SYNOPSIS OF RESEARCH REPORT [redacted]
(PROTOCOL WA18062)

COMPANY: Hoffmann-LaRoche, Inc. NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S): Tocilizumab	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A randomized, double-blind, placebo-controlled, parallel group study of the safety and reduction of signs and symptoms during treatment with MRA versus placebo, in combination with methotrexate (MTX) in patients with moderate to severe active rheumatoid arthritis (RA) and an inadequate response to previous anti-tumor necrosis factor (TNF) therapy. Research Report [redacted]/October 2007		
INVESTIGATORS / CENTERS AND COUNTRIES	128 centers in 13 countries (Australia, Belgium, Canada, France, Germany, Great Britain, Iceland, Italy, Mexico, The Netherlands, Sweden, Switzerland, and the United States)		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	May 27, 2005 to Apr 18, 2007	CLINICAL PHASE	III
OBJECTIVES	1. To assess the efficacy of treatment with tocilizumab (also referred to as myeloma receptor antibody [MRA]) vs placebo, both in combination with MTX, with regard to reduction in signs and symptoms over 6 months of treatment, in patients with moderate to severe active RA who have had an inadequate clinical response to one or more anti-TNF therapies. 2. To assess the safety of tocilizumab vs placebo, both in combination with MTX, with regard to adverse events and laboratory assessments. 3. To explore the pharmacokinetics (PK), immunogenicity, and pharmacodynamic (PD) parameters of tocilizumab in this patient population (reported separately).		
STUDY DESIGN	Three-arm randomized, double-blind, placebo-controlled, parallel group, international multicenter study		
NUMBER OF SUBJECTS	450 patients planned (150 per treatment group); 499 patients enrolled (161 to placebo + MTX, 164 to tocilizumab 4 mg/kg + MTX, and 174 to tocilizumab 8 mg/kg +MTX).		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Adult patients with RA for at least 6 months who had experienced an inadequate clinical response to treatment with one or more anti-TNF therapies (etanercept, infliximab, or adalimumab) within one year prior to randomization and who had received MTX for at least 12 weeks prior to baseline, the last 8 weeks of which being at a stable dose of 10 to 25 mg/week (oral [po] or parenteral).		
TRIAL DRUG / STROKE (BATCH) No.	[redacted] and [redacted]		
DOSE / ROUTE / REGIMEN / DURATION	Tocilizumab: intravenous infusions of 4 or 8 mg/kg given every 4 weeks over a 24-week period (ie, a total of 6 infusions; maximum dose of 1200 mg)		

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	Tocilizumab was given in combination with weekly MTX at a stable dose of 10 to 25 mg/week (po or parenteral)
REFERENCE DRUG / STROKE (BATCH) No.	[redacted]
DOSE / ROUTE / REGIMEN / DURATION	Matching placebo: intravenous infusion given every 4 weeks over a 24-week period (ie, a total of 6 infusions). Matching placebo was given in combination with weekly MTX at a stable dose of 10 to 25 mg/week (po or parenteral)
CRITERIA FOR EVALUATION	
EFFICACY:	**Primary**: - Proportion of patients with an ACR20 response at Week 24 **Secondary**: - Proportion of patients with ACR50 and ACR70 responses at 24 weeks; - Longitudinal generalized estimating equations (GEE) analysis of ACR20, ACR50 and ACR70 responses; - Time to onset of ACR20, ACR50 and ACR70 response; - Changes from baseline in the individual ACR core set parameters at 24 weeks; - Area under the curve (AUC) of the ACRn; - Change from baseline in the Disease Activity Score (DAS) 28 at 24 weeks; - AUC of the mean DAS28 - Proportion of patients with DAS28 < 2.6 at 24 weeks; - Categorical DAS28 responders (EULAR response) at Week 24; - Change from baseline in hemoglobin at 24 weeks; - Change in rheumatoid factor (RF) (IU/mL) at 24 weeks in those patients who were RF positive (+); - Proportion of patients who withdrew due to lack of sufficient therapeutic response; - Proportion of patients in each treatment group who received escape therapy; and - Health Assessment Questionnaire disability index (HAQ-DI), SF36, and Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue scale scores at 24 weeks. **Exploratory**: - Logistic regression analysis of ACR20, ACR50 and ACR70 responses at Week 24 by baseline characteristics; - ACR90; - Categorical changes from baseline in HAQ-DI; and - Proportion of patients with swollen joint counts (SJC) and tender joint counts (TJC) of zero

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PHARMACODYNAMICS/ PHARMACOKINETICS	Serum was obtained for population PK analysis and the analysis of exploratory PD parameters. Exploratory analyses will assess the possible relationship between population PK and PD parameters, including clinical response, interleukin-6 (IL-6), soluble IL-6 receptor (sIL-6R) and laboratory parameters. Results of these analyses will be presented together with data from other studies in a separate report. Serum was obtained for anti-tocilizumab antibody analysis. Exploratory analyses will assess the impact of developing anti-tocilizumab antibodies on safety and efficacy parameters. In addition, the impact of anti-tocilizumab antibodies on PK parameters will also be assessed. Results of these analyses will be presented together with data from other studies in a separate report.
QUALITY OF LIFE:	- SF-36 - FACIT-fatigue These assessments were also considered secondary efficacy parameters
SAFETY:	Adverse events, clinical laboratory results, physical examination, including vital signs and ECGs.

STATISTICAL METHODS

The primary analysis was performed on the intent-to-treat (ITT) population and compared the proportion of patients with an ACR20 response at Week 24 in each tocilizumab arm with the placebo arm using a Cochran-Mantel-Haenszel (CMH) chi-squared test with adjustment for the stratification factor applied at randomization ('site'). The longitudinal probability of an ACR20 response was also compared between treatment groups using a model based on GEE. As supportive analyses, ACR20 response rates were summarized descriptively. Time to first ACR20 response was summarized by treatment group as cumulative incidences over time using Kaplan-Meier estimates. ACR20 response rates were analyzed using logistic regression, including 'region' in the model.

Secondary endpoints of ACR50 and ACR70 responses were analyzed using the same statistical methodology as described for the primary endpoint. Secondary endpoints of AUC of ACRn, changes from baseline in the individual ACR core set parameters, AUC and change from baseline in DAS28, and changes from baseline in the SF-36 and FACIT-fatigue questionnaire scores, hemoglobin values and RF titers were summarized descriptively and compared between the treatment groups using an analysis of variance (ANOVA) model with 'site' included in the model. A comparison between treatment groups of the proportion of patients who achieved remission according to the DAS28 criterion at Week 24 (ie, DAS28 < 2.6) was performed using a CMH chi-squared test adjusting for 'site'. Additionally, the proportions of patients who withdrew from the study due to lack of therapeutic response and the proportions of patients who received escape therapy were compared between treatment groups using logistic regression, including 'region' in the model. In order to control the rate of false positive conclusions, a fixed sequence approach was applied, which enabled the null hypothesis of each secondary endpoint to be tested at the same significance level of α without any adjustment, as the null hypotheses were hierarchically ordered and were tested in a pre-defined sequential order. There was a break in the hierarchically ordered testing of the secondary endpoints. There was no plan to analyze efficacy according to individual anti-TNF therapies.

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For efficacy and quality of life parameters, the primary analysis population was the ITT population. Assessments were also performed on the per protocol (PP) population.

Safety data were listed and summarized by treatment group for the safety population using descriptive statistics.

METHODOLOGY:

Patients received an infusion of tocilizumab or placebo every 4 weeks for a total of 6 infusions, with interim visits scheduled 2 weeks after each of the first 2 infusions and 2 weeks after the fourth infusion. Patients were also receiving stable MTX therapy for at least 8 weeks prior to the first study treatment. Patients who failed to respond to treatment at Week 16 ie, achieved < 20% improvement in both SJC and TJC, and who had received at least 2 scheduled consecutive doses of double-blind study treatment at Weeks 8 and 12, could receive escape therapy consisting of tocilizumab 8 mg/kg + MTX at Weeks 16 and 20. Escape patients were considered nonresponders in the primary efficacy analysis at 24 weeks.

Patients returned for an efficacy and safety assessment 4 weeks after the last infusion of study treatment (Week 24). After completion of the Week 24 visit, patients could choose to enter an open-label long-term extension study (WA18696). Patients who did not enroll into the long-term extension study also returned for additional safety follow-up assessments 8 and 12 weeks after the last infusion of study treatment. Patients who withdrew prematurely from the study returned for follow-up safety assessments 4, 8, and 12 weeks after discontinuing study treatment.

Oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and NSAIDs were permitted during the study if the dose had been stable for at least 6 weeks prior to baseline. Dosage alterations of these medications during the study were strongly discouraged.

STUDY POPULATION:

At baseline, the 3 treatment groups were generally well balanced with respect to demographic and disease severity characteristics. Mean DAS at baseline was 6.8 in all 3 groups, indicating severe disease and most patients (>70%) were rheumatoid factor positive. The treatment groups were well balanced with respect to the proportions of patients with other co-morbidities (eg, hypertension, heart disease, diabetes) including other bone disease (osteoporosis or osteoarthritis). There were differences among the treatment groups regarding baseline ESR and CRP values, with patients in the placebo + MTX group having had higher mean and median CRP and ESR values at baseline than patients in the tocilizumab + MTX groups. Concomitant NSAID use (58% tocilizumab 8 mg/kg + MTX, 63% tocilizumab 4 mg/kg + MTX, and 62% placebo + MTX), corticosteroid use (58%, 59%, and 53%, respectively), and mean MTX dose (16 mg) were also well-balanced across the treatment groups. Patients in the tocilizumab 8 mg/kg + MTX group had a longer duration of RA than patients in the other 2 treatment groups (mean of 12.6 years vs 11 and 9.3 years in the tocilizumab 4 mg/kg + MTX and placebo + MTX groups, respectively). All but 1 patient in the tocilizumab 4 mg/kg + MTX group had discontinued treatment with at least one of the 3 licensed anti-TNF treatments (etanercept, infliximab, and/or adalimumab), and approximately half of the patients in each treatment group failed at least two of these treatments. Most patients failed a previous anti-TNF treatment due to lack of efficacy or both lack of efficacy and toxicity; very few patients in each treatment group (< 5%) failed prior anti-TNF treatment due to toxicity alone.

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Of the 499 patients enrolled, 30 patients (19%) in the placebo + MTX group, 24 patients (15%) in the tocilizumab 4 mg/kg group, and 23 patients (13%) in the tocilizumab 8 mg/kg + MTX group withdrew prematurely from the study treatment to which they were randomized. In addition, 117 patients discontinued initially assigned study treatment due to insufficient therapeutic response, defined as failure to achieve > 20% improvement in both the SJC and TJC at Week 16, and remained in the study by initiating escape therapy: 66 patients (41%) in the placebo + MTX group, 31 patients (19%) in the tocilizumab 4 mg/kg + MTX group, and 20 patients (11%) in the tocilizumab 8 mg/kg + MTX group. Escape therapy consisted of open-label tocilizumab 8 mg/kg + MTX and, if necessary, intra-articular corticosteroids or an increase in oral corticosteroid dosage (maximum dose of 10 mg total dose/day). Four patients withdrew after initiating escape therapy: 2 for adverse events and 2 for insufficient therapeutic response.

The ITT Population comprised 489 patients, the Safety Population comprised 498 patients, and the PP Population comprised 347 patients (71% of the ITT population). The number of patients included in the PP population was balanced across the treatment groups.

EFFICACY RESULTS:

The proportion of patients achieving ACR20, 50, or 70 responses at Week 24 was consistently higher in tocilizumab 8 mg/kg + MTX group than the tocilizumab 4 mg/kg + MTX group or the placebo + MTX group (ACR20: 50% vs 30% and 10%, ACR50: 29% vs 17% and 4%, ACR70: 12% vs 5% and 1%, respectively). In addition, irrespective of the most recently failed anti-TNF medication and the number of previously failed anti-TNF medications, tocilizumab 8 mg/kg + MTX was shown to be beneficial in this difficult-to-treat population in all three of these parameters. Similar results were obtained in the Per Protocol population analysis and in several sensitivity analyses investigating different methods of imputation for missing data. Logistic regression analysis indicated that the odds of achieving an ACR20 response at Week 24 were 9 times higher for patients receiving tocilizumab 8 mg/kg + MTX and 4 times higher for patients receiving tocilizumab 4 mg/kg + MTX than for patients receiving placebo + MTX.

Importantly, a statistically significant and clinically meaningful benefit over placebo + MTX was observed in the tocilizumab 8 mg/kg + MTX group in the higher clinical disease hurdles such as ACR50 and ACR70 response, EULAR 'good' response, and DAS28 remissions rates. These higher clinical hurdles for efficacy represent substantial clinical improvements for the patient. In addition to the demonstrated benefits at Week 24, the onset of response occurred early in the tocilizumab 8 mg/kg + MTX group, with differences from the placebo + MTX group becoming apparent as early as the first scheduled assessment (Week 2). Finally, the benefits of tocilizumab treatment were reflected in the large numbers of placebo + MTX patients who either withdrew from the study due to insufficient therapeutic response (11%) or entered the escape phase at Week 16 (41%) compared with early withdrawal and escape rates of 2% and 11% for patients receiving tocilizumab 8 mg/kg + MTX.

A summary of the key efficacy parameter results at Week 24 for the tocilizumab + MTX groups and the placebo + MTX group is provided below.

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ITT Population Results at Week 24	**Placebo + MTX N = 158**	**Tocilizumab 4 mg/kg + MTX N = 161**		**Tocilizumab 8 mg/kg + MTX N = 170**	
Primary endpoint			p-value*		p-value*
ACR20 (%)	10.1	30.4	< 0.0001	50.0	< 0.0001
Key secondary endpoints					
ACR50 (%)	3.8	16.8	-	28.8	< 0.0001
ACR70 (%)	1.3	5.0	-	12.4	0.0002
ACRn (adjusted mean)	-19.51	13.16	-	25.75	< 0.0001
DAS28 remission < 2.6 (%)	1.6	7.6	-	30.1	0.0001
Change in DAS28 (adjusted mean)	-0.95	-2.04	-	-3.16	< 0.0001
EULAR response (%)					
Good	1.9	9.9	-	37.1	< 0.0001
Moderate	14.6	36.6	-	30.6	-
None	83.5	53.4	-	32.4	-
Change in ACR core set (adjusted mean)					
SJC	-0.5	-6.8	-	-7.8	< 0.0001
TJC	0.3	-10.5	-	-14.8	< 0.0001
Patient's global assessment	-15.4	-25.4	-	-32.8	0.0011
Physician's global assessment	-20.0	-30.5	-	-38.2	< 0.0001
Patient's pain assessment	-8.6	-21.0	-	-32.5	< 0.0001
HAQ-DI	-0.05	-0.31	-	-0.39	< 0.0001
CRP (mg/dL)	-0.0600	-1.4034	-	-2.5807	< 0.0001
ESR (mm/hr)	-3.0	-19.7	-	-37.2	< 0.0001
Hemoglobin (g/L) (adjusted mean)	-2.888	4.480	-	11.904	< 0.0001

*P-values for categorical endpoints from CMH analysis, stratified by 'site'. P-values for continuous endpoints from an analysis of variance, controlling for 'site'. P-values are vs placebo + MTX.

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QUALITY OF LIFE RESULTS:

Mean HAQ-DI scores, which were slightly higher in the tocilizumab 8 mg/kg + MTX group at baseline, decreased (ie, improved) gradually in both tocilizumab + MTX groups until Week 20, after which time they remained constant.

FACIT-fatigue scores improved over time in all treatment groups, although greater mean increases (improvements) were consistently observed for patients in the tocilizumab + MTX groups than for patients in the placebo + MTX group. At Week 24, the adjusted mean change from baseline in FACIT-fatigue scores were 8.83 ($p = 0.0150$), 6.66, and 4.33 in the tocilizumab 8 mg/kg + MTX, tocilizumab 4 mg/kg + MTX, and placebo + MTX groups, respectively.

All treatment groups demonstrated some improvements in physical and mental component scores over time, but the greatest improvements were observed in the tocilizumab + MTX groups, with a separation between the placebo + MTX and the tocilizumab + MTX groups being observed for the physical component summary score (PCS) as early as the first scheduled assessment at Week 8. At Week 24, the difference in the adjusted means for the PCS between the tocilizumab 8 mg/kg + MTX group and the placebo + MTX group at Week 24 was statistically significant ($p = 0.0020$). At Week 24, there was no difference in the adjusted means for the mental component summary score among the treatment groups.

SAFETY RESULTS:

Tocilizumab treatment was generally well tolerated in this trial. The proportion of patients reporting adverse events, serious adverse events, and adverse events leading to withdrawal is described in the table below. No deaths occurred during the 24-week study period.

An overview of adverse events excluding events in patients who received escape therapy is provided below:

Number (%) of patients with:	**Placebo + MTX N = 160**		**Tocilizumab 4 mg/kg + MTX N = 163**		**Tocilizumab 8 mg/kg + MTX N = 175**	
Any adverse event	129	(80.6)	142	(87.1)	147	(84.0)
Severe adverse event	31	(19.4)	22	(13.5)	24	(13.7)
Related adverse event[a]	86	(53.8)	107	(65.6)	111	(63.4)
Serious adverse event	18	(11.3)	12	(7.4)	11	(6.3)
Related serious AE[a]	3	(1.9)	3	(1.8)	5	(2.9)
Adverse event leading to discontinuation	8	(5.0)	10	(6.1)	10	(5.7)
Adverse event leading to dose modification	13	(8.1)	24	(14.7)	12	(6.9)
Death	0	-	0	-	0	-

Source: stae11_2, stae17, stae11_r, staell_s2, stae11_wd, stae11_dmod, stdd11

[a]Events judged by the investigator to be remotely, possibly, or probably related to study treatment

Note: Escape data are excluded.

Some adverse events were reported by a higher proportion of patients treated with tocilizumab + MTX than patients treated with placebo + MTX. These included: diarrhea, upper abdominal pain, dyspepsia, abdominal distention, gastritis, abdominal discomfort, and mouth ulcerations; rash, pruritis, dermatitis, skin

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ulcer, drug eruption, and swelling face; hypercholesteremia, hyperlipidemia, hypertriglyceridemia, and dyslipidemia, headache and dizziness; hypertension; elevated hepatic transaminases; insomnia, anxiety; conjunctivitis. Neutropenia (5 events each of grade 4 and grade 3 neutropenia) occurred only in patients who were receiving tocilizumab + MTX. For the most part these events were non-serious in nature.

The incidence of serious infections was low across the three treatment groups (16 patients [3%]), but was higher in patients treated with tocilizumab 8 mg/kg + MTX than in patients who received tocilizumab 4 mg/kg + MTX or placebo + MTX: tocilizumab 8 mg/kg + MTX group (8 patients [5%]) compared with 3 patients (2%) and 5 patients (3%) in the tocilizumab 4 mg/kg + MTX and placebo + MTX groups, respectively. However, the rate of serious infections expressed per 100 patient years was 9.98, 5.71, and 9.64, respectively in the tocilizumab 8 mg/kg + MTX, 4 mg/kg + MTX, and placebo + MTX groups. All but 1 serious infection, cellulitis, reported in the placebo + MTX group resolved without sequelae. Five serious infections in four patients led to discontinuation of study treatment: septic staphylococcal arthritis in the tocilizumab 8 mg/kg + MTX group; necrotizing pneumonia in the tocilizumab 4 mg/kg + MTX group; urosepsis and osteomyelitis/cellulitis in the placebo + MTX group. No serious infections occurred during escape therapy and no opportunistic infections were reported during the study.

The overall incidence of infusion reactions that occurred during or within 24 hours of an infusion was low. Two infusion reactions led to discontinuation of study treatment: non-serious infusion site reactions in 1 patient each in the tocilizumab 8 mg/kg + MTX and placebo + MTX groups. Both events resolved without sequelae. Although a small proportion of patients in both tocilizumab + MTX groups (more in 4 mg/kg group) experienced non-serious transient rashes, there were no events suggesting anaphylaxis or acute hypersensitivity.

Treatment with tocilizumab was associated with decreases in circulating mean neutrophil counts. The majority of these abnormalities were CTC grade 1 or 2. During treatment, 5 patients experienced a transient CTC grade 4 neutrophil count (4 patients in the tocilizumab 8 mg/kg + MTX group and 1 patient in the 4 mg/kg + MTX group), with no evidence of fever or infection. Per protocol, all of these patients were discontinued from treatment. Neutropenia was transient and neutrophil counts returned to the normal range within 3 to 4 weeks. One patient received 2 doses of filgrastim, despite absence of clinical effects, and her neutrophil counts returned to normal within 1 week. Five additional patients experienced grade 3 neutropenia during treatment (4 patients in the tocilizumab 8 mg/kg + MTX group and 1 patient in the 4 mg/kg + MTX group). Two of these 5 patients discontinued study treatment for reasons unrelated to neutropenia; the other 3 patients did not have recurrence and enrolled in the long-term extension study. There was no identifiable association between low neutrophil counts and the occurrence of infections and no patients experienced a serious infection with a simultaneous low neutrophil count. Decreases in mean platelet counts were also observed in both tocilizumab groups; however, there were no CTC grade 3 or 4 platelet events.

Increases in mean hepatic transaminases and total bilirubin within the normal range were seen in patients in both tocilizumab treatment groups. Small numbers of patients, more in the tocilizumab groups, had a transient increase in ALT and/or AST from normal at baseline to > 3x ULN. Increases in ALT from normal at baseline to > 3x ULN to 5x ULN occurred in 4 patients (2%) in the tocilizumab 8 mg/kg + MTX group, 4 patients (2.5%) in the tocilizumab 4 mg/kg + MTX group, and 1 patient (< 1%) in the placebo + MTX

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group. Shifts in ALT from normal at baseline to > 5x ULN to 8x ULN occurred in 1 patient (< 1%) in each of the tocilizumab + MTX groups and in no patients in the placebo + MTX group. Increased AST from normal at baseline to > 3x ULN occurred in 1 patient (< 1%) in the tocilizumab 4 mg/kg + MTX group. A total of 6 patients, all in the tocilizumab + MTX groups, experienced an increase in ALT and/or AST of ≤ 3x ULN and a simultaneous increase in total bilirubin (< 2x ULN) during the study. None of these 6 patients met the parameters for Hy's rule (simultaneous total bilirubin ≥ 2x ULN and ALT ≥ 3x ULN). In the majority of patients, liver enzyme elevations decreased or normalized after interruption of study treatment, with or without MTX dose alteration. In some patients, values normalized while continuing tocilizumab therapy. Per protocol, three patients discontinued study treatment for hepatic transaminase elevations. Hepatic steatosis diagnosed by ultrasound and/or MRI were reported as adverse events in 2 patients during the study: one patient in the tocilizumab 8 mg/kg + MTX group and one patient in the placebo + MTX group who received escape therapy (tocilizumab 8 mg/kg+ MTX). Neither event lead to discontinuation of study drug. No patients had signs or symptoms of hepatitis or hepatic dysfunction.

An initial increase in fasting mean plasma lipid levels (total cholesterol, HDL, LDL, triglycerides) with stabilization within the normal range was seen in both tocilizumab groups, as was an increase in apoA and apoB and a decrease in lipoprotein(a). Mean triglyceride values in all treatment groups were borderline to high at baseline. In the tocilizumab 8 mg/kg + MTX group, mean triglyceride values rose above the ULN at weeks 6 and 14 and remained above the ULN through week 24. These changes occurred in association with a decrease in Lp(a) lipoprotein and moderate to large decreases in CRP. Although the implications of changes in atherogenic indices are not recognized for RA patients, more patients in the tocilizumab groups had increases in the indices applied to non-RA individuals such as total cholesterol/HDL, LDL/HDL, and non-HDL/HDL with the exception of the more recently characterized ApoB/ApoA index, which exhibited similar proportions of increases (23% - 25%) and decreases (18% - 23%) across the three treatment groups. Additionally, the extent of increases in the ApoB/ApoA index were lower than the other atherogenic indices.

CONCLUSIONS:

- Irrespective of the most recently failed anti-TNF medication and the number of previously failed anti-TNF medications, tocilizumab 8 mg/kg every 4 weeks provides clinically important benefit in patients with moderate to severe, treatment-refractory RA.
- Statistically significant improvements in ACR20 response rates at Week 24 were observed for both tocilizumab + MTX groups in comparison with the placebo + MTX group.
- For additional clinically important efficacy parameters (ACR50 and ACR70 response, ACRn, ACR components, DAS28 remission, change in DAS28, EULAR), and for hemoglobin, improvements for the tocilizumab 8 mg/kg + MTX group in comparison with placebo + MTX were statistically significant.
- Improvements in clinical disease parameters were associated with rapid, clinically relevant and statistically significant improvements in patient-reported outcomes related to physical health (SF-36) and fatigue (FACIT-fatigue), which were sustained throughout the treatment period.
- Onset of benefit was noted as early as Week 2 after treatment initiation with tocilizumab 8 mg/kg + MTX while incremental responses were observed as treatment duration increased.
- Tocilizumab was generally well tolerated in this patient population and the safety profile was consistent with the immunomodulatory properties of the drug. In this study, there was a

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comparable safety profile across the 8 mg/kg + MTX and 4 mg/kg + MTX groups. There were no toxicities indicating a need to restrict the use of tocilizumab in patients receiving commonly prescribed non-biologic MTX background therapy. Importantly, the low and similar incidence of serious infections in the tocilizumab 8 mg/kg + MTX and placebo + MTX groups suggest that tocilizumab does not increase infection risk in this treatment-refractory population.