SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL WA17824)

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, double-dummy, parallel group study of the safety and efficacy of tocilizumab monotherapy, versus methotrexate (MTX) monotherapy, in patients with active rheumatoid arthritis.		
INVESTIGATORS / CENTERS AND COUNTRIES	120 centers in 18 countries worldwide: Argentina (4 centers), Australia (4 centers), China (3 centers), Denmark (1 centers), France (5 centers), Italy (5 centers), Lithuania (5 centers), Mexico (5 centers), Norway (2 centers), Peru (3 centers), Portugal (1 center), Serbia/Montenegro (2 centers), Slovenia (2 centers), South Africa (6 centers) and Spain (5 centers). Patients who were enrolled into the placebo controlled substudy came from centers in Canada (9 centers), Israel (4 centers), and the USA (54 centers), only.		
PUBLICATION (REFERENCE)	None.		
PERIOD OF TRIAL	July 6, 2005 to April 23, 2007	CLINICAL PHASE	III
OBJECTIVES	The primary objectives of this study were: • To assess the efficacy of tocilizumab alone versus MTX alone with regard to reduction in signs and symptoms in patients with active RA. • To assess the safety of tocilizumab alone versus MTX alone with regard to adverse events and laboratory assessments in patients with active RA. The secondary objectives of this study were: • To explore the pharmacokinetics, immunogenicity and pharmacodynamic parameters of tocilizumab in this patient population.		
STUDY DESIGN	Phase III, 2-arm randomized, double-blind, double dummy, parallel group, multi-center study in patients with active RA. Randomized blinded treatment was maintained for 24 weeks. As an internal control the study also included a placebo controlled substudy. Patients in the placebo controlled substudy were enrolled from centers in the USA, Canada and Israel only. The patient population and study procedures were identical at all study centers, however patients enrolled into in the placebo controlled substudy were able to receive escape therapy with 8 mg/kg tocilizumab within the first 8 weeks of double-blind treatment.		

SYNOPSIS OF RESEARCH REPORT [redacted]
(PROTOCOL WA17824)

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

NUMBER OF SUBJECTS	A total of 650 patients were planned for this study (175 patients per arm in the main study and 100 patients per arm in the placebo controlled substudy). In total 673 patients were enrolled.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Men and women ≥ 18 years old, weighing ≤ 150 kg, with active RA of ≥ 3 months duration who had not been treated with MTX within 6 months prior to randomization, and who had not discontinued previous methotrexate treatment as a result of clinically important toxic effects or lack of response as determined by the investigator. Eligible patients were to have ≥ 6 swollen joints and ≥ 8 tender joints. Treatment with all DMARD therapies was to be discontinued prior to study entry. Eligible patients were not to have failed treatment with an anti-TNF agent.
TRIAL DRUG / STROKE (BATCH) No.	Tocilizumab Batch Numbers: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Tocilizumab: intravenous infusions of 8 mg/kg given every 4 weeks over a 24-week period (ie, a total of 6 infusions; maximum dose of 1200 mg).
REFERENCE DRUG / STROKE (BATCH) No.	MTX Batch Numbers: [redacted] Matching placebo MTX: [redacted] Matching placebo tocilizumab: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	MTX was given orally. All patients started on 7.5 mg MTX weekly. At Week 4, if the patient had any swollen or tender joints, the MTX dose was increased to 15 mg once/week (taken as two divided doses 12 hours apart). At Week 8, if the patient had any swollen or tender joints, the MTX dose was increased to 20 mg once/week (taken as 2 divided doses 12 hours apart). Matching placebo tocilizumab was administered intravenously once every 4 weeks and placebo MTX capsules were given once weekly.

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL WA17824)

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

CRITERIA FOR EVALUATION

EFFICACY:

Primary

- The primary endpoint was the proportion of patients with an ACR20 response at Week 24.

Secondary

- Proportion of patients with an ACR20 response at Week 8.
- Proportion of patients with ACR50 and ACR70 responses at Week 24
- Changes from baseline to Week 24 in the individual parameters of ACR core set
- AUC of the ACRn
- Longitudinal (GEE) analysis of ACR20, ACR50 and ACR70 responses
- Proportion of patients that achieved a remission according to the ACR remission criteria by Week 24.
- Change from baseline in Disease Activity Score (DAS28) at Week 24
- Proportion of patients classified as Categorical DAS28 responders (EULAR response) at Week 24
- Change from baseline to Week 24 in DAS28 Score
- Proportion of patients with DAS28 score < 2.6 at Week 24
- AUC of the mean disease activity score (DAS28)
- Health Assessment Questionnaire disability index (HAQ-DI), SF-36, and FACIT fatigue scale scores at Week 24
- Proportion of patients who withdraw due to lack of sufficient therapeutic response.
- Proportion of patients in each treatment group who receive escape therapy.
- Change in rheumatoid factor (IU/mL) to Week 24 in those patients with positive RF.
- Median time to improvement in daily pain VAS (25% decline in pain VAS from baseline).
- Change from baseline in hemoglobin, at Week 24.
- Time to onset of ACR20, 50 and 70 by treatment group

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL WA17824)

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

EFFICACY: Cont'd	**Exploratory**: – Logistic regression analysis of ACR20, ACR50 and ACR70 responses at Week 24 by baseline characteristics – ACR20, ACR50, ACR70 and DAS28 stratified by disease duration (≤ 2 years and > 2 years). ACR response and DAS28 were also analyzed in patients who were MTX naïve. – ACR90 response – Proportion of patients with swollen joint counts (SJC) and tender joint counts (TJC) of zero. – Categorical changes from baseline in HAQ-DI
PHARMACOKINETICS/ PHARMACODYNAMICS:	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:	HAQ-DI, 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.

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL WA17824)

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

STATISTICAL METHODS	The primary efficacy analysis was a non-inferiority comparison of tocilizumab with MTX. The null hypothesis tested was that the proportion of patients with an ACR20 response at Week 24 in the tocilizumab treatment arm was more than 12 percentage points lower than the proportion of patients with an ACR20 response at Week 24 in the MTX arm. Representing the proportion of patients with an ACR20 response at Week 24 for MTX by p1, and by p2 for the tocilizumab treatment arm: the null hypothesis, H_0, is $p2 < p1$. The null hypothesis was to be rejected if the lower limit of the two-sided 95% confidence interval for the difference in proportions of ACR20 responders on tocilizumab minus MTX was not less than -0.12. If tocilizumab was shown to be non-inferior to MTX in ACR20 response at Week 24, testing was also to be conducted for superiority. The analysis was based upon all patients receiving either MTX or tocilizumab and excluded patients who were initially randomized to placebo. Patients who began escape therapy (applied only to patients in the substudy up to Week 8) or withdrew from the study prior to the Week 24 ACR assessment, and all patients in whom the ACR20 response could not be determined due to missing data, were considered non-responders in the primary analyses. To support the conclusions from the primary analysis a comparison (based upon the ITT population) was made at Week 8, between the tocilizumab treatment group and the placebo group, using the extended Mantel-Haenszel statistic. 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' and 'disease duration' in the model.

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL WA17824)

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

STATISTICAL METHODS Cont'd	Secondary endpoints of ACR50 and ACR70 responses were analyzed. 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 and hemoglobin values were summarized descriptively and compared between the treatment groups using an analysis of variance (ANOVA) 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. 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. No non inferiority limits were pre-defined for secondary endpoints however, if the lower limit of 95% CI for treatment difference between tocilizumab and MTX was > 0, superiority had been achieved. In order to control the rate of false positive conclusions, a fixed sequence approach was applied, which allows for the superiority null hypothesis of each secondary endpoint to be tested at the same significance level of α without any adjustment, as long as the null hypotheses to be tested are hierarchically ordered and are tested in a pre-defined sequential order. For efficacy and quality of life parameters, the primary analysis population was the per protocol population (PP) population. Assessments were also performed on the intent-to treat population (ITT) population. Safety data were listed and summarized by treatment group for the safety population using descriptive statistics.

METHODOLOGY:

Study medication was administered as double dummy in order to maintain the blind. Patients received an infusion of tocilizumab 8 mg/kg every 4 weeks plus placebo MTX (oral capsules weekly) or oral MTX (escalating dose regimen: initial dose 7.5 mg, increasing at Week 4 to 15 mg and at Week 8 to 20 mg, given as oral capsules taken weekly) + placebo i.v. every 4 weeks. Patients were also to receive a stable dose of at least 5 mg/week folate (or equivalent) given as either a single dose or divided into daily doses. In the placebo/tocilizumab group, patients were administered with placebo MTX (oral capsules weekly) plus placebo i.v. infusions at 4 weekly intervals for 8 weeks. At Week 8, patients received 8 mg/kg tocilizumab as an i.v. infusion every 4 weeks plus placebo MTX capsules for the remaining 16 weeks of the study.

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL WA17824)

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

Patients in countries participating in the placebo controlled substudy who experienced a 20% increase from baseline in both SJC and TJC at any visit prior to (but not including) the Week 8 visit could, if requested and deemed necessary by the treating investigator, receive escape therapy. Patients who were not enrolled into the substudy were not eligible to receive escape therapy. Escape therapy consisted of open label tocilizumab (8 mg/kg), which was administered at the next scheduled 4 weekly visit where an i.v. infusion was planned. Patients could also receive intra-articular steroids or an increase in oral corticosteroid dosage (maximum dose of 10 mg total dose/day). After completion of 24 weeks of randomized treatment, patients could either enter a 'Transition Phase' in which double-blind treatment was continued or an open-label, long term extension study (WA18696) and receive tocilizumab 8 mg/kg every 4 weeks for up to 5 years. Escape patients were considered non-responders in the primary efficacy analysis at 24 weeks and for all time points beyond the time point at which they first received escape therapy. Patients returned for an efficacy and safety assessment 4 weeks after the last infusion of study treatment(Week 24). 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 RESULTS:

The primary analysis group for the assessment of both safety and efficacy was all patients randomized to receive either MTX or tocilizumab (including those patients initially randomized to receive MTX or tocilizumab in the placebo controlled substudy). Of the 673 patients enrolled into the study, 284 patients were randomized to receive MTX (comprising 192 patients in the main study & 92 patients in the placebo controlled substudy), 288 patients were randomized to receive tocilizumab 8 mg/kg (comprising 200 patients in the main study & 88 patients in the placebo controlled substudy) and 101 patients were randomized to receive placebo for 8 weeks followed by tocilizumab 8 mg/kg for 16 weeks in the placebo controlled substudy. In the primary analysis group, the MTX and tocilizumab groups were well balanced at baseline with respect to their general demographic characteristics, ACR core set component scores and RA disease characteristics (see below). Baseline demographics were characteristic of a relatively early RA population with moderate to severe RA. Approximately 43% of patients in this study were completely DMARD naïve. In the primary analysis group the most common concomitant RA treatments taken at baseline were non-steroidal anti inflammatories (MTX group: 77.1%, tocilizumab group: 79.5%), followed by folic acid (MTX group: 65.8%, tocilizumab group: 64.2%).

SYNOPSIS OF RESEARCH REPORT [redacted]
(PROTOCOL WA17824)

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

Primary Analysis Group (PP population)	MTX N= 259	MRA 8 mg/kg N= 265
Sex		
Female	211 (81%)	219 (83%)
Male	48 (19%)	46 (17%)
Mean Duration of RA (years)	6.31	6.43
Median Duration of RA (years)	3.18	3.24
Mean DAS28 Score	6.7	6.7
Rheumatoid Factor Positive	194 (75%)	194 (75%)
MTX Naive	171 (66%)	176 (66%)
Mean Tender Joint Count	31.1	32.2
Mean Swollen Joint Count	18.9	19.3
Mean Number of Previous DMARDs/Anti-TNFs	1.1	1.2

In the placebo controlled substudy some differences were observed between treatment arms. Median duration of RA was higher in the tocilizumab group (5.08 years) compared with the placebo/tocilizumab group (3.08 years) and the MTX group (3.88 years). A difference was also observed in rheumatoid factor status at baseline, with more patients in the placebo/tocilizumab group being RF+ compared with the MTX and tocilizumab groups (71% patients vs. 59% patients in the MTX group and 61% of patients in the tocilizumab group).

Thirty-two patients in the placebo controlled substudy entered escape therapy by Week 8: 14 patients (14%) in the placebo group, 11 patients (12%) in the MTX group and 7 patients (7%) in the tocilizumab group. Patients who received escape therapy were not classed as withdrawing from initial study treatment, but were non-responders in all analyses. A total of 61 patients withdrew prematurely from the study during the 24 week treatment phase due to reasons of safety or non-safety (including insufficient therapeutic response, protocol violation, refused treatment and failure to return). Of these patients 58 withdrew from initial randomized treatment or following the switch from placebo to tocilizumab at Week 8 (18 patients [18%] randomized to the placebo/tocilizumab group, 22 patients [8%] randomized to receive MTX and 18 patients [6%] randomized to receive tocilizumab) and 3 withdrew from escape therapy. The primary population for the analysis of efficacy was the PP population which comprised 616 patients. The ITT population comprised 669 patients and the safety population comprised 673 patients. The number of patients included in the PP population was balanced across the two treatment groups.

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL WA17824)

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

EFFICACY RESULTS:

The primary endpoint was the proportion of patients with an ACR20 response at Week 24. The proportion of ACR20 responders at Week 24 was 52.1% in the MTX group and 70.6% in the tocilizumab group, with a weighted difference of 0.21 (95% CI 0.13 to 0.29). The lower limit of the CI was 0.13. Since the lower limit is greater than –0.12 (pre-defined non-inferiority limit), treatment with tocilizumab was considered non-inferior to treatment with MTX. As tocilizumab was shown to be at least non inferior to MTX, further testing for superiority to MTX was conducted. For the purposes of this assessment the ITT population was used. The weighted difference in ACR20 response at Week 24 was 0.19 (95% CI 0.11 to 0.27). Since the lower limit of the 95% CI of the treatment difference was greater than 0, treatment with tocilizumab 8 mg/kg was demonstrated to be superior to treatment with MTX. This result was highly statistically significant ($p < 0.0001$). To support the conclusions from the primary analysis a comparison was made between all patients treated with tocilizumab and the placebo treated patients enrolled into the placebo controlled substudy. The ITT population was used for this assessment. As patients in this study received placebo only for the first 8 weeks, this analysis compared proportions of patients achieving an ACR20 response at Week 8. The proportion of ACR20 responders at Week 8 was 13.1% in the placebo/tocilizumab group and 55.6% in the tocilizumab group. The weighted difference in ACR20 response at 8 weeks was 0.43 (95% CI 0.34 to 0.52). Since the lower limit of the 95% CI for the weighted difference was greater than 0, tocilizumab 8 mg/kg is considered to be superior to treatment with placebo at Week 8. In general, all secondary endpoints tested were positive and supported the improved efficacy of tocilizumab compared with MTX observed with the primary efficacy endpoint. Logistic regression analyses showed the odds of achieving an ACR20 response at Week 24 were approximately 3 times higher in the tocilizumab group. In addition to the differences observed at Week 24, onset of response occurred earlier in the tocilizumab group with differences between the two treatment groups apparent as early as Week 2 (ie, first scheduled assessment) for ACR20 response. By Week 2, an increase in mean hemoglobin value of 7 g/L was observed in the tocilizumab group compared with a mean decrease of 3 g/L in the MTX group. A summary of the key efficacy parameter results for the primary analysis group (PP population) at Week 24 is provided below, in addition to a summary of parameters for which treatment with tocilizumab was shown to be statistically superior to MTX (based on the ITT population).

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL WA17824)

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

Results at Week 24-Primary Analysis Group (PP population)	MTX	MRA 8 mg/kg	Treatment Difference [95% CI]	
Primary Endpoint				
ACR20	52.1%	70.6%	0.21 [0.13, 0.29]	Non-inferiority demonstrated
Key Secondary Endpoints				
ACR50	32.8%	43.4%	0.13 [0.04, 0.21]	
ACR70	15.1%	27.5%	0.14 [0.06, 0.22]	
DAS28 Remission [<2.6]	11.4%	31.8%		
Change in DAS28 -adjusted mean	-1.99	-3.29	-1.30 [-1.58, -1.03]	
EULAR Response				
Good	16.2%	38.9%		
Moderate	48.6%	43.8%		
No Response	35.1%	17.4%		
Hemoglobin (g/L) adjusted mean (PP population)	0.498	11.707	11.209 [8.529, 13.889]	

Results at Week 24- Primary Analysis Group (ITT Population)	MTX	MRA 8 mg/kg	Treatment Difference [95% CI]	Superiority Criteria Met
ACR20	52.5%	69.9%	0.19 [0.11, 0.27]	Yes (p< 0.0001)
Key Secondary Endpoints				
ACR50	33.5%	44.1%	0.12 [0.04, 0.20]	Yes (p=0.0023)
ACR70	15.1%	28.0%	0.14 [0.07, 0.22]	Yes (p=0.0002)
Change in ACR core set – adjusted mean				
Swollen Joint Count	-8.2	-11.7	-3.5 [-5.2, -1.7]	Yes
Tender Joint Count	-13.9	-17.2	-3.3 [-5.9, -0.6]	Yes

SYNOPSIS OF RESEARCH REPORT [redacted]
(PROTOCOL WA17824)

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

In the placebo controlled substudy ACR20, ACR50 and ACR70 response at Week 24 was 44.6%, 29.3% and 12.0%, respectively in the placebo/tocilizumab group, 36.7%, 20.3% and 6.3%, respectively in the MTX group and 49.4%, 24.7% and 16.9%, respectively in the tocilizumab group. Despite the fact that patients randomized to the placebo/tocilizumab group received active treatment 8 weeks later than patients randomized to receive MTX or tocilizumab, these patients still responded well in comparison with patients in the MTX group. Non-inferiority was demonstrated for ACR20 response (weighted difference tocilizumab vs. MTX = 0.11, 95% CI -0.06 to 0.29) and there was no evidence of inferiority of tocilizumab to MTX in ACR50 or ACR70 response.

QUALITY OF LIFE:

In addition to improvements in HAQ-DI, patients in the tocilizumab group experienced significant improvement at Week 24 in self-assessments of mental and physical health (based on the SF-36 health survey) and fatigue (based on the FACIT-fatigue assessment results) compared with patients in the MTX group. Clinically relevant improvements in the mean physical component summary scores (≥ 5 points) were recorded at Weeks 16 and 24 in the MTX group compared with Weeks 8, 16 and 24 for the tocilizumab group. Clinically relevant improvements in mental component score were recorded at Week 24 only in the MTX group compared with Weeks 8, 16 and 24 for the tocilizumab group.

A mean increase in FACIT-fatigue score of 5 points or more was observed by the first scheduled assessment at Week 4 in the tocilizumab group (92% of patients in the tocilizumab group) but was only reached at Week 12 in the MTX group (88% of patients in the MTX group).

SAFETY RESULTS:

The overall incidence of adverse events was similar in both treatment groups (77.5% and 79.9% in the MTX and tocilizumab groups, respectively), as was the incidence of serious adverse events (2.8% and 3.8%, respectively). The incidence of adverse events considered to be related to study treatment was slightly higher in patients treated with tocilizumab (56.6%) than in patients receiving MTX (49.6%). The majority of adverse events were mild or moderate in intensity with < 7% of patients in each group experiencing severe events. Adverse events leading to discontinuation and dose modification were reported by slightly more patients in the MTX group (5.3% and 22.2%, respectively) than in the tocilizumab group (3.8% and 19.4%, respectively). Three patients treated with tocilizumab died during the study (the causes of death were gastrointestinal perforation [last treatment Day 29; died on Study Day [redacted]], myocardial ischemia [last treatment Day 36; died on Study Day [redacted] and cardio-respiratory arrest [last treatment Day 142; died on Study Day [redacted]]), while one patient in the MTX group died from lung cancer (last treatment Day 119; died Study Day [redacted]). The gastrointestinal perforation event was considered to be possibly related to treatment.

An overview of adverse events occurring during the 24 weeks of initial treatment (excluding placebo patients and events in patients receiving escape therapy) is provided below.

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL WA17824)

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

Number (%) of patients with:	MTX N = 284		MRA 8 mg/kg N = 288	
Any adverse event	220	(77.5)	230	(79.9)
Severe adverse event	19	(6.7)	20	(6.9)
Related adverse event	141	(49.6)	163	(56.6)
Serious adverse event	8	(2.8)	11	(3.8)
Related serious adverse event	4	(1.4)	4	(1.4)
Adverse event leading to discontinuation	15	(5.3)	11	(3.8)
Adverse event leading to dose modification	63	(22.2)	56	(19.4)
Death	1	(0.4)	3	(1.0)

During the first 8 weeks of the placebo controlled substudy, a higher incidence of adverse events was recorded in the tocilizumab group compared with the placebo and MTX groups (59% vs 44% and 47%, respectively). Serious adverse events were recorded by a similar number of patients in each group (3, 2 and 2 in the placebo, MTX and tocilizumab groups, respectively). The death due to gastrointestinal perforation in a patient treated with tocilizumab occurred during the first [redacted] weeks of treatment in the substudy.

Adverse events which occurred at a higher frequency in the tocilizumab group during the 24 week study included headache (7.3% vs 2.5% in the MTX group), skin disorders (12.8% vs 6.3%, respectively, primarily rash, pruritus and dermatitis), hypertension (5.6% vs 2.1%, respectively), respiratory disorders (9.0% vs 6.7%, respectively, primarily pharyngolaryngeal pain and cough) and psychiatric disorders (6.9% vs 3.9%, respectively, primarily anxiety, depression and insomnia). The most common classes of adverse events during the study were infections, gastrointestinal disorders and investigations (primarily liver function test abnormalities), which each occurred at a similar frequency in the tocilizumab and MTX groups (~35%, ~31% and ~16%, respectively). Serious or severe infections were reported by five patients in the tocilizumab group compared with three patients in the MTX group. In addition, two patients receiving tocilizumab as escape therapy experienced a serious infection.

No anaphylactic or hypersensitivity reactions were seen. Infusion reactions, defined as adverse events occurring during or within 24 hours of infusion, were reported by 16 patients receiving tocilizumab compared with five patients receiving MTX. The most common infusion reaction in the tocilizumab group was hypertension, with most events occurring during or within 24 hours after the first infusion. One patient in each group had their i.v. infusion modified or interrupted as a result of a hypertension adverse event. One patient in the tocilizumab group was withdrawn from the study due to an infusion related reaction.

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL WA17824)

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

Mean neutrophil counts were seen to decrease at two weeks after each tocilizumab infusion, but remained within the normal range and returned towards baseline values by 4 weeks post infusion. This pattern was most apparent during the first two infusions, after which time the decrease in neutrophil counts became more sustained. A higher proportion of patients receiving tocilizumab had downward shifts in neutrophil counts compared with patients receiving MTX. Four patients in the tocilizumab group recorded an adverse event of neutropenia, and two receiving tocilizumab as escape therapy. Of these six patients, two discontinued study medication, despite no clinical events, and four had their study medication modified as per protocol. Approximately 30% of all infections in the tocilizumab group were associated with a decrease in neutrophils, compared with 35% of infections in the MTX group. No serious infections were associated with CTC grade 3 neutropenia in either treatment group. One event of CTC grade 4 neutropenia was reported during the study (1 post week 8 placebo patient). A decrease in mean platelet count within the normal range was observed in the tocilizumab group at Week 2 and was maintained throughout the 24 week treatment period. No clinical symptoms were associated with decreases in platelet counts. Increases in mean values were observed for ALT and AST in both treatment groups during the 24 Week study, while increases in mean total bilirubin and lipid parameters were observed only in the tocilizumab group. The increase in mean ALT values occurred from Week 2 onwards in the tocilizumab group and from approximately Week 8 in the MTX group. Shifts from baseline and marked increases in ALT and AST occurred slightly more frequently in patients receiving MTX than in patients treated with tocilizumab. In most cases enzyme levels returned to normal following interruption or modification of study treatment. There were no clinical manifestations associated with laboratory abnormalities, however, two patients in the tocilizumab group had adverse events reported on the basis of transaminase elevations (cytolytic hepatitis and a worsening of hepatic steatosis).

Increases in fasting mean plasma lipid levels (total cholesterol, HDL, LDL and triglycerides) were observed in the tocilizumab group from Week 6 and remained elevated during continued dosing. Consistent with this, marked increases in total cholesterol, LDL and triglycerides were recorded more frequently in the tocilizumab group than in the MTX group. Seven patients in the tocilizumab group commenced therapy with a lipid-lowering agent during the study compared with five in the MTX group.

Decreases in mean levels of acute phase reactants CRP, ESR, SAA and serum ferritin were observed in both treatment groups however, the decreases were more marked and more rapid in the tocilizumab group. There was no evidence of hemolysis with tocilizumab.

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL WA17824)

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

CONCLUSIONS:

- Monotherapy treatment with tocilizumab 8 mg/kg provided a clinically important benefit in patients with highly active, moderate to severe, relatively early RA.
- Treatment with tocilizumab 8 mg/kg was shown to be non inferior to treatment with the active comparator MTX with respect to ACR20 response at Week 24. Treatment with tocilizumab was also shown to be statistically superior to treatment with MTX (with respect to ACR20/50/70 at 24 weeks).
- Clinical benefit was noted as early as two weeks after treatment initiation and continued to improve over the treatment duration.
- Patient reported outcomes, mirrored the clinical benefits observed.
- Tocilizumab was generally well tolerated in this patient population and the safety profile was consistent with the known mechanism of action and immunomodulatory properties of the drug. There were no toxicities apparent that would limit the use of tocilizumab in this patient population.