19 November 2015
EMA/CHMP/825080/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cimzia

International non-proprietary name: certolizumab pegol

Procedure No. EMEA/H/C/001037/II/0045

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACPA	anticyclic citrullinated peptide antibody
ACR	American College of Rheumatology
ACR20/50/70	American College of Rheumatology response of 20%, 50% or 70%
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bDMARD	biological disease-modifying antirheumatic drug
BMI	body mass index
BRAF-MDQ	Bristol RA fatigue- multdimensional questionnaire
CDAI	clinical disease activity index
CRP	C-reactive protein
CS1	Completer Set Period 1
CZP	certolizumab pegol
DAS28(ESR)	disease activity score based on evaluation of 28 joints and erythrocyte sedimentation rate
DMARD	disease-modifying antirheumatic drug
EQ-5D-3L	EuroQoL-5 Dimension 3 Level Questionnaire
ER	emergency room
ESR	erythrocyte sedimentation rate
EU	European Union
EU-SmPC	European Union- Summary of Product Characteristics
EULAR	European League Against Rheumatism
FAS1	Full Analysis Set Period 1
Fc	fragment crystallizable
HAQ-DI	Health Assessment Questionnaire – Disability Index
HLT	higher level term
HRQoL	health-related quality of life
IgG	immunoglobulin G
ISS	Integrated Summary of Safety
JSN	joint space narrowing
LDA	low disease activity
LFT	liver function test
LS	least squares
MCID	minimum clinically important difference
MACE	major adverse cardiac event
MCS	mental component summary

MedDRA®	Medical Dictionary for Regulatory Activities
mTSS	van der Heijde modified total sharp score
MTX	methotrexate
NEC	not elsewhere classified
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
PASS	Patient Acceptable Symptom State
PBO	placebo
PCS	Physical Component Summary
PEG	polyethylene glycol
PF	Physical Functioning (an SF-36 domain)
PK	pharmacokinetic
PKS1	Pharmacokinetic Set 1
po	per os
PPD	protein purified derivative
PPS1	Per-Protocol Set Period 1
PT	preferred term
pt-yrs	patient-years
PtAAP	Patient Assessment of Arthritis Pain
PtGADA	Patient Global Assessment of Disease Activity
Q2W	every two weeks
RA	rheumatoid arthritis
RAD1	Radiographic Set Period 1
RF	rheumatoid factor
RS1	Randomized Set 1
SAE	Serious Adverse Event
sc	subcutaneous(ly)
SDAI	simplified disease activity index
SF-36	Short-Form 36-item Health Survey
SJC	swollen joint count
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SOC	system organ class
SS1	Safety Set 1
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNFα	tumor necrosis factor alpha

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, UCB Pharma SA submitted to the European Medicines Agency on 4 February 2015 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I

Extension of indication to include treatment of severe, active and progressive rheumatoid arthritis in adults not treated previously with methotrexate or other disease-modifying antirheumatic drugs (DMARDs); as a consequence, sections 4.1, 4.8 and 5.1 of the SmPC were proposed to be revised in order to update the efficacy and safety information.

The requested variation proposed amendments to the Summary of Product Characteristics.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0295/2013 on the agreement of a paediatric investigation plan (PIP) and on the granting of a class waiver.

At the time of submission of the application, the PIP EMEA-C1-001071-PIP02-12-M01 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Kristina Dunder Co-Rapporteur: Agnes Gyurasics

Timetable	Actual dates
Submission date	4 February 2015
Start of procedure:	20 February 2015
CHMP Rapporteur Assessment Report	17 April 2015
CHMP Co-Rapporteur Assessment Report	6 May 2015
CHMP comments	11 May 2015
Rapporteur Revised Assessment Report	13 May 2015
Request for supplementary information (RSI)	21 May 2015
CHMP Joint Rapporteurs Assessment Report	30 October 2015
CHMP comments	9 November 2015
Opinion	19 November 2015

2. Scientific discussion

2.1. Introduction

Cimzia (certolizumab pegol (CZP)), is a monoclonal antibody and biological disease-modifying anti-rheumatic drug (bDMARD). It consists of a recombinant, humanized antibody Fab' fragment expressed in *Escherichia coli* and is conjugated to polyethylene glycol (PEG). In contrast to other members of the class it does not contain an immunoglobulin G (IgG) fragment crystallisable (Fc) region.

CZP selectively neutralises human TNFα, a major pro-inflammatory cytokine contributing to the pathogenesis of RA.

In the EU, Cimzia, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe, active rheumatoid arthritis (RA) in adult patients when the response to disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate, has been inadequate. Cimzia can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Cimiza has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with MTX.

It is now accepted that during early stages of RA, there is a therapeutic opportunity to maximize control of signs and symptoms, limit joint damage, and improve physical function (Sesin and Bingham, 2005; Cush, 2007). In this context, besides MTX and/or other conventional DMARDs, which are recommended as first line therapies, some patients may need to start with a combination of a MTX plus a biologic DMARD. Three TNF-inhibitors are currently approved in the EU for patients with severe, active, and progressive RA not previously treated with MTX (adalimumab, etanercept, golimumab) and 1 for patients not previously treated with MTX or other DMARDs (infliximab).

The current type II variation application was to extend the current indication for CZP to include adult patients with severe, active, and progressive RA not previously treated with MTX or other DMARDs.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

Certolizumab pegol is a recombinant, humanized antibody Fab' fragment against tumour necrosis factor alpha (TNFα), conjugated to polyethylene glycol (PEG) and in accordance with the CHMP guideline on the environmental risk assessment (EMEA/CHMP/SWP/4447/00) is exempted from testing because of its chemical structure.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study title (number)	Objective	Study design	Treatments	Number of subjects	Duration of treatment	Study status
RA0055 (C-EARLY)	Efficacy and safety	A multi-centre randomised double-blind, parallel-group, placebo-controlled	Period 1: 400 mg at weeks 0, 2 and 4 + MTX followed by 200 mg Q2W+MTX or PBO at weeks 0, 2 and 4 +MTX followed by PBO Q2W+MTX Period 2: 200 mg Q2W+ MTX or 200 mg Q4W + MTX or PBO + MTX sc	879 randomised in Period 1	Period 1: 52 weeks Period 2: 52 weeks (from W52 to W104)	Period 1 complete/ Period 2 ongoing
RA0096 (C-OPERA)	Efficacy and safety	A multi-centre randomised double-blind, parallel-group, placebo-controlled	400 mg at Weeks 0, 2, 4 followed by 200 mg Q2W + MTX or PBO + MTX	319 randomised in Period 1	52 weeks with follow-up period extending until week 104	Period 1 complete/ Period 2 ongoing

2.3.2. Pharmacokinetics

The pharmacokinetic profile of CZP has been described previously in healthy subjects and RA patients. Following subcutaneous administration, Tmax is 54 to 171 hours and bioavailability is approximately 80% (range 76% to 88%). The terminal elimination phase half-life is approximately 14 days.

There were no new clinical pharmacology data except for the CZP plasma concentration data and the immunogenicity data from study RA0055 (the study is described in detail under Clinical efficacy).

The PK variable for this study included pre-dose CZP plasma concentration at Baseline and Weeks 2, 4, 8, 12, 20, 24, 36, 40, and 52/Withdrawal Visit. The observed CZP concentrations are summarised in **Table 1**.

Table 1. Summary statistics of observed CZP concentrations in study RA0055

Visit	CZP+MTX N=659					
	n	Geo. mean (µg/mL)	(95% CI)	Geo. CV (%)	Median (µg/mL)	Min, max (µg/mL)
Week 0 (Baseline)	651	0.417	(0.386, 0.451)	1.314	0.205	0.21, 120.09
Week 2	646	26.769	(25.796, 27.779)	0.508	27.720	0.21, 145.00
Week 4	629	37.998	(36.461, 39.599)	0.566	40.160	0.21, 150.66
Week 8	614	29.677	(28.018, 31.434)	0.833	34.035	0.21, 144.12
Week 12	606	21.879	(20.548, 23.297)	0.926	26.255	0.21, 129.40
Week 20	577	18.594	(17.278, 20.011)	1.114	22.670	0.21, 60.48
Week 24	542	19.099	(17.756, 20.542)	1.053	23.055	0.21, 67.92
Week 36	529	17.743	(16.187, 19.448)	1.473	23.350	0.21, 145.27
Week 40	512	18.579	(16.993, 20.313)	1.369	23.470	0.21, 142.91
Week 52	500	17.589	(16.049, 19.277)	1.403	23.055	0.21, 84.47

CI=confidence interval; CV=coefficient of variation; CZP=certolizumab pegol; geo.=geometric; max=maximum; min=minimum; MTX=methotrexate; PKS1=Pharmacokinetics Set 1

Note: Values below the limit of quantification of 0.41µg/mL were set to half the limit of quantification for the calculation of descriptive statistics.

Anti-CZP antibodies were assessed at Baseline, Weeks 2, 4, 8, 12, 20, 24, 36, 40, and 52/Withdrawal Visit. Subjects who were positive for anti-CZP antibodies (63 subjects [9.6%]) had lower mean (geometric) plasma CZP concentrations at Weeks 8 through 52 compared with subjects who were negative for anti-CZP antibodies. The immunogenicity in DMARD-naïve patients was similar to that reported for previous RA placebo-controlled studies (9.6% Section 5.1, SmPC). The trend and magnitude of effect on CZP plasma concentration in anti-CZP antibody positive subjects was consistent with previous experience with CZP.

2.3.3. Conclusions on clinical pharmacology

There were no new clinical pharmacology data except for CZP plasma concentration data and the immunogenicity data from study RA0055. This was acceptable given the available data from previous studies in healthy subjects and RA patients. The PK profile appeared to be consistent with expectations based on previous studies of CZP in RA patients. The effect of anti-CZP antibody formation on CZP plasma

concentration was shown to be consistent with previous experience and thus adequately addressed in the current SmPC text.

2.4. Clinical efficacy

The clinical program to support the expansion of the indication consists of a single study, RA0055 (Period 1) and supportive data from the following sources:

- Japanese study RA0096 in early RA patients who were naïve to MTX, leflunomide, and biological DMARDs.

2.4.1. Main study

RA0055

A multi-centre, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of certolizumab pegol in combination with methotrexate for inducing and sustaining clinical response in the treatment of DMARD-naïve adults with early active rheumatoid arthritis (C-Early).

Methods

Study participants

Inclusion criteria

The main inclusion criteria were:

1. Subject was male or female and must have been at least 18 years old at the Screening Visit.
2. Subjects must have had a time since diagnosis of adult-onset RA less than 1 year as defined by the 2010 ACR/EULAR classification criteria from Screening Visit.
3. Subjects must have been DMARD-naïve at Screening and Baseline (except anti-malarials).
4. Subjects must have had a positive RF or positive anticyclic citrullinated peptide antibody (ACPA) result at Screening.
5. Subjects must have had Active RA disease as defined by:
    - ≥4 swollen joints and ≥4 tender joints (DAS28) at Screening and Baseline
    - DAS28(ESR) >3.2 at Screening and Baseline
    - C-reactive protein (CRP) ≥10mg/L at Screening and/or ESR ≥28mm/h at Screening and Baseline.

Exclusion criteria

The main exclusion criteria are listed below:

1. Female subjects who were breastfeeding, pregnant, or planned to become pregnant during the study or within 6 months following the last dose of study medication.

2. The subject had previously participated in this study and had received CZP treatment, or had previously received CZP in or outside of another clinical study.

3. Subjects must not have received any experimental non-biological therapy in the 3 past months or within 5 half-lives prior to Baseline (whichever was longer).

4. Subjects must not have received any experimental or approved biological agent (eg, anti-TNFα therapy, anti-interleukin 1 [IL1], or interleukin 6 [IL6], etc) prior to Baseline.

5. Subjects must not have had a secondary, noninflammatory type of musculoskeletal condition (eg, osteoarthritis or fibromyalgia) that in the Investigator's opinion was symptomatic enough to interfere with evaluation of the effect of study medication on the subject's primary diagnosis of RA.

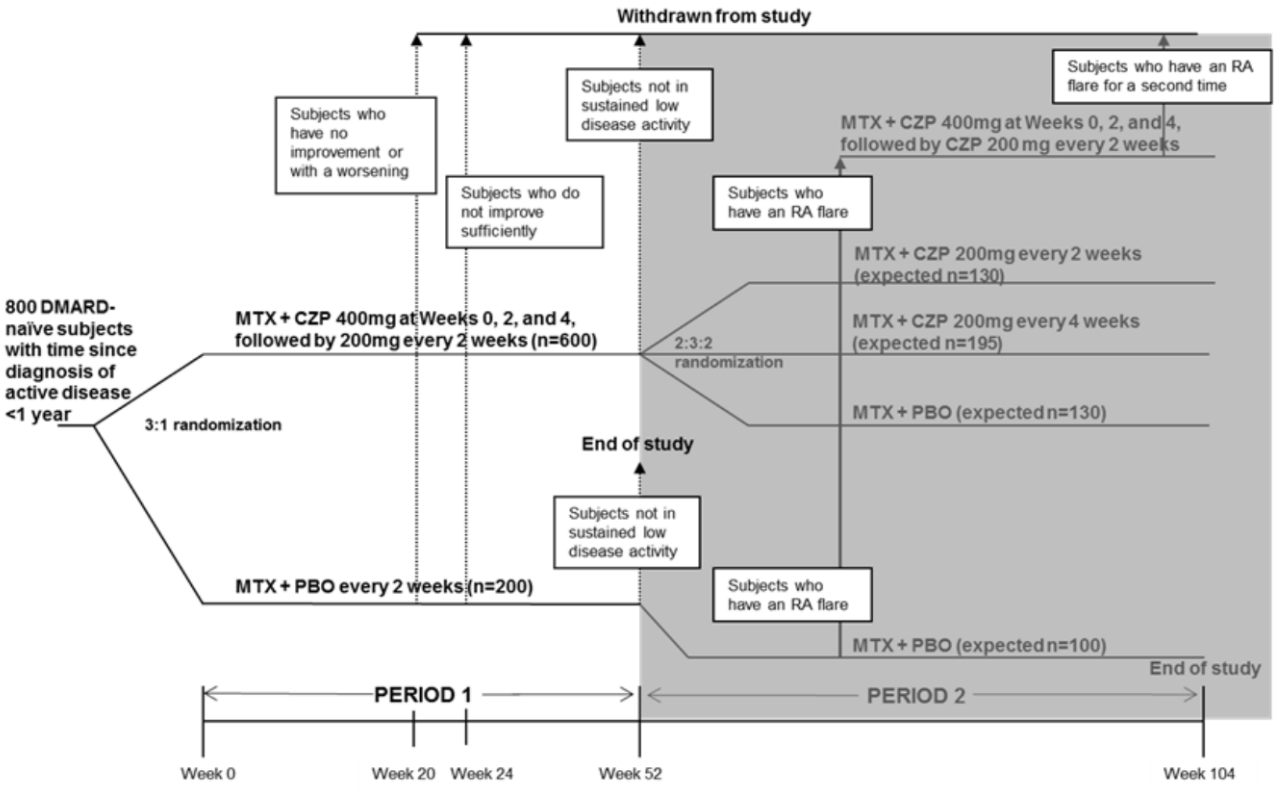
6. Subjects must not have had a diagnosis of any other inflammatory arthritis (eg, psoriatic arthritis or ankylosing spondylitis) nor have had a Steinbrocker IV functional capacity.

Treatments

The study comprised of 2 periods: Period 1 (Week 0 to Week 52) and Period 2 (Week 52 to Week 104) which was ongoing at the time of submission.

The study design is presented **in Figure 1.**

Figure 1. Study design of RA0055



Randomisation was performed centrally and eligible subjects were stratified by the time since diagnosis of RA at Baseline (≤4 months and >4 months). Subjects in each stratum were then randomly assigned to the CZP+MTX or placebo (PBO)+MTX treatment arms in a 3:1 ratio. The treatments and treatment regimens in each arm were as follows:

CZP+MTX treatment arm

- CZP 400mg subcutaneously (sc) at Weeks 0, 2, and 4
- CZP 200mg sc every 2 weeks [Q2W]) from Week 6 until Week 50
- MTX per os (po) once weekly from Week 0 until Week 51

PBO+MTX treatment arm

- Placebo sc Q2W from Week 0 until Week 50
- MTX po once weekly from Week 0 until Week 51

Subjects were to receive CZP or PBO injections at their clinic visits from qualified study personnel at the first 3 visits (Weeks 0, 2, and 4) and were to receive training on how to perform the injections to ensure proper and safe administration of the study drug at home. Subjects who were unable to self- administer CZP or those without a family member/friend/caregiver who could help were not to be discontinued but could continue to visit the site for only study treatment administration.

Subjects were to initiate MTX at 10mg/week and rapidly escalate the dose by 5mg Q2W to a maximum of 25mg/week by Week 6 to 8. Subjects who did not tolerate at least 15mg/week were withdrawn. Subjects maintained the maximum tolerated dose of MTX reached by Week 8 during the remaining study period. The protocol strongly recommended the use of a medicinal formulation of folic acid or leucovorin or antiemetics to control MTX side effects.

Rescue medication

The use of rescue medication was allowed in this study under the conditions described in **Table 2**.

Table 2. Rescue medication in Study RA0055

Drug class	Dose/conditions
Intra-articular corticosteroids	Two injections of up to 80mg methylprednisolone or equivalent each were allowed when needed up to Week 34. Injections must have been separated by at least 1 month and could not have been given in the same joint.
Analgesics or opioids	Any dose regimen higher than Baseline dose was not allowed within 48 hours prior to clinical efficacy assessments.
NSAIDs/COX-2 Inhibitors	If a stable regimen of NSAIDs and COX-2 inhibitors was established at Baseline, tapering/changes may have been done between Week 4 and Week 14 and between Week 24 and Week 34 but at no time was the Baseline dose to have been exceeded. As needed use of NSAIDs and COX-2 inhibitors were permitted. Unless on stable dose NSAIDs/COX-2 inhibitors should not have been used within 24 hours of the clinical efficacy assessments, except for piroxicam, meloxicam, and diflunisal, which may not have been used within 72 hours of the clinical efficacy assessment.
Topical anesthetic creams (eg, lidocaine/prilocaine creams) and licensed NSAID creams	Were permitted except within 24 hours prior to clinical efficacy assessments.

COX-2=cyclooxygenase-2; NSAID=nonsteroidal anti-inflammatory drug

Objectives

The primary objective was to demonstrate that the combination of CZP+MTX was superior to PBO+MTX in achieving sustained remission by Week 52.

The key secondary objective was to demonstrate that in DMARD-naïve subjects with adult-onset, early, active RA present for less than 1 year that the combination therapy of CZP+MTX was superior to PBO+MTX in achieving sustained LDA at Week 52.

Other secondary objectives were to compare the efficacy of CZP+MTX to PBO+MTX based on the following measures:

- Radiographic progression
- Clinical response
- Patient-reported outcomes
- Productivity within and outside home

The PK and immunological objectives were as follows:

- To evaluate the CZP and anti-CZP antibody concentrations during Period 1
- To evaluate the autoantibody (antinuclear antibody [ANA]) levels and anti–double-stranded deoxyribonucleic acid [anti-dsDNA] antibodies) levels

The safety objectives were as follows:

- To evaluate the tolerability and safety of the CZP+MTX combination therapy and PBO+MTX monotherapy

Outcomes/endpoints

The primary endpoint for Period 1 of the study was sustained remission (defined as a disease activity score based on evaluation of 28 joints and erythrocyte sedimentation rate (DAS28 [ESR]) <2.6 at Week 40 and Week 52 Visits) at Week 52.

Key secondary endpoint was sustained low disease activity (DAS28 [ESR]) ≤3.2at Week 40 and Week 52 Visits) at week 52.

Other secondary endpoints (selected)

Radiographic variables assessed from Baseline to Week 52 were as follows:

- The change in the van der Heijde modified total Sharp score (mTSS)
- The proportion of subjects with radiographic nonprogression, defined as change in mTSS ⩽0.5
- The change in joint erosion score
- The change in joint space narrowing (JSN) score

Clinical variables assessed at Weeks 12, 24, and 52/Withdrawal Visit:

- The American College of Rheumatology 20% (ACR20), 50% (ACR50), and 70% (ACR70) response in relation to Baseline
- The proportion of subjects achieving a good or moderate EULAR clinical response (according to the DAS28[ESR]-based EULAR response criteria)

- The changes from Baseline in individual components of the ACR criteria, including TJC, SJC, Health Assessment Questionnaire-Disability Index (HAQ-DI), Patient's Assessment of Arthritis Pain (PtAAP), Patient Global Assessment of Disease Activity (PtGADA), Physician's Global Assessment of Disease Activity (PhGADA), CRP (ratio to Week 0), and ESR (ratio to Week 0)
- The changes from Baseline in DAS28(ESR), Clinical Disease Activity Index (CDAI), and Simplified Disease Activity Index (SDAI)
- The proportion of subjects achieving LDA (DAS28[ESR] $\leqslant$3.2)
- The proportion of subjects in remission as defined by 5 separate criteria:
    - the new ACR/EULAR 2011 remission criteria (TJC ≤1, SJC ≤1, CRP ≤10mg/L, and PtGADA ≤10mm)
    - the new ACR/EULAR 2011 remission criteria simplified for clinical practice (TJC ≤1, SJC ≤1, and PtGADA ≤10mm)
    - DAS28(ESR) <2.6
    - CDAI ≤2.8
    - SDAI ≤3.3

Other efficacy variables (selected):

- The ACR20, ACR50, ACR70 response rate at Weeks 2, 4, 6, 8, 20, 36, and 40.
- Proportion of subjects achieving LDA (DAS28[ESR] ≤3.2) at Weeks 2, 4, 6, 8, 20, 36, and 40.
- The proportion of subjects achieving a good or moderate EULAR clinical response (according to the DAS28(ESR)-based EULAR response criteria) at Weeks 2, 4, 6, 8, 20, 36, and 40.
- The changes from Baseline in individual components of the ACR criteria, including TJC, SJC, HAQ-DI, PtAAP, PtGADA, PhGADA, CRP (ratio to Week 0) and ESR (ratio to Week 0) at Weeks 2, 4, 6, 8, 20, 36, and 40.
- The changes from Baseline in DAS28 (ESR), CDAI, and SDAI at Weeks 2, 4, 6, 8, 20, 36, and 40.
- The proportion of subjects in remission at Weeks 2, 4, 6, 8, 20, 36, and 40 as defined by 5 separate criteria:
    - the new ACR/EULAR 2011 remission criteria (TJC ≤1, SJC ≤1, CRP ≤10mg/L and PtGADA ≤ 10mm [on a scale of 0 to 100mm]);
    - the new ACR/EULAR 2011 remission criteria simplified for clinical practice (TJC ≤1, SJC ≤ 1 and PtGADA ≤ 10mm [on a scale of 0 to 100mm]);
    - DAS28(ESR) <2.6;
    - CDAI ≤2.8;
    - SDAI ≤3.3.

Sample size

A total of 800 subjects were planned to be enrolled in this study. Approximately 1067 subjects were planned to be screened in order to enrol 800.

The sample size calculation was based on the period 1 primary efficacy variable, and, was calculated using a two-group continuity-corrected chi-square test with a 2-sided significance level of 0.05. The calculation was based on an expected proportion of subjects in sustained remission of 50% and 30% in the CZP+MTX treatment group and, the PBO+MTX treatment group, respectively. Given a 3:1 randomization, 600 subjects in the CZP+MTX arm and 200 subjects in the PBO+MTX treatment group, a power of 99% was achieved.

Randomisation

For Period 1, subjects were randomized at Week 0. The randomization schedule was produced by a biostatistician not otherwise involved in this study. Randomisation was performed centrally using an interactive voice/web response system and was stratified by the time since RA diagnosis at Baseline (≤4 months and >4 months). Subjects in each stratum were then randomly assigned to the CZP+MTX or PBO+MTX treatment arms in a 3:1 ratio.

Blinding (masking)

This was a double-blind study.

Statistical methods

For the analysis of Period 1, data were locked and un-blinded after the last subject had completed the Week 52 Visit or the Safety Follow-up phone call (if the subject was withdrawn). The Full Analysis Set Period 1 (FAS1) was used to summarise and analyze all efficacy data except for the radiographic analyses which were based on the Radiographic Set (RAD1). In addition, a per-protocol set (PPS1) and, a Completer Set (CS1) was defined and used for sensitivity analyses of the primary and the key secondary endpoint. For definition of analysis sets, see “Numbers analysed” Section of this Report.

The primary and the key secondary endpoints were analysed using a logistic regression model including terms for treatment, region (Europe/Australia or Latin/North America), and stratification factor (≤4 months or >4 months since RA diagnosis at Baseline). The same model was used also for the analysis of other/secondary dichotomous efficacy endpoints including ACR20, ACR50, and ACR70 response relative to Baseline at Weeks 12, 24, and 52.

For dichotomous efficacy variables including all analyses on sustained remission and LDA rates, missing data was handled using a non-responder imputation (NRI), i.e. a subject having missing data for the time point assessed was counted as a non-remitter or non-responder. This was to be done whether the data were missing, the subject discontinued the study prior to the time point assessed, or the data were considered missing due to use of prohibited or rescue medication. Initially, if a subject met the withdrawal criteria specified in the protocol and was not withdrawn, all efficacy data collected at assessments after the specified time of withdrawal were to be treated as missing. This rule was however changed prior to CRF lock and unblinding, instead, such subjects were considered as having important protocol deviations and excluded from the PPS1, but the assessments were not treated as missing.

The change from Baseline in HAQ-DI at Weeks 12, 24, and 52 was analysed by an analysis of covariance (ANCOVA) model with terms for treatment, region, and time since RA diagnosis at Baseline as factors

and Baseline value as a covariate. The difference in least squares (LS) Means was presented with a 95% 2-sided CI.

The Week 52 change from Baseline for mTSS, joint erosion score and the JSN score respectively was analyzed using an ANCOVA model on the ranks with the terms for treatment, region, and time since RA diagnosis at Baseline as factors and rank Baseline value as a covariate. The treatment effect was estimated by the Hodges-Lehmann point estimate of shift and corresponding asymptotic (Moses) 95% CI. It was planned that the mTSS at Week 52 for early withdrawal subjects would be estimated by linear extrapolation of the scores from the radiographs taken from the Withdrawal Visit. This was changed (after SAP amendment 1) so that, the same methodology was applied to all subjects (not just to those who withdrew early), in order to have a consistent 52-week (364 day) score for every subject and minimize the impact of the differences in follow-up time.

For other secondary endpoints, e.g. HAQ-DI, TJC, SJC and, ETC, missing data was handled using last-observation-carried-forward (LOCF).

In addition to the primary and key secondary efficacy endpoints, statistical analyses accounting for multiplicity were also performed for selected secondary endpoints. A hierarchical test procedure was applied to protect the overall significance level for the multiplicity of endpoints. Hypothesis testing was performed in the following predefined order, each at a 2-sided 5% alpha level.

1. **Primary:** sustained DAS28 (ESR) remission at Week 52
2. **Key secondary:** sustained DAS28 (ESR) LDA at Week 52
3. ACR50 response at Week 52 in relation to Baseline
4. Change from Baseline in HAQ-DI at Week 52
5. Change from Baseline in mTSS at Week 52

No adjustment for multiple comparisons was made for the remaining endpoints outside the hierarchical test procedure. Significance testing was performed for these endpoints and is presented for descriptive purposes only.

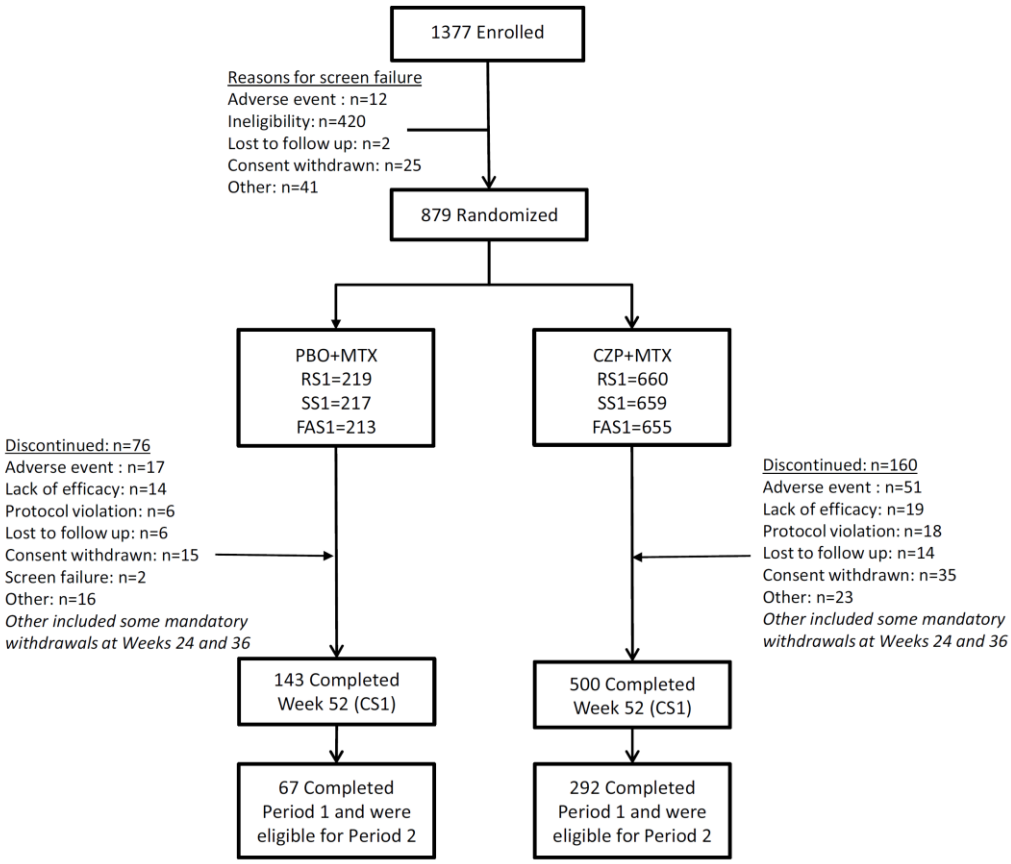
The primary efficacy variable was further analysed to investigate the consistency of treatment effect across regions using the primary logistic regression model including also the treatment by region interaction term. The Period 1 primary endpoint was examined by a number of pre-defined subgroups including e.g. time since RA diagnosis at Baseline (≤4 months and >4 months), gender, region and, age group (<65 years old, ≥65 years old).

Results

Participant flow

A total of 1377 subjects were enrolled, of which 880 subjects were randomized. Three subjects which were randomised in error, were not dosed, and withdrawn shortly afterwards as screen failures. Due to limited data in the database for these subjects, two subjects were included in the Randomized Set 1(RS1) only and one subject, who did not have complete data on informed consent in the database, was conservatively excluded from any output. Therefore, the flowchart of subject disposition (**Figure 2**) reported 879 subjects as being randomised; 660 subjects were randomised to receive CZP+MTX, and 219 subjects were randomised to receive PBO+MTX.

Figure 2. Flowchart of subject disposition



CS1=Completer Set Period 1; CZP=certolizumab pegol; FAS1=Full Analysis Set Period 1; LDA=low disease activity; mand w/d=mandatorily withdrawn subjects; MTX=methotrexate; PBO=placebo; RS1=Randomized Set 1; SS1=Safety Set 1
Notes: Subjects completed Week 52 if they had a Week 52 Visit. Subjects completed Period 1 if they had a Week 52 Visit and were eligible for Period 2 (i.e., in sustained LDA). Two subjects which were randomized in error, were not dosed, and withdrawn shortly afterwards as screen failures. These 2 subjects were included in the RS1.

Per the protocol, subjects were evaluated at Weeks 20, 24, 36 (in Sweden only), and 52. Subjects who had no improvement at Week 20 (i.e. DAS28 (ESR) ≤0) were withdrawn from the study. Those with insufficient improvement were re-evaluated at Week 24 (and also Week 36 for Sweden only) and Week 52. Those subjects who did not have sufficient improvement in their disease activity at Weeks 24, 36, or 52 were withdrawn from the study as summarised in **Table 3.**

Table 3. Mandatory withdrawals per the Interactive Voice/Web Response System (IXRS)

	PBO+MTX	**CZP+MTX**	**All subjects**
	N=219	N=660	N=879
	n (%)	n (%)	n (%)
Week 20	3 (1.4)	3 (0.5)	6 (0.7)
Week 24	9 (4.1)	9 (1.4)	18 (2.0)
Week 36 (Sweden) [a]	1 (0.5)	5 (0.8)	6 (0.7)
Week 52	72 (32.9)	197 (29.8)	269 (30.6)
TOTAL	85 (38.8)	214 (32.4)	299 (34.0)

CZP=certolizumab pegol; IXRS=Interactive Voice/Web Response System; MTX=methotrexate; PBO=placebo
[a] *Fifteen subjects were randomided in Sweden.*

Recruitment

The study was conducted at 181 centres located in North America, Latin America, Europe, and Australia. By geographic region, 53.0% of all subjects came from Europe/Australia and 47.0% of all subjects came from Latin/North America. In the CZP+MTX group, there was a higher proportion of subjects from Europe/Australia compared with Latin/North America (54.0% vs 46.0%). In the PBO+MTX group, a similar proportion of subjects came from each region.

Conduct of the study

The original SAP, dated 31 Jan 2014, was revised. The main changes from the original SAP were:

- The number of regions was reduced due to statistical concerns for the possibility of low cell counts in the logistic regression model, which could result in complete or quasi-complete separation and problems fitting the model.
- Calculated time since diagnosis was specified for use given a discrepancy between the IXRS value and the calculated value, since calculated values are more compatible with model-based analyses.

Post-hoc analyses with the initially 2 regions further divided into sub regions due to that the treatment by region interaction was found to be statistically significant.

Important protocol deviations were identified in 16.8% of subjects, as summarised in (**Table 4**).

Table 4. Important protocol deviations in Study RA0055

Protocol deviation type	PBO+MTX N=219	CZP+MTX N=660	All subjects N=879
	n (%)	n (%)	n (%)
No important protocol deviations	**179 (81.7)**	**552 (83.6)**	**731 (83.2)**
At least 1 important protocol deviation	**40 (18.3)**	**108 (16.4)**	**148 (16.8)**
Important protocol deviation for safety	**23 (10.5)**	**50 (7.6)**	**73 (8.3)**
Exclusion criteria	23 (10.5)	50 (7.6)	73 (8.3)
Important protocol deviation for efficacy [a]	**12 (5.5)**	**48 (7.3)**	**60 (6.8)**
Inclusion criteria	2 (0.9)	14 (2.1)	16 (1.8)
Exclusion criteria	2 (0.9)	6 (0.9)	8 (0.9)
Withdrawal criteria	1 (0.5)	2 (0.3)	3 (0.3)
Study medication compliance	6 (2.7)	28 (4.2)	34 (3.9)
Deviation on visits	1 (0.5)	0	1 (0.1)
Important protocol deviation for conduct	**33 (15.1)**	**80 (12.1)**	**113 (12.9)**
Exclusion criteria	25 (11.4)	55 (8.3)	80 (9.1)
Withdrawal criteria	1 (0.5)	2 (0.3)	3 (0.3)
Study medication compliance	2 (0.9)	12 (1.8)	14 (1.6)
Deviation other	6 (2.7)	12 (1.8)	18 (2.0)

CZP=certolizumab pegol; MTX=methotrexate; PBO=placebo; PPS1=Per-Protocol Set Period 1; RS1=Randomized Set 1
protocol deviation for efficacy [a] Subjects were excluded from the PPS1.

Baseline data

The treatment groups were balanced with respect to demographic characteristics (**Table 5**).

Table 5. Demographics summary at baseline in Study RA0055 (SS1)

	PBO+MTX N=217	CZP+MTX N=659	All subjects N=876
Age (years)			
n	217	659	876
Mean (SD)	51.2 (13.2)	50.4 (13.6)	50.6 (13.5)
Median	52.0	52.0	52.0
Min, max	18, 78	18, 90	18, 90
Age (years), n (%)			
≤18 [a]	1 (0.5)	2 (0.3)	3 (0.3)
>18 to <65	181 (83.4)	560 (85.0)	741 (84.6)
≥65	35 (16.1)	97 (14.7)	132 (15.1)
Gender, n (%)			
Male	43 (19.8)	161 (24.4)	204 (23.3)
Female	174 (80.2)	498 (75.6)	672 (76.7)
Race, n (%)			
American Indian/Alaskan native	4 (1.8)	7 (1.1)	11 (1.3)
Asian	3 (1.4)	10 (1.5)	13 (1.5)
Black or African American	12 (5.5)	26 (3.9)	38 (4.3)
Native Hawaiian/Other Pacific Islander	0	1 (0.2)	1 (0.1)
White	184 (84.8)	572 (86.8)	756 (86.3)
Other/mixed	14 (6.5)	43 (6.5)	57 (6.5)
Ethnicity, n (%)			
Hispanic or Latino	49 (22.6)	135 (20.5)	184 (21.0)
Not Hispanic or Latino	168 (77.4)	524 (79.5)	692 (79.0)
Weight (kg)			
n	217	657	874
Mean (SD)	78.12 (17.64)	76.69 (17.70)	77.04 (17.69)
Median	76.00	74.40	74.90
Min, max	41.9, 131.5	35.3, 167.5	35.3, 167.5

	PBO+MTX N=217	CZP+MTX N=659	All subjects N=876
Height (cm)			
n	217	657	874
Mean (SD)	165.07 (8.95)	165.58 (9.74)	165.45 (9.55)
Median	165.00	165.00	165.00
Min, max	136.0, 200.0	140.0, 207.0	136.0, 207.0
BMI (kg/m^2)			
n	217	656	873
Mean (SD)	28.71 (6.32)	27.95 (6.01)	28.14 (6.10)
Median	28.09	26.96	27.17
Min, max	17.2, 49.8	16.8, 59.3	16.8, 59.3
BMI class (kg/m^2), n (%)			
<18.5	6 (2.8)	13 (2.0)	19 (2.2)
≥18.5 to <25	61 (28.1)	219 (33.2)	280 (32.0)
≥25 to <30	73 (33.6)	217 (32.9)	290 (33.1)
≥30	77 (35.5)	207 (31.4)	284 (32.4)
Missing	0	3 (0.5)	3 (0.3)
Waist circumference (cm)			
n	213	650	863
Mean (SD)	95.2 (15.8)	93.1 (16.5)	93.6 (16.3)
Median	96.0	93.0	94.0
Min, max	58, 137	31, 180	31, 180
Region, n (%)			
Europe and Australia	108 (49.8)	356 (54.0)	464 (53.0)
Latin and North America	109 (50.2)	303 (46.0)	412 (47.0)

BMI=body mass index; CZP=certolizumab pegol; max=maximum, min=minimum, MTX=methotrexate; PBO=placebo; SD=standard deviation; SS1=Safety Set 1

The Study Protocol required that subjects were either RF positive or ACPA positive at Screening. Overall, 96.8% of subjects were RF positive, and 84.0% of subjects were ACPA positive.

Overall, the Baseline characteristics of RA demonstrated that the study population suffered from severe active RA and overall high disease burden. A total of 3.5% were in moderate disease activity, whereas 96.5% were in high disease activity as measured by DAS28 (ESR). More than three-quarters of subjects (77.8%) had erosions present at Baseline.

The treatment groups were also well-balanced with respect to RA history (**Table 6**). Overall, the mean and median (calculated) times since diagnosis for all subjects were 2.87 months and 1.63 months, respectively, with 75.9% of subjects having a (calculated) time since diagnosis of ≤4 months.

The mean and median (calculated) times since first symptoms of RA for all subjects were 11.7 months and 6.0 months, respectively. Time since first symptoms of RA was collected retroactively and was not available for all subjects; this information is highly subjective, so should be interpreted with caution.

A total of 6.1% of subjects had a history of extra-articular feature(s) and 6.7% of subjects had at least 1 extra-articular feature at Screening.

Table 6. Summary of baseline disease characteristics in Study RA0055

	PBO+MTX (SS1; N=217) (FAS1; N=213)	**CZP+MTX (SS1; N=659) (FAS1; N=655)**	**All subjects (SS1; N=876) (FAS1; N=868)**
Disease duration (months)	2.91 (2.93)	2.86 (4.63)	2.87 (4.27)
Baseline characteristics (SS1)			
RF (IU/mL), mean (SD)	244.09 (345.77)	210.02 (365.60)	218.38 (360.94)
ACPA (IU/mL), mean (SD)	724.20 (1444.33)	511.91 (867.96)	564.19 (1043.02)
Disease characteristics (FAS1)			
DAS28 (ESR), mean (SD)	6.797 (0.907)	6.697 (0.893)	6.722 (0.897)
SJC, mean (SD)	13.04 (5.64)	12.37 (5.48)	12.53 (5.52)
TJC, mean (SD)	16.22 (6.45)	15.61 (6.48)	15.76 (6.47)
CRP (mg/L), mean (SD)	21.49 (27.91)	21.73 (29.47)	21.67 (29.08)
ESR (mm/h), mean (SD)	50.76 (22.23)	50.18 (24.67)	50.32 (24.08)
HAQ-DI, mean (SD)	1.688 (0.647)	1.610 (0.607)	1.629 (0.618)
mTSS, mean (SD)	8.5 (17.5)	7.2 (13.8)	7.5 (14.8)
Presence of erosions at baseline, n(%)	169 (79.3)	506 (77.3)	675 (77.8)

ACPA=anticyclic citrullinated peptide antibody; CRP=C-reactive protein; CZP=certolizumab pegol; DAS28(ESR)=disease activity score-28 joint count erythrocyte sedimentation rate; ESR=erythrocyte sedimentation rate; FAS1=Full Analysis Set Period 1; HAQ-DI=Health Assessment Questionnaire-Disability Index; JSN=joint space narrowing; mTSS=modified total Sharp score; MTX=methotrexate; PBO=placebo; RF=rheumatoid factor; SD=standard deviation; SJC=swollen joint count; TJC=tender joint count

Numbers analysed

Analysis sets in addition to the Randomized Set 1 (RS1) included:

- Safety Set 1 (SS1): This set included subjects in the RS1 who received at least 1 dose of study medication (CZP/PBO) and was used to summarize demographic, baseline and safety data.
- Full Analysis Set Period 1 (FAS1): This set included subjects in the RS1 who had valid Baseline and post-Baseline efficacy measurement for the primary efficacy assessment of DAS28(ESR) and was used to summarize and analyse all efficacy data.
- Radiographic Set Period 1 (RAD1): This set included subjects in the FAS1 who had provided valid radiographs (ie, radiographs resulting in a non-missing mTSS score) at Baseline and at Week 52 or the Withdrawal Visit and was used for the radiographic analyses.
- Per-Protocol Set Period 1 (PPS1): This set included subjects in the FAS1 who did not have any important protocol deviations that would have influenced the validity of the data and was used for sensitivity analysis on the Period 1 primary endpoint only.
- Completer Set Period 1 (CS1): This set included subjects in the FAS1 who completed to Week 52 and was used for sensitivity analyses of the Period 1 primary and key secondary endpoints only
- Pharmacokinetic Set 1 (PKS1): This included subjects who received at least 1 dose of CZP and provided at least 1 PK sample.

Table 7. Populations analysed in RA055 study Period 1

	Number of subjects						
	RS1	**SS1**	**FAS1**	**PPS1**	**RAD1**	**CS1**	**PKS1**
All subjects	879	876	868	809	691	643	659
PBO+MTX	219	217	213	201	163	143	0
CZP+MTX	660	659	655	608	528	500	659

Outcomes and estimation

Primary efficacy variable: Sustained remission at Week 52

The Period 1 primary efficacy variable was the proportion of subjects in sustained remission (defined as DAS28 [ESR] <2.6 at both Week 40 and Week 52 Visits) at Week 52.

Table 8. Summary of subjects in sustained remission (FAS1, with NRI, Study RA0055)

Week 52	PBO+MTX N=213 n (%)	CZP+MTX N=655 n (%)	Odds ratio [a] CZP+MTX/ PBO+MTX	Odds ratio [a] 95% CI	p-value [a]
In sustained remission	32 (15.0)	189 (28.9)	2.283	1.503, 3.468	<0.001
Not in sustained remission	181 (85.0)	466 (71.1)	–	–	–

CI=confidence interval; CZP=certolizumab pegol; DAS28(ESR)=disease activity score-28 joint count erythrocyte sedimentation rate; FAS1=Full Analysis Set Period 1; MTX=methotrexate; NRI=nonresponder imputation; PBO=placebo; RA=rheumatoid arthritis

[a] *Odds ratio: CZP+MTX/PBO+MTX (and corresponding p-value) from a logistic regression model with factors form treatment, region, and time since RA diagnosis at Baseline (≤4 months vs >4 months).*

Sensitivity analyses of the primary efficacy variable performed using the PPS1 and the CS1 (**Table 9**) confirmed the primary analysis. Although the sensitivity analysis using the PPS1 was not required since <15% of subjects were excluded from the PPS1, these results (odds ratio favouring CZP+MTX: 2.289; 95% CI: 1.494, 3.509; p-value< 0.001) were similar to those using the FAS1, indicating that subjects with protocol violations did not bias the results. The results using the CS1 were also consistent with those using the FAS1, indicating that the impact of dropouts is similar in both groups.

Table 9. Primary variable: summary of subjects in sustained remission (CS1, with NRI, Study RA0055)

Week 52	PBO+MTX N=143 n (%)	CZP+MTX N=500 n (%)	Odds ratio [a] CZP+MTX/ PBO+MTX	Odds ratio [a] 95% CI	p-value [a]
In sustained remission	32 (22.4)	189 (37.8)	2.109	1.359, 3.272	<0.001
Not in sustained remission	111 (77.6)	311 (62.2)	–	–	–

CI=confidence interval; CS1=Completer Set Period 1; CZP=certolizumab pegol; DAS28(ESR)=disease activity score-28 joint count erythrocyte sedimentation rate; MTX=methotrexate; NRI=non-responder imputation; PBO=placebo; RA=rheumatoid arthritis

[a] *Odds ratio: CZP+MTX/PBO+MTX (and corresponding p-value) from a logistic regression model with factors for treatment, region, and time since RA diagnosis at Baseline (≤4 months vs >4 months)*

Analyses of the primary efficacy variable by subgroups

Treatment with CZP+MTX provided an increase in the proportion of subjects in sustained remission compared with PBO+MTX regardless of gender, age group, RF status, albumin level, or presence of erosions at Baseline (**Table 10**).

Table 10. Summary of subjects in sustained remission at Week 52 by subgroups (FAS1, with NRI, Study RA0055)

In sustained remission at Week 52	PBO+MTX N=213		CZP+MTX N=655		Odds ratio [a]		p-value [a]
	N	n (%)	N	n (%)	CZP+MTX/ PBO+MTX	95% CI	
Overall							
Remitters	213	32 (15.0)	655	189 (28.9)	2.283	1.503, 3.468	<0.001
Time since RA diagnosis at Baseline							
≤4 months	157	22 (14.0)	502	146 (29.1)	2.520	1.529, 4.152	<0.001
>4 months	56	10 (17.9)	153	43 (28.1)	1.782	0.823, 3.856	0.142
Gender							
Male	43	9 (20.9)	158	60 (38.0)	2.348	1.030, 5.355	0.042
Female	170	23 (13.5)	497	129 (26.0)	2.220	1.362, 3.620	0.001
Region							
Europe and Australia	107	18 (16.8)	354	136 (38.4)	3.071	1.771, 5.325	<0.001
Latin and North America	106	14 (13.2)	301	53 (17.6)	1.427	0.754, 2.702	0.275
Age							
<65 years	179	29 (16.2)	558	167 (29.9)	2.230	1.430, 3.478	<0.001
≥65 years	34	3 (8.8)	97	22 (22.7)	2.808	0.774, 10.190	0.116
RF							
≤42 IU/mL	47	8 (17.0)	194	64 (33.0)	2.416	1.038, 5.619	0.041
>42 IU/mL	163	24 (14.7)	460	125 (27.2)	2.161	1.332, 3.505	0.002
Albumin							
<42g/L	93	7 (7.5)	281	66 (23.5)	4.146	1.807, 9.509	<0.001
≥42g/L	120	25 (20.8)	374	123 (32.9)	1.798	1.089, 2.969	0.022
Presence of erosions at Baseline							
Yes	169	27 (16.0)	506	144 (28.5)	2.085	1.314, 3.307	0.002
No	43	5 (11.6)	145	45 (31.0)	3.381	1.232, 9.274	0.018

CI=confidence interval; CZP=certolizumab pegol; DAS28(ESR)=disease activity score-28 joint count erythrocyte sedimentation rate; FAS1=Full Analysis Set Period 1; MTX=methotrexate; NRI=nonresponder imputation; PBO=placebo; RA=rheumatoid arthritis; RF=rheumatoid factor

[a] *Odds ratio: CZP+MTX/PBO+MTX (and corresponding p-value) from a logistic regression model with factors for treatment, region, and time since RA diagnosis at Baseline (≤4 months vs >4 months) (note: this factor was not included in the analysis for the subgroup of time since RA diagnosis at Baseline).*

Key secondary efficacy variable: sustained LDA at Week 52

Sustained low disease activity (LDA) was defined as subjects with DAS28 [ESR] ⩽3.2 at both the Week 40 and Week 52 Visits. A statistically significant difference (p<0.001) in LDA at Week 52 was observed between the CZP+MTX and the PBO+MTX group (**Table 11**). Subjects treated with CZP+MTX were 2.0 times (95% CI: 1.384, 2.767) more likely to achieve sustained LDA (LDA at both Weeks 40 and 52) after 52 weeks of treatment compared with subjects treated with PBO+MTX.

Table 11. Summary of subjects in sustained LDA at Week 52 (FAS1, with NRI. Study RA0055)

Week 52	PBO+MTX N=213 n (%)	CZP+MTX N=655 n (%)	Odds ratio [a] CZP+MTX/ PBO+MTX	Odds ratio [a] 95% CI	p-value [a]
In sustained LDA	61 (28.6)	287 (43.8)	1.957	1.384, 2.767	<0.001
Not in sustained LDA	152 (71.4)	368 (56.2)	–	–	–

CI=confidence interval; CZP=certolizumab pegol; DAS28 (ESR)=disease activity score-28 joint count erythrocyte sedimentation rate; FAS1=Full Analysis Set Period 1; LDA=low disease activity; MTX=methotrexate; NRI=nonresponder imputation; PBO=placebo; RA=rheumatoid arthritis

[a] *Odds ratio: CZP+MTX/PBO+MTX (and corresponding p-value) from a logistic regression model with factors for treatment, region, and time since RA diagnosis at Baseline (≤4 months vs >4 months).*

A sensitivity analysis of the key secondary efficacy variable was performed using the CS1 to assess the impact of missing data. The results using the CS1 were consistent with those using the FAS1, indicating that the impact of dropouts is similar in both groups (data not shown).

Inhibition of progression of structural damage

All radiographic efficacy variables were analysed using the RAD1, which consisted of subjects in the FAS1 who had provided valid radiographs (i.e. radiographs resulting in a non-missing mTSS score) at Baseline and at Week 52 or the Withdrawal Visit (mTSS at Withdrawal Visit linearly extrapolated to Week 52). Radiographs were read centrally and independently by at least 2 experienced readers with a third reader for adjudication, if necessary.

At Baseline, the mean mTSS for subjects in the RAD1 was 6.6 and 9.1 in the CZP+MTX and PBO+MTX groups, respectively and the median Baseline values were 2.5 for each group. Mean changes at Week 52 between the two treatment arms and the difference between the two are presented in **Table 12**.

Table 12. Mean change from Baseline in mTSS at Week 52 (RAD1, with linear extrapolation, Study RA0055)

Visit	PBO+MTX N=163		CZP+MTX N=528	
	Actual	CFB	Actual	CFB
Baseline				
n	163	–	528	–
Mean (SD)	8.7 (18.1)	–	6.6 (12.4)	–
Median (range)	2.5 (0, 161)	–	2.5 (0, 130)	–
Week 52				
n	163	163	528	528
Mean (SD)	10.5 (18.7)	1.8 (4.3)	6.8 (12.5)	0.2 (3.2)
Median (range)	4.5 (-3, 158)	0.5 (-9, 20)	3.0 (-9, 130)	0.0 (-26, 26)
CZP+MTX – PBO+MTX:				
Difference [a]	–	–	–	-0.978
95% CI for difference [a]	–	–	–	-1.005, -0.500
p-value [b]	–	–	–	<0.001

ANCOVA=analysis of covariance; CFB=change from Baseline; CI=confidence interval; CZP=certolizumab pegol; mTSS=modified total Sharp score; MTX=methotrexate; PBO=placebo; RA=rheumatoid arthritis; RAD1=Radiographic Set Period 1; SD=standard deviation
Note: The mTSS has a possible range from 0 to 448 with lower scores meaning less structural damage in the hands and feet.
a Hodges-Lehmann point estimate of shift and 95% asymptotic (Moses) CI.
b p-value was estimated using ANCOVA on the ranks with treatment, region, and time since RA diagnosis at Baseline (≤4 months vs >4 months) as factors and Baseline rank as a covariate.

The proportion of subjects with radiographic non-progression at Week 52 was 70.3% in the CZP+MTX group compared with 49.7% in the PBO+MTX group (p<0.001;**Table 13**).

Table 13. Summary of subjects with radiographic non-progression at Week 52 (RAD1, with linear extrapolation)

Week 52	PBO+MTX N=163 n (%)	CZP+MTX N=528 n (%)	Odds ratio [a] CZP+MTX/ PBO+MTX	95% CI	p-value [a]
Subjects with nonprogression	81 (49.7)	371 (70.3)	2.386	1.665, 3.420	<0.001
Subjects with progression	82 (50.3)	157 (29.7)	–	–	–

CI=confidence interval; CZP=certolizumab pegol; mTSS=modified total Sharp score; MTX=methotrexate; PBO=placebo; RA=rheumatoid arthritis; RAD1=Radiographic Set Period 1 Note: Radiographic nonprogression was defined as a change from Baseline in mTSS of ≤0.5 (based on linearly extrapolated scores).
[a] *Odds ratio: CZP+MTX/PBO+MTX (and corresponding p-value) from a logistic regression model with factors for treatment, region, and time since RA diagnosis at Baseline (≤4 months vs >4 months).*

At Baseline, the mean joint erosion score for subjects in the RAD1 was 3.9 and 4.8 in the CZP+MTX and PBO+MTX groups, respectively and the median Baseline values were 1.5 for each group. Mean changes at Week 52 between the two treatment arms and the difference between the two are presented in **Table 14**.

Additional post-hoc sensitivity analyses were submitted for the changes from Baseline in mTSS at Week 52 using all subjects in the FAS1 with a non-missing baseline mTSS (651 and 212 subjects in the CZP+MTX and PBO+MTX arm, respectively). In all 3 post-hoc sensitivity analyses, for subjects with a valid Withdrawal Visit mTSS, the Week 52 mTSS was imputed by linear extrapolation of the Withdrawal Visit mTSS (as in the predefined primary analysis).

The sensitivity analyses differed with respect to the method of imputation for subjects without a valid Withdrawal Visit mTSS. These were performed as follows:

Sensitivity Analysis 1

- The missing Week 52 mTSS was imputed (for both treatment arms) from the slope estimates obtained from the ANCOVA model on the Week 52 mTSS score for PBO+MTX subjects.

Sensitivity Analysis 2

- The missing change from Baseline in mTSS at Week 52 was imputed using the mean change from Baseline in mTSS at Week 52 for all patients with observed values.

Sensitivity Analysis 3

- The missing change from Baseline in mTSS at Week 52 was imputed using the median change from Baseline in mTSS at Week 52 for all patients with observed values.

As summarized in Table 14, all 3 sensitivity analyses resulted in CZP+MTX – PBO+MTX differences which were still significant (p <0.001).

Table 14. Summary of change from Baseline in mTSS at Week 52 using different imputation methods

mTSS Imputation Method	Mean/Median Change from BL		CZP+MTX - PBO+MTX Difference	95% CI	p-value
	PBO+MTX	CZP+MTX			
RAD1	N=163	N=528			
Primary pre-defined analysis[a]	1.8/0.5	0.2/0.0	-0.978	-1.005, -0.500	<0.001
FAS1	N=212	N=651			
Post-hoc Sensitivity Analysis 1[b]	1.8/1.5	0.5/0.5	-0.619	-1.000, -0.499	<0.001
Post-hoc Sensitivity Analysis 2[c]	1.4/0.2	0.2/0.2	-0.284	-0.503, -0.216	<0.001
Post-hoc Sensitivity Analysis 3[d]	1.4/0.0	0.1/0.0	-0.499	-0.500, 0.000	<0.001

BL=Baseline; CI=confidence interval; CZP=certolizumab pegol; FAS1=Full Analysis Set Period 1; mTSS=van der Heijde modified Total Sharp Score; MTX=methotrexate; PBO=placebo; RAD1=Radiographic Set Period 1

[a] The mTSS at Week 52 for early withdrawal subjects was estimated by linear extrapolation of the scores from the radiographs taken from the Withdrawal Visit. ANCOVA on the ranks with treatment, region, time since RA diagnosis at Baseline (≤4 months vs >4 months) as factors and Baseline rank as covariate (RA0055 Period 1 CSR

[b] For subjects without a valid Withdrawal Visit mTSS, the missing Week 52 mTSS was imputed (for both treatment arms) from the slope estimates obtained from the ANCOVA model on the Week 52 mTSS score for PBO+MTX subjects. ANCOVA on the ranks with treatment, region, time since RA diagnosis at Baseline (≤4 months vs >4 months) as factors and Baseline rank as covariate (RA0055 Period 1 Post-hoc Table 59).

[c] For subjects without a valid Withdrawal Visit mTSS, the missing change from Baseline in mTSS at Week 52 was imputed using the mean change from Baseline in mTSS at Week 52 for all patients with observed values. ANCOVA on the ranks with treatment, region, time since RA diagnosis at Baseline (≤4 months vs >4 months) as factors and Baseline rank as covariate (RA0055 Period 1 Post-hoc Table 128).

[d] For subjects without a valid Withdrawal Visit mTSS, the missing change from Baseline in mTSS at Week 52 was imputed using the median change from Baseline in mTSS at Week 52 for all patients with observed values. ANCOVA on the ranks with treatment, region, time since RA diagnosis at Baseline (≤4 months vs >4 months) as factors and Baseline rank as covariate (RA0055 Period 1 Post-hoc Table 129).

Note: For all sensitivity analyses, for subjects with a valid Withdrawal Visit mTSS, the Week 52 mTSS was imputed by linear extrapolation of the Withdrawal Visit mTSS (as in the original primary analysis)

At Baseline, the mean joint erosion score for subjects in the RAD1 was 4.0 and 5.2 in the CZP+MTX and PBO+MTX groups, respectively and the median Baseline values were 1.5 for each group. Mean changes at Week 52 between the two treatment arms and the difference between the two are presented in **Table 15**.

Table 15. Mean change from Baseline in the joint erosion score at Week 52 (RAD1, with linear extrapolation).

Visit	PBO+MTX N=163		CZP+MTX N=528	
	Actual	CFB	Actual	CFB
Baseline				
n	163	–	528	–
Mean (SD)	4.8 (8.3)	–	3.9 (7.2)	–
Median (range)	1.5 (0, 68)	–	1.5 (0, 65)	–
Week 52				
n	163	163	528	528
Mean (SD)	5.9 (8.8)	1.1 (3.0)	4.0 (7.2)	0.1 (2.1)
Median (range)	3.0 (-0, 68)	0.5 (-7, 20)	1.9 (-7, 72)	0.0 (-22, 13)
CZP+MTX – PBO+MTX:				
Difference [a]	–	–	–	-0.500
95% CI for difference [a]	–	–	–	-0.508, -0.366
p-value [b]	–	–	–	<0.001

ANCOVA=analysis of covariance; CFB=change from Baseline; CI=confidence interval; CZP=certolizumab pegol; MTX=methotrexate; PBO=placebo; RA=rheumatoid arthritis; RAD1=Radiographic Set Period 1; SD=standard deviation

Note: The total joint erosion score has a possible range from 0 to 280 with lower scores meaning less joint erosion in the hands and feet.

[a] *Hodges-Lehmann point estimate of shift and 95% asymptotic (Moses) CI.*

[b] *p-value was estimated using ANCOVA on the ranks with treatment, region, and time since RA diagnosis at Baseline (≤4 months vs >4 months) as factors and Baseline rank as a covariate.*

At Baseline, the mean JSN score for subjects in the RAD1 was 2.6 and 3.9 in the CZP+MTX and PBO+MTX groups, respectively and the median Baseline values were 0.0 for each group. Mean changes at Week 52 between the two treatment arms and the difference between the two are presented in **Table 16**.

Table 16: Mean change from Baseline in the JSN score at Week 52 (RAD1, with linear extrapolation)

Visit	PBO+MTX N=163		CZP+MTX N=528	
	Actual	CFB	Actual	CFB
Baseline				
n	163	–	528	–
Mean (SD)	3.9 (11.3)	–	2.6 (6.0)	–
Median (range)	0.0 (0, 101)	–	0.0 (0, 65)	–
Week 52				
n	163	163	528	528
Mean (SD)	4.6 (11.4)	0.7 (2.3)	2.7 (6.1)	0.1 (1.8)
Median (range)	1.0 (-3, 98)	0.0 (-7, 15)	0.0 (-8, 66)	0.0 (-20, 13)
CZP+MTX – PBO+MTX:				
Difference [a]	–	–	–	0.000
95% CI for difference [a]	–	–	–	0.000, 0.000
p-value [b]	–	–	–	0.001

ANCOVA=analysis of covariance; CFB=change from Baseline; CI=confidence interval; CZP=certolizumab pegol; JSN=joint space narrowing; MTX=methotrexate; PBO=placebo; RA=rheumatoid arthritis; RAD1=Radiographic Set Period 1; SD=standard deviation

Note: The total JSN score has a possible range from 0 to 168 with lower scores meaning less JSN in the hands and feet.

[a] *Hodges-Lehmann point estimate of shift and 95% asymptotic (Moses) CI.*

[b] *p-value was estimated using ANCOVA on the ranks with treatment, region, and time since RA diagnosis at Baseline (≤4 months vs >4 months) as factors and Baseline rank as a covariate.*

Change from baseline in HAQ-DI

At Baseline, the mean HAQ-DI scores were similar between the CZP+MTX (1.6 points) and PBO+MTX (1.7 points) groups. The LS Mean change from Baseline in HAQ-DI improved over time in the CZP+MTX through Week 52; a similar trend was observed in the PBO+MTX group but with a consistently smaller change from Baseline at each time point (**Table 17**).

Table 17. Mean change from Baseline in HAQ-DI at Weeks 12, 24, and 52 (FAS1, with LOCF, Study RA0055)

Visit	PBO+MTX N=213		CZP+MTX N=655		CZP+MTX – PBO+MTX [a]		
	n	LS Mean (SE)	n	LS Mean (SE)	LS Mean (SE)	95% CI	p-value
Baseline mean (SD)	213	1.688 (0.647)	654	1.610 (0.607)	–	–	–
Change from Baseline:							
Week 12	209	-0.690 (0.041)	643	-0.853 (0.026)	-0.163 (0.046)	-0.253, -0.073	<0.001
Week 24	209	-0.825 (0.042)	643	-0.917 (0.026)	-0.092 (0.047)	-0.184, -0.001	0.048
Week 52	210	-0.819 (0.044)	645	-0.997 (0.028)	-0.177 (0.049)	-0.273, -0.082	<0.001

ANCOVA=analysis of covariance; CI=confidence interval; CZP=certolizumab pegol; FAS1=Full Analysis Set Period 1; HAQ-DI=Health Assessment Questionnaire-Disability Index; LOCF=last observation carried forward; LS Mean=least squares mean; MTX=methotrexate; PBO=placebo; RA=rheumatoid arthritis; SD=standard deviation; SE=standard error

Note: Baseline was defined as the latest, nonmissing predose result.

Note: The HAQ-DI total score has a possible range from 0 to 3 with lower scores indicating less disability (ie, physical functioning).

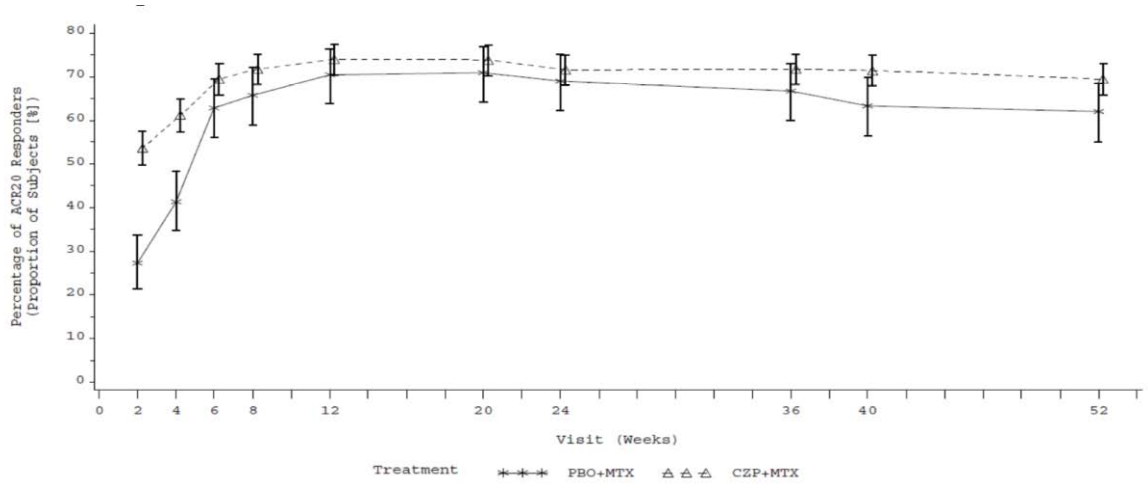
[a] ANCOVA model with treatment, region, and time since RA diagnosis at Baseline (≤4 months vs >4 months) as factors and Baseline value as a covariate.

A greater proportion of subjects reaching normative physical function (HAQ-DI score ≤0.5) was observed in the CZP+MTX group compared with the PBO+MTX group as early as Week 2. At Week 52, 48.1% of subjects in the CZP+MTX group had reached normative physical function compared with 35.7% of subjects in the PBO+MTX group (p=0.002); subjects treated with CZP+MTX were 1.7 times (95% CI: 1.207, 2.305) more likely to reach normative physical function after 52 weeks of treatment compared with subjects treated with PBO+MTX.

ACR20, ACR 50 and ACR70 response by visit

The ACR20 (**Figure 3**), ACR 50 (**Figure 4**) and ACR70 (**Figure 5**) responses with CZP+MTX treatment, showed a separation from PBO+MTX as early as Week 2.

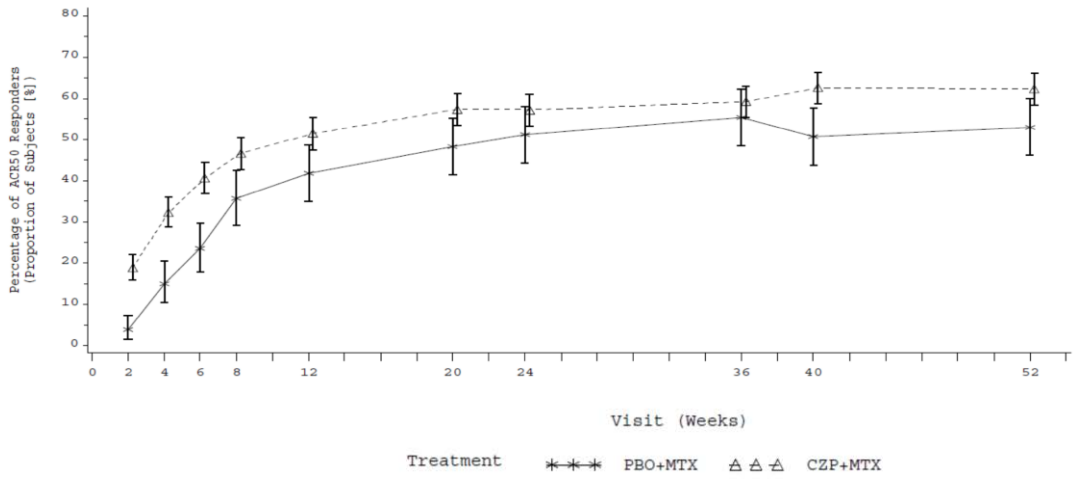
Figure 3 : ACR20 responders (FAS1, with NRI, Study RA0055)



Note: p-value was ⩽0.05 at Weeks 2, 4, and 40.

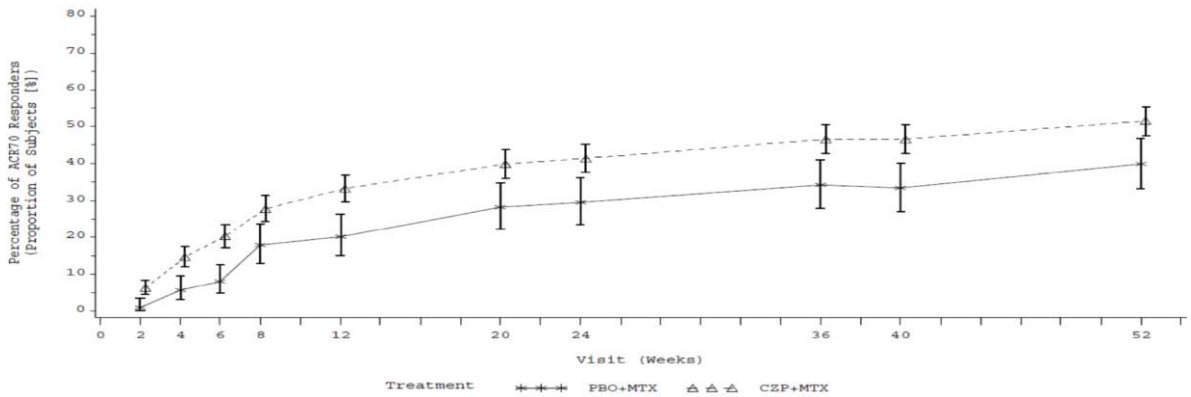
The target treatment responses for clinical practice of 60%, 40%, and 20% for the ACR20, ACR50, and ACR70, respectively, (McInnes and O'Dell, 2010; Kavanaugh et al, 2004) were achieved by at least Week 6 (Week 4 for ACR20) in this study and maintained through Week 52 with CZP+MTX treatment. Both treatment groups achieved these targets by Week 52; however, the proportion of subjects reaching ACR20, ACR50, and ACR70 at Week 52 was greater in the CZP+MTX group compared with the PBO+MTX.

Figure 4. Percentage ACR50 responders by visit (FAS1, with NRI, Study RA0055)



The proportion of ACR50 responders increased over time in both groups; however, the proportion was greater in the CZP+MTX group compared with the PBO+MTX group beginning at Week 2 and continuing through Week 52. At each visit, the p-value for the difference from PBO+MTX was ≤0.05 with the exception of Weeks 24 and 36.

Figure 5. ACR70 responders (FAS1, with NRI, Study RA0055)



Note: p-value was ≤0.05 at all assessment time points (Weeks 2, 4, 6, 8, 12, 20, 24, 36, 40, and 52).
Note: Error bars denote 95% confidence intervals.

Note: p-value was ≤0.05 at all assessment time points (Weeks 2, 4, 6, 8, 12, 20, 24, 36, 40, and 52).
Note: Error bars denote 95% confidence intervals.

ACR components by visit

The changes from Baseline in individual components of the ACR criteria were defined as secondary efficacy variables at Weeks 12, 24, and 52/Withdrawal Visit and as other efficacy variables at Weeks 2, 4, 6, 8, 20, 36, and 40. For each ACR component, a negative change from Baseline indicates improvement such that the larger the negative value, the greater the improvement. Changes in CRP and ESR were assessed as a ratio to Baseline; the smaller the ratio, the greater the reduction and improvement in CRP and ESR. Although ESR was not used in the calculation of ACR scores in this study, ESR was considered an ACR component for the efficacy endpoint.

At Baseline, the mean scores for ACR components were similar between the CZP+MTX and PBO+MTX groups. Mean changes from Baseline in ACR components at Weeks 12, 24, and 52 are summarised in **Table 18**.

MCID from Baseline in PtGADA

The proportion of subjects who achieved an MCID from Baseline (an improvement of ≥10mm from Baseline) in PtGADA in the CZP+MTX group ranged from 68.2% to 76.6%. The proportion of subjects in the PBO+MTX group was generally similar to the CZP+MTX group, with smaller proportions at the early visits (Weeks 2 and 4) and at Weeks 40 and 52. No difference between groups was seen at Week 12 (76.1% vs 76.6% in the placebo group and the Cimzia treated group respectively). At week 52, the proportions were 59.6% and 68.2% respectively.

Table 18. Mean change from Baseline in ACR components at Weeks 12, 24, and 52 (FAS1, with LOCF)

Visit	PBO+MTX N=213		CZP+MTX N=655		CZP+MTX – PBO+MTX [a]		
TJC (based on 28 joints)	**n**	**LS Mean (SE)**	**n**	**LS Mean (SE)**	**LS Mean (SE)**	**95% CI**	**p-value**
Baseline mean (SD)	213	16.22 (6.45)	655	15.61 (6.48)	–	–	–
Change from Baseline:							
Week 12	209	-9.79 (0.40)	644	-10.46 (0.25)	-0.85 (0.44)	-1.71, 0.02	0.055
Week 24	209	-10.86 (0.39)	644	-11.68 (0.24)	-0.81 (0.43)	-1.66, 0.03	0.060
Week 52	210	-11.23 (0.38)	646	-12.55 (0.24)	-1.32 (0.42)	-2.14, -0.49	0.002
SJC (based on 28 joints)	**n**	**LS Mean (SE)**	**n**	**LS Mean (SE)**	**LS Mean (SE)**	**95% CI**	**p-value**
Baseline mean (SD)	213	13.04 (5.64)	655	12.37 (5.48)	–	–	–
Change from Baseline:							
Week 12	209	-7.73 (0.29)	644	-9.23 (0.18)	-1.49 (0.32)	-2.13, -0.86	<0.001
Week 24	209	-8.78 (0.27)	644	-9.86 (0.17)	-1.08 (0.30)	-1.67, -0.50	<0.001
Week 52	210	-9.15 (0.28)	646	-10.52 (0.17)	-1.37 (0.31)	-1.97, -0.77	<0.001
HAQ-DI	**n**	**LS Mean (SE)**	**n**	**LS Mean (SE)**	**LS Mean (SE)**	**95% CI**	**p-value**
Baseline mean (SD)	213	1.688 (0.647)	654	1.610 (0.607)	–	–	–
Change from Baseline:							
Week 12	209	-0.690 (0.041)	643	-0.853 (0.026)	-0.163 (0.046)	-0.253, -0.073	<0.001
Week 24	209	-0.825 (0.042)	643	-0.917 (0.026)	-0.092 (0.047)	-0.184, -0.001	0.048
Week 52	210	-0.819 (0.044)	645	-0.997 (0.028)	-0.177 (0.049)	-0.273, -0.082	<0.001
PtGADA	**n**	**LS Mean (SE)**	**n**	**LS Mean (SE)**	**LS Mean (SE)**	**95% CI**	**p-value**

Visit	PBO+MTX N=213		CZP+MTX N=655		CZP+MTX – PBO+MTX [a]		
Baseline mean (SD)	213	65.3 (22.6)	655	65.3 (21.8)	–	–	–
Change from Baseline:							
Week 12	209	-35.2 (1.7)	644	-39.7 (1.1)	-4.5 (1.9)	-8.2, -0.9	0.015
Week 24	209	-39.1 (1.7)	644	-42.5 (1.0)	-3.4 (1.8)	-7.0, 0.2	0.064
Week 52	210	-42.0 (1.7)	646	-46.7 (1.0)	-4.7 (1.9)	-8.4, -1.1	0.011
PhGADA	**n**	**LS Mean (SE)**	**n**	**LS Mean (SE)**	**LS Mean (SE)**	**95% CI**	**p-value**
Baseline mean (SD)	213	68.6 (17.0)	653	67.5 (16.2)	–	–	–
Change from Baseline:							
Week 12	209	-40.2 (1.4)	642	-45.7 (0.9)	-5.6 (1.5)	-8.6, -2.6	<0.001
Week 24	209	-43.1 (1.3)	642	-49.7 (0.8)	-6.6 (1.5)	-9.5, -3.7	<0.001
Week 52	210	-45.1 (1.4)	644	-53.5 (0.9)	-8.4 (1.6)	-11.5, -5.3	<0.001
PtAAP	**n**	**LS Mean (SE)**	**n**	**LS Mean (SE)**	**LS Mean (SE)**	**95% CI**	**p-value**
Baseline mean (SD)	213	66.4 (22.9)	654	66.0 (22.3)	–	–	–
Change from Baseline:							
Week 12	209	-37.0 (1.7)	643	-41.5 (1.1)	-4.5 (1.9)	-8.2, -0.7	0.019
Week 24	209	-41.1 (1.7)	643	-44.2 (1.0)	-3.1 (1.8)	-6.7, 0.5	0.091
Week 52	210	-44.0 (1.7)	645	-48.5 (1.0)	-4.4 (1.8)	-8.0, -0.8	0.016
CRP (mg/L)	**n**	**Geo. mean (Geo. CV%)**	**n**	**Geo. mean (Geo. CV%)**	**Geo. LS Mean (SE)**	**95% CI**	**p-value**
Baseline	213	10.32 (225.47)	655	10.02 (228.44)	–	–	–
Ratio to Baseline:							

Visit	PBO+MTX N=213		CZP+MTX N=655		CZP+MTX – PBO+MTX [a]		
Week 12	209	0.48 (191.42)	644	0.27 (235.52)	0.55 (0.05)	0.46, 0.66	<0.001
Week 24	209	0.40 (226.61)	644	0.24 (278.86)	0.61 (0.06)	0.50, 0.74	<0.001
Week 52	210	0.43 (243.04)	646	0.24 (319.07)	0.55 (0.05)	0.45, 0.67	<0.001
ESR (mm/h)	**n**	**Geo. mean (Geo. CV%)**	**n**	**Geo. mean (Geo. CV%)**	**Geo. LS Mean (SE)**	**95% CI**	**p-value**
Baseline	213	46.66 (42.30)	655	44.73 (52.83)	–	–	–
Ratio to Baseline:							
Week 12	209	0.58 (71.06)	644	0.45 (90.72)	0.78 (0.05)	0.70, 0.88	<0.001
Week 24	209	0.56 (73.96)	644	0.43 (92.67)	0.78 (0.05)	0.69, 0.87	<0.001
Week 52	210	0.46 (96.92)	646	0.36 (111.74)	0.78 (0.05)	0.68, 0.89	<0.001

ACR=American College of Rheumatology; ANCOVA=analysis of covariance; CI=confidence interval; CRP=C-reactive protein; CV=coefficient of variation; CZP=certolizumab pegol; ESR=erythrocyte sedimentation rate; FAS1=Full Analysis Set Period 1; geo.=geometric; HAQ-DI=Health Assessment Questionnaire-Disability Index; LOCF=last observation carried forward; LS Mean=least squares mean; MTX=methotrexate; PBO=placebo; PhGADA =Physician's Global Assessment of Disease Activity; PtAAP=Patient's Assessment of Arthritis Pain; PtGADA = Patient's Global Assessment of Disease Activity; RA=rheumatoid arthritis; SD=standard deviation; SE=standard error; SJC=swollen joint count; TJC=tender joint count

Note: Baseline was defined as the latest, non-missing pre-dose result.

Note: The TJC and SJC each have a possible range of scores from 0 to 28 with lower scores indicating less tenderness and swelling, respectively. The PtGADA, PhGADA, and PtAAP each have a possible range of scores from 0 to 100 with higher scores indicating a worse state.

[a] *ANCOVA model with treatment, region, and time since RA diagnosis at Baseline (≤4 months vs >4 months) as factors and Baseline value as a covariate. For CRP and ESR only, ANCOVA model on log-transformed data with treatment, region, and time since RA diagnosis at Baseline (≤4 months vs >4 months) as factors and Baseline log-transformed value as a covariate.*

LDA by visit

The proportion of subjects achieving LDA based on DAS28(ESR) ≤3.2 was defined as a secondary efficacy variable at Weeks 12, 24, and 52/Withdrawal Visit and as another efficacy variable at Weeks 2, 4, 6, 8, 20, 36, and 40.

A summary of these results at weeks 12, 24 and 52 are summarised in **Table 19**.

Table 19. Summary of subjects achieving LDA at Weeks 12, 24, and 52 (FAS1, with NRI)

Visit	PBO+MTX N=213 n (%)	CZP+MTX N=655 n (%)	Odds ratio [a] CZP+MTX/ PBO+MTX	Odds ratio [a] 95% CI	p-value [a]
Week 12	40 (18.8)	207 (31.6)	1.992	1.353, 2.934	<0.001
Week 24	65 (30.5)	260 (39.7)	1.475	1.049, 2.073	0.025
Week 52	84 (39.4)	358 (54.7)	1.867	1.345, 2.591	<0.001

CI=confidence interval; CZP=certolizumab pegol; DAS28(ESR)=disease activity score-28 joint count erythrocyte sedimentation rate; FAS1=Full Analysis Set Period 1; LDA=low disease activity; MTX=methotrexate; NRI=nonresponder imputation; PBO=placebo; RA=rheumatoid arthritis Note: LDA was defined as DAS28(ESR) ≤3.2.

[a] *Odds ratio: CZP+MTX/PBO+MTX (and corresponding p-value) from a logistic regression model with factors for treatment, region, and time since RA diagnosis at Baseline (≤4 months vs >4 months).*

Change from Baseline in DAS28 (ESR), CDAI and SDAI by visit

At Baseline, the mean DAS28 (ESR) was similar between the CZP+MTX group and the PBO+MTX group. Subjects in the CZP+MTX group had a greater decrease in DAS28 (ESR) compared with the PBO+MTX group which was observed as early as Week 2 and continued through Week 52. At Week 52, the CZP+MTX group had a greater mean decrease from Baseline in DAS28(ESR) compared with the PBO+MTX group (-3.6 vs -3.0 points).

Remission status as determined by CDAI and SDAI showed also similar trends to the results observed with the DAS28(ESR) criteria in that a greater proportion of subjects in the CZP+MTX group were in remission compared with the PBO+MTX group beginning at Week 2 and continuing through Week 52 for CDAI and SDAI.

The results were consistent across all definitions of remission. For most remission criteria analyses, the difference between treatment groups was less at Week 12 than at other visits. At Week 24, however, maxima could be experienced in odds ratios for all remission criteria. Of note, there was a consistent and clear superiority of the CZP+MTX group over the PBO+MTX group from Week 20 onwards.

EULAR response by visit

A EULAR response of good was defined as an improvement in DAS28 (ESR) of >1.2 and a present score of ≤ 3.2. A EULAR response of moderate was defined as an improvement in DAS28 (ESR) of >0.6 to ≤1.2 and a present score of ≤ 5.1 or an improvement in DAS28 (ESR) of >1.2 and a present score of >3.2. A subject was considered a EULAR responder if their EULAR response was good or moderate.

The proportion of EULAR responders increased over time in the CZP+MTX group from Week 2 (65.2%) through Week 20 (87.2%) reaching a plateau at Week 20 that continued through Week 52; the PBO+MTX group showed the same trend but with a consistently smaller proportion of responders at each time point. At Week 52, the proportion of EULAR responders was 89.9% in the CZP+MTX group compared with 82.2% in the PBO+MTX group.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 20. Summary of Efficacy for trial RA0055

Title: A multicenter, randomized, double-blind, placebo-controlled, study to evaluate the efficacy and safety of certolizumab pegol in combination with methotrexate for inducing and sustaining clinical response in the treatment of DMARD-naïve adults with early active rheumatoid arthritis.		
Study identifier	RA0055	
Design	multicenter, randomized, double-blind, placebo-controlled study	
	Period1 - Run-in+main phase (Period2 - Extension phase)	6 + 46 weeks = 52weeks (52 weeks, Not completed yet)
Hypothesis	Superiority study. CZP plus methotrexate are superior to PBO plus methothrexate also in patients not treated with MTX or other DMARDs.	

Treatments groups	PBO+MTX	Placebo sc Q2W from Week 0 until Week 50, MTX p.os once weekly from Week 0 until Week 51 number of randomized subjects: 219, including 2 subjects randomized by mistake.
	CZP+MTX	CZP 400mg (sc) at Weeks 0, 2, 4, CZP 200mg sc Q2W from Week 6 until Week 50, MTX p.os once weekly from Week 0 until Week 51 number of randomized subjects: 660
	randomization rate	PBO:CZP 1:3
Endpoints and definitions	Primary endpoint	Proportion of subjects in sustained remission (DAS28(ESR)<2.6 at Week 40 *and* Week52)
	Secondary endpoint	Proportion of subjects in sustained LDA (DAS28(ESR≤3.2at Week 40 *and* Week52)
	Secondary endpoints	Change from Baseline in Tender Joint Count (TJC)
		Change from Baseline in Swollen Joint Count (SJC)
		Erythrocyte Sedimentation Rate (ESR) ratio to Baseline
		CRP ratio to Baseline
		Change from Baseline in Patient Global Assessment of Disease Activity (PtGADA):
		Change from Baseline in Physician's Global Assessment of Disease Activity (PhGADA)
		Change from Baseline in Patient Assessment of Arthritis Pain (PtAAP)
		Change from Baseline in Health Assessment Questionnaire−Disability Index (HAQ−DI)
		Change from Baseline in DAS28(ESR)
		Change from Baseline in CDAI and SDAI
		Proportion of subject with good/moderate EULAR response
		ACR 20/50/70 response in relation to Baseline
		Change from Baseline in the mTSS
		Proportion of subject with radiographic nonprogression (Change in mTSS≤0.5)
Endpoints and definitions	Secondary endpoints	Change from Baseline in joint erosion score
		Change from Baseline in joint narrowing score
		Change from Baseline in Short Form 36-items Health Survey (SF-36) PCS (Physical Component Summary) and PF (Physical Functioning) domain scores
		Change from Baseline in BRAF-MDQ total score
Database lock	29 Aug 2014	

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	Full Analysis Set (FAS1): Subjects included in the FAS1 had valid Baseline and post-Baseline DAS28(ESR) score RAD1 Set: subjects in the FAS1 who had provided valid radiographs (ie, radiographs resulting in a nonmissing mTSS score) at Baseline and at Week 52 or the Withdrawal Visit.

Descriptive statistics and estimate variability	Treatment group	CZP+MTX group	PBO+MTX group	CZP+MTX/ PBO+MTX (Odds ratio)
	Number of subject	655	213	-
	n of subjects in sustained remission (odds ratio)	189 (FAS with NRI)	32	2.283
	95 % CI	-	-	1.503, 3.468
	n of subjects in sustained LDA (odds ratio)	287 (FAS with NRI)	61	1.957
	95 % CI	-	-	1.384, 2.767
	n of subjects in remission at w52 - DAS28(ESR) <2.6 (odds ratio)	279 (FAS with NRI)	57	2.039
	95 % CI	-	-	1.437, 2.895
	n of subjects in remission at w52 -ACR-EULAR 2011 remission criteria (odds ratio)	212 (FAS with NRI)	44	1.824
	95 % CI	-	-	1.253, 2.656
	n of subjects in remission at w52 -ACR-EULAR 2011 remission criteria, simplified (odds ratio)	231 (FAS with NRI)	53	1.625
	95 % CI			1.139, 2.319
Descriptive statistics and estimate variability	n of subjects in remission at w52 CDAI≤2.8 (odds ratio)	255 (FAS with NRI)	56	1.771
	95 % CI			1.247, 2.515
	n of subjects in remission at w52 SDAI≤3.3 (odds ratio)	255 (FAS with NRI)	53	1.917
	95 % CI			1.343, 2.736
	n of subjects in DAS28(ESR) LDA at w52 (odds ratio)	358 (FAS with NRI)	84	1.867
	95 % CI			1.345, 2.591
	n of ACR50 responders at w52 (odds ratio)	405 (FAS with NRI)	112	1.446

	95 % CI			1.052, 1.989
	n of ACR70 responders at w52 (odds ratio)	336 (FAS with NRI)	85	1.571
	95 % CI			1.142, 2.163
	n of subjects with radiographic nonprogression at w52 (change from Baseline in mTSS of ≤0.5 units)	371 (RAD1 with linear extrapolation)	81	2.385
	95 % CI			1.664, 3.419
	n of subjects reaching normative physical function at w52 (HAQ-DI score ⩽0.5)	315 (FAS with NRI)	76	1.668
	95 % CI			1.207, 2.305
		CZP+MTX group	PBO+MTX group	CZP-PBO
	Change from the Baseline at w52 DAS28(ESR) CZP-PBO difference (LS mean)	-3.615 (FAS with LOCF)	-3.014	-0.601
	95 % CI			-0.840, -0.363
	Change from the Baseline at w52 CDAI CZP-PBO difference (LS mean)	-33.11 (FAS with LOCF)	-29.09	-4.01
	95 % CI			-5.83, -2.19
Descriptive statistics and estimate variability	Change from the Baseline at w52 SDAI (LS mean) CZP-PBO difference	-34.55 (FAS with LOCF)	-30.24	-4.32
	95 % CI			-6.23, -2.40
	Change from the Baseline at w52 mTSS CZP-PBO difference***	0.2(RAD ANCOVA)	1.8	- 0.978
	95 % CI			-0.500, -1.005

	Change from the Baseline at w52 HAQ-DI, Means (SE) CZP-PBO difference	-0.997(FAS with LOCF)	-0.819	-0.177
	95 % CI			-0.273, -0.082

Effect estimate per comparison	Primary endpoint: n of subjects in ***sustained*** **remission**	CZP+MTX group	PBO+MTX group
		N= 655	N=213
		Odds ratio	2.283
		95 % CI	1.503, 3.468
		P-value* (log regression model)	<0.001
	Secondary endpoint: n of subjects in ***sustained*** **LDA**	CZP+MTX group	PBO+MTX group
		N= 655	N=213
		Odds ratio	1.957
		95 % CI	1.384, 2.767
		P-value* (log regression model)	<0.001
	Secondary endpoint: n of subjects **in remission** at w52 - DAS28(ESR) <2.6	CZP+MTX group	PBO+MTX group
		N= 655	N=213
		Odds ratio	2.039
		95 % CI	1.437, 2.895
		P-value* (log regression model)	<0.001
	n of subjects **in remission** at w52 -ACR-EULAR 2011 remission criteria	CZP+MTX group	PBO+MTX group
		N= 655	N=213
		Odds ratio	1.824
		95 % CI	1.253, 2.656
		P-value* (log regression model)	0.002
	n of subjects **in remission** at w52 -ACR-EULAR 2011 remission criteria, simplified	CZP+MTX group	PBO+MTX group
		N= 655	N=213
		Odds ratio	1.625
		95 % CI	1.139, 2.319
Effect estimate per comparison		P-value* (log regression model)	0.007
	n of subjects **in remission** at w52 CDAI≤2.8	CZP+MTX group	PBO+MTX group
		N= 655	N=213
		Odds ratio	1.771
		95 % CI	1.247, 2.515
		P-value* (log regression model)	0.001
	n of subjects **in remission** at w52 SDAI≤3.3	CZP+MTX group	PBO+MTX group
		N= 655	N=213
		Odds ratio	1.917
		95 % CI	1.343, 2.736
		P-value* (log regression model)	<0.001

	n of subjects **in LDA at w52**	CZP+MTX group	PBO+MTX group
		N= 655	N=213
		Odds ratio	1.867
		95 % CI	1.345, 2.591
		P-value* (log regression model)	<0.001
	n of ACR50**** responders at w52 (odds ratio)	CZP+MTX group	PBO+MTX group
		N=405	N=112
		Odds ratio	1.446
		95 % CI	1.052, 1.989
		P-value* (log regression model)	P=0.023
	n of ACR70 responders at w52 (odds ratio)	CZP+MTX group	PBO+MTX group
		N=336	N=85
		Odds ratio	1.581
		95 % CI	1.142, 2.163
		P-value* (log regression model)	P=0.005
	n of subjects with radiographic nonprogression at w52(change from Baseline in mTSS of ≤0.5 units) (RAD1 with linear extrapolation)	CZP+MTX group	PBO+MTX group
		N=371	N=81
		Odds ratio	2.385
		95 % CI	1.664, 3.419
		P-value* (log regression model)	<0.001
	n of subjects reaching normative physical function at w52 (HAQ-DI score ⩽0.5) (FAS with NRI)	CZP+MTX group	PBO+MTX group
		N=315	N=76
		Odds ratio	1.668
Effect estimate per comparison		95 % CI	1.207, 2.305
		P-value* (log regression model)	0.002
	Change from the Baseline at w52 DAS28(ESR) LS Means (SE), FAS with LOCF	CZP+MTX group	PBO+MTX group
		N=646	N=210
		-3.615 (0.069)	-3.014 (0.109)
		Difference in LS Means (CZP-PBO, SE)	-0.601 (0.121)

		95 % CI	-0.840, -0.363
		P-value** (ANCOVA model)	<0.001
	Change from the Baseline at w52 CDAI LS Means (SE), FAS with LOCF	CZP+MTX group	PBO+MTX group
		644	210
		-33.11 (0.52)	-29.09 (0.84)
		Difference in LS Means (CZP-PBO, SE)	-4.01 (0.93)
		95 % CI	-5.83, -2.19
		P-value** (ANCOVA model)	<0.001
	Change from the Baseline at w52 SDAI LS Means (SE), LOCF	CZP+MTX group	PBO+MTX group
		644	210
		-34.55 (0.55)	-30.24 (0.88)
		Difference in LS Means (CZP-PBO, SE)	-4.32 (0.98)
		95 % CI	-6.23, -2.40
		P-value** (ANCOVA model)	<0.001
	Change from the Baseline at w52 mTSS, Means (SD) linear extrapolation	CZP+MTX group	PBO+MTX group
		528 (RAD1)	163 (RAD1)
		0.2 (3.2)	1.8 (4.3)
		Difference in Mean changes from Baseline (CZP-PBO)	-0.978
		95 % CI*****	-0.500, -1.014
		P-value****** (rank ANCOVA model)	<0.001
	Change from the Baseline at w52 HAQ-DI, Means (SE) (FAS with LOCF)	CZP+MTX group	PBO+MTX group

Notes	*p value was estimated from a logistic regression model with factors for treatment, region, and time since RA diagnosis at Baseline ** ANCOVA model with treatment, region, and time since RA diagnosis at Baseline (≤4 months vs >4 months).as factors and Baseline value as a covariate. *** Hodges-Lehmann point estimate of shift and 95% asymptotic (Moses) CI. **** Changes of individual components of ACR response from Baseline by time are compiled in Table 18. ***** Hodges-Lehmann point estimate of shift and 95% asymptotic (Moses) CI. Note: The mTSS has a possible range from 0 to 448 with lower scores meaning less structural damage in the hands and feet. Radiographic nonprogression was defined as a change from Baseline in mTSS≤0.5. ******ANCOVA on the ranks with treatment, region, and time since RA diagnosis at Baseline (≤4 months vs >4 months) as factors and Baseline rank as a covariate Note: A subject reached normative physical function if he/she had a HAQ-DI score≤0.5

Supportive study

Methods

RA0096 is an ongoing, Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group comparison study in adult subjects with early RA who were MTX-naïve and had poor prognostic factors. After an up to 4-week Screening Period subjects received CZP+MTX or placebo (PBO)+MTX during a 52-week, double-blind, placebo-controlled Treatment Period. Subjects completing the Treatment Period were eligible to enroll in the 52-week Follow-Up Observation Period providing MTX monotherapy. Rescue treatment was available to subjects meeting predefined criteria.

The most notable differences in design between RA0096 and RA0055 were as follows:

- RA onset is defined as the time when continuous symptoms of RA started in RA0096 (versus the time of diagnosis in RA0055);
- RA0096 required no minimum TJC, SJC, CRP, or ESR;
- MTX dosing started at 8mg/week (versus 10mg/week in RA0055) and was escalated to a maximum of 16mg/week by Week 8 (versus a maximum of 25mg/week in RA0055). The minimum MTX dose was 8mg/week (versus a minimum of 15mg/week in RA0055);
- RA0096 excluded for any previous use of MTX, leflunomide or biological DMARD (versus any prior use of all DMARDs except anti-malarials in RA0055);
- The primary endpoint in RA0096 was the change in mTSS at Week 52 (versus sustained remission in RA0055).

Study participants

RA0096 included Japanese adult male and female subjects ≥20 years and <65 years of age who were within their first year of RA since onset (defined as the time when continuous symptoms of arthritis started). Subjects were naïve to MTX and were required to have active disease in a moderate or higher degree of their DAS28[ESR]) ≥3.2. Subjects were to have a high anti-cyclic citrullinated peptide (CCP) antibody titer (see below) and must have met at least 1 of the other 2 criteria for poor prognostic factors.

- High anti-CCP antibody titer: ≥13.5U/mL (3 times the standard range);
- Positive rheumatoid factor: >20IU/mL (standard range);

- Presence of bone erosion (evidenced by the x-ray examination of hands and feet).

Treatments

Subjects meeting the eligibility criteria were allocated to 1 of the following treatment groups:

- Certolizumab pegol administered subcutaneously (sc) at a loading dose of CZP 400mg every second week (Q2W) at Weeks 0, 2, and 4; followed by a dose of CZP 200mg Q2W sc from Week 6 to Week 50 and an oral dose of MTX administered from Week 0 onwards;
- Placebo administered sc Q2W at Weeks 0, 2, and 4; followed by placebo Q2W sc from Week 6 to Week 50 and an oral dose of MTX administered from Week 0 onwards

Rescue treatment was available to subjects who did not achieve an improvement of symptoms at and after Week 24 (Visit 16). The Rescue Treatment Period started after the subject's dropout from the original study schedule and lasted up to Week 104.

Objectives

The objective of this study was to compare the efficacy of certolizumab pegol (CZP) in combination with MTX in subjects with early RA, who were MTX-naïve and had poor prognostic factors, to that of MTX monotherapy with inhibition of joint damage progression after 1 year of treatment as the primary endpoint. In addition, maintenance of the efficacy of CZP is being investigated explorative in a Follow-Up Observation Period for 1 year with MTX monotherapy after CZP withdrawal. The safety, pharmacokinetics, and immunogenicity were also investigated.

Outcomes/endpoints

The change from Baseline in mTSS at Week 52 was the primary endpoint. The DAS28(ESR) and ACR/EULAR remission rates at Week 24 and Week 52 were secondary endpoints.

Results

Baseline data

The mean DAS28(ESR) score was 5.45, and scores were comparable in both treatment groups. Approximately 60% of subjects had high disease activity (DAS28[ESR] score >5.1) and approximately 35% had moderate disease activity (DAS[ESR] score 3.2 to 5.1). Five subjects (3.1%) in the CZP+MTX group and 3 subjects (1.9%) in the PBO+MTX group had a DAS28(ESR) score of <3.2 at Baseline.

No subject had received MTX, leflunomide, or biological products; however, 19% of subjects had received a prior DMARD.

The most notable differences between the RA0055 and RA0096 populations at Baseline were as follows:

- RA0096 included Japanese subjects exclusively.
- RA0096 included a higher proportion of subjects with moderate disease activity.
- RA0096 included subjects (19%) who were not DMARD-naïve; however, all were MTX naïve.

Numbers analysed

A total of 319 subjects were randomized (161 subjects to CZP+MTX and 158 to PBO+MTX).

Two subjects in the CZP+MTX group and 1 subject in the PBO+MTX group did not receive the study drug due to violation of inclusion/exclusion criteria or investigator decision. The percentage of subjects who

completed the Treatment Period was higher in the CZP+MTX group (68.9%) as compared with the PBO+MTX group (46.2%). Lack of efficacy was the major reason for discontinuation, accounting for 22.4% and 44.9% of subjects in the CZP+MTX and PBO+MTX groups.

Outcomes and estimation

The result of the primary analysis of the mTSS at Week 52 for the FAS was statistically significant (p<0.001, **Table 21**).

Table 21. Actual values and changes from Baseline in mTSS scores at Week 52 (FAS, rank ANCOVA, linear extrapolation) in Study RA0096

Parameter	Treatment group				Difference (CZP+MTX vs PBO+MTX)
	PBO+MTX N=157		CZP+MTX N=159		
	Actual	CFB	Actual	CFB	
Baseline					
n	157	-	159	-	-
Mean (SD)	5.95 (15.30)	-	5.16 (8.76)	-	-
Median (range)	1.50 (0.0-120.5)	-	1.50 (0.0-55.5)	-	-
Week 52					
n	157	157	158	158	-
Mean (SD)	7.53 (16.68)	1.58 (4.86)	5.55 (9.35)	0.36 (2.70)	-
Median (range)	2.50 (0.0-125.7)	0.00 (-3.0-47.4)	1.50 (-1.8-57.0)	0.00 (-9.8-25.1)	-
Primary analysis					
Diff. (95% CI)[a]	-	-	-	-	0.00 (0.00, 0.00)
p-value[b]	-	-	-	-	<0.001
Sensitivity analysis					
LS Mean (SE)[c]	-	1.57 (0.31)	-	0.38 (0.31)	-1.19 (0.44)
Diff. 95% CI[c]	-	-	-	-	(-2.06, -0.32)
Diff. p-value[c]	-	-	-	-	0.007

ANCOVA=analysis of covariance; CZP=certolizumab pegol; CFB=change from Baseline; CI=confidence interval; Diff.=difference; FAS=Full Analysis Set; LS Mean=least square means; MTX=methotrexate; mTSS=modified total Sharp score; PBO=placebo, SD=standard deviation; SE=standard error

[a] *The Hodges-Lehmann point estimate of shift and 95% CI was used.*

[b] *The ANCOVA on the ranks with treatment as factors and Baseline rank as covariate was used.*

[c] *The ANCOVA model with the following factors: treatment and Baseline value was used.*

The percentage of subjects with non-progression at Week 52 was higher in the CZP+MTX group as compared to the PBO+MTX group for the mTSS (82.9% vs 70.7%) as summarised in **Table 22**.

Table 22. Subjects with non-progression of joint damage at Week 52 (FAS, linear extrapolation) in Study RA0096

Parameter	Treatment group				Difference (CZP+MTX vs PBO+MTX)
	PBO+MTX N=157		CZP+MTX N=159		
	n (%)	95% CI[a]	n (%)	95% CI[a]	
mTSS					
n	157	-	158	-	-
Subjects with nonprogression	111 (70.7)	(62.9, 77.7)	131 (82.9)	(76.1, 88.4)	-
Subjects with progression	46 (29.3)	-	27 (17.1)	-	-
p-value[b]	-	-	-	-	0.011

CZP=certolizumab pegol; CI=confidence interval; FAS=Full Analysis Set; MTX=methotrexate; mTSS=modified total Sharp score; PBO=placebo
Note: nonprogression was defined as a change from Baseline of ≤0.5.
[a] *A 95% CI for the progression rate was used.*
[b] *Fisher's exact test with CZP+MTX and PBO+MTX was used.*

At Week 24, the percentage of subjects meeting DAS28 (ESR) remission criteria was 52.8% in the CZP+MTX group compared with 30.6% in the PBO+MTX group. This difference between the treatment groups was maintained at Week 52 (57.2% versus 36.9%), and statistical significance (p<0.001) was achieved at both time-points.

At Week 24, the percentage of subjects meeting SDAI-based ACR/EULAR remission criteria in the CZP+MTX group was 48.4% compared with 29.3% in the PBO+MTX group. This difference between the treatment groups was maintained at Week 52 (57.9% versus 33.8%). Statistical significance (p<0.001) was achieved at both time-points.

At Week 24, the percentage of subjects meeting Boolean-based ACR/EULAR remission criteria in the CZP+MTX group was 36.5% compared with 22.3% the PBO+MTX group. This difference between the treatment groups was maintained at Week 52 (45.3% versus 28.0%). Statistical significance (p=0.007 at Week 24 and p=0.002 at Week 52) was achieved at both time-points.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Cimzia is currently approved for the treatment of the following conditions: axial spondyloarthritis (axSpA), psoriatic arthritis (PsA), and moderate to severe Rheumatoid arthritis when the response to disease –modifying DMARDs including MTX has been inadequate.

The MAH submitted an application to register an extended indication in severe, active and progressive RA in adults not previously treated with MTX or other DMARDs. The proposed wording for this indication was in line with other TNF-blockers who have achieved approval for this indication. To support the application, efficacy data from a pivotal globally conducted study (RA0055) and a supportive Japanese study (RA0096) were provided. Both studies compared MTX-treatment to MTX in combination with Cimzia. Study RA0055 primarily aimed to show higher proportion of sustained remission in the Cimzia-treated group at week 52, whereas study RA0096 was designed to show a difference in change from baseline in mTSS at week 52 between groups.

Study RA0055 was a 24-month (104 week) randomised, double-blind, parallel-group, placebo-controlled

Phase 3 study to evaluate the efficacy and safety of CZP in combination with MTX for inducing and sustaining clinical response in the treatment of DMARD-naïve adults with early active RA. The study consisted of 2 consecutive periods of 52 weeks each. The primary endpoint, the proportion of subjects in sustained remission (defined as DAS28 (ESR) <2.6 at both Week 40 and Week 52 Visits) at Week 52. Key secondary endpoint was the proportion of subjects in sustained LDA (defined as DAS28 (ESR) ≤3.2 at Week 40 and Week 52 Visits) at Week 52. Thus, subjects in sustained remission were included among subjects in sustained LDA.

The study design employed a fast titration of MTX (within 8 weeks, with a starting dose of 10mg/week) and the mean doses achieved in each treatment group were >20mg/week. These doses were close to the maximum allowed MTX dose (25mg/week achieved by Weeks 6 to 8, as per the protocol) and were in line with current recommendations. MTX treatment was therefore considered to be optimised.

Methods to achieve and maintain blinding were acceptable as was the randomisation procedure. Subjects were randomly assigned to the CZP+MTX or PBO+MTX treatment arm in a 3:1 ratio with randomisation stratified by the time since RA diagnosis at Baseline (≤4 months or >4 months).

The analysis approach and the statistical methods planned were overall acceptable. The primary analysis set was the FAS1 excluding subjects without a post-baseline assessment. FAS1 was used for all analyses of efficacy data except for the radiographic analyses which were based on the Radiographic Set (RAD1) and comprised the subset of subjects in FAS1 who had valid radiographs (i.e. resulting in a non-missing mTSS score) at baseline and at week 52 or the withdrawal visit.

Missing data was handled using a non-responder imputation (dichotomous variables), LOCF (change from baseline) or, for mTSS, linear extrapolation. Few sensitivity analyses were planned and those performed were mainly based on analyses excluding subjects with protocol deviations or those who did not complete through week 52 (i.e. PP1, CS1).

For the primary, the key and, three additional secondary endpoints a hierarchical test procedure was applied. Although no justification for the choice or ordering of secondary endpoints 3-5 (ACR50, change from baseline in HAQ-DI and change from baseline in mTSS) has been found the multiplicity approach is per se acceptable. A few changes were made to the planned analyses but they were considered minor.

Overall, 23.7% (155/655); CZP+MTX and 32.9% (70/213); PBO+MTX of subjects included in the full analysis set (FAS1) discontinued before week 52. No subjects used any prohibited medication and the proportion of subjects that used rescue were similar between groups; 16.5% (108/655) CZP+MTX and, 16.0% (34/213), PBO+MTX).

Efficacy data and additional analyses

The proportion of subjects in sustained remission at Week 52 in the CZP+MTX group was 28.9% compared with 15.0% (p<0.001) in the PBO+MTX group (FAS1 with non-responder imputation). The proportion of subjects in sustained LDA at week 52 in the CZP+MTX group was 43.8% compared with 28.6% (p<0.001) in the PBO+MTX group. It is acknowledged that sustained remission or LDA are clinically important endpoints, and this difference was considered to be clinically meaningful.

By age group, the proportion of subjects ≥65 years in sustained remission was not different between groups (p=0.116); however, the odds ratio was 2.808, which was similar to the odds ratio for subjects <65 years of age (2.230), indicating that the response was similar in both subgroups. Due to the comparatively small sample size in the ≥65 years subgroup, these results should be interpreted with caution.

ACR response

61.8% of subjects in the CZP+MTX group compared with 52.6% in the PBO+MTX group were ACR50 responders at Week 52 (p=0.023). The proportion of ACR50 responders increased over time in both groups; however, the proportion was greater in the CZP+MTX group compared with the PBO+MTX group. At each visit, the p-value for the difference from PBO+MTX was ≤0.05 with the exception of Weeks 24 and 36. However, the CHMP considered that the lack of statistical difference at week 24 and 36 could be reflective of a difference in the time course of effect of CZP and MTX. In addition the CHMP noted that the proportion of responders at all the time points was higher in the CZP+MTX group than in the PBO+MTX group. Moreover, there was a significant difference between the groups for the most stringent ACR70. Therefore, the observed results were considered to be of clinical relevance.

The CHMP noted that difference in the proportion of ACR20 responders between the two treatment arms did not reach significance, however, the Applicant's view that this goal is not very hard to achieve when treatment is initiated early in the disease, was endorsed by the CHMP.

Functional improvement

After 52 weeks, HAQ-DI had decreased more in the CZP-treated group. However, the difference, 0.177 was not very large as MCID has in literature been estimated to be 0.22. The relatively small difference was due to a relatively large proportion of improved patients in the placebo group, mean -0.819 at week 52, as compared to -0.997 in the Cimzia-treated group.

Inhibition of progression of structural damage

The radiographic analyses (e.g. mTSS, radiographic non-progression) were based on the Radiographic Set (RAD1) including only subjects who had valid radiographs at baseline and at the Week 52 or early Withdrawal visit. In those analyses 20% (132/660) and 25% (56/219) of randomised subjects in the CZP+MTX and PBO+MTX arm respectively, were excluded. Additional/sensitivity analyses based on FAS1 were therefore requested and were provided by the Applicant.

The change from Baseline in mTSS was lower in the CZP+MTX group compared to the PBO+MTX group, with mean changes from Baseline of 0.2 and 1.8, respectively (p<0.001), indicating a protective effect of Cimiza on joint destruction in this population of early RA with poor prognostic factors. Although the difference between the CZP+MTX arm and the PBO+MTX arm was smaller in all the sensitivity analyses ranging from -0.284 to -0.619 as compared to the outcome in the primary pre-defined analysis, -0.978, the difference was still statistically significant in favour of CZP+MTX over PBO+MTX with the p-value being <0.001 in all three sensitivity analyses.

Consistently, the proportion of subjects with radiographic non progression at Week 52 (defined as a change from Baseline to Week 52 in mTSS of ≤0.5) was greater in the CZP+MTX (70.3%) group compared with the PBO+MTX group (49.7%; p<0.001).

As requested, the Applicant also submitted sensitivity analysis of the proportion of subjects with radiographic non-progression at Week 52 based on FAS1 and using a non-responder imputation. In this analysis the proportion of subjects with radiographic non progression, decreased from 70.3% (371/528) to 57.0% (371/651) in the CZP+MTX arm and from 49.7% (81/163) to 38.2% (81/212) in the PBO+MTX. The difference between the two treatment arms was however still in favour of CZP+MTX (OR: 2.12; 95% CI 1.54, 2.91; p<0.001) supporting the outcome as shown in the primary pre-defined analysis (OR: 2.38; 95% CI 1.66, 3.42; p<0.001) where subjects without valid radiographs were excluded.

In addition, information on time points for x-rays in early withdrawals was provided by the Applicant. Overall, more subjects in the PBO+MTX arm than in the CZP+MTX arm had radiographs taken at the

early withdrawal visit; 18.4% (30/163) and 9.5% (50/528) in the PBO+MTX and the CZP+MTX arm respectively.

Taken together, these observations provided further evidence in support of the claim that CZP+MTX is superior to PBO+MTX in the inhibition of the progression of structural damage after 52 weeks of treatment in DMARD-naïve subjects with severe, active, and progressive RA.

Other efficacy endpoints
For subjects who achieved an improvement of ≥10mm from Baseline (MCID) in patients global assessment of disease activity (PtGADA), no difference between groups was seen at Week 12 (76.1% vs 76.6% in the placebo group and the Cimzia treated group respectively). At week 52, the proportions were however 59.6% and 68.2% respectively. The CHMP considered that this observation could be explained by the fact that MCID in PtGADA is not difficult to achieve, in particular in previously DMARD-naïve subjects initiating MTX treatment and that is not a very sensitive tool for capturing changes between different treatments. In addition, CZP-treated subjects achieved higher levels above the MCID threshold than only MTX-treated subjects indicating a better clinical improvement in the CZP group.

At Week 52, the proportion of EULAR responders was 89.9% in the CZP+MTX group compared with 82.2% in the PBO+MTX group (p=0.003). The difference is modest, but it was noted that for subjects with a "good" EULAR response, the proportion of subjects increased over time in the CZP+MTX group from Week 2 (8.2%) through Week 52 (60.6%); whereas the PBO+MTX group increased with 1.4% at Week 2 and 43.7% at Week 52.

Finally, the results from the Japanese study RA0096 supported the claim that initial treatment with CZP+MTX may inhibit progression of structural damage and reduce clinical signs and symptoms better than initial treatment with PBO+MTX.

2.4.3. Conclusions on the clinical efficacy

Study RA0055 has provided results that support efficacy of Cimzia in combination with MTX in an early DMARDs-naïve RA population with poor prognostic factors such as CCP and elevated RF or presence of bone erosions in the hands or feet. The effect was in general better for signs and symptoms, and a significantly larger group achieved sustained remission, a clinically meaningful primary endpoint that is used for the first time in a study on a TNF-blocker. A beneficial effect on joint destruction has also been shown, and these results were further supported by the Japanese study RA0096.

2.5. Clinical safety

Introduction

The safety data corresponding to Period 1 from RA0055 and RA0096 were supported, where relevant, by long-term safety data from the overall RA pool, which comprised of 2 sets of data:

- The Placebo-Controlled (PC) Data: consisting of data from PC studies or PC study phases: C87002 (PC phase), C87004 (PC phase), C87011, C87014, C87027, C87050, C87076, C87077 (PC phase), C87094 (PC phase), and RA0017 (PC phase).
- All Studies Data: consisting of data from all studies/all phases: PHA001, C87002, C87004, C87011, C87014, C87015, C87027, C87028, C87050, C87051, C87076, C87077, C87094, and RA0017.

For the PC Data Pool, the following treatment groups were summarised: Placebo; CZP 200mg every 2 weeks (Q2W; following a 400mg loading regimen); CZP 400mg every 4 weeks (Q4W); and All CZP in PC. For the All Data Pool, the All CZP in PC and All CZP in All Studies treatment groups were summarized.

A subgroup of 401 subjects, the early RA sub-pool, was created from the overall RA pool to include only those subjects with RA disease of less than 1 year duration. This early RA sub-pool was created to explore the long-term safety of CZP treatment in a larger population of subjects which more closely matched the RA0055 population, however unlike RA0055, the subjects in the early RA sub-pool were not DMARD naïve.

Study RA0055

Patient exposure

A total of 1377 subjects were enrolled (i.e. screened and signed an Informed Consent form) in the study, of which 880 subjects were randomised. The most common reason for screen failure was ineligibility (420/1377, 30.5%).

Exposure of these patients to treatment in this study is summarised in **Table 23**.

Table 23. Extent of exposure during Period 1 of Study RA0055 (SS1)

	PBO+MTX N=217	CZP+MTX N=659
Period 1 patient time at risk (days) [b]		
n	217	659
Mean (SD)	324.1 (113.0)	335.5 (102.1)
Median	364.0	364.0
Min, max	15, 431	16, 427
Total Period 1 patient-years at risk [c]	192.6	605.3
Average weekly dose of MTX after Week 8 [d] **(mg)**		
n	200	615
Mean (SD)	22.3 (3.6)	21.1 (4.2)
Median	25.0	22.7
Min, max	14, 25	7, 25

CZP=certolizumab pegol; max=maximum; min=minimum; MTX=methotrexate; PBO=placebo; SD=standard deviation; SS1=Safety Set 1

[b] *Patient time at risk=date of last Period 1 injection (not including the Week 52 injection) – date of first Period 1 injection + 70 days, censored at last patient contact (if withdrawn) or first Period 2 injection (if continuing).*

[c] *Patient-years at risk was the total patient time at risk divided by 365.25.*

[d] *Calculated from Week 8 (end of MTX Titration Period). Subjects with no MTX dosing data after Week 8 were not included.*

The mean weekly dose of MTX following the Titration Period (up to Week 8) was similar between the groups (21.1 and 22.3mg/week, in the CZP+MTX and PBO+MTX groups, respectively). These mean values were close to the maximum allowed MTX dose (per the protocol) of 25mg/week.

Subjects who had no improvement at Week 20 (i.e., DAS28 (ESR) ≤0) were withdrawn from the study (**Table 24**). Those with insufficient improvement were re-evaluated at Week 24 (and also at Week 36

for Sweden only) and Week 52. Those subjects who did not have sufficient improvement in their disease activity (i.e. DAS28 (ESR) ≤3.2 and/or improvement in DAS28 (ESR) of ≥1.2 points since Baseline) at Weeks 24, 36, or 52 were withdrawn from the study.

Table 24. Mandatory withdrawals per the IXRS in Study RA0055

	PBO+MTX	CZP+MTX	All subjects
	N=219	N=660	N=879
	n (%)	n (%)	n (%)
Week 20	3 (1.4)	3 (0.5)	6 (0.7)
Week 24	9 (4.1)	9 (1.4)	18 (2.0)
Week 36 (Sweden) [a]	1 (0.5)	5 (0.8)	6 (0.7)
Week 52	72 (32.9)	197 (29.8)	269 (30.6)
TOTAL	85 (38.8)	214 (32.4)	299 (34.0)

CZP=certolizumab pegol; IXRS=Interactive Voice/Web Response System; MTX=methotrexate; PBO=placebo
[a] *Fifteen subjects were randomized in Sweden.*

Adverse events

A summary of adverse events observed in Period 1 of study RA0055 is presented in **Table 25**.

Table 25. Overall summary of adverse events during Period 1 of RA0055 (SS1)

	PBO+MTX N=217	CZP+MTX N=659
	n (%)	n (%)
Any TEAEs	158 (72.8)	525 (79.7)
Severe TEAEs	20 (9.2)	47 (7.1)
Drug-related TEAEs	69 (31.8)	278 (42.2)
Serious TEAEs	20 (9.2)	70 (10.6)
Discontinuation due to TEAEs	20 (9.2)	57 (8.6)
TEAEs requiring dose change of MTX	14 (6.5)	73 (11.1)
TEAEs leading to death	1 (0.5)	2 (0.3)

CZP=certolizumab pegol; MTX=methotrexate; PBO=placebo; SS1-Safety Set 1
TEAE=treatment-emergent adverse event
Note: n=number of subjects reporting at least 1 TEAE in that category.
Note: Treatment emergence was defined as an adverse event starting on or after the date of first study medication administration and up to 70 days after the last (most recent) CZP or PBO dose.
Note: TEAEs having a serious flag as missing were counted as serious. TEAEs with a missing relationship to study medication were counted as related. TEAEs with a missing intensity were counted as severe.

The incidence of TEAEs was 79.7% in the CZP+MTX group and 72.8% in the PBO+MTX group. The incidence rate was 250.77/100 pt-yrs in the CZP+MTX group and 195.66/100 pt-yrs in the PBO+MTX group.

In the CZP+MTX group, TEAEs were most frequently reported in the following System Organ Classes (SOCs, summarised in **Table 26**):

- Infections and infestations (45.2% vs 35.0% for PBO+MTX),
- Gastrointestinal disorders (31.3% vs 24.4% for PBO+MTX)
- Investigations (20.8% vs 19.4% for PBO+MTX)

The incidence rates were higher in the CZP+MTX group compared with the PBO+MTX group for the following SOCs:

- Infections and infestations (71.77 vs 52.70/100 pt-yrs) and
- Gastrointestinal disorders (44.72 vs 33.99/100 pt-yrs)
- General disorders and administration site conditions (20.19 vs 15.44/100 pt-yrs)
- Metabolism and nutrition disorders (10.02 vs 6.46/100 pt-yrs)

Table 26. Incidence and exposure-adjusted incidence rates of TEAEs in all SOCs and common PTs (at least 3% of subjects in any treatment group) during Period 1 of RA0055 (SS1)

System Organ Class **Preferred term**	**PBO+MTX** **N=217**		**CZP+MTX** **N=659**	
Patient-years at risk (per 100 pt-yrs) [a]	1.93		6.05	
	n (%)	**IR [b]**	**n (%)**	**IR [b]**
Any TEAEs	**158 (72.8)**	**195.66**	**525 (79.7)**	**250.77**
Blood and lymphatic system disorders	13 (6.0)	6.92	45 (6.8)	7.76
Cardiac disorders	6 (2.8)	3.15	16 (2.4)	2.68
Congenital, familial, and genetic disorders	0	0	1 (0.2)	0.17
Ear and labyrinth disorders	3 (1.4)	1.57	9 (1.4)	1.50
Endocrine disorders	0	0	5 (0.8)	0.83
Eye disorders	13 (6.0)	7.03	24 (3.6)	4.08
Gastrointestinal disorders	53 (24.4)	33.99	206 (31.3)	44.72
Nausea	22 (10.1)	12.34	83 (12.6)	15.16
Diarrhoea	4 (1.8)	2.11	31 (4.7)	5.32
Dyspepsia	7 (3.2)	3.73	12 (1.8)	2.01
General disorders and administration site conditions	27 (12.4)	15.44	108 (16.4)	20.19
Drug intolerance	7 (3.2)	3.69	13 (2.0)	2.18
Hepatobiliary disorders	2 (0.9)	1.05	13 (2.0)	2.17
Immune system disorders	1 (0.5)	0.52	15 (2.3)	2.52
Infections and infestations	76 (35.0)	52.70	298 (45.2)	71.77
Upper respiratory tract infection	11 (5.1)	5.95	72 (10.9)	12.88
Urinary tract infection	16 (7.4)	8.63	48 (7.3)	8.34
Nasopharyngitis	13 (6.0)	7.05	46 (7.0)	8.00
Bronchitis	7 (3.2)	3.71	29 (4.4)	4.90
Sinusitis	5 (2.3)	2.63	24 (3.6)	4.04
Gastroenteritis	7 (3.2)	3.74	4 (0.6)	0.66

System Organ Class Preferred term	PBO+MTX N=217		CZP+MTX N=659	
Patient-years at risk (per 100 pt-yrs) [a]	1.93		6.05	
	n (%)	IR [b]	n (%)	IR [b]
Injury, poisoning, and procedural complications	15 (6.9)	8.20	62 (9.4)	10.90
Investigations	42 (19.4)	25.20	137 (20.8)	26.35
Alanine aminotransferase increased	9 (4.1)	4.80	42 (6.4)	7.24
Aspartate aminotransferase increased	5 (2.3)	2.65	20 (3.0)	3.37
Metabolism and nutrition disorders	12 (5.5)	6.46	57 (8.6)	10.02
Hypercholesterolaemia	5 (2.3)	2.63	20 (3.0)	3.37
Musculoskeletal and connective tissue disorders	36 (16.6)	20.51	114 (17.3)	21.18
Rheumatoid arthritis	10 (4.6)	5.29	21 (3.2)	3.53
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	3 (1.4)	1.57	12 (1.8)	1.99
Nervous system disorders	26 (12.0)	14.87	92 (14.0)	17.06
Headache	8 (3.7)	4.31	45 (6.8)	7.88
Dizziness	8 (3.7)	4.28	17 (2.6)	2.86
Pregnancy, puerperium, and perinatal conditions	0	0	1 (0.2)	0.17
Psychiatric disorders	4 (1.8)	2.12	25 (3.8)	4.24
Renal and urinary disorders	2 (0.9)	1.04	20 (3.0)	3.37
Reproductive system and breast disorders	2 (0.9)	1.04	17 (2.6)	2.85
Respiratory, thoracic, and mediastinal disorders	22 (10.1)	12.26	76 (11.5)	13.58
Cough	7 (3.2)	3.73	26 (3.9)	4.40
Skin and subcutaneous tissue disorders	31 (14.3)	18.19	119 (18.1)	22.45
Alopecia	7 (3.2)	3.75	26 (3.9)	4.42
Rash	10 (4.6)	5.39	24 (3.6)	4.06
Social circumstances	1 (0.5)	0.52	0	0
Surgical and medical procedures	0	0	5 (0.8)	0.83
Vascular disorders	9 (4.1)	4.83	39 (5.9)	6.72

CZP=certolizumab pegol; IR=incidence rate; MTX=methotrexate; PBO=placebo; PT=Preferred term; pt-yrs=patient-years; SOC=System Organ Class; SS1=Safety Set 1; TEAE=treatment-emergent adverse event

Note: n=number of subjects reporting at least 1 TEAE in that category.

Note: Treatment emergence was defined as an adverse event starting on or after the date of first study medication administration and up to 70 days after the last (most recent) CZP or PBO dose.

Note: Preferred terms are listed by descending order of frequency in the CZP+MTX group according to SOC. System Organ Classes for which no events were reported are not presented.

[a] *Patient-years at risk was based on the time from the first Period 1 injection to the last Period 1 injection (excluding the Week 52 injection) +70 days divided by 365.25, censored at last clinical contact or first Period 2 injection.*

[b] *Exposure-adjusted incidence rate=incidence of new cases (subjects experiencing the event at least once) per 100 pt-yrs.*

In the CZP+MTX group, the most commonly (i.e., those with an incidence of ≥5% in any group) reported TEAEs by PT were nausea, upper respiratory tract infection, urinary tract infection, nasopharyngitis, headache, and ALT increased. Most TEAEs were reported at a similar (<2% difference between groups) or lower incidence in the CZP+MTX group compared with the PBO+MTX group. The TEAEs that occurred in a higher percentage of subjects in the CZP+MTX group compared with the PBO+MTX group (difference of ≥2% between groups) were nausea (12.6% vs 10.1%), upper respiratory tract infection (10.9% vs 5.1%), headache (6.8% vs 3.7%), ALT increased (6.4% vs 4.1%), diarrhoea (4.7% vs 1.8%), and fatigue (2.1% vs 0); for each of these PTs, the incidence rate was also higher in the CZP+MTX group compared with the PBO+MTX group.

Severe adverse events

The incidence of any severe TEAE (**Table 27**) was slightly lower in the CZP+MTX group compared with the PBO+MTX groups (7.1% and 9.2%, respectively). The most frequently reported severe TEAE by PT was latent TB, which was reported by 5 subjects overall (3 subjects (0.5%) for CZP+MTX and 2 subjects (0.9%) for PBO+MTX). All other severe TEAEs by PT were reported at <1.0% and were similar between groups

Table 27. Incidence of severe TEAEs in all SOCs and any PTs reported by more than 1 subject during Period 1 of RA0055 (SS1)

System Organ Class **Preferred term**	**PBO+MTX** **N=217**	**CZP+MTX** **N=659**
	n (%)	**n (%)**
Any severe TEAEs	**20 (9.2)**	**47 (7.1)**
Blood and lymphatic system disorders	0	5 (0.8)
Anaemia	0	2 (0.3)
Pancytopenia	0	2 (0.3)
Cardiac disorders	1 (0.5)	6 (0.9)
Gastrointestinal disorders	0	4 (0.6)
General disorders and administration site conditions	3 (1.4)	1 (0.2)
Hepatobiliary disorders	1 (0.5)	2 (0.3)
Immune system disorders	0	1 (0.2)
Infections and infestations	6 (2.8)	13 (2.0)
Latent tuberculosis	2 (0.9)	3 (0.5)
Pneumonia	1 (0.5)	2 (0.3)
Cellulitis	1 (0.5)	1 (0.2)
Injury, poisoning, and procedural complications	3 (1.4)	5 (0.8)
Investigations	1 (0.5)	2 (0.3)
Metabolism and nutrition disorders	0	2 (0.3)
Musculoskeletal and connective tissue disorders	5 (2.3)	6 (0.9)
Osteoarthritis	1 (0.5)	2 (0.3)
Rheumatoid arthritis	2 (0.9)	1 (0.2)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	0	3 (0.5)
Nervous system disorders	1 (0.5)	3 (0.5)
Pregnancy, puerperium, and perinatal conditions	0	1 (0.2)
Renal and urinary disorders	0	1 (0.2)
Reproductive system and breast disorders	0	1 (0.2)

System Organ Class Preferred term	PBO+MTX N=217 n (%)	CZP+MTX N=659 n (%)
Respiratory, thoracic, and mediastinal disorders	4 (1.8)	4 (0.6)
Dyspnoea	1 (0.5)	2 (0.3)
Pulmonary embolism	2 (0.9)	1 (0.2)
Cough	1 (0.5)	1 (0.2)
Respiratory failure	1 (0.5)	1 (0.2)
Skin and subcutaneous tissue disorders	0	1 (0.2)
Surgical and medical procedures	0	2 (0.3)
Vascular disorders	2 (0.9)	1 (0.2)
Deep vein thrombosis	1 (0.5)	1 (0.2)

CZP=certolizumab pegol; MTX=methotrexate; PBO=placebo; PT=Preferred term; SOC=System Organ Class; SS1=Safety Set 1; TEAE=treatment-emergent adverse event
Note: n=number of subjects reporting at least 1 TEAE in that category.
Note: Treatment emergence was defined as an adverse event starting on or after the date of first study medication administration and up to 70 days after the last (most recent) CZP or PBO dose.
Note: TEAEs with a missing intensity were counted as severe.
Note: Preferred terms are listed by descending order of frequency in the CZP+MTX group according to SOC. System Organ Classes for which no events were reported are not presented.

Serious adverse event / deaths / other significant events

Serious adverse events

The incidence of SAEs was 10.6% in the CZP+MTX group and 9.2% in the PBO+MTX group The incidence rate was 12.06/100 pt-yrs in the CZP+MTX group and 10.74/100 pt-yrs in the PBO+MTX group. The incidence of SAEs leading to hospitalization or death was 8.6% in the CZP+MTX group and 7.4% in the PBO+MTX group. Most commonly reported PTs in Study RA0055 are presented in **Table 28**.

Table 28. Incidence and exposure-adjusted incidence rates of serious TEAEs in all SOCs and common PT reported by more than 1 subject in any group during Period 1 of RA0055 (SS1)

System Organ Class Preferred term	PBO+MTX N=217		CZP+MTX N=659	
Patient-years at risk (per 100 pt-yrs) [a]	1.93		6.05	
	n (%)	IR [b]	n (%)	IR [b]
Any SAEs	**20 (9.2)**	**10.74**	**70 (10.6)**	**12.06**
Blood and lymphatic system disorders	0	0	7 (1.1)	1.16
Anaemia	0	0	3 (0.5)	0.50
Pancytopenia	0	0	2 (0.3)	0.33
Cardiac disorders	1 (0.5)	0.52	6 (0.9)	1.00
Gastrointestinal disorders	0	0	9 (1.4)	1.50
Hepatobiliary disorders	0	0	3 (0.5)	0.50
Cholelithiasis	0	0	2 (0.3)	0.33
Immune system disorders	0	0	1 (0.2)	0.17
Infections and infestations	7 (3.2)	3.69	20 (3.0)	3.34
Cellulitis	1 (0.5)	0.52	2 (0.3)	0.33

System Organ Class Preferred term	PBO+MTX N=217		CZP+MTX N=659	
Patient-years at risk (per 100 pt-yrs) [a]	1.93		6.05	
	n (%)	IR [b]	n (%)	IR [b]
Pneumonia	3 (1.4)	1.57	4 (0.6)	0.66
Latent tuberculosis	2 (0.9)	1.04	1 (0.2)	0.17
Injury, poisoning, and procedural complications	1 (0.5)	0.52	8 (1.2)	1.33
Joint dislocation	0	0	2 (0.3)	0.33
Metabolism and nutrition disorders	0	0	1 (0.2)	0.17
Musculoskeletal and connective tissue disorders	2 (0.9)	1.04	6 (0.9)	0.99
Osteoarthritis	0	0	4 (0.6)	0.66
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	2 (0.9)	1.04	5 (0.8)	0.83
Nervous system disorders	3 (1.4)	1.57	4 (0.6)	0.66
Pregnancy, puerperium, and perinatal conditions	0	0	1 (0.2)	0.17
Renal and urinary disorders	1 (0.5)	0.52	2 (0.3)	0.33
Reproductive system and breast disorders	0	0	2 (0.3)	0.33
Menorrhagia	0	0	2 (0.3)	0.33
Respiratory, thoracic, and mediastinal disorders	6 (2.8)	3.14	6 (0.9)	0.99
Interstitial lung disease	0	0	2 (0.3)	0.33
Pulmonary embolism	2 (0.9)	1.04	1 (0.2)	0.17
Pneumonitis	2 (0.9)	1.04	0	0
Skin and subcutaneous tissue disorders	1 (0.5)	0.52	0	0
Surgical and medical procedures	0	0	3 (0.5)	0.50
Vascular disorders	3 (1.4)	1.57	3 (0.5)	0.50

CZP=certolizumab pegol; IR=incidence rate; MTX=methotrexate; PBO=placebo; PT=Preferred term; pt-yrs=patient-years; SAE=serious adverse event; SOC=System Organ Class; SS1=Safety Set 1; TEAE=treatment-emergent adverse event
Note: n=number of subjects reporting at least 1 SAE in that category.
Note: Treatment emergence was defined as an adverse event starting on or after the date of first study medication administration and up to 70 days after the last (most recent) CZP or PBO dose.
Note: TEAEs having a serious flag as missing were counted as serious.
Note: Preferred terms are listed by descending order of frequency in the CZP+MTX group according to SOC. System Organ Classes for which no events were reported are not presented.
[a] *Patient-years at risk was based on the time from the first Period 1 injection to the last Period 1 injection (excluding the Week 52 injection) +70 days divided by 365.25, censored at last clinical contact or first Period 2 injection.*
[b] *Exposure-adjusted incidence rate=incidence of new cases (subjects experiencing the event at least once) per 100 pt-yrs.*

Deaths

A total of 3 subjects experienced TEAEs leading to death during Period 1 of RA0055; 2 subjects in the CZP+MTX group (pulmonary TB, TB gastrointestinal, and acute respiratory distress syndrome in 1 subject and cerebrovascular accident in 1 subject) and 1 subject in the PBO+MTX group (respiratory failure).

In the CZP+MTX group, the total patient-years at risk was 6.05 per 100 pt-yrs, resulting in a mortality rate of 0.33 deaths per 100 pt-yrs, or 1 death per approximately 333 pt-yrs of exposure. In the PBO+MTX group, the total patient-years at risk was 1.93 per 100 pt-yrs, resulting in a mortality rate of 0.52 deaths per 100 pt-yrs, or 1 death per approximately 192 pt-yrs of exposure.

Other significant events

Serious infections

The incidence of TEAEs in the Infections and infestations SOC was similar between the CZP+MTX group (3.0%) and the PBO+MTX group (3.2%). The incidence rate was similar in the CZP+MTX group compared with the PBO+MTX group (3.34 vs 3.69/100 pt-yrs).

The most common (i.e. those reported by more than 1 subject in any group) Infection and infestation SAEs (by PT) in the CZP+MTX group were as follows:

- Pneumonia (0.6% vs 1.4% for PBO+MTX)
- Cellulitis (0.3% vs 0.5% for PBO+MTX)
- Latent tuberculosis (TB) (0.2% vs 0.9% for PBO+MTX)

All PTs were reported at similar or lower incidences and incidence rates in the CZP+MTX group compared with the PBO+MTX group.

Opportunistic infections (including active TB)

One subject in the CZP+MTX group had active TB and later died. No subjects in the PBO+MTX group presented with opportunistic infections.

Herpetic infections

The incidence of herpetic infections was slightly higher in the CZP+MTX group compared to PBO+MTX (3.6% vs 2.3%, respectively). All of the herpetic infections in both treatment groups were non-serious, with the exception of 1 event of herpes zoster in a subject in the CZP+MTX group.

Malignancies

The TEAE incidence of malignancies, including lymphoma, (as defined by the standardised MedDRA query (SMQ)="Malignancies") was 1.5% in the CZP+MTX group and 0.9% in the PBO+MTX group. No malignancies were reported for subjects ≤30 years of age.

A total of 1.2% CZP+MTX-treated subjects and 0.9% PBO+MTX-treated subjects reported malignancies during Period 1 of RA0055. The exposure-adjusted incidence rate was comparable in the CZP+MTX group compared with the PBO+MTX group (1.33/100 pt-yrs vs 1.04/100 pt-yrs) suggesting no overall increased risk for malignant tumors with CZP exposure over the treatment duration covered by this study (52 weeks).

Autoimmune disorders

There were 2 TEAEs of autoimmune disorders, including lupus and lupus-like illness; 1 event in the

CZP+MTX group (0.2%) and 1 event in the PBO+MTX group (0.5%)

Cardiovascular events
Two subjects (0.3%) in Period 1 of RA0055 had SAEs considered to be major adverse cardiovascular events (MACE), both were in the CZP+MTX group. Neither was drug-related nor led to study discontinuation, and both events resolved.

Neurological disorders
There were no TEAEs suggestive of demyelinating disorders or notable neurological SAEs reported during RA0055 Period 1. One SAE of cerebrovascular accident was reported in1 subject in the CZP+MTX group.

Hematopoietic cytopenia
There were no serious events of isolated neutropenia, leukopenia, or thrombocytopenia.
The incidence of hematopoietic cytopenia treatment-emergent SAEs (defined using SMQ="Haematopoietic cytopenias") was 0.9% in the CZP+MTX group and 0% in the PBO+MTX group. There was no meaningful difference in the incidence rate between the CZP+MTX and PBO+MTX groups (0.99 vs 0/100 pt-yrs), suggesting no overall increased risk for hematopoietic cytopenia with CZP exposure during the 52 weeks covered by this study.

In the CZP+MTX group, the incidences and incidence rates of treatment-emergent SAEs of aplastic anemia, pancytopenia, and bone marrow toxicity were low (≤0.5% and ≤0.50/100 pt-yrs, respectively). Of note, the bone marrow toxicity was considered related to MTX by the Investigator. Only the SAEs of pancytopenia were considered to be related to study medication. Both SAEs of pancytopenia and the SAE of bone marrow toxicity led to discontinuation from the study

Serious bleeding events
The incidence of treatment-emergent serious bleeding events (defined using the SMQ="Haemorrhages") was 0.6% in the CZP+MTX group and 0.5% in the PBO+MTX group. The exposure adjusted incidence rate in the CZP+MTX group was similar to the PBO+MTX group (0.66 vs 0.52/100 pt-yrs), suggesting no overall increased risk for serious bleeding events with CZP exposure over the 52 weeks of the study.

All hepatic events
The TEAE incidence of hepatic events was 13.1% in the CZP+MTX group and 12.0% in the PBO+MTX group. The exposure adjusted incidence rate in the CZP+MTX group was similar compared with the PBO+MTX group (15.54 vs 14.64/100 pt-yrs), suggesting no overall increased risk for hepatic disorders with CZP exposure over the 52 weeks of the study.
In the CZP+MTX group, the most frequently reported hepatic TEAEs were as follows:

- ALT increased (6.4% vs 4.1% for PBO+MTX)
- Aspartate aminotransferase (AST) increased (3.0% vs 2.3% for PBO+MTX)
- Hepatic enzyme increased (2.4% vs 2.8% for PBO+MTX)

All other hepatic TEAEs were reported at an incidence <2.0%. All hepatic events had a similar incidence and incidence rate between the CZP+MTX and PBO+MTX groups with the exception of ALT increased, which was higher in the CZP+MTX group compared with the PBO+MTX group (7.24 vs 4.80/100 pt-yrs).

All subjects were using MTX concomitantly. Among the subjects who had an hepatic event, in the PBO+MTX group, the majority of subjects had received >20mg/week MTX at any time (65.4%), whereas in the CZP+MTX group, a similar percentage of subjects with hepatic events had received 10 to 20mg/week MTX (46.5%) or >20mg/week MTX (44.2%).

Of the 51 subjects with ALT increased, 17 subjects reduced the dose of MTX as a result of this event. Of the 25 subjects with AST increased, 8 subjects reduced the dose of MTX as a result of this event.
The incidences of all post-Baseline marked elevations in liver function tests (LFTs) were low (<7.0%) and similar between the CZP+MTX and PBO+MTX groups. No subjects had both elevations of bilirubin ≥1xULN and AST or ALT ≥3xULN.

Local injection site reactions
Local injection site reactions, as determined by the Investigator, were reported in 6.4% of subjects in the CZP+MTX group and 2.3% in the PBO+MTX group. All injection site reactions were mild or moderate in severity and non-serious.

Systemic hypersensitivity injection reactions
One subject reported 1 TEAE of acute systemic hypersensitivity injection reaction (pre-syncope in the CZP+MTX group (0.2%); the event was mild and non-serious). The incidence of delayed systemic hypersensitivity injection reactions was also low (1.1% in the CZP+MTX group and 0.5% in the PBO+MTX group). No delayed systemic hypersensitivity injection reactions were reported in more than 1 subject. All delayed systemic hypersensitivity injection reactions were mild or moderate in severity and non-serious.

Adverse events by anti-CZP antibody status
A total of 63 of 659 subjects (9.6%) were positive for anti-CZP antibodies. The overall incidence of TEAEs was 90.5% in subjects who were anti-CZP antibody positive compared with 78.5% in subjects who were anti-CZP antibody negative.

The incidences of severe TEAEs, drug-related TEAEs, TEAEs requiring a change in MTX dose, SAEs, and discontinuation due to TEAEs were higher in anti-CZP antibody positive subjects compared with anti-CZP antibody negative subjects (**Table 29**).

Table 29. Overall summary of TEAEs by overall anti-CZP antibody status for subjects with CZP exposure during Period 1 of RA0055 (SS1)

	Overall anti-CZP antibody status	
	Negative N=596	Positive N=63
	n (%)	n (%)
Any TEAEs	468 (78.5)	57 (90.5)
Severe TEAEs	38 (6.4)	9 (14.3)
Drug-related TEAEs	249 (41.8)	29 (46.0)
Serious TEAEs	61 (10.2)	9 (14.3)
Discontinuation due to TEAEs	50 (8.4)	7 (11.1)
TEAEs requiring dose change of MTX	64 (10.7)	9 (14.3)
All deaths	2 (0.3)	0
TEAEs leading to death	2 (0.3)	0

CZP=certolizumab pegol; MTX=methotrexate; SS1=Safety Set 1;
TEAE=treatment-emergent adverse event
Note: n=number of subjects reporting at least 1 TEAE in that category.
Note: Treatment emergence was defined as an adverse event starting on or after the date of first study medication

administration and up to 70 days after the last (most recent) CZP or PBO dose.
Note: TEAEs having a serious flag as missing were counted as serious. TEAEs with a missing relationship to study medication were counted as related. TEAEs with a missing intensity were counted as severe.
Note: A subject was overall positive to anti-CZP antibodies if the level was >2.4units/mL on at least 1 visit in Period 1 (no samples were taken after the last/Withdrawal Visit). A subject was overall negative to anti-CZP antibodies if the level was ⩽2.4units/mL at all visits in Period 1 (excluding Safety Follow-Up Visits).

In the anti-CZP antibody positive group, the incidence of TEAEs with a difference of difference of >10% compared with the anti-CZP antibody negative group was observed in the SOCs of Skin and subcutaneous tissue disorders (30.2% vs 16.8%).

Adverse events associated with MTX use

The incidence of MTX-associated events was similar between the treatment groups (5.3% [35 subjects] and 5.5% [12 subjects], for CZP+MTX and PBO+MTX, respectively). The AEs reported to be associated with MTX by the Investigators were in line with what is known for this drug.

Laboratory findings
No clinically meaningful changes in haematology values, serum biochemistry values, or urinalysis values were observed. Overall, the incidence of markedly abnormal haematology values was higher than the incidence of markedly abnormal biochemistry values.

The percentage of subjects with any markedly abnormal post-Baseline haematology value overall was lower in the CZP+MTX group compared with the PBO+MTX group whereas the percentage of subjects with any markedly abnormal post-baseline biochemistry parameter was slightly higher in the CZP+MTX group compared to the PBO+MTX group. Treatment-emergent AEs related to biochemistry were most frequently reported in the HLT of liver function analyses; the incidence was similar between treatment groups (11.7% for CZP+MTX and 11.1% for PBO+MTX.

Discontinuation due to adverse events

The overall incidence of TEAEs leading to discontinuation (i.e. study withdrawal) was low (8.6% in the CZP+MTX group vs 9.2% in the PBO+MTX group), although slightly higher than that seen in the overall RA pool (4.4% in the All CZP in PC group but the median duration of exposure was less in the overall RA pool (112 days vs 364 days in RA0055). The most common TEAEs leading to discontinuation were in the SOC of Infection and infestations (1.7% in the CZP+MTX group).

Supportive study RA0096

The key inclusion and exclusion criteria in this study were similar to those in RA0055. Subjects in RA0096 were excluded for any previous use of MTX or leflunomide, whereas subjects in RA0055 were excluded for any prior use of all DMARDs, with the possible exception of an antimalarial drug.

Incidences of TEAEs, SAEs, drug-related TEAEs, severe TEAEs, and TEAEs leading to study medication discontinuation during the Treatment Period were generally similar in both treatment groups (**Table 30**). No deaths occurred.

Table 30. Overall summary of TEAEs during the Treatment Period of RA0096 (SS)

Category	Treatment group	
	PBO+MTX N=157 n (%)	CZP+MTX N=159 n (%)
Any TEAEs	148 (94.3)	153 (96.2)
Intensity		
Mild	141 (89.8)	149 (93.7)
Moderate	36 (22.9)	41 (25.8)
Severe	8 (5.1)	4 (2.5)
Any drug-related TEAEs	105 (66.9)	113 (71.1)
Any SAE (serious TEAEs)	14 (8.9)	13 (8.2)
Any TEAEs leading to death	0	0
Any TEAEs leading to study drug discontinuation	7 (4.5)	9 (5.7)

CZP=certolizumab pegol; MTX=methotrexate; PBO=placebo; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: n is the number of subjects reporting at least 1 TEAE in that category.
Note: Percentages are based on the number of subjects in the SS.
Note: TEAEs having serious flag as missing were counted as "serious." TEAEs with a missing relationship to study drug were counted as "related." TEAEs with missing intensity were counted as "severe."
Note: There were no TEAEs with missing information regarding relationship to study drug or intensity; therefore, no imputation for a worst case scenario was needed.

2.5.1. Discussion on clinical safety

The MAH has presented safety data for the early RA indication from the pivotal study RA0055 and the supportive Japanese study RA0096.

To supplement this data, comparison, where relevant, with long-term safety data from the overall RA pool were also analysed. The overall RA pool comprised 2 sets of data:

- The Placebo-Controlled (PC) Data: consisting of data from 10 PC studies or PC study phases.
- All Studies Data: consisting of data from all studies/all phases including the 10 PC studies or PC study phases and another 4 studies.

In RA0055, study medication exposure was well-balanced between groups. The total mean duration of CZP/PBO exposure during Period 1 was 307.0 days for the CZP+MTX group and 288.3 days for the PBO+MTX group. The mean patient time at risk was similar between the CZP+MTX and PBO+MTX groups (335.5 and 324.1 days, respectively).

Consistent with RA0055, in the overall RA pool there were more TEAEs in the CZP groups (69.1% in the All CZP in PC group) compared with the placebo group (62.7%). However, the percentage of subjects with severe TEAEs was comparable across the CZP (8.6%) and placebo (8.2%) groups in the overall RA pool and slightly lower in the CZP+MTX group (7.1%) compared with the PBO+MTX group (9.2%) in RA0055.

Of the most common TEAEs (≥5% of subjects in any treatment group), the following AEs showed the largest difference in percentage between groups: nausea (12.6% vs 10.1%), upper respiratory tract infection (10.9% vs 5.1%), headache (6.8% vs 3.7%), ALT increased (6.4% vs 4.1%), and fatigue (2.1% vs 0). The frequency and pattern of TEAEs were in line with previous experience of Cimzia, with the exception of diarrhoea which occurred more frequently in subjects treated with CZP compared to placebo-treated subjects (4.7% vs 1.8%). However, the CHMP considered that there was not enough

evidence at this stage to establish a causal association between CZP use and diarrhoea, as in the total overall RA population in placebo controlled studies, diarrhoea was observed more frequently in patients treated with placebo (3.6%, compared to 2.6% for patients treated with CZP).

In addition, despite the higher incidence rates of diarrhoea in patients treated with CZP in Study RA0055, the incidence rates (incidence of new cases per 100 subject-years) and their associated 95% confidence intervals were 2.11 (0.57, 5.40) and 5.32 (3.62, 7.56) respectively. The overlapping 95% confidence intervals indicated that a statistical difference in the incidence of diarrhoea between these 2 groups could not be confirmed.

The most common SAEs were in the SOC of Infections and infestations (3.0% for the CZP+MTX group vs 3.2% for PBO+MTX) and Respiratory, thoracic, and mediastinal disorders (0.9% for CZP+MTX vs 2.8% for PBO+MTX); for all other SOCs, the incidence of SAEs was <1.5%. This is consistent with results in the overall RA pool where SAEs occurred most often in the SOC of Infections and infestations (3.1% in the All CZP in PC group vs 0.8% for placebo) and for all other SOCs the incidence of SAEs was <1.5%, and is as expected for this class of drug.

The most frequently reported severe TEAE by PT was latent TB. The risk of infections and in particular that of tuberculosis is well established for CZP with extensive warnings and instructions in the SmPC for physicians in cases were latent tuberculosis is suspected.

The TEAEs leading to death in RA0055 were in line with the known risks with anti-TNFα agents, and did not present a new safety signal. The mortality rate of 0.33 deaths per 100 pt-yrs was slightly lower than that observed in the overall RA pool (0.84 deaths per 100 pt-yrs) in the All CZP in PC group.

A total of 1.2% CZP+MTX-treated subjects and 0.9% PBO+MTX-treated subjects reported malignancies during Period 1 of RA0055. The exposure-adjusted incidence rate was comparable in the CZP+MTX group compared with the PBO+MTX group (1.33/100 pt-yrs vs 1.04/100 pt-yrs) suggesting no overall increased risk for malignant tumours with CZP exposure over the treatment duration covered by this study (52 weeks).

The overall SAE pattern was also in line with previous experience of Cimzia.

Regarding the incidence of TEAS in relation to the formation of anti-CZP antibodies, a difference of >10% was observed for Skin and subcutaneous tissue disorders in the anti-CZP antibody positive group over the anti-CZP antibody negative group. However, as there were no serious skin reactions reported in this study, and also considering the overall small number of subjects in the anti-CZP antibody positive group, the CHMP considered that the current SmPC adequately reflected the risks related to CZP skin toxicity.

No new safety signals in laboratory findings have emerged in the early RA population.

In study RA0096, incidences of TEAEs and SAEs were generally similar in both treatment groups. No deaths occurred.

2.5.2. Conclusions on clinical safety

The safety profile of certolizumab pegol is established through the clinical development program in its currently approved indications and experience in the post-marketing setting. This includes several potentially serious risks, such as infections, and potential risks of malignancies, congestive heart failure and demyelinating disorders. Risk minimisation as well as pharmacovigilance activities are in place from previous procedures. Review of the submitted data, it was concluded that the adverse event (AE) incidence and profile of Cimzia in the early RA-population was as expected for an anti-TNF-therapy and

consistent with previous experience with Cimzia. No new safety signals emerged from the analysis of the data in the studies with early RA.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR refers to the EURD list which remains unchanged.

2.6. Risk management plan

The application was to expand the RA indication and based on the current review of the data in support of this indication, no additional risks to the patient were identified. Therefore the MAH considered that an update to the RMP was not warranted and that the currently approved RMP version for Cimzia was still sufficient to adequately minimise the risks associated with certolizumab use.

The justification provided by the MAH for not updating the RMP was considered acceptable by the CHMP.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable, as the introduced changes are not considered to impact the readability of the package leaflet.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Certolizumab pegol is a biologic disease-modifying drug belonging to the class of TNF-inhibitors. In the current submission, the MAH submitted data from a pivotal study with sustained remission at Week 52 as the primary endpoint. The proportion of subjects achieving this in the CZP+MTX group was 28.9% compared with 15.0% ($p<0.001$) in the PBO+MTX group (FAS1 with non-responder imputation). The proportion of subjects achieving the key secondary endpoint sustained LDA at Week 52 was 43.8% in the CZP+MTX group vs 28.6% in the PBO+MTX group ($p<0.001$). These were considered to be stringent endpoints and the difference between the MTX-treated group and the MTX+CZP treated group was therefore clinically meaningful.

The proportion of subjects with radiographic non progression at Week 52 (defined as a change from Baseline to Week 52 in mTSS of ≤0.5) was greater in the CZP+MTX (70.3%) group compared with the PBO+MTX group (49.7%; $p<0.001$).Thus, the submitted data also supported a joint protective effect of Cimzia in combination with MTX.

Finally, the proportion of ACR 50 and 70 responders was higher in the Cimzia treated group providing further evidence of a positive effect of CZP in disease activity status.

Uncertainty in the knowledge about the beneficial effects

At Week 24, the difference in ACR 20/50 between the groups was not statistically different. However, for the more stringent ACR 70, a statistical significance was observed. In addition at all time-points CZP was superior to placebo all 3 measures and therefore the statistical insignificance for one time-point was not expected to be of clinical importance.

For subjects who achieved an improvement of ≥10mm from Baseline (MCID) in PtGADA, no difference between groups was seen at Week 12 (76.1% vs 76.6% in the placebo group and the CZP treated group respectively). At week 52, the proportions were however 59.6% and 68.2% respectively. The CHMP considered that this observation could be explained by the fact that MCID in PtGADA is not difficult to achieve, in particular in previously DMARD-naïve subjects initiating MTX treatment and that is not a very sensitive tool for capturing changes between different treatments. In addition, CZP-treated subjects achieved higher levels above the MCID threshold than only MTX-treated subjects indicating a better clinical improvement in the CZP group.

Information on time points for x-rays in early withdrawals and sensitivity analyses of change from baseline in mTSS at Week 52 and proportion of subjects with radiographic non-progression at Week 52 were also submitted and all supported the positive findings in the primary pre-defined analyses in favour of CZP compared to placebo.

Risks

Unfavourable effects

The safety profile of certolizumab is well established and is characterised by several potentially serious risks, including but not limited to infections and potential risks of malignancies, congestive heart failure and demyelinating disorders. Risk minimisation as well as pharmacovigilance activities are in place and detailed in the currently approved RMP for CZP. Upon review of the submitted data, it was concluded that the AE incidence and profile of Cimzia in the early RA-population was consistent with previous experience with Cimzia and no new safety signals emerged.

Uncertainty in the knowledge about the unfavourable effects

Subjects who developed CZP-antibodies achieved low disease activity at Week 52 to a lesser extent than subjects who did not develop antibodies. However, there was no difference between these groups regarding the need for rescue medication. Furthermore, the percentage of subjects with a positive antibody response to CZP was consistent with the overall percentage in previous RA-studies. Overall, the findings on immunogenicity were consistent with the current product information.

Effects Table

Table 31. Effects Table for Cimzia in severe, active and progressive rheumatoid arthritis in adults not treated previously with MTX or other disease-modifying anti-rheumatic drugs

Effect	Short Description	Unit	CZP+MTX	PBO+MTX	Uncertainties/ Strength of evidence	References
Favourable Effects						
Sustained remission	DAS28(ESR) <2.6 at weeks 40 and 52	%	28.9	15.0	Sustained LDA (DAS28 ((ESR) <=3.2), showed similar trends of differences between treatment arms	RA0055
Protection of joint destruction	Change from BL to Week 52 in mTSS of ≤0.5	%	70.3	49.7	Element of subjectivity in the assessment	RA0055

Effect	Short Description	Unit	All CZP in PC	PBO	Uncertainties/ Strength of evidence	References
Unfavourable Effects						
Infections	Any serious infection	%	0.8	3.1	Results do not include subjects for early RA studies	Integrated summary of RA Safety data (data cutoff: 30 Nov 2011)
Malignancies	Any, including unspecified	%	0.6	0.7		
Congestive HF	HF NEC HLT	%	0	0.2		

Abbreviations: DAS28=Disease activity score 28 joints, ESR= erythrocyte sedimentation rate, LDA=low disease activity, BL=baseline, mTSS= van der Heijde modified total sharp score, CZP=certolizumab pegol, PC=placebo controlled studies, PB)=placebo, HF=heart failure, NEC=Not elsewhere classified, HLT=High Level Term

Benefit-Risk Balance

Importance of favourable and unfavourable effects

There is a convincing evidence of the beneficial effects of early intervention in RA, and it is increasingly accepted to use TNF-blockers together with MTX early on in the disease's course, especially in cases with poor prognostic factors, such as high disease activity, presence of CCP-antibodies, and/or RF, or presence of erosions on hand/feet x-ray.

A number of TNF-inhibitors are approved for use in patients with, active and progressive RA not previously treated with MTX (adalimumab, etanercept, and golimumab) or other DMARDs (infliximab). The higher sustained (over 12 weeks) remission rate and the joint protective effect which were demonstrated with CZP in the studies in early RA are considered of value in this population.

In addition, no new safety concerns were identified in this particular population and the known risks of CZP are adequately minimised with the risk minimisation activities detailed in the Risk Management Plan and the SmPC of the product.

Benefit-risk balance

Discussion on the Benefit-Risk Balance

Robust and clinically relevant efficacy has been shown for CZP in the treatment of severe, active and progressive RA in adults not previously treated with MTX or other DMARDs. Unfavourable effects typical of anti-TNF treatments have been observed, including infections, but the incidence rate was similar in the CZP and the PBO groups.

Based on the data available, CZP is approvable for the treatment of severe, active and progressive RA in adults not previously treated with MTX or other DMARDs.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIb

Extension of indication to include treatment of severe, active and progressive rheumatoid arthritis in adults not treated previously with methotrexate or other disease-modifying anti-rheumatic drugs (DMARDs); as a consequence, sections 4.1 and 5.1 of the SmPC are revised in order to update the efficacy and safety information. The Package Leaflet is updated accordingly.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include treatment of severe, active and progressive rheumatoid arthritis in adults not treated previously with methotrexate or other disease-modifying anti-rheumatic drugs (DMARDs); as a consequence, sections 4.1 and 5.1 of the SmPC are revised in order to update the efficacy and safety information. The Package Leaflet is updated accordingly.

Summary

Please refer to the scientific discussion Cimzia EMEA/H/C/001037/II/0045