SYNOPSIS OF RESEARCH REPORT

Protocol ML22012

COMPANY: Roche Oy, Pharma affiliate Finland NAME OF FINISHED PRODUCT: RoActemra® NAME OF ACTIVE SUBSTANCE(S): TOCILIZUMAB	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY:	Local Open-Label Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients with Active Rheumatoid Arthritis on Background Non-biologic DMARDs who have an Inadequate Response to Current Non-biologic DMARDs
EUDRA CT No.: REPORT NUMBER: DATE OF REPORT:	2008-004126-16 Protocol ML22012 – CSR synopsis/Final 17.4.2011
INVESTIGATORS CENTERS AND COUNTRIES:	A total of five centers in Finland
PUBLICATION (REFERENCE):	Not applicable.

PERIOD OF TRIAL: First Patient First Visit (FPFV): Last Patient Last Visit LPLV):	 14 Nov 2008 26 May 2010	CLINICAL PHASE	Phase IIIb

OBJECTIVES:	Primary objective: • To assess the safety of tocilizumab (TCZ) monotherapy or in combination with non-biologic disease-modifying antirheumatic drugs (DMARDs) Secondary objective: • To assess the efficacy of TCZ monotherapy or in combination with non-biologic DMARDs
STUDY TRIAL DESIGN:	Local, phase IIIb, open-label single-arm study with a treatment duration of 24 weeks (6 infusions from baseline to week 20 plus follow-up visit at week 24)
NUMBER OF SUBJECTS: PLANNED: ENROLLED:	 25 14
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:	Male or non-pregnant, non-nursing female, aged ≥ 18 years of age at the time of providing informed consent, who had a diagnosis of RA and moderate to severe disease activity defined as ≥6 swollen and ≥6 tender joints (66 and 68 joints assessed for swelling and tenderness, respectively) and CRP ≥ 10 mg/l and/or ESR ≥ 28 mm/hr, and received treatment on an outpatient basis. Patients on ≥ 1 non-biologic DMARDs at a stable dose for a period ≥ 8 weeks prior to treatment (baseline). Patients with inadequate clinical response to a stable dose of non-biologic DMARD. Patients who failed a previous DMARD for safety or tolerability reasons were allowed to discontinue the DMARD and start TCZ monotherapy. If patients received an oral corticosteroid, the dose must have been stable for at least 25 out of 28 days prior to treatment (baseline). Eligible patients were those who were able and willing to provide

	written informed consent and to comply with the requirements of the study protocol.
INVESTIGATIONAL MEDICINAL PRODUCT(S)/STUDY DRUG: STROKE (BATCH) No.:	Tocilizumab RO487-7533/F01
CONCOMITANT/REFERENCE THERAPY:	Concomitant non-biologic DMARD therapy was allowed at a stable dose. To minimize potential methotrexate (MTX) toxicity, all patients being treated with MTX received either folic acid or leucovorin according to the manufacturer's recommendations.
DOSE / ROUTE / REGIMEN / DURATION:	TCZ 8 mg/kg IV, 60-minute infusion period, every 4 weeks for a total of 6 infusions.
REFERENCE DRUG / STROKE (BATCH) No.:	Not applicable; no comparator group.
DOSE / ROUTE / REGIMEN / DURATION:	Not applicable, no comparator group.
MAIN CRITERIA FOR EVALUATION:	
SAFETY:	The following parameters were assessed for safety: • Adverse events (AEs) • Serious adverse events (SAEs) • Discontinuation of TCZ because of (an) AE(s) • Discontinuation of TCZ for any reason • Infusion reactions • Major adverse cardiac events (MACE), strokes • Elevation of transaminases • Elevation of lipids • Hematology
EFFICACY:	• Disease activity as measured by DAS28 at every visit • Number of patients achieving DAS28 remission (DAS28 < 2.6) at every visit • Number of patients achieving ACR20, ACR50 and ACR70 response at every visit • CRP and ESR at every visit • Improvement in physical functioning as measured using HAQ
STATISTICAL METHODS:	This exploratory, single-arm clinical study aimed primarily at identifying safety and efficacy signals in a routine clinical practice. Descriptive statistics was used. Clinical scores and similar variables followed over time (e.g. DAS28) were displayed graphically.

METHODOLOGY:	This was a phase IIIb, local, open-label, single-arm study with treatment duration of 24 weeks in patients with moderate to severe active RA who had an inadequate clinical response to current non-biologic DMARD therapy. The sequence of assessments and procedures were as follows: At screening (visit 1), after providing written Informed Consent, patients were screened for eligibility. Physical examination, including pulse rate, systolic and diastolic blood pressure, body temperature, vital signs, body weight, electrocardiogram (ECG), chest X-ray (CXR) and physician's global assessment of disease status were carried out. Blood samples were collected to screen CRP, ESR, hematology, blood chemistry and lipid panel. Swollen and tender joints were counted. Tuberculin skin test was performed as per local guidelines and HIV test if deemed necessary by the investigator. All baseline (visit 2) evaluations were performed within 2 weeks ± 7 days after the screening visit and treatment with TCZ was initiated. Vital signs were taken at least once during the infusion. Patients were advised to return to the clinic for assessments and treatment at weeks 4, 8, 12, 16, and 20 (visits 3 to 7), or when withdrawing prematurely. All study visits following the baseline visit had to occur within ± 5 days of the scheduled visit. At all visits, physician's and patient's global assessment of disease status were measured, physical examination was carried out as described above and diagnosis of new abnormalities were recorded as AEs if appropriate. Blood samples were collected for laboratory testing and swollen and tender joints counted. Patients returned to the clinic for assessments at week 24 (visit 8), within ±5 days of scheduled visit.

SAFETY RESULTS: The primary objective of this study was to assess safety with the primary endpoint being the incidence of AEs and SAEs over the 24-week period. Overall, 13 (92.9 %) of 14 patients experienced 65 AEs, and 14.3 % of patients had an AE which was considered by the investigator to be related to study medication. One patient (7.1 %) experienced SAE, (erysipelas), which was considered to be related to TCZ. One patient (7.1 %) withdrew from the study after visit 3 due to an AE (destructive left coxitis) not considered related to TCZ. Three patients (21.4%) experienced mild infusion related reaction, two (14.3 %) were considered to be possibly related to the study medication. No major adverse cardiac events were reported.

The majority of changes in laboratory parameters were observed within the first 4 weeks of initiating treatment with TCZ and most remained within a clinically acceptable range and stabilized by Week 24. One patient (7.1%) experienced >1.5 ULN ALT elevation at week 4 and one patient (7.7%) >1.5 ULN AST elevation at week 24. Total cholesterol level was ≥ 240 mg/dl in 7.1 % of patients at baseline (visit 2) vs. 42.9 to 30.8 % of patients at visits 3 to 8. LDL cholesterol level increased from normal range at baseline to high level (160-189 mg/dl) in 35.7 % to 15.4 % of patients at visits 3 to 8. HDL cholesterol was at high level (≥ 60 mg/dl) in 42.8 % of patients at baseline vs. 85.7 to 69.2 % of patients at visits 3 to 8. One patient (7.1 %) experienced neutrophil count of [redacted] $x10^9$/l at visits 4 and 7.

EFFICACY RESULTS: Improvement in disease status (DAS28) was shown after 4 weeks of treatment (mean DAS28 decrease 3.14 [SD ± 1.01]). Improvement continued from baseline to week 24 with some fluctuation (mean DAS28 decrease 3.88 [SD ± 1.93] at week 24). Mean DAS28 decreased from 5.99 at baseline to 2.85 at week 4 and 1.98 at week 24. Mean DAS28 remained below 2.6 from week 8 to 24.

The percentage of patients who achieved DAS28 remission (DAS28 <2.6) increased over time with some fluctuation: Baseline (0%), Week 4 (42.9%), Week 8 (69.2%), Week 12 (83.3%), Week 16 (76.9%), Week 20 (84.6%), and Week 24 (69.2%). The proportion of patients achieving ACR20, 50 and 70 responses also increased over time with some fluctuations: Week 4 (57, 29, 0 %), Week 8 (100, 77, 46 %), Week 12 (77, 62, 31 %), Week 16 (100, 77, 46 %), Week 20 (85, 77, 54 %), Week 24 (100, 62, 62 %), respectively. Mean CRP decreased from 35.8 mg/l at baseline to 1.29 mg/l at week 4 and remained below 3.0 mg/l throughout the study. Mean ESR decreased from 37.1 mm/h at baseline to 3.71 mm/h at week 4 and remained below 10 mm/h.

The results of the quality of life assessments show that both patients and investigating physicians deemed there to be an improvement in the condition over the 24 weeks. The HAQ-DI score decreased steadily over time, indicating an improvement in condition. The mean HAQ score decreased from 2.37 at baseline to 1.45 at week 24 (corresponding to an overall 39% improvement).

CONCLUSIONS:

- TCZ at a dose of 8 mg/kg (IV) every 4 weeks appears to be well-tolerated in patients with moderate to severe RA as studied in a routine clinical practice setting.
- Response to treatment was fast: An improvement in disease status was shown after 4 weeks demonstrated by improvements in DAS28, ACR, and HAQ-DI, and continued to week 24 with some fluctuations.