

Supplemental information for: efficacy and safety of bimekizumab as add-on therapy for rheumatoid arthritis in patients with inadequate response to certolizumab pegol: a proof-of-concept study

Sophie Glatt,¹ Peter C. Taylor,² Iain B. McInnes,³ Georg Schett,⁴ Robert Landewé,⁵ Dominique Baeten,^{5,6} Lucian Ionescu,⁶ Foteini Strimenopoulou,⁷ Mark I. L. Watling,¹ Stevan Shaw⁸

¹Translational Medicine, UCB Pharma, Slough, UK

²Botnar Research Centre, University of Oxford, Oxford, UK

³Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, UK

⁴Department of Internal Medicine 3, Friedrich Alexander University Erlangen-Nurnberg and Universitätsklinikum Erlangen, Erlangen, Germany

⁵University Medical Centre, Amsterdam Rheumatology and Immunology Center, the Netherlands & Zuyderland Medical Centre, Heerlen, the Netherlands

⁶Patient Value Practices Development and Medical, UCB Pharma, Slough, UK

⁷New Medicines, UCB Pharma, Slough, UK

⁸Immunology Patient Value Unit, UCB Pharma, Brussels, Belgium

Corresponding author: Sophie Glatt

Address: Translational Medicine, UCB Pharma, Slough, UK

Email: Sophie.Glatt@ucb.com

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Methods

Statistical methods

Calculation of sample size

Sample size calculations were based on the Bayesian evaluation of the primary endpoint. The study was designed to have a high probability to pass the study efficacy success criterion of a $\geq 97.5\%$ probability that the change in Disease Activity Score 28-joint count C-reactive protein (DAS28[CRP]) from Week 8 for the certolizumab pegol-IR plus bimekizumab group was greater than for the certolizumab pegol-IR plus placebo group. Assuming a 5% drop out rate, and that 15% of patients would achieve low disease activity following treatment with certolizumab pegol and would therefore be ineligible for randomisation, up to 180 patients were enrolled in order to randomise at least 82 patients to study treatment at Week 8. Rates for withdrawal and missing data between randomisation and Week 20 were assumed to be 23% and 5% respectively, resulting in a total of 60 patients across both treatment groups available for analysis at Week 20. With a total sample size of 60 patients across both treatment groups and a common standard deviation (SD) of 0.94, the study would have an 89% probability of detecting a difference of 0.7 in DAS28(CRP) change from Week 8 between the treatment groups at Week 20.

Bayesian analysis of primary efficacy endpoint

The analysis of the primary efficacy endpoint was performed using an augmented Bayesian control model which allowed information borrowing from previous studies to augment the data on the control group (certolizumab pegol-IR plus placebo). At the design stage of the study, it was planned using data from the RAPID 1 study (NCT00175877).¹ The Bayesian model assumed an informative prior distribution for the DAS28(CRP) change from Week 8 in the certolizumab pegol-IR plus placebo group to be normal, with mean -0.54 and SD 0.26. This prior distribution contributed an approximate effective sample size of 13 patients to the certolizumab pegol –IR plus placebo group.

A linear model with normally distributed errors, including the centred Week 8 data as a covariate and treatment as a factor, was fitted to the change from Week 8 in DAS28(CRP). If errors were not normally distributed, then a t-distribution was considered as an alternative to the Gaussian model. The posterior distribution of the treatment effect and the posterior distribution of the response of the two treatment arms was summarised using means, medians, SD, 95% credible intervals, and 95% highest density intervals. The posterior probability of the change from Week 8 in DAS28(CRP) with certolizumab pegol plus bimekizumab being greater than certolizumab pegol plus placebo was also calculated. For

the mean response of the certolizumab pegol-IR plus bimekizumab group, and for the coefficient of model covariate, a vague prior distribution was assumed; for the certolizumab pegol-IR plus placebo group, an informative prior distribution was assumed. Patients that did not have available data were included in the analysis as a random variable in the Bayesian framework.

Sensitivity analyses of the primary efficacy endpoint

Sensitivity analyses were conducted to assess the strength of evidence when the informative prior was replaced with a vague prior, thus remove the leveraging of historical data. A sensitivity analysis was conducted by repeating the primary analysis assuming vague priors for all parameters of the model. A second sensitivity analysis was conducted by repeating the primary analysis for all randomised patients in the per protocol set (PPS; patients in the FAS who had no major protocol deviations) to evaluate the effect of important protocol deviations. The third sensitivity analyses repeated the primary analysis assuming vague priors for all parameters of the model for all randomised patients in the PPS to evaluate the effect of the influence of the prior distribution on the PPS. The fourth sensitivity analysis used a mixed model with repeated measures (MMRM) to evaluate the change from Baseline 2 in DAS28(CRP) at Week 20. This used all available change from Week 8 in DAS28(CRP) at all visits up to and including Week 20, incorporated as repeated measures within each subject. Treatment group, visit, and treatment group by visit interaction were included as fixed effects. The Week 8 values in DAS28(CRP) were used as a covariate and an unstructured covariance matrix was utilised.

Bayesian analysis of secondary efficacy endpoints

DAS28(CRP) remission at Week 20 was analysed using a logistic regression model to evaluate treatment response at Week 20. Treatment group, visit, and treatment group by visit interaction were included as fixed effects and the DAS28(CRP) value at Week 8 as a covariate in the model. A Bayesian analysis using a logistic model with vague prior distributions was conducted for DAS28(CRP) remission at Week 20.

Additional efficacy analyses

Additional analyses were performed to determine if the improvement in DAS28(CRP) at Week 20 could be attributed to one of the components. This analytical approach aimed to determine the drivers of remission by removing any potential over-influence of the patient global assessments or the CRP response and by utilising direct calculation of DAS28(CRP) remission and Boolean remission.

For the purpose of these analyses, an alternative version of DAS28(CRP), known as DAS28(CRP)[3], was used to evaluate the influence of the patient global assessment component in DAS28(CRP) improvement at Week 20 and was defined as:

$$\text{DAS28(CRP)[3]} = 0.56\sqrt{\text{TJC}} + 0.28\sqrt{\text{SJC}} + (0.36\ln(\text{CRP} + 1))^{1.10} + 1.15$$

with remission defined as a DAS28(CRP) score of ≤ 2.6 . Similarly, the Clinical Disease Activity Index (CDAI), a composite score frequently used in RA, was used as a measure of remission that excludes CRP, and was defined as:

$$\text{CDAI} = \text{SJC}(28) + \text{TJC}(28) + (\text{PtGADA}/10) + (\text{PhGADA}/10)$$

with remission defined as ≤ 2.8 . Boolean remission is a categorical variable, which prevents any one component from exerting too much influence on the analysis of disease remission. Boolean remission is based on a 28-joint count when all of the following criteria are met: swollen joint count (SJC) ≤ 1 , tender joint count (TJC) ≤ 1 , CRP ≤ 1 mg/dL and patient's global assessment of disease activity (PtGADA) score ≤ 10 mm.

Results

Sensitivity analysis of the primary efficacy variable

The results of the four sensitivity analyses at Week 20 were consistent with and supportive of the primary analysis of the primary efficacy variable. The estimated posterior mean treatment difference in DAS28(CRP) change from Week 8 to Week 20 for the randomised set using a vague prior distribution was 0.38 (95% credible interval [CrI]: -0.16, 0.92) with strong evidence that the true treatment difference was >0 (posterior probability of 91.6%). The estimated posterior mean treatment difference in DAS28(CRP) change from Week 8 to Week 20 for the PPS using an informative prior distribution was 0.61 (95% CrI: 0.15, 1.08) with very strong evidence that the true treatment difference was >0 (posterior probability of 99.6%). The estimated posterior mean treatment difference in DAS28(CRP) change from Week 8 to Week 20 for the PPS using a vague prior distribution for the certolizumab pegol and placebo model parameter was 0.43 (95% CrI: -0.11, 0.98) with strong evidence that the true treatment difference was >0 (posterior probability of 94.0%). The sensitivity analysis of change from Week 2 at Week 20 in DAS28(CRP) using MMRM showed a larger mean decrease in the certolizumab pegol-IR plus bimekizumab group compared with the certolizumab pegol-IR plus placebo group, mean difference from placebo -0.44 (95% CI: -0.98, 0.10); $p=0.110$.

ACR20, ACR50 and ACR70 response

The Bayesian analysis of ACR20 response indicated a posterior probability of 69.0% for a greater improvement in ACR20 in the certolizumab pegol-IRplus bimekizumab group compared with the certolizumab pegol plus placebo group at Week 20; estimated posterior mean treatment difference in ACR20 response was 6.3% (95% CrI -17.7, 30.6).

The posterior probability for improvement in ACR50 and ACR70 in the certolizumab pegol-IR plus bimekizumab group compared with certolizumab pegol-IR plus placebo group at Week 20 by Bayesian analysis was 99.6% and 100% respectively. The estimated posterior mean treatment differences in ACR50 and ACR 70 response was 26.5% (95% CrI 8.0, 43.7) and 13.9% (95% CrI 5.4, 25.6), respectively. However, since the ACR70 model didn't converge, these results should be interpreted with caution.

Safety profile of the certolizumab pegol responders group

In the certolizumab pegol responders group, the incidence of treatment-emergent adverse events (TEAEs) was 67.5% (54/80), with serious TEAEs reported for 8.8% (7/80).

Throughout the course of the study, 11.3% (9/80) of patients discontinued due to TEAEs. Severe TEAEs were reported for 3.8% (3/80) of patients; two patients experienced severe TEAEs of rheumatoid arthritis and one patient experienced a severe TEAE of pregnancy. There were no deaths in the certolizumab pegol responders group.

A summary of TEAEs reported in the certolizumab pegol responders group is shown in Supplementary Table S6. The most frequent TEAEs in the certolizumab pegol responders group were infections and infestations (32.5% [26/80]). Serious infections were experienced by three patients, all of whom withdrew from the study; one patient experienced serious infective bursitis 180 days after the first certolizumab pegol dose and 11 days after the most recent dose; one patient experienced serious pneumonia 29 days after the first certolizumab pegol dose and 15 days after the most recent dose; one patient experienced serious disseminated tuberculosis 146 days after the first certolizumab pegol dose and 5 days after the most recent dose. The most common non-serious infections reported by $\geq 5\%$ of patients were nasopharyngitis, upper respiratory tract infection and herpes viral infection. No new safety signals were observed in any laboratory parameters or vital signs.

References

1. Keystone E, Heijde D, Mason D, Jr., et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 2008;58(11):3319-29. doi: 10.1002/art.23964

Supplemental Table S1. Prohibited medications used for the treatment of RA

Drug class*	Exclusion criteria
Intramuscular/ intravenous /intra-articular corticosteroids	Use in the 28 days prior to the baseline visit and during the study
Intra-articular hyaluronic acid	Use in the 28 days prior to the baseline visit and during the study
Specific DMARDs Azathioprine, cyclosporine, cyclophosphamide, mycophenolic acid	Use in the 28 days prior to the baseline visit and during the study
Biologicals Abatacept, rituximab (or other B-cell depleting agents), anakinra, ustekinumab, anti-CD20, anti-IL-6 therapies, any other investigational biological drug	Any previous use of a marketed biological drug Previous use in a clinical trial for the same indication was allowed, provided that: use within 6 months prior to Baseline Visit (Week 0), or pharmacodynamic effect of the agent, if any, had returned to baseline at the time of enrollment and during the study
TNF inhibitors Infliximab, adalimumab, etanercept golimumab	Any previous exposure whether in clinical treatment or an investigational study and during the study
IL-17 inhibitors	Any previous exposure whether in clinical treatment or an investigational study and during the study

*Any dose

CD, cluster of differentiation; DMARDs, disease-modifying anti-rheumatic drugs; IL, interleukin; TNF, tumour necrosis factor

Supplemental Table S2. Disease characteristics at Week 8

	Certolizumab pegol-IR plus bimekizumab (n=52)	Certolizumab pegol-IR plus placebo (n=27)	Certolizumab pegol responders (n=80)
SJC,* mean (SD)	6.2 (4.2)	8.5 (7.1)	1.4 (2.1)
TJC,* mean (SD)	12.4 (11.0)	17.0 (11.4)	3.3 (3.3)
PtAAP , mean (SD)	53.4 (21.9)	46.0 (24.2)	21.5 (18.8)
PtGADA , mean (SD)	53.7 (22.5)	45.6 (22.4)	21.7 (17.2)
HAQ-DI , mean (SD)	1.3 (0.5)	1.3 (0.6)	0.87 (0.57)
DAS28(CRP) , mean (SD)	4.7 (0.8)	4.7 (1)	2.65 (0.69)

*SJC and TJC were based on 66 and 68 counts, respectively.

DAS28(CRP), Disease activity score 28 joint count (C-reactive protein); HAQ-DI; Health Assessment Questionnaire – Disability Index; PtAAP, patient's assessment of arthritis pain; PtGADA, patient's assessment of global disease activity; SJC, swollen joint count; TJC, tender joint count

Supplemental Table S3. Change from Week 8 in components of DAS28(CRP)

	Certolizumab pegol-IR plus bimekizumab (N=52)	Certolizumab pegol-IR plus placebo (N=27)
SJC*, mean (SD)		
Week 20	-3.9 (3.7)	-5.2 (5.0)
Week 32	-4.3 (4.2)	-5.6 (7.1)
TJC*, mean (SD)		
Week 20	-6.2 (8.8)	-8.9 (10.1)
Week 32	-6.7 (10.2)	-10.3 (10.0)
PtGADA, mean (SD)		
Week 20	-26.5 (29.0)	-13.8 (15.2)
Week 32	-31.0 (26.6)	-17.2 (26.9)
CRP†, geometric mean (GeoCV[%])		
Week 20	0.55 (4.6)	0.77 (1.2)
Week 32	0.43 (2.6)	0.78 (1.8)

†Ratio to Week 8

*SJC and TJC were based on 66 and 68 counts, respectively.

DAS28(CRP), Disease activity score 28 joint count (C-reactive protein); PtGADA, patient's assessment of global disease activity; SJC, swollen joint count; TJC, tender joint count

Supplemental Table S4. Additional efficacy analyses

	Certolizumab pegol-IR plus bimekizumab (N=52)	Certolizumab pegol-IR plus placebo (N=27)
Boolean remission, n (%)		
Week 8	0	0
Week 20	5 (10.9)	1 (4.2)
Week 32	5 (11.6)	4 (17.4)
DAS28(CRP)[3] change from Week 8, mean (SD)		
Week 20	-1.05 (1.1)	-0.85 (0.8)
Week 32	-1.24 (1)	-1.0 (1.2)
DAS28(CRP)[3] remission, n (%)		
Week 8	0	0
Week 20	12 (26.1)	2 (8.3)
Week 32	16 (37.2)	8 (34.8)
CDAI change from Week 8, mean (SD)		
Week 20	-12.4 (10.2)	-10.8 (8.4)
Week 32	-13.9 (10.7)	-11.8 (13.1)
CDAI remission, n (%)		
Week 8	0	0
Week 20	7 (15.2)	1 (4.2)
Week 32	9 (20.9)	3 (13.0)

CDAI, Clinical Disease Activity Index; DAS28(CRP), Disease activity score 28 joint count (C-reactive protein)

Supplemental Table S5. Percentage of patients with DAS28(CRP) remission and ACR20, ACR50 and ACR70 responders based on Week 8 values

	Certolizumab pegol-IR plus bimekizumab (n=52)	Certolizumab pegol-IR plus placebo (n=27)
DAS28(CRP) remission, % (95% CI) [n]		
Week 10	9.8 (4.3, 21.0) [51]	3.8 (0.7, 18.9) [26]
Week 12	22.4 (13.0, 35.9) [49]	7.7 (2.1, 24.1) [26]
Week 14	23.5 (14.0, 36.8) [51]	11.5 (4.0, 29.0) [26]
Week 16	21.6 (12.5, 34.6) [51]	0.0 (0.0, 13.3) [25]
Week 18	27.1 (16.6, 41.0) [48]	12.0 (4.2, 30.0) [25]
Week 20	26.1 (15.6, 40.3) [46]	8.3 (2.3, 25.8) [24]
Week 22	28.9 (17.7, 43.4) [45]	12.5 (4.3, 31.0) [24]
Week 24	20.0 (10.9, 33.8) [45]	4.2 (0.7, 20.2) [24]
Week 26	33.3 (21.4, 47.9) [45]	8.3 (2.3, 25.8) [24]
Week 28	31.1 (19.5, 45.7) [45]	37.5 (21.2, 57.3) [24]
Week 30	25.0 (14.6, 39.4) [44]	30.4 (15.6, 50.9) [23]
Week 32	37.2 (24.4, 52.1) [43]	34.8 (18.8, 55.1) [23]
Week 44	23.4 (13.6, 37.2) [47]	25.0 (12.0, 44.9) [24]
ACR20, % (95% CI) [n]		
Week 10	32.7 (21.2, 46.6) [49]	15.4 (6.2, 33.5) [26]
Week 12	46.8 (33.3, 60.8) [47]	30.8 (16.5, 50.0) [26]
Week 14	54.2 (40.3, 67.4) [48]	38.5 (22.4, 57.5) [26]
Week 16	47.9 (34.5, 61.7) [48]	32.0 (17.2, 51.6) [25]
Week 18	55.6 (41.2, 69.1) [45]	52.0 (33.5, 70.0) [25]
Week 20	60.5 (45.6, 73.6) [43]	54.2 (35.1, 72.1) [24]
Week 22	52.4 (37.7, 66.6) [42]	54.2 (35.1, 72.1) [24]
Week 24	54.8 (39.9, 68.8) [42]	50.0 (31.4, 68.6) [24]
Week 26	61.9 (46.8, 75.0) [42]	62.5 (42.7, 78.8) [24]
Week 28	59.5 (44.5, 73.0) [42]	75.0 (55.1, 88.0) [24]
Week 30	63.4 (48.1, 76.4) [41]	69.6 (49.1, 84.4) [23]

Week 32	62.5 (47.0, 75.8) [40]	65.2 (44.9, 81.2) [23]
Week 44	38.6 (25.7, 53.4) [44]	41.7 (24.5, 61.2) [24]

ACR50, % (95% CI) [n]

Week 10	12.2 (5.7, 24.2) [49]	7.7 (2.1, 24.1) [26]
Week 12	27.7 (16.9, 41.8) [47]	3.8 (0.7, 18.9) [26]
Week 14	25.0 (14.9, 38.8) [48]	7.7 (2.1, 24.1) [26]
Week 16	27.1 (16.6, 41.0) [48]	12.0 (4.2, 30.0) [25]
Week 18	28.9 (17.7, 43.4) [45]	16.0 (6.4, 34.7) [25]
Week 20	34.9 (22.4, 49.8) [43]	8.3 (2.3, 25.8) [24]
Week 22	33.3 (21.0, 48.4) [42]	20.8 (9.2, 40.5) [24]
Week 24	33.3 (21.0, 48.4) [42]	25.0 (12.0, 44.9) [24]
Week 26	31.0 (19.1, 46.0) [42]	37.5 (21.2, 57.3) [24]
Week 28	35.7 (23.0, 50.8) [42]	37.5 (21.2, 57.3) [24]
Week 30	36.6 (23.6, 51.9) [41]	43.5 (25.6, 63.2) [23]
Week 32	40.0 (26.3, 55.4) [40]	26.1 (12.5, 46.5) [23]
Week 44	31.8 (20.0, 46.6) [44]	25.0 (12.0, 44.9) [24]

ACR70, % (95% CI) [n]

Week 10	2.0 (0.4, 10.7) [49]	0.0 (0.0, 12.9) [26]
Week 12	12.8 (6.0, 25.2) [47]	0.0 (0.0, 12.9) [26]
Week 14	12.5 (5.9, 24.7) [48]	0.0 (0.0, 12.9) [26]
Week 16	12.5 (5.9, 24.7) [48]	0.0 (0.0, 13.3) [25]
Week 18	11.1 (4.8, 23.5) [45]	8.0 (2.2, 25.0) [25]
Week 20	14.0 (6.6, 27.3) [43]	0.0 (0.0, 13.8) [24]
Week 22	19.0 (10.0, 33.3) [42]	4.2 (0.7, 20.2) [24]
Week 24	14.3 (6.7, 27.8) [42]	4.2 (0.7, 20.2) [24]
Week 26	19.0 (10.0, 33.3) [42]	4.2 (0.7, 20.2) [24]
Week 28	19.0 (10.0, 33.3) [42]	8.3 (2.3, 25.8) [24]
Week 30	24.4 (13.8, 39.3) [41]	13.0 (4.5, 32.1) [23]
Week 32	27.5 (16.1, 42.8) [40]	21.7 (9.7, 41.9) [23]
Week 44	18.2 (9.5, 32.0) [44]	16.7 (6.7, 35.9) [24]

Data are Wilson's 95% CI. ACR20, ACR50, ACR70, American College of Rheumatology 20%, 50%, and 70% improvement criteria; DAS28(CRP), Disease Activity Score 28-joint count (C-reactive protein).

Supplemental Table S6. Most common ($\geq 5\%$ of patients) TEAEs reported in the certolizumab pegol responders group

TEAE by SOC and PT, n* (%)	Certolizumab pegol responders (n=80)
Infections and infestations	26 (32.5)
Nasopharyngitis	8 (10.0)
Upper respiratory tract infection	5 (6.3)
Herpes viral infection	4 (5.0)
Musculoskeletal and connective tissue disorders	14 (17.5)
Rheumatoid arthritis	7 (8.8)
Investigations	11 (13.8)
Alanine aminotransferase increased	6 (7.5)
Injury, poisoning and procedural complications	10 (12.5)
Skin and subcutaneous disorders	6 (7.5)
Gastrointestinal disorders	5 (6.3)
Blood and lymphatic system disorders	4 (5.0)

*n = number of patients reporting at least one TEAE within the SOC/PT

TEAEs during treatment were defined as an adverse event that started or worsened on or after the first dose of certolizumab pegol. TEAEs were coded using MedDRA v 19.0

PT, preferred term; SOC, system organ class; TEAE, treatment emergent adverse event