pharmacodynamic (PD) activity, enabling a shorter duration of therapy of 3 to 5 days.

A multiple dose study was conducted to compare plasma, epithelial lining fluid (ELF) and alveolar macrophage (AM) concentrations of nafithromycin (800 mg administered once daily for 3 days) in healthy adult subjects. Each subject underwent one standardized bronchoscopy with bronchoalveolar lavage (BAL) at 3, 6, 9, 12, 24 or 48 h after the third oral dose of nafithromycin. Concentrations of nafithromycin were significantly higher in ELF and AM than simultaneous plasma concentrations throughout the 48 h period after 3 days of once-daily dosing. The ratios of ELF to plasma concentrations and of AM to plasma concentrations based the mean AUC_{0-24} values were 13.8 and 527, respectively.

Pharmacokinetic (PK) sampling:

Blood samples for PK analysis will be collected from all subjects on Day 3 and Day 4 at sites

	<p>where PK sampling is possible. Time points for PK sample collection will be:</p> <ul style="list-style-type: none"> • Pre-dose: pre-dose PK sample will be collected within 10 minutes before dosing. • Post-dose at 2-4 h (Day 3) and 24-28 h (Day 4). Subjects who have been hospitalized are also required to have a post-dose PK sample at 6-10 h (Day 3).
Inclusion Criteria	<p>Subjects are required to meet all of the following inclusion criteria:</p> <ol style="list-style-type: none"> 1. Male or female ≥ 18 years of age 2. Willing to participate in the study and provide written informed consent before any protocol specific assessment is performed 3. Meet the following clinical criteria for CABP: <ol style="list-style-type: none"> a. Have at least TWO of the following symptoms (new or worsening): <ul style="list-style-type: none"> • Dyspnea (shortness of breath) • Cough • Production of purulent sputum • Pleuritic chest pain b. Have at least TWO of the following vital sign abnormalities: <ul style="list-style-type: none"> • Fever or hypothermia documented by the Investigator (oral, rectal, or tympanic temperature $> 38.0^{\circ}\text{C}$ [100.4°F] or $< 36.0^{\circ}\text{C}$ [95.5°F]) • Hypotension, defined as systolic blood pressure < 90 mm Hg • Tachycardia, defined as heart rate > 90 beats per minute • Tachypnea, defined as respiratory rate > 20 breaths per minute c. Have at least ONE of the following laboratory abnormalities: <ul style="list-style-type: none"> • Hypoxemia defined as arterial oxygen saturation $< 90\%$ by pulse oximetry or partial pressure of arterial oxygen (PaO_2) < 60 mm Hg by arterial blood gas (ABG) • Auscultatory findings on pulmonary examination consistent with bacterial pneumonia or pulmonary consolidation (e.g., rales, dullness on percussion, bronchial breath sounds, or egophony) • Elevated total white blood cell (WBC) count ($> 10,000$ cells/mm^3) or leucopenia (WBC $< 4,000$ cells/mm^3) • Elevated immature neutrophils ($> 15\%$ band forms), regardless of total peripheral WBC count d. Radiographic evidence of CABP: <ul style="list-style-type: none"> • Radiographically-confirmed pneumonia, i.e., new or progressive pulmonary infiltrate(s) on chest X-ray (CXR) or chest computed tomography (CT) scan consistent with acute bacterial pneumonia within 48 h prior to randomization e. PORT score of 51 to 105 (PORT Risk Class of II, III or IV) 4. All females must have a negative urine or serum pregnancy test (β-human chorionic gonadotropin [β-HCG]) at Screening AND agree to the use of one of the following acceptable methods of contraception from Screening through TOC: surgical sterilization (defined as bilateral oophorectomy or bilateral salpingectomy, but excluding bilateral tubal occlusion), post-menopausal (defined by amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments), barrier contraception (e.g., condom, intrauterine device), levonorgestrel intrauterine system (e.g., Mirena[®]), regular medroxyprogesterone injections (e.g., Depo-Provera[®]), sexual intercourse with only vasectomised partners, or abstinence. Note that oral contraceptives should not be used as the sole method of birth control because the effect of nafcithromycin on the efficacy of oral contraceptives has not yet been established; subjects who take oral contraceptives must also use one of the acceptable forms of birth control (listed above) from Screening through TOC. Males must agree to use an acceptable barrier method of birth control (i.e., condom) with female partner(s) and must not donate sperm from Screening through TOC. 5. Ability to ingest oral study drug (e.g., able to swallow large capsules intact, and no significant nausea, vomiting, diarrhea, or any other condition that might impair ingestion or absorption of oral study drug)
Exclusion Criteria	<ol style="list-style-type: none"> 1. Subjects with any of the following confirmed or suspected types of pneumonia: <ul style="list-style-type: none"> • Aspiration pneumonia

	<ul style="list-style-type: none"> • Hospital-acquired bacterial pneumonia (HABP), defined as pneumonia with onset of clinical signs and symptoms after at least 48 h hospitalization in an acute inpatient health care facility. • Healthcare-associated bacterial pneumonia (HCAP), defined as pneumonia acquired in a long-term care or subacute healthcare facility (e.g., nursing home) or pneumonia with onset after recent hospital discharge (within 90 days of current admission and previously hospitalized for ≥ 48 h) • Ventilator-associated bacterial pneumonia (VABP), defined as pneumonia with onset of clinical signs and symptoms after at least 48 h endotracheal intubation • Pneumonia that may be caused by pathogen(s) resistant to either study drug (nafithromycin or moxifloxacin), including viral, mycobacterial, or fungal pneumonia (e.g., <i>Pneumocystis jiroveci</i> pneumonia, active pulmonary tuberculosis) • Post-obstructive pneumonia • Pneumonia associated with cystic fibrosis <ol style="list-style-type: none"> 2. Suspected or confirmed pleural empyema (a parapneumonic pleural effusion is not an exclusion criterion) or lung abscess 3. Suspected or confirmed non-infectious causes of pulmonary infiltrates (e.g., pulmonary embolism, hypersensitivity pneumonia, congestive heart failure) 4. Receipt of 1 or more dose(s) of a potentially effective systemic antibacterial treatment for treatment of the current CABP within 72 h prior to randomization with the exception of: <ul style="list-style-type: none"> • Receipt of a single dose of a short-acting antibacterial agent within 72 h of randomization (Appendix I) OR • Failure (worsening of symptoms) of at least 48 h of treatment for the current episode of CABP with an antibacterial agent other than a ketolide or fluoroquinolone 5. Subjects requiring concomitant adjunctive or additional potentially-effective systemic antibacterial treatment for management of CABP 6. Evidence of significant immunologic disease determined by any of the following: <ul style="list-style-type: none"> • Current or anticipated neutropenia defined as < 500 neutrophils/mm³ • Known infection with human immunodeficiency virus (HIV) (prior to Screening) and a cluster of differentiation 4 (CD4) count that is unknown or documented to be < 200 cells/mm³ within the last year, or an Acquired Immune Deficiency Syndrome (AIDS)-defining illness; note that neither HIV nor CD4 testing is required at Screening • History of heart, lung, or kidney transplant • The receipt of cancer chemotherapy, radiotherapy, or potent, non-corticosteroid immunosuppressant drugs (e.g., cyclosporine, azathioprine, tacrolimus, immunomodulating monoclonal antibody therapy) within the past 3 months, or the receipt of corticosteroids equivalent to or greater than 40 mg of prednisone per day for more than 14 days in the 30 days prior to randomization 7. Known or suspected primary or metastatic neoplastic lung disease, bronchiectasis, bronchial obstruction, chronic neurological disorder preventing clearance of pulmonary secretions, or severe chronic obstructive pulmonary disease (COPD) (severe COPD is defined as known [prior to Screening] forced expiratory volume in one second/forced vital capacity ratio [FEV₁/FVC] < 0.70 and FEV₁ $< 50\%$ normal); note that pulmonary function tests are not required at Screening 8. Compromised hepatic or renal function, including but not limited to: clinical evidence of end-stage liver disease (e.g., ascites, hepatic encephalopathy), screening serum total bilirubin > 2 times the upper limit of normal (ULN) (unless associated with an elevated indirect bilirubin typical of Gilbert syndrome), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 times ULN, serum creatinine > 2.0 mg/dl and/or blood urea nitrogen (BUN) > 30 mg/dl. Other clinically-significant abnormal laboratory findings should be discussed with the Medical Monitor prior to the subject's entry. 9. History of <i>Clostridium difficile</i>-associated disease within 6 months prior to enrolment 10. History of hypersensitivity, known contraindication (e.g. lactose intolerance, lactase deficiency and glucose-galactose malabsorption etc.) or allergic reaction (e.g., anaphylaxis, urticaria, other significant reaction) to any ketolide, any fluoroquinolone
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	<p>antibiotic medicinal products or any of their excipients.</p> <ol style="list-style-type: none"> 11. Current second- or third-degree atrioventricular block or sick sinus syndrome, uncontrolled atrial fibrillation, severe or unstable angina, congestive heart failure, myocardial infarction within 3 months of the Screening visit, clinically significant ECG abnormalities including QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 msec (males) or > 470 msec (females), or requirement for medications known to cause QT prolongation 12. Prior (within 14 days prior to randomization) or concomitant use of cytochrome P450 liver enzyme inducers (e.g., phenobarbital, carbamazepine, griseofulvin, sulfonyleureas, phenytoin, or rifampin) 13. History of tendon rupture 14. Current peripheral neuropathy or myasthenia gravis 15. Known or suspected seizure disorder or other central nervous system (CNS) disorders that may predispose the subject to seizures or lower the seizure threshold 16. Nursing mother or pregnant female 17. Subjects who received any experimental drug within 30 days prior to enrolment 18. Require admission to in intensive care unit for any reason, life expectancy of less than 2 months, or any concomitant condition that, in the opinion of the Investigator, is likely to interfere with evaluation of the response of the infection under study, determination of AEs, or completion of the expected course of treatment
Study Visits (Calendar Days)	<ul style="list-style-type: none"> • Screening Visit (within 24 h prior to randomization) • Day 1: Randomization and 1st dose of study drug • Day 2 • Day 3: Includes PK sampling • Day 4: Includes PK sampling • Day 5 • Day 6 • Day 7 (EOT is on Day 7 or within 2 days following Day 7) • TOC: Day 15 ±3 days (inclusive) • FU: Day 31 ±3 days (may be conducted via telephone contact or by another interactive technology for subjects who were considered to be clinical successes and had no AEs or clinically significant laboratory or ECG abnormalities noted at or after the TOC visit; otherwise, the visit must be conducted in person)
Investigational Medicinal Product (IMP): Test Product and Matching Placebo	<p>Nafithromycin:</p> <ul style="list-style-type: none"> • Strength and pharmaceutical dosage form: 400 mg tablet • Dose: 800 mg once daily (2 tablets of 400 mg each) for 3 days (Arm A) or for 5 days (Arm B) • Route of administration: Oral <p>Placebo to match Nafithromycin:</p> <ul style="list-style-type: none"> • Pharmaceutical dosage form: Tablet • Dose: 2 tablets daily for 4 days following active nafithromycin (Arm A), for 2 days following active nafithromycin (Arm B), or for 7 days (Arm C) • Route of administration: Oral
IMP: Reference Therapy and Matching Placebo	<p>Moxifloxacin:</p> <ul style="list-style-type: none"> • Strength and pharmaceutical dosage form: 400 mg capsule (i.e. over-encapsulated tablet) • Dose: 400 mg once daily for 7 days (Arm C) • Route of administration: Oral (parenteral moxifloxacin is not allowed) <p>Placebo to match Moxifloxacin:</p> <ul style="list-style-type: none"> • Pharmaceutical dosage form: Capsule • Dose: 1 capsule daily for 7 days (Arm A and Arm B) • Route of administration: Oral
Study Duration	Each subject will remain in the study for approximately one month. This will include a Screening visit (within 24 h of randomization), a 7-day oral treatment period, and post

	treatment assessments at TOC (Day 12 to Day 18) and FU (Day 28 to Day 34).
Sample Size	Approximately 225 adult subjects (75 subjects per arm) diagnosed with CABP. Subjects with a PORT Risk Class of II (PORT score 51-70; see Appendix II) will be capped at 50% of the subjects randomized. Prior antibiotic use will be restricted to a single dose of a short-acting antibacterial drug within 72 h of enrolment (Appendix I), and this prior antibiotic use will be capped at 25%.
Statistical Methods	<p>Efficacy</p> <p>Efficacy will be analyzed in the following populations according to the random treatment assignment:</p> <ul style="list-style-type: none"> • ITT population: All subjects who were randomized • micro-ITT population: All ITT subjects who have at least one baseline Gram-positive or atypical bacterial pathogen known to cause CABP, including bacterial pathogens identified by respiratory specimen culture, blood culture, urinary antigen test (<i>S. pneumoniae</i>, <i>L. pneumophila</i>), or atypical bacterial serologic response (<i>M. pneumoniae</i>, <i>C. pneumoniae</i>, <i>L. pneumophila</i>). Subjects with sole baseline Gram-negative bacterial infection will be excluded from this population. • Clinically evaluable (CE) population: ITT population that follows important components of the trial (criteria provided in Section 16.1.4) • ME population: Micro-ITT population that follows important components of the trial (criteria provided in Section 16.1.5) <p>This study is not powered for inferential statistical analyses. All data will be summarized separately by study drug (nafithromycin for 3 days, nafithromycin for 5 days, and moxifloxacin). Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables. Frequency distributions (counts and percentages) will be presented for categorical variables. All summaries will be presented within each treatment group. The 95% confidence intervals, obtained using the Clopper-Pearson method, for the proportions of subjects with a favorable response in each treatment group will be presented.</p> <p>Safety: Safety data will be summarized for the Safety population, which includes all randomized subjects who received any amount of study drug, analyzed according to the treatment received. The subject incidence of serious adverse events (SAEs), including deaths and discontinuations due to adverse events (AEs) will be presented by system organ class and preferred term according to the Medical Dictionary of Regulatory Activities (MedDRA[®]), relationship to study drug, and severity.</p> <p>PK: The PK data acquisition and analysis strategy entails the use of a sparse PK sampling schedule. Efforts will be made to obtain PK samples from all subjects at sites where PK sampling is possible. Plasma concentrations of nafithromycin will be listed for each subject in the PK Population. Nafithromycin plasma concentration data, along with other information including demographic data, will be combined with appropriate data from other clinical studies and analyzed using a population PK approach and reported separately.</p>

Table 3–1. Schedule of Assessments and Procedures.

Visits	Screening Visit (Day -1) ^a	Day 1 ^b	Day 2	Day 3	Day 4	Day 5	Day 6	EOT (Day 7 (+2 days) ^c	TOC (Day 15 ±3 days ^d	FU Day 31 ±3 days ^e
Informed Consent ^f	√									
Medical history & demography	√									
Physical exam, incl. CABP symptom severity ^g	√	√	√	√	√	√		√	√	
Vital signs, incl. oximetry ^h	√	√	√	√	√	√		√	√	
12 Lead ECG ⁱ	√	√		√		√		√	√ ⁱ	√ ⁱ
CXR or chest CT scan ^j	√									
PORT score calculation ^k	√									
Inclusion/exclusion criteria	√	√								
Randomization		√								
Laboratory Assessments:										
Hematology, coagulation, serum chemistry ^l	√					√		√	√	√
Atypical pathogen serology ^m	√								√	
Urine tests ⁿ	√									
Urinary antigen testing ^o	√									
Pregnancy test ^p	√								√	
Respiratory specimen Gram stain/culture ^q	√	As clinically indicated								
Blood culture ^r	√	Repeat the blood cultures as necessary until negative blood cultures are obtained								
Blood for PK sampling ^s				√	√					
Study drug administration and accountability ^t		√	√	√	√	√	√	√		
Adverse Events ^u	√	√	√	√	√	√	√	√	√	√
Prior and concomitant medications ^v	√	√	√	√	√	√	√	√	√	√
Clinical outcome assessment								√	√	

Abbreviations: CABP = Community-acquired bacterial pneumonia; CT = Computed tomography; CXR = chest x-ray; ECG = electrocardiogram; EOT = End-of-Therapy; FU = Follow-up; PK = Pharmacokinetic; PORT = Pneumonia Outcomes Research Team; TOC = Test-of-Cure.

^a Following the signing of the informed consent form, all Screening evaluations should be completed within 24 h prior to randomization.

^b Day 1 is the first day of study drug administration. Subsequent study days are consecutive calendar days. If feasible, Screening and randomization procedures (Screening Visit and Day 1) can be performed on same day. Standard of care data from within 24 h (laboratory) and 48 h prior (radiology) to randomization can be used as Screening Visit procedures.

^c EOT is to be conducted on the day of, or within 2 days following, Day 7. EOT should also be conducted for any premature withdrawal from study or study drug.

^dTOC is to be conducted on Day 15 \pm 3 days.

^eFU is to be conducted on Day 31 \pm 3 days. The FU assessment may be conducted via telephone contact or by another interactive technology for subjects who were considered to be Clinical Cures ([Section 13.2.2](#)) and had no AEs or clinically significant laboratory or ECG abnormalities noted at or after the TOC visit; otherwise, the visit must be conducted in person.

^fWritten and signed informed consent must be obtained before any protocol assessment is performed.

^gComplete physical exam—consisting of general appearance, skin, eyes, ears, nose, throat, lungs, heart, abdomen, back, extremities, lymph nodes, vascular, and neurological exams—will be conducted at Screening and daily between Day 1 and Day 5 (whether inpatient or outpatient), EOT, and TOC. As part of the complete physical exam, the Investigator should assess the severity of the subject's CABP symptoms of dyspnea, cough, production of purulent sputum, and pleuritic chest pain, based upon the CABP Symptom Severity Guidance for Investigator Assessment in [Appendix III](#).

^hVital signs—including body temperature (oral, rectal, or tympanic), blood pressure, heart rate, respiratory rate, and pulse oximetry—will be collected at Screening and daily between Day 1 and Day 5 (whether inpatient or outpatient), EOT, and TOC. Height, weight, and creatinine clearance (CrCl) will also be collected at the Screening Visit.

ⁱA 12-lead ECG will be performed at Screening, Day 1, Day 3, Day 5, and EOT. A 12-lead ECG will be performed at TOC or FU if prior ECG(s) showed any clinically-significant abnormality ([Sections 11.9 and 11.10](#)).

^jSubjects must have a confirmatory CXR or chest CT scan consistent with acute bacterial pneumonia within 48 h prior to randomization.

^kSubjects with a PORT score of 51 to 105 (PORT Risk Class of II, III or IV) are eligible for enrolment ([Appendix II](#)).

^lAt Screening, local laboratory evaluations required for assessing subject eligibility include serum transaminase (ALT and AST) and total bilirubin levels, serum creatinine and BUN (or urea), peripheral WBC count, absolute neutrophil count, coagulation, and immature neutrophil percentage. Blood will be collected for central laboratory testing at the Screening, Day 5, EOT and TOC visits (including serum β -HCG in females; full list of central laboratory tests available in [Appendix IV](#)); blood will also be collected for central laboratory testing at FU in subjects with clinically significant laboratory abnormalities noted at or after the TOC visit.

^mCollect blood for acute (Screening) and convalescent (TOC) atypical pathogen serology, including *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*, for central laboratory testing.

ⁿAt Screening, a urine dipstick will be performed locally; if results are abnormal and deemed clinically significant by the Investigator, a urinalysis will be sent to the central laboratory.

^oAt Screening, urine will be tested locally for *Streptococcus pneumoniae* and *Legionella pneumophila* using provided rapid antigen test kits.

^pAt Screening, local laboratory urine or serum pregnancy test (females only) is required to confirm study eligibility. In addition, blood will be collected from all female subjects for serum β -HCG pregnancy test by the central laboratory at the Screening and TOC visits.

^qAt Screening, collection of expectorated sputum or other deep respiratory sample should be attempted in all subjects. Gram stain will be performed on all sputum specimens and quality assessed. Culture will be performed on all adequate sputum samples or deep respiratory specimens. Post-baseline respiratory specimens should be collected as clinically indicated and from subjects who are clinical failures and require alternative antibacterial treatment for CABP ([Section 12.6](#)).

^rTwo sets of blood cultures (each set consists of 1 aerobic and 1 anaerobic blood culture bottle) will also be collected at Screening. Repeat post-baseline blood cultures should be collected on the day that the positive blood culture is detected. If subsequent blood cultures are also positive, repeat the blood cultures as necessary until negative blood cultures are obtained ([Section 12.6](#)).

^sBlood samples for PK analysis will be collected from all subjects at sites where PK sampling is possible on Day 3, including within 10 minutes before study drug administration, and post-dose at 2-4 h and 24-28 h. Subjects who have been hospitalized are also required to have a post-dose PK sample at 6-10 h (Day 3).

^tStudy drug should be administered q24h (\pm 4 h) between Day 1 and Day 7, with the exception of Day 2 in which an additional window of 4h may be utilized, depending on the randomization time on day 1.

^uAEs and SAEs will be recorded and reported from signing of the informed consent to the FU visit.

^vPrior medications that have been administered within 14 days prior to the date of signing the informed consent or during the Screening phase will be recorded in the electronic Case Report Form (eCRF). All medications administered after the first dose of study drug must be recorded in the eCRF.

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5.0 **LIST OF ABBREVIATIONS**

ABG	arterial blood gas
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AM	alveolar macrophage
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC ₀₋₂₄	area under the plasma concentration versus time curve over 24 hours
BAL	bronchoalveolar lavage
β-HCG	β-human chorionic gonadotropin
BUN	blood urea nitrogen
CABP	community-acquired bacterial pneumonia
CBC	complete blood count
CD4	cluster of differentiation 4
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CrCl	creatinine clearance
CT	computed tomography
CXR	chest x-ray
eCRF	electronic case report form
ECG	electrocardiogram
EDC	electronic data capture
ELF	epithelial lining fluid
EOT	End-of-Therapy
ESCMID	European Society for Clinical Microbiology and Infectious Diseases
fAUC/MIC	free drug area under the plasma concentration versus time curve/minimum inhibitory concentration
FEV ₁	forced expiratory volume in one second
FU	Follow-Up
FVC	forced vital capacity
GCP	Good Clinical Practice
h	Hours
HABP	hospital-acquired bacterial pneumonia
HCAP	healthcare-associated pneumonia
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDSA	Infectious Diseases Society of America
IMP	Investigational Medicinal Product

IMPD	Investigational Medicinal Product Dossier
ITT	Intent-to-Treat
IV	intravenous(ly)
IXRS	interactive voice/web response system
LPF	low power field
MDR	multidrug-resistant
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
micro-ITT	Microbiological Intent-to-Treat population
MLS _B	macrolide, lincosamide and streptogramin B
PaO ₂	partial pressure of arterial oxygen
PD	pharmacodynamic
PK	pharmacokinetic
PMN	polymorphonuclear cell
PO	per os (by mouth)
PORT	Pneumonia Outcomes Research Team
QT	time from electrocardiogram Q wave to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
rRNA	ribosomal ribonucleic acid
SAE	serious adverse event
SI	Système International d'Unités
T _½	half-life
TEAE	treatment-emergent adverse event
T _{max}	time at which drug is present at maximum concentration in serum
TOC	Test-of-Cure
ULN	upper limit of normal
US	United States
VABP	ventilator-associated bacterial pneumonia
WBC	white blood cell

6.0 **BACKGROUND AND RATIONALE**

6.1 **COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA AND UNMET MEDICAL NEED**

Lower respiratory tract infection, including community-acquired bacterial pneumonia (CABP), remains the second largest cause of death and years of life lost worldwide; its associated age-standardized death rate was 41.7 per 100,000 population in 2013 ([GBD, 2015](#)). The global incidence of pneumonia is estimated to be between 1.5 and 14.0 cases per 1000 person-years, varying by region, season, and patient characteristics ([File, 2010b; Millett, 2013](#)). Short-term mortality (in-hospital and 30-day mortality) for hospitalized patients with CABP ranges from 4.0% to 18.0% ([Arnold, 2013; File, 2010b](#)). Costs related to community-acquired pneumonia are high, and few approaches (such as reducing the length-of-stay, adequate use of antibiotics, and the introduction of vaccines) have reduced these costs to date ([Prina, 2015](#)). *Streptococcus pneumoniae* remains the most common pathogen of CABP worldwide, independent of age. Other frequent causes of CABP include *Haemophilus influenzae*, *Moraxella catarrhalis*, and atypical bacteria (including *Mycoplasma*, *Chlamydia*, and *Legionella* spp.).

A major therapeutic challenge impacting the treatment of CABP is the widespread resistance of *S. pneumoniae* to β -lactams (especially penicillins and 1st and 2nd-generation cephalosporins) and macrolide antibiotics. For example, the prevalence of *S. pneumoniae* macrolide resistance on a global scale is estimated to be 25% to 40%, varying by region ([Farrell, 2008; Reinert, 2009](#)). The prevalence of multidrug-resistant (MDR) *S. pneumoniae*, defined by penicillin nonsusceptibility plus resistance to two additional non- β -lactam antibiotic classes, is also worrisome. For example, in the US, an analysis of 1498 clinical pneumococci strains collected between 2012 and 2013 found that 21.0% were MDR ([Richter, 2014](#)). Community-acquired MDR *S. pneumoniae* poses treatment challenges for outpatient CABP—most notably the lack of effective oral antibacterial options—because of resistance to the most commonly-used oral penicillins, cephalosporins, and/or macrolides. Failure of therapy due to resistance will continue to contribute to the morbidity and mortality of CABP, and treatment failures of mild disease will result in increased hospitalizations and contribute to increased healthcare costs.

The development of oral nafithromycin (described below in [Section 6.2](#)), which has activity against MDR *S. pneumoniae*, *Streptococcus pyogenes*, respiratory Gram-negative pathogens, and atypical pathogens, would provide clinicians with a new treatment option for CABP caused by the most common etiologies of CABP, including MDR *S. pneumoniae*, while maintaining an acceptable safety profile.

6.2 NAFITHROMYCIN

Nafithromycin (previously known as WCK 4873) is an IV and oral antibacterial agent of the ketolide class that is structurally related to the macrolide class. Diverse in vitro, in vivo, preclinical pharmacokinetic (PK) and safety studies have provided strong scientific evidence of the therapeutic potential of nafithromycin for difficult to treat respiratory tract infections caused by MDR pathogens. [REDACTED]

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- [Redacted list item]

Refer to the current nafithromycin Investigator's Brochure (IB) for additional information regarding relevant nonclinical, microbiology, pharmacology and clinical studies.

6.3 CLINICAL EXPERIENCE

[Redacted text block]

[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

Additional details for each study are available in the IB.

6.4 STUDY DRUG DOSE RATIONALE

In this study, study drug is defined as oral nafithromycin tablet or oral moxifloxacin capsule (i.e., over-encapsulated tablet). Relevant matching placebo formulations (tablets and capsules) are used to maintain the blind.

6.4.1 Nafithromycin

Rationale for 800 mg of nafithromycin once daily for 3 – 5 days:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6.4.2 Moxifloxacin

Moxifloxacin was selected as the optimal comparator for this Phase II CABP study, given its long history of efficacy and tolerability in this infection. The proposed dose regimen and treatment scheme (400 mg once daily for 7 days) has been selected for consistency purposes worldwide as this study is planned to be conducted in different regions, such as Europe, US and South Africa.

Moxifloxacin has a similar spectrum of activity to that of nafcithromycin, with coverage against the most common typical and atypical causes of CABP (e.g., *S. pneumoniae* [including penicillin-resistant and macrolide-resistant isolates], *H. influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*). This broad spectrum of activity along with its once-daily dosage allows for the double-blind monotherapy design of this trial, obviating the need for combination therapy in either treatment arm. The use of moxifloxacin for CABP is consistent with the current treatment guidelines by IDSA/ATS and ESCMID ([Mandell, 2007](#); [Woodhead, 2005](#)). In conclusion, the 7-day oral treatment duration of moxifloxacin, allowed in this study was selected to be generally consistent with clinical guideline recommendations as well as the duration of therapy recommended in the package inserts for the oral switch agent (moxifloxacin package inserts) from different regions, and can thus be considered a globally appropriate treatment duration from both efficacy and safety standpoints.

7.0 STUDY OBJECTIVES

7.1 PRIMARY OBJECTIVES

The primary objectives of this study are:

- To assess the overall safety and tolerability of oral nafithromycin
- To assess the clinical response in the ITT population at Day 4

7.2 SECONDARY OBJECTIVES

The secondary objectives of this study are:

- To assess the clinical response in the micro-ITT population at Day 4
- To assess the clinical outcome in the ITT and CE populations at EOT and TOC
- To assess early improvement in clinical symptoms and normalization of vital signs in the ITT population at Day 4
- To assess clinical outcome in micro-ITT population at TOC
- To assess by-subject and by-pathogen microbiological response in micro-ITT and ME populations at TOC
- To assess readmission to the hospital (or admission to the hospital if not previously hospitalized) for any reason prior to FU

7.3 EXPLORATORY OBJECTIVES

Additional exploratory and subgroup analyses may be conducted, as described in the Statistical Analysis Plan.

8.0 STUDY DESIGN

8.1 TYPE OF STUDY

This is a Phase II prospective, multicenter, multinational, randomized (1:1:1), double-blind, comparative study to determine the efficacy, safety, tolerability, and PK of oral nafithromycin versus oral moxifloxacin for treatment of adults with CABP. Study drug is defined as oral nafithromycin tablets or oral moxifloxacin capsules. Relevant matching placebo formulations (tablets and capsules) are used to maintain the blind.

Subjects providing informed consent and meeting all study eligibility criteria will be randomized into the study in a 1:1:1 ratio to either of the following 3 treatment arms:

- Arm A: Nafithromycin 800 mg (two 400 mg tablets) PO q24h for 3 days; subjects will receive matching placebo (two nafithromycin placebo tablets PO q24h) on Days 4 through Day 7, and one moxifloxacin placebo capsule PO q24h on Days 1 through 7, to maintain the blind
- Arm B: Nafithromycin 800 mg (two 400 mg tablets) PO q24h for 5 days; subjects will receive matching placebo (two nafithromycin placebo tablets PO q24h) on Day 6 and Day 7, and one moxifloxacin placebo capsule PO q24h on Days 1 through 7, to maintain the blind
- Arm C: Moxifloxacin 400 mg (one 400 mg over-encapsulated tablet) PO q24h for 7 days; subjects will also receive two nafithromycin placebo tablets PO q24h on Days 1 through Day 7, to maintain the blind

Baseline assessments for study eligibility will occur within 24 h prior to randomization using IXRS, stratified by region (US vs. ex-US) and PORT Risk Class (II vs. III/IV), will be used to assign subjects (1:1:1) to Arm A, Arm B or Arm C. Study Day 1 is defined as the day that the study drug is first administered, and subsequent study days are defined by the number of consecutive calendar days thereafter.

Subjects may be treated in the study as inpatients or outpatients based on their clinical condition, at the discretion of the Investigator; however, only oral study drug will be administered (i.e., parental moxifloxacin will not be administered). Subjects will be assessed daily by the Investigator between Day 1 and Day 5, whether being treated for CABP in the inpatient or outpatient setting. Investigators will assess for clinical outcome on EOT (Day 7) and TOC (Day 15 ± 3 days). Vital signs, physical exam, assessment of CABP symptom severity, and other study procedures are detailed in [Table 3-1](#). A FU visit will be conducted on Day 31 ±3 days from the start of treatment. The FU visit may be conducted via telephone contact or by another interactive technology for subjects who were considered to be clinical successes and had no AEs or clinically significant laboratory or ECG abnormalities noted at or after the TOC visit; otherwise, the visit must be conducted in person.

8.2 RANDOMIZATION

Block randomization using an IXRS, stratified by region (US vs. ex-US) and PORT Risk Class (II vs. III/IV), will be used to assign subjects (1:1:1) to Arm A, Arm B or Arm C.

After informed consent has been obtained and study eligibility established, a study pharmacist or designee will obtain the study drug assignment from the IXRS. Subjects are considered randomized when the pharmacist or designee receives the IXRS-generated treatment assignment.

8.3 NUMBER OF SUBJECTS

Approximately 225 adult subjects (75 subjects per arm) diagnosed with CABP will be enrolled in this study.

Enrolment of PORT Risk Class II (PORT score 51 to 70; [Appendix II](#)) will be capped at 50% and enrolment of subjects with allowed prior systemic antibiotic use ([Appendix I](#)) will be capped initially at 25% (subject to change during study conduct).

8.4 EXPECTED DURATION OF SUBJECT PARTICIPATION

Each subject will remain in the study for approximately one month. This will include a Screening visit (within 24 h of randomization), a 7-day oral treatment period, and post treatment assessments at TOC (Day 12 to Day 18) and FU (Day 28 to Day 34).

9.0 SELECTION, DISCONTINUATION, AND WITHDRAWAL OF SUBJECTS

9.1 STUDY POPULATION

Adult subjects (≥ 18 years) with CABP will be enrolled in this study. Based on recent Phase III CABP study experience, subjects of at least 65 years of age will constitute approximately 48% of randomized subjects ([File, 2010a](#)).

9.2 INCLUSION CRITERIA

Subjects are required to meet all of the following inclusion criteria:

1. Male or female ≥ 18 years of age
2. Willing to participate in the study and provide written informed consent before any protocol specific assessment is performed
3. Meet the following clinical criteria for CABP:
 - a. Have at least TWO of the following symptoms (new or worsening):
 - Dyspnea (shortness of breath)
 - Cough
 - Production of purulent sputum
 - Pleuritic chest pain
 - b. Have at least TWO of the following vital sign abnormalities:
 - Fever or hypothermia documented by the Investigator (oral, rectal, or tympanic temperature $> 38.0^{\circ}\text{C}$ [100.4°F] or $< 36.0^{\circ}\text{C}$ [95.5°F])
 - Hypotension, defined as systolic blood pressure < 90 mm Hg
 - Tachycardia, defined as heart rate > 90 beats per minute
 - Tachypnea, defined as respiratory rate > 20 breaths per minute
 - c. Have at least ONE of the following laboratory abnormalities:
 - Hypoxemia defined as arterial oxygen saturation $< 90\%$ by pulse oximetry or $\text{PaO}_2 < 60$ mm Hg by ABG
 - Auscultatory findings on pulmonary examination consistent with bacterial pneumonia or pulmonary consolidation (e.g., rales, dullness on percussion, bronchial breath sounds, or egophony)
 - Elevated total WBC count ($> 10,000$ cells/ mm^3) or leucopenia (WBC $< 4,000$ cells/ mm^3)
 - Elevated immature neutrophils ($> 15\%$ band forms), regardless of total peripheral WBC count
 - d. Radiographic evidence of CABP:

- Radiographically-confirmed pneumonia, i.e., new or progressive pulmonary infiltrate(s) on CXR or CT scan consistent with acute bacterial pneumonia within 48 h prior to randomization
- e. PORT score of 51 to 105 (PORT Risk Class of II, III or IV) ([Appendix II](#))
4. All females must have a negative urine or serum pregnancy test (β -HCG) at Screening AND agree to the use of one of the following acceptable methods of contraception from Screening through TOC: surgical sterilization (defined as bilateral oophorectomy or bilateral salpingectomy, but excluding bilateral tubal occlusion), post-menopausal (defined by amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments), barrier contraception (e.g., condom, intrauterine device), levonorgestrel intrauterine system (e.g., Mirena[®]), regular medroxyprogesterone injections (e.g., Depo-Provera[®]), sexual intercourse with only vasectomised partners, or abstinence. Note that oral contraceptives should not be used as the sole method of birth control because the effect of nafithromycin on the efficacy of oral contraceptives has not yet been established; subjects who take oral contraceptives must also use one of the acceptable forms of birth control (listed above) from Screening through TOC. Males must agree to use an acceptable barrier method of birth control (i.e., condom) with female partner(s) and must not donate sperm from Screening through TOC.
 5. Ability to ingest oral study drug (e.g., able to swallow large capsules intact, and no significant nausea, vomiting, diarrhea, or any other condition that might impair ingestion or absorption of oral study drug)

9.3 EXCLUSION CRITERIA

1. Subjects with any of the following confirmed or suspected types of pneumonia:
 - Aspiration pneumonia
 - HABP, defined as pneumonia with onset of clinical signs and symptoms after at least 48 h hospitalization in an acute in-subject health care facility.
 - HCAP, defined as pneumonia acquired in a long-term care or subacute healthcare facility (e.g., nursing home) or pneumonia with onset after recent hospital discharge (within 90 days of current admission and previously hospitalized for \geq 48 h)
 - VABP, defined as pneumonia with onset of clinical signs and symptoms after at least 48 h endotracheal intubation
 - Pneumonia that may be caused by pathogen(s) resistant to either study drug (nafithromycin or moxifloxacin), including viral, mycobacterial, or fungal pneumonia (e.g., *Pneumocystis jiroveci* pneumonia, active pulmonary tuberculosis)
 - Post-obstructive pneumonia
 - Pneumonia associated with cystic fibrosis

2. Suspected or confirmed pleural empyema (a parapneumonic pleural effusion is not an exclusion criterion) or lung abscess
3. Suspected or confirmed non-infectious causes of pulmonary infiltrates (e.g., pulmonary embolism, hypersensitivity pneumonia, congestive heart failure)
4. Receipt of 1 or more dose(s) of a potentially-effective systemic antibacterial treatment for treatment of the current CABP within 72 h prior to randomization with the exception of:
 - Receipt of a single dose of a short-acting antibacterial agent within 72 h of randomization ([Appendix I](#)), OR
 - Failure (worsening of symptoms) of at least 48 h of treatment for the current episode of CABP with an antibacterial agent other than a ketolide or fluoroquinolone
5. Subjects requiring concomitant adjunctive or additional potentially effective systemic antibacterial treatment for management of CABP
6. Evidence of significant immunologic disease determined by any of the following:
 - Current or anticipated neutropenia defined as < 500 neutrophils/mm³
 - Known infection with HIV (prior to Screening) and a CD4 count that is unknown or documented to be < 200 cells/mm³ within the last year, or an AIDS-defining illness; note that neither HIV nor CD4 testing is required at Screening
 - History of heart, lung, or kidney transplant
 - The receipt of cancer chemotherapy, radiotherapy, or potent, non-corticosteroid immunosuppressant drugs (e.g., cyclosporine, azathioprine, tacrolimus, immune-modulating monoclonal antibody therapy) within the past 3 months, or the receipt of corticosteroids equivalent to or greater than 40 mg of prednisone per day for more than 14 days in the 30 days prior to randomization
7. Known or suspected primary or metastatic neoplastic lung disease, bronchiectasis, bronchial obstruction, chronic neurological disorder preventing clearance of pulmonary secretions, or severe COPD (severe COPD is defined as known [prior to Screening] FEV₁/FVC < 0.70 and FEV₁ $< 50\%$ normal); note that pulmonary function tests are not required at Screening
8. Compromised hepatic or renal function, including but not limited to: clinical evidence of end-stage liver disease (e.g., ascites, hepatic encephalopathy), screening serum total bilirubin > 2 times ULN (unless associated with an elevated indirect bilirubin typical of Gilbert syndrome), AST or ALT > 3 times ULN, serum creatinine > 2.0 mg/dl and/or BUN > 30 mg/dl. Other clinically-significant abnormal laboratory findings should be discussed with the Medical Monitor prior to the subject's entry.
9. History of *Clostridium difficile*-associated disease within 6 months prior to enrolment

10. History of hypersensitivity, known contraindication (e.g. lactose intolerance, lactase deficiency and glucose-galactose malabsorption etc.) or allergic reaction (e.g., anaphylaxis, urticaria, other significant reaction) to any ketolide, any fluoroquinolone antibiotic medicinal products or any of their excipients.
11. Current second- or third- degree atrioventricular block or sick sinus syndrome, uncontrolled atrial fibrillation, severe or unstable angina, congestive heart failure, myocardial infarction within 3 months of the Screening visit, clinically significant ECG abnormalities including QTcF > 450 msec (males) or > 470 msec (females), or requirement for medications known to cause QT prolongation
12. Prior (within 14 days prior to randomization) or concomitant use of cytochrome P450 liver enzyme inducers (e.g., phenobarbital, carbamazepine, griseofulvin, sulfonyleureas, phenytoin, or rifampin)
13. History of tendon rupture
14. Current peripheral neuropathy or myasthenia gravis
15. Known or suspected seizure disorder or other CNS disorders that may predispose the subject to seizures or lower the seizure threshold
16. Nursing mother or pregnant female
17. Subjects who received any experimental drug within 30 days prior to enrolment
18. Require admission to in intensive care unit for any reason, life expectancy of less than 2 months, or any concomitant condition that, in the opinion of the Investigator, is likely to interfere with evaluation of the response of the infection under study, determination of AEs, or completion of the expected course of treatment

9.4 CRITERIA FOR PREMATURE DISCONTINUATION OF STUDY DRUG OR SUBJECT WITHDRAWAL FROM STUDY

Subjects should be encouraged to complete all study assessments. However, subjects may discontinue study drug or withdraw consent to participate in this study at any time without penalty or loss of benefits to which the subject is otherwise entitled.

9.4.1 Premature Discontinuation from Study Drug Administration

9.4.1.1 Discontinuations Due to Safety

Possible reasons for premature discontinuation from study drug administration due to safety include, but are not limited to, the following:

- Occurrence of an AE that, in the opinion of the Investigator, warrants the subject's permanent discontinuation from study drug administration.
- Meets Hy's law criteria, defined by at least 3-fold elevations of ALT or AST above the ULN, elevation of serum total bilirubin to > 2 times ULN without elevated serum alkaline phosphatase, and no other disease or condition can be found to explain the liver test abnormalities

- Known pregnancy or breastfeeding during the study drug administration period. Female subjects whose pregnancy test is positive post-baseline must be followed through the immediate postnatal period or until termination of the pregnancy. Study center personnel must report every pregnancy as soon as possible (within 24 h of learning of the pregnancy, as described in [Section 14.1.6](#)).

Assessments and Procedures: Subjects who are prematurely discontinued from study drug administration (i.e., before the anticipated full course of study drug required for effective treatment of the CABP) for safety reasons should continue to undergo study assessments at every study visit ([Section 11.0](#)). If a subject is discontinued from study drug on Day 3 or Day 4, an attempt should be made to collect any remaining PK blood samples scheduled for that day.

Clinical Outcome Assessment: Subjects prematurely discontinued from any study drug for safety reasons and for whom further antibacterial therapy is not required for treatment of the primary infection (i.e., the CABP has resolved completely or improved to the point where no further antibacterial therapy is necessary), may be assessed as a clinical cure at the EOT and TOC visits.

Subjects prematurely discontinued from any study drug for safety reasons and who require further antibacterial therapy for the CABP should be assessed as a clinical failure on the day of discontinuation and automatically assigned an outcome of clinical failure at the next outcome evaluation time point.

9.4.1.2 *Discontinuations Due to Insufficient Therapeutic Effect*

Possible reasons for discontinuation from study drug due to insufficient therapeutic effect include, but are not limited to, the following:

- Clinical worsening: Subjects who show systemic or local signs of clinical worsening may be prematurely discontinued from study drug administration at any time. If the Investigator deems the benefit-to-risk ratio of study drug continuance acceptable, study drug administration of at least 48 h is encouraged before discontinuation from study drug therapy.
- Lack of clinical progress: For subjects who are stable, yet do not show signs of improvement, the Investigator is encouraged to continue study drug therapy for at least 48 h before such subjects are considered clinical failures and prematurely discontinued from study drug therapy.

Assessments and Procedures: Subjects who are prematurely discontinued from study drug due to insufficient therapeutic effect should have EOT assessments conducted ([Section 11.8](#)) on the day of discontinuation and undergo safety assessments at TOC ([Section 11.9](#)). Prematurely discontinued subjects should also be encouraged to attend the FU visit. If a subject is discontinued from study drug on Day 3 or Day 4, an attempt should be made to collect any remaining PK blood samples scheduled for that day. If a subject is discontinued from study drug administration due to insufficient therapeutic effect and is switched to an alternative antibiotic, that therapy should be documented.

Clinical Outcome Assessment: Subjects who are prematurely discontinued from study drug administration due to insufficient therapeutic effect should be assessed as clinical failure on the day of discontinuation. Subjects prematurely discontinued from study drug administration due to insufficient therapeutic effect will be automatically assigned an outcome of clinical failure at the next outcome evaluation time point.

9.4.2 Withdrawal from Study

Reasons: Possible reasons for withdrawal from study include, but are not limited to, the following:

- Withdrawal of consent
- Significant subject noncompliance, defined as refusal or inability to adhere to the prescribed dosing and follow-up regimen
- Investigator determines that it is in the best interest of the subject to withdraw from the study protocol, due to reasons other than an AE

Assessments and Procedures: Subjects may withdraw from the study or be withdrawn at the request of the Investigator or Sponsor at any time. Subjects who wish to withdraw completely from this clinical study during the treatment period should be encouraged to undergo safety assessments at the time of withdrawal. Additionally, if a subject is withdrawn on Day 3 or Day 4, an attempt should be made to collect any remaining PK blood samples scheduled for that day. Subjects withdrawn from the study need not undergo TOC or FU assessments.

Clinical Outcome Assessment: Subjects who withdraw from the study and are not assessed as clinical failures should be assessed as indeterminate for all remaining scheduled clinical assessments.

9.5 REPLACEMENT OF SUBJECTS

Randomized subjects who are withdrawn from the study will not be replaced.

9.6 STUDY TERMINATION BY SPONSOR AND TERMINATION CRITERIA

The Sponsor reserves the right to terminate an investigational site or this clinical study at any time. Reasons for termination may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies of nafithromycin or moxifloxacin indicate a potential health hazard to subjects
- Serious or persistent noncompliance by the Investigators with the protocol, clinical research agreement, Form FDA 1572, or applicable regulatory guidelines in conducting the study
- Relevant ethics committee(s) or regulatory agency(ies) decision to terminate or suspend approval for the Investigator or clinical conduct at site

- Investigator request to withdraw from participation
- Subject enrolment is unsatisfactory

9.7 GUIDANCE TO INVESTIGATORS ON WHEN TO END STUDY DRUG THERAPY

The duration of study drug in this study is a fixed 7-day course in all three Treatment Arms; therefore, subjects who are improving clinically will receive no less or no more than 7 days of the study treatment regimen. At Day 7 (EOT), an assessment of clinical outcome will be performed by the Investigator. A subject will be determined as a clinical cure at EOT if the subject is alive and the infection is sufficiently resolved such that further antibacterial therapy is not needed ([Section 13.2.2](#)). Note that subjects with CABP may have some residual findings related to infection (i.e., cough) requiring non-antibiotic ancillary treatment (e.g., expectorant) at EOT and still meet criteria for clinical cure.

If additional antibacterial therapy is required for the index CABP (e.g., progressively worsening CABP between Day 1 and Day 7, or gradually improving CABP that requires additional antibacterial therapy beyond 7 days), study drug should be discontinued, the subject will be deemed a clinical failure on the day of study drug discontinuation, and open-label antibacterial therapy will be started at the discretion of the Investigator. Administration of blinded study drug will not be allowed beyond Day 7. In cases of premature discontinuation of study drug, subjects should not be discontinued from the study itself; subjects should remain in the study and undergo all scheduled assessments at EOT, TOC and FU ([Section 11.0](#)).

The Investigator may use culture and susceptibility results from the local microbiology laboratory to help guide therapy; however, decisions to continue or discontinue study drug should be based on clinical response rather than susceptibility results (as nafithromycin susceptibility testing is not available at the local site). If the index CABP is caused by a microorganism that is not susceptible to fluoroquinolones, macrolides, or ketolides in vitro, the decision to continue or discontinue study treatment should be based on the subject's clinical course and the Investigator's clinical judgment. These cases should be discussed with the Medical Monitor prior to prematurely discontinuing study drug, and the rationale for this decision should be recorded in the source documents.

10.0 TREATMENT OF SUBJECTS

Subjects will be randomized 1:1:1 to receive either oral nafithromycin tablets or oral moxifloxacin capsules (over-encapsulated tablets). The duration of therapy is 7 days (3 or 5 days of active oral nafithromycin followed by placebo to complete 7 days of therapy [Arms A and B, respectively] or 7 days of active oral moxifloxacin [Arm C]). Relevant matching placebo formulations (tablets and capsules) are used to maintain the blind.

10.1 STUDY DRUG

10.1.1 Oral Nafithromycin & Matching Placebo

Each subject randomized to receive nafithromycin (Arm A or Arm B) will receive oral nafithromycin administered as two 400 mg tablets — for a total of 800 mg — once daily.

Nafithromycin is a novel IV and oral antibacterial agent of ketolide class (molecular weight 859 Daltons), which is structurally related to macrolide class. The chemical nomenclature is: (11S, 21R)-3-Decladinosyl-11, 12-dideoxy-6-O-methyl-3-oxo-12, 11-{oxycarbonyl-[E-N-[1-(5-pyridin-2-yl)-1,3,4-thiadiazol-2-yl)-(S)-ethoxy]-carboxamidino]methylene}-erythromycin-A.

The nafithromycin and matching placebo tablets have been manufactured under GMP conditions and have undergone stability studies in compliance with regulatory norms. Oral nafithromycin 400 mg tablets and corresponding clinical placebo tablets are of white color, oval shaped, biconvex film coated, scored on both sides and debossed with W and 755 on either side of the score on one side (IB).

Storage and dispensing of nafithromycin tablets can be undertaken at room temperature (below 25°C) in its packaging (while protected from moisture). Detailed instructions regarding storage are presented in the Investigational Medicinal Product Dossier (IMPD).

The blinded products will be packaged in subject-specific blister wallets. Tablets are to be swallowed with water in an upright position.

10.1.2 Oral Moxifloxacin & Matching Placebo

Each subject randomized to receive moxifloxacin (Arm C) will receive oral moxifloxacin administered as a single 400 mg capsule (i.e., over-encapsulated tablet) once daily.

All other subjects, randomized to receive nafithromycin (Arms A and B), will receive moxifloxacin matching placebo.

The blinded products will be packaged in subject-specific blister wallets. Capsules are to be swallowed with water in an upright position.

Consult the summary of products characteristics or prescribing information ([Appendix V](#)) or other local dosing guidelines regarding preparation, storage, administration, maximum doses, contraindications, warnings, precautions, and AEs reported with the use of moxifloxacin.

10.2 TREATMENT COMPLIANCE

Treatment compliance will be documented in the eCRF by recording the date, time, and whether or not each oral dose of study drug was administered.

10.3 PRIOR AND CONCOMITANT MEDICATIONS

All prior systemic or inhaled antimicrobial agents (administered within 14 days prior to randomization) and all systemic or inhaled concomitant antimicrobial agents (administered during the study) will be documented.

A subject who received more than a single dose of any potentially-effective, short-acting, systemic antibacterial therapy for the current episode of CABP within 72 h before randomization will be excluded from the study ([Section 9.3](#)), unless there is unequivocal clinical evidence of treatment failure of the current episode of CABP (e.g., worsening signs and symptoms) after administration of an antibacterial agent other than a ketolide or fluoroquinolone.

Concomitant use of potentially effective systemic antibacterials or potentially effective inhaled antibacterials is not permitted.

Nafithromycin is a weak inhibitor of human cytochrome P450 (CYP) isoforms such as CYP3A4; specifically, nafithromycin is a 2-5x and 14-60x less potent inhibitor of CYP3A4 than telithromycin and solithromycin, respectively (details in IB). Nafithromycin is not an inhibitor of CYP2D6. In addition, nafithromycin does not induce enzyme activity or mRNA levels of CYP1A2, CYP2B6, or CYP3A4. Concomitant medications that induce P450 enzymes are contraindicated in this study. Specifically, prior (within 14 days prior to randomization) or concomitant use of cytochrome P450 liver enzyme inducers (e.g., phenobarbital, carbamazepine, griseofulvin, sulfonylureas, phenytoin, or rifampin) are excluded.

All other concomitant medications and nutrients necessary for the health and well-being of the subject are permitted.

10.4 ACCOUNTABILITY PROCEDURES

It is the responsibility of the Investigator or designee to ensure that current records of study drug inventory and accountability are maintained. Records must be readily available for inspection by the Sponsor or Sponsor's Representative and are open to inspection at any time by applicable regulatory authorities.

Upon receipt of study therapy drugs, the Investigator or designee must acknowledge receipt, visually inspect the shipment, verify the number of tablets or capsules shipped are received, and document the condition of the drugs received.

10.5 STUDY DRUG HANDLING AND DISPOSAL

All study drugs provided by the Sponsor should be retained at the investigational site until otherwise instructed in writing by the Sponsor. Upon completion of the study or termination of the investigational site, all unused and partially used study drugs supplied by the Sponsor will be either disposed of at the site level or shipped to a site designated by the Sponsor as per local regulatory requirement. For additional information, please refer to current version of the Pharmacy manual.

10.6 BLINDING AND UNBLINDING PROCEDURES

This study will be double-blinded with regard to study drug treatment. After written informed consent has been obtained and eligibility established, the study center's pharmacist/designee will obtain the randomization code using IXRS. The IXRS system will also confirm the study drug assignment including the unique identification number(s) of the kits to be prepared for the subject's oral therapy. The pharmacist/designee will be responsible for maintaining accountability and dispensing the oral study drug according to the handling instructions. Study center personnel will remain blinded to the identity of study drug until the database has been locked and the study has been unblinded. In the case of a medical emergency requiring the Investigator to know the identity of the oral study drug, the Investigator will follow the procedures outlined below.

Individual treatment codes, indicating the treatment for each randomized subject, will be available to the Investigators or pharmacists from IXRS. Interactive voice/web response system procedures will be described in the IXRS user manual that will be provided to each center. To maintain investigator blinding, the treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomization. In such a case, the subject should receive all appropriate medical care. Prior to any unblinding, the Investigator should contact the Sponsor Medical Monitor to discuss options. The unblinding procedure will be done through the IXRS system. As soon as possible and without revealing the subject's study drug assignment (unless important to the safety of subjects remaining in the study), the Investigator must notify the Sponsor if the blind is broken for any reason and the Investigator was unable to contact the Sponsor prior to unblinding. The Investigator will record in the source documentation the date and reason for revealing the blinded treatment assignment for that subject; the treatment assignment itself should not be entered into source documentation. The Sponsor may break the code for SAEs that are unexpected and are believed to be causally related to study drug and that potentially require expedited reporting to regulatory authorities. In such cases, the minimum number of Sponsor personnel will be unblinded. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented and databases have been locked.

11.0 STUDY PROCEDURES

The Schedule of Assessments and Procedures is located in [Table 3-1](#).

11.1 SCREENING VISIT

Screening visit procedures must be completed within 24 h prior to randomization, in order to determine study eligibility. Potential subjects who do not meet entrance criteria may, as appropriate, be rescreened and undergo repeat the baseline assessments within 72 h of initial screening for possible enrolment into the study.

Local or regional laboratory results will be used to determine subject eligibility for study enrolment. Any protocol-required eligibility laboratory or radiological evaluations already performed as part of the subject's regular medical care or site's standards of care within 24 h (laboratory) and 48 h (radiology) before randomization do not have to be repeated to determine subject eligibility. In addition, laboratory assessments ([Table 3-1](#)) must be sent to the central laboratory as part of baseline safety assessments. *If local or regional laboratory results are not confirmed by central laboratory results, the subject should not be automatically withdrawn from the study or study drug.* The subject should be assessed for safety and the Medical Monitor must be contacted to confirm subject eligibility to remain on study.

Written and signed informed consent must be obtained before any protocol assessment is performed.

Clinical Assessments:

- Verify inclusion and exclusion criteria
- Obtain a complete medical and surgical history, including all active conditions and all conditions diagnosed within the previous 5 years
- Record all prior medications that have been administered within 14 days prior to the date of signing the informed consent
- Record height and weight, and estimate creatinine clearance (CrCl) using the following Cockcroft-Gault formula (use actual body weight):

For serum creatinine in mg/dL:

$$\text{Males: CrCl} = \frac{(140 - \text{age in years}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

$$\text{Females: CrCl} = \frac{(140 - \text{age in years}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

If the serum creatinine value reported is in Système International d'Unités (SI) units (i.e., $\mu\text{mol/L}$), convert to conventional units (mg/dL) using the following formula:

$$\text{Conventional units (mg/dL)} = \frac{\text{SI units } (\mu\text{mol/L})}{88.4}$$

- Record vital signs of body temperature (oral, rectal, or tympanic), blood pressure, heart rate, respiratory rate, and pulse oximetry; the highest daily temperature should be recorded, and attempts should be made to measure temperatures using the same methodology throughout the study
- Perform a complete physical examination, including general appearance, skin, eyes, ears, nose, throat, lungs, heart, abdomen, back, extremities, lymph nodes, vascular, and neurological exams
- Assess CABP symptom severity ([Appendix III](#))
- Obtain a 12-lead ECG
- Identify, assess and record any AEs (since the time of informed consent)

Radiographic Evaluation

- Obtain a CXR or chest CT scan for all subjects at Screening. If a CXR is performed, anteroposterior and lateral views are preferred, and confirmation of new or progressive pulmonary infiltrates consistent with CABP may occur with either (or both) CXR view; however, posteroanterior (i.e., portable) views are also acceptable. Chest radiography may be obtained as part of routine, non-study evaluation of a subject presenting with signs and symptoms of CABP and therefore may be performed in some circumstances before informed consent is obtained for participation in this study; radiological evaluations already performed as part of the subject's regular medical care or site's standards of care within 48 h before randomization do not have to be repeated to determine subject eligibility. Radiologic evaluation(s) will be performed locally and interpreted by appropriately qualified personnel who are certified or licensed to interpret chest radiographs according to applicable regional requirements, and the evaluations will be reviewed by the Investigator or qualified personnel during the Screening Visit; the conclusions of the Investigator's review will be the basis for subject inclusion. The written radiography report (i.e., formal interpretation of the radiographic image or film) should be included in the source documents; however, the radiography images or films are not needed in the source documents.

Local or Regional Laboratory Assessments for Study Eligibility:

- Obtain serum transaminase (ALT, AST) and total bilirubin levels, coagulation profile, serum creatinine and blood urea nitrogen (or urea), peripheral WBC count, absolute neutrophil count, and immature neutrophil percentage to determine eligibility. ABG is recommended, but not required, to measure blood pH and partial pressure of oxygen (PaO₂) for the PORT score calculation.
- Obtain serum or urine sample for pregnancy test (β-HCG) in all females and ensure that the test is negative before randomization.
- Obtain a urine dipstick test; a standard urine dipstick includes detection of specific gravity, pH, leukocytes, blood (hemoglobin), nitrite, ketones, bilirubin, urobilinogen, protein, and glucose. If any results is abnormal (e.g., not negative) and deemed clinically significant by the Investigator, a urinalysis will be sent to the central lab.

PORT Score

- Calculate the PORT score using local laboratory and radiographic results ([Appendix II](#)). As part of the Inclusion Criteria to this study, subjects must have a PORT score between 51 and 105 (PORT Risk Class of II, III, or IV) at randomization. For subjects without an optional ABG at Screening, no points will be added for pH or PaO₂; however, oxygen saturation results can be used in place of PaO₂ ([Appendix II](#)).

Central Laboratory Assessments:

- Obtain complete blood count (CBC), chemistry panel, urinalysis (only if local urine dipstick results are abnormal and deemed clinically significant by the Investigator), and serum β-HCG test ([Appendix IV](#))
- Collect blood to test serology for *Legionella pneumophila*, *Mycoplasma pneumoniae* and *Chlamydomphila pneumoniae* by the central laboratory

Local or Regional Microbiological Assessments:

- Attempt to collect an adequate quality expectorated or induced sputum or other respiratory specimen reflecting fluid from the lower respiratory tract from every subject (e.g., respiratory fluid obtained by bronchoalveolar lavage or bronchoscopy; pleural fluid obtained by thoracentesis; or expectorated or induced sputum meeting adequacy criteria) and submit the specimen to the local microbiology laboratory for Gram stain and culture (see Section 12.0 for additional details). A Gram stain slide and an unstained slide should be submitted to the central laboratory for the confirmation of white cell and epithelial cell counts. Attempts should be made to collect quality respiratory specimens prior to the first dose of study drug. Respiratory specimens might be obtained as part of routine, non-study evaluation of a subject being evaluated for CABP and therefore could be obtained prior to obtaining informed consent. An adequate quality sputum specimen will be defined as having the following 2 findings as reported by the local laboratory:
 - < 10 squamous epithelial cells/low power field (LPF) (i.e., 100×)
 - > 25 PMNs/LPF

Processing: Sputum and tracheal samples will be rejected if they contain ≥ 10 squamous epithelial cells/LPF and should NOT be processed. All sputum and tracheal samples with < 10 SECs will be processed, irrespective of the PMN count.

Resubmission: sputum /tracheal aspirate samples should be resubmitted (if possible):

- If both criteria i.e., < 10 squamous epithelial cells/LPF and > 25 PMNs/LPF are not met
 - If specimen meets the first criterion, i.e., < 10 squamous epithelial cells/LPF, but not the second i.e., > 25 PMNs/LPF
- Obtain blood (1 aerobic bottle and 1 anaerobic bottle from 2 separate venipuncture sites, for a total of 4 bottles)
 - Collect a urine specimen to test for the presence of *Legionella pneumophila* and *Streptococcus pneumoniae* antigens. Testing will be performed at the local laboratory using kits supplied by the Sponsor.

Randomize the subject using IXRS after verifying that the subject meets all study inclusion criteria ([Section 9.2](#)) and no exclusion criteria ([Section 9.3](#)).

11.2 STUDY DAY 1

Day 1 is the first calendar day of study drug administration. Subsequent study days are consecutive calendar days. If feasible, Screening and randomization procedures (Screening Visit and Day 1) can be performed on the same day. Standard of care laboratory and radiological data from within 24 h (laboratory) and 48 h (radiology) prior to randomization can be used as Screening Visit procedures. If the Screening Visit and Day 1 occur on different calendar days or on the same day, verify all Inclusion Criteria and Exclusion Criteria prior to randomization. All Day 1 procedures described below and in [Table 3-1](#) are to be conducted after the first administration but before the second administration of study drug.

Administer study drug per the schedule in [Section 10.1](#).

Clinical Assessments:

- Record one set of vital signs, including body temperature (highest daily oral, rectal, or tympanic temperature), blood pressure, heart rate, respiratory rate, and pulse oximetry
- Perform a complete physical examination
- Assess CABP symptom severity ([Appendix III](#))
- Obtain a 12-lead ECG
- Identify, assess and record any AEs
- Record any concomitant medications

11.3 STUDY DAY 2

Administer study drug per the schedule in [Section 10.1](#).

Clinical Assessments:

- Record one set of vital signs, including body temperature (highest daily oral, rectal, or tympanic temperature), blood pressure, heart rate, respiratory rate, and pulse oximetry
- Perform a complete physical examination
- Assess CABP symptom severity ([Appendix III](#))
- Identify, assess and record any AEs
- Record any concomitant medications

Microbiological Assessments:

- If prior blood cultures are positive, repeated post-baseline blood cultures should be collected on the day that the positive blood culture is detected
- Repeated respiratory specimens should be obtained only if clinically indicated

11.4 STUDY DAY 3

Administer study drug per the schedule in [Section 10.1](#).

Clinical Assessments:

- Record one set of vital signs, including body temperature (highest daily oral, rectal, or tympanic temperature), blood pressure, heart rate, respiratory rate, and pulse oximetry
- Perform a complete physical examination
- Assess CABP symptom severity ([Appendix III](#))
- Obtain a 12-lead ECG
- Identify, assess and record any AEs
- Record any concomitant medications

Microbiological Assessments:

- If prior blood cultures are positive, repeated post-baseline blood cultures should be collected on the day that the positive blood culture is detected
- Repeated respiratory specimens should be obtained only if clinically indicated

PK Assessments:

- Blood samples for PK analyses will be taken from all subjects at sites where PK sampling is possible on Day 3 at the following times:
 - Within 10 minutes before study drug administration
 - 2-4 h after study drug administration
 - subjects who have been hospitalized are also required to have a post-dose PK sample at 6-10 h (Day 3)

11.5 STUDY DAY 4

Administer study drug per the schedule in [Section 10.1](#).

Clinical Assessments:

- Record one set of vital signs, including body temperature (highest daily oral, rectal, or tympanic temperature), blood pressure, heart rate, respiratory rate, and pulse oximetry
- Perform a complete physical examination
- Assess CABP symptom severity ([Appendix III](#)). CABP symptom severity information entered into the eCRF will be used to programmatically determine clinical response at Day 4 ([Section 13.2.1](#)); note this is not an Investigator-determined clinical outcome.
- Identify, assess and record any AEs
- Record any concomitant medications

Microbiological Assessments:

- If prior blood cultures are positive, repeated post-baseline blood cultures should be collected on the day that the positive blood culture is detected
- Repeated respiratory specimens should be obtained only if clinically indicated

PK Assessments:

- A single blood sample for PK analyses will be taken from all subjects at sites where PK sampling is possible on Day 4 at 24-28 h following study drug administration on Day 3

11.6 STUDY DAY 5

Administer study drug per the schedule in [Section 10.1](#).

Clinical Assessments:

- Record one set of vital signs, including body temperature (highest daily oral, rectal, or tympanic temperature), blood pressure, heart rate, respiratory rate, and pulse oximetry
- Perform a complete physical examination
- Assess CABP symptom severity ([Appendix III](#))
- Obtain a 12-lead ECG
- Identify, assess and record any AEs
- Record any concomitant medications

Central Laboratory Assessments:

- Obtain hematology, coagulation and chemistry panel ([Appendix IV](#))

Microbiological Assessments:

- If prior blood cultures are positive, repeated post-baseline blood cultures should be collected on the day that the positive blood culture is detected
- Repeated respiratory specimens should be obtained only if clinically indicated

11.7 STUDY DAY 6

Administer study drug per the schedule in [Section 10.1](#).

Clinical Assessments:

- Identify, assess and record any AEs
- Record any concomitant medications

Microbiological Assessments:

- If prior blood cultures are positive, repeated post-baseline blood cultures should be collected on the day that the positive blood culture is detected
- Repeated respiratory specimens should be obtained only if clinically indicated

11.8 STUDY DAY 7 (END-OF-THERAPY [EOT])

Perform EOT assessments at any time during Day 7 after the final dose of study drug, or within 2 days following Day 7. Additional guidance on when to end study drug therapy is provided in [Section 9.7](#).

Administer study drug per the schedule in [Section 10.1](#).

Clinical Assessments:

- Record one set of vital signs, including body temperature (highest daily oral, rectal, or tympanic temperature), blood pressure, heart rate, respiratory rate, and pulse oximetry
- Perform a complete physical examination
- Assess CABP symptom severity ([Appendix III](#))
- Obtain a 12-lead ECG
- Identify, assess and record any AEs

- Record any concomitant medications
- Conduct clinical outcome assessment ([Section 13.2.2](#))

Central Laboratory Assessments:

- Obtain CBC, coagulation and chemistry panel ([Appendix IV](#))

Microbiological Assessments:

- If prior blood cultures are positive, repeated post-baseline blood cultures should be collected on the day that the positive blood culture is detected
- Repeated respiratory specimens should be obtained only if clinically indicated

11.9 TEST-OF-CURE (TOC)

Perform TOC assessments on Day 15 \pm 3 days.

Clinical Assessments:

- Record one set of vital signs, including body temperature (highest daily oral, rectal, or tympanic temperature), blood pressure, heart rate, respiratory rate, and pulse oximetry
- Perform a complete physical examination
- Assess CABP symptom severity ([Appendix III](#))
- Obtain a 12-lead ECG only if prior study ECG(s) showed any clinically-significant abnormality
- Identify, assess and record any AEs
- Record any concomitant medications
- Conduct clinical outcome assessment ([Section 13.2.2](#))

Central Laboratory Assessments:

- Obtain CBC, coagulation, chemistry panel, and serum β -HCG test ([Appendix IV](#))
- Collect blood to test serology for *Legionella pneumophila*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* by the central laboratory

Microbiological Assessments:

- If prior blood cultures are positive, repeated post-baseline blood cultures should be collected on the day that the positive blood culture is detected

- Repeated respiratory specimens should be obtained only if clinically indicated

11.10 FOLLOW-UP (FU)

FU is to be conducted on Day 31 \pm 3 days. The FU assessment may be conducted via telephone contact or by another interactive technology for subjects who were considered to be Clinical Successes and had no AEs or clinically significant laboratory or ECG abnormalities noted at or after the TOC visit; otherwise, the visit must be conducted in person.

Clinical Assessments:

- Assess for clinical relapse or recurrence of CABP, including new hospitalization for any reason within 30 days from initiation of treatment (a secondary endpoint, see [Section 13.2.4](#))
- Obtain a 12-lead ECG only if prior ECG(s) showed any clinically-significant abnormality
- Identify, assess and record any AEs

Central Laboratory Assessments:

- Obtain CBC, coagulation, and/or chemistry panel only if prior study laboratory results showed any clinically-significant abnormality ([Appendix IV](#)); previously-normal (or abnormal but not clinically-significant) laboratory tests do not need to be repeated.

Microbiological Assessments:

- If prior blood cultures are positive, repeated post-baseline blood cultures should be collected on the day that the positive blood culture is detected
- Repeated respiratory specimens should be obtained only if clinically indicated, e.g., if clinical relapse or recurrence of CABP

12.0 MICROBIOLOGICAL ASSESSMENTS

Microbiology specimens will be collected by sites. All microbiological assessments will be initiated at the local or regional laboratory, including Gram stain, organisms identification, local susceptibility testing, and shipment of isolates and Gram stain slides to Central Microbiology Laboratory. Additional details with regard to handling and processing of microbiological specimens at the local laboratory vs. central laboratory are provided in the Microbiology Laboratory Manual.

12.1 SCREENING RESPIRATORY SPECIMENS

An attempt should be made to collect an adequate-quality expectorated or induced sputum or other deep respiratory specimen reflecting fluid from the lower respiratory tract from every subject (e.g., respiratory fluid obtained by bronchoalveolar lavage or bronchoscopy; pleural fluid obtained by thoracentesis; or expectorated or induced sputum meeting adequacy criteria) at Screening. The respiratory specimen should be submitted to the local microbiology laboratory for Gram stain and culture. A Gram stain slide and an unstained slide should be submitted to the central laboratory for the confirmation of white cell and epithelial cell counts. Attempts should be made to collect quality respiratory specimens prior to the first dose of study drug. Respiratory specimens might be obtained as part of routine, non-study evaluation of a subject being evaluated for CABP and therefore could be obtained prior to obtaining informed consent.

An adequate quality sputum specimen will be defined as meeting the following 2 criteria, as reported by the local laboratory:

1. < 10 squamous epithelial cells/ LPF (magnification, x100)
2. > 25 PMNs/LPF

In the event that a sputum specimen is determined to be inadequate, or cannot be obtained prior to the first dose of study drug, repeated collection of a specimen should be attempted as early as possible, not later than 24 h after the first dose of study drug.

If pleural fluid is collected for culture, collect the pleural fluid sample in 1 aerobic blood culture bottle and 1 anaerobic blood culture bottle for a total of 2 bottles (if limited pleural fluid is available, collect the fluid in the aerobic bottle at a minimum). Pleural fluid can be collected in sterile caps for Gram stain and culture. Pleural fluid cultures must be obtained during thoracentesis or initial chest tube placement; cultures are not acceptable if obtained from an indwelling chest tube.

Respiratory specimens should be processed (i.e., Gram's stain and initiation of overnight cultures) within 2 hours of sampling at ambient temperature. Refrigerated samples should be processed within 12 hours. Refer to the Microbiology Laboratory Manual for details.

Culture results are to include identification of organisms to the level of genus and species. Susceptibility testing for nafcithromycin will not be available to the local laboratory. Nafcithromycin minimum inhibitory concentrations (MICs) will be assessed at the central laboratory; however, these MIC results will not be available to the Investigator during real-time management of the subjects, and MICs will not be associated with

formal breakpoints for susceptibility vs. resistance. Therefore, decisions related to subject care (e.g., study drug discontinuation) will be based on the evolution of the clinical signs and symptoms of CABP, rather than specific nafithromycin MIC data (see [Section 9.7](#) for additional guidance). Susceptibility testing for moxifloxacin (or other fluoroquinolones) may be performed locally using local laboratory methods usually employed by the laboratory. Results of this testing can be used by Investigators along with clinical findings to help guide therapy.

With the exception of respiratory “contaminants” listed below, all isolates identified by the local laboratory from expectorated or induced sputum specimens and/or that are isolated from respiratory specimens or blood or pleural fluid and are potential pathogens as defined in the local/regional Microbiology Laboratory Manual, will be submitted to the central laboratory for verification of genus and species and for standardized MIC testing performed for nafithromycin, moxifloxacin, and a panel of currently approved antibiotics. In the event that local laboratory genus and species identification are not consistent with central laboratory results, a back-up isolate should be sent to the central laboratory. All isolates submitted to the central laboratory must also be retained by the local/regional laboratory.

For the purposes of this study, the following respiratory specimen isolates are considered “contaminants” and should not to be sent to the central laboratory:

- Normal respiratory microflora, mixed respiratory microflora, or equivalent (including, but not limited to viridans group streptococci, coagulase-negative staphylococci, *Corynebacterium* spp.)
- Fungal spp. (e.g., *Candida* spp., molds)

Refer to the study-specific Microbiology Laboratory Manual for further detail, including specific procedures pertaining to the collection, processing, storage, and shipment of microbiological samples.

12.2 SCREENING BLOOD CULTURES

At Screening, one aerobic blood culture bottle and one anaerobic blood culture bottle from two separate sites for a total of four bottles must be collected for culture (i.e., 1 aerobic and 1 anaerobic bottle from 2 separate venipuncture sites, for a total of 4 bottles).

Either an automated or a manual system can be used for blood and pleural fluid culture methods according to the preference of the local microbiological laboratory performing the testing. Refer to the Microbiology Laboratory Manual for details.

Culture results are to include identification of pathogens to the level of genus and species. Susceptibility testing for nafithromycin will not be available to the local laboratory; MICs will be assessed at the central laboratory. Therefore, decisions related to subject care (e.g., study drug discontinuation) will be based on the evolution of the clinical signs and symptoms of CABP.

12.3 SCREENING URINARY ANTIGEN TESTS

At the Screening visit, urine will be collected to test for *Legionella pneumophila* and *Streptococcus pneumoniae* antigens. Testing will be performed at the local laboratory using kits supplied by the Sponsor and the results will be recorded on the eCRF.

12.4 SEROLOGY FOR ATYPICAL BACTERIAL TITERS

At the Screening Visit and at TOC, blood samples will be collected to conduct acute and convalescent serology, respectively, for *Legionella pneumophila*, *Mycoplasma pneumoniae* and *Chlamydomphila pneumoniae* by the central laboratory.

12.5 POST-BASELINE MICROBIOLOGICAL ASSESSMENTS

At any time after the Screening Visit, respiratory specimen and blood cultures should be obtained as clinically indicated. As CABP responds to therapy, obtaining repeated specimens for culture or examination may not be clinically appropriate and/or there may be no material for culture.

If study drug is prematurely discontinued due to insufficient effect of study drug (e.g., failure at EOT or TOC, or clinical relapse at any time), an appropriate respiratory specimen and blood should be obtained for culture on the day of discontinuation; if new antibacterial therapy is administered to treat the current CABP after premature discontinuation of study drug, it is preferred that respiratory specimens and blood be collected for culture after stopping the study drug but before new treatment is started.

Blood cultures should be repeated upon knowledge of a positive result from any previous collection until sterilization is confirmed ([Table 3-1](#)).

Repeat, post-baseline urinary antigen tests for *L. pneumophila* or *S. pneumoniae* should not be performed.

12.6 CENTRAL LABORATORY PROCEDURES

With the exception of “contaminants” defined above ([Section 12.1](#)), all cultured bacterial isolates collected at each visit will be forwarded to the designated central laboratory for each study site. Central laboratory services will perform the following procedures:

1. Re-identify all bacterial isolates to the genus and species level
2. Test all bacterial isolates for nafithromycin and moxifloxacin MICs using standardized testing methodologies
3. Test Screening and TOC blood samples for atypical acute and convalescent serology, respectively, for *Legionella pneumophila*, *Mycoplasma pneumoniae* and *Chlamydomphila pneumoniae* ([Section 12.4](#))

Any questions regarding microbiological procedures, interpretation of results, or storage of isolates should be discussed with the Sponsor or designee. Additional detail is available in the Microbiology Laboratory Manual.

13.0 EFFICACY EVALUATION

13.1 PRIMARY AND SECONDARY EFFICACY VARIABLES

Primary efficacy variable:

- Clinical response at Day 4 (ITT population)

Secondary efficacy variables:

- Clinical response at Day 4 (micro-ITT population)
- Clinical outcome at EOT and TOC (ITT and CE populations)
- Improvement in CABP symptoms and normalization of vital signs at Day 4 (ITT population)
- Clinical outcome at TOC (micro-ITT population)
- By-subject and by-pathogen microbiological response at TOC (micro-ITT and ME populations)
- Hospitalization prior to FU (ITT population)

13.2 CLINICAL OUTCOME ASSESSMENTS

13.2.1 Clinical Response at Day 4

The primary efficacy endpoint is clinical response (response, non-response, or indeterminate) at Day 4, tested in the ITT Population. Clinical response (response, non-response, or indeterminate) at Day 4 will also be tested in the micro-ITT Population as a secondary efficacy endpoint. Clinical response is determined programmatically using the Investigator's determination of CABP symptoms entered into the eCRF ([Table 13.2.1-1](#)). The Investigator is not responsible for categorizing subjects as clinical response, non-response, or indeterminate at Day 4. The severity of the subject CABP symptoms of dyspnea (shortness of breath), cough, production of purulent sputum, and pleuritic chest pain will be evaluated on a 4-point scale (absent, mild, moderate, or severe) based upon the CABP Symptom Severity Guidance in [Appendix III](#).

Table 13.2.1.-1. Clinical Outcome Assessment at Day 4.

Outcome	Definition
Clinical Response	Alive and programmatically-determined improvement of at least 1 level (e.g., severe to moderate, moderate to mild, mild to absent) in at least 2 CABP symptoms (dyspnea, cough, production of purulent sputum, and pleuritic chest pain) compared to Screening, without worsening in any other symptom. Severity of symptoms is based on a 4-point scale (absent, mild, moderate, or severe) (Appendix III).
Clinical Non-Response	Meets any of the following criteria: <ul style="list-style-type: none"> • No programmatically-determined improvement of at least 1 level in at least 2 CABP symptoms compared to Screening

Table 13.2.1.-1. Clinical Outcome Assessment at Day 4.

Outcome	Definition
	<ul style="list-style-type: none"> Worsening in any of the 4 CABP symptoms compared to Screening Requires alternative rescue antibacterial therapy for CABP prior to Day 4 Death from any cause prior to Day 4
Indeterminate	Study data are missing for evaluation of efficacy at Day 4 for any reason, including lost to follow-up.

Abbreviations: CABP = community-acquired bacterial pneumonia.

13.2.2 Clinical Outcome at EOT or TOC

An assessment of clinical outcome (cure, failure, or indeterminate) will be made by the Investigator at EOT (conducted on the day of, or within 2 days following, Day 7) or TOC (Day 15 \pm 3 days). Clinical outcome at EOT and TOC will be analyzed as secondary endpoints in the ITT and CE populations, and at TOC in the micro-ITT population.

Clinical success and clinical failure are defined in [Table 13.2.2-1](#). Clinical failure determined at any visit prior to TOC will be carried forward to subsequent assessment visits.

Table 13.2.2-1. Clinical Outcome Assessments at EOT and TOC.

Outcome	Definition
Clinical Cure	Alive and CABP is sufficiently resolved such that further antibacterial therapy is not needed. These subjects may have some residual findings related to infection (i.e., cough) requiring non-antibiotic ancillary treatment (e.g., expectorant). Criteria for clinical failure or indeterminate (below) should not be met.
Clinical Failure	Meets any of the following criteria: <ul style="list-style-type: none"> Requires alternative rescue antibacterial treatment for CABP prior to the assessment (EOT or TOC) related to progression or worsening of CABP symptoms, development of infectious complications of CABP (e.g., empyema, lung abscess), or development of a TEAE that required discontinuation of study therapy Death from any cause prior to the assessment (EOT or TOC)
Indeterminate	Study data are missing for evaluation of efficacy at the assessment visit (EOT or TOC) for any reason, including lost to follow-up

Abbreviations: CABP = community-acquired bacterial pneumonia; EOT = End-of-Therapy; TEAE = treatment-emergent adverse event; TOC = Test-of-Cure.

13.2.3 Improvement in CABP Symptoms and Normalization of Vital signs at Study Day 4

An assessment of improvement in CABP symptoms and normalization in vital signs at Study Day 4 will be made programmatically on Day 4. Improvement in CABP symptoms and normalization in vital signs is defined in [Table 13.2.3-1](#).

Table 13.2.3-1 Improvement in CABP Symptoms and Normalization of Vital signs at Study Day 4.

<i>Outcome</i>	<i>Definition</i>
Improvement in CABP Symptoms and Normalization of Vital signs at Study Day 4	Meets all of the following criteria: <ul style="list-style-type: none"> • Programmatically-determined improvement of at least 1 level in at least 2 CABP symptoms (dyspnea, cough, production of purulent sputum, and pleuritic chest pain) compared to Screening, without worsening in any other symptom (Appendix III) • Normalization of all vital signs: <ul style="list-style-type: none"> ○ Temperature (oral, rectal, or tympanic) between 35.0°C and 38.0°C ○ SBP between 90 and 140 mm Hg, or return to baseline SBP \pm 5 mm Hg ○ Heart rate less than 100 beats per minute ○ Respiratory rate less than 20 breaths per minute ○ Oxygen saturation \geq 90% by pulse oximetry at room air • Ability to maintain oral intake • Normal mental status
No Improvement in CABP Symptoms and Normalization of Vital signs at Study Day 4	Does not meet all criteria for improvement in CABP symptoms and normalization in vital signs as defined above
Indeterminate	Study data are missing for evaluation of efficacy at Day 4 for any reason, including lost to follow-up.

Abbreviations: CABP = community-acquired bacterial pneumonia; SBP = systolic blood pressure.

13.2.4 Hospitalization Prior to the Follow-Up Visit

An assessment of hospitalization (defined as readmission to the hospital if previously hospitalized on or after study drug initiation [Day 1], or initial hospital admission (if not previously hospitalized) for any reason between the initiation of study drug (Day 1) and FU will be made programmatically based on information collected in the eCRF.

For the purposes of this secondary efficacy assessment, “hospital admission” is defined as inpatient admission for at least 24 h in an acute care facility (including inpatient hospital ward or emergency room); in contrast, admission to nursing homes, assisted living facilities, rehabilitation units, or acute care facilities (hospital wards or emergency rooms) for less than 24 h is not considered a formal hospital admission. The assessment of hospitalization within 30 days of study drug initiation is defined in [Table 13.2.4-1](#).

Of note, adverse events that lead to readmission or new admission to the hospital will meet SAE criteria, as defined in [Section 14.1.4](#).

Table 13.2.4-1 Hospitalization Prior to the Follow-Up Visit

<i>Outcome</i>	<i>Definition</i>
Hospitalization Prior to FU	Meets any of the following criteria: <ul style="list-style-type: none"> • Hospital readmission for any reason between Day 1 and FU Visit, if previously hospitalized and discharged • Initial hospital admission for any reason between Day 2 and FU Visit, if not previously hospitalized on Day 1

Table 13.2.4-1 Hospitalization Prior to the Follow-Up Visit

Outcome	Definition
No Hospitalization Prior to FU	Does not meet the criteria for hospitalization within 30 days of study drug initiation as defined above, or till FU whichever is earlier.
Indeterminate	Study data are missing for evaluation of efficacy at FU Visit for any reason, including lost to follow-up.

Abbreviations: FU = Follow-Up

13.3 MICROBIOLOGICAL OUTCOMES

13.3.1 Microbiological Outcomes at TOC

An assessment of by-subject and by-pathogen microbiological response (favorable, unfavorable, or indeterminate) will be made at TOC (Day 15 \pm 3 days) in the micro-ITT and ME populations. Microbiological outcome categories at TOC are defined in [Table 13.3.1-1](#). Favorable microbiological outcomes include eradication or presumed eradication.

The by-subject microbiological outcome at TOC will be determined based on individual outcomes for each baseline pathogen; specifically, for a subject to have a favorable microbiological outcome, the outcome for each baseline pathogen must be favorable (eradicated or presumed eradicated). If the outcome for any pathogen is unfavorable (persistence or presumed persistence), the subject will be considered to have an unfavorable microbiological outcome.

As CABP responds to therapy, obtaining repeated specimens for culture or examination may not be clinically appropriate and/or there may be no respiratory material for culture. However, if study drug is prematurely discontinued due to insufficient effect of study drug (e.g., failure at EOT or TOC, or clinical relapse at any time), an appropriate respiratory specimen and blood should be obtained for culture on the day of discontinuation ([Section 12.6](#)).

Table 13.3.1-1. Microbiological Outcome Categories at TOC

Outcome	Definition
Eradication	Post-baseline respiratory specimen (e.g., respiratory fluid obtained by bronchoalveolar lavage or bronchoscopy; pleural fluid obtained by thoracentesis; or expectorated or induced sputum meeting adequacy criteria) culture or blood culture demonstrates absence of the original baseline pathogen
Presumed eradication	Post-baseline respiratory specimen culture or blood culture was not available and the subject was assessed as a clinical cure at TOC
Persistence	Post-baseline respiratory specimen culture or blood culture demonstrates continued presence of the original baseline pathogen. Note that post-baseline urinary antigen tests for <i>L. pneumophila</i> or <i>S. pneumoniae</i> should not be performed (Section 12.3), and positive post-baseline urinary antigen tests (if performed) will not be considered as persistence.
Presumed persistence	Post-baseline respiratory specimen culture or blood culture was not

	available and the subject was assessed as a clinical failure at EOT or TOC
Indeterminate	Post-baseline respiratory specimen culture or blood culture was not available and the subject's clinical response was assessed as indeterminate

Abbreviations: EOT = End-of-Therapy; TOC = Test-of-Cure.

CABP caused by pathogens first appearing after Screening (emergent infections) will be categorized as either superinfections or new infections as defined in [Table 13.3.1-2](#). Emergent infections will not be considered in the by-subject or by-pathogen microbiological response analyses described above.

Table 13.3.1-2 Emergent Infections

Category	Definition
Superinfection	Isolation of a new pathogen(s) (other than the original CABP pathogen[s]) from an appropriate post-baseline respiratory specimen (e.g., respiratory fluid obtained by bronchoalveolar lavage or bronchoscopy; pleural fluid obtained by thoracentesis; or expectorated or induced sputum meeting adequacy criteria) culture or blood culture, which is accompanied by signs and symptoms of infection requiring alternative systemic antimicrobial therapy during the period <i>up to and including</i> EOT
New infection	Isolation of a new pathogen(s) (other than the original CABP pathogen[s]) from an appropriate post-baseline respiratory specimen culture or blood culture, which is accompanied by signs and symptoms of infection requiring alternative systemic antimicrobial therapy in the time period <i>after</i> EOT (e.g., TOC)

Abbreviations: CABP = community-acquired pneumonia; EOT = End of Treatment; TOC = Test-of-Cure.

14.0 SAFETY EVALUATION

Subjects must be evaluated by a physician or an appropriately trained healthcare professional at every study visit, and the evaluation must be documented. The procedures discussed below will be completed at the designated visits as outlined in [Section 11.0](#).

14.1 ADVERSE EVENTS

14.1.1 Adverse Event Definition

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH-E2A guideline).

Adverse events may also include post-treatment complications that occur as a result of protocol-mandated procedures (e.g. invasive procedures such as venipuncture and biopsy). Pre-existing events that increase in severity or change in nature during, or as a consequence of, use of a medicinal product in a human clinical study will also be considered AEs.

Any preexisting medical condition or diagnosis associated with a clinically significant laboratory abnormality should be documented in the CRF.

An AE does not include the following:

- Medical or surgical procedures (e.g. surgery, endoscopy, tooth extraction, transfusion); the condition that necessitates the procedure is an AE. Any pre-existing medical condition that necessitates a procedure during the study should not be captured as an AE, and the condition should be listed in the medical history.
- Any pre-existing disease or condition or laboratory abnormality present or detected prior to the start of the study treatment regimen that does not worsen
- Laboratory abnormalities without clinical manifestations, which do not require medical intervention, or that do not result in termination or delay of study drug administration
- Situations where an untoward medical occurrence has not occurred (e.g. hospitalization for elective surgery, social and/or convenience admissions)
- Overdose of any study treatment or concomitant medication without any signs or symptoms, unless the subject is hospitalized for observation
- Progression of the index CABP or insufficient therapeutic effect of study drug, which is captured as an efficacy outcome (i.e., clinical failure at EOT or TOC)

- Progression of disease or insufficient therapeutic effect which causes new hospitalization (in subjects not previously hospitalized for the index CABP), rehospitalization (in subjects that were previously hospitalized for the index CABP and discharged); however, if this leads to death, it should be recorded as a serious adverse event (SAE) ([Section 14.1.3](#)).

A TEAE is defined as an AE or SAE that occurs during or after the first administration of study drug and up through the FU visit.

A life-threatening AE is an AE that, in the view of either the Investigator or Sponsor, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

An AE is considered “unexpected” if it is not listed in the IB or is not listed at the specificity or severity that has been observed; or, if an IB is not available, is not consistent with the risk information described in the general investigational plan. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation. Progressive worsening of the index CABP or insufficient therapeutic effect of study drug that leads to hospitalization or death (i.e., SAE criteria, [Section 14.1.4](#)) is considered expected—as part of potential disease progression—and not unexpected.

Some AEs are listed in the IB as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered unexpected until they have been observed with the drug under investigation.

The list of AEs included in the current version of the Investigator’s Brochure will be used as reference safety information.

14.1.2 Relatedness to Study Drug

For each reported AE, the Investigator must make an assessment of the relationship of the event to the study drug using the following scale:

- **Unrelated:** The event is definitely not associated with administration of the study treatment, and is judged clearly due to causes other than the study treatment. Clinical failure of CABP due to insufficient therapeutic effect of study drug is also considered “unrelated” to study drug.
- **Related:** The event is possibly or probably associated with administration of study treatment. Possibly-related events follow a reasonable temporal sequence from administration of study treatment, but may be due to another cause and could also be reasonably explained by the subject's clinical state or other modes of therapy

administered to the subject. Probably-related events follow a reasonable temporal sequence from administration of the study treatment, but are not easily explained by another cause such as known characteristics of the subject’s clinical state or other treatment, and are confirmed by improvement after stopping the study treatment.

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment. If the event is believed to be unrelated to the study treatment, then an alternative explanation should be provided.

14.1.3 Severity Assessment

The Investigator will be asked to provide an assessment of the severity of the AE using the following categories: mild, moderate, or severe ([Table 14.1.3-1](#)). This assessment is subjective and the Investigator should use medical judgment to compare the reported AE to similar types of events observed in clinical practice. *Severity*, which is a description of the intensity of manifestation of the AE, is distinct from *seriousness*, for which specific SAE criteria are met ([Section 14.1.4](#)).

Table 14.1.3-1: Severity Assessments of Adverse Events.

Mild	Symptom(s) barely noticeable to the subject or does not make the subject uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).
Moderate	Symptom(s) of a sufficient severity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) may be needed.
Severe	Symptom(s) of a sufficient severity to cause the subject severe discomfort. Severity may cause cessation of treatment with the drug. Treatment for symptom(s) needed.

Abbreviation: AE = Adverse event.

14.1.4 Serious Adverse Events

An SAE is any adverse experience that occurs from the signing of the informed consent to the FU visit and that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received study treatment
- Events that jeopardize the subject sufficiently that medical or surgical intervention may be required to prevent one of the above outcomes. Examples may include, but are not limited, to:

- Intensive treatment in an emergency room for allergic bronchospasm
- Blood dyscrasias that do not result in hospitalization
- Seizures that do not result in hospitalization

Progression of disease or insufficient therapeutic effect which causes new hospitalization (in subjects not previously hospitalized for the index CABP), rehospitalization (in subjects that were previously hospitalized for the index CABP and discharged) is not a SAE; however, if this leads to death, it should be recorded as a serious adverse event (SAE) ([Section 14.1.3](#))

The Sponsor is required to inform worldwide regulatory authorities of SAEs that meet specific criteria. Therefore, the Sponsor must be notified immediately regarding any SAE that occurs after informed consent is obtained. All SAEs and follow-up information must be reported within 1 business day, or 24 h as required by local regulations, by faxing a completed SAE Report Form to the fax number below (Table 14.1.4-1) or emailing a completed SAE Report Form to the [REDACTED] at [REDACTED].

Table 14.1.4-1: Toll-free Safety Line Numbers for SAE Reporting*

Country	Toll-free Safety Line Numbers
Bulgaria	[REDACTED]
Georgia	[REDACTED]
Latvia	[REDACTED]
Republic of South Africa	[REDACTED]
Romania	[REDACTED]
	[REDACTED]
Russia	[REDACTED]
	[REDACTED]
	[REDACTED]
USA	[REDACTED]
	[REDACTED]
	[REDACTED]

*Any fax sent to these lines will be routed to [REDACTED].

Supplemental information for each SAE should be submitted as soon as available and may include laboratory results, radiology reports, progress notes, hospital admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

The Investigator is expected to take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded in the eCRF. All SAEs are to be followed until resolution or until the SAE is deemed stable. The Sponsor may contact the study center to solicit additional information or follow up on the event.

14.1.5 Recording and Reporting Adverse Events

All AEs and SAEs will be recorded and reported from the signing of the informed consent form (ICF) to the time of the FU Visit. The Investigator must instruct the subject to report AEs and SAEs during this time period. Reports of death within 30 days after the last contact with the subject will be reported to the Sponsor and additional information relative to the cause of death will be sought and documented.

All AEs and SAEs must be recorded on source documents. All AEs and SAEs for subjects who receive a treatment assignment will be recorded in the eCRF.

The Investigator must follow-up as medically necessary on all AEs and SAEs until the events have subsided, the condition has returned to baseline, or in case of permanent impairment, until the condition stabilizes.

AEs should be based on the signs or symptoms detected during the physical examination and on clinical evaluation of the subject. In addition to the information obtained from those sources, the subject should be asked the following nonspecific question: "How have you been feeling since your last visit?" Signs and symptoms should be recorded using standard medical terminology.

Any unanticipated risks to the subjects must be reported promptly to the relevant ethics committee(s) and regulatory agency(ies).

14.1.6 Reporting of Pregnancies Occurring During the Study

Study center personnel must report every pregnancy from the time the subject signs the ICF through the FU Visit. Within 24 h of learning of the pregnancy, the study center personnel must report the event on the Clinical Trial Pregnancy Form and fax or email it to the SAE/Pregnancy fax number or email provided in [Section 14.1.4](#), even if no AE has occurred. Pregnancies in female partners of male subjects occurring during the time frame described above must also be reported.

The pregnancy must be followed to term and the outcome reported by completing the Clinical Trial Pregnancy Form. If the pregnancy is associated with an SAE (e.g., if the mother is hospitalized for hemorrhage), a separate SAE Form for Clinical Trials must be filed as described in [Section 14.1.4](#) with the appropriate serious criterion (e.g., hospitalization) indicated, in addition to the Clinical Trial Pregnancy Form.

14.2 CLINICAL ASSESSMENTS

Safety parameters will be monitored according to standard medical practice and guidelines for oral administration of study drug. Vital sign assessments (temperature, blood pressure, pulse, respiratory rate, and oxygen saturation), medical history, prior and concomitant medications, height, weight, and physical examination findings will be conducted at the specified time points outlined in the Schedule of Assessments and Procedures ([Table 3-1](#)) and [Section 11.0](#).

14.3 LABORATORY ASSESSMENTS

Blood samples for clinical laboratory tests and blood/urine samples for pregnancy tests will be collected at baseline and throughout the study according to the Schedule of Assessments and Procedures ([Table 3-1](#)) and [Section 11.0](#).

Unscheduled clinically-indicated laboratory tests (emergency or unscheduled tests) should be conducted at the local or regional laboratory on an as-needed basis.

14.4 DATA MONITORING COMMITTEE

An internal, blinded Data Monitoring Committee (DMC) will be utilized in this study. The DMC will perform periodic reviews of blinded data from the study to evaluate subject safety, compliance with the study protocol, and the quality of data. Safety of study drug will be monitored by reviewing AEs, SAEs, and the safety laboratory assessments on a regular basis. If specific issues are identified that warrant more extensive review, the DMC will recommend that experts external to the company review the data and provide a formal opinion of their significance and recommend any necessary interventions.

15.0 PHARMACOKINETIC EVALUATION

The PK data acquisition and analysis strategy entails the use of a sparse PK sampling schedule. Pharmacokinetic samples will be obtained from all subjects at sites where PK sampling is possible (for which a study center has been identified by the Sponsor as ineligible to perform PK assessments).

Pharmacokinetic sample handling and shipping procedures are described in the PK Sample Handling and Shipping Manual.

15.1 PHARMACOKINETIC BLOOD SAMPLE COLLECTION

Efforts will be made to obtain PK samples from all subjects on Day 3 and Day 4 at sites where PK sampling is possible, as described below. Blood samples for PK analyses will be collected at the following times:

- Day 3: Pre-dose sample will be collected within 10 minutes before administration of study drug
- Day 3: Post-dose at 2-4 h; subjects who have been hospitalized are also required to have a post-dose PK sample at 6-10 h
- Day 4: 24-28 h after the Day 3 dose.

Refer to the PK Manual for additional details regarding PK sample collection times and handling instructions.

15.2 PHARMACOKINETIC ANALYSES

Plasma samples from nafithromycin-treated subjects will be analyzed to determine concentrations of nafithromycin using a validated assay.

The PK Population in this study will include all subjects in the Safety Population who received at least 1 dose of oral nafithromycin and had at least 1 analyzable plasma PK sample ([Section 16.1.6](#)).

16.0 STATISTICAL METHODS

16.1 STUDY POPULATIONS

16.1.1 Safety Population

The safety population will include all randomized subjects who receive any amount of study drug (nafithromycin or moxifloxacin). Subjects will be analyzed according to the treatment actually received.

16.1.2 Intent-to-Treat Population (ITT)

The ITT population will include all subjects who were randomized.

16.1.3 Microbiological Intent-to-Treat Population (micro-ITT)

The micro-ITT population will include all ITT subjects who have at least one baseline Gram-positive or atypical bacterial pathogen known to cause CABP, including bacterial pathogens identified by respiratory specimen culture (e.g., respiratory fluid obtained by bronchoalveolar lavage or bronchoscopy; pleural fluid obtained by thoracentesis; or expectorated or induced sputum meeting adequacy criteria), blood culture, urinary antigen test (*S. pneumoniae*, *L. pneumophila*), or atypical bacterial serologic response (*M. pneumoniae*, *C. pneumoniae*, *L. pneumophila*). Subjects with sole baseline Gram-negative bacterial infection will be excluded from this population.

16.1.4 Clinically-Evaluable Population (CE)

The CE population will include all ITT subjects who follow important components of the trial. Sufficient information regarding the clinical course of CABP must be available to determine the subject's clinical outcome at TOC, and the subject must not have confounding factors that interfere with the assessment of that outcome.

In order to be included in the CE population, subjects must meet all of the following criteria:

- Meet the clinical disease criteria for CABP as described in Inclusion Criterion #3 (Inclusion Criteria 3a–3e; [Section 9.2](#))
- Receive at least 1 dose of study drug
- Do not receive non-study, potentially-effective, systemic antibacterial therapy between Day 1 and TOC (except in cases of treatment failure)
- Have an Investigator-determined clinical response of clinical cure or clinical failure at TOC (unless determined to be a prior clinical failure at EOT)
- Receive at least 80% of the intended doses of study drug therapy

- Receive at least 48 h of study drug therapy in order to be considered an evaluable clinical failure and at least 72 h of study drug therapy in order to be considered an evaluable clinical success

16.1.5 Microbiologically-Evaluable Population (ME)

The ME population will include all subjects who meet both micro-ITT population ([Section 16.1.3](#)) and CE population ([Section 16.1.4](#)) criteria.

16.1.6 Pharmacokinetic Population

The PK Population includes all subjects in the Safety Population who received at least 1 dose of oral nafithromycin and had at least 1 analyzable plasma PK sample.

16.2 METHODS OF ANALYSIS

This is an exploratory study and, therefore, is not powered for inferential statistical analyses and no formal comparisons between the treatment groups will be conducted.

All data will be summarized separately by study drug (nafithromycin for 3 days, nafithromycin for 5 days, and moxifloxacin). Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables for each study drug. Frequency distributions (counts and percentages) will be presented for categorical variables.

A comprehensive Statistical Analysis Plan will be prepared and finalized prior to database lock.

16.2.1 Determination of Sample Size

Approximately 225 adult subjects with CABP will be enrolled in this study. Randomization will have a 1:1:1 (Arm A: Arm B: Arm C) allocation ratio; therefore, approximately 150 subjects will be randomized to receive active oral nafithromycin. The objectives of this Phase 2 study are to collect initial efficacy data and to evaluate the safety and PK of oral nafithromycin in subjects with CABP. The sample size chosen for this study is considered to be adequate to achieve the study objectives and provide sufficient data to inform the design of future definitive studies, including Phase 3 studies, of nafithromycin. Assuming a 78% clinical response rate at Day 4 in the oral nafithromycin treatment arms, the sample size of 75 subjects per treatment arm will yield a 95% confidence interval around the response rate of 66.9% to 86.7%.

16.2.2 Analysis of Disposition and Subject Characteristics

Subject disposition (enrolment, discontinuations from the study), study drug administered, premature discontinuations from study medication, withdrawals from the study, and major protocol deviations will be summarized by treatment group in the ITT Population.

Demographics and baseline characteristics such as age, sex, race, weight, and medical history will be summarized by treatment group in the ITT using means, standard deviations, medians, minima and maxima for continuous variables, and counts and percentages for categorical variables.

16.2.3 Efficacy Analyses

16.2.3.1 Primary Efficacy Analysis

The primary efficacy evaluation will be the by-subject clinical response at Day 4 in the ITT population. Each subject will be classified programmatically as a responder, non-responder, or indeterminate based on CABP symptom data entered in the e-CRF ([Section 13.2.1](#)).

The number and percentage of subjects in each treatment group classified programmatically as a responder, non-responder and indeterminate will be reported. Exact 95% confidence intervals around the percentage of subjects classified as responders will be calculated for each treatment group using the Clopper-Pearson Method. The treatment difference will also be determined and a 95% confidence for the difference will be calculated using the method of Miettinen-Nurminen. Individual subject data will also be displayed as a listing.

16.2.3.2 Secondary Efficacy Analyses

The secondary analysis variables are listed in [Section 13.1](#).

For analyses of the variables above that measure clinical success on a per-subject basis (i.e., clinical cure, improvement in CABP symptoms and normalization in vital signs at Day 4, lack of readmission or new admission to the hospital), the number and percentage of subjects in each treatment group in the specified population(s) classified as clinical success, clinical failure, and indeterminate (as applicable to each secondary analysis; [Section 13.2](#)) at the specified time point(s) will be tabulated. The difference between treatment groups in clinical success and 2-sided 95% CI for the difference also will be included in the tabulation.

The per-pathogen and per-subject microbiological efficacy analyses will be conducted in the micro-ITT and ME Populations at TOC. Per-subject responses will be based on per-pathogen outcomes ([Section 13.3](#)). These responses include eradication, presumed eradication, persistence, and presumed persistence. Of these responses, eradication and presumed eradication will be regarded as a favorable outcome. Persistence and presumed persistence will be regarded as an unfavorable outcome. To have an overall favorable microbiologic response, the outcome for each baseline pathogen must be favorable. Microbiological outcomes in the ME Population, by definition, will not include subjects with indeterminate responses.

The number and percentage of subjects in each treatment group recorded as having a favorable and unfavorable microbiologic response will be tabulated. Since this is an exploratory study, no statistical comparison between treatment groups is planned. In addition, a table summarizing the number and percent of all responses for each treatment group will be displayed. Individual subject data will also be displayed as a listing.

Emergent infections (i.e., superinfection, new infection) will not be considered in the by-subject or by-pathogen microbiological response and will be provided in separate listings ([Section 13.3.1](#); [Table 13.3.1-2](#)).

16.2.4 Safety Analyses

Evaluation of the safety and tolerability of oral nafithromycin for 3 or 5 days in the treatment of CABP is an important primary objective for this Phase II study. Safety will be analyzed in the Safety Population ([Section 16.1.1](#)). Subjects in the Safety Population will be analyzed according to the treatment actually received.

Safety will be evaluated by presenting summaries of AEs, physical examinations, vital signs, laboratory evaluations (hematology evaluation, chemistry panel, UA, and ECG parameters). For each safety parameter, the last assessment made prior to the first administration of study drug will be used as the baseline value for all analyses.

The incidence of TEAEs (defined in [Section 14.1.1](#)) will be presented by system organ class and preferred term according to MedDRA®, by relationship to the administration of study drug, and by severity. In addition, the incidence of SAEs and AEs leading to discontinuation of study drug will be presented by system organ class, preferred term, and relationship to study drug. If the incidence of SAEs and AEs leading to discontinuation of study drug is low, only a listing will be provided.

Descriptive statistics of vital signs at each time point measured, as well as the change from baseline and PCS changes, will be presented. Descriptive statistics for ECGs and physical examinations will also be presented for each time point measured. The number and percentage of subjects with a normal physical exam result at baseline and an abnormal physical examination result at a follow-up assessment will be provided for each time point. Descriptive statistics for clinical laboratory tests and vital signs and for the change from baseline will be presented by study visit. Potentially clinically significant clinical laboratory results will be determined based on normal limits and percent change from baseline.

16.2.5 Pharmacokinetic Analyses

See [Section 15.0](#).

16.3 INTERIM ANALYSIS

No interim analysis is planned for this study.

16.4 HANDLING OF DROPOUTS AND MISSING DATA

Every effort will be made to collect all data at specified times. A detailed description of the handling of dropouts and missing data for all efficacy and safety evaluations will be provided in the SAP.

17.0 INVESTIGATOR REQUIREMENTS

17.1 PROTOCOL ADHERENCE

Each Investigator must adhere to the protocol as detailed in this document and agree that the Sponsor or Sponsor representative must approve any change to the protocol before seeking approval from the relevant ethics committee(s) and regulatory agency(ies). Each Investigator will be responsible for enrolling only those subjects who have met the protocol inclusion and exclusion criteria.

17.2 ELECTRONIC CASE REPORT FORMS AND DATA CAPTURE SYSTEM

Data collection will involve the use of an Electronic Data Capture (EDC) system, to which only authorized personnel will have access. Electronic case report forms will be used to capture study data in an EDC system. Entering of eCRFs should be handled in accordance with instructions from the Sponsor or Sponsor representative. All eCRFs must be completed by qualified study center personnel. Each Investigator is responsible for ensuring that accurate data are entered into the EDC system in a timely manner.

Before the first subject is dosed at the investigational site, the Sponsor or Sponsor representative will meet with the Investigator and the study center's personnel to train them on recording the data on the eCRFs using the EDC system. The Investigator or designee will be responsible for reviewing eCRFs, resolving data queries generated by the Sponsor via the system, providing missing or corrected data, approving all changes performed on the subject data, and endorsing these data within the EDC system. This approval method will include applying an electronic signature, a uniquely assigned user name, and a password that together will represent a traditional handwritten signature.

Queries may be issued electronically to the clinical study center and answered electronically by that study center's personnel. The identifying information (assigned user name, date, and time) for both the originator of the query and the originator of the data change (if applicable) will be collected.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records.

17.3 SOURCE DOCUMENT MAINTENANCE

Source documents may include, but are not limited to, study progress notes, study- or subject-specific e-mail correspondence, computer printouts, laboratory data, and recorded data from automated instruments, study drug accountability records. The original signed ICF for each participating subject shall be filed with records kept by the Investigator. All documents produced in this study will be maintained by the Investigator and made available for inspection by the Sponsor or Sponsor representative and applicable regulatory authorities.

17.4 STUDY MONITORING REQUIREMENTS

The Sponsor or Sponsor representative will conduct center visits to inspect study data, subjects' medical records, and eCRFs in accordance with current ICH E6 Good Clinical Practice (GCP) guideline, and the respective US, EU and local regulations and guidelines, as applicable. The Sponsor or Sponsor representative will also be able to review query status remotely, which may warrant additional communication with the Investigator and the study center's personnel. The Investigator will make available to the Sponsor, or Sponsor representative, source documents, signed ICFs, and all other study-related documents.

The Investigator will allow the Sponsor or Sponsor representative and applicable regulatory authorities to inspect facilities and records relevant to this study.

17.5 STUDY COMPLETION

The Sponsor requires the following data and materials before the study can be considered complete or terminated:

- Clinical and laboratory results from Screening through TOC
- eCRFs properly completed by appropriate study personnel and signed and dated by the Investigator within the EDC system. This approval method will include applying an electronic signature, a uniquely assigned user name, and a password that together will represent a traditional handwritten signature
- Copies of complete study drug accountability records (e.g., study drug inventory logs and shipment and return records)
- Copies of all relevant ethics committee(s) and regulatory agency(ies) approvals and acknowledgements
- A summary of the study prepared by the Investigator (an ethics committee or regulatory agency summary letter is acceptable)

18.0 PROTECTION OF HUMAN SUBJECTS AND GENERAL STUDY ADMINISTRATION

18.1 STATEMENT OF COMPLIANCE

This study will be conducted in compliance with the current ICH E6 GCP guideline, the ethical principles of the Declaration of Helsinki, current FDA, European Union clinical trials related guidelines, and any additional relevant ethics committee or regulatory agency-required procedures, whichever represents the greater protection for the individual.

Investigators will apply due diligence to avoid protocol deviations. No authorized deviations or protocol waivers will be permitted. All significant protocol deviations will be recorded and reported in the clinical study report.

18.2 SUBJECT CONFIDENTIALITY

The Sponsor, its designee, the Investigator and all parties involved will comply with applicable subject data privacy regulations/guidance as per international and local requirements. The Investigator must assure that the privacy of the subjects, including their identity and all personal medical information, will be maintained at all times. In eCRFs and other documents or image material submitted to the Sponsor, subjects will be identified not by their names, but by an identification code (e.g., initials and identification number).

Personal medical information may be reviewed for the purpose of subject safety and/or verifying data in the source and transcribed onto the eCRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the Sponsor, the quality assurance unit, and/or regulatory authorities. Personal medical information will always be treated as confidential.

18.3 INFORMED CONSENT

This study will be conducted in compliance with the current ICH E6 GCP guideline pertaining to informed consent, the current US CFR (Title 21, Parts 50 Subparts B and D, 56 and 312) as well as relevant European and local guidelines. Subjects will give written consent to participate in the study at the first visit, before initiation of any study-related procedures, after having been informed about the nature and purpose of the study, participation and termination conditions, risks, and benefits. If a subject is unable to provide written informed consent, the subject's legally acceptable representative(s) may provide written consent, as approved according to institution specific guidelines. The ICF must be signed and dated by the subject, or the subject's legally authorized representative(s), before study participation. An original copy of the signed ICF must be provided to the subject or legally acceptable representative(s). If applicable, the ICF will be provided in certified translation (native language) for non-English-speaking subjects. Signed ICFs must remain in the subjects' study files and be available for verification by the Sponsor or Sponsor representative at any time.

18.4 ETHICS COMMITTEE APPROVAL

The relevant ethics committee(s) and regulatory agency(ies) must approve the protocol or amended protocol (if applicable) and the corresponding ICF before the study may be initiated as per local requirements; any recruiting materials before use; and subsequent amended protocols and corresponding ICFs, before instituting amendment-specified changes to the study, unless required for subject safety following the local legislation.

The Investigator is responsible for informing the relevant ethics committees and regulatory authorities of any changes made to the protocol, and to advise the relevant ethics committees and regulatory authorities, at least once a year, about the progress of the study. The Investigator (or Sponsor, if applicable) is also responsible for notifying the relevant ethics committees and regulatory authorities of any significant AEs that occur during the study according to local ethics committee requirements.

19.0 DATA HANDLING AND RECORD KEEPING

Training sessions, regular monitoring of the investigative center by the Sponsor or Sponsor representative, instruction manuals, and data verification, crosschecking, and auditing will be provided or performed to ensure quality of all study data. One or more Investigator meetings will be held to prepare the Investigator and other study personnel for appropriate collection of study data.

The Sponsor or Sponsor representative will review and validate study data as defined in the monitoring plan.

It will be the responsibility of the Investigator to ensure that the essential documents are available in the Investigator's files or at the institutional center. Any or all of these documents should be available for monitoring by the Sponsor or Sponsor representative and inspection by the regulatory authorities as defined in the monitoring plan.

19.1 STUDY DRUG ACCOUNTABILITY

It is the responsibility of the Investigator or designee to ensure that current records of study drug inventory and accountability are maintained. Records must be readily available for inspection by the Sponsor or Sponsor's Representative and open to inspection at any time by applicable regulatory authorities.

19.2 RETENTION AND REVIEW OF RECORDS

Records and documents pertaining to the conduct of this study in all formats (including, but not limited to, written, electronic, magnetic, and optical records and scans/X-rays) must be retained by the Investigator for a period of at least 15 years after study completion unless local regulations or institutional policies require a longer retention period or otherwise notified in writing by the Sponsor. These records include CRFs, source documents, ICFs, regulatory documents, clinical reports and laboratory results (including, but not limited to, all local and central laboratory and microbiology results), and medication inventory records.

No study records shall be destroyed without notifying the Sponsor and providing the Sponsor the opportunity to arrange long-term storage for such study records or authorizing in writing the destruction of these records after the required retention period.

The Investigator must permit access to any documentation relating to the study upon request of the Sponsor or Sponsor representative, the corresponding relevant ethics committee(s) or regulatory agency(ies). If the Investigator for the study retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a suitable alternate custodian employee of the institution or to a suitably qualified and responsible third party. The Sponsor must be notified in writing of the name and address of the new custodian in advance of the transfer.

The Investigator agrees by his or her participation that the results of this study may be used for submission to national or international registration. If required, these authorities will be provided with the name of the Investigator and his or her address, qualifications, and extent of involvement.

Data generated by this study must be available for inspection by applicable regulatory authorities, the Sponsor or Sponsor representative, and the relevant ethics committee(s) and regulatory agency(ies) as appropriate. At the request of a subject's parent(s) or legally acceptable representative(s), medical information may be given to the subject's personal physician or other appropriate medical personnel responsible for the subject's welfare.

19.3 DECLARATION OF THE END OF STUDY AND CLINICAL STUDY REPORT

For clinical investigational centers located in the EU, a declaration of the end of the clinical study will be made according to the procedures outlined in Directive 2001/20/ED, Article 10(c); for other countries, local regulations will be followed.

Last subject last visit is defined as completion of the FU visit for the final subject enrolled in the study. This will be considered the end of the trial for global clinical trial submission.

Whether the study is completed or prematurely terminated, the Sponsor will ensure that the clinical study reports are prepared and provided to the regulatory authority(ies) as required by the applicable regulatory requirement(s). The Sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH Harmonised Tripartite Guideline E3: Structure and Content of Clinical Study Reports. Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report. Upon completion of the clinical study report, the Sponsor will provide the Investigators with the full summary of the study results. The study results summary will also be made publicly available according to applicable FDA/EU requirements.

20.0 FINANCING AND INSURANCE

The financing and insurance for this study are outlined in the Clinical Trial Agreement.

21.0 PUBLICATION POLICY

The data generated in this clinical study are the exclusive property of the Sponsor and are confidential. The Sponsor will make all reasonable efforts to publish the results of the study in an appropriate peer-reviewed journal. Authorship on the primary publication of the results from this study will be based on contributions to study design, enrolment, data analysis, and interpretation of results.

22.0 **REFERENCES**

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23.0 **APPENDICES**

APPENDIX I ALLOWED AND DISALLOWED PRIOR ANTIBIOTICS

Allowed Antibiotics (One dose within 72 h prior to randomization*)	Disallowed Antibiotics
<u>Penicillins</u>	
Amoxicillin Amoxicillin-Clavulanate Amoxicillin-Sulbactam Ampicillin Ampicillin-Sulbactam Dicloxacillin	Nafcillin Oxacillin Penicillin-G or -V Piperacillin Piperacillin-Tazobactam Ticarcillin-Clavulanate Benzathine/Penicillin-G Procaine
<u>Cephalosporins</u>	
Cefaclor Cefadroxil Cefazolin Cefdinir Cefepime Cefixime (200 mg) Cefditoren Cefotaxime	Cefpodoxime Cefprozil Ceftaroline Ceftazidime Ceftibuten Cefuroxime Cephalexin Loracarbef Cefixime (400 mg) Ceftriaxone
<u>Carbapenems</u>	
Doripenem Imipenem Meropenem	Ertapenem
<u>Glycopeptides</u>	
Televancin Vancomycin	Dalbavancin Oritavancin
<u>Fluoroquinolones</u>	
Ciprofloxacin	Levofloxacin Moxifloxacin
<u>Macrolides</u>	
Clarithromycin Erythromycin	Azithromycin Clarithromycin XL
<u>Tetracyclines</u>	
Doxycycline (100 mg) Minocycline	Doxycycline (200 mg) Minocycline Extended Release Tigecycline
<u>Oxazolidinones</u>	
Linezolid	Tedizolid
<u>Miscellaneous</u>	
Clindamycin Metronidazole Trimethoprim-sulfamethoxazole/Co-trimoxazole	

*Prior (within 72 h prior to randomization) administration of potentially effective systemic antibacterial therapy is an Exclusion Criterion ([Section 9.3](#)); however, subjects may be eligible for the study despite prior antimicrobial therapy if they received a single dose of a single short-acting systemic antibiotic within 72 h prior to randomization. For the purposes of this protocol, short-acting is defined as having a dosage frequency of more than once a day. If a subject received a prior short-acting systemic antibiotic that is not listed here, the Investigator must contact the Medical Monitor to ensure subject eligibility.

APPENDIX II PORT SCORE CALCULATION

Subject Characteristic	Point Assignment
Age	
Male	Age (years)
Female	Age (years) -10
Nursing home resident ¹	+10
Coexisting illnesses	
Neoplastic disease ²	+30
Liver disease ³	+20
Congestive heart failure ⁴	+10
Cerebrovascular disease ⁵	+10
Renal disease ⁶	+10
Physical-examination findings	
Altered mental status ⁷	+20
Respiratory rate ≥ 30 /minute	+20
Systolic blood pressure < 90 mm Hg	+20
Temperature $< 35^{\circ}\text{C}$ (95°F) or $\geq 40^{\circ}\text{C}$ (104°F)	+15
Pulse ≥ 125 /minute	+10
Laboratory and radiographic findings	
Arterial pH < 7.35 ⁸	+30
Blood urea nitrogen ≥ 30 mg/dL (11 mmol/L) ⁶	+20
Sodium < 130 mmol/L	+20
Glucose ≥ 250 mg/dL (14 mmol/L)	+10
Hematocrit $< 30\%$	+10
Partial pressure of arterial oxygen < 60 mm Hg or oxygen saturation $< 90\%$ (by pulse oximetry) ⁸	+10
Pleural effusion	+10
PORT Score	Sum of numbers above

PORT Risk Class	PORT Score
I (ineligible for study)	0-50
II (eligible)	51-70
III (eligible)	71-90
IV (score of 91-105 eligible and 106-130 ineligible)	91-130
V (ineligible for study)	≥ 131

- Subjects that reside in a nursing home are excluded from the study and should not be enrolled per Exclusion Criterion #1.
- Neoplastic disease is defined as any cancer, except basal or squamous cell cancer of the skin that was active at the time of presentation or diagnosed within one year of presentation. Subjects with neoplastic lung disease are excluded from the study and should not be enrolled per Exclusion Criterion #7.
- Liver disease is defined as a clinical or histologic diagnosis of cirrhosis or another form of chronic liver disease, such as chronic active hepatitis. Subjects with liver test abnormalities or evidence of end-stage liver disease as defined in Exclusion Criterion #8 should not be enrolled.
- Congestive heart failure is defined as systolic or diastolic ventricular dysfunction documented by history, physical examination, and chest radiograph, echocardiogram, multiple gated acquisition scan,

- or left ventriculogram. Subjects with acute congestive heart failure are excluded from the study and should not be enrolled per Exclusion Criterion #11.
5. Cerebrovascular disease is defined as a clinical diagnosis of stroke or transient ischemic attack or stroke documented by magnetic resonance imaging or CT.
 6. Renal disease is defined as a history of chronic renal disease or abnormal blood urea nitrogen and creatinine concentrations documented in the medical record. Subjects with compromised renal function are excluded from the study and should not be enrolled per Exclusion Criterion #8.
 7. Altered mental status is defined as disorientation with respect to person, place, or time that is not known to be chronic, stupor, or coma.
 8. For subjects without an optional ABG at Screening, no points will be added for pH or PaO₂; however, oxygen saturation results should be used in place of PaO₂.

Reference: Fine, 1997.

APPENDIX III CABP SYMPTOM SEVERITY GUIDANCE FOR INVESTIGATOR ASSESSMENT

CABP Symptom	Absent	Mild	Moderate	Severe
Dyspnea (Shortness of Breath [SOB])	No CABP-associated SOB; or return to pre-CABP baseline SOB	SOB with only strenuous activity but it <u>does not</u> interfere with subject’s usual daily activities; or mild SOB above pre-CABP baseline	SOB with usual activities and it <u>does</u> interfere with some of the subject’s usual daily activities; or moderate SOB above pre-CABP baseline	SOB with minimal exertion or at rest and it <u>limits most</u> of the subject’s usual daily activities; or severe SOB above pre-CABP baseline
Cough	Resolution of cough; or return to pre-CABP baseline cough	Cough present, infrequent, and it <u>does not</u> interfere with subject’s usual daily activities; or mild cough above pre-CABP baseline	Cough present, frequent, and it <u>does</u> interfere with some of the subject’s usual daily activities; or mild cough above pre-CABP baseline	Cough is present throughout the day and night; it <u>limits most</u> of the subjects’ usual daily activities and sleep patterns; or mild cough above pre-CABP baseline
Production of Purulent Sputum	No production of purulent sputum; or return to pre-CABP baseline productive cough	Production of small amount of purulent sputum; or minimal amount of sputum production above pre-CABP baseline	Production of moderate amount of purulent sputum; or moderate amount of sputum production above pre-CABP baseline	Production of large amount of purulent sputum; or large amount of sputum production above pre-CABP baseline
Pleuritic Chest Pain	No CABP-associated pleuritic chest pain	CABP-associated pleuritic chest pain present occasionally with deep breathing but it <u>does not</u> interfere with subject’s usual daily activities	CABP-associated pleuritic chest pain is present with normal breaths, and it <u>does</u> interfere with the subject’s usual daily activities	CABP-associated pleuritic chest pain is present at rest and/or with shallow breathing, and it <u>limits most</u> of the subject’s usual daily activities

APPENDIX IV SAFETY LABORATORY TESTS CONDUCTED BY THE CENTRAL LABORATORY

<p>Hematology:</p> <ul style="list-style-type: none"> • Hemoglobin • Hematocrit • Erythrocyte count • Mean red blood cell volume • Mean red blood cell hemoglobin • Mean red blood cell hemoglobin concentration • Leukocyte count (WBC) • Neutrophils (including immature neutrophils [bands] and absolute neutrophil count) • Lymphocytes • Monocytes • Eosinophils • Basophils • Platelets • Reticulocytes <p>Coagulation:</p> <ul style="list-style-type: none"> • Prothrombin time/International normalized ratio (PT/INR) • Partial thromboplastin time <p>Urinalysis (only if local urine dipstick test abnormal and deemed clinically significant by the Investigator; see Section 11.1):</p> <ul style="list-style-type: none"> • Specific gravity • pH • Protein • Glucose • Ketones • Bilirubin • Occult blood • Nitrites • Urobilinogen • Leukocyte esterase 	<p>Chemistry (Serum Concentrations):</p> <ul style="list-style-type: none"> • Glucose • Calcium • Albumin • Total protein • Sodium • Potassium • Carbon dioxide • Chloride • Blood urea nitrogen (BUN) • Creatinine • Alkaline phosphatase • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Total and direct bilirubin • Magnesium • Lactate dehydrogenase (LDH) • Phosphorus • Uric acid • Creatine kinase • Gamma-glutamyl transferase (GGT) • β-Human chorionic gonadotropin (β-HCG) for females
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**APPENDIX V ORAL MOXIFLOXACIN SUMMARY OF PRODUCT
CHARACTERISTICS**

Insert SPC from Bayer plc, updated 26-August-2015,
<http://www.medicines.org.uk/emc/print-document?documentId=11841>

NDA 021085 AVELOX FDA Approved 8 May 2015 - Merck
https://www.merck.com/product/usa/pi_circulars/a/avelox/avelox_pi.pdf

APPENDIX VI INVESTIGATOR SIGNATURE PAGE

I have read and understand the protocol. I agree to the following:

1. To conduct the study in compliance with Good Clinical Practice, with applicable regulatory requirement(s), and with the protocol agreed to by the Sponsor and given approval/favorable opinion by the Institutional Review Board, Independent Ethics Committee, or Competent Authority
2. To comply with procedures for data recording and reporting
3. To permit monitoring, auditing, and inspection by the Sponsor, its designated representatives, and regulatory authorities
4. To retain the essential documents in the Investigator/Institution files until the Sponsor informs the Investigator or Institution that these documents are no longer needed

Investigator Signature

Date (DD Mmm YYYY)

Investigator Name (printed)

Site Name

Street Address

City, State/Province, Country, and Zip/Postal Code