CLINICAL STUDY REPORT
PROTOCOL ML22413

Open label, multicentric phase IIIb study to evaluate the effect of tocilizumab in combination with DMARDs in the inhibition of progression of synovitis, bone marrow edema, and erosions evaluated by dedicated magnetic resonance imaging (MRI) in the hand of patients with rheumatoid arthritis (RA)

Date of Report:	22 April 2013
Study Sponsor(s)	ROCHE S.p.A.
Study Dates:	22 Oct 2009 – 30 Apr 2012
Trial Phase:	IIIb
Indication:	Adult patients with moderate to severe active rheumatoid arthritis (RA), who are inadequate responders to DMARDs.

Signature of Principal Investigator

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Signature: [redacted] Date: 06 Jun 2013

GCP Compliance: **This study was conducted in accordance with GCP guidelines**

SYNOPSIS OF RESEARCH REPORT PROTOCOL ML 22413

COMPANY: Roche S.p.A. NAME OF FINISHED PRODUCT: RoACTEMRA NAME OF ACTIVE SUBSTANCE(S): Tocilizumab	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY: / REPORT No.:	Open label, multicentric phase IIIb study to evaluate the effect of tocilizumab in combination with DMARDs in the inhibition of progression of synovitis, bone marrow edema, and erosions evaluated by dedicated magnetic resonance imaging (MRI) in the hand of patients with rheumatoid arthritis (RA)	
DATE OF REPORT:	02 April 2013	
INVESTIGATORS / CENTERS AND COUNTRIES:	11 investigational study sites in Italy	
PUBLICATION (REFERENCE):	Not applicable	
PERIOD OF TRIAL:	22 Oct 2009 – 30 Apr 2012	22 Oct 2009 – 30 Apr 2012
OBJECTIVES:	The primary objective of this study was to assess the effects of tocilizumab in changes of the synovial membrane enhancement in the wrist joints of RA patients with inadequate clinical response to treatment with traditional DMARDs, defined as a baseline DAS28 > 3.2. The secondary objectives of the study were to assess the effects of tocilizumab on the following parameters: 1. Extent of bone marrow edema, and the number and extent of erosions in the wrist and metacarpo-phalangeal (MCP) joints using dedicated MRI; 2. Radiographic changes in the hands evaluated by the modified Sharp score; 3. Ritchie articular index; 4. HAQ; 5. Pain by using a visual-analogue scale; 6. General health by using a visual-analogue scale; 7. DAS-28 CRP; 8. VEGF concentration; 9. ESR and hsCRP concentration; 10. Haemoglobin (Hb) and soluble transferrin receptors concentrations; 11. Changes in immunological and inflammatory parameters; 12. Tolerability and safety parameters; 13. Bone erosion. To assess early effects (Day 2) of tocilizumab on immunological and inflammatory parameters, an additional laboratory assessment was performed in patient who gave a supplementary written informed consent.	
STUDY DESIGN:	This was a phase IIIb, open-label, national, multicentric, single arm study to evaluate the effect of tocilizumab in combination with DMARDs in the inhibition of progression of synovitis, bone marrow edema, and erosions evaluated by dedicated MRI in the hand of patients with active RA. The study duration was 48 weeks (12 infusions from baseline to week 44 plus follow-up visit at week 48).	
NUMBER OF SUBJECTS	Total enrolled/ITT: 58	
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Inclusion criteria: This study included men and women ≥ 18 years of age with a diagnosis of RA of ≥ 6 months duration, who were currently experiencing moderate to severe active RA (DAS28 > 3.2) and an inadequate clinical response to a stable dose of non-biologic DMARD therapy. Inclusion criteria were: 1. Male or non-pregnant, non-nursing female; 2. Age ≥ 18 years; 3. Patients with diagnosis of RA of ≥ 6 months duration; 4. Patients currently experiencing moderate to severe active RA (DAS28 > 3.2); 5. Patients with: SJC ≥ 6 and TJC ≥ 8 6. Patients receiving treatment on an outpatient basis; 7. Patients with inadequate clinical response to a stable dose of non-biologic DMARD for at least 2 months; 8. If patients were receiving an oral corticosteroid, the dose had to have been stable for at least 25 out of 28 days prior to treatment (day 1); 9. Subjects able and willing to give written informed consent and comply with the requirements of the study protocol.	

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	Main exclusion criteria: *Disease-specific criteria* 1. Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery within 6 months following randomization; 2. Rheumatic autoimmune disease other than RA, including systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), systemic sclerosis, polymyositis, or significant systemic involvement secondary to RA (e.g. vasculitis, pulmonary fibrosis or Felty's syndrome). Patient with interstitial pulmonary fibrosis and still able to tolerate MTX therapy could be included in the study. Patients with secondary Sjögren's syndrome associated with RA could be included in the study; 3. Functional class IV as defined by the ACR Classification of Functional Status in RA (largely or wholly incapacitated with patient bedridden or confined to wheel chair, permitting little or no self-care); 4. Prior history of or current inflammatory joint disease other than RA (e.g. gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy, Lyme disease); *Drug-specific criteria* 5. Treatment with any investigational agent within 4 weeks (or 5 half-lives of investigational agent, whichever is longer) before screening; 6. Previous inadequate response to treatment with biologic DMARDs; 7. Intraarticular or parenteral corticosteroids within 6 weeks prior to baseline; 8. Immunization with a live/attenuated vaccine within 4 weeks prior to baseline; 9. Previous treatment with tocilizumab (an exception to this criterion could be granted for single-dose exposure upon application to the sponsor on a case by case basis); 10. Any previous treatment with alkylating agents, such as cyclophosphamide or chlorambucil, or with total lymphoid irradiation.
TRIAL DRUG / STROKE (BATCH) No.	Tocilizumab batch No. M8H21, B0007, B0010 and B0016.
DOSE / ROUTE / REGIMEN / DURATION	Tocilizumab 8 mg/kg (but no more than 800 mg) IV was administered in a 60-minute infusion period, every 4 weeks for a total of 12 infusions. The number of vials to be used depended on the patient's body weight as follows: 1. Two 200 mg vials were used for patients with a body weight $\leq$ 50 kg; 2. Three 200 mg vials were used for patients with a body weight >50 and $\leq$ 75 kg; 3. Four 200 mg vials were used for patients with a body weight >75 and $\leq$100 kg. The maximum single dose in any given patient was 800 mg, i.e. patients with a body weight of more than 100 kg received a dose of less than 8 mg/Kg.
CRITERIA FOR EVALUATION EFFICACY:	Primary efficacy variables: • Extension and degree of synovitis of the wrist at week 4 according to the RAMRIS score developed by OMERACT; • Quantitative assessment of the degree of synovitis by dynamic, gadolinium-enhanced MRI of the wrist as rate of early enhancement (initial curve slope, REE) and relative enhancement (curve steady state, RE) at week 4. Secondary efficacy variables: • Extension and degree of synovitis of the wrist at day 15, week 4, 12, 24 and 48 according to RAMRIS score developed by OMERACT; • Quantitative assessment of the degree of synovitis by dynamic, gadolinium-enhanced MRI of the wrist as rate of early enhancement (initial curve slope, REE) and relative enhancement (curve steady state, RE) at day 15, week 4, 12, 24 and 48; • Extension and degree of synovitis of the wrist and MCP joints evaluated on STIR sequences with a modification of the RAMRIS score at day 15, week 4, 12, 24 and 48; • Number of bone with, and extent of erosion in the wrist and MCP joints at day 15, week 4, 12, 24 and 48 according to RAMRIS score developed by OMERACT; • Number of bone with, and extent of bone marrow edema in the wrist and MCP joints at day 15, week 4, 12, 24 and 48 according to RAMRIS score developed by OMERACT;

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	• Radiographic changes in the hands evaluated by the modified Sharp score; • Ritchie articular index; • Pain visual-analogue scale; • General health visual-analogue scale; • Stanford Health Assessment Questionnaire (HAQ) disability index; • DAS-28 CRP; • VEGF; • ESR, CRP; • Immunological/Inflammatory parameters; • Haemoglobin concentration and soluble transferring receptor (STR) concentration; • Dynamika® parameters (IRE, ME, Ntotal, Npersistent, Nplateau, Nwash-out, Ntotal*IRE, Ntotal*ME). Explorative analyses: Correlation among between variables was explored graphically and, if appropriate, by means of Pearson's correlation coefficient. An explorative analysis was carried out in order to investigate a possible correlation between: 1) the primary efficacy endpoints, VEGF, ESR and CRP concentrations; 2) early changes in selected immunological and inflammatory parameters and a) clinical response at week 4 (DAS-28) b) changes in the RAMRIS score at both early (week 2) and later time points (LOCF method); 3) changes from baseline to week 4 of RAMRIS and Dynamika® parameters; 4) changes in STR and haemoglobin, RBCs and their changes at week 2 and 4.
PHARMACODYNAMICS:	Not applicable for this study
PHARMACOKINETICS:	Not applicable for this study
SAFETY:	• Treatment-emergent adverse events (TEAEs); • Physical examination; • Vital signs (weight, BMI, blood pressure, heart rate, body temperature); • Laboratory parameters (haematology, biochemistry).
STATISTICAL METHODS:	The following populations were considered for data analysis: safety/intent-to-treat (ITT) population (all subjects who received at least one dose of treatment); per-protocol population (all patients in the ITT population excluding major protocol violators). Continuous variables were summarized by descriptive statistics (number of cases, mean, standard deviation, median, minimum and maximum). Categorical variables were summarized using counts of subjects and percentages. Proc univariate was used to check for normality assumption and graphical normality check was carried out. A rank transformation of original data was performed if assumption of normal distribution was not met. For each primary endpoint a Student's paired t-test was carried out to test the null hypothesis that there was not a significant change from baseline to week 4. The same test was used in the analysis of changes from baseline to week 48 of Stanford HAQ disability index. Repeated measure analyses of variance (ANOVA) to assess the significance between time points was performed using mixed models. Contrasts between each visit and baseline were also calculated. Bonferroni's adjustment was used for pairwise comparisons. Correlation between pre-defined variables was explored graphically and, if appropriate, by means of Pearson's correlation coefficient. Adverse events were assigned a Preferred Term (PT) and were categorized into System Organ Class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) classification. Laboratory tests values (haematology and blood chemistry) and the associated changes from baseline were summarized using descriptive statistics. A shift-table of the changes from baseline to any post-baseline visit according to the classification of low/normal/high value with respect to the normal range was produced. Vital signs were evaluated by means of descriptive statistics.

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EFFICACY RESULTS:

Primary variables:

- *Extension and degree of synovitis of the wrist at week 4 (RAMRIS score)*

ITT population:

The mean and median RAMRIS score decreased from baseline to week 4. The mean (± SD) change was -0.88 ± 1.56 (median -1.00, range -5.0 to 2.0). In the LOCF analysis, the mean (± SD) change from baseline to week 4 was -0.804 ± 1 575 (95% CI: -1.247 to -0.361), and was statistically significant (adjusted p value = 0.018).

Per-protocol population:

In the LOCF analysis, the mean (± SD) change from baseline to week 4 was -0.975 ± 1.687 (95% CI: -1.514 to -0.436), and was statistically significant (p = 0.018).

- *Relative enhancement (RE) of synovitis of the wrist at week 4*

ITT population:

The mean and median RE slightly decreased from baseline to week 4. The mean (± SD) change was -0.48 ± 47.85 (median -6.50, range -130.3 to 121.5). In the LOCF analysis, the mean (± SD) change from baseline to week 4 was 2.628 ± 50.465 (95% CI: -11.714 to 16.970), and was not statistically significant.

Per-protocol p population:

In the LOCF analysis, the mean (± SD) change from baseline to week 4 was 2.178 ± 53.827 (95% CI: -15.037 to 19.392), and was not statistically significant.

- *Rate of early enhancement (REE) of synovitis of the wrist at week 4*

ITT population:

The mean and median REE did not substantially change from baseline to week 4. The mean (± SD) change was -0.10 ± 0.86 (median 0.00, range -2.6 to 1.6). In the LOCF analysis, the mean (± SD) change from baseline to week 4 was -0.046 ± 0.890 (95% CI: -0.299 to 0.207), and was not statistically significant.

Per-protocol population:

In the LOCF analysis, the mean (± SD) change from baseline to week 4 was -0.113 ± 0.945 (95% CI: -0.415 to 0.190), and was not statistically significant.

Secondary variables:

- *Extension and degree of synovitis of the wrist (RAMRIS score) at any time point*

The mean RAMRIS score decreased from baseline to any post-baseline time point. The mean change from baseline to week 48/end of study was -1.60 ± 2.42 (median -2.00, range -6.0 to 3.0). The results of the repeated measure ANOVA showed that the decrease from baseline was statistically significant at any time point, except at week 2 (adjusted p value = 0.0028 at week 4, 0.0003 at week 12, <0.0001 at week 24 and 0.0006 at week 48/end of study).

- *Relative enhancement (RE) of synovitis of the wrist at any time point*

The mean RE slightly increased from baseline to week 2 and then progressively decreased from baseline up to the end of study. The mean change from baseline to week 48/end of study was -19.74 ± 74.08 (median -20.40, range -164.5 to 108.8). The results of the repeated measure ANOVA (Statistical Table 14.2.48) showed that the decrease from baseline was statistically significant at week 24 (adjusted p value = 0.0046).

- *Rate of early enhancement (REE) of synovitis of the wrist at any time point*

The mean REE did not substantially change from baseline to week 2 and then progressively decreased from baseline up to the end of study. The mean change from baseline to week 48/end of study was -0.66 ± 1.24 (median -0.30, range -3.8 to 1.9). The results of the repeated measure ANOVA showed that the decrease from baseline was statistically significant at week 12 (adjusted p value = 0.0113), week 24 (adjusted p value = 0.0026) and week 48/end of study (adjusted p value = 0.0020).

- *Extension and degree of synovitis of the wrist and metacarpo-phalangeal joints*

The mean wrist distal radio-ulnar joint score progressively decreased from baseline up to the end of study. The mean change from baseline to week 48/end of study was -0.48 ± 1.05 (median 0.00, range -3.0 to 2.0).

The mean wrist distal radio-carpal joint score progressively decreased from baseline up to the end of study. The mean change from baseline to week 48/end of study was -0.51 ± 0.93 (median 0.00, range -3.0 to 2.0).

The mean wrist intercarpal CMCJ joint score progressively decreased from baseline up to the end of study. The mean change from baseline to week 48/end of study was -0.55 ± 0.90 (median 0.00, range -2.0 to 1.0).

The mean MCP joint 2 score did not change from baseline to week 2 and then slightly but progressively decreased from baseline up to the end of study. The mean change from baseline to week 48/end of study was -0.34 ± 0.96 (median 0.00, range -3.0 to 1.0).

The mean MCP joint 3 score did not substantially change from baseline up week 12 and then slightly but progressively decreased from baseline up to the end of study. The mean change from baseline to week 48/end of study was -0.32 ± 0.86 (median 0.00, range -3.0 to 1.0).

The mean MCP joint 4 score did not substantially change from baseline to week 2 and then slightly but progressively decreased from baseline up to the end of study. The mean change from baseline to week 48/end of study was -0.27 ± 0.92 (median 0.00, range -3.0 to 1.0).

The mean MCP joint 5 score slightly but progressively decreased from baseline up to the end of study. The mean change from baseline to week 48/end of study was -0.41 ± 0.84 (median 0.00, range -2.0 to 1.0).

- *Extension and degree of synovitis of the wrist and metacarpo-phalangeal joints evaluated on STIR sequences (modified RAMRIS score)*

The mean wrist global modified RAMRIS score did not substantially change from baseline to week 2 and then progressively decreased from baseline up to the end of study. The mean change from baseline to week 48/end of study was -1.23 ± 2.28 (median -1.00, range -6.0 to 4.0). The results of the repeated measure ANOVA showed that the decrease from baseline was statistically significant at week 24 (adjusted p value = 0.0052) and at week 48 (adjusted p value = 0.0034).

The mean wrist distal radio-ulnar joint modified RAMRIS score did not substantially change from baseline to week 2 and then progressively decreased from baseline up to the end of study. The mean change from baseline to week 48/end of study was -0.58 ± 0.94 (median -1.00, range -3.0 to 1.0).

The mean wrist distal radio-carpal joint modified RAMRIS score did not substantially change from baseline up to week 4 and then slightly but progressively decreased from baseline up to the end of study. The mean change from baseline to week 48/end of study was -0.38 ± 0.92 (median 0.00, range -2.0 to 2.0).

The mean wrist intercarpal CMCJ joint modified RAMRIS score did not change from baseline up to week 4 and then slightly but progressively decreased from baseline up to the end of study. The mean change from baseline to week 48/end of study was -0.34 ± 0.96 (median 0.00, range -2.0 to 2.0).

The mean MCP joint modified score progressively decreased from baseline up to the end of study. The mean change from baseline to week 48/end of study was -1.25 ± 2.53 (median -1.00, range -11.0 to 4.0). The results of the repeated measure ANOVA showed that the decrease from baseline was statistically significant at week 48/end of study (adjusted p value = 0.0323).

The mean wrist and MCP aggregate modified score progressively decreased from baseline up to the end of study. The mean change from baseline to week 48/end of study was -2.49 ± 3.59 (median -2.00, range -14.0 to 5.0). The results of the repeated measure ANOVA showed that the decrease from baseline was statistically significant at week 24 (corrected p value = 0.0032) and week 48/end of study (adjusted p value = 0.0002).

- *Number of bones with and extent of erosion in the wrist and metacarpo-phalangeal joints*

The mean erosion wrist score did not substantially change from baseline up to week 12 and then slightly increased at week 24 and week 48/end of study. The mean change from baseline to week 48/end of study was 0.34 ± 3.67 (median 0.00, range -7.0 to 20.0).

The mean erosion MCP score did not substantially change from baseline up to the end of study. The mean change from baseline to week 48/end of study was 0.09 ± 1.18 (median 0.00, range -3.0 to 5.0).

The mean erosion aggregate score did not substantially change from baseline up to the end of study. The mean change from baseline to week 48/end of study was 0.36 ± 4.17 (median 0.00, range -7.0 to 22.0). The results of the repeated ANOVA did not show statistically significant changes from baseline to any post-baseline time point.

The mean number of bones with erosion did not substantially change from baseline up to the end of study. The mean change from baseline to week 48/end of study was -0.04 ± 2.81 (median 0.00, range -13.0 to 7.0).

- *Number of bones with and extent of bone marrow edema in the wrist and metacarpo-phalangeal joints*

The mean bone marrow edema wrist score progressively decreased from baseline up to the end of study. The mean change from baseline to week 48/end of study was -6.45 ± 11.90 (median -2.00, range -43.0 to 31.0).

The mean bone marrow edema MCP score progressively decreased from baseline up to the end of study. The mean change from baseline to week 48/end of study was -1.98 ± 4.13 (median 0.00, range -16.0 to 5.0).

The mean bone marrow edema aggregate score progressively decreased from baseline up to the end of study. The mean change from baseline to week 48/end of study was -8.30 ± 13.06 (median -4.00, range -39.0 to 29.0). The results of the repeated measure ANOVA showed that the decrease from baseline was statistically significant at week 24 (adjusted p value = 0.0022) and week 48/end of study (adjusted p value = 0.0008).

The mean number of bones with bone marrow edema progressively decreased from baseline up to the end of study. The mean change from baseline to week 48/end of study was -3.56 ± 5.07 (median -2.50, range -16.0 to 7.0).

- *Radiographic changes in the hands evaluated by the modified Sharp score*

The mean Total Modified Sharp Score (TMSS) did not substantially change from baseline to week 24 and slightly increased at week 48/end of study. The mean change from baseline to week 48/end of study was 1.46 ± 5.66 (median 0.00, range -10.0 to 31.0). The results of the repeated measure ANOVA did not show statistically significant changes from baseline to both week 24 and week 48/end of study.

The mean erosion score did not substantially change from baseline to week 24 and slightly increased at week 48/end of study. The mean change from baseline to week 48/end of study was 0.31 ± 1.07 (median 0.00, range -1.0 to 4.0).

The mean Joint Space Narrowing (JSN) score did not substantially change from baseline to week 24 and slightly increased at week 48/end of study. The mean change from baseline to week 48/end of study was 1.15 ± 5.42 (median 0.00, range -11.0 to 29.0).

- *Ritchie Articular index*

The mean Ritchie articular index decreased from baseline to any post-baseline time point. The mean change from baseline to week 48/end of study was -12.09 ± 6.95 (median -13.00, range -30.0 to 9.0). The results of the repeated measure ANOVA showed that the decrease from baseline was statistically significant at any time point (adjusted p value <0.0001 at any time).

- *Pain and general health visual-analogue scale*

The mean and median patient's assessment of pain (PP-VAS) score decreased from baseline to any post-baseline time point. The mean change from baseline to week 48/end of study was -39.44 ± 25.26 (median -41.00, range -87.0 to 12.0). The results of the repeated measure ANOVA showed that the decrease from baseline was statistically significant at any time point (adjusted p value <0.0001 at any time).

The mean and median patient's global assessment of disease activity (PGDA-VAS) score decreased from baseline to any post-baseline time point. The mean change from baseline to week 48/end of study was -40.41 ± 25.69 (median -46.00, range -91.0 to 19.0). The results of the repeated measure ANOVA showed that the decrease from baseline was statistically significant at any time point (adjusted p value <0.0001 at any time).

The mean and median Investigator's global assessment of disease activity (IGDA-VAS) score decreased from baseline to any post-baseline time point. The mean change from baseline to week 48/end of study was -44.72 ± 18.98 (median -42.00, range -87.0 to -2.0). The results of the repeated measure ANOVA showed that the decrease from baseline was statistically significant at any time point (adjusted p value <0.0001 at any time).

- *Stanford Health Assessment Questionnaire disability index(HAQ-DI)*

The mean HAQ-DI decreased from baseline to any post-baseline time point. The mean change from baseline to week 48/end of study was -0.67 ± 0.61 (median -0.63, range -2.1 to 0.5). In the LOCF analysis, the mean (± SD) change from baseline to week 48/end of study was -0.675 ± 0.626 (95% CI: -0.841 to -0.509), and was statistically significant (p<0.0001). The results of the repeated measure ANOVA showed that the decrease from baseline was statistically significant at any time point (adjusted p value = 0.0024 at week 2 and <0.001 at the other time points).

- *DAS-28 CRP*

The mean DAS-28 CRP decreased from baseline to any post-baseline time point. The mean change from baseline to week 48/end of study was -3.07 ± 1.27 (median -3.21, range -6.1 to 0.2). The results of categorical response of DAS-28 CRP based on EULAR criteria showed that the rate of patients with good response progressively increased over time up to the end of study (77.3% at week 48/end of study).

The mean TJC-28 decreased from baseline to any post-baseline time point. The mean change from baseline to week 48/end of study was -9.94 ± 5.75 (median -10.50, range -22.0 to 5.0).

The mean SJC-28 decreased from baseline to any post-baseline time point. The mean change from baseline to week 48/end of study was -8.46 ± 4.84 (median -8.00, range -22.0 to 4.0).

- *Tender joint count 68 (TJC-68) and swollen joint count 66 (SJC-66)*

The mean TJC-68 decreased from baseline to any post-baseline time point. The mean change from baseline to week 48/end of study was -16.11 ± 10.78 (median -15.50, range -47.0 to 20.0). The results of the repeated measure ANOVA showed that the decrease from baseline was statistically significant at any time point (adjusted p value <0.0001 at any time).

The mean SJC-66 decreased from baseline to any post-baseline time point. The mean change from baseline to week 48/end of study was -11.06 ± 6.80 (median -10.00, range -29.0 to 11.0). The results of the repeated measure ANOVA showed that the decrease from baseline was statistically significant at any time point (adjusted p value <0.0001 at any time).

- *Laboratory parameters*

The mean VEGF concentration decreased from baseline to any post-baseline time point. The mean change from baseline to week 48/end of study was -29.35 ± 183.46 pg/mL (median -45 98 pg/mL, range -568.3 to 663.8). The results of the repeated measure ANOVA showed that the decrease from baseline was statistically significant at week 2 (adjusted p value = 0.0074), week 4 (adjusted p value = 0.0002), week 12 (adjusted p value = 0.0046) and week 24 (adjusted p value = 0.0006), while the decrease at week 48/end of study was not statistically significant.

The mean ESR decreased from baseline to any post-baseline time point. The mean change from baseline to week 48/end of study was -27.22 ± 21.79 mm/h (median -24.00 mm/h, range -70.0 to 25.0). The results of the repeated measure ANOVA showed that the decrease from baseline was statistically significant at any time point (adjusted p value <0.0001 at any time).

The mean and median hsCRP levels decreased from baseline to any post-baseline time point. The mean change from baseline to week 48/end of study was -10.49 ± 12.31 mg/L (median -6.30 mg/L, range -48.8 to 4.0). The results of the repeated measure ANOVA showed that the decrease from baseline was statistically significant at any time point (adjusted p value <0.0001 at any time).

The mean and median haemoglobin levels increased from baseline to any post-baseline time point. The mean change from baseline to week 48/end of study was 7.17 ± 8.28 g/L (median 8.00 g/L, range -10.0 to 35.0).

The mean RBCs count did not substantially change from baseline to any post-baseline time point. The mean change from baseline to week 48/end of study was 0.03 ± 0.21 x 10^{12}/L (median 0.08 x 10^{12}/L, range -0.4 to 0.5).

The mean STR concentration did not substantially change from baseline to any post-baseline time point (day 2, week 2 and week 4). The mean change from baseline to week 4 was -89722.7 ± 959232.1 pg/mL (median -212135 pg/mL, range -2159160 to 2151940).

- *Immunological/inflammatory parameters*

The most evident changes from baseline were observed for sIL6R. The mean and median sIL6R (pg/mL) markedly increased from baseline to both week 2 and week 4: the mean change from baseline to week 4 was 303037.2 ± 253261.4 (median 295394.0, range -50677 to 951645).

There were no substantial changes from baseline to any post-baseline time point for the other tested immunological/inflammatory parameters, including bone markers.

- *Dynamika® parameters*

The mean IRE slightly decreased from baseline to any post-baseline time point: the mean change from baseline to week 48/end of study was -0.00246 ± 0.00363 (median -0.00204, range -0.01150 to 0.00449). The mean ME slightly decreased from baseline to week 48/end of study and did not substantially change at the other time point: the mean change from baseline to week 48/end of study was -0.177 ± 0.416 (median -0.112, range -1.633 to 0.878). The mean N total progressively decreased from baseline to any post-baseline time point: the mean change from baseline to week 48/end of study was -974.16 ± 1606.14 (median -1108.00, range -5041 to 2590). The mean N persistent did not substantially change from baseline to any post-baseline time point: the mean change from baseline to

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week 48/end of study was -0.53 ± 219.74 (median 5.00, range -785 to 613). The mean N plateau slightly increased from baseline to week 2 and then progressively decreased from week 4 up to the end of study: the mean change from baseline to week 48/end of study was -635.72 ± 1019.13 (median -676.00, range -2986 to 1680). The mean N wash-out decreased from baseline to any post-baseline time point (except for no substantial changes at week 2): the mean change from baseline to week 48/end of study was -358.25 ± 798.88 (median -307.50, range -2043 to 1355).

The mean N total*IRE decreased from baseline to any post-baseline time point (except for no substantial changes at week 2): the mean change from baseline to week 48/end of study was -4.84 ± 6.13 (median -3.49, range -19.38 to 4.85). The mean N total*ME decreased from baseline to any post-baseline time point (except for an increase in mean values and no substantial changes in median values at week 2): the mean change from baseline to week 48/end of study was -793.59 ± 1168.57 (median -761.48, range -4118.68 to 1157.70).

The results of the repeated measure ANOVA of Dynamika® parameters showed that the decrease from baseline was statistically significant for the following parameters: IRE at week 48/end of study (adjusted p value = 0.0013); ME at week 24 (adjusted p value = 0.0025) and week 48/end of study (adjusted p value = 0.0017); N total at week 48/end of study (adjusted p value = 0.0043); N plateau at week 48/end of study (adjusted p value = 0.0252); N wash-out at week 12 (adjusted p value = 0.0096) and week 48/end of study (adjusted p value = 0.0287); N total*IRE at week 12 (adjusted p value = 0.0339), week 24 (adjusted p value = 0.0165) and week 48/end of study (adjusted p value = 0.0001); and N total*ME at week 24 (adjusted p value = 0.0138) and week 48/end of study (adjusted p value = 0.0002). No statistically significant changes from baseline were observed for N persistent.

Exploratory analyses:

The following statistically significant correlations were observed:

Correlation of Th17 absolute number (% change baseline-week 4) with synovitis wrist RAMRIS score (% change baseline-week 2): Pearson's correlation coefficient = 0.542; p = 0.0451;

Correlation of Treg absolute number (% change baseline-week 4) with DAS-28 (week 4): Pearson's correlation coefficient = -0.342; p = 0.0288;

Correlation of ICTP-I collagen fragment (% change baseline-week 2) with synovitis wrist RAMRIS score (% change baseline-week 2): Pearson's correlation coefficient = 0.330; p = 0.0373;

Correlation of ICTP-I collagen fragment (% change baseline-week 2) with synovitis wrist RAMRIS score (% change baseline-week 48 [LOCF]): Pearson's correlation coefficient = 0.327; p = 0.0303.

No other statistically significant or at least moderate positive or negative linear correlations were observed for the other tested parameters.

PHARMACODYNAMIC RESULTS: Not applicable for this study.

PHARMACOKINETIC RESULTS: Not applicable for this study.

SAFETY RESULTS:

- *Extent of exposure to study treatments*

The mean (± SD) extent of exposure to tocilizumab was 288.7 ± 74.8 days (median 311.0 days, range 1-351). Most of patients received 12 (33 patients, 56.9%) or 11 (12 patients, 20.7%) infusions.

- *Adverse events*

Fifty patients (86.2%) in the safety population had at least one TEAE. Drug-related TEAEs were observed in 49 patients (84.5%). Treatment-emergent SAEs were observed in 5 patients (8.6%): none of them was fatal. Two patients (3.4%) prematurely discontinued the study due to TEAEs. Dose modification due to TEAEs was required in 27 patients (46.6%).

With regard to drug-related TEAEs, infections and infestations (23 patients, 39.7%), investigations (21 patients, 36.2%), metabolism and nutrition disorders (12 patients, 20.7%) and skin and subcutaneous tissue disorders (12 patients, 20.7%) were the most commonly involved SOCs.

Hypercholesterolemia (11 patients, 19.0% [3 patients reported blood cholesterol increased]), neutropenia (8 patients, 13.8%; [one patient reported neutrophil count decreased]) and blood triglycerides increased (8 patients, 13.8% [2 patients reported hypertriglyceridemia]) were the most commonly reported drug-related TEAEs by PT.

The TESAEs consisted of tachycardia, upper limb fracture, non-Hodgkin's lymphoma, renal colic and hypertension, each in one patient. Only the case of hypertension was considered as drug-related.

- *Laboratory safety parameters*

The results of haematology parameters showed a decrease from baseline to any post-baseline time point in mean WBCs, neutrophils and platelets count. There were no important changes from baseline in the other haematology parameters.

The results of blood chemistry showed an increase from baseline to any post-baseline time point in mean values of AST, ALT, bilirubin (total, direct and indirect), total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides, and a decrease from baseline in mean alkaline phosphatase. There were no important changes from baseline in the other blood chemistry parameters.

- *Vital signs*

A small decrease from baseline to any post-baseline time point was observed in mean DBP and heart rate. There were no important changes from baseline in the other vital signs parameters, (except a small increase in mean body weight at any post-baseline time point).

CONCLUSIONS:

A 48-week treatment period with tocilizumab 8 mg/kg (but no more than 800 mg) in combination with DMARDs in RA patients not responsive to DMARDs therapy was associated with a statistically significant decrease from baseline to week 4 in wrist synovitis

SYNOPSIS OF RESEARCH REPORT PROTOCOL ML 22413

COMPANY: Roche S.p.A. NAME OF FINISHED PRODUCT: RoACTEMRA NAME OF ACTIVE SUBSTANCE(S): Tocilizumab	(FOR NATIONAL AUTHORITY USE ONLY)

evaluated with RAMRIS score developed by OMERACT. The improvements from baseline were observed as early as at two weeks from the start of treatment and were sustained up to week 48/end of study.

The quantitative assessment of the degree of synovitis by dynamic, gadolinium-enhanced MRI of the wrist showed statistically significant improvements in rate of early enhancement (initial curve slope, REE) from baseline to week 12, 24 and 48/end of study, and in relative enhancement (curve steady state, RE) from baseline to week 24. Statistically significant improvements from baseline to week 48/end of study were also observed in MRI parameters measured with the Dynamika® software (initial rate of enhancement [IRE], maximal enhancement [ME], total number of enhancing voxel [Ntotal], number of voxels with plateau [Nplateau], number of voxels with wash-out [Nwash-out], Ntotal*IRE and Ntotal*ME).

Mean bone marrow edema at the wrist and metacarpo-phalangeal sites significantly decreased from baseline to week 48/end of study, while bone erosion score did not progress.

A marked decrease from baseline in mean DAS-28 CRP (as well as in its components) was evident just after two weeks of treatment and was sustained up to week 48/end of study.

Significant improvements from baseline to week 48/end of study were observed for clinical parameters (Ritchie articular index, patient's and investigator's assessment of pain and disease activity, Stanford HAQ disability index, TJC-68 and SJC-66).

Mean VEGF concentration, ESR and hsCRP significantly decreased from baseline to any post-baseline time point, while mean haemoglobin levels rapidly increased from baseline and the increase was sustained up to the end of study.

The safety results were consistent with the known safety profile of tocilizumab.

Therefore, treatment with tocilizumab given in combination with DMARDs in patients with moderate to severe RA not responsive to DMARDs therapy was highly effective in the low-field dedicated MRI evaluation of changes from baseline of the synovial membrane enhancement in the wrist joints, and in improvements of clinical parameters, with no progression in bone erosion, and with an acceptable toxicity profile.