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CLINICAL STUDY REPORT NO: 1

STUDY INFORMATION

TITLE:	**PROSPECTIVE EVALUATION OF RHEUMATOID ARTHRITIS ACTIVITY USING DAS28 IN PATIENTS TREATED WITH SUBCUTANEOUSLY ADMINISTERED TOCILIZUMAB ON LOCAL LEVEL**
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STUDIED MEDICINAL PRODUCT:	RoActemra
COUNTRY OF STUDY POPULATION:	Slovakia
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1. SYNOPSIS/ABSTRACT

This clinical trial was early terminated by the Sponsor. Significant delay caused by pending approvals from Health's Insurance Companies, strict timelines for enrollment period required by the local legislation and pending recruitment led the Sponsor to the decision of early termination of the trial in Dec 2015 with two patients enrolled, completing just one and two visits, respectively. Collected data before the study termination represent less than 0,01 % of originally expected ones with no AE or SAE reported during that period. Such data do not allow evaluation of any primary or secondary objectives, therefore no statistical analysis was performed. Abbreviated Clinical Study report for the study ML29712 has been written to describe this situation.

Title

PROSPECTIVE EVALUATION OF RHEUMATOID ARTHRITIS ACTIVITY USING DAS28 IN PATIENTS TREATED WITH SUBCUTANEOUSLY ADMINISTERED TOCILIZUMAB ON LOCAL LEVEL.

Dr. Alan Majerník, Head of Clinical Operations, Roche Slovensko

Keywords

Tocilizumab s.c., Rheumatoid Arthritis, DAS 28 evaluation

Research Question and Objectives

Study objectives

- The assessment of RA activity based on the change in DAS 28 in Slovakia
- The assessment of joint function impairment based on HAQ in Slovakia

Study design

A prospective, non-interventional, multicentric phase IV clinical trial. Our goal is to perform a competitive recruitment up to the total number of 60 treated patients. Competitive screening (days -60 - 0) should last 12 months. When the number of patients reaches 60, they will be enrolled in the study (day 1 – commencement of the treatment) and the recruitment period will be closed. In some patients, the recruitment period may be extended by 3 months (-90 - 0) due to the positive quantiferon test. The treatment period is scheduled for 48 weeks. Day 1 is the day on which the 1st dose of tocilizumab is administered in the healthcare institution under the supervision of the healthcare staff.

Target Population• Signed informed consent

• Patients with moderate to severe active rheumatoid arthritis (DAS28 $\geqslant$ 3.2) who did not respond sufficiently to or did not tolerate previous treatment with one or several disease-modifying antirheumatic drugs (DMARDs), irrespective of whether they were of biological or synthetic nature.

• Patients eligible for the treatment with subcutaneously administered tocilizumab, as decided by the doctor in accordance with SPC and standard therapeutic procedures, who were not previously treated with tocilizumab and did not receive any other biological treatment for RA in the past either. Assignment of patients for observation using the treatment described above is clearly separated from the physician's decision to prescribe the treatment to the patient.

• Age ≥18

• Pulmonologist's consent with commencement of biological treatment. Pulmonary examination must include chest X-ray and quantiferon test.

Study size

In this study 2 patients have been enrolled across 3 open sites.

Studied medicinal product

RoActemra (tocilizumab) 162 mg solution for injection in a pre-filled syringe for subcutaneous use.

Variables

- RA activity evaluated based on the DAS 28 score – average change of the baseline values after 24 and of the baseline values after 48 weeks
- Percentage of participants achieving clinical remission defined as a DAS28 <2.6 at 12, 24, 36, and 48 week
- Percentage of participants achieving a DAS28 >=3.2 at 12, 24, 36, and 48 week
- Evaluation of participant's pain using visual analogue scale (VAS)
- Evaluation of the disease activity by participant using VAS
- Evaluation of the disease activity by Doctor using VAS
- Absolute and percentage change in the Health Assessment Questionnaire (HAQ). Data Sources

Source of study data will be the patient's medical records which include patient hospital/outpatient records, physician's and nurse's notes, original copies of laboratory findings, X-ray scans, pathology and other specialized reports, signed informed consent forms, HAQ questionnaire and other questionnaires, etc.

Statistical and Epidemiological Methods

All parameters investigating treatment efficiency will be evaluated using descriptive statistic methodologies and presented in sequence in summary tables.

Results

This clinical trial was early terminated by the Sponsor. Only two patients were enrolled, completing just one and two visits, respectively. Collected data before the study termination represent less than 0,01 % of originally expected ones with no AE or SAE reported during that period. Such data do not allow evaluation of any primary or secondary objectives, therefore no statistical analysis was performed.

Conclusions

This clinical trial was early terminated by the Sponsor. Significant delay caused by pending approvals from Health's Insurance Companies, strict timelines for enrollment period required by the local legislation and pending recruitment led the Sponsor to the decision of early termination of the trial in Dec 2015 with two patients enrolled, completing just one and two visits, respectively. Collected data before the study termination represent less than 0,01 % of originally expected ones with no AE or SAE reported during that period. Such data do not allow evaluation of any primary or secondary objectives, therefore no statistical analysis was performed. Abbreviated Clinical Study report for the study ML29712 has been written to describe this situation.

2. LIST OF ABBREVIATIONS

Abbreviation	Deffinition
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CRF	Case Report Form
CRP	C-reactive protein
CYP	cytochrome P
DAS 28	disease activity score
DMARDS	disease-modifying antirheumatic drugs
ESR	erythrocyte sedimentation rate
GMT	glutamate transaminase
HbsAg	hepatitis B antigen
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HAQ	Health Assessment Questionnaire for the assessment of joint function impairment
ICH	International Conference on Harmonisation
IL-6	interleukin 6
CBC	complete blood count
MTX	methotrexate
AE	adverse event
QFN	quantiferon
RA	rheumatoid arthritis
X-ray	pertaining to X-ray exam
RF	rheumatoid factor
SAE	Serious adverse event
SPC	Summary of Product Characteristics
SIDC	State Institute for Drug Control
TNF	tumour-necrosis factor
VAS	Visual Analogue Scale

3. MILESTONES

Milestone	Planned Date
Approval of the protocol by EC	13-Jan-2015
Start of data collection	01-Jul-2015
End of data collection	01-Dec- 2015
Study Progress Report No. 1	NA
Study Progress Report No. 2	NA
Study Progress Report No. 3	NA
Interim Report No. 1	NA
Interim Report No. 2	NA
Interim Report No. 3	NA
Registration in the EU PAS registry	NA
Final Report of Study Results	NA, study was early terminated by Sponsor
{Any other important timeline in the conduct of the study}	Abbreviated CSR 22-Sep 2016

4. RATIONALE AND BACKGROUND

Rheumatoid arthritis (RA) is a chronic progressive disease. Clinical manifestations, course and prognosis are very heterogeneous, usually with a progressive impairment of joint function, development of deformities and gradual transition to functional incapability (disability) which significantly affects the quality of life,[1] incapability to work and restricts social activities of patients. Ten years of disease leads to the functional impairment and joint abnormalities in more than 80% of patients[2] with less than 50% being employed.[3] The estimated life expectancy is shortened by 3-10 years.[4]

Treatment paradigms in case of RA are as follows: early initiation of treatment because irreversible destructive changes appear early; monitoring of disease activity is essential for therapeutic judgement,[5] the treatment goal is disease activity control and achievement of remission.

From July 1, 2009, Professional Guideline of the Ministry of Health of the Slovak Republic on impartial judgement of the activity and joint function destruction in RA patients became valid. Evaluation of RA treatment effectiveness requires impartial judgement of the activity and joint function before treatment and in regular, 12- to 24-week intervals in the course of the treatment.[6]

Patients with moderate to severe RA often require modifications of the treatment regimen with moving to the biological therapy at regular intervals. Patients must actively cooperate in evaluation of RA activity using questionnaires.

Since 2009, RoActemra with tocilizumab as the active substance is available for biological treatment of RA. Inhibition of interleukin 6 represents unique mechanism of action with rapid onset and high anti-inflammatory effect on systemic manifestations of the disease.[7] According to experience with tocilizumab obtained to date, more than 90% of patients in clinical trials wished to continue treatment after study completion. According to an international study (Summacta[8]), the subcutaneous form of the drug is just as effective as its intravenous form of application. Based on this we assume that in real clinical practice patients would adhere to the tocilizumab therapy and cooperate so that we can obtain data on the assessment of RA activity in accordance with the Expert Guideline of the Ministry of Health of the Slovak Republic No. 10646/2009.

5. RESEARCH QUESTIONS AND OBJECTIVES

Primary effectiveness objective in this trial is:

- The assessment of RA activity based on the change in DAS 28 in Slovakia

Secondary effectiveness objectives in this trial are:

- The assessment of joint function impairment based on HAQ in Slovakia.

6. AMENDMENTS AND UPDATES TO PROTOCOL

Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	15-Jan-2015	8.1.3	Update	Administrative - Change of participating site
2	06-Feb-2015	Several parts	Amendment	Substantial Amendment of observed procedures, study population criteria and statistical analysis

7. RESEARCH METHODS

This clinical trial was early terminated by the Sponsor. Collected data before the study early termination represent less than 0,01 % of originally expected with no AE or SAE reported during that period. Such data do not allow evaluation of any primary or secondary objectives, therefore no statistical analysis was performed.

7.1 STUDY DESIGN

Prospective, non-interventional, multicentric clinical study. Patients with moderate to severe active rheumatoid arthritis who are eligible for the treatment with tocilizumab in accordance with SPC and standard therapeutic procedures as decided by the physician will be enrolled in the clinical trial.

7.2 SETTING

Week	SCREENING 8 (12*) weeks Before commencement of the treatment	VISITS						FINAL VISIT Early termination of the clinical trial[A]
		BASELINE (commencement of the tocilizumab treatment)	Week 4 ± 7 days	Week 8 ± 7 days	Week 12 ± 14 days	Week 24 ± 14 days	36 ± 14 days	48 ± 14 days
Day	-60 (-90)* to 0	1	28 ± 7 days	56 ± 7 days	84 ± 14 days	168 ± 14 days	252 ± 14 days	336 (±14 days)

7.3 PATIENTS

Patients with moderate to severe RA often require modifications of the treatment regimen with moving to the biological therapy at regular intervals. Patients must actively cooperate in evaluation of RA activity using questionnaires.

Inclusion criteria:

- Signed informed consent
- Patients with moderate to severe active rheumatoid arthritis (DAS28 ≥ 3.2) who did not respond sufficiently to or did not tolerate previous treatment with one or several disease-modifying antirheumatic drugs (DMARDs), irrespective of whether they were of biological or synthetic nature.
- Patients eligible for the treatment with subcutaneously administered tocilizumab, as decided by the doctor in accordance with SPC and standard therapeutic procedures, who were not previously treated with tocilizumab and did not receive any other biological treatment for RA in the past either. Assignment of patients for observation using the treatment described above is clearly separated from the physician's decision to prescribe the treatment to the patient.
- Age ≥18
- Pulmonologist's consent with commencement of biological treatment. Pulmonary examination must include chest X-ray and quantiferon test.

Exclusion criteria:

- Known hypersensitivity to the drug or any of its ingredients
- Age < 18 years
- Pregnancy and breastfeeding
- Active infection
- Active tuberculosis
- HBsAg, HCV or HIV positivity
- History of severe allergic or anaphylactic responses to human or humanized murine monoclonal antibodies
- History of intestinal ulcerations or diverticulitis

- Active hepatopathy with more than threefold increase of ALT or AST
- Thrombocytes < 100,000/mm^3, Le < 3,000 mm^3, absolute neutrophil count < 2,000 mm^3
- Uncontrolled hyperlipoproteinemia
- Demyelinating diseases
- Serious cardiovascular diseases
- Patients with history of malignancy in the previous 5 years
- Women of childbearing age (without medically confirmed sterility, e.g. following hysterectomy, ovariectomy, menopause lasting 2 years) who do not accept the use of a suitable form of contraception (e.g. barrier methods of contraception in the patient and partner, contraceptive pills or patches, hormonal implants, spermicidal agents in combination with barrier method of contraception, intrauterine device)
- Current treatment with TNF inhibitors
- Overlap syndrome – moderate and extremely serious RA in combination with health status or diseases mentioned in SmPC (special warnings and precautions for use)

7.4 VARIABLES

7.4.1 Primary Effectiveness Variable

- RA activity evaluated based on the DAS 28 score – average change of the baseline values after 24 and of the baseline values after 48 weeks.

7.4.2 Secondary Effectiveness Variable

- Percentage of participants achieving clinical remission defined as a DAS28 <2.6 at 12, 24, 36, and 48 week
- Percentage of participants achieving a DAS28 >=3.2 at 12, 24, 36, and 48 week
- Evaluation of participant's pain using visual analogue scale (VAS)
- Evaluation of the disease activity by participant using VAS
- Evaluation of the disease activity by Doctor using VAS
- Absolute and percentage change in the Health Assessment Questionnaire (HAQ)

7.4.3 Safety Variables

Collected data before the study early termination represent less than 0,01 % of originally expected ones with no AE or SAE reported during that period.

7.4.4 Other Variables of Interest Not applicable

7.5 DATA SOURCE(S) AND MEASUREMENT

This clinical trial was early terminated by the Sponsor. Collected data before the study early termination represent less than 0,01 % of originally expected with no AE or SAE reported during that period. Such data do not allow evaluation of any primary or secondary objectives, therefore no statistical analysis was performed.

7.6 BIAS

NA, see the above section

7.7 DATA TRANSFORMATION

NA, see the above section

7.7.1 Safety Analyses

This clinical trial was early terminated by the Sponsor. Collected data before the study early termination represent less than 0,01 % of originally expected with no AE or SAE reported during that period. Such data do not allow evaluation of any safety analysis, therefore no statistical analysis was performed.

7.7.2 Effectiveness Analyses

This clinical trial was early terminated by the Sponsor. Collected data before the study early termination represent less than 0,01 % of originally expected with no AE or SAE reported during that period. Such data do not allow any effectiveness analyses, therefore no statistical analysis was performed.

7.7.3 Other Analyses

7.7.4 Interim and Final Analysis and Timing of Analyses

This clinical trial was early terminated by the Sponsor. Collected data before the study early termination represent less than 0,01 % of originally expected with no AE or SAE reported during that period. Such data do not allow evaluation of any primary or secondary objectives, therefore no statistical analysis was performed.

7.8 STATISTICAL METHODS

Not applicable - No statistical analysis was performed.

7.8.1 Amendments to the Statistical Analysis Plan

Not applicable - No amendments statistical analysis was performed.

7.8.2 Statistical Considerations and Planned Sample Size

Bilateral 95% confidence interval corresponding with bilateral 5% significance level was planned to be used in the analysis. All relevant data should have been collected in tabular form and described using descriptive statistics with the following structure: average value and standard error for continuing variables and frequencies for category variables. Due to early termination of trial no statistical consideration was performed.

7.8.3 Sample size justification

Study has been planned as s open label, explorative trial; therefore the analysis of primary effectiveness had to be assessed by methods of descriptive statistics. Since this is an exploratory trial, the sample size of enrolled patient has not been calculated. Decision on the number of enrolled patients is based on practical and real assumptions regarding the possibility of individual sites to enroll suitable patients into the study.

This clinical trial was early terminated by the Sponsor. Collected data before the study early termination represent less than 0,01 % of originally expected with no AE or SAE reported during that period. Such data do not allow evaluation of any primary or secondary objectives, therefore no statistical analysis was performed.

7.9 QUALITY CONTROL

Not applicable - No statistical analysis was performed.

8. RESULTS

This clinical trial was early terminated by the Sponsor. Only two patients were enrolled, completing just one and two visits, respectively. Collected data before the study termination represent less than 0,01 % of originally expected ones with no AE or SAE reported during that period. Such data do not allow evaluation of any primary or secondary objectives, therefore no statistical analysis was performed.

8.1 PATIENT POPULATION

Only two patients were enrolled, completing just one and two visits, respectively.

8.2 DESCRIPTIVE DATA

Patients were female and male, age categories 40 - 50 and 50 – 60 years old. RA was diagnosed more than 12 months before enrollment.

8.3 OUTCOME DATA

Not applicable - No statistical analysis performed.

8.4 MAIN RESULTS

This clinical trial was early terminated by the Sponsor. Significant delay caused by pending approvals from Health's Insurance Companies, strict timelines for enrollment period required by the local legislation and pending recruitment led the Sponsor to the decision of early termination of the trial in Dec 2015 with two patients enrolled, completing just one and two visits, respectively. Collected data before the study termination represent less than 0,01 % of originally expected ones with no AE or SAE reported during that period. Such data do not allow evaluation of any primary or secondary objectives, therefore no statistical analysis was performed.

8.5 OTHER ANALYSES

Not applicable - No other analysis performed.

8.6 ADVERSE EVENTS AND ADVERSE REACTIONS

No adverse event, no serious adverse event and no adverse reaction were reported.

9. DISCUSSION

9.1 KEY RESULTS

This clinical trial was early terminated by the Sponsor. Significant delay caused by pending approvals from Health's Insurance Companies, strict timelines for enrollment period required by the local legislation and pending recruitment led the Sponsor to the decision of early termination of the trial in Dec 2015 with two patients enrolled, completing just one and two visits, respectively. Collected data before the study termination represent less than 0,01 % of originally expected ones with no AE or SAE reported during that period. Such data do not allow evaluation of any primary or secondary objectives, therefore no statistical analysis was performed. Abbreviated Clinical Study report for the study ML29712 has been written to describe this situation.

9.2 LIMITATIONS

Not applicable.

9.3 INTERPRETATION

Not applicable - This clinical trial was early terminated by the Sponsor. Collected data before the study early termination represent less than 0,01 % of originally expected with no AE or SAE reported during that period. Such data do not allow evaluation of any primary or secondary objectives, therefore no statistical analysis was performed.

9.4 GENERALIZABILITY

Not applicable - This clinical trial was early terminated by the Sponsor. Collected data before the study early termination represent less than 0,01 % of originally expected with no AE or SAE reported during that period. Such data do not allow evaluation of any primary or secondary objectives, therefore no statistical analysis was performed.

10. OTHER INFORMATION

Not applicable.

11. CONCLUSION

This clinical trial was early terminated by the Sponsor. Significant delay caused by pending approvals from Health's Insurance Companies, strict timelines for enrollment period required by the local legislation and pending recruitment led the Sponsor to the

decision of early termination of the trial in Dec 2015 with two patients enrolled, completing just one and two visits, respectively. Collected data before the study termination represent less than 0,01 % of originally expected ones with no AE or SAE reported during that period. Such data do not allow evaluation of any primary or secondary objectives, therefore no statistical analysis was performed. Abbreviated Clinical Study report for the study ML29712 has been written to describe this situation.

12. REFERENCES

1. Čalfová A. Interná med. 2009; 9 (12): 574-577
2. Burton et al. Occup Med (Lond) 2006;56:18–27
3. NICE Rheumatoid Arthritis Consultation Document 2006; www.nice.org.uk
4. Gaffo A, et al. Am J Health Syst Pharm 2006; 63:2451–2465
5. Rovenský J. a spol. Klinická reumatológia. 2000, s. 237
6. Expert Guideline issued by the Ministry of Health of the Slovak Republic on impartial judgement of activity and joint function destruction in patients with rheumatoid arthritis. Official Journal of the Ministry of Health of the Slovak Republic 2009: No. 10646, item 25: 178-188
7. Smolen J, et al. Lancet 2008; 371:987–997 (OPTION Study)
8. Burmester GR, et al. Ann Rheum Dis 2014;73: 69-74