

ORIGINAL RESEARCH

The MIDORA trial: a phase II, randomised, double-blind, placebo-controlled, mechanistic insight and dosage optimisation study of the efficacy and safety of dazodalibep in patients with rheumatoid arthritis

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ABSTRACT

Objectives To evaluate the safety, efficacy and response duration of four different dosing regimens of dazodalibep (DAZ), a non-antibody biological antagonist of CD40L, in patients with rheumatoid arthritis (RA).

Methods This double-blind study included adult patients with moderate-to-severe active RA with a positive test for serum rheumatoid factor and/or anticitrullinated protein antibodies, an inadequate response to methotrexate, other conventional disease-modifying antirheumatic drugs or tumour necrosis factor- α inhibitors, and no prior treatment with B-cell depleting agents. Eligible participants were randomised equally to five groups receiving intravenous infusions of DAZ or placebo. The primary endpoint was the change from baseline in the Disease Activity Score-28 with C reactive protein (DAS28-CRP) at day 113. Participants were followed through day 309.

Results The study randomised 78 eligible participants. The change from baseline in DAS28-CRP (least squares means \pm SE) at day 113 was significantly greater for all DAZ groups (-1.83 ± 0.28 to -1.90 ± 0.27 ; $p<0.05$) relative to PBO (-1.06 ± 0.26); significant reductions in DAS28-CRP were also observed for all DAZ groups at day 309. The distribution of adverse events was generally balanced among DAZ and PBO groups (74% and 63%, respectively). There were four serious adverse events deemed by investigators to be unrelated to study medication.

Conclusions DAZ treatment for all dosage regimens significantly reduced DAS28-CRP at day 113 relative to PBO. The safety data suggest an acceptable safety and tolerability profile. Treatment effects at day 113 and the prolonged duration of responses after DAZ cessation support the use of longer dosing intervals.

Trial registration number NCT04163991

INTRODUCTION

The CD40/CD40L pathway has been implicated as a key driver in mounting cellular and humoral immune responses and likely

plays a role in the pathophysiology of several autoimmune diseases.^{1–3} The CD40 receptor is a member of the tumour necrosis factor (TNF) family and is expressed on the plasma membrane of antigen-presenting cells, including macrophages, dendritic cells and B cells.^{4–5} The cognate ligand for CD40 is CD40L (also known as CD154), which is expressed on the plasma membrane of T cells and other cell types, including platelets.^{6–7} The CD40/CD40L pathway plays a critical role in B cell and T cell activation.^{1,8} Activation of CD40 is critical for germinal centre (GC) formation, immunoglobulin-class switching and expression of cytokines such as interferon- α , TNF α and interleukin (IL)-6.^{1,9,10} While the potential therapeutic utility of inhibiting the CD40/CD40L pathway was suggested in previous studies of anti-CD40L monoclonal antibodies (mAbs) in patients with lupus and other autoimmune disorders, the development of these biologics was halted more than two decades ago due to thromboembolic complications found to be secondary to platelet activation mediated by the Fc portion of the mAb.^{11–16}

Dazodalibep (DAZ), a novel non-antibody biological antagonist of CD40L, was designed to circumvent Fc-dependent platelet activation. It comprises two Tn3 proteins fused to human serum albumin.^{17,18} Tn3, derived from the third fibronectin type III domain of human tenascin-C, is structurally similar to immunoglobulins and exhibits protein folds analogous to the complementarity-determining regions of an antibody. Notably, DAZ was designed to lack an Fc

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Dazodalibep (DAZ) is a novel non-antibody biological antagonist of CD40L under investigation for the treatment of autoimmune disorders.
- ⇒ The CD40/CD40L pathway plays a critical role in mounting cellular and humoral immune responses and has been implicated in the pathophysiology of rheumatoid arthritis and other autoimmune disorders.
- ⇒ Prior studies of anti-CD40L monoclonal antibodies (mAb) targeting the CD40/CD40L pathway were associated with thromboembolic complications related to the Fc portion of their mAb structure.
- ⇒ Treatment with DAZ led to higher, durable response rates compared with placebo in a double-blind, phase Ib study in patients with moderate-to-severe rheumatoid arthritis and was not associated with thrombotic complications or other major safety concerns.

WHAT THIS STUDY ADDS

- ⇒ In MIDORA (Mechanistic Insight and Dose Optimization in Rheumatoid Arthritis), a randomised, phase II trial of different dosage regimens of DAZ therapy for moderate-to-severe rheumatoid arthritis, the primary efficacy endpoint was achieved with statistical significance at all DAZ dosage regimens relative to placebo.
- ⇒ DAZ was associated with an acceptable safety and tolerability profile with no reported thromboembolic events; however, there was an imbalance in COVID-19 infections.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ The results provide further evidence of the potential therapeutic benefits of targeting the CD40/CD40L pathway in rheumatoid arthritis and other autoimmune disorders.
- ⇒ The safety data from this study are reassuring and suggest that DAZ therapy has an acceptable balance of potential risks and benefits.

domain; instead, human serum albumin was covalently linked to the bivalent CD40L binding domain to avoid any Fc-mediated effects and extend its half-life.¹⁸ DAZ did not induce platelet aggregation in non-clinical studies,¹⁹ and no platelet-related safety concerns have been observed thus far in treated subjects.¹⁸

In a phase Ib trial of DAZ in 53 patients with moderate-to-severe rheumatoid arthritis (RA), intravenous DAZ 1000 mg and 1500 mg administered every other week for 12 weeks rapidly improved RA disease activity compared with placebo (PBO), with maintenance of clinical responses during the 3-month follow-up period.²⁰ Here, we report the results of a phase II trial (MIDORA; NCT04163991) of DAZ in adult patients with moderate-to-severe RA assessing the safety, efficacy and duration of clinical response after treatment with four different dosage regimens of DAZ. Additionally, we assessed the impact of DAZ treatment on exploratory biomarkers of RA disease activity and biomarkers related to its presumed mechanism of action.

METHODS

Study design

This was a multicentre, randomised, double-blind, PBO-controlled, parallel-cohort clinical trial to evaluate the

safety and efficacy of DAZ in adult patients with active, moderate-to-severe, adult-onset RA who tested positive for serum rheumatoid factor (RF) and/or anticitrullinated protein antibodies (ACPA), had an inadequate response to methotrexate (MTX), other conventional disease-modifying antirheumatic drugs (cDMARDs) or an anti-TNF α agent, and had not previously received a B-cell depleting agent.

Eligible participants were randomly allocated to five groups in a 1:1:1:1:1 ratio to receive one of four intravenous dosage regimens of DAZ or PBO (online supplemental figure S1) in addition to their ongoing baseline treatment. An interactive web response system was used for block randomisation (block size=5). A participant was considered randomised when the investigator had notified the system that they had met eligibility criteria and the system provided the assignment of treatment group. Participants, investigators, site staff, sponsor and evaluating staff were blinded to treatment assignment.

No change in background treatment was allowed for 12 weeks (day 85), at which time rescue therapy could be instituted if they had persistently active disease. Rescue therapy was considered as any new or intensified cDMARD therapy or initiation of biological DMARD (bDMARD) treatment for RA, including initiation of any new cDMARD or increase in dose of a concomitant cDMARD therapy, initiation of a bDMARD or JAK inhibitor, increase in baseline corticosteroid dose, an intra-articular steroid injection >40 mg methylprednisolone (or its equivalent) or more than one intra-articular steroid injection of any dose. One intra-articular steroid injection \leq 40 mg methylprednisolone in one joint was permitted and not considered rescue therapy. All participants were followed at least through the primary analysis (day 113), and those who had not instituted rescue therapy, were followed through day 309 to determine the duration of clinical response. Study visits occurred on days 1, 15, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281 and 309.

Participants randomised to PBO or DAZ 1500 mg \times 4 received four infusions of saline or DAZ, respectively, on days 1, 15, 29 and 57. DAZ infusions were administered on day 1 for the DAZ 3000 mg \times 1 group and on days 1 and 57 for the DAZ 1500 mg \times 2 and DAZ 3000 mg \times 2 groups. PBO was given on dosing days when DAZ was not administered.

Patients

Key inclusion criteria

The study population included adult participants with a confirmed RA diagnosis at least 6 months prior to screening according to the EULAR/American College of Rheumatology 2010 criteria.²¹ Participants were required at screening to have moderate-to-severe disease activity as defined by a Disease Activity Score-28 with C reactive protein (DAS28-CRP) score >3.2, tender joint count (TJC) \geq 4 and swollen joint count (SJC) \geq 4, and to be positive for RF and/or ACPA. Participants were also required

to have been treated with MTX (7.5–25.0 mg/week), with or without a concomitant cDMARD via the same route of administration for at least 12 weeks and without a change in dose for at least 6 weeks prior to screening. If not receiving MTX therapy due to intolerance or contraindication, participants must have been treated with one or more cDMARD for at least 12 weeks prior to screening without a change in dose during the past 6 weeks.

Key exclusion criteria

Participants were excluded if they had a prior or current inflammatory joint disease other than RA, severe interstitial lung disease or prior use of B-cell depleting or anti-CD40L agent. Participants were also excluded if they had received any anti-TNF α biological agent within 8 weeks prior to screening (discontinuation could have been for any reason: lack of efficacy, safety/tolerability issues or lack of access to drug). In addition, participants were excluded if they had received any bDMARD with a mechanism of action other than direct TNF blockade, including, abatacept, anti-IL-6R (tocilizumab, sarilumab), rituximab or any JAK inhibitor, within 12 weeks or within five half-lives of the drug (whichever is longer) prior to screening. Additionally, participants were excluded if they had received any experimental therapy within 12 weeks or within five half-lives of the drug (whichever is longer) prior to screening.

Other exclusion criteria included a history of confirmed deep venous thrombosis or arterial thromboembolism within 2 years of enrolment, history of recurrent deep venous thrombosis or arterial thromboembolism and participants with risk factors for venous thromboembolism or arterial thrombosis (eg, immobilisation or major surgery within 12 weeks before screening), prothrombotic status (including, but not limited to, known congenital or inherited deficiency of antithrombin III, protein C, protein S or confirmed diagnosis of catastrophic antiphospholipid syndrome).

Assessments

Efficacy

The primary endpoint was the change from baseline to day 113 in DAS28-CRP. DAS28-CRP was assessed at each study visit through day 309. The DAS28-CRP is a composite score that includes an assessment of 28 specified joints for TJC and SJC, a patient global assessment of disease activity (PGA) and CRP level (mg/L).

Secondary endpoints included the proportion of participants at day 113 with DAS28-CRP-defined clinical remission (DAS28-CRP <2.6) and time to institution of rescue medication. Established definitions of remission and high disease activity are DAS28-CRP <2.6 and DAS28-CRP >5.1, respectively.^{22 23} Exploratory efficacy assessments through day 309 included the change in Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), TJC, SJC, physician global assessment of disease activity (MDGA), PGA and Health Assessment Questionnaire (including pain) score.

See online supplemental information for pharmacokinetic (PK), immunogenicity and biomarker methodology.

Safety

Safety was monitored through day 309 and included the incidence of treatment-emergent adverse events (AEs), serious adverse events (SAEs) and adverse events of special interest (AESI).

Statistical analysis

The planned sample size of 75 participants (15 participants per treatment group) provided approximately 80% power to detect a difference of 1.2 in the primary efficacy endpoint between the DAZ and PBO treatment groups assuming an SD of 1.25, at a two-sided statistical significance level of 0.10 using a two-sample t-test.

The primary efficacy endpoint and other continuous endpoints were analysed using a mixed model for repeated measures (MMRM) analysis with treatment, visit, visit by treatment interaction and corresponding baseline value included in the model. Data collected after administration of rescue medication were not included in the analysis. Data were included if they were collected after treatment discontinuation for reasons other than rescue. Missing data were handled by the MMRM approach.

For the primary efficacy endpoint analysis, the type I error rate was controlled at the 0.1 level (two-sided) using the following sequential testing strategy: step 1—the primary endpoint was tested for the DAZ 1500 mg \times 4 groups compared with PBO; step 2—if the p value was \leq 0.1 in step 1, the primary endpoint was tested for the DAZ 3000 mg \times 2 groups compared with PBO; step 3—if the p value was \leq 0.1 in both step 1 and step 2, the primary endpoint was tested for the DAZ 1500 mg \times 2 and DAZ 3000 mg \times 1 group compared with PBO using the Hochberg's method.²⁴

The proportion of participants achieving clinical remission at day 113 was analysed using a logistic regression model, with treatment and baseline value included in the model. Participants who received rescue medication before day 113 or had prematurely discontinued before day 113 were considered non-responders. Time to start of rescue medication for RA was analysed using the Cox proportional hazards model with treatment group included in the model; participants not receiving rescue medication were censored at their end of study date.

Safety data were summarised descriptively and by treatment group.

RESULTS

Baseline demographics and disease characteristics and disposition of participants

MIDORA was conducted at 19 sites in the USA and Poland from December 2019 to December 2021. Of 175 patients screened, 78 were randomised and dosed. The mean (SD) age of participants was 56.3 (12.7) years, and the majority were female (79.5%), white (93.6%) and not Hispanic or Latino (96.2%). Demographics and baseline

Table 1 Demographic and baseline disease characteristics

Parameter	PBO N=16	DAZ 3000 mg×1 N=16	DAZ 1500 mg×2 N=16	DAZ 3000 mg×2 N=15	DAZ 1500 mg×4 N=15	Total N=78
Age, mean (SD)	56.3 (14.0)	53.2 (10.7)	59.0 (12.2)	56.5 (12.2)	56.4 (15.2)	56.3 (12.7)
Female, n (%)	12 (75.0)	14 (87.5)	11 (68.8)	13 (86.7)	12 (80.0)	62 (79.5)
Race, n (%)						
Black/African-American	2 (12.5)	0	0	1 (6.7)	1 (6.7)	4 (5.1)
White	14 (87.5)	16 (100)	15 (93.8)	14 (93.3)	14 (93.3)	73 (93.6)
Other	0	0	1 (6.3)	0	0	1 (1.3)
Ethnicity, n (%)						
Hispanic or Latino	1 (6.3)	1 (6.3)	1 (6.3)	0	0	3 (3.8)
Non-Hispanic or Latino	15 (93.8)	15 (93.8)	15 (93.8)	15 (100)	15 (100)	75 (96.2)
BMI, mean (SD), kg/m ²	27.6 (5.5)	27.6 (3.8)	28.0 (4.8)	30.0 (6.0)	30.1 (7.6)	28.6 (5.6)
DAS28-CRP, mean (SD)	5.4 (1.1)	5.5 (0.9)	5.9 (0.7)	5.5 (0.6)	5.8 (0.7)	5.6 (0.8)
CRP, mean (SD), mg/mL	17.6 (23.7)	7.2 (12.4)	14.9 (16.1)	8.8 (9.2)	14.1 (13.9)	12.6 (16.0)
RF+, n (%)	14 (87.5)	12 (75.0)	15 (93.8)	12 (80.0)	8 (53.3)	61 (78.2)
CDAI, mean (SD)	36.5 (10.5)	39.0 (10.2)	43.5 (10.7)	35.7 (8.8)	39.3 (8.8)	38.9 (10.0)
SDAI, mean (SD)	38.3 (11.6)	39.7 (10.7)	45.0 (10.8)	36.6 (8.9)	40.7 (9.3)	40.1 (10.4)
TJC, mean (SD)	13.3 (5.0)	14.9 (5.1)	17.5 (5.3)	13.9 (4.1)	15.3 (4.8)	15.0 (5.0)
SJC, mean (SD)	10.5 (4.0)	9.8 (4.5)	11.9 (5.1)	9.3 (3.8)	9.9 (4.1)	10.3 (4.3)
PGA, mean (SD), mm VAS	56.6 (21.2)	71.3 (13.0)	65.9 (18.9)	64.6 (16.9)	69.0 (16.4)	65.4 (17.8)
MDGA, mean (SD), mm VAS	71.0 (15.3)	71.9 (12.6)	75.3 (14.7)	59.9 (18.3)	72.4 (12.0)	70.2 (15.3)

BMI, body mass index; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; DAS28-CRP, Disease Activity Score in 28 joints using C reactive protein; DAZ, dazodalibep; MDGA, physician global assessment of disease activity; PBO, placebo; PGA, patient global assessment of disease activity; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.

disease characteristics were generally similar across arms, except for RF+ proportion and mean CRP levels (table 1). The average (SD) disease duration was 12.5 (9.8) years.

At baseline, all participants were receiving at least one cDMARD with almost 90% (70/78) receiving MTX. The mean (SD) MTX dose was 17.46 (4.49) mg/week. Approximately 42% (33/78) were receiving a glucocorticoid for the treatment of RA at a mean (SD) prednisone-equivalent dose of 6.09 (2.43) mg/day. Baseline use of any cDMARD was balanced between the treatment groups; however, there was an imbalance in glucocorticoid use (PBO: 50.0%; DAZ groups: 33.3%–43.8%). Approximately 21% (16/78) of participants had received prior anti-TNF α agents. A total of 73 (94%) participants completed treatment, and 65 (83%) completed the study follow-up to day 309 (figure 1). Thirteen participants discontinued the study (AE: 1 (1.3%); death: 1 (1.3%); lost to follow-up: 1 (1.3%); withdrawal: 7 (9.0%); other: 3 (3.8%)).

Efficacy

A statistically significant improvement in DAS28-CRP score at day 113, the primary endpoint, was observed in all DAZ groups relative to PBO (LS mean \pm SE); DAZ 3000 mg \times 1: -1.90 ± 0.27 ($p=0.0296$); DAZ 1500 mg \times 2: -1.87 ± 0.27 ($p=0.0355$); DAZ 3000 mg \times 2: -1.87 ± 0.27 ($p=0.0364$); DAZ 1500 mg \times 4: -1.83 ± 0.28 ($p=0.0478$); PBO: -1.06 ± 0.26 (figure 2, table 2). The DAS28-CRP

component scores are presented in online supplemental figure S2. Reductions from baseline in DAS28-CRP were also found in all DAZ groups at day 309. In the DAZ 3000 mg \times 2 groups, separation from PBO was achieved at all timepoints after day 113.

The secondary efficacy endpoints are presented in table 2. DAS28-CRP clinical remission rates were low and similar in all groups (PBO: 18.8%; DAZ groups: 6.3%–18.8%), but fewer DAZ participants had high disease activity at day 113 (PBO group: 40.0%; DAZ groups: 7.1%–14.3%). Few participants (PBO: $n=1/16$; DAZ: $n=6/62$) received rescue medication (none before day 113), and time to rescue medication did not differ between DAZ and PBO.

The change from baseline (LS mean \pm SE) scores for exploratory efficacy endpoints are presented in table 3. A greater reduction in SDAI score at day 113 was achieved in all DAZ groups and ranged from -21.20 to -23.99 ($p=0.0944$ for DAZ 1500 mg \times 4; $p<0.05$ for all other DAZ groups) compared with PBO (-14.17). The ranges were similar for CDAI scores. The magnitude of improvement in SJC at day 113 was greater in the four DAZ groups (-6.5 to -8.2) compared with PBO (-4.4) with separation from PBO occurring in the DAZ 3000 mg \times 1 ($p=0.0895$), DAZ 1500 mg \times 2 ($p=0.0081$) and DAZ 3000 mg \times 2 ($p=0.0317$) groups. Improvement in TJC at day 113 in the DAZ groups ranged from -8.0 to -9.8 (PBO: -5.8); separation from

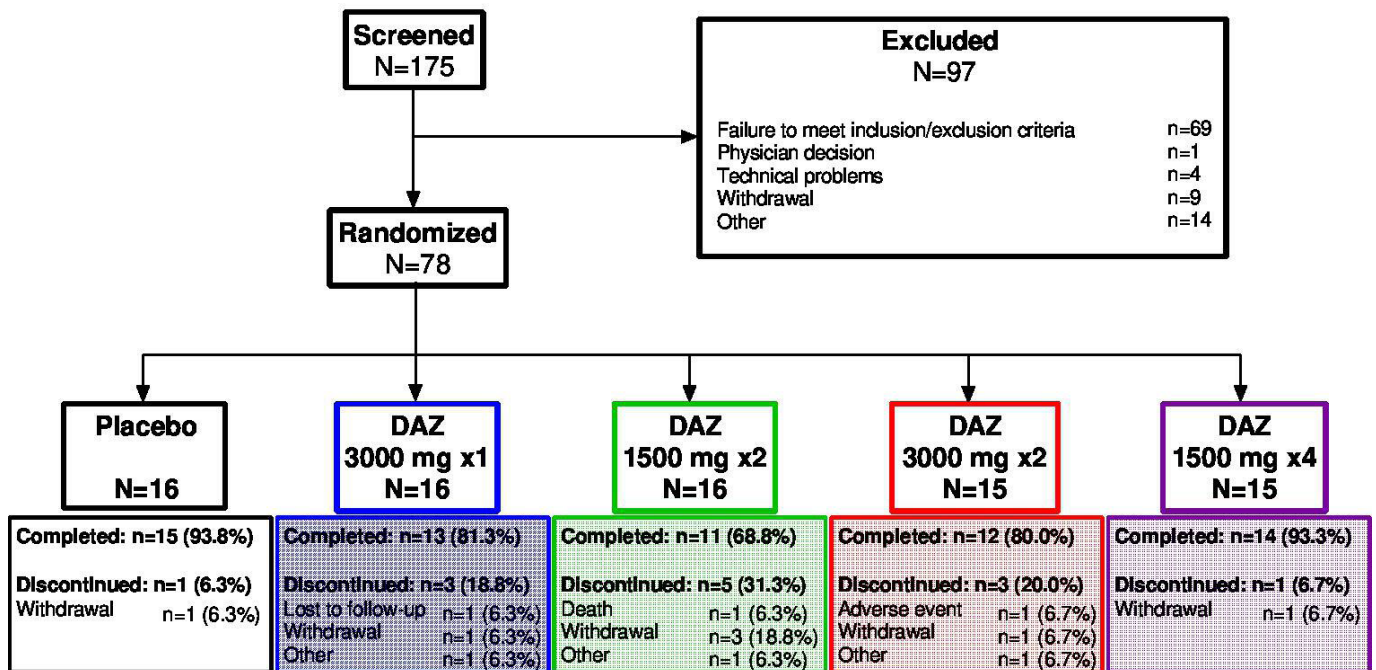


Figure 1 Disposition of MIDORA participants. Data reported as n (%). DAZ, dazodalibep.

PBO was achieved for the DAZ 3000 mg×1 ($p=0.0542$) and DAZ 3000 mg×2 ($p=0.0712$) groups.

At day 113, there was a greater magnitude of improvement in PGA score in each of the DAZ groups (−15.4 to −21.9) compared with PBO (−7.1); separation from PBO was achieved for the DAZ 3000 mg×2 and DAZ 1500 mg×4 groups ($p=0.0612$ and $p=0.0588$, respectively). Similarly, there was numerically greater improvement from baseline in MDGA score at day 113 in DAZ groups (−38.0 to −42.1) relative to PBO (−26.1), with separation from PBO in the DAZ 1500 mg×2 groups ($p=0.0642$) and DAZ 1500 mg×4 groups ($p=0.0425$). A substantially greater change from baseline in HAQ-Pain score at day 113 was observed in the DAZ 1500 mg×4 groups relative to PBO (−21.8 vs −8.8; $p=0.0754$). The magnitude of change from baseline in HAQ-Pain score at day 113 was −14.1, −9.9 and −19.7 in the DAZ 3000 mg×1, DAZ 1500 mg×2 and DAZ 3000 mg×2 groups, respectively.

Pharmacokinetics and immunogenicity

Mean plasma concentration-time profiles for DAZ are shown in [figure 3](#), and a summary of the PK parameters is shown in online supplemental table S1. DAZ plasma concentrations were below the limit of quantification for all participants receiving PBO. Following infusion of DAZ (1500 and 3000 mg), the mean concentration-time profiles showed parallel terminal phase and DAZ area under the concentration-time curve (AUC) and maximal concentration (C_{max}) that increased in an approximately dose-proportional manner. After the first dose, the mean C_{max} values ranged from 421 to 476 $\mu\text{g}/\text{mL}$ and 860–877 $\mu\text{g}/\text{mL}$ in DAZ 1500 mg and 3000 mg groups, respectively; the mean AUC from time 0 to day 56 was 4280 hours× $\mu\text{g}/\text{mL}$ and 7280–7870 hours× $\mu\text{g}/\text{mL}$.

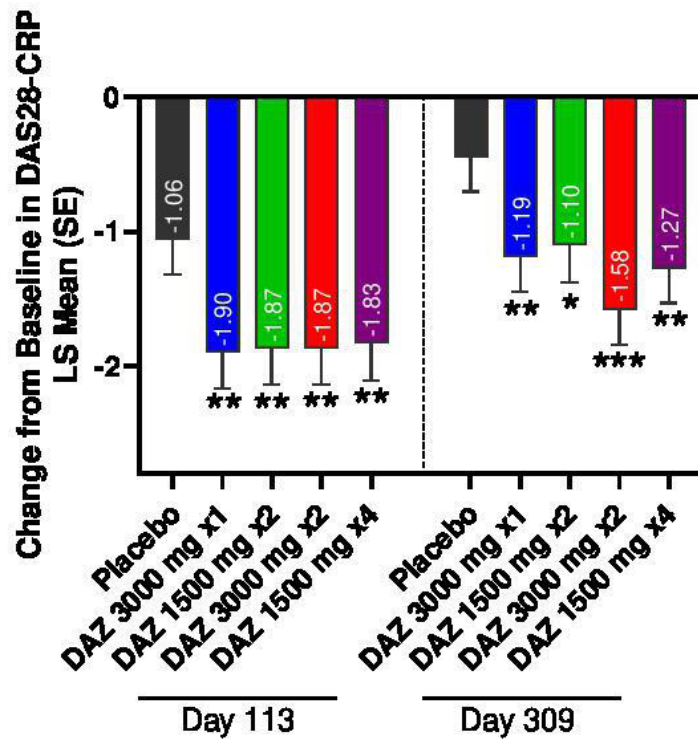
The terminal elimination half-life ($t_{1/2}$) was comparable across all DAZ groups (9–10 days).

None of the 62 participants treated with DAZ had ADA detected at baseline, and no participants in the PBO group tested ADA positive. A total of 19 participants (30.6%) tested ADA positive postbaseline (online supplemental table S2), with the earliest detectable ADA observed at day 85. Titres ranged from <60 to 480. Participants with positive ADA results had slightly lower exposure and slightly higher total body clearance (CL) when compared with participants with negative ADA results (online supplemental table S3 and online supplemental figure S3), however, there was no clear impact of ADAs on the PK profile based on a comparison of CL between the first and second dose.

Biomarkers

The impact of DAZ treatment on RF and ACPA levels (adjusted geometric mean ratio to baseline (90% CI)) is shown in [figure 4A–B](#). At day 113, RF levels dropped and separated from PBO for all DAZ groups ($p\leq 0.0007$) with values ranging from 0.57 (0.49 to 0.66) to 0.77 (0.66 to 0.89) IU/mL for DAZ groups relative to 1.20 (1.04 to 1.39) IU/mL for PBO. Separation was observed starting at day 57 and sustained through day 113 ($p\leq 0.0035$) for all DAZ dosage regimens. The changes in RF isotype levels are presented in online supplemental figure S4. ACPA levels were reduced for the DAZ 3000 mg×1 group (0.69 (0.52 to 0.91) U/mL; $p=0.0584$) and DAZ 1500 mg×4 groups (0.62 (0.47 to 0.82) U/mL; $p=0.0199$) compared with PBO (1.08 (0.83 to 1.42)) at day 113. The groups receiving DAZ 1500 mg×2 and DAZ 3000 mg×2 showed a reduction in ACPA levels relative to PBO at day 113 (0.82 (0.62 to 1.07) and 0.84 (0.63 to 1.11) U/mL,

A



B

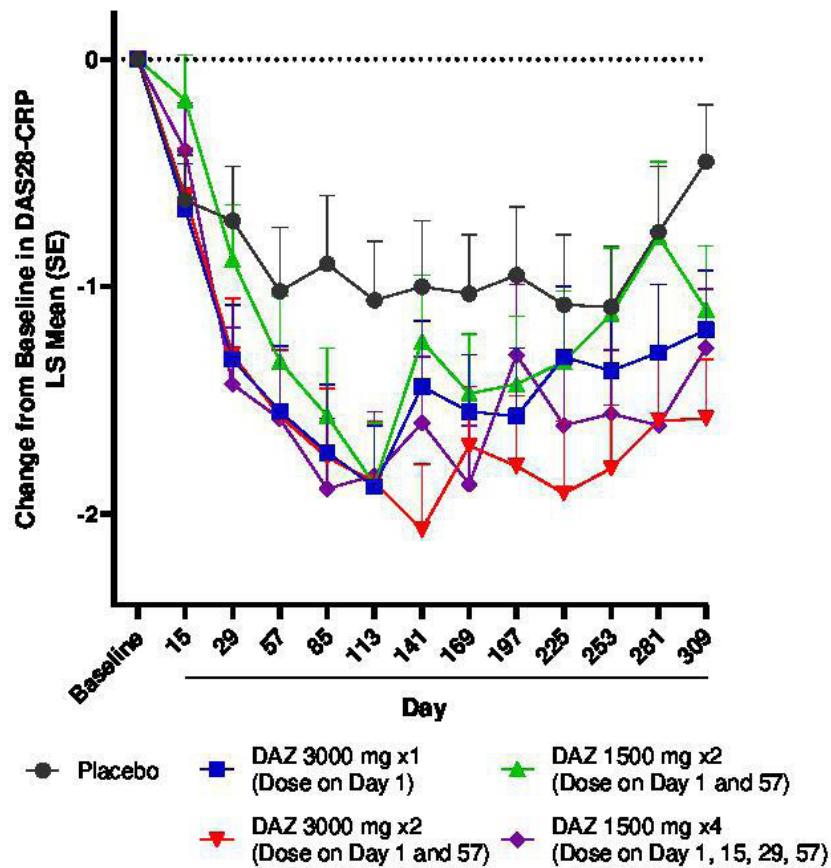


Figure 2 Change from baseline in DAS28-CRP. (A) MMRM results for DAS28-CRP at day 113 and day 309; * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$. (B) Change from baseline in DAS28-CRP plotted by study visit. DAS28-CRP, Disease Activity Score in 28 joints using C reactive Protein; DAZ, dazodalibep; LS, least squares; MMRM, mixed model for repeated measures.

Table 2 Primary and secondary efficacy endpoints

	PBO N=16	DAZ 3000 mg×1 N=16	DAZ 1500 mg×2 N=16	DAZ 3000 mg×2 N=15	DAZ 1500 mg×4 N=15
DAS28-CRP, n	15	14	15	14	14
LS mean CFB (SE)	-1.06 (0.26)	-1.90 (0.27)	-1.87 (0.27)	-1.87 (0.27)	-1.83 (0.28)
LS mean difference (SE)		-0.84 (0.38)	-0.81 (0.38)	-0.81 (0.38)	-0.77 (0.38)
P value		0.0296	0.0355	0.0364	0.0478
DAS28-CRP <2.6, n	16	16	16	15	15
Responder, n (%)	3 (18.8)	3 (18.8)	1 (6.3)	2 (13.3)	2 (13.3)
OR (90% CI)		1.4 (0.2 to 8.0)	0.6 (<0.1 to 5.5)	0.9 (0.1 to 5.7)	0.9 (0.2 to 5.1)
P value		0.7750	0.6974	0.9318	0.9108
Time to start rescue medication					
Rescued, n (%)	1 (6.3)	1 (6.3)	1 (6.3)	3 (20.0)	1 (6.7)
Censored, n (%)	15 (93.8)	15 (93.8)	15 (93.8)	12 (80.0)	14 (93.3)
HR (90% CI)		1.04 (0.10 to 10.60)	1.04 (0.10 to 10.60)	3.01 (0.45 to 20.09)	1.04 (0.10 to 10.60)
P value		0.9805	0.9805	0.3407	0.9805

DAS28-CRP score (primary endpoint) and DAS28-CRP-defined clinical remission (DAS28-CRP <2.6; secondary endpoint) at day 113; time to start rescue medication (secondary endpoint) through day 309.
CFB, change from baseline; DAS28-CRP, Disease Activity Score in 28 joints using C reactive protein; LS, least-squares; PBO, placebo.

respectively), but these differences were modest and not statistically significant. Serum total IgG, IgA and IgM is presented in online supplemental figure S5.

The effect of DAZ treatment on total soluble CD40L (sCD40L) and C-X-C motif chemokine ligand 13 (CXCL13) levels is presented in figure 4C–D. Increases from baseline in total sCD40L (median±median absolute deviation) were observed in all DAZ dosage groups at day 15, the earliest sampling timepoint. Increases peaked about day 85 in the groups receiving multiple doses of DAZ and returned to baseline values by day 197. In the 3000 mg×1 group, sCD40L levels peaked at day 57 and returned to baseline earlier, at day 141. Maximum reduction in CXCL13 levels was observed in all DAZ groups at day 29 ($p \leq 0.0013$ for all DAZ groups) with DAZ 1500 mg×4 maintaining reduction at day 57. An additional reduction in CXCL13 levels was observed relative to PBO at day 85 in cohorts receiving DAZ at day 57 (DAZ 1500 mg×2: $p=0.0017$, DAZ 3000 mg×2: $p=0.0006$ and DAZ 1500 mg×4; $p=0.0002$). CXCL13 levels in these groups began to recover after day 85 and returned to baseline levels by day 141, while in the DAZ 3000 mg×1 group, CXCL13 levels returned by baseline by approximately day 85.

Safety

Treatment-emergent AEs are summarised in table 4. The majority (91.0% (71/78)) of participants received all four doses of study medication (DAZ groups: 80.0%–93.8%; PBO: 93.8%). The proportion of participants reporting at least one AE was relatively balanced among treatment groups (DAZ groups: 74.2% (46/62); PBO: 62.5% (10/16)). Similarly, the proportion of participants with AEs deemed by investigators to be related to study medication was similar between DAZ groups (14.3%–23.5%) and PBO (25.0%). There were four SAEs in three

participants randomised to a DAZ group, all considered by the investigators to be unrelated to study drug: one nephrolithiasis, one COVID-19 infection that occurred the evening of dose 1 (also an AESI) and one participant hospitalised for COVID-19 pneumonia (also an AESI) who died from unknown cause 3 days after discharge (233 days after last dose). Full safety narratives pertaining to the SAEs observed on study are presented in the online supplemental information. There were no SAEs in the PBO group.

There was no imbalance of events in the infection and infestation system organ class between DAZ and PBO (32.3% and 31.3%, respectively); however, an imbalance in COVID-19 infections was observed, with COVID-19 infection reported by 12.9% (8/62) of DAZ recipients compared with 6.3% (1/16) who received PBO. In DAZ groups, one COVID-19 event occurred on the evening of dose 1, the others 51–279 days after dose 1 (16–223 days from most recent dose). Except for the two SAEs related to COVID-19 (COVID-19 and COVID-19 pneumonia), which were considered to be severe, other COVID-19 AEs were mild-to-moderate in severity. No participant with a COVID-19 infection during the trial was intubated or treated in an intensive care unit.

DISCUSSION

In this phase II trial of adults with moderate-to-severe RA, DAZ treatment significantly improved RA disease activity in all dosage groups as assessed by the change from baseline in DAS28-CRP at day 113 (primary endpoint). The observed improvement with DAZ treatment in DAS28-CRP scores was supported by the favourable effects of this agent on multiple components of the composite score. Although with some fluctuation, much of the improvement in disease activity appeared to be

Table 3 Exploratory efficacy endpoints

	PBO N=16	DAZ 3000 mg×1 N=16	DAZ 1500 mg×2 N=16	DAZ 3000 mg×2 N=15	DAZ 1500 mg×4 N=15
CDAI, n	15	14	15	14	14
LS mean CFB (SE)	-13.47 (2.87)	-22.22 (2.89)	-23.28 (2.93)	-22.98 (2.94)	-20.84 (2.98)
LS mean difference (SE)		-8.74 (4.07)	-9.81 (4.13)	-9.50 (4.09)	-7.36 (4.14)
P value		0.0356	0.0204	0.0233	0.0799
SDAI, n	15	14	15	14	14
LS mean CFB (SE)	-14.17 (2.87)	-22.61 (2.90)	-23.99 (2.93)	-22.95 (2.94)	-21.20 (2.98)
LS mean difference (SE)		-8.44 (4.07)	-9.82 (4.12)	-8.78 (4.10)	-7.03 (4.14)
P value		0.0424	0.0202	0.0360	0.0944
TJC, n	15	14	15	14	14
LS mean CFB (SE)	-5.8 (1.5)	-9.8 (1.5)	-9.1 (1.5)	-9.6 (1.5)	-8.0 (1.5)
LS mean difference (SE)		-4.1 (2.1)	-3.4 (2.1)	-3.8 (2.1)	-2.3 (2.1)
P value		0.0542	0.1168	0.0712	0.2849
SJC, n	15	14	15	14	14
LS mean CFB (SE)	-4.4 (1.0)	-6.8 (1.0)	-8.2 (1.0)	-7.5 (1.0)	-6.5 (1.0)
LS mean difference (SE)		-2.4 (1.4)	-3.8 (1.4)	-3.1 (1.4)	-2.1 (1.4)
P value		0.0895	0.0081	0.0317	0.1429
PGA, n	15	14	15	14	14
LS mean CFB (SE)	-7.1 (5.3)	-19.8 (5.5)	-15.4 (5.3)	-21.6 (5.5)	-21.9 (5.5)
LS mean difference (SE)		-12.7 (7.7)	-8.4 (7.6)	-14.5 (7.6)	-14.9 (7.7)
P value		0.1030	0.2724	0.0612	0.0588
MDGA, n	15	14	15	14	14
LS mean CFB (SE)	-26.1 (5.3)	-38.0 (5.4)	-40.4 (5.4)	-38.2 (5.6)	-42.1 (5.6)
LS mean difference (SE)		-12.0 (7.6)	-14.3 (7.6)	-12.1 (7.7)	-16.0 (7.7)
P value		0.1215	0.0642	0.1213	0.0425
HAQ, n	15	14	15	14	14
LS mean CFB (SE)	-0.27 (0.10)	-0.31 (0.11)	-0.16 (0.10)	-0.27 (0.11)	-0.26 (0.11)
LS mean difference (SE)		-0.04 (0.15)	0.11 (0.15)	-0.01 (0.15)	0.00 (0.15)
P value		0.7692	0.4784	0.9641	0.9749
Pain, n	15	14	15	14	14
LS mean CFB (SE)	-8.8 (5.0)	-14.1 (5.0)	-9.9 (4.9)	-19.7 (5.1)	-21.8 (5.1)
LS mean difference (SE)		-5.3 (7.1)	-1.1 (7.0)	-10.9 (7.1)	-13.0 (7.2)
P value		0.4598	0.8739	0.1284	0.0754

Exploratory efficacy endpoints at day 113.

CDAI, Clinical Disease Activity Index; CFB, change from baseline; DAZ, dazodalibep; HAQ, Health Assessment Questionnaire; LS, least-squares; MDGA, physician global assessment of disease activity; PBO, placebo; PGA, patient global assessment of disease activity; SDAI, Simplified Disease Activity Index; SJC, swollen joint count; TJC, tender joint count.

sustained in the DAZ treatment groups relative to PBO through day 197, despite receipt of the last dose at day 57 by participants in the 1500 mg×2, 3000 mg×2 and 1500 mg×4 groups and administration of a single dose at day 1 in the 3000 mg×1 group. A dose-response relationship was previously demonstrated in the phase Ib trial of DAZ in patients with RA that investigated doses ranging from 75 to 1500 mg administered every other week.¹⁸ The current study was not designed to formally test dose-response but to expand on the findings of the phase Ib study and explore the potential efficacy of higher doses of DAZ administered at intervals substantially longer than the every 2-week dosing interval tested in the phase Ib study. The efficacy observed across all dosage regimens strongly supports further investigation of dosing intervals

of 4 weeks and longer, particularly at the 3000 mg dose. Notably, the improvement in RA disease activity was achieved without evidence of thromboembolic complications, as expected based on the lack of an Fc domain in DAZ and consistent with previous non-clinical/clinical studies.^{18 19}

During the study, we observed an imbalance in COVID-19 infections between the PBO and DAZ groups. It is possible that DAZ treatment may increase the risk for COVID-19 infection, which would comport with its known mechanisms of action. However, given the small sample size, particularly in the PBO group, the potential differences in epidemiological risk and other possible confounding factors (study began in the pre-COVID-19 era, and COVID-19 disease activity varied widely by

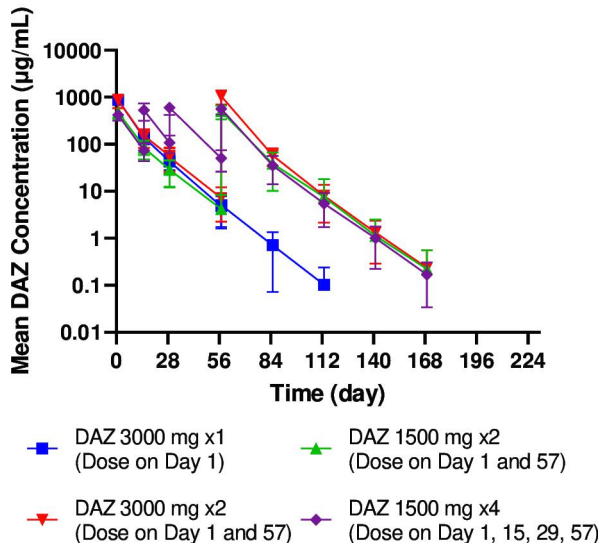


Figure 3 Concentration-time profile of DAZ. The mean (\pm SD) concentration-time profiles of DAZ following intravenous infusion. DAZ, dazodalibep.

region), we are uncertain about the extent to which DAZ therapy predisposes to COVID-19-related illness and its severity; we will closely monitor for COVID-19 infection in future studies with appropriate safety guidelines in place. SARS-CoV2 vaccination became available during the study period (later in Poland than in the USA) and as a result, only 44.9% of participants randomised to DAZ treatment were vaccinated before or during the study; only one of the participants who developed a COVID-19 infection during the trial reported having been vaccinated

prior to developing this infection. Despite this lack of protective immunity to the SARS-CoV2 virus, no participant was severely ill due to COVID-19. An autopsy was not performed on the participant experiencing the SAE of death, and the cause of death could not be determined.

DAZ PK exposures (AUC and C_{max}) were dose-proportional over the twofold dose range tested and the $t_{1/2}$ was comparable across groups. Approximately 31% of participants receiving DAZ had detectable ADAs, which were, at most, only four-fold greater than the lowest minimum detectable titre level (60); there was no clear impact of ADAs on the PK profile based on a comparison of CL between the first and second dose. Moreover, ADA-positive participants exhibited lower exposures after the first dose on day 15, which was much earlier than when ADAs were first detected (the earliest positive ADA time-point was day 85), suggesting many ADA-positive participants exhibited overall high CL initially, and that the occurrence of ADA is unlikely to impact efficacy. Interestingly, the clinical effect on disease activity seemed to be maintained beyond the last detectable level of DAZ in the circulation, particularly in the DAZ 3000 mg \times 2 groups, where most of the clinical response was maintained to at least day 253.

Total sCD40L and CXCL13 levels were evaluated as biomarkers of proximal and distal target engagement relevant to the CD40L/CD40 pathway. CXCL13, a biomarker of GC activity, is secreted by T follicular helper cells and is a key factor in the regulation of lymphoid organ development, ectopic GC development and plasma cell differentiation.²⁵ Elevated plasma levels are found in patients

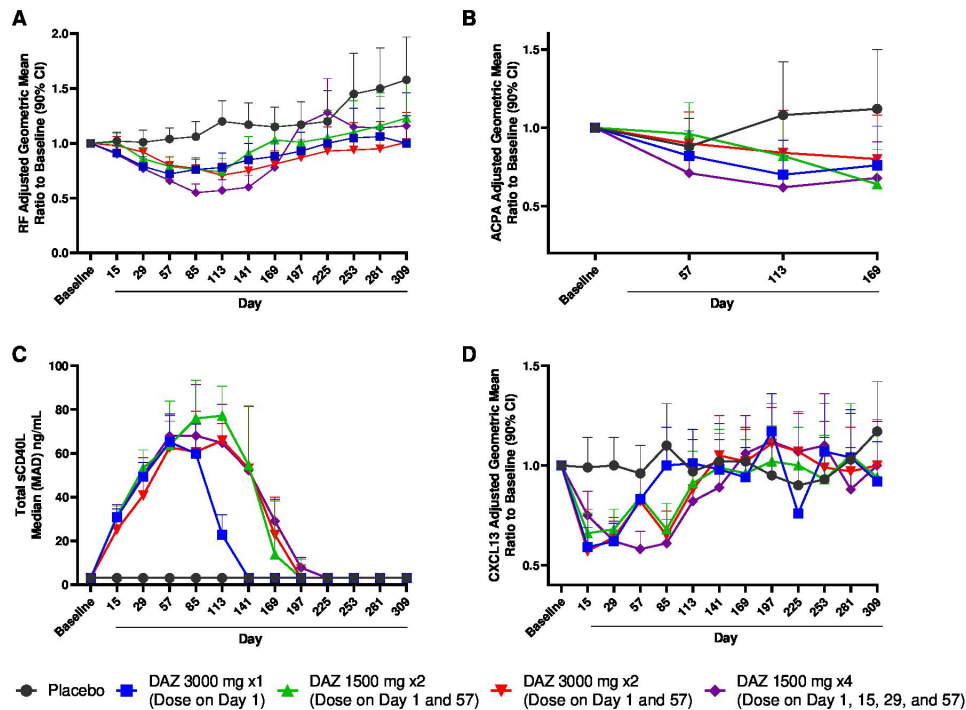


Figure 4 DAZ biomarkers. Line plots of DAZ biomarkers by study visit for (A) RF, (B) ACPA, (C) total sCD40L and (D) CXCL13. ACPA, anticitrullinated protein antibody; CXCL13, C-X-C motif chemokine ligand 13; DAZ, dazodalibep; MAD, median absolute deviation; RF, rheumatoid factor; sCD40L, soluble CD40L.

Table 4 Treatment-emergent AEs

Parameter, n (%) preferred term	PBO N=16	DAZ 3000 mg×1 N=18	DAZ 1500 mg×2 N=17	DAZ 3000 mg×2 N=13	DAZ 1500 mg×4 N=14	DAZ total N=62
≥1 AE	10 (62.5)	10 (55.6)	14 (82.4)	11 (84.6)	11 (78.6)	46 (74.2)
≥1 AE related to study drug	4 (25.0)	3 (16.7)	4 (23.5)	2 (15.4)	2 (14.3)	11 (17.7)
≥1 AE leading to death	0	0	1 (5.9)	0	0	1 (1.6)
≥1 AE leading to discontinuation	0	1 (5.6)	0	0	0	1 (1.6)
≥1 SAE	0	1 (5.6)	1 (5.9)	0	1 (7.1)	3 (4.8)
≥1 SAE related to study drug	0	0	0	0	0	0
≥1 AESI	0	1 (5.6)	1 (5.9)	0	0	2 (3.2)
Most common AEs*						
COVID-19	1 (6.3)	2 (11.1)	3 (17.6)	0	3 (21.4)	8 (12.9)
Rheumatoid arthritis	1 (6.3)	0	3 (17.6)	2 (15.4)	1 (7.1)	6 (9.7)
Alanine aminotransferase increased	0	1 (5.6)	2 (11.8)	1 (7.7)	0	4 (6.5)
Spinal osteoarthritis	0	2 (11.1)	2 (11.8)	0	0	4 (6.5)
Upper respiratory tract infection	1 (6.3)	1 (5.6)	0	3 (23.1)	0	4 (6.5)
Hypertension	0	1 (5.6)	0	1 (7.7)	1 (7.1)	3 (4.8)
Nasopharyngitis	0	0	1 (5.9)	1 (7.7)	1 (7.1)	3 (4.8)
Osteoarthritis	0	0	0	3 (23.1)	0	3 (4.8)
Pharyngitis	0	0	0	2 (15.4)	1 (7.1)	3 (4.8)
Anaemia	1 (6.3)	2 (11.1)	0	0	0	2 (3.2)
Arthralgia	0	0	1 (5.9)	0	1 (7.1)	2 (3.2)
Aspartate aminotransferase increased	0	0	2 (11.8)	0	0	2 (3.2)
Back pain	0	1 (5.6)	1 (5.9)	0	0	2 (3.2)
Hypercholesterolaemia	0	1 (5.6)	0	1 (7.7)	0	2 (3.2)
Lymphopenia	0	0	2 (11.8)	0	0	2 (3.2)
Pyrexia	0	0	1 (5.9)	0	1 (7.1)	2 (3.2)
Cystitis	2 (12.5)	0	0	0	1 (7.1)	1 (1.6)
Urinary tract infection	2 (12.5)	0	1 (5.9)	0	0	1 (1.6)

*Reported in ≥2 participants in PBO group or ≥2 participants in combined DAZ groups.

AE, adverse event; AESI, adverse event of special interest; PBO, placebo; SAE, serious adverse event.

with active RA and other autoimmune diseases.^{26,27} DAZ, in binding to CD40L, prevents the interaction between B and T cells through this pathway and has been shown to dissolve established GCs.¹⁹ Total sCD40L levels increased from baseline through day 85, indicative of DAZ binding sCD40L. The increase in total sCD40L levels was independent of DAZ dose consistent with maximum accumulation being reached at doses >300 mg.¹⁸ The reduction in serum CXCL13 levels likely reflects at least in part the inhibitory effect of DAZ on GCs and may be a leading indicator of clinical and serological responses. CXCL13 is also secreted by synovial plasmacytoid dendritic cells and T peripheral helper cells²⁸; however, the impact of DAZ on these signalling pathways remains to be fully elucidated. Significant reductions in RF were seen in all dosage cohorts by day 113, with modest reductions in ACPA levels by day 113 to day 169. These reductions

reached their nadir and were sustained after CXCL13 had returned to baseline. Taken together, the clinical efficacy and biomarker responses, the results suggest that the interval between DAZ doses could be greater than every 2 weeks and yet produce a significant treatment benefit in RA.

The study population assessed was predominantly white, and not Hispanic or Latino, and therefore, the results reported here may not be generalisable to other racial or ethnic groups. Moreover, this study was designed to explore the effect of a short (8 weeks or less) treatment period on the duration of clinical responses. Longer studies with repeated treatments at extended intervals are needed to establish the efficacy of DAZ for the chronic treatment of RA. Notably, the small sample sizes in each of the dosage groups prevent us from making any definitive interpretations about the effect of treatment

on the secondary and exploratory endpoints, although positive trends (greater numerical improvement in DAZ groups relative to PBO) were observed for many of the exploratory efficacy endpoints. Additionally, a total of 13 (16.7%) participants discontinued the study (DAZ groups: 12; PBO: 1), which may have impacted our interpretation of the results during the follow-up period at timepoints after day 113.

In summary, the initially observed efficacy of DAZ therapy for RA shown in a phase Ib study was confirmed by the results here and provides additional information regarding its dosing, PK, duration of clinical response and impact on biomarkers related to its mechanism of action. These study results support the continued evaluation of DAZ for the treatment of RA and other autoimmune disorders. DAZ dosing with more widely spaced intervals should be investigated in future clinical trials as they may be sufficient to provide sustained clinical benefits and allow for a greater margin of safety.

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Data availability statement Data are available on reasonable request. These data are not available in a repository but available on reasonable request.

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