SYNOPSIS

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Name of Sponsor/Company	Janssen Research & Development
Name of Finished Product	To be determined
Name of Active Ingredient(s)	JNJ-38518168

Protocol No.: 38518168ARA2001

Title of Study: A Phase IIa Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of JNJ-38518168 in Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy With Synovial Biopsy Substudy

EudraCT Number: 2009-012118-27

Study Center(s): The trial was conducted at 26 sites in 9 countries: Russia, Czech Republic, South Korea, Poland, United Kingdom, Netherlands, Taiwan, Spain, and Ireland.

Publication (Reference): None.

Study Period: 09 December 2009 to 17 November 2010

Phase of Development: 2a

Objectives and Modifications due to Early Termination of Study:

Modifications: The sponsor terminated this trial on 28 October 2010 because of a serious adverse event (SAE) with a fatal outcome. The trial did not complete enrollment and the majority of subjects did not complete the planned 12 weeks of treatment. Because of the early termination of the study, the study objectives were modified and the scope of the protocol-specified efficacy analysis was reduced. The modified analysis included a complete assessment of safety and tolerability of JNJ-38518168 as defined in the protocol and a descriptive summary of selected efficacy endpoints (swollen joint count, tender joint count, patient's assessment of pain, Health Assessment Questionnaire-Disability Index (HAQ-DI), patient's and physician's assessment of disease activity, C-reactive protein [CRP], and erythrocyte sedimentation rate [ESR]) with minimum data handling rules.

After review of the descriptive efficacy summary results, an exploratory analysis of efficacy was planned and documented in a supplemental statistical analysis plan (SAP). The objective of the post-hoc efficacy analysis was to evaluate the treatment effects of JNJ-38518168 as defined in the protocol and included the analyses of the composite scores for the Disease Activity Index Score (28 joints) [DAS28 (CRP)] and the American College of Rheumatology (ACR) 20, 50, 70, 90 response rates. While the objectives of the post-hoc efficacy analysis was the same as those stated in the protocol, the analysis population, the statistical analysis method, and data handling rules were modified to reflect the premature termination of the study. Throughout this report, the term "protocol-defined" is used to describe objectives and methods described in the original protocol and before the termination of the study. The term "modified" is used to describe objectives and methods defined in the SAP dated 18 December 2010; the term "post-hoc" is used to describe objectives and methods in post-hoc efficacy analyses as detailed in the Exploratory Analysis SAP dated 18 February 2011.

Objectives: The protocol-specified primary, secondary, and exploratory objectives of this study included the following:

Primary Objective: To assess the safety, tolerability, and efficacy (in terms of change from baseline DAS28 using CRP) of JNJ-38518168 at a dose of 100 mg/day for up to 12 weeks compared with placebo in subjects with active rheumatoid arthritis (RA) despite methotrexate (MTX) therapy.

Secondary Objective: To assess the efficacy of JNJ-38518168 as measured by ACR component scores and ACR 20, 50, and 70 response rates at Week 12.

Exploratory Objectives: To assess the effect of JNJ-38518168 on various biomarkers detected in synovial biopsy tissue and blood samples and to characterize the population pharmacokinetics (PK) of JNJ-38518168 in adults with active RA despite MTX therapy.

Modified Primary Objective: As noted in the Statistical Analysis Plan (SAP) dated18 December 2010, the primary objective of the study analysis was modified to evaluate the safety and tolerability of JNJ-38518168 at a dose of 100 mg/day for up to 12 weeks compared with placebo. Additionally, because of the premature termination of the study, the scope of the efficacy analysis was reduced; therefore, the planned analyses of composite RA endpoints (DAS28 and ACR) were removed.

Post-Hoc Efficacy Objectives: As noted in the Exploratory Analysis SAP (18 February 2011), the objectives of the post-hoc efficacy analysis, which were the same as those stated in the protocol, to evaluate the treatment effects of JNJ-38518168 with composite RA endpoints (DAS28 and ACR); however, data handling rules were modified to reflect the premature termination of the study.

Methodology: This was a multi-center, randomized, double-blind, placebo-controlled, parallel-group study in subjects with active RA despite MTX therapy with a synovial biopsy substudy. A target of 90 subjects were to be randomly assigned to treatment, with 60 and 30 subjects planned for the active and placebo treatment groups, respectively. A substudy for detecting biomarkers in synovial biopsy tissue was planned at selected sites in up to 18 subjects, with 12 and 6 subjects planned for the active and placebo treatment groups, respectively.

Upon satisfying the screening procedures, during Visit 2 eligible subjects were randomly allocated in a 2:1 ratio to receive 1 of the following treatments:

- JNJ-38518168 100 mg once daily for 12 weeks
- Matching placebo capsules once daily for 12 weeks

The treatment period lasted 12 weeks. Study visits were conducted at the end of Weeks 1, 2, 4, 6, 8, and 12 (Visits 3, 4, 5, 6, 7 and 8, respectively).

Subjects who completed treatment had a study termination visit at the end-of-treatment Week 12 (Visit 8). Subjects returned to the clinic for a safety follow-up visit (Visit 9) 4 weeks after the completion of treatment. Subjects who discontinued the study prematurely completed the Visit 8 termination procedures at the time of discontinuation or as soon thereafter as possible.

A Data Monitoring Committee (DMC) composed of sponsor clinicians and statisticians were to review the study data for safety purposes on an ongoing basis. Interim analyses of unblinded safety and efficacy data were to be performed and reviewed by the DMC on 2 occasions: when approximately 20% of subjects completed Week 12 (review of safety data only) and when approximately 50% of subjects completed Week 12 (review of safety and efficacy data). Because of the early termination of the study, the second interim analysis was not performed.

Number of Subjects (planned and analyzed): Approximately 90 men and women aged 18 to 75 years, inclusive, with active RA (per ACR criteria) for at least 6 months despite MTX therapy were planned for enrollment. At the time of early termination, a total of 86 subjects had been enrolled; 36 subjects completed the study and 86 subjects were included in the safety and intent-to-treat (ITT) population for analyses.

Diagnosis and Main Criteria for Inclusion: Subjects were eligible for this study if they had a diagnosis of RA functional Class I to III according to the ACR criteria for a minimum of 6 months prior to screening, have active disease at the time of screening and at baseline, and were on MTX treatment at dosages between 7.5 to 25 mg/week for at least 4 months, with a stable dose for a minimum of 4 weeks prior to randomization. Subjects were allowed to continue stable doses of oral steroids (prednisone ≤10 mg/day, or equivalent corticosteroid) and stable doses of non-steroidal anti-inflammatory drugs (NSAIDs). Subject must not have been treated with more than a total of 3 antirheumatic biologic agents or a total of 5 conventional disease modifying anti-rheumatic drugs (DMARDs) that proved ineffective before screening.

Test Product, Dose and Mode of Administration, Batch No.: JNJ-38518168, 2 x 50 mg oral tablets**.** The following batch numbers of JNJ-38518168 were supplied for use in the study: 361326, 361704, 362055, 362341, 363238, A00702.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo, 2 x 50 mg oral tablets. The following batch numbers of placebo were supplied for use in the study: 361326, 361704, 362055, 362341, 363238, A00703.

Duration of Treatment: The study consisted of a screening period, a 12-week treatment period, and a follow-up visit 4 weeks after the last dose.

Criteria for Evaluation: All randomized subjects were included in the summary of baseline demographics and disease characteristics. The ITT population was used for the primary efficacy and selected secondary analyses. All randomized subjects were included in the safety evaluation.

Statistical Methods: As specified in the protocol, all efficacy analyses were based on the ITT population, which included all subjects who were assigned to a randomized treatment and who had at least 1 efficacy measurement after baseline during the treatment phase for the primary efficacy variable, the DAS28 (using CRP) score. Missing values were to be imputed using the last observation carried forward (LOCF) approach. Additionally, analyses were to be performed to evaluate the impact of missing data.

In the post-hoc efficacy analysis, the baseline-adjusted analysis of covariance (ANCOVA) models were used to estimate treatment effects for DAS28 and the other efficacy endpoints at each time point after baseline. Statistical significance testing for non-normally distributed endpoints and ACR numeric score (ACR-N) used the Kruskal Wallis test. The Cochran Mantel Haenszel test (CMH) was used to determine statistical significance of categorical measures. Nominal statistical significance was assessed with respect to 2-sided testing at $p \leq 0.05$.

The post-hoc analyses were based on ‘observed cases while on treatment’ with treatment failure rules applied. The “observed cases” means no imputation was performed for missing study visits. However, missing measurements for a non-missing visit were imputed using LOCF with the exception of baseline values. No imputation was performed for a missing baseline value. The “while on treatment” means that only observed data within 20 days of the last treatment with study drug were included. If a subject met 1 or more of the treatment failure criteria, the subject was considered a treatment failure for all efficacy endpoints from the earliest date of the treatment failure. The measurements from last visit before treatment failure were carried forward.

Pharmacokinetic data were listed for all subjects with available plasma concentrations by collection time and descriptive statistics were calculated for the plasma concentrations of JNJ-38518168 at each sampling time. Population pharmacokinetic analysis of plasma concentration-time data of JNJ-38518168 was performed using nonlinear mixed-effects model.

Safety data were summarized using descriptive statistics.

RESULTS: The trial was conducted at 26 sites. At the time of early termination, 86 subjects had been enrolled in 9 countries as follows: Russia (37 subjects), Czech Republic (22 subjects), South Korea (11 subjects), Poland (4 subjects), United Kingdom (3 subjects), Netherlands (3 subjects), Taiwan (3 subjects), Spain (2 subjects), and Ireland (1 subject).

The percentage of subjects who completed 12 weeks of treatment was relatively balanced between treatments. Overall, the main reason for early study withdrawal was the sponsor's early termination of the study. Early termination for reasons other than sponsor's decision occurred at a similar frequency in the 2 treatment groups. Other reasons for withdrawal in the 100-mg JNJ-38518168 group included lack of efficacy, withdrawal of consent, and adverse events; and in the placebo group, other reasons for withdrawal included only adverse events.

Study Completion/Withdrawal Information
(Study 38518168ARA2001: All Randomized Subjects)

Population Reason Withdrawn	PLACEBO (N=28) n (%)	JNJ-38518168 100 mg (N=58) n (%)	Total (N=86) n (%)
Randomized population	28 (100)	58 (100)	86 (100)
Safety population	28 (100)	58 (100)	86 (100)
ITT population	28 (100)	58 (100)	86 (100)
Completed	12 (43)	24 (41)	36 (42)
Withdrawn	16 (57)	34 (59)	50 (58)
Adverse event	3 (11)	4 (7)	7 (8)
Lost to follow-up	0	0	0
Withdrawal of consent	0	1 (2)	1 (1)
Study terminated by sponsor	13 (46)	28 (48)	41 (48)
Lack of efficacy	0	1 (2)	1 (1)

Note: Percentages calculated with the number of subjects in each group as denominator.
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The distributions of subject age, height, weight, and body mass index were similar across the 2 treatment groups. Overall, the study enrolled more women (68 [79%] subjects) than men (18 [21%] subjects). The overall mean age was 51.6 years, ranging from 21 to 74 years. The overall median age was 53 years.

Overall, the baseline disease characteristics were comparable across treatment groups. The JNJ-38518168 group had more subjects with Class III Global Functional Status at baseline than placebo (21 [36%] subjects versus 7 [25%] subjects). The median number of years since the diagnosis of RA was also longer for JNJ-38518168 group (5.75 years) than for the placebo group (4.90 years).

A total of 16 (28%) subjects in the JNJ-38518168 group and 5 (18%) subjects in the placebo group had 1 or more protocol deviations.

Of the 86 subjects who were randomly assigned to treatment, 58 subjects were assigned to receive 100-mg JNJ-38518168 and 28 subjects were assigned to receive placebo. All 86 subjects received at least 1 dose of their assigned randomized study drug. The average number of doses of the study drug that were received and the average duration of exposure were similar between the 2 treatment groups. Two (7.1%) subjects in the placebo group had study drug dose reduction compared with 1 (1.8%) subject in the JNJ-38518168 group. The average weekly dose of MTX was also similar between the 2 treatment groups (14.2 mg/week vs 15.5 mg/week for placebo and JNJ–38518168 100-mg group respectively).

EFFICACY RESULTS: All efficacy results discussed are based on post-hoc efficacy analysis since the key endpoint to evaluate treatment effects of JNJ-38518168 were the composite RA endpoints (DAS28 and ACR) included in the post-hoc efficacy analysis. Other efficacy endpoints (swollen joint count, tender joint count, patient's assessment of pain, HAQ-DI, patient's and physician's assessment of disease activity, CRP, and ESR) were summarized in the 'modified analysis', but were evaluated for treatment effect in the post-hoc efficacy analysis. In addition, in the post-hoc efficacy analysis, the analysis population, the statistical analysis method, and data handling rules were defined to appropriately evaluate the treatment effects of JNJ-38518168, while reflecting the premature termination of the study.

The post-hoc efficacy analysis was conducted using an analysis set composed of observations made while on treatment (ie, within 20 days of the last dose), with LOCF data imputation performed for the last value before treatment failure for 4 subjects who received prohibited medications due to worsening of RA while participating in the study. For all exploratory analysis, the statistical significance should be considered as nominal.

In the post-hoc efficacy analysis, the baseline-adjusted ANCOVA of change from baseline in DAS28 (CRP) showed statistically significant treatment benefits from Week 2 that persisted through Week 12. The adjusted mean treatment differences (LS Means) (JNJ-38518168 minus placebo) at Week 12 was −0.853, which was statistically significant (p=0.037) despite the small sample size (31 subjects on JNJ-38518168 versus 14 subjects on placebo) due to early termination of the study. The CMH analysis of DAS28 (CRP) response also showed statistically significant improvement from Week 2 that persisted through Week 12, and a higher proportion of subjects in the JNJ-38518168 group achieved moderate or good response from Week 1 through Week 12. The baseline-adjusted ANCOVA analysis of change from baseline in DAS28 (ESR) showed treatment benefits at Week 4 and Week 12.

The CMH analysis of ACR20 response showed statistically significant improvement at Weeks 2, 4, and 12. A higher proportion of subjects in the JNJ-38518168 group achieved an ACR20 response from Week 1 through Week 12. Trends of improvement in ACR50 response was also observed at Weeks 4, 6 and 8, but the proportion at Week 12 was similar for the JNJ-38518168 group (3 [9.7%]) compared with the placebo group [1 (7.1%)]. Analysis of ACR-N index of improvement showed statistically significant results from Week 2 through Week 8, but the median ACR-N value at Week 12 was 18.2 for the JNJ-38518168 group compared with −7.8 for placebo group, which was not statistically significant (p=0.122).

The CMH analysis of HAQ-DI response showed statistically significant results at Weeks 1, 2, 4 and 8. A higher proportion of subjects in the JNJ-38518168 group achieved HAQ-DI response from Week 1 through Week 12. However, the placebo response rate was variable over time resulting in a reduced treatment benefit at Weeks 6 and 12.

PHARMACOKINETIC RESULTS: Following administration of multiple oral overencapsulated tablet doses of 100 mg/day for up to 12 weeks in subjects with active RA, the mean trough concentrations of JNJ-38518168 in plasma were 377, 403, 396, 382, and 338 ng/mL at Weeks 1, 2, 4, 6, and 8, respectively. Pharmacokinetic steady state appeared to be reached by the end of Week 2. Therefore, at steady state

(Weeks 2 through 8), the average trough concentration in subjects with RA was approximately 385 ng/mL.

SYNOVIAL BIOPSY SUBSTUDY: Because of the early termination of the study, there were not enough tissue samples available for analyses.

SAFETY RESULTS: The number of subjects who had 1 or more adverse events was higher in the 100-mg JNJ-38518168 group (34 [59%]) than in the placebo group (14 [50%]). More adverse events were reported within the musculoskeletal and connective tissue disorders, infections and infestations, and gastrointestinal disorders system organ classes for the JNJ-38518168 group than for the placebo group. Adverse events that occurred in at least 5% of subjects in either group were: arthralgia (6 [10%]) versus 1 [4%]), back pain (4 [7%] versus 0), RA (3 [5%] versus 1 [4%]), nasopharyngitis (3 [5%] versus 1 [4%]) and nausea (3 [5%] versus 0) for the JNJ-38518168 and placebo groups, respectively.

One subject (Subject [redacted]) died 21 days after starting treatment with JNJ-38518168 100 mg daily. The death of this subject led to the early termination of the study by the sponsor. Based upon a review of all available information for Subject [redacted] the most likely cause of death was considered to be secondary hemophagocytic lymphohistiocytosis (sHLH), a disorder characterized by an uncontrolled proliferation of cytotoxic T cells and activated macrophages, leading to dramatic increases in inflammatory cytokines and subsequent organ dysfunction. All of the serious adverse events (SAEs) experienced by Subject [redacted] were considered by the investigator to be possibly related to JNJ-38518168 administration. Based on the pathogenesis of sHLH, the known mechanisms of action of H_4R antagonism, the toxicological profile, and the current clinical data for JNJ-38518168 and a second H_4R antagonist (JNJ-39758979), the sponsor deemed that Subject [redacted]'s death was unlikely related to JNJ-38518168 or H_4R antagonism.

A total of 7 subjects experienced SAEs during the study, with more subjects in the JNJ-38518168 group (6 [10%] subjects) experiencing serious adverse events than in the placebo group (1 [4%] subject). The SAEs experienced by 3 out of 6 subjects treated with JNJ–38518168 100-mg were exacerbations of RA that led to hospitalization for intravenous steroid treatment. Other significant adverse events were those that led to interruption, reduction, or cessation of dosing, and these events were experienced by a similar number of subjects in each treatment group.

The overall safety and tolerability profile of JNJ-38518168 is consistent with the Phase 1 data for this compound. There is no clear explanation for the increase in musculoskeletal or gastrointestinal adverse events in subjects who received JNJ-38518168. Future research will determine if this effect is related to the compound. Similar to Phase 1 studies, an increase in serum creatinine was observed. The current hypothesis is that this is a result of inhibition of human organic cation transport 2 (hOCT2)-mediated creatinine secretion by JNJ–38518168 rather than an indication of nephrotoxicity. Additional studies are underway to further evaluate this issue.

Dose-dependent prolongation of the QTcF interval was observed in a previous Phase 1 study, but only a slight QTcF prolongation effect was observed in the present trial. There were no other notable effects on vital signs, other laboratory parameters, or ECG parameters, suggesting that overall JNJ-38518168 is safe and well-tolerated, and appropriate for further development in subjects who have RA.

STUDY LIMITATIONS: The study was terminated by the sponsor prematurely due to the death in the study. While the DAS28 and ACR20 results are encouraging for future development of JNJ-38518168 or other H_4R antagonists for RA, these data should be interpreted cautiously. In particular, the effect size cannot be accurately determined due to the small sample size.

CONCLUSION(S): Despite the early termination of this clinical trial and the substantial level of missing data, a post-hoc analysis indicates that treatment with 100 mg of JNJ-38518168 daily for up to 12 weeks

was associated with a reduction of signs and symptoms of RA, based on improvements observed in DAS28 and ACR scores as well as in all components of these scores, in subjects who had active RA despite treatment with MTX. The safety and tolerability profile of JNJ-38518168 is consistent with the Phase 1 data for this compound, and the 1 death due to sHLH did not appear to be related to the study drug. The data from this study should be interpreted cautiously because of the sponsor's early termination of the study and the resultant small sample size; however, these results support the future research of H_4R antagonists in RA.

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