SYNOPSIS

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Name of Sponsor/Company	Janssen Research & Development
Name of Finished Product	TBD
Name of Active Ingredient(s)	Sirukumab (CNTO 136)

Protocol No.: C1377T04

Title of Study: A Phase 2, 2-Part, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Proof-of-concept, Dose-finding Study Evaluating the Efficacy and Safety of CNTO 136 Administered Subcutaneously in Subjects With Active Rheumatoid Arthritis Despite Methotrexate Therapy

EudraCT Number: 2007-006603-20

NCT No.: NCT00718718

Clinical Registry No.: CR015214

Coordinating Investigator: Michael E. Weinblatt, MD – Harvard Medical School, [redacted]

Study Center(s): Part A, 8 investigative sites. Part B, 36 investigative sites.

Publication (Reference): None

Study Period: 24 Jul 2008 to 03 Mar 2011

Phase of Development: 2

Objectives:

Part A

The objective of Part A was to evaluate efficacy and safety of CNTO 136 (sirukumab) 100 mg subcutaneous (SC) every 2 weeks (q2w) in reducing signs and symptoms in subjects with active rheumatoid arthritis (RA) despite methotrexate (MTX) therapy.

Part B

The objectives of Part B were to determine efficacious and safe dose regimens of CNTO 136 SC in reducing signs and symptoms of active RA, describe the pharmacokinetic (PK) profile of CNTO 136 SC in subjects with RA, and assess the pharmacodynamic (PD) effects of CNTO 136 SC in subjects with RA despite MTX therapy.

Methodology: This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled, proof-of-concept, dose-finding study to evaluate the efficacy and safety of CNTO 136 SC in subjects with active RA despite MTX therapy. The study was to be conducted in 2 parts; Part A (proof-of-concept portion), and Part B (dose finding portion). All subjects were to remain on a stable dose of MTX through Week 24 unless the dose needed to be adjusted for signs/symptoms of MTX toxicity.

Part A was to consist of 2 treatment groups (CNTO 136 100 mg q2w or placebo). At the Week 0 visit, subjects were to be randomized into 1 of the 2 treatment groups in a 1:1 ratio. The randomization in Part A was to be stratified by site and weight (< 75 kg or ≥ 75 kg). Subjects were to receive either CNTO 136 100 mg or placebo SC injections q2w through Week 10. At Week 12, subjects randomized to CNTO 136 were to receive placebo and subjects randomized to placebo were to receive CNTO 136 100 mg SC injections q2w through Week 22.

Part B was to be initiated only after safety and efficacy was demonstrated at the Week 12 interim analysis in Part A. Part B was to consist of 5 treatment groups (placebo or CNTO 136 100 mg q2w, 100 mg every 4 weeks [q4w], 50 mg q4w, or 25 mg q4w). At the Week 0 visit, subjects were to be randomized into 1 of the 5 treatment groups in a 1:1:1:1:1 ratio. The randomization in Part B was to be stratified by site and weight (< 65 kg, 65 kg to 85 kg, > 85 kg). At Week 12, subjects randomized to the placebo group were to receive CNTO 136 100 mg SC injections q2w through Week 24. A second interim analysis was to be conducted after approximately 10 subjects in each of the 25 mg q4w and 50 mg q4w groups reached Week 2 to assess the degree of serum C-reactive protein (CRP) suppression. The decision to continue randomization into those respective treatment groups was to be based upon the review of this data.

All subjects were to be followed for safety for approximately 4 months after their last administration of study agent. The safety and efficacy of the study was to be monitored by the unblinded Data Monitoring Committee and by the blinded sponsor's medical monitor on an ongoing basis throughout the study.

The primary endpoint of this study was American College of Rheumatology (ACR) 50 response at Week 12 in Part B.

The major secondary endpoints in this study were:

1. The main endpoint for Part A, change from baseline in Disease Activity Index Score 28 based on CRP (DAS28 [CRP]) score at Week 12 in Part A was the endpoint for the proof-of-concept portion and was compared between the placebo and the active treatment groups.
2. Change from baseline in DAS28 (CRP) score at Week 12 in Part B was compared between the placebo and the active treatment groups at Week 12, excluding dose groups closed to further enrollment from the analysis.
3. ACR 50 response at Week 12 in Part A was summarized and compared between the placebo and the CNTO 136 100 mg group.
4. Serum CNTO 136 concentrations were summarized in Part A and Part B.
5. Percent change from baseline in serum CRP at Week 2 was compared between the placebo and the active treatment groups in Part A and Part B

Number of Subjects (planned and analyzed): This study was to include approximately 40 subjects in Part A and up to an additional 150 subjects in Part B (including 30 subjects from Japanese sites). In Part A, 36 subjects were analyzed. In Part B, 151 subjects were analyzed.

Diagnosis and Main Criteria for Inclusion: Men and women 18 years of age or older (20 years or older at Japanese sites) were eligible to participate if they had a diagnosis of active RA with at least 6 swollen and 6 tender joints despite MTX therapy at a dose of ≥ 15 mg/week (≥ 8 mg/week at Japanese sites) for at least 4 months prior to screening. Subjects eligible for the study were also required to be anti-cyclic citrullinated peptide antibody-positive or rheumatoid factor positive at screening and were to have a screening CRP ≥ 1.0 mg/dL (International System of Units [SI]: 10 mg/L).

Test Product, Dose and Mode of Administration, Batch No.: CNTO 136 (100 mg, 50 mg, 25 mg) was to be administered by SC injection. CNTO 136 was supplied as a single-use, sterile, white, lyophilized solid containing 50 mg CNTO 136 in a 2 mL glass vial. Following reconstitution with 1.0 mL sterile water for injection, each 1 mL of the solution contained 50 mg CNTO 136, sucrose, L-histidine, and polysorbate 80, at a pH of 5.0 to 6.0. No preservatives were present. Lot Numbers: C08.1611-C08.1613, C08.1752-C08.1754, 436029, 4360443, 4360445, 4361256, C09.2105-C09.2107, C09.2117-C09.2119, C09.2111-C09.2113, and 362630.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was to be administered by SC injection. Liquid placebo was supplied as a single use, sterile liquid in a 2 mL glass vial. Each 1 mL of the placebo solution contained L-histidine and L-histidine monohydrochloride, sucrose, and polysorbate 80, at a pH of 6.0. Lot Numbers: C08.1614-C08.1616, C08.1755-C08.1757, 436330, 4360444, 4360446, 4360912, 4361456, C09.2114-C09.2116, C09.2108-C09.2110, C09.2120-C09.2122, and 4362708.

Duration of Treatment: Subjects were to be randomized to study drug within 1 month of screening. The duration of treatment (interval between first and last administration of CNTO 136 or placebo) was to be 22 weeks in Part A and 24 weeks in Part B.

Criteria for Evaluation:

All randomized subjects were included in the summary of baseline demographics and disease characteristics. All randomized subjects were included in the primary efficacy and selected secondary analyses. Subjects were analyzed according to their randomized treatment group. Secondary efficacy analyses were based on all randomized subjects according to their randomized group. Safety evaluations included subjects who received at least 1 study agent administration; subjects were analyzed according to the actual treatment received.

Pharmacokinetics: CNTO 136 pharmacokinetic PK parameters were calculated from serum concentration versus time data using noncompartmental analyses. Pharmacokinetic parameters evaluated included observed maximum serum concentration (C_{max}), observed time to reach maximum serum concentration (T_{max}), area under the serum concentration versus time curve between two defined sampling timepoints, t1 and t2 ($AUC_{(t1-t2)}$), terminal half life ($T_{1/2}$), apparent total systemic clearance of drug after SC administration (CL/F), apparent volume of distribution during terminal phase after SC administration (V_z/F), accumulation ratio calculated from C_{max} after the last dose of multiple doses and C_{max} after the first dose (R_{Cmax}), and accumulation ratio calculated from $AUC_{(t1-t2)}$ after the last dose of multiple doses and $AUC_{(t1-t2)}$ after the first dose ($R_{AUC(t1-t2)}$).

Immunogenicity: Serum samples for evaluating antibodies to CNTO 136 were analyzed using a validated bridging immunoassay. The incidence of antibodies to CNTO 136 was summarized for all subjects who had received at least one administration of CNTO 136 and had evaluable serum samples for the detection of antibodies to CNTO 136 (ie, at least one serum sample collected after drug administration).

Pharmacodynamics: Pharmacodynamic assessments were to be based on the assessment of serum based PD markers, cellular based PD markers, metabolic PD markers, and anemia PD markers.

Whole Blood Gene Expression and Pharmacogenomics: All subjects had the option to have blood samples collected for deoxyribonucleic acid (DNA) and ribonucleic acid analysis. Results for pharmacogenomic analysis were to be reported in a separate technical report.

Efficacy:

The primary efficacy endpoint was ACR 50 response at Week 12 in Part B. Major secondary efficacy endpoints included change from baseline in DAS28 (CRP) score at Week 12 in Part A (the main endpoint for Part A) and Part B, and ACR 50 response at Week 12 in Part A. Other secondary efficacy endpoints

included DAS28 (CRP) response at Week 12 in Part A and Part B, ACR 20, ACR 70, and ACR 90 responses at Week 12 in Part A and Part B, DAS28 (CRP) remission at Week 12 in Part A and Part B, percent improvement from baseline in ACR components at Week 12 in Part A and Part B, change from baseline in duration of morning stiffness at Week 12 in Part A and Part B, change from baseline in physical and mental component summary scores of 36-item short form health survey (SF-36) scales at Week 12 in Part A and Part B, and change from baseline in norm-based scores of SF-36 scales at Week 12 in Part A and Part B. The relationship between clinical efficacy and antibodies to CNTO 136 status was also to be explored.

Health Economics: Health economics assessments included subject's self-reported work productivity data.

Safety: The safety of CNTO 136 was to be assessed through Week 38 by measurement of vital signs, assessment of adverse events (AEs) and serious AEs (SAEs), study agent injection-site evaluations, routine laboratory evaluations (hematology, chemistry, and lipids), and the presence of antinuclear antibodies /anti-double-stranded DNA, and antibodies to CNTO 136. The relationship between clinical safety and systemic exposure to CNTO 136 based on PK analysis and antibodies to CNTO 136 was to be explored.

Statistical Methods: Descriptive statistics (eg, mean, median, standard deviation [SD], interquartile [IQ] range, minimum, and maximum) were to be used to summarize continuous variables. Counts and percentages were to be used to summarize categorical variables. The proportion of subjects responding to treatment were to be compared using a Cochran Mantel Haenszel chi-square test stratified by weight group (< 75 kg and ≥ 75 kg for Part A; < 65 kg, 65 kg to 85 kg, and > 85 kg for Part B) if ≥ 5 subjects in any cell defined by treatment group and weight group or using Fishers Exact test if < 5 subjects in any cell defined by treatment group and weight group. Continuous response parameters (such as change from baseline in DAS28 [CRP] score) were to be compared using an analysis of variance on the van der Waerden normal scores with weight group (< 75 and ≥ 75 kg for Part A; < 65, 65 – 85, and > 85 kg for Part B) as a covariate. All statistical tests were to be performed at 2-sided α level of 0.05. In addition, graphical data displays (eg, line plots) and subject listings could also be summarized.

RESULTS:

STUDY POPULATION:

A total of 36 subjects were randomized to treatment in Part A. Of the 36 subjects, 17 (including 3 subjects from site [redacted] were randomized to CNTO 136 and 19 were randomized to placebo (including 2 subjects from site [redacted] Among these 36 subjects, 3 (8.3%) subjects (1 in the placebo group and 2 in the CNTO 136 group) discontinued study agent prior to Week 22. All of these discontinuations occurred prior to Week 12 and were due to AEs. A higher proportion of female subjects were randomized to the CNTO 136 group (82.4%) compared with the placebo group (57.9%). Other baseline demographics were comparable between the placebo and CNTO 136 groups.

A total of 151 subjects were randomized to treatment in Part B. Of these 151 subjects, 30 each were randomized to the CNTO 136 100 mg q2w, 100 mg q4w, and 50 mg q4w and placebo groups and 31 were randomized to the CNTO 136 25 mg q4w. Among these 151 subjects, 20 (13.2%) subjects discontinued study agent prior to Week 24; 11 (7.3%) of which discontinued study agent administrations prior to Week 12. Of the 20 subjects who discontinued study agent administrations prior to Week 24, 11 subjects discontinued due to an AE (5 [16.7%] in the CNTO 136 100 mg q4w group, 3 [10.0%] in the CNTO 136 50 mg q4w group, 2 [6.7%] in the placebo group, and 1 [3.3%] in the CNTO 136 100 mg q2w group). Asian subjects constituted about 20% of all randomized subjects. A higher proportion of male subjects was enrolled into the CNTO 136 25 mg q4w group (25.8%) compared with the other CNTO 136 groups and the placebo group. Other baseline demographics were comparable among the 5 treatment groups.

EFFICACY RESULTS:

Part A

- Proof-of-concept for CNTO 136 in RA was established.
- A greater average improvement from baseline in DAS28 (CRP) was observed at Week 12 in the CNTO 136 group compared with the placebo group; statistical significance (p-value ≤0.05) was achieved.
- A higher proportion of subjects achieved ACR 50 response at Week 12 in the CNTO 136 group (29%) compared with the placebo group (6%); statistical significance (p-value ≤ 0.05) was not achieved.
- A greater proportion of subjects achieved ACR 20 response at Week 12 in the CNTO 136 group (71%) compared with the placebo group (18%); statistical significance (p-value ≤ 0.05) was achieved.
- Overall, efficacy, measured by improvement from baseline in DAS28 (CRP), proportions of subjects with DAS28 (CRP) moderate or good responses, proportions of subjects with ACR 20/50/70 responses, improvement from baseline in ACR core components (except CRP), improvement from baseline in duration of morning stiffness, improvement from baseline in Health Assessment Questionnaire (HAQ) index score, proportions of subjects with HAQ responses, and improvement from baseline in Clinical Disease Activity Index (CDAI) in the CNTO 136 group, generally was observed as early as Week 2, after the first study agent administration, increased over time through Week 12, and then, after crossover to receive placebo starting from Week 12, was maintained through Week 24 (ie, 12 weeks after receiving placebo). Efficacy in the placebo group generally increased rapidly after crossover to receive CNTO 136 starting from Week 12 and became comparable to the CNTO 136 group at Week 24. The CNTO 136 group generally had better efficacy over time than the placebo group.
- CRP was profoundly suppressed by Week 2 after treatment with CNTO 136 100 mg q2w and this level of CRP suppression was maintained through Week 24, 12 weeks after crossover to receive placebo.

Part B

- A higher proportion of subjects achieved ACR 50 response at Week 12 in each of the 4 CNTO 136 treatment groups (CNTO 136 100 mg q2w, 27%; 100 mg q4w, 23%; 50 mg q4w, 27%; 25 mg q4w 19%) compared with the placebo group (3%); statistical significance (p-value ≤ 0.05) was achieved in the CNTO 136 100 mg q2w and 50 mg q4w treatment groups.
- A greater proportion of subjects achieved ACR 20 response at Week 12 in each of the 4 CNTO 136 groups (CNTO 136 100 mg q2w, 63%; 100 mg q4w, 60%; 50 mg q4w, 57%; 25 mg q4w, 61%) compared with the placebo group (30%).; statistical significance (p-value ≤ 0.05) was achieved in the CNTO 136 100 mg q2w, 100 mg q4w, and 25 mg q4w treatment groups.
- A greater average improvement from baseline in DAS28 (CRP) was observed at Week 12 in each of the 4 CNTO 136 groups compared with the placebo group; all 4 of the CNTO 136 treatment groups achieved statistical significance (p-value ≤ 0.05).
- Throughout Part B, 23 subjects achieved ACR/The European League Against Rheumatism remission by the Boolean-based criteria, and 32 subjects by the simplified disease activity index (SDAI)-based criteria. Remission by SDAI-based criteria was observed as early as Week 2, increased over time through Week 24, and was then maintained in all 5 groups through Week 30, which was 6 weeks after the last administration of CNTO 136.

- Overall, efficacy, measured by improvement from baseline in DAS28 (CRP), proportions of subjects with DAS28 (CRP) moderate or good responses, proportions of subjects with ACR 20/50/70 responses, improvement from baseline in ACR core components (except CRP), improvement from baseline in duration of morning stiffness, improvement from baseline in HAQ index score, proportions of subjects with HAQ responses, and improvement from baseline in CDAI across the 5 treatment groups, generally was observed as early as Week 2, after the first study agent administration, increased over time through Week 24, and then was maintained through Week 30 (ie, 6 weeks after receiving last study agent). Efficacy in the placebo group generally increased rapidly after crossover to receive CNTO 136 starting from Week 12 and became comparable to the CNTO 136 group at Week 38. An apparent loss of efficacy generally was observed at Week 38 in the CNTO 136 25 mg and 50 mg q4w groups. The CNTO 136 100 mg q2w group generally had better efficacy over time than the placebo group and the other 3 CNTO 136 groups.
- Observed CRP suppression was similar to Part A.

PHARMACOKINETIC, IMMUNOGENICITY, AND PHARMACODYNAMIC RESULTS:

Pharmacokinetics

Part A

Following SC administration of CNTO 136 100 mg q2w, the median T_{max} ranged from 3.9 to 4.0 days. Mean C_{max} and $AUC_{0\text{-}14d}$ values were 7.50 µg/mL and 80.63 µg•day/mL, and 20.01 µg/mL and 232.43 µg•day/mL following the first and last doses, respectively. Serum CNTO 136 concentration appeared to achieve steady state by Week 12 with a mean trough concentration of 14.31 µg/mL at Week 12. Mean accumulation ratios following SC administration of CNTO 136 100 mg q2w were 2.67 for C_{max} and 2.68 for $AUC_{0\text{-}14d}$. The mean values of CL/F and V_z/F were 6.27 mL/day/kg and 162.63 mL/kg, respectively. The mean $T_{1/2}$ value was 18.3 days.

Mean (SD) CNTO 136 pharmacokinetic parameters following SC administration in Part A

PK Parameters	Dose 1	Dose 6
n	14	11
C_{max} (µg/mL)	7.50 ± 2.91	20.01 ± 4.40
T_{max} (day) [b]	3.9 (2.2, 13.8)	4.0 (3.0, 7.0)
$AUC_{0\text{-}14d}$ (µg·day/mL)	80.63 ± 25.66	232.43 ± 48.90
$T_{1/2}$ (day)	NA	18.32 ± 4.51
CL/F (mL/day/kg)[a]	NA	6.27 ± 1.36
V_z/F (mL/kg)[a]	NA	162.63 ± 46.28
R_{Cmax}	NA	2.67 ± 1.08
$R_{AUC(0\text{-}14d)}$	NA	2.68 ± 0.52

[a] Body-weight adjusted value.
[b] Median (Min, Max) was reported for T_{max}.
NA: Not applicable.

Part B

Following SC administration of CNTO 136, the median T_{max} ranged from 4.0 to 5.5 days. Mean C_{max} values for the 25 mg q4w, 50 mg q4w and 100 mg q4w groups increased in an approximately dose-proportional manner following administration of both the first (1.86, 2.99 and 6.73 µg/mL) and last doses (2.93, 4.26 and 9.34 µg/mL) of CNTO 136. Similarly, mean $AUC_{0\text{-}28d}$ values for the 25 mg q4w, 50 mg q4w and 100 mg q4w groups increased in an approximately dose-proportional manner following administration of both the first (29.08, 49.38 and 107.88 µg•day/mL) and last doses (52.02, 83.52 and 172.04 µg•day/mL) of CNTO 136. Mean values of CL/F and V_z/F were dose independent and ranged from 8.05 to 16.90 mL/day/kg, and 165.35 to 285.71 mL/kg, respectively. For the 100 mg q2w group,

mean C_{max} and AUC_{0-14d} values following the first and last doses were 6.60 µg/mL and 66.03 µg•day/mL, and 15.68 µg/mL and 188.67 µg•day/mL, respectively. Mean values of CL/F and V_z/F were 9.51 mL/day/kg and 245.01 mL/kg, respectively. Mean $T_{1/2}$ values ranged from 14.9 to 19.1 days across all treatment groups. Serum CNTO 136 concentrations achieved steady state by Week 12 with mean trough concentrations of 0.99, 1.79, 3.10, and 11.63 µg/mL at Week 12 for the 25 mg q4w, 50 mg q4w, 100 mg q4w and 100 mg q2w groups, respectively. Mean accumulation ratios following SC administrations of CNTO 136 at 25 q4w, 50 mg q4w, 100 mg q4w or 100 mg q2w were 1.62, 1.66, 1.51 and 2.55, respectively, for C_{max}; and 1.68, 1.81, 1.57, and 3.01, respectively, for $AUC_{(t1-t2)}$.

Mean (SD) CNTO 136 pharmacokinetic parameters following SC administration in Part B

PK Parameters	25 mg q4w	50 mg q4w	100 mg q4w	100 mg q2w	Placebo → 100 mg q2w
First Dose					
n	31	28	29	29	NA
C_{max} (µg/mL)	1.86 ± 1.11	2.99 ± 1.51	6.73 ± 2.73	6.60 ± 3.03	NA
T_{max} (day)	5.0 (2.9, 27.8)	5.4 (2.9, 12.6)	5.0 (3.0, 13.9)	4.9 (2.8, 10.7)	NA
$AUC_{(t1-t2)}$ (µg.day/mL)[a]	29.08 ± 10.65	49.38 ± 23.15	107.88 ± 43.05	66.03 ± 31.62	NA
Last Dose					
n	28	21	22	26	22
C_{max} (µg/mL)	2.93 ± 1.29	4.26 ± 1.73	9.34 ± 4.31	15.68 ± 7.07	16.26 ± 5.92
T_{max} (day)	4.0 (2.8, 11.7)	5.0 (0.0, 7.0)	4.0 (0.0, 7.1)	5.0 (0.0, 9.7)	5.5 (2.9, 7.2)
$AUC_{(t1-t2)}$ (µg.day/mL)[a]	52.02 ± 22.03	83.52 ± 35.17	172.04 ± 86.17	188.67 ± 90.43	188.84 ± 68.20
$T_{1/2}$ (day)	14.89 ± 4.54	16.12 ± 4.75	16.00 ± 4.11	19.01 ± 4.32	19.10 ± 4.30
CL/F (mL/day/kg)[b]	8.05 ± 2.66	16.90 ± 30.97	11.00 ± 4.37	9.51 ± 4.87	9.05 ± 3.97
V_z/F (mL/kg)[b]	165.35 ± 57.55	285.71 ± 251.63	237.03 ± 71.69	245.01 ± 104.45	240.06 ± 98.73
R_{Cmax}	1.62 ± 0.57	1.66 ± 0.65	1.51 ± 0.87	2.55 ± 1.03	NA
$R_{AUC(t1-t2)}$[a]	1.68 ± 0.37	1.81 ± 0.65	1.57 ± 0.83	3.01 ± 1.23	NA

[a] AUC_{0-14d} was reported for q2 Weeks treatment group; AUC_{0-28d} was reported for q4 Weeks treatment groups.
[b] Body-weight adjusted value.
[c] Median (Min, Max) was reported for T_{max}.
NA not applicable

Immunogenicity

In Part A, a total of 31 subjects received CNTO 136 and had appropriate serum samples for the evaluation of antibodies to CNTO 136. The incidence of antibodies to CNTO 136 in Part A was 0% (0/31).

In Part B, a total of 142 subjects received CNTO 136 and had appropriate serum samples for the evaluation of antibodies to CNTO 136. The incidence of antibodies to CNTO 136 in Part B was 1.4% (2/142).

The overall incidence of antibodies to CNTO 136 in this study was 1.2% (2/173).

Pharmacodynamics

Part A

- The concentration of CRP and serum amyloid A decreased significantly in the CNTO 136-treated subjects to at or near the lower limit of quantification (LLOQ). This decrease was maintained through Week 24.
- Serum vascular endothelial growth factor, haptoglobin, and intercellular adhesion molecule-1 were significantly decreased by CNTO 136 treatment.
- A collagen synthesis marker (type IIA collagen N-propeptide) decreased in CNTO 136-treated subjects at Week 2 and Week 4.
- In the majority of anemic subjects treated with CNTO 136, hemoglobin levels were normalized by Week 24.

Part B

- The concentration of CRP and serum amyloid A decreased significantly in the CNTO 136-treated subjects to at or near the LLOQ. This decrease was maintained through Week 24.
- At Week 24, 21/37 (56.8%) of subjects with anemia at baseline achieved normal hemoglobin levels.

HEALTH ECONOMICS RESULTS:

There was a trend toward a greater decrease in self-reported impact of disease on productivity in the CNTO 136 treatment group than in the placebo group at Week 12, but the difference was not statistically significant.

SAFETY RESULTS:

- No dose response was observed for overall treatment emergent adverse events (TEAEs) or for laboratory abnormalities.
- The overall incidence of TEAEs was higher in subjects who received CNTO 136 than in subjects receiving placebo.
- The three most frequently reported system-organ classes of TEAE were Infections and infestations, Investigations (ie, laboratory abnormalities), and General disorders and administration site conditions.
- In Part A through Week 12, the rate of TEAEs was slightly higher in the CNTO 136 group; TEAEs were reported by 12 of 17 subjects (70.6%) in the CNTO 136 group versus 12 of 19 subjects (63.2%) in the placebo group.
- In Part A, a single SAE of staphylococcal cellulitis occurred in a subject in the CNTO 136 100 mg q2w group after receiving 4 doses of CNTO 136.
- In Part B during the initial 12-week, placebo-controlled period, 7 subjects experienced SAEs. There was 1 malignancy (fibrosarcoma). The proportion of RA subjects with treatment-emergent SAEs was higher in the placebo group (13.3%) compared with the combined CNTO 136 treatment groups (2.5%) and any individual CNTO 136 treatment group. After Week 12, 10 additional SAEs were reported. There was no dose relationship among the SAEs, when considered by type or timing.
- One death due to cerebral aneurysm occurred 6 weeks after the subject completed Week 24 and received CNTO 136 100 mg q2w for 12 weeks.

- Subjects in the treatment groups who received CNTO 136 had a greater number of infections compared with those in the placebo group (33.3% versus 13.3%). Most of the infections were upper respiratory tract infections. There were no opportunistic infections or tuberculosis.
- Injection-site reactions occurred more frequently in CNTO 136-treated subjects (15.6% in Part B) than in placebo group subjects (3.3%). The proportion of injections resulting in injection-site reactions was highest in the CNTO 136 100 mg q2w treatment groups. No subject discontinued study agent because of an injection-site reaction. The 2 subjects who were positive for antibodies to CNTO 136 did not have injection site reactions.
- No hypersensitivity or anaphylactic reactions were reported.
- Laboratory abnormalities commonly observed in CNTO 136 treatment groups included:
  - Decreased white blood cells, absolute neutrophil count, and platelets within the first 2 weeks of treatment that were sustained through at least 24 weeks in Part B.
  - Transient alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increases, usually within 4 weeks of receiving CNTO 136. In most cases, ALT and AST levels declined or returned to normal without interruption of dosing. One subject had toxicity Grade 3 AST and 9 subjects had toxicity Grade 3 ALT.
  - Increased total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides by Week 2 of receiving CNTO 136 with sustained elevation in cholesterol fractions through the last dose of study agent. Cholesterol levels returned toward baseline levels 14 weeks after the last dose of CNTO 136 in Part A.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

- CNTO 136, in combination with MTX, demonstrated good efficacy in subjects with active RA and inadequate response to MTX.
- CNTO 136 administered between 25 mg SC q4w up to 100 mg SC q2w, in combination with MTX, was clinically well tolerated in subjects with RA and inadequate response to MTX.
- The safety profile of CNTO 136 in subjects with RA includes increased risk of infection, injection site reactions, transient liver enzyme elevations, increases in lipid parameters, and decreases in hematological parameters. Overall these events were not related to serious AEs.
- CNTO 136 exhibited linear pharmacokinetics at dose levels ranging from 25 mg to 100 mg following q4w SC administration.
- The accumulation ratio following repeated dosing of 100 mg q2w was higher than the accumulation ratios from 25 mg q4w, 50 mg q4w, and 100 mg q4w.
- Mean $T_{1/2}$ values ranged from 14.9 to 19.1 days across all dose regimens.
- CNTO 136 pharmacokinetics were consistent between Part A and Part B.
- The overall incidence of antibodies to CNTO 136 in this study was low (1.2%, 2/173).
- Serum CRP concentration decreased significantly with all CNTO 136 doses to at or near the lower limit of detection. The decrease was observed by Day 5 and was maintained generally at this level through Week 24 in all 4 CNTO 136 groups in Part B of the study.