2. RHAK Synopsis

Approval Date: 03-Jun-2013 GMT

Clinical Study Report Synopsis: Study I1F-MC-RHAK

Title of Study: A Phase 2 Dose-Ranging Study of Multiple Subcutaneous Doses of LY2439821 (an Anti-IL-17 Antibody) in Patients with Active Rheumatoid Arthritis on Concomitant DMARD Therapy

Number of Investigators: This multicenter study included 80 principal investigators.

Study Centers: This study was conducted at 80 study centers in 11 countries.

Publications Based on the Study:

Genovese M, Greenwald M, Cho C-S, Berman A, Jin L, Cameron G, Xie L, Braun D, Banerjee S. A phase 2 study of multiple subcutaneous doses of LY2439821, an anti-IL-17 monoclonal antibody, in patients with rheumatoid arthritis in two populations: naïve to biologic therapy or inadequate responders to tumor necrosis factor alpha inhibitors. *Arthritis Rheum*. 2011;63(suppl 10):2591.

Genovese M, Greenwald M, Cho C-S, Berman A, Jin L, Cameron G, Wang L, Xie L, Braun D, Berclaz P-Y, Banerjee S. A phase 2 study of multiple subcutaneous doses of LY2439821, an anti-IL-17 monoclonal antibody, in patients with rheumatoid arthritis in two populations: naïve to biologic therapy or inadequate responders to tumor necrosis factor alpha inhibitors. *Ann Rheum Dis*. 2012;71(suppl 3):59.

Length of Study:	**Phase of Development:** 2
Date of first patient enrolled (randomized): 16 September 2009 Date of last patient completed, Part A: 10 February 2011 Date of last patient completed, Part B: 06 June 2012	

Objectives:

The **primary objective** of the study was as follows:

Biologic disease modifying anti-rheumatic drug (bDMARD)-Naive Population ONLY

- To determine the dose-response relationship of ixekizumab (LY2439821) at Week 12, as measured by the proportion of ACR20 responders.

The **secondary objectives** of the study were as follows:

Tumor necrosis factor alpha–inadequate responder (TNFα-IR) Population ONLY

- To evaluate the efficacy of ixekizumab at Week 12 compared to placebo as measured by the proportion of ACR20 responders.

bDMARD-Naive Population ONLY

- To estimate the smallest doses that achieve 10%, 50%, and 90% of the maximum ACR20 response (ED10, 50, and 90, respectively) at Week 12.
- To evaluate the ixekizumab dose-response relationship at Week 12 and the doses that achieve 10%, 50%, and 90% of the maximum response (ED10, 50, and 90, respectively) at Week 12, as measured by the Disease Activity Score based on the 28 diarthroidal joint count (DAS28) and the ACR50 response rates.

BOTH bDMARD-Naive AND TNFα-IR Populations, separately

- To evaluate the efficacy of ixekizumab compared to placebo as measured by the individual components of the ACR Core Set, the ACR20/50/70/N indices, the DAS28, European League Against Rheumatism Responder Index based on the 28 joint count (EULAR28), and morning stiffness at all time points where the measures were collected.
- To evaluate the effect of treatment with ixekizumab compared to placebo on patient-reported health outcomes, as measured by the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale and the Health Assessment Questionnaire-Disability Index (HAQ-DI; part of the ACR Core Set) at all time points where the measures were collected.
- To characterize relationships between ixekizumab dose, exposure, and response of selected disease activity measures including: individual components of the ACR Core Set, ACR20/50/70/N endpoints, DAS28, and EULAR28 at all time points where the measures were collected.

- To evaluate the safety and tolerability of ixekizumab compared to placebo as measured by deaths, serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), discontinuations due to adverse events (AEs), laboratory results, vital signs, electrocardiograms (ECGs), and additional safety measures at all time points where the measures were collected.
- To characterize pharmacokinetic (PK) data after multiple doses of ixekizumab at all time points where the measures were collected.
- To explore the potential development of anti-ixekizumab antibodies following subcutaneous (SC) dosing at all time points where immunogenicity samples were collected.

The **exploratory objective** of the study was as follows:

- To explore the potential associations between selected biomarkers (measured at baseline and in response to study treatment) and selected disease activity measures at selected time points where the measures were collected.

Additional **post-hoc analyses** were also performed:

- To evaluate the efficacy of ixekizumab compared to placebo as measured by the DAS28-erythrocyte sedimentation rate (ESR).
- To evaluate the efficacy of ixekizumab compared to placebo as measured by the Clinical Disease Activity Index (CDAI), which is a composite score of the sum of tender joint count (TJC; 28 joints), swollen joint count (SJC; 28 joints), patient's global assessment of disease activity, and physician's global assessment of disease activity.

Study Design: Study I1F-MC-RHAK (RHAK) was a multicenter study in bDMARD-naive and TNFα-IR patients with active rheumatoid arthritis (RA) on concomitant conventional disease modifying anti-rheumatic drug (DMARD) therapy. The study was a Phase 2 study with 2 parts: Part A was a randomized, double-blind, placebo-controlled, parallel-group, dose-ranging design, and Part B was an optional, open-label extension design.

Part A: Each patient received multiple SC injections of ixekizumab (bDMARD-naive patients: 3, 10, 30, 80, or 180 mg; TNFα-IR patients: 80 or 180 mg) or placebo at Weeks 0, 1, 2, 4, 6, 8, and 10. Total study participation for a patient was approximately 16 to 34 weeks in Part A and included an entry period (up to 4 weeks), a treatment period (12 weeks, including an additional 2 weeks after the last injection at Week 10), and a follow-up period (4 weeks for patients entering Part B, and up to 22 weeks for patients who did not enter Part B). Only patients who needed to be followed for neutropenia returned for a safety visit (SV) 24 weeks after the last injection (Week 34).

Part B: All patients who completed the treatment period in Part A were eligible to enter Part B at Week 16. All patients choosing to continue participation into Part B were assigned to receive 160 mg of ixekizumab SC at Weeks 16, 18, and 20 and every 4 weeks (Q4W) thereafter through Week 60. Treatment assignment in Part B was independent of patient population or previous treatment assignment. For Part B, total study participation for a patient was approximately 56 to 68 weeks and included an unblinded treatment period (48 weeks, including an additional 4 weeks after the last injection at Week 60) and a follow-up period (8 to 20 weeks). Only patients who needed to be followed for neutropenia returned for an SV 24 weeks after the last injection (Week 84).

Therefore, for patients who completed both Part A and Part B of Study RHAK, total study participation was up to approximately 72 to 84 weeks.

Number of Patients:
Planned: 753 (screen); 429 (randomize) (252 bDMARD-naive and 177 TNFα-IR)
Randomized: 448 (260 bDMARD-naive and 188 TNFα-IR)
Treated (at least 1 dose): Part A = 330 ixekizumab (206 bDMARD-naive and 124 TNFα-IR), 118 placebo (54 bDMARD-naive and 64 TNFα-IR)
Part B = 390 ixekizumab (232 bDMARD-naive and 158 TNFα-IR); of the 390 patients, 97 were on placebo in Part A (46 bDMARD-naive and 51 TNFα-IR)
Completed: Part A = 397 (236 bDMARD-naive and 161 TNFα-IR)
Part B = 301 (202 bDMARD-naive and 99 TNFα-IR)

Diagnosis and Main Criteria for Inclusion: This study enrolled bDMARD-naive and TNFα-IR patients with active RA on concomitant conventional DMARD therapy. For inclusion in this study, male or female patients were ambulatory with an established diagnosis of RA according to the American Rheumatism Association (ARA) 1987 Revised Criteria for the Classification of RA; were in an ACR Functional Class I, II, or III; had active RA defined as the presence of at least 6 tender and at least 6 swollen joints; had a C-reactive protein (CRP) measurement greater than the upper limit of normal (ULN) or ESR (by Westergren method) of at least 28 mm/h; and were between the ages of 18 and 75 years, inclusive, at time of study entry.

Patients enrolled in the bDMARD-naive population were required to have been taking methotrexate (MTX) for ≥12 weeks and at a stable dose (7.5 to 25 mg/week) for ≥8 weeks prior to baseline and throughout the study. Patients taking hydroxychloroquine and/or sulfasalazine in addition to MTX had to be on a stable dose for ≥8 weeks prior to baseline. Patients enrolled in the TNFα-IR population had to have been treated with ≥1 biologic TNFα inhibitor therapy, and in the opinion of the investigator, either had stopped treatment due to insufficient efficacy after ≥3 months of therapy at approved doses, or had been intolerant of such treatment, regardless of treatment duration. Patients could not have used etanercept or anakinra <28 days, infliximab or adalimumab <56 days, abatacept <3 months, rituximab <12 months, or any other bDMARD for a duration equivalent to <5 half-lives prior to baseline. In addition, patients had to have been regularly treated with ≥1 conventional DMARD in a stable treatment regimen that could include any combination of 1 or more of MTX, hydroxychloroquine, and sulfasalazine; all other conventional DMARDs were allowed as single-agent use only. If on MTX, regular use for ≥12 weeks and stable dose level (7.5 to 25 mg/week) for ≥8 weeks prior to baseline was required.

Test Product, Dose, and Mode of Administration:
Ixekizumab was administered at the following dose levels in Part A: 3, 10, 30, 80, or 180 mg and in Part B at 160 mg. SC injections were given by study site personnel in Part A at Weeks 0, 1, 2, 4, 6, 8, and 10 for a total of 7 doses and in Part B at Weeks 16, 18, and 20 and Q4W thereafter through Week 60 for a total of 13 doses. Doses were administered as 2 x 1.5 mL SC injections.

Reference Therapy, Dose, and Mode of Administration: Placebo was administered SC by study site personnel in Part A at Weeks 0, 1, 2, 4, 6, 8, and 10. Doses were administered as 2 x 1.5 mL SC injections. There was no reference therapy in Part B.

Duration of Treatment:
The planned duration of treatment was approximately 12 weeks in Part A and approximately 48 weeks in Part B.

Variables:
Efficacy: The primary objective in this study was the dose-response relationship of ixekizumab as measured by ACR20 response in the bDMARD-naive population at Week 12. Secondary efficacy measures included ACR20 (TNFα-IR population), ACR50, ACR70, and ACR-N responder indices, individual components of the ACR Core Set (TJC, SJC, patient's assessment of arthritis pain, patient's global assessment of disease activity, physician's global assessment of disease activity, HAQ-DI, CRP, and ESR), EULAR28, DAS28-CRP, and morning stiffness. Post-hoc efficacy measures included DAS28-ESR and CDAI.
Health Outcomes/Quality of Life: HAQ-DI (part of the ACR Core Set) and FACIT Fatigue Scale.
Pharmacokinetic: Serum for ixekizumab concentrations.
Pharmacodynamic: Disease-related biomarkers including rheumatoid factor (RF), CRP, ESR, and [redacted]

Safety: AEs, TEAEs, Deaths, SAEs, discontinuations due to AEs, AEs of special interest (AESIs), laboratory results, immunogenicity, vital signs, ECGs, and other physical findings.

Statistical Evaluation Methods:

A total sample size of approximately 252 bDMARD-naive patients randomized into Part A was estimated to obtain approximately 224 evaluable bDMARD-naive patients at Week 12, assuming a dropout rate of approximately 10% (48, 32, 32, 32, 48, and 32 patients per group in the 0- [placebo], 3-, 10-, 30-, 80-, and 180-mg treatment groups, respectively). This provided at least 94% unadjusted power to detect a statistically significant dose-response relationship across the ixekizumab and placebo treatment groups at a 2-sided significance level of 0.10 based on the ACR20 response.

A total sample size of approximately 177 TNFα-IR patients randomized into Part A was estimated to obtain approximately 159 evaluable TNFα-IR patients at Week 12, assuming a dropout rate of approximately 10% (53 patients per group in the 0- [placebo], 80-, and 180-mg treatment groups). This provided at least 80% power to detect a difference of 25% in the ACR20 response between each of the ixekizumab dose groups versus the placebo group using a 1-sided Pearson Chi-square test at the 0.05 significance level with no adjustment for multiple comparisons.

All analyses were conducted using the Full Analysis Set (FAS; also known as modified intent-to-treat patient set). This set included all data from all randomized patients who received at least 1 dose of study drug based on actual treatment received, irrespective of treatment assignment. Unless otherwise specified, missing data for the primary time point, Week 12, was imputed by the last observation carried forward (LOCF) method. For ACR20, ACR50, and ACR70 patients who discontinued treatment before reaching Week 12, non-responder imputation (NRI) method was used for analysis at Week 12. Separate analyses were done within each population (bDMARD-naive and TNFα-IR patients); the combined population was used in exploratory analyses.

Primary Efficacy Analysis: The primary efficacy variable was the proportion of bDMARD-naive responders as measured by the ACR20 response at Week 12. A logistic regression model with dose and dose2 as continuous predictor variables was used with dose equal to 0 defined for placebo. A 2-sided maximum likelihood ratio test was used at the 0.1 significance level to test the dose-response relationship. The primary efficacy analysis was repeated using the Per Protocol Analysis Set (PPAS). This set included all data from all randomized patients without major protocol deviations.

Secondary Efficacy Analyses: The main efficacy variable for the TNFα-IR population was the proportion of responders as measured by the ACR20 response at Week 12.

Within both the bDMARD-naive and TNFα-IR populations, the ACR20/50/70/N, DAS28, and EULAR28 were analyzed using 1-sided tests. All other secondary efficacy variables were analyzed using 2-sided tests. Unless otherwise specified, for the visit values and the changes from baseline values, comparisons between ixekizumab dose groups and the placebo group were analyzed using an analysis of covariance (ANCOVA) with treatment as the fixed factor and the baseline value as a covariate. Differences in least squares means (LS Means) and p-value from the comparisons via ANCOVA were presented. Pairwise comparisons of each ixekizumab dose group to the placebo group in each categorical parameter were performed using Pearson Chi-square test unless assumptions of the test were violated, and in that case, Fisher's exact test was used. Analyses were performed for all time points where data was collected. Spearman rank correlation method was used to explore the potential associations between biomarkers and disease activity measures.

For the open-label extension period (Part B), the efficacy data were summarized descriptively across all patients from Part A who entered into Part B without formal statistical analysis.

Health Outcomes/Quality-of-Life Analyses: Observed values and changes from baseline in HAQ-DI, HAQ-DI reduction from baseline ≥0.22, and FACIT Fatigue Scale were analyzed using the same methods as described for the efficacy analyses.

Pharmacokinetics/Pharmacodynamics: Ixekizumab PK data were analyzed using a population approach via nonlinear mixed effects modeling with the NONMEM software. In the population PK model, the parameter for absolute bioavailability (F) for the SC route was fixed to a value estimated from an earlier study (Study I1F-MC-RHAG). Population PK parameters were examined for relationships with age, gender, origin, RA treatment duration at study entry, body mass index (BMI), body surface area (BSA), weight, dose, Cockcroft-Gault creatinine clearance, modification of diet in renal disease estimated glomerular filtration rate (MDRD eGFR), treatment-emergent anti-drug antibody (TE-ADA), anti-drug antibody (ADA) titer, and RA patient cohort (bDMARD-naive or TNFα-IR).

A separate PK/pharmacodynamic (PD) or exposure-efficacy model was built for each RA patient cohort using patient-level data via a sequential PK/PD modeling approach. This logistic regression model has the ability to model the relationships between ixekizumab concentrations, a continuous but assumed (not measured) latent-dependent variable (American College of Rheumatology latent [ACRL]) representing RA disease progression in signs and symptoms, and the time-course of the binary variables ACR20, ACR50, and ACR70 for clinical efficacy. Factors that were assessed as covariates on population PD parameters included CRP, ESR, RF, TJC, SJC, geographical location, origin, RA treatment duration at entry, DAS28, TE-ADA, and ADA titer.

Estimates of PK as well as PD model parameters and covariate effects and corresponding 90% confidence intervals (CIs) were reported.

Safety: Safety and tolerability were evaluated across all populations in terms of AEs, TEAEs, AESIs, discontinuations due to AEs, SAEs, deaths, changes in clinical laboratory test results (including neutrophils and immunogenicity), ECGs, vital signs, and other physical findings for Part A and Part B. Unless otherwise specified, safety data in Part A were analyzed using a 2-sided test with a t-test for continuous variables and Fisher's exact test for categorical variables. For the open-label extension period (Part B), the safety data were summarized descriptively across all patients from Part A who entered into Part B without formal statistical analysis.

Summary:

Patients: A total of 448 RA patients were randomized into 2 population cohorts, 260 bDMARD-naive and 188 TNFα-IR patients. Of the 448 randomized patients, 397 patients completed Part A. Of these 397 patients, 391 patients entered Part B, and 301 patients completed Part B. Overall, the mean age of enrolled patients was 53 years, 86% were women, and the mean duration of RA diagnosis was 8.7 years. Within each population, the distribution of most demographic characteristics, including age, gender, race, and BMI was comparable across treatment groups. A total of 17 (7%) patients in the bDMARD-naive population and 19 (10%) patients in the TNFα-IR population discontinued before the Week 12 visit. The most common reasons for discontinuation from the study during Part A were subject decision and AEs. The most common reasons for discontinuation from the study during Part B were lack of efficacy and subject decision.

Efficacy: All efficacy and health outcomes/quality-of-life analyses were conducted using the FAS (also known as modified intent-to-treat patient set).

Part A

bDMARD-Naive Population

- This study met its primary objective as a statistically significant dose-response relationship was detected for ACR20 responses at Week 12 with ixekizumab treatment in the bDMARD-naive population.

- Although not powered for pair-wise comparisons, significantly greater percentages of patients achieved an ACR20 response with multiple doses of ixekizumab compared with placebo at various time points; the response was statistically significantly greater at Week 12 in the 30-mg ixekizumab dose group.
- The clinical efficacy response was characterized by a rapid onset of action, with statistically significantly greater percentages of patients achieving an ACR20 response by Day 3 in the 30- and 180-mg ixekizumab dose groups versus the placebo group, and by Week 1 in the 3-, 30-, and 180-mg ixekizumab dose groups versus the placebo group.
- At Week 12, the proportions of patients achieving ACR50 and ACR70 responses in the ixekizumab dose groups were statistically significantly greater compared with those in the placebo group; although no clear dose response was observed.
- Changes in most ACR component scores were significantly better in the 30-, 80-, and 180-mg ixekizumab dose groups compared with those in the placebo group at Week 12.
- Mean CRP values decreased rapidly in all ixekizumab dose groups versus the placebo group, with near-nadir values achieved at Week 1. Patient CRP values were relatively stable in the 30-, 80-, and 180-mg ixekizumab dose groups after Week 1; CRP levels in all ixekizumab dose groups were statistically significantly lower versus the placebo group at Week 12 with no clear dose-related differences.
- Decreases in mean ESR values from baseline already reached statistical significance across all ixekizumab dose groups compared to the placebo group at Week 1 with continued decline thereafter. At Week 12, mean ESR values in the 3- and 30-mg ixekizumab dose groups were significantly lower versus the placebo group, while statistically significant differences versus the placebo group were observed through Week 16 for all ixekizumab dose groups except for the 10-mg ixekizumab dose group; no clear dose-related differences were observed.
- Using EULAR response criteria at Week 12, a statistically significant response was observed in the 80- and 180-mg ixekizumab dose groups versus the placebo group.
- A reduction in disease activity was observed using DAS28-CRP scores with improvements seen by Day 3 in the 10- and 180-mg ixekizumab dose groups versus the placebo group, and by Week 1, across all ixekizumab dose groups versus the placebo group. These improvements versus placebo persisted through Week 12 (statistically significant for all ixekizumab dose groups at all time points except for 10 mg at Week 2 and for 3 mg at Weeks 2, 4, and 8).
- Although the combined ixekizumab dose group had higher percentages of patients with DAS28-CRP $\leq$3.2 and DAS28-CRP <2.6 versus the placebo group at most time points, statistical significance was observed only for DAS28-CRP $\leq$3.2 in the 80-mg ixekizumab dose group at Week 16 and in the 180-mg ixekizumab dose group at Weeks 2, 4, 8, 12, and 16 versus the placebo group.
- Statistically significant reductions were observed in morning stiffness duration in the 80- and 180-mg ixekizumab dose groups versus the placebo group at Week 12.
- Statistically significant reductions were observed in DAS28-ESR scores for all ixekizumab dose groups versus the placebo group at all time points except for 30 mg at Day 3, 80 mg at Day 3 and Week 2, 10 mg at Weeks 2 and 4, and 3 mg at all time points.
- Statistically significant decreases from baseline were observed in mean CDAI scores in the 30-, 80-, and 180-mg ixekizumab dose groups versus the placebo group at most time points, with statistically significant improvements seen as early as by Day 3 in the 180-mg ixekizumab dose group and by Week 1 in the 80- and 180-mg ixekizumab dose groups versus the placebo group.

TNFα-IR Population

- Statistically significant differences in ACR20 responses were observed in each of the ixekizumab dose groups versus the placebo group by Week 1 in TNFα-IR patients (statistically significant responses seen as early as Day 3 in the 180-mg ixekizumab dose group) that persisted through Week 12.
- At Week 12, ACR50 and ACR70 responses in the ixekizumab dose groups were numerically higher compared with those in the placebo group, with statistically significant differences observed in the 80-mg ixekizumab dose group for the ACR50 response; no clear dose response was observed.

- Changes in most ACR component scores were significantly better in each of the ixekizumab dose groups compared with those in the placebo group at Week 12.
- Mean CRP values decreased significantly in each of the ixekizumab dose groups versus the placebo group, beginning by Day 3 and reaching near-nadir values by Week 1. CRP levels in each of the ixekizumab dose groups were statistically significantly lower versus the placebo group at Week 12 with no clear dose-related differences.
- Mean ESR values did not change significantly through Week 1 in either of the ixekizumab dose groups; however, ESR levels in each of the ixekizumab dose groups were statistically significantly lower versus the placebo group at Week 12 with no clear dose-related differences.
- Using EULAR response criteria at Week 12, a statistically significant response was observed in each of the ixekizumab dose groups versus the placebo group.
- Decreases in DAS28-CRP from baseline were observed in each of the ixekizumab dose groups versus the placebo group by Day 3 and persisted through Week 12 (statistically significant for both ixekizumab doses at each time point).
- Although each of the ixekizumab dose groups had higher percentages of patients with DAS28-CRP $\leq$3.2 and DAS28-CRP <2.6 versus the placebo group, only the 180-mg ixekizumab dose group reached statistical significance for both DAS28-CRP thresholds at Week 12.
- Statistically significant reductions were observed in morning stiffness duration in the 80-mg ixekizumab dose group versus the placebo group at Week 12.
- Decreases in DAS28-ESR from baseline were observed in each of the ixekizumab dose groups versus the placebo group (statistically significant for both ixekizumab dose groups at all time points except for 80 mg at Day 3 and Week 8).
- For CDAI scores, statistically significant decreases from baseline were observed as early as by Day 3 in the 180-mg ixekizumab dose group and by Week 1 in the 80-mg ixekizumab dose group versus the placebo group that persisted through Week 12.

Part B

bDMARD-Naive and TNFα-IR Populations

- For patients originally randomized to the ixekizumab dose groups in Part A, maintenance of response was observed for ACR20, ACR50, and ACR70 in both populations through Week 64 in Part B.
- For patients originally randomized to placebo in Part A, ACR20, ACR50, and ACR70 response levels in Part B beyond Week 12 were comparable to those observed for patients originally randomized to the ixekizumab dose groups in Part A in both populations.
- For patients originally randomized to placebo in Part A, a rapid decline in disease activity scores and CRP values was observed in Part B comparable to those observed for patients in the ixekizumab dose groups in Part A. At the end of Part B, these patients obtained results similar to those patients having received ixekizumab from the start of the study.
- Of patients with a good/moderate EULAR response at Week 16, this response was maintained through Week 64 in both populations in Part B.
- Improvements in DAS28-CRP observed at Week 16 were maintained or improved after switching to 160 mg ixekizumab Q4W through Week 64 in Part B in both populations.
- Mean improvement in the duration of morning stiffness was observed in all patients at all time points in Part B in both populations regardless of original treatment group randomization in Part A.

Health Outcomes/Quality of Life:

Part A

bDMARD-Naive and TNFα-IR Populations

- Statistically significant improvements in HAQ-DI scores were observed in the 30-, 80-, and 180-mg ixekizumab dose groups versus the placebo group in the bDMARD-naive population at Week 12.

- There were no statistically significant improvements in HAQ-DI scores in the ixekizumab dose groups versus the placebo group in the TNFα-IR population at Week 12.
- There were no statistically significant improvements in FACIT Fatigue Scale scores in the ixekizumab dose groups versus the placebo group for either population at Week 12.

Part B

bDMARD-Naive and TNFα-IR Populations

- Improvement in HAQ-DI scores was observed in all patients at all time points in Part B in both populations regardless of original treatment group randomization in Part A.
- Improvement in FACIT Fatigue Scale scores was observed in most patients at various time points in Part B in both populations regardless of original treatment group randomization in Part A.

Pharmacokinetics/Pharmacodynamics:

bDMARD-Naive and TNFα-IR Populations

- A 2-compartment PK model with first-order SC absorption and elimination adequately described ixekizumab disposition characteristics. As the PK concentration profiles were very similar between the bDMARD-naive and TNFα-IR populations, a common set of PK parameters were estimated.
- Population mean (95% CI) of absorption rate constant (Ka) and central (V2) and peripheral (V3) volumes of distribution were estimated to be 0.0104/hr [0.00817, 0.0130], 4.25 L [2.99, 5.26], and 2.1 L [1.51, 2.64], respectively. Both Ka and V2 showed moderate to high inter-individual variabilities of 53.9% and 66.3% for Ka and V2, respectively. Inter-individual variability was not estimated for V3. Ixekizumab V2 closely approximated total plasma volume. Ixekizumab population mean (95% CI) for clearance (CL) and inter-individual variability were 0.0142 L/h [0.0133, 0.0151] and 38.5%, respectively. The range of ixekizumab CL values is consistent with CL reported for monoclonal antibodies in general.
- Age was identified as a significant covariate on V2. V2 was found to increase with increasing age and a patient aged 70 years was estimated to have a V2 of 5.93 L, 40% higher than a typical patient of median age 53.6 years in this study. At the highest age of 75.3 years, as permissible for entry into this study, V2 was estimated to be 56% higher than the typical patient of median age 53.6 years.
- Higher doses (≥80 mg) and BMI were identified to have significant effects on ixekizumab CL. CL in patients given ixekizumab ≥80 mg was estimated to be 14% higher compared to patients who were administered ixekizumab doses <80 mg. A patient with a BMI of 40 kg/m^2 (morbid obesity) is estimated to have 19.6% higher CL than a typical RA patient with a median BMI of 27.3 kg/m^2. However, for 1 patient with an extreme BMI of 64 kg/m^2, the CL is estimated to be 49.1% higher than that of a typical RA patient with a BMI of 27.3 kg/m^2.
- The dose-concentration- response relationships for ACR20, ACR50, and ACR70 responses were modeled separately for the bDMARD-naive and TNFα-IR populations. Each model incorporated data for the same population for simultaneous modeling of ACR20, ACR50, and ACR70 responses within a population.
- Baseline TJC was found to be a common and significant covariate in both populations accounting for reducing some of the variability in probability of ACR20, ACR50, and ACR70 response rates. Increasing baseline TJC above the study median of 25 was related to a reduction in ACR response rates.
- Patients of Native American origin demonstrated a trend for higher ACR response rates when compared to patients from all other racial origins combined.
- These trends in response rates by TJC and origin apply to both the placebo group and the ixekizumab dose groups for the bDMARD-naive and TNFα-IR populations but need to be further confirmed with additional data in other studies.
- No conclusive dose-response relationships between incidence of TE-ADA and ADA titer, and ixekizumab dose, were observed based on data from Part A.
- No conclusive relationship between incidence of TE-ADA or ADA titer and ixekizumab PK concentrations or PD effects (ACR20, ACR50, ACR70 response rates) was identified through PK/PD modeling with the available data.

- Dose-related trends were not observed for the disease-related biomarkers RF and [redacted]

Safety: Ixekizumab was well-tolerated overall following multiple administrations over the dose range of 3 to 180 mg SC in patients with RA. The mean days of exposure was similar across treatment groups in Part A for both populations.

Part A through Week 16

bDMARD-Naive and TNFα-IR Populations

- The proportions of patients experiencing TEAEs were similar across all treatment groups in both the bDMARD-naive (59% ixekizumab-treated patients, 56% placebo-treated patients) and TNFα-IR (65% ixekizumab-treated patients, 66% placebo-treated patients) populations.
- There was no clear dose-relatedness of TEAE severity across the 2 populations.
- Overall, infections were the most common type of TEAE in both populations (bDMARD-naive: 29% ixekizumab-treated patients, 20% placebo-treated patients; TNFα-IR: 32% ixekizumab-treated patients, 30% placebo-treated patients), with infections of the upper respiratory tract and urinary tract the most frequent types.
- No patient died in Part A of the study.
- SAEs occurred in 3% (bDMARD-naive) and 9% (TNFα-IR) of ixekizumab-treated patients, and in 2% (bDMARD-naive) and 2% (TNFα-IR) of placebo-treated patients. Infection-related SAEs were reported in 1% (bDMARD-naive) and 4% (TNFα-IR) of ixekizumab-treated patients.
- The reported incidences of AEs leading to discontinuation were 2% (bDMARD-naive) and 5% (TNFα-IR) for ixekizumab-treated patients, and 4% (bDMARD-naive) and 0% (TNFα-IR) for placebo-treated patients.
- The incidence of potentially systemic allergic/hypersensitivity TEAEs was higher in ixekizumab-treated patients versus the placebo-treated patients in both populations (bDMARD-naive: 6% versus 0%, respectively; TNFα-IR: 5% versus 3%, respectively). All but 1 event of this type were mild or moderate in severity in Part A.
- No mycobacterial or invasive fungal infections were reported in either population.
- Similar to other SC biologic therapies, injection-site reactions were more frequent in patients administered ixekizumab than in those given placebo (bDMARD-naive: 6% versus 2%, respectively; TNFα-IR: 21% versus 8%, respectively). No patient experienced an injection-site reaction that led to discontinuation from the study in Part A.
- Among ixekizumab-treated patients through the end of treatment at Week 12, mean absolute neutrophil counts decreased 11% to 17% in bDMARD-naive patients, with a decline of 4% to 5% in TNFα-IR patients. There was no clear dose-dependence across the 2 populations. No patients experienced a Common Terminology Criteria for AEs (CTCAE) Grade 3 or 4 neutrophil counts.
- Changes in mean white blood cell counts were similar to those observed in mean absolute neutrophil counts in both populations in Part A, and appeared to be due primarily to changes in neutrophil counts.
- Mean serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels did not show statistically or clinically significant changes in any ixekizumab dose groups ≤80 mg compared to the placebo group in either population. The 180-mg ixekizumab dose group in both populations showed small, nonclinically significant increases of ALT and AST at isolated time points.
- There were no CTCAE Grade 3 or 4 elevations of serum ALT or AST in ixekizumab-treated patients in either population. No patient experienced a Hy's Law elevation of serum transaminases and total bilirubin.
- Among ixekizumab-treated patients, 16% in the bDMARD-naive and 20% in the TNFα-IR populations developed TE-ADAs in Part A; 12% (bDMARD-naive) and 13% (TNFα-IR) of placebo-treated patients in each population also developed TE-ADAs in Part A. No relationship of ixekizumab doses to frequency or titers of ADAs was observed, and no relationship of ADAs to safety was identified in either population. There were no neutralizing TE-ADAs detected in either population.

- There were no consistent dose-related trends or patterns in mean vital signs over time in the various ixekizumab dose groups compared to the placebo group across the 2 populations. In the bDMARD-naive patients, the 180-mg ixekizumab dose group showed statistically significant increases in mean postbaseline systolic and diastolic blood pressures compared to the placebo group at isolated time points. However, the magnitude of absolute increases were <3 mm Hg in all instances, and observed changes were not considered clinically meaningful.
- There were no statistically significant increases in any mean ECG intervals for any ixekizumab dose groups compared to the placebo group in either population.

Part A, Weeks 16 through 34

For the limited total number of patients in the combined populations (30) who continued follow-up in Part A beyond Week 16 without entering Part B:

- The incidence of TEAEs was 31% (4 patients) in the bDMARD-naive population and 18% (3 patients) in the TNFα-IR population. All reported TEAEs were in ixekizumab-treated patients. The only system organ class (SOC) with more than 1 patient reporting a TEAE was Infections and Infestations (2 patients in each population).
- Two patients (both bDMARD-naive) experienced an SAE (strongyloidiasis and breast cancer stage III); there were no deaths.
- One patient (TNFα-IR) was reported to have discontinued follow-up due to an AE (worsening of RA).
- There were no notable laboratory findings in the Part A follow-up period through Week 34.

Part B

bDMARD-Naive and TNFα-IR Populations

- During the nearly year-long treatment period in Part B to Week 64, TEAEs occurred at similar frequencies in both populations, with 72% of bDMARD-naive patients and 73% of TNFα-IR patients experiencing TEAEs.
- The SOC with the highest incidences of TEAEs was Infections and Infestations, with these TEAEs reported in 41% of patients in both populations.
- There were 3 deaths (<1% of all patients) in Part B, with 2 in the bDMARD-naive population (meningitis and unknown cause) and 1 in the TNFα-IR population (metastatic lung adenocarcinoma). Two of the deaths (meningitis and unknown cause) occurred 5 or more months after discontinuation of ixekizumab.
- The incidences of SAEs in Part B in the bDMARD-naive and TNFα-IR populations were 7% and 11%, respectively. In the bDMARD-naive population, SAEs were most frequent in the Infections and Infestations SOC, with an incidence of 2%. In the TNFα-IR population, the highest incidences of SAEs were reported in the Infections and Infestations (3%), and Injury, Poisoning, and Procedural Complications (3%) SOCs.
- One percent of bDMARD-naive patients and 6% of TNFα-IR patients reported AEs that led to discontinuation. In the bDMARD-naive population, there was no more than 1 patient with an AE leading to discontinuation in any SOC. In the TNFα-IR population, AEs leading to discontinuation were most common in the Infections and Infestations SOC (3% of patients).
- Potentially systemic allergic/hypersensitivity reactions occurred in 8% of bDMARD-naive and 6% of TNFα-IR patients. All events of this type were mild or moderate in severity in Part B.
- As in Part A, there were no mycobacterial or invasive fungal infections reported in either population.
- Injection-site reactions occurred in comparable proportions of all patients in both populations in Part B (bDMARD-naive patients: 7%; TNFα-IR patients: 15%) compared to the ixekizumab dose groups in Part A; those switching from placebo to ixekizumab in Part B having the highest rates (bDMARD-naive patients: 13%; TNFα-IR patients: 20%). No patient experienced an injection-site reaction that led to discontinuation from the study in Part B.

- bDMARD-naive patients showed a decrease of 9% overall (range: -1% to -18% for the various Part A treatment groups, including placebo) in mean absolute neutrophil count from Baseline A values (defined as the last available value before the first dose in Part A) at Week 64, and an increase of 4% overall (range: -3% to +13% for the various Part A treatment groups, including placebo) from Baseline B values (defined as the available value measured at Visit 11 [Week 16] before the first dose in Part B) at Week 64. TNFα-IR patients showed a decrease of 5% overall (range: -1% to -8% for the various Part A treatment groups, including placebo) in mean absolute neutrophil count from Baseline A values at Week 64, and an increase of 1% overall (range: -5% to +7% for the various Part A treatment groups, including placebo) from Baseline B values at Week 64. There was no clear relationship of changes in mean absolute neutrophil count in Part B relative to the original treatment group randomization in Part A in either population.
- One bDMARD-naive patient experienced a CTCAE Grade 3 absolute neutrophil count at Week 48 during Part B. This patient, who was also receiving 3 concomitant conventional DMARDs at the time, had spontaneous recovery to Grade 2 while on treatment until Week 64 and then to Grade 1 by the Week 72 follow-up visit. There were no Grade 4 neutrophil counts in either population.
- As in Part A, changes in mean white blood cell counts in Part B were similar to those seen in mean absolute neutrophil counts in both populations, and appeared to be secondary to changes in neutrophil counts.
- Mean serum ALT and AST were essentially unchanged for patients overall in both the bDMARD-naive and TNFα-IR populations at the end of treatment at Week 64 compared to Baseline B at Week 16. As in Part A, no patient had a Hy's Law elevation of serum transaminases and total bilirubin.
- During Part B, 8% of bDMARD-naive and 9% of TNFα-IR patients developed TE-ADAs. No relationship of ADAs to safety was identified in the combined populations. There were no neutralizing TE-ADAs detected in either population.
- Mean vital signs did not show clinically significant changes from Baseline B at Week 16 through the end of treatment at Week 64 for patients overall in either population.

Conclusions:

Ixekizumab significantly improved RA signs and symptoms compared with placebo in both the bDMARD-naive and TNFα-IR populations.

A significant dose-response relationship in bDMARD-naive patients was observed with ACR20 responses at Week 12. For TNFα-IR patients, ACR20 responses at Week 12 were significantly better with ixekizumab than placebo. Significant decreases in CRP, DAS28-CRP, and CDAI from baseline were observed at Week 12 in the ixekizumab dose groups versus the placebo group in both populations. Onset of action was rapid, with significant improvements in ACR20, CRP, DAS28-CRP, and CDAI observed by Day 3 in both populations.

Clinical improvements observed with ixekizumab treatment in the double-blind period (Part A) were maintained or improved in those patients that participated in the open-label extension period (Part B) through Week 64.

For bDMARD-naive patients, HAQ-DI scores at Week 12 were significantly better with ixekizumab than placebo. Improvements in HAQ-DI and FACIT Fatigue Scale scores were observed in Part B in both populations.

Ixekizumab's V2 closely approximated total plasma volume, and CL was consistent with values reported for monoclonal antibodies in general. Age was identified as a significant covariate on V2, whereby V2 increased with increasing age. This effect of age on V2 may influence the shape of the concentration-time curve, but it's unlikely to have an impact on actual area under the concentration-time curve. Doses ≥80 mg and BMI were identified to have significant effects on ixekizumab CL. A marginal increase in CL of 14% was estimated for doses ≥80 mg. A patient with a BMI of 40 kg/m^2 (morbid obesity) was estimated to have 19.6% higher CL than a typical RA patient

with a median BMI of 27.3 kg/m^2. The estimated inter-individual variability for CL and overall residual error from the proportional error component alone was 38.5% and 28.1%, respectively. As the increase in CL is small at doses ≥80 mg and the BMI range for morbid obesity is within the estimated variabilities from the PK model, these variables are unlikely to result in clinically significant increases in CL causing substantial lowering of drug exposures. Both covariates identified for effects on CL do not necessitate dose adjustments for these groups at this point of development. PK of ixekizumab was not appreciably affected by age, gender, origin, RA treatment duration at study entry, BSA, weight, Cockcroft-Gault creatinine clearance, MDRD eGFR, TE-ADA, ADA titer, and RA patient cohort (bDMARD-naive or TNFα-IR).

While baseline TJC and patients of Native American origin were identified as covariates on the probability of ACR20, ACR50, and ACR70 response rates, the impact of these covariates needs to be confirmed with a larger dataset. These effects on response rates apply to both the placebo group and the ixekizumab dose groups for the bDMARD-naive and TNFα-IR populations, so they do not affect the difference in response between ixekizumab treatment and placebo. The time-courses of ixekizumab's ACR20, ACR50, and ACR70 response rates were not found to be appreciably influenced by CRP, ESR, RF, SJC, geographical location, RA treatment duration at entry, DAS28, TE-ADA, and ADA titer.

No conclusive dose-response relationship with ADA formation was observed.

Ixekizumab was well-tolerated, and the safety profile was similar to other biologics with no unexpected safety findings. No dose-related trends in AE incidence rate or event severity were observed across the 2 populations.

The significant beneficial effects on signs and symptoms of RA and patient-reported health outcomes as well as the acceptable safety profile of ixekizumab demonstrated in this study in both the bDMARD-naive and TNFα-IR populations support further clinical development of ixekizumab in Phase 3 studies.