SYNOPSIS OF ABBREVIATED RESEARCH REPORT [redacted] (PROTOCOL WI18273)

COMPANY: NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A Phase II, prospective, randomized, double-blind, active-controlled, parallel group, multi-center 'proof of concept' trial in adult patients with community-acquired pneumonia requiring hospitalization without evidence of *Legionella*.		
INVESTIGATORS / CENTERS AND COUNTRIES	Patients were recruited from 44 centers in 11 countries: - Latvia, USA, Peru, Argentina, Chile, Lithuania, Bulgaria, Hungary, Croatia, Slovakia and Romania		
PUBLICATION (REFERENCE)	N/A		
PERIOD OF TRIAL	March 29, 2005 to July 10, 2006	CLINICAL PHASE	II
OBJECTIVES	***Primary*** • To compare the safety, tolerance and efficacy of parenteral RO4908463 to ceftriaxone in patients with community acquired pneumonia requiring hospitalization. ***Secondary*** • To obtain *in vitro* susceptibility data on RO4908463 on the pathogenic organisms isolated from patients participating in the study. • To evaluate the pharmacokinetics of RO4908463 in the patient population including the influence of covariates. • To explore the relationship of drug exposure (time above MIC) to clinical cure rates in the bacteriologically evaluable population.		
STUDY DESIGN	Randomized, prospective double-blind, active-controlled, parallel group, multi-center 'proof of concept' trial.		
NUMBER OF PATIENTS	A total of 302 patients were randomized to receive one of the following IV study drug treatments for at least 3 to a maximum of 14 days: • Arm A: RO4908463 750 mg (n= 101 patients) • Arm B: RO4908463 1500 mg (n= 104 patients) • Arm C: ceftriaxone 1000 mg (n= 97 patients)		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Male or female patients $\geq$ 18 years of age who required hospitalization with community-acquired pneumonia or developed pneumonia within 48 hours of hospitalization for another condition.		
TRIAL DRUG / STROKE (BATCH) No.	RO4908463 was provided as sterile, single-use, vials containing 750 mg lyophilisate of RO4908463, 81.5 mg sodium chloride, 375 mg lactose, pH 6.0. Batch Nos: [redacted]		

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DOSE / ROUTE / REGIMEN / DURATION	Patients randomized to Arm A received RO4908463 750 mg reconstituted in 100 mL of 0.9% NaCl q 12 h, as an intravenous infusion over 60 minutes. Patients randomized to Arm B received RO4908463 1500 mg reconstituted in 100 mL of 0.9% NaCl q 12 h IV, as an intravenous infusion over 60 minutes.
REFERENCE DRUG / STROKE (BATCH) No.	Ceftriaxone was supplied by Roche to the participating study centers and packaged and labeled according to local specifications. Lot numbers for ceftriaxone 1 g/10 mL vials used in this study were [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Patients randomized to Arm C received 1000 mg ceftriaxone q 24 hours and the site pharmacist prepared a "dummy infusion" of 0.9% NaCl to mimic the q 12 hour infusion of RO4908463.
CRITERIA FOR EVALUATION	
EFFICACY:	• *Primary Endpoint*: clinical cure rate as determined by the Investigator Assessment of Pneumonia Therapy (IAPT) at the End of Study Evaluation (EOSE) visit. • *Planned Secondary Endpoints*: time to resolution of signs and symptoms of pneumonia, bacteriologic outcome, respiratory rate, body temperature, chest X-ray and category of signs and symptoms of pneumonia.
SAFETY:	Adverse events, vital signs, physical exams, ECGs and clinical laboratory tests: CBC, haptoglobin, PT/PTT, Coomb's test (direct and indirect) and reticulocytes, blood chemistry, urinalysis and urinary hemosiderin, urine protein/creatinine ratio and β-NAG index (U/g Cr)
STATISTICAL METHODS	Ninety-five percent confidence intervals were produced for the clinical cure rate within each treatment arm. The 95% confidence intervals for the clinical cure rate was calculated by the Wilson score method without continuity correction as recommended by Newcombe. The difference in clinical cure rates between each of the RO4908463 dose arms and the ceftriaxone arm was calculated and 95% confidence intervals were produced for the differences. The 95% confidence interval for the difference between clinical cure rates was calculated by use of a method based upon the Wilson score method for the single proportion without continuity correction as described by Newcombe.

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STATISTICAL METHODS Cont'd	The 95% confidence interval (a one-sided 2.5% significance level) for the difference in cure rates between the RO4908463 and the control arms was used to test the following statistical hypotheses evaluating the non-inferiority of each of the RO4908463 arms to the ceftriaxone arm: H_0: $\pi_E - \pi_C \leq -0.14$ H_1: $\pi_E - \pi_C > -0.14$ whereπ_E and π_C were the clinical cure rates for the patients in the RO4908463 and the ceftriaxone arms, respectively. The bacteriologic eradication rate was assessed as the proportion of patients in each treatment group who had a bacteriologic outcome of eradication or presumed eradication at the EOSE visit. The non-inferiority of each RO4908463 arm as compared with ceftriaxone was assessed in a similar manner to that of the primary endpoint.

METHODOLOGY:

Patients were to receive IV study drug treatment for 3 - 14 days and were followed for 7-10 days from last dose of antibiotic (IV study drug or oral study antibiotics). Patients underwent a Community Acquired Pneumonia Clinical Evaluation (CAPCE) twice daily (q 12 ± 2 hours) and an IAPT daily (except Day 1) while receiving IV study drug. In addition, patients underwent a CAPCE and IAPT at the Early Follow-up and at the EOSE visit. Chest X- rays (CXRs) were required for the determination of the IAPT. All CXRs were read by a radiologist blinded to study treatment. The CXR was considered to show improvement if the radiologist reported a reduction in lung infiltrate/consolidation in the affected lobe(s).

Patients who had completed 3 days (6 doses) of IV study drug treatment and who met the 'clinical improvement or clinical cure' criteria could be switched to oral amoxicillin/clavulanate (Augmentin® 875 mg, supplied by Roche) to complete their antibiotic treatment as outpatients. A different oral antibiotic was permitted, if based upon the investigator's review of patient history and culture and sensitivity results of the causative pathogen(s) oral Augmentin® was deemed inadequate or inappropriate. All patients were to receive at a minimum a total course of antibiotic therapy (IV plus follow-on PO) of 7 days. The EOSE served as the test of cure visit and was to occur 7-10 days from the last day the patient had received study antibiotics, and no later than study Day 39.

All clinical isolates (blood and respiratory secretions) were sent to a central microbiology laboratory for confirmatory susceptibility, speciation and routine testing. The clinical and bacteriologic course of the infection were carefully monitored during and after completion of treatment.

Patients who developed a skin rash meeting the following criteria:

- developed while on IV antibiotics or within 24 hours of the last dose and
- persisted for longer than 4 hours and
- did not appear to be resolving.

were to be entered into an ancillary evaluation of rash to characterize and compare the histopathology of cutaneous skin reactions seen in patients receiving intravenous study medication

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EFFICACY RESULTS:

The primary efficacy parameter was the clinical cure rate at the EOSE visit, as assessed by the IAPT in both co-primary populations (clinically modified intent-to-treat [cMITT] and clinically evaluable [CE] populations). In the cMITT population the highest cure rate was observed in the RO4908463 1500 mg b.i.d group where 89 patients (87%) were assessed as clinically cured, compared with 78 patients (78%) in the RO4908463 750 mg b.i.d group and 80 patients (82%) in the ceftriaxone group. Similar results were observed in the CE population. The 95% confidence interval (a one-sided 2.5% significance level) for the difference in cure rates between the RO4908463 arms and the ceftriaxone arm was calculated to evaluate the non-inferiority of each of the RO4908463 groups to ceftriaxone. A non-inferiority margin of –14% (delta) was set. In the cMITT population the difference in the clinical cure rate between the RO4908463 750 mg b.i.d group and the ceftriaxone group was -4.5% (95% CI –15.5% to 6.7%) and the difference between the RO4908463 1500 mg b.i.d group and the ceftriaxone group was 4.8% (95% CI –5.3% to 14.9%). Since the lower limit of the CI for the RO4908463 750 mg b.i.d group was –15.5% and therefore lower than –14%, non-inferiority to ceftriaxone 1000 mg q.d. could not be concluded. The RO4908463 1500 mg b.i.d group however was regarded as clinically non-inferior to ceftriaxone 1000 mg q.d, since the lower limit of the CI (-5.3%) was greater than the non-inferiority margin of –14%. Similar results were observed for the CE population. The difference in clinical cure rate between the RO4908463 groups and ceftriaxone was -5.7 % (95% CI –17.2% to 6.3%) for the RO4908463 750 mg b.i.d group and 3.3% (95% CI –7.1% to 14.2%) for the RO4908463 1500 mg b.i.d group. An analysis of the clinical cure rate using the last post-baseline efficacy assessment carried forward method was supportive of the primary analysis.

The majority of patients had a bacteriologic outcome of eradication or presumed eradication in the bMITT population. Bacteriologic eradication rates were similar across the three treatment groups and the differences in eradication rates between the RO4908463 treatment groups and ceftriaxone were generally in line with the clinical cure rates (difference in bacteriologic eradication rate for RO4908463 750 mg treatment group and ceftriaxone: -2.4% [95% CI -13.7% to 8.3%], difference in bacteriologic eradication rate for RO4908463 1500 mg treatment group and ceftriaxone: -0.6% [95% CI -12.0% to 9.8%]. The BE population showed similar results. All bacterial isolates, independent of their sensitivity/resistance to other antibiotics such as penicillin, cefuroxime/axetil, azithromycin, tetracycline and trimeth/ sulfa were susceptible to RO4908463.

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SAFETY RESULTS:

RO4908463 was generally well tolerated in this study with no significant safety concerns. Of the 299 patients in the safety population 137 (46%) experienced at least one AE. The overall incidence of AEs was highest in the RO4908463 1500 mg group (51% vs. 41% in the RO4908463 750 mg group and 45% in the ceftriaxone group). The most frequently reported AEs by system organ class were gastrointestinal disorders. The most common AEs were headache, diarrhea and pleural effusion, although each individual AE was experienced relatively infrequently (<8% of patients in any treatment group). The vast majority of all AEs reported during this study were mild or moderate in intensity (RO4908463 750 mg group, 97%; RO4908463 1500 mg, 95%; ceftriaxone, 95%) and were mostly considered unrelated to study drug by the trial investigator (RO4908463 750 mg, 76% of AEs; RO4908463 1500 mg, 70% of AEs; ceftriaxone, 76% of AEs). A total of 18 serious adverse events (SAEs) were reported in 15 patients across all three treatment groups, with the highest incidence of SAEs reported in the RO4908463 1500 mg b.i.d group (RO4908463 750 mg group: 5 patients, 6 SAEs; RO4908463 1500 mg group: 6 patients, 7 SAEs; ceftriaxone group: 4 patients, 5 SAEs) . The most common types of SAE were respiratory, thoracic and mediastinal disorders, followed by cardiac disorders. Only two SAEs were considered related to study drug by the trial investigator (small intestinal hemorrhage and delirium) and both resolved with no sequelae.

One death was reported during the study (RO4908463 1500 mg group: metastatic bronchial carcinoma) however this death was considered unrelated to study drug by the trial investigator.

AEs such as rash, hypersensitivity, severe cutaneous reactions and renal toxicity were carefully monitored during the study and standardized MedDRA queries (SMQs)/adverse event grouped terms (AEGTs) were utilized to detect safety issues. The analyses applying the SMQs did not identify any severe cutaneous reactions however an acute renal failure AE (renal impairment) was identified in the ceftriaxone group. One patient in the RO4908463 1500 mg group had an AE of renal failure which was not detected in the SMQ. This renal failure AE, which was mild in severity and considered probably related to RO4908463, resolved after discontinuation of RO4908463. The analyses using the AEGTs for hypersensitivity and rash identified six events in five patients in the RO4908463 groups and two events in two patients in the ceftriaxone group. The RO4908463 1500 mg group had the highest incidence of hypersensitivity or rash adverse event grouped terms (hypersensitivity events 4%, rash events 3%). Nine patients had AEs of transaminase elevation or hepatitis. Six of these patients were receiving RO4908463 1500 mg b.i.d, one was receiving RO4908463 750 mg b.i.d and two were receiving ceftriaxone 1000 mg q.d. All of these events were considered possibly or probably related to study drug except for the two unrelated events of transaminases increased and alcoholic hepatitis, both in patients receiving ceftriaxone. All of these events resolved with no sequelae. The number of patients with confirmed positive Coomb's test results was similar in the RO4908463 1500 mg group and ceftriaxone group. One patient in the RO4908463 750 mg group had a post baseline positive urine hemosiderin test, but this was not associated with a confirmed positive Coomb's test. Four patients receiving RO4908463 experienced AEs of anemia. No AEs of hemolysis, leucopenia, neutropenia or thrombocytopenia were observed.

Other than a higher incidence of increased ALAT and ASAT in the RO4908463 treatment groups there were no clinically significant changes noted in laboratory parameters tested. Similarly, there were no clinically significant differences between the treatment groups with respect to vital signs or ECG changes.

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CONCLUSIONS:

Treatment with RO4908463 1500 mg b.i.d was shown to be non-inferior to treatment with ceftriaxone 1000 mg q.d., however, non-inferiority of the RO4908463 750 mg b.i.d dosing regimen could not be concluded.

No clinically significant safety concerns were identified with RO4908463 treatment, however more adverse events were reported with RO4908463 1500 mg b.i.d compared with RO4908463 750 mg b.i.d.