SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL WA17822)

COMPANY: NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A randomized, double-blind, parallel group study of the safety and reduction of signs and symptoms during treatment with tocilizumab vs placebo, in combination with methotrexate (MTX), in patients with moderate to severe active rheumatoid arthritis (RA). Research Report [redacted] / May 2007		
INVESTIGATORS / CENTERS AND COUNTRIES	73 centers in 17 countries worldwide: Argentina (3 centers), Australia (3 centers), Austria (4 centers), Brazil (2 centers), Bulgaria (3 centers), Canada (11 centers), France (7 centers), Germany (8 centers), Hong Kong (3 centers), Hungary (3 centers), Israel (6 centers), Italy (5 centers), Mexico (6 centers), Singapore (2 centers), Slovakia (1 center), Switzerland (2 centers), Thailand (4 centers).		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	Feb 16, 2005 to Nov 13, 2006	CLINICAL PHASE	III
OBJECTIVES	1. To assess the efficacy of tocilizumab (also referred to as myeloma receptor antibody [MRA]) vs placebo, 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 had previously had an inadequate clinical response to MTX. 2. To assess the safety of tocilizumab vs placebo, in combination with MTX, with regard to adverse events and laboratory assessments. 3. To explore the pharmacokinetics, immunogenicity and pharmacodynamic parameters of tocilizumab in this patient population (reported separately).		
STUDY DESIGN	Randomized, double-blind, controlled, parallel group study with three treatment arms: placebo + MTX, tocilizumab 4 mg/kg + MTX, and tocilizumab 8 mg/kg + MTX. Patients who failed to respond to treatment during the study ie, achieved < 20% improvement in both the swollen joint count (SJC) and tender joint count (TJC) at week 16, and who had received at least two scheduled consecutive doses of double-blind study treatment, could receive open-label escape therapy consisting of tocilizumab 8 mg/kg + MTX at weeks 16 and 20. Patients who completed the study could enter an open-label long-term extension study (WA18695) and receive tocilizumab 8 mg/kg every 4 weeks for up to 5 years.		
NUMBER OF SUBJECTS	630 patients planned (210 per treatment group); 623 patients enrolled (204 to placebo + MTX, 213 to tocilizumab 4 mg/kg + MTX and 206 to tocilizumab 8 mg/kg + MTX).		
DIAGNOSIS AND MAIN CRITERIA FOR	Adult patients with RA for at least 6 months who had previously		

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INCLUSION	experienced an inadequate clinical response to treatment with MTX and who had received MTX for at least 12 weeks immediately 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.	Tocilizumab / batch no.s [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) 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.:	Matching placebo / batch no.s [redacted]
DOSE / ROUTE / REGIMEN / DURATION:	Matching placebo: intravenous infusions 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 – Mean 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. – Mean 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 – Health Assessment Questionnaire disability index (HAQ-DI), SF-36, and Functional Assessment of Chronic Illness Therapy

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(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
- Proportion of patients with SJC and TJC of zero

PHARMACOKINETICS/ PHARMACODYNAMICS:

Serum was obtained for population PK analysis and for 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. The 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. The 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.

PHARMACOECONOMICS:

- EQ-5D
- Medical resource utilization (MRU)
- Work productivity and activity impairment (WPAI)

These data were collected for use in separate pharmacoeconomic analyses.

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 the treatment groups using a model based on GEE. As supportive analyses, ACR20 response rates were

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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 'site' 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 achieve 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 a lack of therapeutic response and the proportions of patients who received escape therapy were compared between treatment groups using logistic regression, including 'site' 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 no break in the hierarchically ordered testing of the secondary endpoints, therefore, all p-values reported in the following sections can be considered to be statistically valid.

For efficacy and quality of life parameters, the primary analysis population was the intent-to-treat (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 six infusions, with interim visits scheduled 2 weeks after the first two infusions and 2 weeks after the fourth infusion.

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 two scheduled consecutive doses of double-blind study treatment, could receive escape therapy consisting of tocilizumab 8 mg/kg + MTX at weeks 16 and 20. Escape patients were considered as non-responders 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 enter an open-label long-term extension study (WA18695). 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 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 three treatment groups were well balanced with respect to their general demographic characteristics, baseline ACR core set component scores and their RA disease characteristics, including concomitant NSAID use (approximately 68%), corticosteroid use (approximately 55%) and mean MTX dose (15 mg). Mean DAS28 in each group was 6.8, indicating severe disease. Mean disease duration was

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approximately 7.5 years, but the median duration was approximately 5 years, indicating that patients with relatively early disease were also included.

Of the 623 patients enrolled, 50 patients (12 [6%] in the placebo + MTX group, 25 [12%] in the tocilizumab 4 mg/kg + MTX group and 13 [6%] in the tocilizumab 8 mg/kg + MTX group) withdrew prematurely from initial study treatment due to reasons of safety or non-safety (including insufficient therapeutic response, protocol violation, refused treatment, failure to return, non-compliance to medication, and received wrong study medication). In addition, 118 patients were switched from their initially assigned study treatment to escape therapy due to insufficient therapeutic response ie, failure to achieve > 20% improvement in both the SJC and TJC at week 16: 68 patients (33%) in the placebo + MTX group, 31 patients (15%) in the tocilizumab 4 mg/kg + MTX group and 19 patients (9%) in the tocilizumab 8 mg/kg + MTX group. Patients who entered the escape phase were not classified as withdrawing from initial study treatment. Seven patients withdrew prematurely from escape therapy (4 due to adverse events and 2 due to insufficient therapeutic response).

The ITT and safety populations comprised 622 patients and the PP population (predominantly the patients who received at least 4 doses and who received no excluded concomitant medications) comprised 501 patients (81% of the ITT population). The number of patients included in the PP population was balanced across the treatment groups.

EFFICACY RESULTS:

The proportion of ACR20 responders at week 24 was 27% in the placebo + MTX group, 48% in the tocilizumab 4 mg/kg + MTX group and 59% in the tocilizumab 8 mg/kg + MTX group. For both tocilizumab + MTX groups, there was a highly statistically significant difference from the placebo + MTX group in the proportion of ACR20 responders at week 24 ($p < 0.0001$ for both groups). Similar results were obtained for the ITT robustness and PP population analyses of the primary efficacy parameter. Logistic regression analysis showed that the odds of achieving an ACR20 response at week 24 were 3 times higher for patients receiving tocilizumab 4 mg/kg + MTX and 6 times higher for patients receiving tocilizumab 8 mg/kg + MTX than for patients receiving placebo + MTX. ACR20 response rates were higher in the tocilizumab + MTX groups compared with the placebo + MTX group at all time points from the first scheduled assessment at week 2, with the highest rates being consistently observed in the tocilizumab 8 mg/kg + MTX group.

Secondary endpoint analyses supported the primary efficacy findings. At week 24, statistically significant differences from the placebo + MTX group were achieved for both tocilizumab + MTX groups for all secondary endpoints related to disease activity. In addition to the differences observed at week 24, the onset of response occurred early in the tocilizumab + MTX groups and differences between the tocilizumab + MTX groups and the placebo + MTX group were apparent by week 2 (ie, the first scheduled assessment) or week 4 for a number of clinical parameters including ACR50, change from baseline in ACR core set components, DAS28 and EULAR response.

A highly statistically significant increase in hemoglobin was also observed in the tocilizumab + MTX groups compared with the placebo + MTX group. The increase in mean hemoglobin values in the tocilizumab + MTX groups was first observed at the first scheduled assessment for hemoglobin at week 2.

For the primary and secondary efficacy endpoints, at week 24 and throughout the 24-week treatment period, the greatest responses were consistently observed in the tocilizumab 8 mg/kg + MTX group.

A summary of some of the key efficacy parameter results at week 24 for the tocilizumab + MTX groups vs the placebo + MTX group is provided below:

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ITT population results at week 24	**Placebo + MTX N = 204**	**MRA 4 mg/kg + MTX N = 213**		**MRA 8 mg/kg + MTX N = 205**	
Primary endpoint			p-value*		p-value*
ACR20 (%)	26.5	47.9	< 0.0001	58.5	< 0.0001
Key secondary endpoints					
ACR50 (%)	10.8	31.5	< 0.0001	43.9	< 0.0001
ACR70 (%)	2.0	12.2	< 0.0001	22.0	< 0.0001
ACRn (adjusted mean)	13.55	31.64	0.0034	39.94	< 0.0001
DAS28 remission < 2.6 (%)	0.8	13.5	0.0002	27.5	< 0.0001
Change in DAS28 (adjusted mean)	-1.55	-2.68	< 0.0001	-3.43	< 0.0001
EULAR response (%)					
Good	2.9	21.1	< 0.0001	38.0	< 0.0001
Moderate	31.9	40.8	-	41.5	-
None	65.2	38.0	-	20.5	-
Change in ACR core set (adjusted mean)					
SJC	-4.3	-8.5	< 0.0001	-10.5	< 0.0001
TJC	-7.4	-14.5	< 0.0001	-17.1	< 0.0001
Patient's global assessment	-17.8	-28.8	0.0005	-32.7	< 0.0001
Physician's global assessment	-32.7	-38.3	0.0229	-41.6	0.0002
Patient's pain assessment	-14.0	-25.0	0.0004	-29.8	< 0.0001
HAQ-DI	-0.34	-0.52	0.0296	-0.55	0.0082
CRP	-0.353	-1.656	0.0004	-2.509	< 0.0001
ESR	-7.1	-25.5	< 0.0001	-39.5	< 0.0001
Hemoglobin (g/L) (adjusted mean)	-0.286	9.244	< 0.0001	12.439	< 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.

QUALITY OF LIFE RESULTS:

In addition to the HAQ-DI, patients in both tocilizumab + MTX groups experienced a statistically significant improvement at week 24 in self-assessments of fatigue (based on the FACIT-fatigue assessment results) and mental and physical health (based on the SF-36 health survey) compared with patients in the placebo + MTX group. A separation between the placebo + MTX and the tocilizumab + MTX groups in mean mental and physical health scores was apparent as early as the first scheduled assessment for SF-36 at week 8. Based on mean changes from baseline, clinically relevant improvements in physical health score (change of > +5.42) were observed by the first scheduled SF-36 assessment (week 8) in both tocilizumab + MTX groups and was maintained until week 24, while a clinically relevant improvement in mental health score (change of > +6.33) was only recorded in the tocilizumab 8 mg/kg + MTX group at week 24. In the

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placebo + MTX group, clinically relevant mean changes in physical or mental health scores were not achieved at any time point. Clinically meaningful improvements in fatigue (based on mean changes from baseline in the FACIT-fatigue score of ≥ 5 points) were also achieved by the first scheduled FACIT-fatigue assessment (week 4) in the tocilizumab 8 mg/kg + MTX group and by week 8 in the tocilizumab 4 mg/kg + MTX group. In comparison, in the placebo + MTX group, a mean change in FACIT-fatigue score of ≥ 5 points was only achieved at week 20.

A summary of SF-36 and FACIT-fatigue results at week 24 is provided below:

ITT population results at week 24	**Placebo + MTX N = 204**	**MRA 4 mg/kg + MTX N = 213**		**MRA 8 mg/kg + MTX N = 205**	
Change in SF-36 domains (adjusted mean)			p-value*		p-value*
Mental health	2.7	5.7	0.0394	7.3	0.0012
Physical health	5.0	9.7	< 0.0001	9.5	< 0.0001
Change in FACIT-fatigue (adjusted mean)	4.01	7.29	0.0063	8.60	< 0.0001

*P-values from an analysis of variance, controlling for 'site'. P-values are vs placebo + MTX.

SAFETY RESULTS:

The incidence of adverse events that occurred on the patient's initially assigned treatment was similar in the tocilizumab 4 mg/kg + MTX and 8 mg/kg + MTX groups but was slightly higher than in the placebo + MTX group, as was the incidence of adverse events considered to be related to study treatment as determined by the investigator. In all three groups, the majority of adverse events were of mild or moderate intensity. The incidence of serious adverse events was similar across the groups, while adverse events leading to discontinuation or dose modification were more frequent in the tocilizumab + MTX groups than in the placebo + MTX group. One patient in the placebo + MTX group died during the 24-week study period as a result of a coronary artery thrombosis.

Serious adverse events were experienced by a further eight patients on escape therapy, three of which led to discontinuation of study treatment. One additional patient was withdrawn from escape therapy due to a non-serious adverse event.

A summary of adverse experience on initial study treatment is provided below:

Number (%) of patients with:	**Placebo + MTX N = 204**		**MRA 4 mg/kg + MTX N = 212**		**MRA 8 mg/kg + MTX N = 206**	
Any adverse event	129	(63.2)	151	(71.2)	143	(69.4)
Severe adverse event	9	(4.4)	13	(6.1)	16	(7.8)
Related adverse event	61	(29.9)	90	(42.5)	96	(46.6)
Serious adverse event	12	(5.9)	13	(6.1)	13	(6.3)
Adverse event leading to discontinuation	5	(2.5)	14	(6.6)	13	(6.3)
Adverse event leading to dose modification	16	(7.8)	23	(10.8)	23	(11.2)
Death	1	(< 1)	0		0	

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The overall incidence of infusion reactions that occurred during or within 24 hours of an infusion was low (5% to 7% across the groups). Most infusion reactions were single, self-limiting, non-specific events and very few (< 6 patients per group) required treatment. Three specific infusion reactions led to discontinuation of tocilizumab (allergic dermatitis and anaphylactic reaction in the 4 mg/kg + MTX group and infusion-related reaction on escape therapy), the latter two being serious adverse events. All were treated successfully and had resolved by the patient's last assessment.

For the following adverse events, higher incidences were reported in patients treated with tocilizumab 4 mg/kg + MTX and 8 mg/kg + MTX than in patients who received placebo + MTX: gastrointestinal disorders of dyspepsia and abdominal pain (8% and 10%, respectively, vs 5%), skin and subcutaneous tissue disorders (mainly rash, dermatitis and pruritus) (13% and 18%, respectively, vs 7%), and adverse events within the investigation system organ class (mainly elevations in liver function tests) (12% and 15%, respectively, vs 5%). Musculoskeletal and connective tissue disorders were more frequent in the placebo + MTX group (16% vs 14% [4 mg] and 12% [8 mg]), driven largely by a higher incidence of worsening of RA in this group.

The incidence of infections was similar across the treatment groups (28% in the placebo + MTX group, 31% in the tocilizumab 4 mg/kg + MTX group and 32% in the tocilizumab 8 mg/kg + MTX group) as was the number of infections per 100 patient years (96 for placebo + MTX, 99 for tocilizumab 4 mg/kg + MTX and 102 for tocilizumab 8 mg/kg + MTX). Almost all infections were of mild or moderate intensity. Skin and subcutaneous tissue infections were slightly more frequent in the tocilizumab + MTX groups (4% to 6%) than in the placebo + MTX group (2%). The incidence of serious infections was low (ovarian abscess and urinary tract infection in the placebo + MTX group; pneumonia, *Pneumocystis jiroveci* pneumonia and gastroenteritis in the tocilizumab 4 mg/kg + MTX group; and cellulitis [2 events], pneumonia, empyema, peridiverticular abscess and upper respiratory tract infection in the 8 mg/kg + MTX group). Of these, four infections led to discontinuation of study treatment (urinary tract infection, *Pneumocystis jiroveci* pneumonia, empyema and peridiverticular abscess). Serious infections were also experienced by three patients on escape therapy (gastrointestinal infection, urinary tract infection and pneumococcal infection), the latter of which led to discontinuation of study treatment. All but two serious infections (*Pneumocystis jiroveci* pneumonia in the tocilizumab 4 mg/kg + MTX group and gastrointestinal infection on escape therapy) had resolved by the patients' last observation.

Decreases in mean neutrophil counts (within the normal range) were observed after treatment with tocilizumab; however, this did not result in discontinuation of tocilizumab and there was no clear association between low neutrophil counts and the occurrence of infections.

Decreases in mean platelet counts (within the normal range) were observed after treatment with tocilizumab. Only one event of thrombocytopenia was reported, which was not associated with clinical symptoms and resolved with continued tocilizumab dosing.

There was an increase in mean liver enzymes, within the normal range, in the tocilizumab treatment groups. However, only a small number of patients had a shift in ALT or AST from normal at baseline to > 3x the upper limit of normal (ULN) (6, 9 and 16 patients in the placebo + MTX and tocilizumab 4 mg/kg + MTX and 8 mg/kg + MTX groups, respectively) and only a few of these patients had a shift to > 5x ULN (2, 2 and 6 patients, respectively). None of the cases was associated with a concomitant increase in bilirubin nor did any of the patients experience signs or symptoms of hepatic disease. After discontinuation of study treatment, in all cases but two (one in the placebo + MTX group and one in the tocilizumab 8 mg/kg + MTX group) liver enzyme values were reduced or had normalized by the patient's last observation.

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In addition to a reduction in the acute phase reactants CRP and ESR, a reduction in mean levels of serum amyloid a (SAA), serum ferritin and haptoglobin was observed in the tocilizumab + MTX groups, as was a reduction in C3 and C4 titers within the normal range.

An increase in mean plasma lipid levels (total cholesterol, HDL, LDL, triglycerides) was observed, generally within the normal range, upon treatment with tocilizumab, as was an increase in apoA and apoB and a decrease in lipoprotein(a). The majority of patients (> 60%) in all three treatment groups experienced either no change or a decrease in atherogenic indices. A higher proportion of patients in the tocilizumab + MTX groups experienced an increase in the following atherogenic indices: LDL/HDL (12%, 18% and 22% of patients in the placebo + MTX and tocilizumab 4 mg/kg + MTX and 8 mg/kg + MTX groups, respectively), total cholesterol/HDL (5%, 8% and 17%, respectively) and non-HDL/HDL (11%, 16%, 24%, respectively); however, there was no meaningful change in the atherogenic index as determined by apoB/apoA1. In the tocilizumab + MTX groups, increases in total cholesterol, LDL and HDL and in the ratios of LDL/HDL, total cholesterol/HDL and non-HDL/HDL appeared to be coincident with a moderate to large decrease in CRP (of approximately -3 to -12 mg/dL). Only a few patients commenced therapy with a lipid lowering agent during the study (1 in the placebo + MTX group and 3 in each of the tocilizumab + MTX groups). Despite increases in mean lipid levels, there was no increase in cardiovascular adverse events nor any increases in clinically significant mean blood pressure recordings.

CONCLUSIONS:

- Treatment with tocilizumab 4 mg/kg and 8 mg/kg in combination with MTX significantly decreased disease activity over 24 weeks in this population of RA patients who had previously experienced an inadequate response to MTX
- Statistically significant improvements from placebo + MTX for both tocilizumab + MTX arms were observed for all clinical disease parameters (ACR20, ACR50 and ACR70 response, ACRn, ACR components, DAS28 remission, change in DAS28, EULAR) and for increase in hemoglobin
- The greatest improvements in disease activity parameters, reduction in markers of inflammation, and increases in hemoglobin were consistently achieved with tocilizumab 8 mg/kg + MTX
- Statistically significant improvements were also observed on tocilizumab 4 mg/kg and 8 mg/kg + MTX compared with placebo + MTX for patient reported outcomes related to physical and mental health (SF-36) and fatigue (FACIT-fatigue)
- Tocilizumab was well tolerated in this patient population with a comparable safety profile across the 4 mg/kg + MTX and 8 mg/kg + MTX groups. Of particular note were the following:
    - Serious infections were reported infrequently, although slightly more often in the tocilizumab 8 mg/kg + MTX group (6 events vs 2 and 3 events in the placebo and 4 mg/kg + MTX groups). There was one opportunistic infection of *Pneumocystis jiroveci* pneumonia in a patient with COPD. All but one of the serious infections resolved without sequelae, and the majority of patients continued in the study without a recurrence
    - Infusion reactions were also infrequent and most represented non-specific untoward reactions which did not require treatment
    - Non serious rash events (including dermatitis and pruritus) occurred at a higher incidence in the tocilizumab + MTX groups without change or discontinuation of study treatment
    - As expected from the mechanism of action, tocilizumab treatment was associated with decreases in mean absolute neutrophil and platelet counts within the normal range. The majority of individual neutrophil abnormalities were transient and were not of clinical significance
    - Elevations in lipid parameters (LDL and HDL, and triglycerides) were observed in a minority of

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patients. These elevations stabilized on continuation of tocilizumab treatment, were not associated with the occurrence of cardiovascular events, and the majority were not associated with changes in atherogenic indices

- Elevations in liver enzymes were transient and episodic and were managed by simple or no intervention. Few patients required discontinuation per protocol and there was no evidence of clinical hepatitis.