2 Synopsis

<table>
<tr><td>Name of Sponsor/Company:
Furiex</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
JNJ-32729463 Tablets & JNJ-32729463 for Injection</td></tr>
<tr><td>Name of Active Ingredient:
JNJ-32729463</td></tr>
<tr><td colspan="3">Title of study: A Randomized, Controlled, Double-Blind, Multicenter, Phase 2 Study of the Safety/Tolerability and Efficacy of JNJ-32729463 Compared With Moxifloxacin for the Treatment of Subjects Requiring Hospitalization for Community-Acquired Bacterial Pneumonia (CABP) With a PORT Score of II or Greater</td></tr>
<tr><td colspan="3">Investigator(s) and study center(s): 16 investigators at 16 investigative sites in 5 countries.</td></tr>
<tr><td colspan="3">Publication(s) (reference): None.</td></tr>
<tr><td colspan="2">Studied period (years):
February 2011 to October 2011</td><td>Phase of development:
2</td></tr>
<tr><td colspan="3">Objectives:

The primary objective of this study was to demonstrate noninferiority in clinical success rates between JNJ-32729463 and moxifloxacin for subjects with community-acquired bacterial pneumonia (CABP).

The secondary objectives of this study were to evaluate the effect of JNJ-32729463 versus moxifloxacin on the following:

1. The daily signs and symptoms of CABP
2. The percentage of subjects with resolution of the signs and symptoms of CABP at Day 3 and Day 4
3. The per-pathogen microbiological response at Test of Cure (TOC)
4. The per-subject microbiological response at TOC
5. The clinical outcome at TOC in subjects with Streptococcus pneumoniae
6. The rate of superinfections or new infections
7. The time to oral switch
8. All-cause mortality within 30 days of start of study medication
9. The safety and tolerability profiles of JNJ-32729463 in subjects with CABP</td></tr>
</table>

Name of Sponsor/Company: Furiex	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Finished Product: JNJ-32729463 Tablets & JNJ-32729463 for Injection		
Name of Active Ingredient: JNJ-32729463		

10. Evaluation of adverse events (AEs) of special interest, including diarrhea, skin rash, elevated lipase, and elevated liver function tests

The exploratory objective was to determine the clinical success rate in subjects with *Staphylococcus aureus* CABP after treatment with JNJ-32729463.

Methodology: Approximately 120 total subjects requiring hospitalization for CABP with a PORT (Patient Outcomes Research Team) score of II or greater as defined in the inclusion and exclusion criteria were planned for random assignment to double-blind treatment with moxifloxacin or JNJ-32729463 in a 1:1 ratio. Additional subjects with suspected or confirmed *S. aureus* CABP may have been entered at selected sites and assigned to open-label treatment with JNJ-32729463.

Eligible subjects were stratified by PORT score (PORT II/III [≤90] or PORT IV/V [≥91]) and age (≥50 or <50). The study was terminated early after enrollment of a total of 31 subjects into the JNJ-32729463 or moxifloxacin double-blind treatment arms and 1 subject into the open-label JNJ-32729463 treatment arm. Study termination was due to business reasons only and was not based on safety concerns.

Subjects received treatment with intravenous (i.v.) study medication for a minimum of 72 hours, including a minimum of 24 hours after absence of fever. Subjects could be switched to oral study medication once the following criteria were met: clinical improvement in respiratory status, as evidenced by a respiratory rate <24 breaths/min and an oxygen saturation (measured by cutaneous pulse oximetry) of >90% on room air; hemodynamically stable, with a heart rate <100 beats/min, and a systolic blood pressure of >90 mm Hg; ability to maintain oral intake; and normal mental status, or has returned to baseline mental status.

Study medication could be stopped when the infection was considered clinically cured with a minimum treatment period of 7 days and a maximum treatment period of 14 days. Subjects

Name of Sponsor/Company: Furiex	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use Only)**
Name of Finished Product: JNJ-32729463 Tablets & JNJ-32729463 for Injection	**Volume:**	
Name of Active Ingredient: JNJ-32729463	**Page:**	

who needed antibiotic treatment beyond 14 days were considered clinical failures. The maximum duration of a subject's participation was approximately 31 days. This included the baseline visit, up to a 2-week treatment period, and up to a 3-week follow-up period. Subjects could have up to 17 study visits (Baseline, Days 2 to 14, end of therapy [EOT], TOC, and a follow-up visit).

Number of subjects (planned and analyzed):
Approximately 120 subjects were planned for randomization: 60 subjects were planned for randomization in each treatment group. A total of 15 subjects were randomly assigned to receive JNJ-32729463; a total of 16 subjects were randomly assigned to receive moxifloxacin. One subject received open-label JNJ-32729463.

Diagnosis and main criteria for inclusion:
Male or nonpregnant, nonlactating females aged 18 to 85 years, inclusive, with CABP that required hospitalization with a PORT score of II or greater and 3 or more of the following clinical signs or symptoms were eligible for enrollment: cough with production of purulent sputum, dyspnea or tachypnea, chest pain, fever or hypothermia, and clinical findings of pulmonary consolidation. Subjects must also have had chest x-ray findings consistent with bacterial pneumonia and had been able to generate adequate sputum specimens via deep expectoration or bronchoscopy. Subjects were not eligible if they had received systemic antibiotics within the last 96 hours prior to randomization (except a single dose of a short-acting antibiotic within 24 hours before randomization); prior non-fluoroquinolone antibiotic use was also allowed in specified cases of clinical failure as stated in the exclusion criteria. Other exclusion criteria included contraindications for moxifloxacin or other fluoroquinolones or contraindications as specified in the JNJ-32729463 investigator's brochure, or medical conditions or concomitant therapies that may have interfered with the evaluation of efficacy or safety or impacted the subject's ability to participate in the study.

Name of Sponsor/Company: **Furiex**	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Finished Product: **JNJ-32729463 Tablets & JNJ-32729463 for Injection**		
Name of Active Ingredient: **JNJ-32729463**		

Test product, dose and mode of administration, batch number(s):

JNJ-32729463, 150 mg administered intravenously every 12 hours for a minimum of 72 hours including a minimum of 24 hours after absence of fever and then 250 mg administered orally approximately every 12 hours for a total treatment time of 7 to 14 days.

Product	Lot Number
JNJ-32729463 100 mg/100 mL sterile vial	[redacted]
JNJ-32729463 250 mg capsule	[redacted]
JNJ-32729463 100 mL inject solvent	[redacted]

Duration of treatment:

All subjects were to be treated for a minimum of 7 days and a maximum of 14 days.

Name of Sponsor/Company: Furiex	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use Only)**
Name of Finished Product: JNJ-32729463 Tablets & JNJ-32729463 for Injection	**Volume:**	
Name of Active Ingredient: JNJ-32729463	**Page:**	

Reference therapy, dose and mode of administration, batch number(s):
Moxifloxacin, 400 mg once daily administered intravenously for a minimum of 72 hours including a minimum of 24 hours after absence of fever and then administered orally once daily for a total treatment time of 7 to 14 days. To maintain the blind, subjects assigned to moxifloxacin received moxifloxacin once daily with a matching placebo dosed approximately 12 hours apart.

Product	Lot Number
Moxifloxacin 400 mg capsules	[redacted]
Moxifloxacin 400 mg Injection (i.v. 250 mL bag)	[redacted]
Placebo capsule	[redacted]

Criteria for evaluation:
Efficacy: Clinical efficacy was measured through evaluation of the signs and symptoms of CABP. Microbiological assessments included culture and susceptibility testing of bacterial isolates.
Safety: Safety assessments included AE monitoring, clinical laboratory evaluations (hematology and serum chemistry), vital sign measurements, at-home body temperature measurements, electrocardiogram (ECG) results, and physical examination findings. Subjects were monitored for AEs of special interest, including diarrhea, skin rash, elevated lipase, and elevated liver function tests.

Name of Sponsor/Company: Furiex	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use Only)**
Name of Finished Product: JNJ-32729463 Tablets & JNJ-32729463 for Injection	**Volume:**	
Name of Active Ingredient: JNJ-32729463	**Page:**	

Statistical methods:

General: All analyses were conducted using SAS software, Version 9.1 or higher (SAS Institute Inc, Cary, North Carolina).

Six analysis sets were generated for analysis: All Randomized Set, Intent-to-Treat (ITT) Set, Microbiological ITT (m-ITT) Set, Clinically Evaluable (CE) Set, Microbiologically Evaluable (ME) Set, and Safety Set. Subjects in the All Randomized Set, ITT Set, m-ITT Set, ME Set, and CE Set were analyzed according to randomized treatment assignment. Subjects in the Safety Set were analyzed according to the treatment actually received.

Primary Efficacy: The primary efficacy endpoint of clinical outcome was classified as either clinical success or clinical failure. Clinical success was defined as a subject who was alive and had resolution of disease-specific signs and symptoms present at enrollment and no new symptoms or complications attributable to CABP. Any other outcome was defined as a clinical failure. Subjects designated as clinical failures at an early time point were designated as clinical failures for all subsequent follow-up visits. Missing clinical response was classified as unevaluable. At the TOC visit, when the clinical response was documented, the number and percentage of subjects in each response category (clinical success, clinical failure, or unevaluable) are summarized by treatment and overall. Clinical outcome was evaluated via a logistic regression model with treatment group as a main effect and age as a covariate for the ITT Set. The odds ratio and the 95% Wald confidence intervals (CIs) for the treatment group effect were computed. All noninferiority tests were 1-sided hypothesis tests performed at the 2.5% level of significance. These noninferiority tests were based on the lower limit of the 2-sided 95% CI. A noninferiority test for the risk difference analysis was also conducted for the primary efficacy endpoint for the ITT Set. A sensitivity analysis of the primary endpoint on the m-ITT Set was conducted using the method described for the primary efficacy endpoint on the ITT Set.

Name of Sponsor/Company: Furiex	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: JNJ-32729463 Tablets & JNJ-32729463 for Injection	Volume:	
Name of Active Ingredient: JNJ-32729463	Page:	

Secondary Efficacy: All signs and symptoms of CABP except fever or hypothermia were assessed via 4-point numeric rating items--response scales of 0 (none), 1 (mild), 2 (moderate), and 3 (severe). Summary statistics for each sign or symptom by visit, by treatment, and overall are summarized in a table including the change from Baseline for the ITT Set.

Fever or hypothermia was derived from vital signs and/or temperature log.

Treatment groups were compared in the ITT Set using a logistic regression model as described for the primary analysis. A response of unevaluable was considered clinical failure for the purposes of this analysis. A sensitivity analysis of the clinical outcomes on the m-ITT Set was also conducted. Microbiological response was generated at the TOC assessment at both the subject and pathogen levels. The following responses were considered: eradication, presumed eradication, superinfection, persistence, presumed persistence, and new infection. The by-subject microbiologic outcome was analyzed for m-ITT Set using a logistic regression model as described for the primary analysis with treatment group as main effects and age as a covariate. Microbiological success was considered a microbiological response of eradicated or presumed eradicated. Responses of persistence, presumed persistence, or unevaluable were considered failure. Similar analyses were performed on the subset of subjects with infections caused by *S. pneumoniae*. Other secondary efficacy endpoints included time to oral switch and all-cause mortality within 30 days of start of study medication. A summary of clinical response at TOC by baseline pathogen is presented for the m-ITT Set for the double-blind treatment groups.

Susceptibility to JNJ-32729463 and moxifloxacin of *S. pneumoniae* isolates from the sputum specimens and blood specimens are summarized at TOC visit for the m-ITT Set for double-blind treatment groups. Susceptibility was determined by the central laboratory and isolates were categorized as susceptible, intermediate, resistant, not susceptible, not tested, or

Name of Sponsor/Company: Furiex	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: JNJ-32729463 Tablets & JNJ-32729463 for Injection	Volume:	
Name of Active Ingredient: JNJ-32729463	Page:	

no interpretation.

Exploratory Efficacy: The exploratory efficacy endpoint was the clinical success rate in subjects with *S. aureus* CABP after treatment with JNJ-32729463.

Safety: Adverse event summaries include all AEs, AEs of special interest, AEs by relationship to study medication, AEs by severity, serious AEs (SAEs), and AEs leading to discontinuation of study drug. Only TEAEs collected through the follow-up visit are summarized in tables by system organ class and preferred term; however, all AEs are presented in data listings. Serum chemistry and hematology laboratory results are summarized in tables by treatment group using the Safety Set for Baseline, Visit 4 (Day 4), Visit 7 (Day 7), EOT, and TOC.

C-reactive protein levels, vital sign measurements, and ECG measurements are summarized in tables by visit and treatment group using the Safety Set. Physical examination results are summarized in a table by visit and by treatment group and overall. Details of all nondrug therapies and re-hospitalizations due to CABP including admission date and discharge date are presented in data listings.

Summary and conclusions:

Efficacy results: The rates of clinical success in the ITT Set were similar for the double-blind JNJ-32729463 and moxifloxacin treatment groups, with 86.7% (13 of 15) and 81.3% (13 of 16) subjects in each treatment group, respectively, achieving clinical success; the OR (95% CI) was 1.54 (0.22, 10.97). The study was not powered and conclusions regarding noninferiority cannot be made based on the small sample size.

Daily improvement in the baseline signs and symptoms of CABP were noted in all treatment groups. No subjects in any treatment group had resolution of all baseline signs and symptoms

Name of Sponsor/Company: Furiex	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: JNJ-32729463 Tablets & JNJ-32729463 for Injection	Volume:	
Name of Active Ingredient: JNJ-32729463	Page:	

of CABP at Day 3. One subject in the moxifloxacin group and no subjects in the JNJ-32729463 groups had resolution of the signs and symptoms of CABP at Day 4. Overall, symptoms were resolved or mild in intensity by EOT.

At Baseline, 8 subjects in the double-blind JNJ-32729463 group and 5 subjects in the moxifloxacin group had fever. The majority of subjects with fever at Baseline had resolution of fever by Day 3 in both groups.

Thirteen subjects in each double-blind treatment group and the 1 subject in the open-label group had *S. pneumoniae* isolated from sputum or identified by PCR at Baseline. The rate of clinical success for subjects with *S. pneumoniae* isolated from sputum at Baseline was similar in the treatment groups, with 11 subjects in the double-blind JNJ-32729463 group, 10 subjects in the moxifloxacin group, and 1 subject in the open-label JNJ-32729463 group achieving clinical success at the TOC visit.

Cultures of postbaseline sputum (if available) were all negative for pathogens; therefore, the eradication or persistence of baseline pathogens was presumed based on clinical response. A higher proportion of subjects in the double-blind JNJ-32729463 group (85.7%) had presumed eradication of the baseline pathogen compared with the moxifloxacin group (76.9%) based on a clinical outcome of clinical success. The open-label JNJ-32729463 subject also had presumed eradication.

A total of 86.7% of subjects in the double-blind JNJ-32729463 and 81.3% of subjects in the moxifloxacin treatment group switched from i.v. to oral medication. The mean (50% quartile) time to oral switch was similar between the treatment groups (JNJ-32729463: 4.8 [4.6] days; moxifloxacin: 5.1 [4.0] days). The time to oral switch for the subject in the open-label

Name of Sponsor/Company: Furiex	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: JNJ-32729463 Tablets & JNJ-32729463 for Injection	Volume:	
Name of Active Ingredient: JNJ-32729463	Page:	

JNJ-32729463 group was 3.2 days.

No subjects reported any superinfection or new infection.

No subjects in the JNJ-32729463 groups died within 30 days of start of study medication. Two subjects in the moxifloxacin treatment group died within 30 days of start of study medication, 1 each due to a fatal AE of shock and myocardial infarction.

In the double-blind JNJ-32729463 treatment group, 53.3% of subjects (8 of 15) were both clinically stable and met the criteria for symptoms success at Day 4 compared with the moxifloxacin group (43.8% [7 of 16]); the OR for the combined endpoint was 1.34 (0.22, 8.14). The open-label JNJ-32729463 subject was both clinically stable and met the criteria for symptoms success at Day 4.

Safety results: In the double-blind JNJ-32729463 group, 10 subjects experienced a total of 27 AEs of which 2 AEs in 2 subjects were considered severe. In the moxifloxacin group, 12 subjects experienced a total of 22 AEs of which 4 AEs in 4 subjects were considered severe. The only AEs experienced by more than 1 subject overall were diarrhea, hypokalemia, oral candidiasis, and elevated γ-glutamyltransferase. The open-label JNJ-32729463 subject did not experience any AEs during the study.

In the double-blind JNJ-32729463 group, 1 nonfatal SAE of acute respiratory failure requiring intubation and ventilation was reported; the event occurred on Day 2 of treatment, resulted in treatment discontinuation, and was considered unrelated to study medication. No other events leading to treatment discontinuation were reported.

In the moxifloxacin group, a total of 4 SAEs in 4 subjects, including 2 deaths, were reported: 1 subject each with a fatal AE of shock and myocardial infarction, and 1 subject each with a

Name of Sponsor/Company: Furiex	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: JNJ-32729463 Tablets & JNJ-32729463 for Injection	Volume:	
Name of Active Ingredient: JNJ-32729463	Page:	

nonfatal AE of pseudomembranous colitis and noncardiac chest pain.

Five subjects treated with double-blind JNJ-32729463 experienced a total of 6 AEs of special interest, including events categorized as diarrhea in 2 subjects, elevated liver enzyme in 2 subjects, and skin rash in 1 subject; no events of elevated lipase were reported. Three subjects treated with moxifloxacin experienced a total of 4 AEs of special interest, including events classified as diarrhea in 2 subjects (includes a single subject with 2 events of pseudomembranous colitis) and elevated liver function tests in 1 subject.

With few exceptions, in general, results for laboratory parameters including hematology and serum chemistry, vital sign measurements, and ECGs were consistent with the subject population and did not show any remarkable between-treatment differences or changes from Baseline to the end-of-treatment.

Mean (SD) and median C-reactive protein levels were high in both treatment groups at Baseline (152.94 [125.65] mg/L and 130.45 mg/L in the double-blind JNJ-32729463 group, respectively; 173.32 [178.73] mg/L and 69.05 mg/L in the moxifloxacin group, respectively) and decreased over time. Mean values were variable in both treatment groups at all time points with large standard deviations. At EOT, C-reactive protein levels ranged from 2.0 to 13.7 mg/L in the JNJ-32729463 group and 1.3 to 242.1 mg/L in the moxifloxacin group, and median values were higher in the moxifloxacin (10.20 mg/L) group than the JNJ-32729463 group (5.55 mg/L).

Conclusion:

Overall, although the study was terminated early for business reasons after enrollment of only 32 subjects, the rate of clinical success in the JNJ-32729463 group was comparable to

Name of Sponsor/Company: **Furiex**	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Finished Product: **JNJ-32729463 Tablets & JNJ-32729463 for Injection**		
Name of Active Ingredient: **JNJ-32729463**		
the rate of clinical success in the moxifloxacin group, and daily improvement in the baseline signs and symptoms of CABP was noted for all treatment groups. The safety profile of JNJ-32729463 was generally similar to that of moxifloxacin and consistent with the subject population. Most AEs were mild or moderate in intensity, and occurred in only 1 subject in either group. One nonfatal SAE of acute respiratory failure was reported for 1 subject in the JNJ-32729463 group. A total of 4 SAEs in 4 subjects, including 2 deaths, were reported in subjects treated with moxifloxacin: 1 subject each with a fatal AE of shock and myocardial infarction, and 1 subject each with a nonfatal AE of pseudomembranous colitis and noncardiac chest pain.		
Date of report: 31 May 2012		