Name of Finished Product	To be determined
Name of Active Ingredient(s)	JNJ-40346527

Protocol No.: 40346527ARA2001

Title of Study: A Phase 2a, Randomized, Multicenter, Double-blind, Placebo-controlled, Parallel-Group Study of JNJ-40346527 in Subjects With Active Rheumatoid Arthritis Despite Disease-Modifying Antirheumatic Drug Therapy

EudraCT Number: 2011-004529-28

NCT No.: NCT01597739

Clinical Registry No.: CR100801

Principal Investigator: None

Study Centers: The study was conducted at 35 sites in 9 countries: Argentina, Bulgaria, Chile, Czech Republic, Hungary, South Korea, Poland, Russia and Ukraine.

Publication (Reference): None

Study Period: 30 May 2012 to 30 April 2013

Phase of Development: 2a

OBJECTIVES:

The primary objective of the study was to assess the safety, tolerability, and efficacy (change from baseline in Disease Activity Score 28 [DAS28] using C-reactive protein [CRP]) of JNJ-40346527 200 mg/day (100 mg twice daily) for 12 weeks compared with placebo in subjects with active rheumatoid arthritis (RA) despite disease-modifying antirheumatic drug (DMARD) therapy.

The secondary objectives of the study were:

- To assess the efficacy of JNJ-40346527 as measured by American College of Rheumatology (ACR) 20 and 50 response rates at Week 12.
- To characterize the population PK of JNJ-40346527 in adults with active RA despite DMARD therapy.

The exploratory objective of this study was to assess the PD of JNJ-40346527 in adults with active RA despite DMARD therapy.

METHODS:

This was a randomized, double-blind, placebo-controlled, parallel-group study that evaluated JNJ-40346527 in subjects with RA despite DMARD therapy. Approximately 90 subjects were to be randomly assigned in a 2:1 ratio to 1 of 2 treatment groups (JNJ-40346527 at 200 mg/day [100 mg BID] or placebo BID, respectively) stratified by baseline methotrexate (MTX) usage (yes or no) and country/site. Subjects were to receive study drug for 12 weeks.

Subjects were to continue their permitted, stable DMARD therapy (MTX, sulfasalazine [SSZ], and/or hydroxychloroquine [HCQ]) through Week 12; but these therapies were not to be initiated during the study. Plasma PK samples were to be collected from all subjects in this study, according to the Time and Events Schedule in the protocol (Appendix 1). An optional PK substudy was planned to be conducted in

approximately 20 study subjects, who were to sign a separate consent form. Additional blood samples were to be collected for the substudy at Week 8 study visit. A follow-up visit for all randomized subjects was to occur 4 weeks after dosing was complete.

The study duration was to be approximately 16 weeks, including a 12 week placebo-controlled period and a 4-week follow-up period between the last dose and the last visit. The maximum length of subject participation was to be approximately 22 weeks, including a 6-week screening period. The end of the study was defined as the last follow-up visit of the last subject. Study visits were to occur at the time points specified in the Time and Events Schedule in the protocol (Appendix 1).

An internal Data Monitoring Committee was to be commissioned for this study.

Number of Subjects:

Approximately 90 subjects were to be randomly assigned in a 2:1 (active: placebo) ratio to 1 of 2 treatment groups.

Diagnosis and Main Criteria for Inclusion:

The study population was to include male or female subjects aged between 18 to 80 years (inclusive). Subjects had to have RA according to the revised 1987 American Rheumatism Association criteria for at least 6 months, and had active disease despite MTX, SSZ, and/or HCQ therapy at the time of screening. Active RA defined for the purpose of the study as persistent disease activity with at least 6 swollen/6 tender joints at screening and baseline and a CRP level of $\geq$0.8 mg/dL at screening. Subjects had to be on MTX, SSZ, and/or HCQ therapy for at least 6 months prior to screening, with a stable dose for a minimum of 8 weeks prior to screening. Subjects had to be positive for either anti-cyclic citrullinated peptide (anti-CCP) antibody or rheumatoid factor in serum.

In addition subjects had to meet criteria for concomitant medications, screening laboratory test results, TB history and TB testing results, and have agreed to use adequate birth control measures.

Complete inclusion and exclusion criteria are listed in the protocol (Appendix 1).

Test Product, Dose and Mode of Administration, Batch No.:

JNJ-40346527 was supplied as 50 mg gray-colored, hard, gelatin capsules.

All subjects were to receive 4 capsules daily, 2 in the morning and 2 in the evening. Subjects were to be instructed to take study drug with or without food in the morning and the evening at approximately the same times each day, and to finish taking all of the capsules from one bottle of study drug prior to taking study drug from a new bottle.

For subjects with poor tolerability, the dose could be reduced twice during the study (reduced to 1 capsule in morning and 1 capsule in evening). A dose reduction could occur after an initial AE. The dose could be returned to baseline after resolution of this event. A second dose reduction was permitted due to an AE; however, the dose could not be returned to baseline a second time. Subjects, those who were on a proton pump inhibitor (PPI) or a histamine 2 receptor (H_2R) antagonist were instructed to take their dose of study agent BID with a meal within approximately 30 minutes after breakfast in the morning and within approximately 30 minutes after their evening meal. Antacids, such as PPIs and H_2R antagonists significantly raise stomach pH and thereby were hypothesized to potentially decrease the dissolution and absorption of the JNJ-40346527. The administration of JNJ-40346527 with a meal triggers the release of bile salt, which in turn could potentially create an acidic environment required for better dissolution and absorption of the JNJ-40346527.

Reference Therapy, Dose and Mode of Administration, Batch No.:

A placebo oral capsule was to be supplied to match the active capsule in size, shape, and appearance. Batch/formulation numbers and expiration date for reference therapy are provided.

Duration of Treatment:

For each subject, the total duration of the study was to be approximately 22 weeks, including a 6-week screening period, a 12-week placebo-controlled treatment period and a 4-week follow-up period between the last dose and the last visit.

Criteria for Evaluation:

Efficacy assessments were to include the following: joint assessments (swollen and tender joint counts), Subject's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, Health Assessment Questionnaire-Disability Index (HAQ-DI), subject's assessment of pain, serum CRP, and erythrocyte sedimentation rate (ESR) as outlined in the Time and Events Schedule in the protocol (Appendix 1).

Efficacy Criteria

Primary Endpoint

- Change from baseline in DAS28 (using CRP) at Week 12.

Major Secondary Endpoints

- ACR 20 response rates at Week 12.
- DAS28 (using CRP) response rates at Week 12.

Other Secondary Endpoints

- ACR 50/70 response rates at Week 12.
- Change from baseline in DAS28 (using ESR) at Week 12.
- DAS28 (using ESR) response rates at Week 12.
- Health Assessment Questionnaire – Disability Index (HAQ DI) response at Week 12.
- Change from baseline in HAQ DI score at Week 12.
- Percent change from baseline in ESR levels at Week 12.
- Percent change from baseline in ACR components at Week 12.
- Change from baseline in Simplified Disease Activity Index (SDAI) at Week 12.
- Change from baseline in Clinical Disease Activity Index (CDAI) at Week 12.
- Number of Subjects with DAS28 (CRP) Remission Over Time.

Exploratory Endpoints

- Hybrid ACR response at Week 12.
- ACR/EULAR remission at Week 12.
- Changes from baseline in biomarkers at Week 12.

- Refer to SAP (Appendix 9) for the detailed description of the analyses planned for the study.

Pharmacokinetic evaluations: Blood samples were to be collected for the measurement of plasma concentrations of JNJ-40346527 and metabolites prior to the next administration of study agent from all subjects at the visits specified in the Time and Events Schedule in the protocol (Appendix 1). To evaluate any potential differences in the absorption of JNJ-40346527 between subjects receiving or not receiving PPIs or H_2R antagonists, Week 1 PK levels were to be analyzed and the calculated parameters will be addressed in the Advanced Modeling and Simulation report. In addition, population PK analysis was to be performed to predict the overall PK profile of JNJ-40346527 when PK samples collected from all subjects through Week 12 become available (ie, snapshot PK data) and the analysis and results of the analysis will be presented in the Advanced Modeling and Simulation report.

For all subjects, based on the individual plasma concentration-time data, using actual sampling times, plasma PK parameters were to be determined from the plasma concentration data collected from the intensive PK substudy (Week 8). PK parameters were calculated via non-compartmental analysis with validated WinNonlin software (v 5.3, Pharsight Corporation, Mountain View, California). PK parameters that were calculated, but were not limited to the following:

C_{max} maximum plasma JNJ-40346527 and metabolite concentration during a dosing interval at steady state.

Cmin minimum plasma JNJ-40346527 concentration during a dosing interval at steady state (may or may not be the trough concentration).

tmax time to reach the maximum plasma JNJ-40346527 concentration.

Biomarker evaluations: Blood samples (whole blood and serum) and urine were to be collected from all subjects at the times specified in the Time and Events Schedule (Appendix 1) for measurement of biomarkers. Biomarkers could include, but were not limited to, inflammatory markers, auto-antibodies, cartilage/bone markers, and other categories of biomarkers potentially involved in the development and the progression of RA or related to the JNJ-40346527 mechanism of action.

Pharmacogenomic evaluations: A pharmacogenomic blood sample was to be collected to allow for pharmacogenomic research (where local regulations permit) from subjects who sign a separate consent form.

Safety evaluations: Safety assessments were to include vital signs, general physical examination, AEs, concomitant medication review, ECGs, pregnancy testing, routine laboratory testing, urine protein testing, anemia markers testing, and fasting lipid measurements.

Statistical Methods:

Sample Size Determination: Sample size calculation was based on two positive RA trials (C0524T06 and 38518168ARA2001) with other compounds conducted by the sponsor. In those trials, the mean treatment difference of change in DAS28 (CRP) from baseline was approximately 0.8 with a common SD of about 1.15 to 1.3 for both the active and placebo groups. Under the assumption that the treatment difference of change in DAS28 (CRP) from baseline is 0.8 and the SD is 1.25, it was determined that a total of 90 subjects (30 and 60 subjects in the placebo and JNJ-40346527 groups, respectively) would provide approximately 80% power to detect the difference between the two treatment groups by using a 2 sided t-test at $\alpha = 0.05$.

Efficacy Analyses: Efficacy analyses were to be based on the modified intent-to-treat population (m-ITT), defined as all randomized subjects who had received at least one study agent administration and who had a baseline and at least one postbaseline value. Subjects included in the efficacy analyses were to be summarized according to their assigned treatment group regardless of whether or not they received the assigned treatment. Missing postbaseline values or missing components of composite endpoints were to

be imputed using the last-observation-carry-forward (LOCF) approach. All hypothesis testing were to be 2-sided and conducted at $\alpha = 0.05$.

- Primary Endpoint Analyses: Change from baseline in DAS28 (CRP) at Week 12 was to be compared between the JNJ-40346527 group and the placebo group using an analysis of covariance (ANCOVA) model with treatment as a fixed factor and baseline DAS28 (CRP) score as covariate. Subgroups analyses were to be performed using the same ANCOVA model, if number of subjects in the subset permits. Sensitivity analyses were to be performed with a similar model with change from baseline in the DAS28 (CRP) at Week 12 as the dependent variable, treatment and site as fixed factors and baseline DAS28 (CRP) score as a covariate. Sites without at least 1 subject per treatment group would be pooled with other similar sites for analysis purposes.
- Major Secondary Endpoints Analyses: ACR and DAS28 response rates were to be analyzed using Fisher Exact test.
- Other Secondary/Exploratory Endpoints Analyses: All the secondary endpoints except for responder rate were to be analyzed using the ANCOVA models with treatment group as a fixed factor and baseline values as covariate. Hybrid ACR response was to be analyzed using an ANCOVA model with treatment group as a fixed factor. Summary statistics were to be provided for each assessment except for responder rate. Ninety-five percent confidence interval (CI) and p-values were to be calculated.

Of note, in the protocol, all (above) analyses were to be conducted to incorporate MTX stratification. However, due to only 4 subjects without MTX in the placebo group, the statistical plan was written to remove MTX from the ANCOVA model and to replace Cochran Mantel Haenszel test with Fisher Exact test.

PK Analyses: Data were to be listed for all subjects in the intensive PK visit (Week 8) with available plasma concentrations. Subjects were to be excluded from the PK analysis if missing data or deviations to the data did not allow for accurate assessment of the PK.

All plasma concentrations below the lowest quantifiable concentration or missing data were to be labeled as such in the concentration data presentation for the intensive PK visit (Week 8). Concentrations below the lowest quantifiable concentration were to be treated as zero for the calculation of PK parameters on Week 8. All subjects and samples excluded from the analysis were to be clearly documented in the study report.

For the intensive PK visit only (Week 8), descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, and maximum values were to be calculated for the JNJ-40346527 plasma concentrations at each sampling time and for all PK parameters of JNJ-40346527.

The JNJ-40346527 plasma concentration-time data from all subjects were to be pooled and subjected to population PK analysis using nonlinear mixed effects modeling. If appropriate, data could be combined with those of other studies. Data handling rules for the population PK analysis and the assessment of H_2R antagonists and PPI were to be addressed in the Advanced Modeling and Simulation report. The influence of potential covariates (eg, demographics, laboratory variables) on key PK model parameters could be tested.

Biomarker Analyses: Changes in the concentration of individual biomarkers from baseline to the selected posttreatment time points were to be summarized. Associations between baseline levels and changes from baseline in selected markers and clinical response were to be explored. The biomarker analysis would characterize the response of subjects to JNJ-40346527 and loss of response, to determine if response to JNJ-40346527 could be predicted and to further our understanding of RA. The RNA and DNA analyses were to be summarized in separate technical reports.

Pharmacogenomic Analyses: Pharmacogenomic analyses will not be performed or reported**.**

RESULTS:

STUDY POPULATION:

A total of 96 subjects were enrolled into the study: 63 subjects in the JNJ-40346527 group and 33 subjects in the placebo group. One subject in the placebo group did not receive study drug due to a randomization error (Appendix 13).

Of the 95 subjects who were treated with study drug, 2 subjects from the placebo group (1 subject due to an AE and 1 subject due to lack of efficacy) and 6 subjects from the JNJ-40346527 group (3 subjects due to an AE and 3 subjects due to lack of efficacy) discontinued from the study agent through Week 12. The summary of study completion/withdrawal information is shown in Table 1**.**

Table 1: Number of Subjects Who Discontinued Study Agent Through Week 12 by Reason for Discontinuation; Randomized Subjects

(Study 40346527ARA2001)

	Placebo	JNJ40346527 100 mg BID	Total
Subjects randomized	33	63	96
Subjects treated	32	63	95
Subjects who discontinued study agent	2	6	8
Reason for discontinuation			
Adverse Event	1 (3.1%)	3 (4.8%)	4 (4.2%)
Withdrawal of consent	0	0	0
Product quality complaint	0	0	0
Death	0	0	0
Lost to follow-up	0	0	0
Physician decision	0	0	0
Pregnancy	0	0	0
Initiation of protocol prohibited medications	0	0	0
Lack of efficacy	1 (3.1%)	3 (4.8%)	4 (4.2%)
Other	0	0	0

Note: Percentage was calculated based on subjects treated.

Lists of subjects who discontinued the study agent through Week 12, who discontinued study participation early, who were unblinded, and who received more than 1 JNJ-40346527 dose during the study are provided in Appendix 13..

Demographic characteristics of the study population are presented in Table 2. Overall, the majority of subjects were female (87.5%) and Caucasian (89.6%). The median age was 54.5 years, ranging from 27 to 78 years. Subject demographic characteristics were generally similar between 2 treatment groups.

Table 2: Summary of Demographics at Baseline; Randomized Subjects

(Study 40346527ARA2001)

	Placebo	JNJ40346527 100 mg BID	Total
Subjects randomized	33	63	96
Age (years)			
N	33	63	96
Mean (SD)	54.7 (10.58)	54.2 (11.05)	54.3 (10.84)
Median	55.0	54.0	54.5
Range	(28; 77)	(27; 78)	(27; 78)
Age at Screening, n (%)			
N	33	63	96

Table 2: Summary of Demographics at Baseline; Randomized Subjects

(Study 40346527ARA2001)

	Placebo	JNJ40346527 100 mg BID	Total
< 45	5 (15.2%)	9 (14.3%)	14 (14.6%)
45 - 65	24 (72.7%)	45 (71.4%)	69 (71.9%)
> 65	4 (12.1%)	9 (14.3%)	13 (13.5%)
Sex, n (%)			
N	33	63	96
Male	4 (12.1%)	8 (12.7%)	12 (12.5%)
Female	29 (87.9%)	55 (87.3%)	84 (87.5%)
Race, n (%)			
N	33	63	96
Caucasian	30 (90.9%)	56 (88.9%)	86 (89.6%)
Asian	3 (9.1%)	7 (11.1%)	10 (10.4%)
Other	0	0	0
American Indian or Alaska Native	0	0	0
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	0	0	0
Unknown	0	0	0
Not Reported	0	0	0
Ethnicity, n (%)			
N	33	63	96
Hispanic or Latino	3 (9.1%)	8 (12.7%)	11 (11.5%)
Not Hispanic or Latino	30 (90.9%)	55 (87.3%)	85 (88.5%)
Unknown	0	0	0
Not Reported	0	0	0
Baseline Weight (kg)			
N	33	63	96
Mean (SD)	72.49 (13.662)	71.91 (14.005)	72.11 (13.819)
Median	71.00	72.00	71.60
Range	(45.3; 97.0)	(40.0; 103.0)	(40.0; 103.0)
Baseline Height (cm)			
N	33	63	96
Mean (SD)	162.44 (9.396)	162.35 (8.355)	162.38 (8.678)
Median	162.00	162.00	162.00
Range	(142.0; 187.0)	(149.0; 188.0)	(142.0; 188.0)
BMI (kg/m^2)			
N	33	63	96
Mean (SD)	27.581 (5.3105)	27.269 (4.9250)	27.376 (5.0351)
Median	27.854	26.273	26.691
Range	(16.53; 38.79)	(17.31; 38.96)	(16.53; 38.96)
Geographic region, n (%)			
N	33	63	96
Asia	3 (9.1%)	7 (11.1%)	10 (10.4%)
South Korea	3 (9.1%)	7 (11.1%)	10 (10.4%)
Europe	27 (81.8%)	48 (76.2%)	75 (78.1%)
Bulgaria	1 (3.0%)	5 (7.9%)	6 (6.3%)
Czech Republic	4 (12.1%)	2 (3.2%)	6 (6.3%)
Hungary	6 (18.2%)	6 (9.5%)	12 (12.5%)
Poland	2 (6.1%)	7 (11.1%)	9 (9.4%)
Russia	12 (36.4%)	25 (39.7%)	37 (38.5%)
Ukraine	2 (6.1%)	3 (4.8%)	5 (5.2%)
South America	3 (9.1%)	8 (12.7%)	11 (11.5%)
Argentina	2 (6.1%)	5 (7.9%)	7 (7.3%)

Table 2: Summary of Demographics at Baseline; Randomized Subjects

(Study 40346527ARA2001)

	Placebo	JNJ40346527 100 mg BID	Total
Chile	1 (3.0%)	3 (4.8%)	4 (4.2%)

Summary of baseline disease characteristics of randomized subjects are provided in Attachment TSIDEM02. The baseline disease characteristics of RA were similar between both treatment groups. Mean number of years since initial diagnosis of RA was 6.6 and 7.7 in the placebo and the JNJ-40346527 group, respectively. Mean tender joint count was 22.9 and 24.6 and the mean swollen joint count was 14.7 and 14.8 in the placebo and the JNJ-40346527 group, respectively. Approximately 88% and 94% of subjects were using MTX at baseline in the placebo and the JNJ-40346527 group, respectively; 24% and 29% of subjects were using PPIs or H_2R antagonists at baseline in the placebo and the JNJ-40346527 group, respectively. The mean baseline ESR was 50.7 mm/hour in the placebo group and 47.3 mm/hour in the JNJ-40346527 group. Mean baseline CRP was 2.26 mg/dL in the placebo group and 2.22 mg/dL in the JNJ-40346527 group.

Summary of medical history and diagnosis at baseline are presented in Attachment TSIDEM03. The most common conditions reported (in ≥10% of subjects in total population) were hypertension (44.8%), osteoporosis (15.6%), hyperlipidemia (14.6%) and diabetes mellitus (11.5%).

Concomitant Therapies

Summary of baseline concomitant medications used for RA is provided in Attachment TSICM01. The most common concomitant medication used for RA was MTX (90.6% in the placebo group; 93.7% in the JNJ-40346527 group) followed by nonsteroidal anti-inflammatory drugs (87.5% in the placebo group; 79.4% in the JNJ-40346527 group). More than 50% of subjects (53.1% in the placebo group and 61.9% in the JNJ-40346527 group) were using corticosteroid at baseline. RA concomitant medications are listed by subject in Attachment LSICM02.

Summary of non-RA concomitant medications is provided in Attachment TSICM03. The most common (reported in ≥10% of subjects in both the treatment groups) non-RA drug treatments were folic acid and derivatives (87.5% and 93.7% in the placebo and JNJ-40346527 groups respectively), angiotensin-converting enzyme inhibitors (28.1% and 27% in the placebo and JNJ-40346527 groups respectively), and PPIs (18.8% and 17.5% in the placebo and JNJ-40346527 groups respectively). Non-RA concomitant medications are listed by subject in Attachment LSICM04.

List of subjects using H_2R antagonists and PPIs is presented in Attachment LSICM06. List of subjects who met 1 or more treatment failure criteria prior to Week 12 is presented in Attachment LSICM05.

Protocol Deviations

Overall, major protocol deviations were reported in 9 subjects (5 subjects in the placebo group and 4 subjects in the JNJ-40346527 group). The most common major protocol deviation recorded was deviations related to selection criteria (3 [9.4%] subjects in the placebo group and 2 [3.2%] subjects in the JNJ-40346527 group). Of the 5 subjects who reported protocol deviation related to selection criteria, 4 subjects (2 subjects each in the placebo and the JNJ-40346527 group) took a drug (omeprazole) that potently inhibits CYP2C19 isoforms within 2 weeks or within 5 half-lives of the drug, prior to the first dose of study agent.

A summary of protocol deviations based in the safety analysis set is provided in Table 3. Listing of subjects with major protocol deviations are provided in Appendix 14.

Table 3: Number of Subjects with a Major Protocol Deviation; Safety Analysis Set

(Study 40346527ARA2001)

	Placebo	JNJ40346527 100 mg BID	Total
Subjects treated	32	63	95
Subjects with a major protocol deviation	5	4	9
Selection criteria not met	3 (9.4%)	2 (3.2%)	5 (5.3%)
Subject not withdrawn as per protocol	0	0	0
Excluded concomitant medication	0	0	0
Treatment deviation	1 (3.1%)	0	1 (1.1%)
Other	1 (3.1%)	2 (3.2%)	3 (3.2%)

Treatment Compliance and Extent of Exposure

Summary of treatment exposure and compliance through Week 12 is provided in Attachment TSIEXP01. The majority of subjects (>93%) had treatment compliance between 80% and 100%. The mean duration of study treatment administration was 81.1 days and 79.8 days in the placebo and the JNJ-40346527 groups, respectively. The mean dose received by the JNJ-40346527 group was 198.1 mg/day.

EFFICACY RESULTS:

Primary Endpoint

The m-ITT analysis set was used for the analysis of primary efficacy endpoint. The primary efficacy variable was compared between the JNJ-40346527 group and the placebo group, using an ANCOVA model with treatment as a fixed factor and baseline DAS28 (CRP) score as a covariate.

Summary of improvement from baseline in DAS28 (CRP) score at Week 12 is presented in Table 4. At Week 12, a mean (SD) improvement in DAS28 (CRP) score from baseline was observed in the JNJ-40346527 group (1.15 [1.186]) and the placebo group (1.42 [1.187]). However, no statistically significant (p=0.303) difference was observed between 2 treatment groups at Week 12.

Table 4: **Summary of Improvement from Baseline in DAS28 (CRP) Score at Week 12; Modified Intent-to-treat Analysis Set**

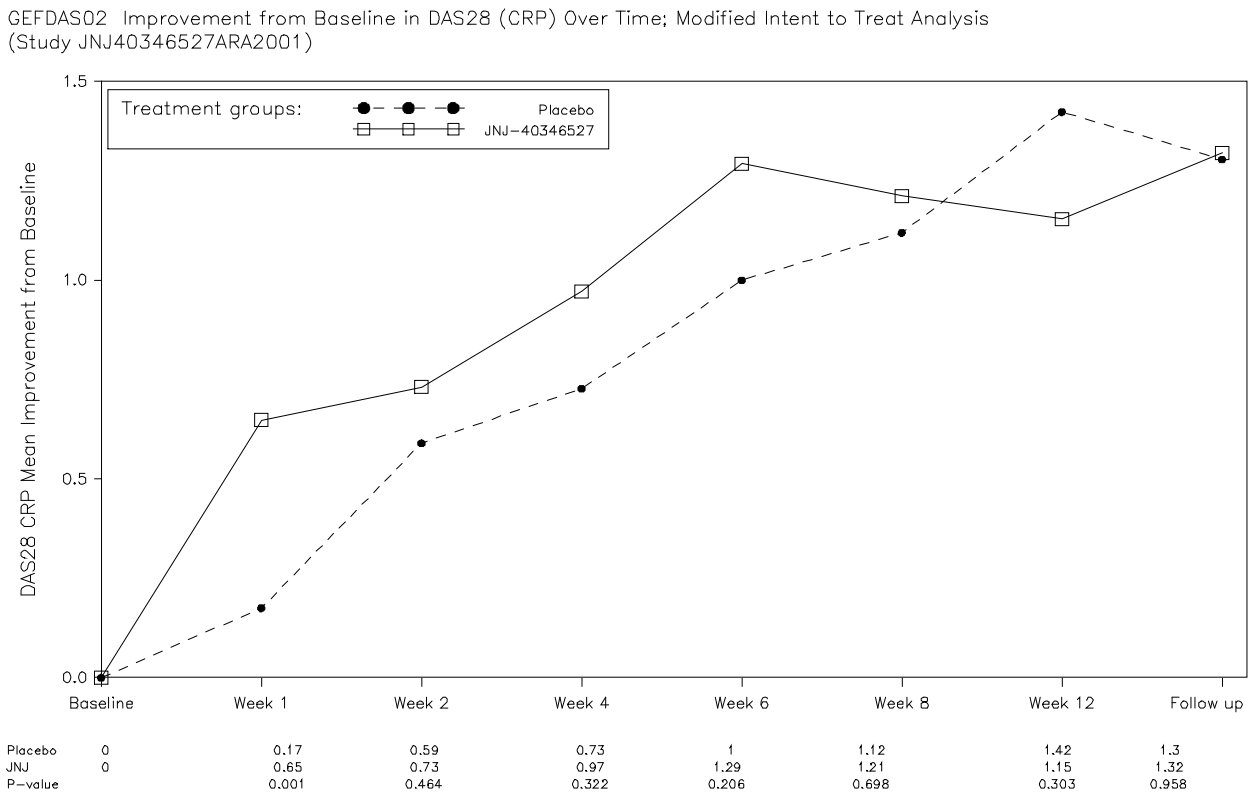
(Study 40346527ARA2001)

	Placebo	JNJ40346527 100 mg BID	p-value
Week 12			
n	31	61	
Mean (SD)	1.42 (1.187)	1.15 (1.186)	0.303
Median	1.32	0.99	
IQ range	(0.50; 2.29)	(0.38; 1.76)	
Range	(-0.7; 4.4)	(-0.8; 4.5)	

Note: Improvement from baseline was analyzed using an ANCOVA model with treatment as a fixed factor and baseline DAS28 score as a covariate.

Summary of improvement from baseline in DAS28 (CRP) score over time is provided in Attachment TEFDAS05. At Week 1, a nominally significant treatment difference was observed in the JNJ-40346527 group compared with the placebo group (p=0.001). However, this difference did not persist at consecutive time points. The improvements observed in both treatment groups were of similar magnitude from Week 2 onwards (Figure 1).

Figure 1: Improvement from Baseline in DAS28 (CRP) over Time; Modified Intent to Treat Analysis Set
(Study 40346527ARA2001)



Subgroup analyses were performed on the primary endpoint. The number of subjects in each of the subgroups was too small to draw a valid conclusion in relation to efficacy. Forest plot of mean difference in improvement from baseline in DAS28 (CRP) at Week 12 for subgroups defined by demographic characteristics are provided in Attachments GEFDAS03A_Normal and GEFDAS03D_Normal, and by disease characteristics are provided in Attachments GEFDAS03B_Normal and GEFDAS03E_Normal. Forest plot of mean difference in improvement from baseline in DAS28 (CRP) at Week 12 for subgroups defined by median values are provided in Attachment GEFDAS03C_Normal.

Results of the sensitivity analyses #1, #2, and #3, to evaluate the effect of site, MTX usage(Y/N), and violations of protocol respectively, are provided in Attachment TEFDAS04. Result of the sensitivity analysis #4, using longitudinal statistical method is provided in Attachment TEFDAS06. None of the sensitivity analyses showed statistically significant difference between the treatment groups at any point of time**.** Sensitivity analyses #5, #6, and #7, using more computing intensive statistical methods were not performed due to robustness of the other sensitivity analysis.

Major Secondary Endpoints

ACR 20 response at Week 12

At Week 12, the percentage of subjects who achieved ACR 20 response was not significantly different between 2 treatment groups (placebo: 41.9%; JNJ-40346527: 49.2%, p=0.659). Number of subjects who achieved ACR 20, ACR 50 and ACR 70 response over time is provided in Attachment TEFACR02.

Subgroup analyses were performed on the secondary endpoint, ACR 20. The number of subjects in each of the subgroups was too small to draw a valid conclusion in relation to efficacy. Forest plot of difference and 95% CI for comparing proportion of subjects who achieved ACR 20 response at Week 12 for

subgroups defined by demographic characteristics, baseline disease characteristics and by median values are provided in Attachments GEFACR01A, GEFACR01B, and GEFACR01C, respectively.

DAS28 (CRP) response at Week 12

At Week 12, the proportion of subjects who achieved DAS28 (using CRP) response was similar in both treatment groups (placebo group: 64.5%; JNJ-40346527 group: 55.7%; p=0.504). Number of subjects who achieved DAS28 (CRP) response over time is provided in Attachment TEFDAS07.

Other Secondary Endpoints

ACR Responses of 50 and 70 at Week 12: No significant difference was observed between 2 treatment groups for the number of subjects who achieved ACR 50 (placebo: 19.4%; JNJ-40346527: 14.8%; p=0.565) and ACR 70 (placebo: 12.9%; JNJ-40346527: 6.6%; p=0.435; Attachment TEFACR02) responses at Week 12.

DAS28 (ESR) at Week 12: At Week 12, no significant difference was observed between the two treatment groups for the improvement from baseline in DAS28 (ESR) score (placebo median: 1.17; JNJ-40346527 median: 1.13; Attachment TEFDAS08). Similarly, there was no significant difference between 2 treatment groups for the number of subjects who achieved DAS28 (ESR) response at Week 12 (placebo: 48.4%; JNJ-40346527: 54.1%; p=0.662; Attachment TEFDAS09).

HAQ-DI Response (Defined as Improvement from Baseline ≥0.25) at Week 12: The percentage of subjects achieving a clinically meaningful ≥0.25 improvement in HAQ at Week 12 was similar in both treatment groups (placebo group: 53.1%; JNJ-40346527 group: 61.9%; p=0.509; Attachments TEFHAQ01 and TEFHAQ03). Improvement in HAQ at Week 12 was similar in both treatment groups (placebo median: 0.25; JNJ-40346527 median: 0.38; p=0.21; Attachment TEFHAQ02_A and TEFHAQ04_A).

ACR components at Week 12: The direction and magnitude of improvement in each ACR component and ESR were consistent with that of ACR 20 (Attachment TEFACR04_A).

Change from Baseline in Simplified Disease Activity Index (SDAI) at Week 12: No significant difference was observed between 2 treatment groups for change from baseline in SDAI at Week 12 (placebo median: 17.02; JNJ-40346527 median: 16.00; p=0.609; Attachment TEFSDAI01_A).

Change from Baseline in Clinical Disease Activity Index (CDAI) at Week 12: No significant difference was observed between 2 treatment groups for change from baseline in CDAI at Week 12 (placebo median: 15.50; JNJ-40346527 median: 15.50; p=0.687; Attachment TEFCDAI01).

DAS28 (CRP) Remission Over Time: There was no significant difference between 2 treatment groups in the number of subject who achieved remission for DAS28 at any time points analyzed (Attachment TEFDAS10).

Exploratory Endpoints

Hybrid ACR response at Week 12: At Week 1, a nominally significantly higher hybrid ACR response rate was observed in the JNJ-40346527 group compared with the placebo group (placebo: 1.02; JNJ-40346527: 11.07; p=0.008). However, no significant response rates were observed in the consecutive weeks (Attachment TEFACR03).

ACR/EULAR remission at Week 12: There was no significant difference between 2 treatment groups in the number of subject who achieved ACR/EULAR remission over time (Attachment TEFACR05).

PHARMACOKINETIC RESULTS

Sparse PK Sampling (Week 1, 2, 4, 6, 8, and 12) Results:

Results of the Population PK analyses and the assessment of the effect on H_2R antagonists and PPIs on JNJ-40346527 plasma concentration for these samples are presented in a separate Advanced Modeling and Simulation report (Population PK/PD analysis of JNJ-40346527 from 40346527EDI1001 and 40346527ARA2001).

Intensive PK Substudy (Week 8) Results:

Analytical Performance

Plasma samples were analyzed to determine concentrations of JNJ-40346527 using a validated, specific and sensitive liquid chromatography coupled to mass spectrometry/mass spectrometry (LC-MS/MS) method. All batches of bioanalytical runs met the predefined acceptance criteria. The bioanalytical method for JNJ-40346527 in plasma had a validated calibration range of 1 ng/mL to 1,000 ng/mL. Plasma samples were analyzed to determine concentrations of the metabolites of JNJ-40346527 (JNJ-54368249 [M7] and JNJ-54382458 [M2]) using a qualified LC-MS/MS method. The bioanalytical method for the metabolites of JNJ-40346527 in plasma had a qualified calibration range of 5 ng/mL to 1,000 ng/mL. The assay validation and performance data for plasma JNJ-40346527 and its metabolites concentration analysis are available in Appendix 17.

Datasets Analyzed

Twenty-eight subjects had blood samples taken in the intensive PK substudy on Week 8. All subjects received 100 mg BID JNJ-40346527 with the exception of Subject 007004-2003 and Subject 359004-2054. These two subjects received 100 mg once daily and were not included in the descriptive statistics for concentration and PK parameters. All subjects were to have samples collected predose, 1, 2, 3, and 4 hours post-dose on Week 8; Subject 007015-2029 had 2 predose samples collected and no 4 hour sample collected and therefore was not included in the calculation of PK parameters or in the descriptive statistics for concentration. All subjects who received placebo had no JNJ-40346527 or metabolite concentrations above the LLOQ (5 ng/mL).

Pharmacokinetics

A summary of plasma PK parameters for subjects receiving 100 mg BID JNJ-40346527 at Week 8 is presented in Table 5. The key observations are summarized as follows:

- The mean C_{max} of JNJ-40346527 within 4 hours post-dose was 347 ng/mL.
- T_{max} for JNJ-40346527 included all time points sampled at Week 8 (pre-dose to 4 hours post-dose). The median t_{max} occurred at 2 hours post-dose.
- The mean metabolite-to-parent C_{min} ratios for JNJ-54368249 (M7) and JNJ-54382458 (M2) on Week 8 were 1.41 and 0.407, respectively.
- When the C_{min} values for the parent and two metabolites were combined (PMCMIN), the mean value (468 ng/mL) was greater than the target C_{min} (160 ng/mL) of the parent drug based on rat pharmacology.

Table 5: Summary of Plasma JNJ-40346527 and Metabolite Pharmacokinetic Parameters receiving 100 mg BID JNJ-40346527 on Week 8

PK	JNJ-40346527			JNJ-54368249	JNJ-54382458	M:P Ratio	M:P Ratio	PMCMIN[c]
Parameter/ Unit	C_{max}, ng/mL	t_{max}[a] h	C_{min}, ng/mL	C_{min}, ng/mL	C_{min}, ng/mL	C_{min1}[b]	C_{min2}[b]	ng/mL

N	25	25	25	25	25	24[d]	24[d]	25
Mean	347	2.0	167	229	71.1	1.41	0.407	468
SD	109	(0.0-4.0)	89.1	116	53.7	0.374	0.285	231

Cross-Reference: Attachment TablePK3

[a] median and range reported instead of mean and SD

[b] M:P Ratio $Cmin_1$ is JNJ-54369249:JNJ-40346527 and M:P Ratio $Cmin_2$ is JNJ:54382458:JNJ-40346527 based on ng/mL

[c] PMCMIN is the total C_{min} calculated as the sum of the C_{min} concentrations of parent (JNJ-403464527) and its metabolites (M7 and M2)

[d] As the C_{min} value for Subject 359004-2056 was BQL for the denominator, the ratio could not be calculated

.

Pharmacokinetic Attachments and Appendices

Actual sampling times relative to study drug administration in hours were used in graphing the composite and individual concentration-time profiles. Nominal sampling times relative to study drug administration in hours were used in plotting the mean (+SD) concentration-time profiles of JNJ-40346527 and metabolites (Attachment FigurePK1). Blood sampling times in hours relative to dose administration are available in Attachment TablePK1. Individual subject plasma concentration-time data of JNJ-40346527 and metabolites and descriptive statistics for each treatment are presented in Attachment TablePK2. Composite plots of all subjects for each treatment and individual subject plasma JNJ-40346527 and its metabolites concentration-time profiles are presented in Attachment FigurePK3 and Attachment FigurePK2, respectively. Scatterplots of metabolite vs. JNJ-40346527 concentrations are shown in Attachment FigurePK4. Individual subject JNJ-40346527 and metabolites' plasma PK parameters and descriptive statistics for each treatment are presented in Attachment TablePK3.

PHARMACODYNAMIC RESULTS

Results of pharmacodynamic analyses are presented in a separate report (Immunology Biomarker Exploratory Report: 40346527ARA2001). This report contains the exploratory protein analysis performed on the Somalogics platform, the RNA expression analysis performed on the Agilent platform and whole blood cell phenotype analysis performed by Covance using flow cytometry. The report will contain CSF-1 protein pharmacodynamic results as well.

PHARMACOGENOMIC RESULTS:

Pharmacogenomic analyses were not conducted.

SAFETY RESULTS:

All subjects, who received at least 1 dose of the study drug, were included in the safety analysis set.

Number of subjects with 1 or more treatment-emergent AEs (TEAEs) by MedDRA Version 15.0, system organ class (SOC) and preferred term (PT) is provided in Table 6.

Overall, 16 (50.0%) of the 32 subjects from the placebo group and 37 of the 63 (58.7%) subjects from the JNJ-40346527 group reported at least 1 TEAE. The most common TEAEs by SOC were observed in the Investigations SOC (2 [6.3%] subjects in the placebo group and 14 [22.2%] subjects in the JNJ-40346527 group).

The most frequently reported (observed in ≥5% of subjects in any of the treatment group) TEAEs by PT included blood lactate dehydrogenase increased (1 [3.1%] subject in the placebo group and 9 [14.3%] subjects in the JNJ-40346527 group), abdominal pain upper (3 [9.4%] subjects in the placebo group and 1 [1.6%] subject in the JNJ-40346527 group), and urinary tract infection (2 [6.3%] subjects in the placebo group and 1 [1.6%] subject in JNJ-40346527 group).

Table 6: Number of Subjects with 1 or More Treatment-emergent Adverse Event by MedDRA System Organ Class and Preferred Term; Safety Analysis Set

(Study 40346527ARA2001)

	Placebo	JNJ40346527 100 mg BID
Subjects treated	32	63
Total no. subjects with adverse events, n (%)	16 (50.0%)	37 (58.7%)
Body System Organ Class/Preferred Term		
Investigations	2 (6.3%)	14 (22.2%)
Blood lactate dehydrogenase increased	1 (3.1%)	9 (14.3%)
Alanine aminotransferase increased	0	3 (4.8%)
Aspartate aminotransferase increased	0	2 (3.2%)
Blood creatine phosphokinase increased	0	1 (1.6%)
Blood glucose increased	0	1 (1.6%)
Gamma-glutamyltransferase increased	1 (3.1%)	1 (1.6%)
Haemoglobin decreased	0	1 (1.6%)
Red blood cell sedimentation rate increased	0	1 (1.6%)
Gastrointestinal disorders	5 (15.6%)	10 (15.9%)
Dyspepsia	0	2 (3.2%)
Nausea	1 (3.1%)	2 (3.2%)
Vomiting	0	2 (3.2%)
Abdominal pain upper	3 (9.4%)	1 (1.6%)
Colonic polyp	0	1 (1.6%)
Constipation	0	1 (1.6%)
Diarrhoea	0	1 (1.6%)
Gastrooesophageal reflux disease	0	1 (1.6%)
Rectal haemorrhage	0	1 (1.6%)
Dental caries	1 (3.1%)	0
Gastritis	1 (3.1%)	0
Musculoskeletal and connective tissue disorders	2 (6.3%)	8 (12.7%)
Arthralgia	1 (3.1%)	2 (3.2%)
Rheumatoid arthritis	0	2 (3.2%)
Bursitis	0	1 (1.6%)
Fibromyalgia	0	1 (1.6%)
Muscle contracture	0	1 (1.6%)
Myofascial pain syndrome	0	1 (1.6%)
Muscular weakness	1 (3.1%)	0
Myositis	1 (3.1%)	0
Infections and infestations	5 (15.6%)	7 (11.1%)
Acute tonsillitis	0	1 (1.6%)
Erysipelas	1 (3.1%)	1 (1.6%)
Nasopharyngitis	0	1 (1.6%)
Respiratory tract infection viral	1 (3.1%)	1 (1.6%)
Tonsillitis	0	1 (1.6%)
Upper respiratory tract infection	0	1 (1.6%)
Urinary tract infection	2 (6.3%)	1 (1.6%)
Viral upper respiratory tract infection	1 (3.1%)	1 (1.6%)
Blood and lymphatic system disorders	0	6 (9.5%)
Anaemia	0	3 (4.8%)
Iron deficiency anaemia	0	2 (3.2%)

Table 6: Number of Subjects with 1 or More Treatment-emergent Adverse Event by MedDRA System Organ Class and Preferred Term; Safety Analysis Set

(Study 40346527ARA2001)

	Placebo	JNJ40346527 100 mg BID
Neutropenia	0	1 (1.6%)
Nervous system disorders	2 (6.3%)	4 (6.3%)
Headache	0	2 (3.2%)
Dysaesthesia	0	1 (1.6%)
Sciatica	0	1 (1.6%)
Hypoaesthesia	1 (3.1%)	0
Loss of consciousness	1 (3.1%)	0
General disorders and administration site conditions	0	2 (3.2%)
Asthenia	0	1 (1.6%)
Face oedema	0	1 (1.6%)
Skin and subcutaneous tissue disorders	1 (3.1%)	2 (3.2%)
Ecchymosis	0	1 (1.6%)
Erythema	0	1 (1.6%)
Pruritus	1 (3.1%)	0
Cardiac disorders	1 (3.1%)	1 (1.6%)
Bundle branch block left	0	1 (1.6%)
Atrial fibrillation	1 (3.1%)	0
Eye disorders	0	1 (1.6%)
Keratitis	0	1 (1.6%)
Hepatobiliary disorders	0	1 (1.6%)
Hepatic function abnormal	0	1 (1.6%)
Immune system disorders	0	1 (1.6%)
Hypersensitivity	0	1 (1.6%)
Injury, poisoning and procedural complications	1 (3.1%)	1 (1.6%)
Wound	0	1 (1.6%)
Femur fracture	1 (3.1%)	0
Metabolism and nutrition disorders	0	1 (1.6%)
Hyperglycaemia	0	1 (1.6%)
Psychiatric disorders	0	1 (1.6%)
Insomnia	0	1 (1.6%)
Renal and urinary disorders	2 (6.3%)	1 (1.6%)
Pyuria	0	1 (1.6%)
Calculus ureteric	1 (3.1%)	0
Haematuria	1 (3.1%)	0
Respiratory, thoracic and mediastinal disorders	0	1 (1.6%)
Dyspnoea	0	1 (1.6%)
Vascular disorders	2 (6.3%)	0
Hypotension	1 (3.1%)	0
Thrombophlebitis	1 (3.1%)	0

Note: Percentages calculated with the number of subjects in each treatment group as denominator.
Note: n is the number of subjects experiencing at least one adverse event, not the number of events.
MedDRA 15.0

Number of subjects with 1 or more TEAEs by severity is provided in Attachment TSFAE02. The majority of TEAEs were mild to moderate in intensity. No subjects reported severe TEAEs in the JNJ-40346527 group; 1 subject in the placebo group reported a severe TEAE (dental caries).

Number of subject with 1 or more TEAEs by the investigator's assessment of relationship to study drug is provided in Attachment TSFAE03. None of the TEAEs were considered very likely related to the study

drug by the investigator. The most common possibly related TEAE was blood lactate dehydrogenase increased (1 subject in the placebo group and 7 subjects in the JNJ-40346527 group) followed by abdominal pain upper (3 subjects in the placebo group 1 subject in the JNJ-40346527 group).

Number of subjects with 1 or more TEAEs by action taken and outcome is provided in Attachments TSFAE05 and TSFAE06, respectively. The majority of the TEAEs reported were TEAEs from which subjects recovered. There were no events which had a fatal outcome.

Number of subjects with a change in dose due to TEAEs is provided in Attachment TSFAE08. The percentage of subjects who experienced interruption, reduction, or withdrawal of dosing due to TEAEs was similar between the placebo group (5 subjects) and the JNJ-40346527 group (7 subjects). Overall, 4 subjects discontinued due to TEAEs (3 from the JNJ-40346527 group and 1 from the placebo group). The TEAEs that led to treatment discontinuation in the JNJ-40346527 group were dyspnoea, RA, and red blood cell sedimentation rate increased. The TEAE that led to treatment discontinuation in the placebo group was muscular weakness. All events that led to discontinuation were mild in severity. All events were considered not related to the study drug by the investigators. A by-subject listing for subjects who experienced an interruption, reduction or withdrawal of dosing due to TEAEs is presented in Appendix 19 [LSFAE09]. Narratives for subjects who discontinued due to AEs are presented below:

- **Subject 036001-2091:** A 66-year-old white male, randomized to the JNJ-40346527 group, experienced a mild event of dyspnoea on 22 Sep 2012 (Study Day 18). The subject's RA concomitant medications included MTX and methylprednisolone and non-RA concomitant medications included perindopril, alendronate sodium, calcium citrate, ciprofloxacin, folic acid, acetylsalicylic acid, pantoprazole, indapamid, colecalciferol, and aminophylline. The study drug was withdrawn due to the event. The outcome of the event was reported as resolved in 1 day. The investigator considered the event as not related to the study drug.
- **Subject 036002-2060:** A 64-year-old white female, randomized to the JNJ-40346527 group, experienced a mild event of worsening of RA on 19 Sep 2012 (Study Day 43). The subject's RA concomitant medications included meloxicam, MTX and methylprednisolone and non-RA concomitant medications included ramipril, metoprolol succinate, amlodipine besilate and folic acid. The study drug was withdrawn due to the event. The outcome of the event was reported as resolving. The investigator considered the event as not related to the study drug.
- **Subject 054003-2132**: A 60-year-old white female, randomized to the JNJ-40346527 group, experienced a mild event of red blood cell sedimentation rate increased on 09 Oct 2012 (Study Day 15). The subject's RA concomitant medications included etoricoxib, meprednisone, MTX, sulfasalazine and non-RA concomitant medications included losartan, benzathine penicillin, bactrim, norfloxacin, folic acid, ranitidine, ferrous sulfate, iron, calcium with Vitamin D, tizanidine, omeprazole, hydrochlorothiazide and levothyroxin. The study drug was withdrawn due to the event. The event was not resolved at the time of reporting. The investigator considered the event as not related to the study drug.
- **Subject 036001-2095:** A 59-year-old white female with a medical history of muscular weakness, was randomized to the placebo group. The subject experienced a mild event of muscular weakness in right arm which led to discontinuation. The subject's RA concomitant medications included MTX, and methylprednisolone and non-RA concomitant medications included perindopril, amoxicillin with clavulanate potassium, folic acid, nadroparin, human insulin, clindamycin, moduretic, glyceryl trinitrate, piracetam, and furosemide. The subject also experienced serious events of thrombophlebitis and myositis. The narrative for this subject is provided along with the narratives for serious TEAEs (Subject 036001-2095).

Number of subjects with 1 or more serious TEAEs is presented in Table 7. Incidence of serious TEAEs were slightly higher in the placebo group than the JNJ-40346527 group. Three subjects (9.4%) in the placebo group and 1 subject (1.6%) in the JNJ-40346527 group reported serious TEAEs during the study.

The serious TEAE reported in the JNJ-40346527 group was gastroesophageal reflux disease and, in the placebo group were thrombophlebitis, myositis, calculus ureteric, and femur fracture. The serious TEAEs were mild in intensity except the events of femur fracture and calculus ureteric which were considered to be of moderate severity. All these events were recovered and considered not related to the study drug by the investigators.

Table 7: **Number of Subjects with 1 or More Serious Treatment-emergent Adverse Event by MedDRA System Organ Class and Preferred Term; Safety Analysis Set**

(Study 40346527ARA2001)

	Placebo	JNJ40346527 100 mg BID
Subjects treated	32	63
Total no. subjects with adverse events, n (%)	3 (9.4%)	1 (1.6%)
Body System Organ Class/Preferred Term		
Gastrointestinal disorders	0	1 (1.6%)
Gastrooesophageal reflux disease	0	1 (1.6%)
Injury, poisoning and procedural complications	1 (3.1%)	0
Femur fracture	1 (3.1%)	0
Musculoskeletal and connective tissue disorders	1 (3.1%)	0
Myositis	1 (3.1%)	0
Renal and urinary disorders	1 (3.1%)	0
Calculus ureteric	1 (3.1%)	0
Vascular disorders	1 (3.1%)	0
Thrombophlebitis	1 (3.1%)	0

Note: Percentages calculated with the number of subjects in each treatment group as denominator.
Note: n is the number of subjects experiencing at least one adverse event, not the number of events.
MedDRA 15.0

By-subject listing of serious TEAEs is provided in Appendix 19. Narratives for subjects with serious TEAEs are presented below:

- **Subject 007003-2067**: A 53-year-old white female, with a medical history of hypertension, was randomized to the placebo group. The subject's RA concomitant medications included MTX, nimesulide, prednisolone and sulfasalazine and non-RA concomitant medications included sodium chloride, omeprazole, folic acid, celecoxib, vitamin D and/or other calcium D3, blood transfusion and auxiliary products, capiven, and bisoprolol fumarate. On 29 Nov 2012 (Study Day 95), the subject experienced a moderate event of femur facture in the left thigh. The event was considered serious due to hospitalization. The action taken with the study drug was reported as not applicable as the subject completed the treatment period prior to the event. The outcome of the event was reported as resolved in 49 days. The investigator considered the event not related to the study drug.
- **Subject 036001-2095:** A 59-year-old white female, with a medical history of muscular weakness, was randomized to the placebo group. The subject's RA concomitant medications included MTX, and methylprednisolone and non-RA concomitant medications included perindopril, amoxicillin with clavulanate potassium, folic acid, nadroparin, human insulin, clindamycin, moduretic, glyceryl trinitrate, piracetam, and furosemide. On 27 Sep 2012 (Study Day 23), experienced mild event of muscular weakness. The study drug was withdrawn due to the event on the same day. The event was not resolved and was ongoing at the time of reporting. The subject also experienced serious TEAEs of thrombophlebitis on 04 Oct 2012 (Study Day 30) and myositis on 09 Oct 2012 (Study Day 35) and was hospitalized. The action taken with the study drug was reported as not applicable as the study drug was stopped prior to the onset of these events. The outcomes of the events thrombophlebitis and myositis were reported as resolved in 12 days and 17 days, respectively.

The investigator considered the events of muscular weakness, thrombophlebitis and myositis as not related to the study drug.

- **Subject 359004-2054**: A 57-year-old white female, with medical history of RA, hypertension, diabetes mellitus, hyperlipidemia, osteoporosis, peptic ulcer disease, and irritable bowel syndrome was randomized to the JNJ 40346527 group. The subject's RA concomitant medications included methylprednisolone, sulfasalazine, and non RA concomitant medications included pancreatin, famotidine, ferrous sulfate, ferric hydroxide polymaltose complex, pantoprazole, and saccharated iron oxide. On Study Day 99, 15 days after the last dose of the study drug, the subject experienced mild gastroesophageal reflux disease and was hospitalized on the same day. The action taken with the study drug was reported as not applicable. The outcome of the event was reported as resolved in 7 days. The investigator considered the event to be not related to the study drug. The subject also had increased ALT (58 U/L [1.7xULN]) on the last day of dosing (Week 12). Her ALT level was normal during the hospitalization for the event of gastroesophageal reflux disease, but was increased to 349 U/L (10xULN) at the follow-up visit (Week 16). The elevation in ALT was not associated with clinical symptoms or elevated total bilirubin and the repeat laboratory test after one week showed an ALT level of 66 U/L.
- **Subject 420005-2156**: A 56-year-old white female, with no history of renal colic, kidney, ureteral disease or surgery, was randomized to the placebo group. The subject's RA concomitant medications included MTX, and tiaprofenic acid, and non-RA concomitant medications included bactrim, folic acid, nadroparin and levothyroxine sodium. She also received a combination analgesic drug containing metamizole sodium, fenpiverinium bromide and pitofenone hydrochloride. On 19 Jan 2013 (Study Day 66), the subject experienced a moderate event of calculus ureteric and was hospitalized. The event was considered serious because of the hospitalization. The outcome of the event was reported as resolved in 8 days. The study drug was interrupted due to the event. The investigator considered the event not related to the study drug.

No treatment-emergent deaths occurred during the study (Appendix 19 [LSFAE 10]).

Other Safety Observations

Chemistry

Change from baseline in clinical chemistry laboratory values over time is provided in Attachment TSFLAB02. At Week 12, there was no meaningful difference between the 2 treatments groups with regards to any of the chemistry laboratory values, except the following:

- Higher mean increase in creatine kinase was observed in the JNJ-40346527 group (91.3 U/L) than the placebo group (3.7 U/L).
- Higher mean increase in lactate dehydrogenase was observed in the JNJ-40346527 group (89.9 U/L) than the placebo group (3.3 U/L).
- Higher mean increase in ALT was observed in the JNJ-40346527 group (5.8 U/L) than the placebo group (2.0 U/L).
- Higher mean increase in AST was observed in the JNJ-40346527 group (7.3 U/L) than the placebo group (2.9 U/L).

Number of subjects with postbaseline clinical chemistry laboratory values by National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grade is presented in Attachment TSFLAB10A. Based on postbaseline values by maximum NCI-CTCAE toxicity grade, Grade I and Grade II toxicities were reported by >90% of subjects in both treatment groups. Grade III toxicities were reported in 2 (6.3%) subjects in the placebo group and 2 (3.2%) subjects in the JNJ-40346527 group. There were no Grade IV toxicities observed. The distribution of subjects with

toxicity grades was comparable between the JNJ-40346527 and placebo groups, with exceptions noted below:

- For creatine kinase, there were no Grade III toxicities reported. The percentage of subjects with toxicity Grade I (placebo: 6.3%, JNJ-40346527: 42.9%) and Grade II (placebo: 0, JNJ-40346527: 3.2%) was higher in the JNJ-40346527 group than the placebo group.
- For ALT, 1 subject (1.6%) in the JNJ-40346527 group reported Grade III toxicity (ALT = 349 U/L). The percentages of subjects with toxicity Grade I (placebo: 25.0%, JNJ-40346527: 36.5%) and Grade II (placebo 0, JNJ-40346527: 4.8%) toxicities were higher in the JNJ-40346527 group compared with the placebo group.
- For AST, 2 subjects (3.2%) in the JNJ-40346527 group reported Grade II toxicity. The percentage of subjects with toxicity Grade I was higher in the JNJ-40346527 group (placebo: 15.6%, JNJ-40346527: 44.4%) compared with the placebo group.
- For lactate dehydrogenase, there were no Grade III or Grade II toxicities reported. The percentage of subjects with toxicity Grade I was higher in the JNJ-40346527 group (50.8%) compared with the placebo group (3.1%) (Attachment TSFLAB18A).

Number of subjects with postbaseline clinical chemistry laboratory values by maximum NCI-CTCAE toxicity grade in subjects with normal baseline values is presented in Attachment TSFLAB10B. Number of subjects with postbaseline lactate dehydrogenase and serum uric acid laboratory values by maximum rheumatology common toxicity grade in subjects with normal baseline is provided in Attachment TSFLAB18B. By-subject listing of postbaseline clinical chemistry laboratory values of NCI-CTCAE Toxicity Grade 1 or higher is provided in Appendix 20 [LSFLAB12].

Summary of post baseline liver function tests is provided in Attachment TSFLAB14. Three (4.8%) subjects (Subject 007009-2039, Subject 082004-2051, and Subject 048004-2170) in the JNJ-40346527 group experienced a maximum postbaseline ALT>=3 and <5 times the upper limit of normal (ULN) as compared to none in the placebo group. Of these, 2 subjects (Subject 007009-2039 and Subject 082004-2051) had ALT elevations at the follow-up visit (4 weeks after the last dose of study drug), and 1 subject (Subject 048004-2170) had elevations at Study Week 4. The dose was reduced per protocol, and the ALT levels normalized for remainder of the study. One (1.6%) subject (Subject 359004-2054) in the JNJ-40346527 group had a maximum postbaseline ALT>=8×ULN (349 U/L) at the follow up visit. Narrative for this subject (Subject 359004-2054) is included along with the narratives for serious TEAEs.

List of subjects with ALT or AST>=3 times the ULN is provided in Appendix 20 [LSFLAB19].

Shift in clinical chemistry laboratory values over time is provided in Attachment TSFLAB16. Number of subjects with abnormal postbaseline clinical chemistry laboratory values is presented in Attachment TSFLAB07.

Hematology

Change from baseline in hematology laboratory values over time is provided in Attachment TSFLAB01. At Week 12, there were no meaningful differences in any of the hematology parameters between the treatment groups, except in total leukocytes and neutrophils. At Week 12, higher mean decreases in leukocyte (-1.20x10E9/L in the JNJ-40346527 group and -0.58x10E9/L in the placebo group) and neutrophil (-1.19x10E9/L in the JNJ-40346527 group and -0.79x10E9/L in the placebo group) levels were observed in the JNJ-40346527 group relative to the placebo group. No clinically meaningful change in hemoglobin level was observed at Week 12. One subject (Subject 007001-2100) in the JNJ-40346527 group had neutrophil count 0.83x10E9/L (Grade III toxicity) at Week 12 (Appendix 20 [LSFLAB06]). Narrative for this subject is included below:

- **Subject 007001-2100**: A 50-year-old white female, randomized to the JNJ-40346527 group, experienced decreased neutrophil count (0.83x10E9/L) at the last day of dosing (Week 12). The subject's RA concomitant medications included MTX, and nimesulide and non-RA concomitant medications included ferrous sulfate and folic acid. After two weeks (Week 14), neutrophil count returned to the normal level (2.93x10E9/L).

Number of subjects with postbaseline hematology laboratory values by maximum NCI-CTCAE toxicity grade is presented in Attachment TSFLAB09A. Based on postbaseline values by maximum NCI-CTCAE toxicity grade, Grade I and Grade II toxicities were observed in > 70% of subjects in both treatment groups. There were no Grade IV toxicities observed. One subject each from the placebo group and the JNJ-40346527 group experienced Grade III toxicity. The distribution of subjects with toxicity grades was comparable between the JNJ-40346527 group and the placebo group, with the exceptions as noted below:

- For hemoglobin decreased, there were no Grade III toxicities reported. The percentage of subjects with toxicity Grade I (placebo: 37.5%; JNJ-40346527: 50.8%) and Grade II (placebo: 15.6%; JNJ-40346527: 15.9%) was higher in the JNJ-40346527 group than the placebo group.
- For lymphocyte decreased, the percentage of subjects with toxicity Grade II was higher in the JNJ-40346527 group (placebo: 6.3%, JNJ-40346527: 14.3%) compared to the placebo group.

Small increase in the frequency of Grade I toxicity was also observed for leukocytes in the JNJ-40346527 group compared with the placebo group.

Number of subjects with postbaseline hematology laboratory values by maximum NCI-CTCAE toxicity grade in subjects with normal baseline values is presented in Attachment TSFLAB09B. Number of subjects with abnormal postbaseline hematology laboratory values is provided in Attachment TSFLAB08. Shift in hematology laboratory values over time is provided in Attachment TSFLAB15. List of subjects with any postbaseline hematology laboratory values of NCI-CTCAE toxicity Grade 1 or higher is provided in Appendix 20.

Urinalysis

Shift in continuous urinalysis laboratory values over time is provided in Attachment TSFLAB17. Summary of observed values and change from baseline in continuous and categorical urinalysis laboratory values over time are provided in Attachments TSFLAB04 and TSFLAB05, respectively. There were no clinically relevant changes urinalysis laboratory values observed in the both the treatment groups during the study.

By-subject listing of abnormal postbaseline laboratory values (in chemistry, hematology, immunology and urinalysis) is provided in Appendix 20 .

Electrocardiogram

Summary of observed values and change from baseline in ECG parameters is provided in Attachment TSFECG01. Distribution of maximum postbaseline and maximum change from baseline in QTC values is provided in Attachment TSFECG02. List of subjects with 1 or more significant ECG abnormality or QTcB/QTcF interval prolongation is provided in Attachment LSFECG03.

Abnormal high heart rate was observed in 2 subjects (Subject 007004-2131 in the placebo group and Subject 007009-2070 in the JNJ-40346527 group). There were no treatment-emergent abnormal PR and QT intervals in both treatment groups. Few cases of abnormal QRS was observed in both the treatment groups. There were no clinically relevant changes in ECG values observed in both treatment groups during the study.

Vital Signs

Summary of observed values and change from baseline in vital signs over time is provided in Attachment TSFVS01. Number of subjects with abnormal postbaseline vital sign values is provided in Attachment TSFVS02. There were no clinically relevant changes vital signs observed in both treatment groups during the study.

By-subject listing of 1 or more abnormal postbaseline vital sign values is provided in Attachment LSFVS03.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

No consistent evidence of efficacy was observed in the JNJ-40346527 group compared with the placebo group in subjects with active RA despite DMARD therapy. No statistical difference was observed between the JNJ-40346527 group and the placebo group in any of the efficacy parameters analyzed.

JNJ-40346527 was generally well-tolerated with no dose limiting AEs. The most common AEs in JNJ-40346527 group were within Investigations SOC, with elevation of LDH being the most frequent single AE. No new or unexpected safety findings emerged during this study.

The following appendices are available on request.

1 Protocol and Amendments
2 Sample Case Report Form(s)
3 List of IECs or IRBs and Sample Consent Forms
4 List and Description of Investigators and Sites
5 Signature of Sponsor's Responsible Medical Officer
6 Listing of Patients Receiving Test Drug(s) from Specified Batch (Not applicable)
7 Randomization Scheme
8 Audit Certificates
9 Documentation of Statistical Methods and Interim Analysis Plans
10 Documentation of Interlaboratory Standardization Methods and Quality Assurance Procedures if Used
11 Publications Based on the Study (Not applicable)
12 Important Publications Referenced in the Report (Not applicable)
13 Discontinued Patients
14 Protocol Deviations
15 Patients Excluded From the Efficacy Analysis (Not applicable)
16 Demographic Data
17 Compliance and/or Drug Concentration Data
18 Individual Efficacy Response Data (Not applicable)
19 Adverse Event Listings
20 Listing of Individual Laboratory Measurements by Patient

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.