Effectiveness and safety of anti-tumour necrosis factor therapy with certolizumab pegol observed in real-life rheumatoid arthritis patients in Germany: results from the non-interventional FαsT study

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Abstract

Objective

To report the tolerability and effectiveness of certolizumab pegol (CZP) for the treatment of patients with active rheumatoid arthritis (RA) in a routine clinical practice setting.

Methods

FαsT (NCT01069419) was a non-interventional, observational 104-week (wk) study performed at 163 sites in Germany. RA patients were treated according to the treating physician's discretion. Clinical remission (DAS28-CRP<2.6) at wk 104 was the primary endpoint of the study. Remission data based on ESR (DAS28-ESR<2.6) were also assessed. Secondary endpoints included the effect of CZP treatment on pain, physical function and disease activity. Safety data were collected at all study visits.

Results

1,117 patients were enrolled in the FαsT study (78% female, mean age: 55 years). Rapid responses were observed at wk 6 (18.7% and 12.9% patients in DAS28-CRP and DAS28-ESR remission, respectively) with improvements sustained over 2 years (20.0% and 13.9% patients achieved DAS28-CRP and DAS28-ESR remission, respectively at wk 104). Anti-TNF naïve patients exhibited greater improvements than anti-TNF experienced patients (mean DAS28-ESR change from baseline [CfB] -1.3, -1.5 and -1.7 for patients with ≥2, 1 and no anti-TNFs, respectively at wk104). Improvements were reported in all secondary endpoint measures. 1,111 patients were exposed to CZP for a total of 1,538 patient-years during the study. 2,000 treatment-emergent adverse events (TEAEs) were reported in 745 patients (67.1%); 9 (0.8%) experienced TEAEs with fatal outcome.

Conclusion

CZP demonstrated efficacy and safety outcomes reflective of those observed in trial settings. Rapid reductions in disease activity and improvements in physical function were maintained up to wk 104.

Key words

rheumatoid arthritis, certolizumab pegol, efficacy, safety

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Introduction

Rheumatoid arthritis (RA) is a chronic, immune-mediated, inflammatory disease characterised by the inflammation of synovial tissue, which in turn causes pain, stiffness and swelling of joints. Due to its chronic nature, RA treatment must help to achieve long-term effectiveness and must have an acceptable long-term safety profile (4, 5). Tumour necrosis factor (TNF) inhibitors have been shown to reduce signs and symptoms of RA, improving physical function, limiting radiographic progression and reducing disease activity (1, 2, 6-10). Certolizumab pegol (CZP) is a PEGylated anti-TNF which does not contain a fragment-crystallisable (Fc) region and is approved to treat a range of indications including adults with moderate to severe RA in Europe (9). In January 2018, the CZP label was updated in Europe, making it the first anti-TNF for potential use during both pregnancy and breastfeeding (3, 11).

A large number of randomised clinical trials (RCTs), including the pivotal RAPID-1 and RAPID-2 studies, have demonstrated a fast clinical response and excellent safety profile in CZP-treated RA patients which is comparable with other anti-TNFs (12-14). However, whilst RCTs provide important results regarding the efficacy and tolerability of a drug, the selective nature of their design and subsequent under-representation of particular patient demographics can result in a lack of external validity (15). The Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT) registry of RA patients treated with bDMARD (biological disease-modifying anti-rheumatic drugs) in Germany found that only 21–33% of the RA population are eligible to participate in RCTs investigating the disease (16). Observational studies are therefore important to investigate the 'real-life' treatment effect and gain further drug safety data in a clinical, routine setting.

Etanercept, adalimumab and infliximab, were well established anti-TNF options before the approval of CZP in 2009. FαsT was voluntarily initiated by UCB in Germany immediately after the drug's approval (11). In addition, the anti-TNF biologic golimumab received approval from the EMA in October of the same year.

Here we report effectiveness and safety results over 104 weeks' continuous CZP treatment in adults with active RA. This represents the outcome of the first non-interventional, post-authorisation study to be conducted over a comparatively long study period (two years) in CZP-treated patients to date.

Materials and methods

Study design

The FαsT study (NCT01069419) was a two-year, multicentre, observational, non-interventional study conducted at 163 sites in Germany between October 2009 and December 2014. According to guidelines provided by the German Society of Rheumatology (17), the therapeutic decision and dose determination were left exclusively within the discretion of the physician (with consideration of the product label). CZP was self-administered subcutaneously by patients or by the treating physician. Patient procedures and assessments were performed in the frame of current standard clinical practice, in accordance with the Summary of Product Characteristics (SmPC) and local marketing authorisation requirements.

Patients who discontinued CZP treatment were followed up for 12 weeks. Adverse events (AEs) were managed according to German and European Union drug safety regulations for observational studies, and strict safety monitoring was used to ensure data quality (sites were inspected once a year). FαsT was conducted in accordance with EMA requirements for post-authorisation safety studies, the Declaration of Helsinki and all applicable German regulations (18). Information regarding study conduct was provided to the local German authority and approved by the Institutional Review Board and Independent Ethics Committee. All participants provided signed informed consent forms.

Patients

Patients eligible for inclusion in the study were aged ≥18 years and had been diagnosed with moderate to severe active

RA, in accordance with the 2010 American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) RA Classification Criteria (19). Patients were excluded from participation if they had been previously treated with CZP or had known hypersensitivity to any components of the drug. All concomitant treatments were permitted, doses of which could be increased, withdrawn or altered by the treating physician at their own discretion based on standard medical practice and in accordance with the marketing authorisation.

Study procedures and evaluations

The primary objective of the FαsT study was to assess the clinical effectiveness of CZP in achieving clinical remission (defined as Disease Activity Score examined in 28 joints [DAS28]-CRP<2.6) after 104 weeks of CZP treatment according to ACR recommendations (20). The secondary objectives were to assess the effect of CZP treatment on patients' pain, physical function and disease activity after 104 weeks of therapy. Other objectives included assessment of safety, patient-reported outcome measures and identification of clinical responders and non-responders to CZP treatment. Evaluation of effectiveness and safety was conducted and reported by the treating physician during routine clinical visits. Visits were expected around weeks 6, 12, 24, 36, 52, 64, 76, and 104, and a safety follow-up occurred around week 116.

DAS28 was computed in the database for analysis purposes. Therefore, DAS28-CRP and DAS28-ESR could be computed if ESR and/or CRP values were available. DAS28 change from baseline (CfB) scores, baseline and post-baseline values were only derived if the scores at both visits were based on the same measurement. DAS28-ESR remission rates (DAS28-ESR<2.6[21]) were analysed post-hoc. DAS28-ESR was used to establish whether patients had high, moderate or low disease activity post-hoc. Early DAS28-ESR response was defined as decrease in score of ≥1.2 up to week 12 compared with the baseline value, in accordance with EULAR RA treatment recommendations (4). Early EULAR response was defined as a decrease in DAS28-ESR score of ≥3.2 up to week 12 compared with the baseline value.

Arthritis pain was reported using Patient's Assessment of Arthritis Pain (PAAP) scores which used a 0–100 mm visual analogue scale (VAS) (22). Physical function was calculated using Health Assessment Questionnaire Disability Index (HAQ-DI) scores (23). Disease activity was calculated using Clinical Disease Activity Index (CDAI) scores (24) which were calculated using the sum of Tender Joint Count (TJC), Swollen Joint Count (SJC), Physician's Global Assessment of Disease Activity (PhGADA) (25) and Patient's Global Assessment of Disease Activity (PtGADA) (25). Possible CDAI scores ranged between 0–76, with no disease activity defined as 0 and the highest disease activity defined as 76. Fatigue was measured using the Fatigue Assessment Scale (ranging from 0–10) (26). Health-related quality of life was reported using the EuroQol-5 dimension (EQ-5D) questionnaire and a 0–100 mm VAS scale, with the worst quality of life defined as 0 and the best quality of life as 100. Morning stiffness was evaluated at each visit and defined as the time elapsed between the time of usual awakening and the time taken by patients to achieve a typical level of mobility.

Safety data, including AEs of special interest, were collected at all study visits. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 17.1 and reported using System Organ Class (SOC) and preferred term (27). Treatment emergent adverse events (TEAEs) were defined as AEs occurring within 5 half-lives of the last dose (70 days) (3).

Statistical analysis

Effectiveness data are presented for the full analysis set (FAS), which included all patients who received ≥1 dose of CZP, with a DAS28-CRP≥2.6 at baseline and ≥1 valid post-baseline DAS28-CRP assessment. Safety data are presented for the Safety Set (SS), which consisted of all patients who received ≥1 CZP dose at any point during the study.

The sample size calculation was based on the precision of the 95% confidence interval around the DAS28-CRP remission rate (RR) after two years. A precision of at least ±3.0% was assumed to be sufficient for estimating a reliable RR. An overall RR of 50.0% was calculated to yield a precision of ±3.0%, if at least 1,068 patients were included into the study. Furthermore, for any subgroups analysed in the study, around 500 patients were sufficient to estimate the remission rate for each subgroup with an adequate precision (±4.5%).

Non-responder imputation (NRI) was used to impute missing data of binary variables; patients with missing data were classified as non-responders. Mixed model with repeated measures (MMRM) is a special case of the mixed-effects regression model and was used as an alternative imputation for binary variables, as well as to impute missing values for multinomial and continuous variables. The model consisted of visit, gender, disease duration, patient status at termination, and rheumatoid factor as fixed categorical effects. For change from baseline variables, the baseline values of the variable were included as covariate. The multiple patient visits were treated as repeated measures and random effects for patients were used to account for the fact that correlation between pairs of visits were unlikely to be the same. The covariance of the within-patient errors was assumed to be unstructured. If the covariance structure did not allow for a stable solution, an autoregressive first order structure was used. The resulting estimates of the regression model were used to replace missing values of a variable. The imputed values for a derived variable were based upon imputed values of the individual components for that variable.

Exposure-adjusted incidence rates (EAIRs) and event rates (EAERs) were calculated per 100 patient-years; EAIRs were calculated with 95% confidence intervals (CIs). Post-hoc subgroup analyses, defined by prior anti-TNF use, were carried out on primary and secondary outcomes. Time to early discontinuation data was assessed using Kaplan-Meier analysis. Statistical comparisons of remission rates at week 104 were conducted using Wald tests. All

Table I. Patient characteristics at baseline.

Characteristic	Full Analysis Set				Safety Set
	All patients n=851	No prior anti-TNFs n=527	1 prior anti-TNF n=186	≥2 prior anti-TNFs n=138	All patients n=1111
Demographics					
Mean age, years (SD)	55.4 (12.1)	55.4 (11.8)	55.8 (11.7)	54.8 (13.5)	55.1 (12.4)
Female, n (%)	669 (78.6)	406 (77.0)	144 (77.4)	119 (86.2)	865 (77.9)
Disease characteristics					
Disease duration, years, median (min, max)	7.3 (0–66)	5.4 (0–66)	8.4 (0–50)	12.7 (0–43)	7.1 (0–66)
<2 years, n (%)	160 (18.8)	131 (24.9)	25 (13.4)	4 (2.9)	209 (18.9)
≥2 years, n (%)	691 (81.2)	396 (75.1)	161 (86.6)	134 (97.1)	897 (81.1)
Rheumatoid factor positive, n (%)	575 (70.3)	363 (72.3)	125 (69.4)	87 (64.0)	750 (70.2)
aCCP positive, n (%)	500 (66.9)	328 (71.0)	105 (62.9)	67 (56.8)	642 (66.0)
MCV positive, n (%)	75 (10.0)	37 (8.0)	21 (12.6)	17 (14.4)	95 (9.8)
DAS28-ESR, mean (SD)[a]	5.3 (1.1)	5.4 (1.1)	5.2 (1.1)	5.5 (1.3)	5.1 (1.3)
Moderate disease activity[b]: >3.2 to ≤5.1, n (%)	333 (42.4)	208 (43.1)	77 (44.8)	48 (36.6)	398 (41.8)
High Disease Activity[b]: >5.1, n (%)	436 (55.5)	271 (56.1)	88 (51.2)	77 (58.8)	483 (50.7)
CDAI, mean (SD)[c]	29.7 (12.6)	29.42 (12.0)	28.47 (12.6)	32.09 (14.6)	28.0 (13.3)
HAQ-DI, mean (SD)[d]	1.38 (0.70)	1.29 (0.68)	1.44 (0.69)	1.60 (0.73)	1.38 (0.70)
SDAI, mean (SD)[e]	31.41 (12.99)	31.08 (12.39)	30.03 (12.83)	34.43 (14.90)	NA
TJC (28 joints), mean (SD)	10.3 (7.0)	10.0 (6.6)	9.8 (7.2)	11.9 (8.1)	9.5 (7.2)
SJC (28 joints), mean (SD)	7.4 (5.7)	7.4 (5.5)	7.0 (5.7)	7.6 (6.1)	6.9 (5.8)
ESR (mm/hr), median (min, max)[a]	24.0 (1.0, 120.0)	25.0 (1.0, 120.0)	20.5 (2.0, 90.0)	25.0 (1.0, 120.0)	22.0 (1.0, 120.0)
CRP (mg/L), median (min, max)[f]	8.0 (0.0, 520.0)	8.4 (0.0, 170.0)	7.3 (0.2, 180.0)	7.9 (0.2, 520.0)	8.0 (0.0, 520.0)
PAAP, mean (SD)[d]	57.9 (21.8)	57.3 (22.0)	56.7 (21.2)	61.5 (21.9)	55.3 (23.5)
PtGADA, mean (SD)	59.3 (20.6)	58.2 (20.6)	58.2 (20.9)	65.0 (19.2)	57.1 (22.2)
EQ-5D, mean (SD)	46.5 (20.4)	NA	NA	NA	46.5 (20.4)
Prior/concomitant medication/treatment, n (%)					
Other biologics					
Prior	117 (13.7)	NA	NA	NA	153 (13.8)
Concomitant	6 (0.7)	NA	NA	NA	8 (0.7)
MTX					
Prior	622 (73.1)	352 (66.8)	152 (81.7)	118 (85.5)	809 (72.8)
Concomitant	337 (39.6)	NA	NA	NA	450 (40.5)
Other synthetic DMARDs					
Prior	685 (80.5)	NA	NA	NA	895 (80.6)
Concomitant	601 (70.6)	NA	NA	NA	782 (70.4)
Corticosteroids					
Prior	617 (72.5)	NA	NA	NA	770 (69.3)
Concomitant	701 (82.4)	NA	NA	NA	892 (80.3)

[a]: n=786; [b]: For no previous anti-TNFs, n=483, for 1 previous anti-TNF, n=172, and for ≥2 anti-TNFs, n=131 (based on DAS28[ESR] values; [c]: n=846 (observed value); [d]: n=845 (observed value); [e]: n=832 (observed value); [f]: n=837. SD: standard deviation; aCCP: antibodies against cyclic citrullinated peptides; MCV: mutated citrullinised vimentines; NA: not available; DAS28: disease activity score 28-joint count; ESR: erythrocyte sedimentation rate; CDAI: clinical disease activity index; HAQ-DI: health assessment questionnaire disability index; SDAI: simple disease activity index; TJC: tender joint count; SJC: swollen joint count; CRP: C-reactive protein; PAAP: patient's assessment of arthritis pain; PtGADA: patient's global assessment of disease activity; EQ-5D: EuroQol-5 dimension questionnaire; TNF: tumour necrosis factor; MTX: methotrexate; DMARDs: disease-modifying anti-rheumatic drugs.

p-values were nominal in nature and should be interpreted in an exploratory manner. Statistical analyses were conducted using Statistical Analysis System (SAS®) v. 9.1.3 or higher.

Results

Patient disposition and baseline characteristics

Of 1,117 patients who were enrolled in the study, 1,111 received at least one CZP dose during the study and were included in the SS. Of those, 851 patients were included in the FAS and 402 (36.2%) patients had ongoing treatment at week 104. 837 patients had CRP assessments at baseline whilst 786 had ESR assessments.

Patient characteristics at baseline were similar for the FAS and SS (Table I). In the FAS, mean age was 55.4 years, with 205 (24.1%) patients ≥65 years old at study initiation. The median disease duration was 7.3 years, with 81.2% (691/851) of patients experiencing a disease duration ≥2 years at baseline. The majority of patients in the FAS were female (78.6%) and 38.1% (324/851) of patients had been previously treated with at least one other anti-TNF medication; 21.9% (186/851) of patients had used one anti-TNF prior to study commencement and 16.2% (138/851) had been treated with two or more anti-TNFs. The majority of patients in anti-TNF experienced and an-

Table II. Disposition and discontinuation reasons.

	All patients (SS) n=1111 n (%)	No prior anti-TNFs n=674 n (%)	1 prior anti-TNF n=251 n (%)	≥2 prior anti-TNFs n=186 n (%)
Completed study	402 (36.2)	270 (40.1)	91 (36.3)	41 (22.0)
Discontinuations	696 (62.6)	394 (58.5)	157 (62.5)	145 (78.0)
Reason for discontinuation				
Adverse event*	232 (20.9)	127 (18.8)	55 (21.9)	50 (26.9)
Lack of effectiveness	332 (29.9)	188 (27.9)	71 (28.3)	73 (39.2)
Lost to follow-up	49 (4.4)	32 (4.7)	10 (4.0)	7 (3.8)
Remission of disease	11 (1.0)	7 (1.0)	3 (1.2)	1 (0.5)
Consent withdrawn	31 (2.8)	17 (2.5)	7 (2.8)	7 (3.8)
Other	41 (3.7)	23 (3.4)	11 (4.4)	7 (3.8)
Missing data	13 (1.2)	10 (1.5)	3 (1.2)	0

*Please note that discontinuations due to adverse event data were collected using two different sections of the case report form ('Terminations' and 'Adverse Events'). These data were collected using the 'Terminations' section, therefore, these data differ from the figures quoted in Table III, which were collected using the 'Adverse Events' section. SS: safety set; TNF: tumour necrosis factor.

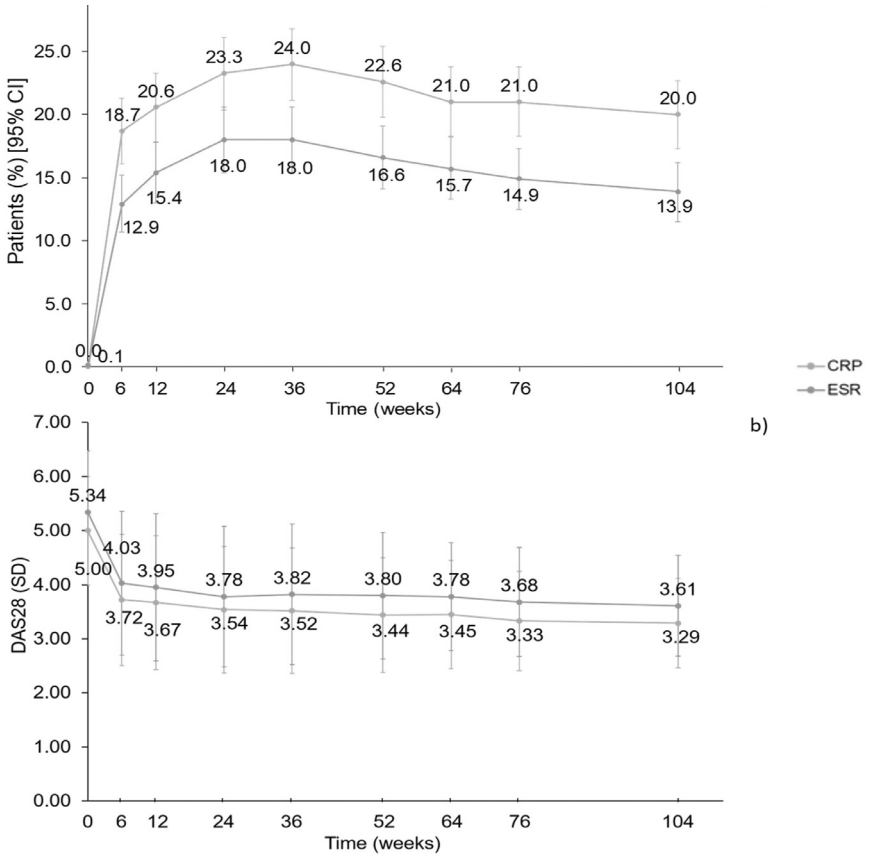

Fig. 1. Clinical remission. **a**) Patients achieving remission (DAS28-ESR<2.6 and DAS28-CRP<2.6; MMRM) up to week 104 and **b**) mean DAS28-CRP and -ESR scores up to week 104 (MMRM). Full analysis set. Clinical remission defined as DAS28-ESR<2.6 and DAS28-CRP<2.6. 95% confidence intervals were constructed based on the approximation to the normal distribution. DAS28: Disease activity score 28-joint count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MMRM: mixed model with repeated measures; CI: confidence interval; SD: standard deviation.

ti-TNF naïve subgroups exhibited high disease activity (DAS28-ESR>5.1) at baseline (54.5% [165/303] and 56.1% [271/483], respectively).

CZP treatment was discontinued by 696 patients prior to study completion/site closure (62.6%; Table II); main reasons for discontinuation were lack of CZP effectiveness (29.9%, n=332) and discontinuation due to an AE (20.9%, n=232; SS). Kaplan-Meier analyses show that a higher percentage of anti-TNF experienced patients had discontinued by week 104 compared with anti-TNF naïve patients (Supplementary Fig. 1). Of the 674 anti-TNF naïve patients in the Safety Set, 58.5% had discontinued by week 104 compared with 62.5% of patients who had taken one prior anti-TNF and 78.0% of patients who had taken ≥2 anti-TNFs.

Effectiveness

At week 104, 20.0% (170/851) of patients achieved the primary endpoint of disease remission (DAS28-CRP<2.6; MMRM). In comparison, 13.9% (118/851) of patients achieved disease remission defined by DAS28-ESR at week 104 (MMRM; Fig. 1). Rapid responses to CZP treatment were observed with 18.7% and 12.9% of patients achieving DAS28-CRP and DAS28-ESR remission, respectively at week 6. Remission rates appeared to peak between weeks 24 and 36, with 18.0% patients achieving DAS28-ESR remission at each timepoint, before exhibiting a slight decrease to week 104. At study completion, 15.3% (57/373) of patients with early DAS28-ESR response had achieved clinical remission compared with 6.7% (32/478) of patients with no early response (NRI). 79.4% (676/851) of patients achieved an early EULAR response; of these 5.3% (36/676) achieved EULAR remission at week 104 compared with 1.1% (2/175) of patients who did not achieve an early EULAR response (p=0.0312; NRI).

Patients who had received ≥2 prior anti-TNFs generally showed less improvement than those having taken one or no prior anti-TNFs (Fig. 2). DAS28-ESR CfB scores at week 104 were -1.3 (standard deviation [SD]: 0.8) for patients who had received ≥2 prior anti-TNFs, -1.5 (1.0) for those who had received one prior anti-TNF and -1.7 (1.0) for the anti-TNF naïve group (MMRM). DAS28-ESR<2.6 at week 104 was achieved by 7.1% (23/324) of anti-TNF experienced patients; 9.7% (18/186) of patients treated with 1 prior anti-TNF achieved remission, com-

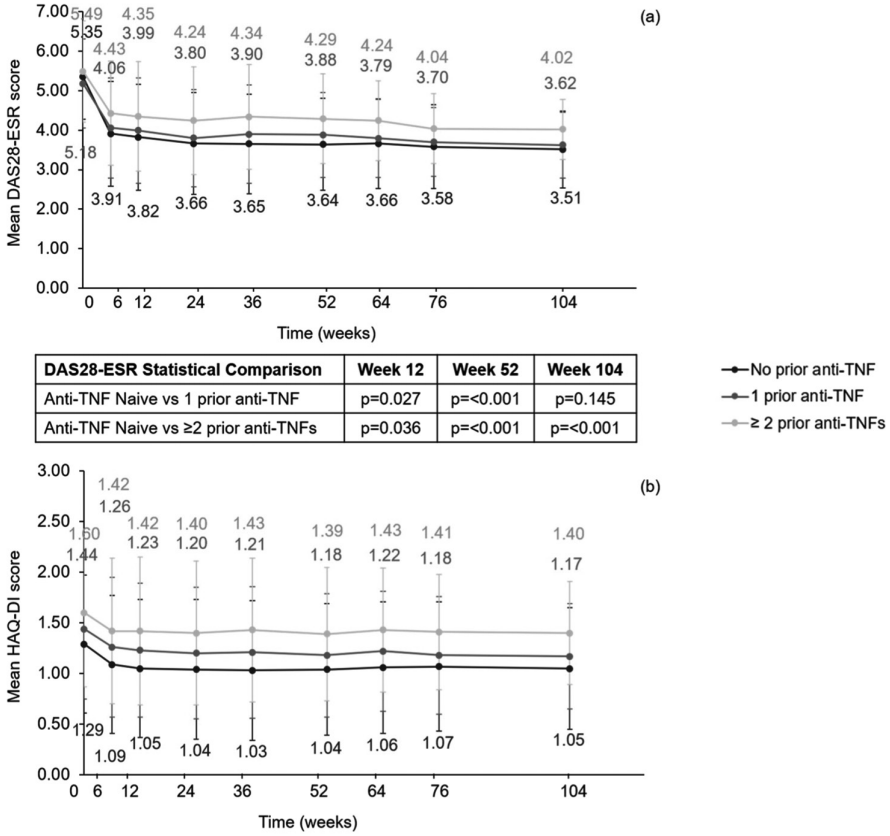

Fig. 2. (a) **Mean DAS28-ESR and (b) HAQ-DI scores up to week 104, stratified by prior anti-TNF usage.**

Full analysis set. Error bars denote standard deviation. All *p*-values are nominal in nature and should be interpreted in an exploratory manner. DAS28: disease activity score 28-joint count; ESR: erythrocyte sedimentation rate; HAQ-DI: health assessment questionnaire disability index; TNF: tumour necrosis factor; MMRM: mixed model with repeated measures.

pared with 3.6% (5/138) of patients who had received two or more prior anti-TNFs (MMRM).

Substantial improvement was reported in pain, physical function and disease activity outcomes at week 104 (Fig. 3 and Suppl. Fig. 2). Reductions were seen at week 6 in PAAP (CfB: -14.5 [SD: 22.7]; MMRM), fatigue (CfB: -0.9 [2.2]; MMRM), HAQ-DI (CfB: -0.2 [0.4]; MMRM), PtGADA (CfB: -14.0 [22.4]; MMRM). These reductions were maintained or further improved at week 104 in PAAP (CfB: -16.4 [20.3]; MMRM), fatigue (CfB: -1.1 [1.9]; MMRM), HAQ-DI (CfB: -0.3 [0.4]; MMRM), and PtGADA (CfB: -17.6 [19.9]; MMRM). Reductions were also observed in CDAI and SDAI scores at week 6 (CfB: -12.0 [11.8] and -12.6 [12.2], respectively. These were maintained up to week 104 with corresponding scores of -14.6 [10.2] and -15.2 [10.6]. The percentage of patients reporting a problem in the EQ-5D dimensions decreased across all five categories in patients remaining in the study (Suppl. Fig. 3).

Safety

Patients included in the SS were exposed to CZP for a total of 1,538 patient-years during the study (Table II). Median duration of CZP treatment was 383 days. TEAEs (2,000) were reported in 745 patients (67.1%; Table III). 306 TEAEs in 212 patients were classified as serious and 319 of these events resulted in 253 patients discontinuing the study. Nine patients experienced TEAEs with fatal outcome (0.8%; 0.6 per 100 patient-years [EAIR]), three of which (0.3%) were deemed to be drug-related; causes of death were reported to be sepsis in two cases and unknown in one case. For the latter, a causality assessment of CZP for the event was not reported by the treating physician and was therefore classed as drug-related as per convention. Neoplasms, including malignancies were reported in 10 patients (0.9%); neoplasms reported in only 1 patient were: breast cancer, cervix carcinoma (stage 0), endometrial adenocarcinoma, squamous cell carcinoma, bronchial carcinoma, small cell lung cancer, malignant melanoma and thyroid cancer (recurrent). Basal cell carcinoma was the only neoplasm to be reported in more than 1 patient (2 patients; 0.2%).

The most commonly reported TEAEs were infections and infestations (353 patients [31.8%]) and skin and subcutaneous tissue disorders (175 patients [15.8%]). Serious infections and infestations (53 events) were reported by 43 patients (3.9%); these included five cases of tuberculosis (including one case of latent tuberculosis). Local reactions at the injection site were experienced by 24 patients; 75 patients had systemic reactions.

Discussion

The FαsT study is the first non-interventional, post-authorisation study, conducted after the launch of the drug in 2009 in Germany, to investigate the effectiveness and safety profile of CZP in a routine, clinical setting, using a 'real-life' patient population with a high sample size (n=1,117). Due to the non-interventional, observational nature of the study, the data may be more reflective of the typical experience of RA patients treated with anti-TNFs. In the RABBIT registry, lower response rates were generally observed among patients who would not have been eligible for inclusion in RCTs (16).

Rapid responses to CZP treatment were observed as early as week 6 (13% patients and 19% were in DAS28-ESR and DAS28-CRP remission, respectively at this timepoint) with improvements sustained over two years of treatment (14% patients had achieved DAS28-ESR remission at week 104). Between weeks 24 and 36, a peak in remission rates was observed with 18% and 23% of patients achieved clinical remission (DAS28-ESR<2.6 and DAS28-CRP<2.6, respectively; MMRM) at week 24, which is compa-

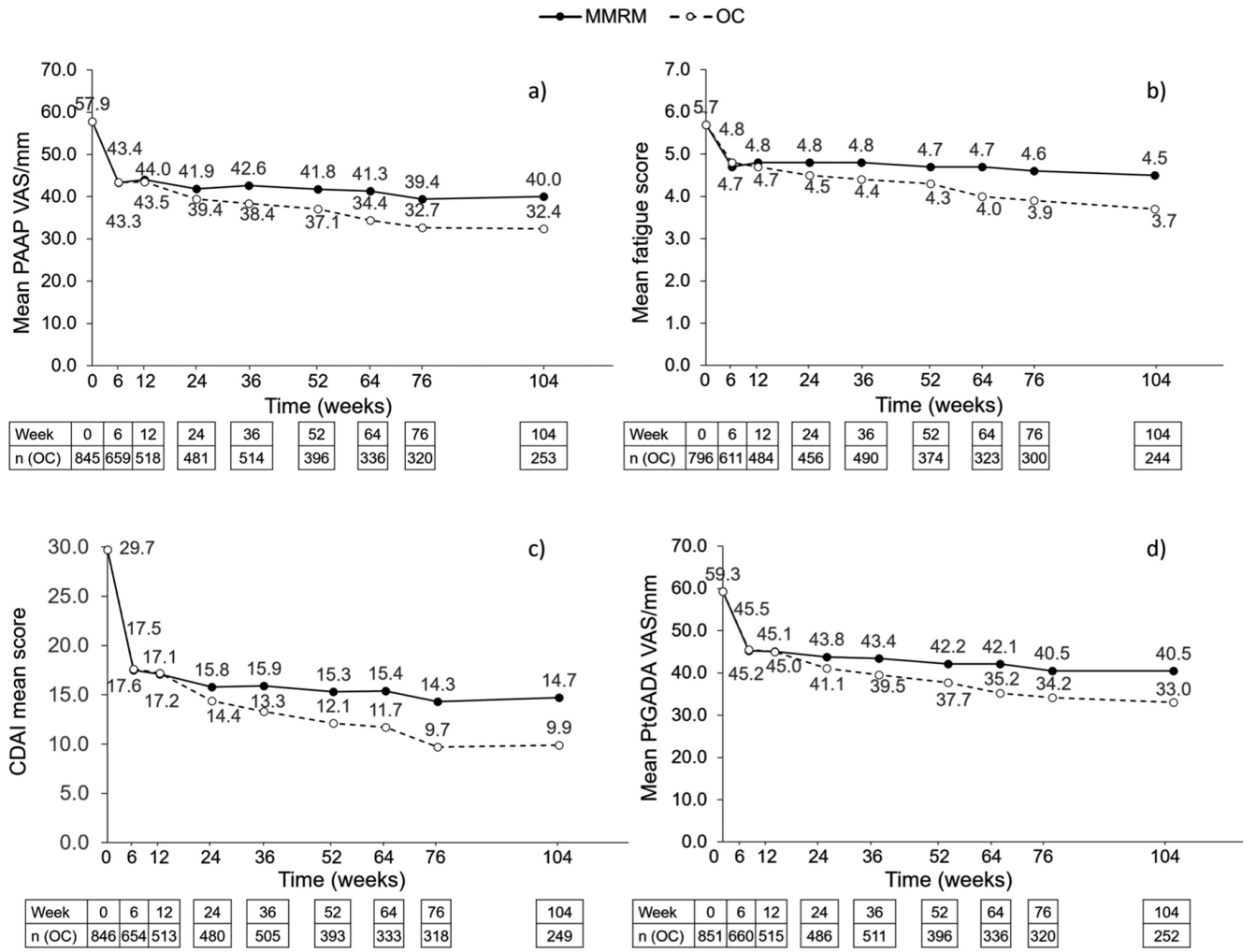

Fig. 3. Secondary outcomes up to week 104. Mean **a**) PAAP, **b**) Fatigue, **c**) CDAI and **d**) PtGADA scores imputed using MMRM and OC analyses. Full analysis set. PAAP: patient's assessment of arthritis pain; CDAI: clinical disease activity index; PtGADA: patient's global assessment of disease activity; MMRM: mixed model with repeated measures; OC: observed case; VAS: visual analogue scale.

rable with a 6-month post-marketing surveillance trial conducted by Koike *et al*. investigating the effectiveness of tocilizumab (28) (19% achieved DAS28-ESR remission at week 24). Similarly, 17% and 23% of patients achieved DAS28-ESR and DAS28-CRP remission, respectively at week 52 in FαsT, compared with 19% in the non-interventional adalimumab study conducted by Kleinert *et al*., (29) 19% of patients who had previously demonstrated inadequate response to anti-TNFs in the Italian RUBINO (rituximab) study (30) and 13% of patients with moderate disease activity in the Italian MODERATE trial (in the latter two trials, DAS28 was calculated using CRP or ESR according to site practice) (7). Baseline characteristics of FαsT were broadly comparable with other clinical RA studies (31-35).

Anti-TNF naïve patients appeared to be more likely to achieve low disease activity or remission at week 104 than anti-TNF experienced patients. Within the anti-TNF experienced subgroup, patients with one prior anti-TNF showed a better response than those who had taken two or more anti-TNFs previously, which is consistent with other RA observational studies (29, 34). In the 5-year non-interventional ReAlise study, (n=3,435), a numerical trend was observed for higher response rates in anti-TNF naïve patients. Harrold *et al*. observed that patients with moderate/high disease activity were much more likely to achieve remission if they had only had one prior anti-TNF compared with ≥2 prior anti-TNF treatments which corresponds with data from the FαsT study (34). One could hypothesise that an anti-TNF experienced patient is likely to have a longer disease duration, which has been shown to increase the risk of non-response to anti-TNFs (36). It is important to note that patients were not excluded from the study in the event of primary non-response to previous anti-TNF therapy. After receiving two years of CZP treatment, 402 (36%) patients completed the study. In a systematic review and meta-analysis investigating RA registry discontinuation rates, registries investigating anti-TNF treatments over two years exhibited survival rates ranging between 49–81% (37). At the time of the older studies included in this meta-analysis, fewer biologic options, including anti-TNFs, were available. Therefore, patients may have been more likely to continue with a particular anti-

Table III. Safety data.

	SS n=1111 no. of patients (%) [EAER]
Total exposure (patient-years)	1537.8
Any TEAEs	745 (67.1) [130.1]
TEAEs (≥5% in any SOC[a])	
Gastrointestinal disorders	137 (12.3)
General disorders and administration site conditions	120 (10.8)
Infections and infestations	353 (31.8)
Injury, poisoning and procedural complications	64 (5.8)
Musculoskeletal and connective tissue disorders	160 (14.4)
Nervous system disorders	111 (10.0)
Respiratory, thoracic and mediastinal disorders	80 (7.2)
Skin and subcutaneous tissue disorders	175 (15.8)
Severe TEAEs[b]	135 (12.2) [13.8]
Drug-related TEAEs	485 (43.7) [62.2]
Serious TEAEs	212 (19.1) [19.9]
TEAEs with fatal outcome	9 (0.8) [0.6]
Myocardial infarction	1 (0.1)
Haemorrhagic diarrhea	1 (0.1)
Sepsis	3 (0.3)
Multiple injuries	1 (0.1)
Bronchial carcinoma	1 (0.1)
Small cell lung cancer	1 (0.1)
Unknown	1 (0.1)
Discontinuation due to TEAEs[c]	253 (22.8) [20.7]

[a]: System organ class; b: Severe TEAEs were defined as those that have clear clinical effects or cause a patient to be unable to perform their daily activities; [b]: Please note that discontinuations due to adverse event data were collected using two different sections of the case report form ('Terminations' and 'Adverse Events'). These data were collected using the 'Adverse Events' section, therefore, these data differ from the figures quoted in Table II, which were collected using the 'Terminations' section. EAER is given per 100 patient-years. SS: safety set; EAER: exposure-adjusted event rate; TEAE: treatment-emergent adverse event; SOC: system organ class.

TNF treatment in the absence of alternative therapy.

Notably, this long-term, observational study (two years) assured a high level of monitoring in terms of data quality (each site was inspected once per year). This enhanced rate of safety collection enabled an extensive evaluation of the CZP safety profile at a level similar to those of RCTs. However, it is possible that the consequent burden on the investigator could have resulted in an increase of withdrawals from the study. In addition, increased levels of monitoring could change the everyday routine of a clinic, and therefore data may no longer be representative of standard practice.

Overall, the incidence of TEAEs was consistent with the known safety profile of CZP and did not reveal any new safety signals. The EAIR for AEs with fatal outcome was 0.6 per 100 patient-years which is in line with the identified incidence rate of deaths in a pooling of RA CZP studies, with a cut-off date of 31st Dec 2014 (0.5 per 100 patient-years) and is comparable with an EAIR of 0.7 per 100 patient-years from the RABBIT registry (unpublished report).

It is important to note the limitations of the FαsT study; non-interventional studies have an inherent known risk of selection bias (38), since patients who experience effective or tolerable therapy are likely to continue treatment and therefore the impact of bias is likely to increase over time. Bias is also introduced through missing observations caused by premature discontinuation when using observed data. This effect can become more prominent in long-term studies such as this one, however, much of the data collected during this study were imputed using MMRM analysis. This assumes that patients who discontinued would behave similarly to other patients in the same treatment group, whilst taking into account patient status (*e.g.* lack of effectiveness, AE) at termination. Data were considered to be missing at random, which is reasonable to assume in this study. Use of MMRM is atypical for non-interventional studies, as many use no imputation in data analyses. NRI imputation has been found to consistently underestimate within-group changes in efficacy whilst observed data are often found to over-estimate results (39, 40).

It is also important to highlight the use of the pre-defined clinical remission cut-off score (2.6) for the DAS28-CRP analysis (the primary endpoint of the study), and its associated limitations. Both DAS28-CRP and DAS28-ESR are used regularly in clinical practice, however, at the initiation of the study, it was believed that CRP was used more regularly in clinical practice and could be assessed more easily. In addition, CRP is regarded as a more direct measure of inflammation than ESR, with more sensitivity to short-term changes, and was therefore preferably selected for this study (41). Though the data cut-off of <2.6 has only been validated previously for DAS28-ESR (21) and not for DAS28-CRP, ACR guidelines for use of disease activity indicators recommend the use of both measures with an equal threshold for clinical remission of 2.6 (20).

The larger number of CRP assessments compared with ESR conducted during this trial suggests that CRP is indeed more widely used in clinical practice. This may be due to practical reasons: CRP can be measured from stored specimens of plasma or serum whereas ESR requires a fresh whole blood specimen and more manual work at the site of collection (42). In addition, ESR levels are more likely to be affected by confounding factors than CRP levels (43). As the two measures are regularly used in conjunction, it is important to establish a relationship between them. The Dutch RhEumatoid Arthritis Monitoring (DREAM) registry found that CRP and ESR exhibited a linear relationship and that DAS28-CRP scores were 0.2 points lower than DAS28-ESR scores (44). Our study showed a similar result, with DAS28-CRP scores consistently 0.3 points lower than their ESR counterparts, suggesting that DAS28-ESR is

likely to underestimate the number of patients in remission.

In conclusion, CZP was found to be an effective and well-tolerated treatment with no new or unexpected safety concerns identified during two years of therapy in a routine clinical practice setting in Germany. Rapid reductions in disease activity and improvements in physical function were maintained over two years in patients with moderate to severe active RA.

Key messages

What is already known about this subject?

- Several controlled clinical trials have demonstrated the efficacy and safety of certolizumab pegol (CZP), a PEGylated fragment crystallisable (Fc)-free anti-TNF (1, 2), which has subsequently been approved to treat adults with moderate to severe rheumatoid arthritis (RA) in Europe (3).

What does this study add?

- FαsT was the first non-interventional, post-authorisation study to be conducted over 2 years in CZP-treated patients.
- In a routine clinical practice setting in Germany, CZP was found to be an effective treatment with no new safety concerns up to week 104.
- Rapid reductions in disease activity and improvements in physical function were maintained up to week 104.

How might this impact on clinical practice?

- Here, we show that CZP is an effective and well-tolerated treatment option for patients with moderate to severe active RA in Germany.

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