The MIDORA Trial: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Mechanistic Insight and Dosage Optimization Study of the Efficacy and Safety of Dazodalibep in Patients with Rheumatoid Arthritis

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Supplemental Information

Pharmacokinetic, Immunogenicity and Biomarker Assessments Methodology

Plasma samples for pharmacokinetic (PK) assessment of DAZ were collected at each study visit pre- and post-dosing through Day 225. Plasma samples for immunogenic assessment of anti-drug antibodies (ADA) were collected on Days 1, 15, 29, 85, 169, 253 and 309. DAZ PK and ADA were measured as described previously [1].

Noncompartmental analysis was performed on the PK concentration-time data from all participants who received DAZ using Phoenix® WinNonlin® (Version 8.3, Certara, Princeton, NJ). PK concentrations and parameters were summarized by group with descriptive statistics.

ADA data was summarized descriptively and by treatment group

Serum and plasma samples were collected at each study visit through Day 309 to evaluate the impact of DAZ on RF and ACPA levels. ACPA was assayed using a commercially available kit (Eagle Biosciences, Inc.). Total sCD40L was determined as a measure of target engagement (free sCD40L and sCD40L bound to DAZ) and was assessed using a modified human sCD40L Platinum ELISA kit [eBioscience]). CXCL13 levels were measured as a biomarker of GC activity.

Safety Assessments

For the assessment of adverse events of special interest (AESI), AESIs included: thrombotic and embolic events, anaphylaxis and clinically significant (Grade 3 or higher) hypersensitivity reactions, severe (Grade 3 or higher) infusion related reactions, immune complex disease, severe (Grade 3 or higher) and/or opportunistic infections, hepatic function abnormality meeting

the definition of Hy's Law, and malignant neoplasm. Vital signs, laboratory parameters, electrocardiograms, and physical examinations were assessed; if abnormal and clinically relevant, they were recorded as an AE or SAE.

Safety

The participant experiencing the SAE of COVID-19 pneumonia who later died was in their late seventies, had a baseline BMI of 30.2 kg/m^2, and a 14-year history of RA. Prior medical history included arterial hypertension, coronary atherosclerosis, type 2 diabetes, bronchial asthma, and hypothyroidism. Concomitant medications included MTX, dexamethasone, ciclesonide, formoterol, lercanidipine, nebivolol, and metformin. The participant had received their second dose of COVID-19 vaccine 42 days prior to the event. The participant was randomized to the DAZ 1500 mg x2 group and received all doses of study medication. A Grade 3 SAE of COVID-19 pneumonia was reported 223 days after the last dose of study medication that led to hospitalization. Physical examination upon admission revealed average overall condition, and vesicular sounds with numerous crackles bilaterally over the lung fields on auscultation. Chest X-ray was remarkable for inflammatory lesions of virus etiology. Treatment included, among other medications and supportive measures, corticosteroids, oxygen therapy, and anticoagulants. The participant was discharged after an 8-day hospital stay in good overall condition. The participant died 3 days after discharge (233 days after the last dose of study medication). No autopsy was conducted, and no further information was available pertaining to this death.

The participant experiencing the SAE of nephrolithiasis was in their late fifties and had an 8-year history of RA. Prior medical history included arterial hypertension, fatty liver, dyslipidemia, vitamin D3 deficiency, osteoarthrosis, obesity, and nephrolithiasis requiring surgery. Concomitant medications included methotrexate, folic acid, methylprednisolone, diclofenac sodium, pantoprazole, perindopril arginine, and cholecalciferol. The participant was randomized to the DAZ 1500 mg x4 group and received all doses of study medication. A Grade 2 SAE of nephrolithiasis was reported 185 days after the last dose of study medication that resulted in hospitalization. The participant was admitted with an elevated body temperature (38°C), and blood test findings showed abnormal levels of CRP and ALT, and reduced glomerular filtration rate. A urinalysis showed hematuria. Computed tomography revealed a stone in the upper calyx of the left kidney. The participant was treated with antibiotics and analgesics, and then discharged after a 9-day hospital stay in good clinical status.

The participant experiencing the SAE of COVID-19 infection was in their late fifties with a baseline BMI of 27.3 kg/m^2 and a 10-year history of RA. Prior medical history included hypertension, non-alcoholic fatty liver, probable lung infection, and mild pulmonary fibrosis. Concomitant medications included sulfasalazine, etoricoxib, antihypertensive drugs (indapamide, and perindopril arginine), and pantoprazole. The participant was randomized to the DAZ 3000 mg x1 group and received the first dose of study medication. A Grade 3 SAE of COVID-19 infection was reported for this participant after receiving the first dose of study

medication. On the evening of dose 1, the participant developed a fever (maximum 38°C), which persisted for 2 weeks, along with symptoms of cough and generalized weakness. The initial chest X-ray was interpreted as normal. Thirteen days after receiving dose 1, the participant began cefuroxime and a repeat chest X-ray showed “inflammatory changes” in both lungs. Nineteen days after receiving dose 1, the participant was admitted via the emergency room with increased body temperature as the only symptom; a SARS-CoV-2 polymerase chain reaction test was positive. The participant had elevated levels of acute inflammatory plasma markers (D-dimer = 1300 mg/L [ULN = 500 mg/L]); ferritin = 907 ng/mL [ULN = 400 ng/mL]; fibrinogen = 880 mg/dL [ULN = 400 mg/dL]) and was treated with IV ceftriaxone and SC enoxaparin. The participant remained stable and was discharged to complete the required period of isolation and treatment with levofloxacin.

Supplemental Table 1. Summary of DAZ Plasma Pharmacokinetic Parameters

Treatment	**Dose No.** (Patients)	**T_{max}** (day)	**C_{max}** (µg/mL)	**AUC_{last}** (µg·day/mL)	**AUC_{0-56D}** (µg·day/mL)	**CL** (mL/day)	**$t_{1/2}$** (day)
DAZ 3000 mg x 1	Dose 1 n = 16	0.0899 (0.0868, 0.100)	877 ± 204 (23.2)	7350 ± 1380 (18.7)	7280 ± 1370 (18.8)	430 ± 91.9 (21.4)	9.27 ± 1.61 (17.3)
DAZ 1500 mg x 2	Dose 1 n = 17	0.0875 (0.0847, 0.0951)	476 ± 127 (26.7)	3980 ± 1580 (39.8)	4280 ± 1280 (29.9)	371 ± 92.5 (24.9)	9.06 ± 1.98 (21.8)
	Dose 2 n = 15	0.0681 (0.0646, 0.0847)	504 ± 162 (32.1)	5280 ± 2000 (37.9)	5310 ± 1910 (35.9)	314 ± 104 (33.2)	9.55 ± 1.51 (15.8)
DAZ 3000 mg x 2	Dose 1 n = 13	0.0875 (0.0840, 0.0917)	860 ± 275 (32.0)	7870 ± 2570 (32.6)	7870 ± 2570 (32.6)	417 ± 144 (34.6)	9.02± 1.06 (11.8)
	Dose 2 n = 13	0.0667 (0.0486, 0.0882)	1050 ± 349 (33.3)	10000 ± 3320 (33.1)	9910 ± 3250 (32.7)	340 ± 140 (41.0)	9.88 ± 1.41 (14.3)
DAZ 1500 mg x 4	Dose 1 n = 13	0.0903 (0.0840, 0.108)	421 ± 102 (24.2)	2960 ± 604 (20.4)	NA	NC	NC
	Dose 2 n = 13	0.0486 (0.0437, 0.0521)	564 ± 163 (28.9)	4060 ± 1290 (31.8)	NA	NC	NC
	Dose 3 n = 14	0.0472 (0.0438, 0.0486)	601 ± 181 (30.1)	6350 ± 1840 (28.9)	NA	NC	NC
	Dose 4 n = 14	0.0667 (0.0486, 0.0708)	568 ± 140 (24.7)	5770 ± 1110 (19.1)	NA	294 ± 49.8 (16.9)	10.5 ± 2.06 (19.6)

Parameters presented as arithmetic mean ± standard deviation (CV%) except T_{max}, which is presented as median (range). On Day 57, two participants missed dose 2 in the DAZ 1500 mg x 2 group. Sample collection at the end of infusion was missed for three participants: one in the DAZ 1500 mg x 4 group after the first and second doses, and two in the DAZ 3000 mg x 1 group after the first dose. All PK parameters from the related doses were excluded from group summary statistics. In CL, column, CL_{ss} values are reported for doses 2-4.

AUC, area under the concentration-time curve; AUC_{0-56D}, AUC from Time 0 to Day 56; AUC_{last}, AUC from Time 0 to the last quantifiable concentration; CL, total body clearance; CL_{ss}, total body clearance at steady state; NA, not applicable; NC, not calculable; C_{max}, maximum observed concentration; $t_{1/2}$ = terminal elimination half-life; T_{max}, time to the maximum concentration

Supplemental Table 2. Summary of Anti-drug Antibody Results

Parameter	DAZ 3000 mg x 1 N=18	DAZ 1500 mg x 2 N=17	DAZ 3000 mg x 2 N=13	DAZ 1500 mg x 4 N=14
Baseline ADA positive, n	0	0	0	0
Post-Baseline ADA positive, n (%)	8 (44.4)	2 (11.8)	5 (38.5)	4 (28.6)
Minimum, maximum titer	60, 480	120, 120	60, 480	60, 120

ADA, anti-drug antibodies

Supplemental Table 3. Impact of Anti-drug Antibodies on DAZ Pharmacokinetics

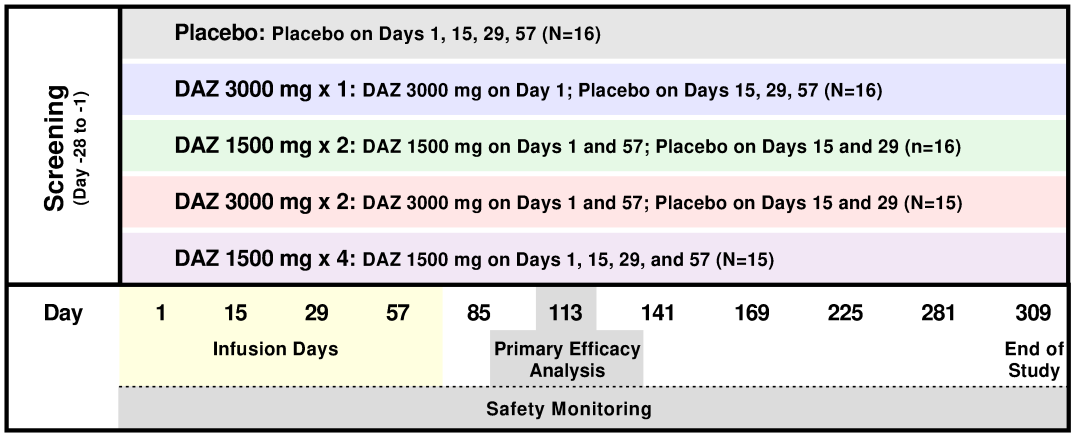
Treatment	Dose No. No. of Participants	ADA Status[1]	CL (mL/day)	R_CL_{21}
DAZ 3000 mg x 1	Dose 1 n = 16	Negative (n = 9)	404 ± 83.6 (20.7)	NA
		Positive (n = 7)	469 ± 97.5 (20.8)	NA
DAZ 1500 mg x 2	Dose 1 n = 17	Negative (n = 15)	352 ± 80.6 (22.9)	NA
		Positive (n = 2)	498 ± 67.8 (13.6)	NA
	Dose 2 n = 15	Negative (n = 14)	295 ± 100 (34.0)	0.873 ± 0.180 (20.6)
		Positive (n = 2)	425 ± 37.4 (8.8)	0.863 ± 0.191 (22.2)
DAZ 3000 mg x 2	Dose 1 n = 13	Negative (n = 8)	385 ± 106 (27.7)	NA
		Positive (n = 5)	468 ± 193 (41.3)	NA
	Dose 2 n = 13	Negative (n = 8)	340 ± 162 (47.5)	0.860 ± 0.234 (27.2)
		Positive (n = 5)	341 ± 113 (33.1)	0.746 ± 0.108 (14.4)
DAZ 1500 mg x 4	Dose 4 n = 14	Negative (n = 10)	291 ± 46.0 (15.8)	NA
		Positive (n = 4)	302 ± 65.6 (21.7)	NA

[1] For participants with a CL value.

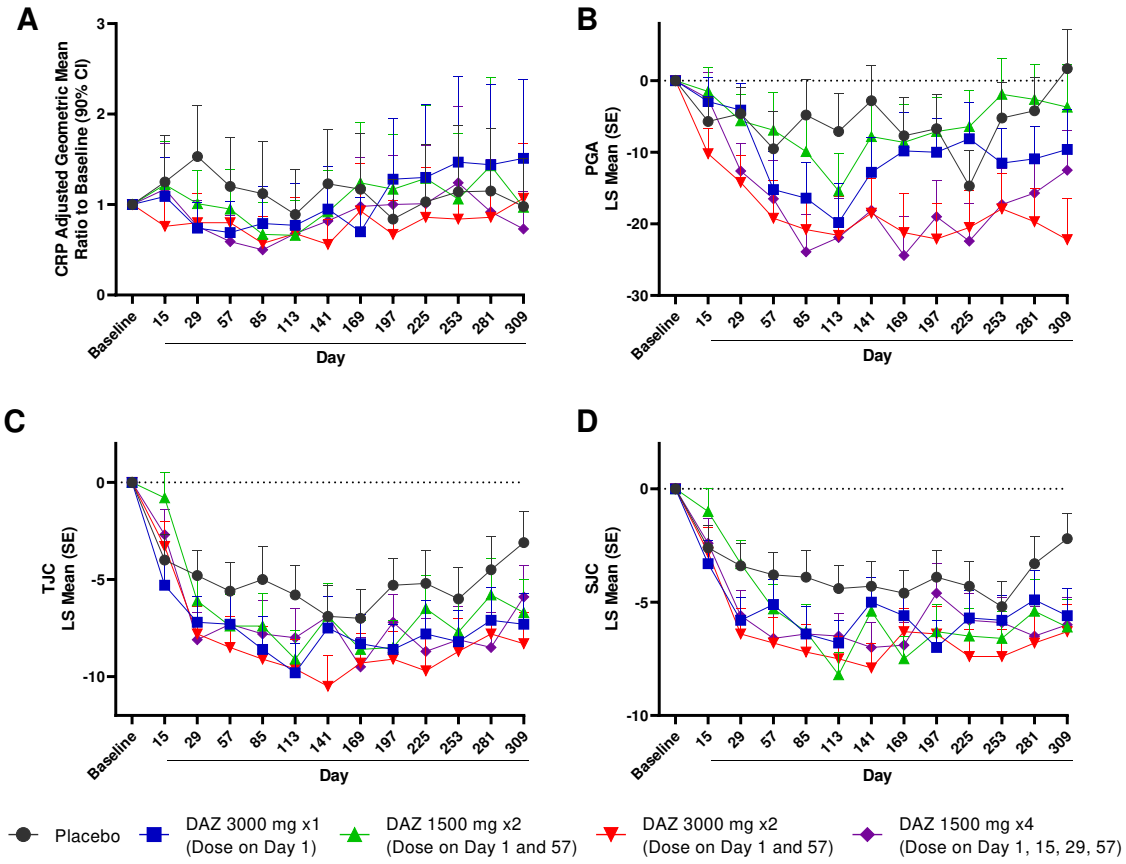
Parameters are presented as arithmetic mean ± standard deviation (percent coefficient of variation). On Day 57, two participants missed dose 2 in the DAZ 1500 mg x 2 group. PK Sample collection at the end of infusion was missed for three participants: one in the DAZ 1500 mg x 4 group after the first and second doses, and two in the DAZ 3000 mg x 1 group after the first dose. All PK parameters from the related doses were excluded from group summary statistics.

ADA, anti-drug antibody; CL, total body clearance; NA, not applicable; R_CL_{21}, clearance ratio of Dose 2 versus Dose 1 (DAZ 1500 mg x 2 and DAZ 3000 mg x 2 groups)

Supplemental Figure 1. Study Schematic

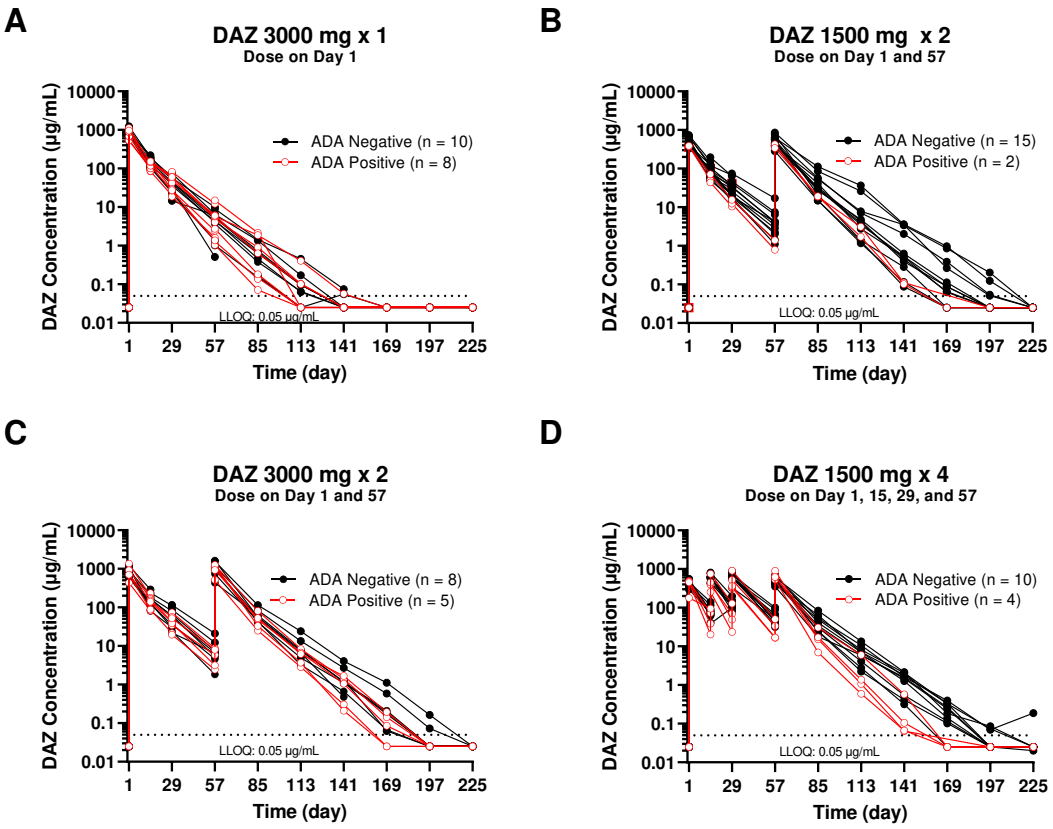


Supplemental Figure 2. Component Scores of DAS28-CRP



Longitudinal data presented by study visit for(A) CRP, (B) PGA, (C) TJC, and (D) SJC. CI, confidence interval; CRP, C-reactive protein;LS, least squares; PGA, patient global assessment of disease activity; SE, standard error; SJC, swollen joint count; TJC, tender joint count.

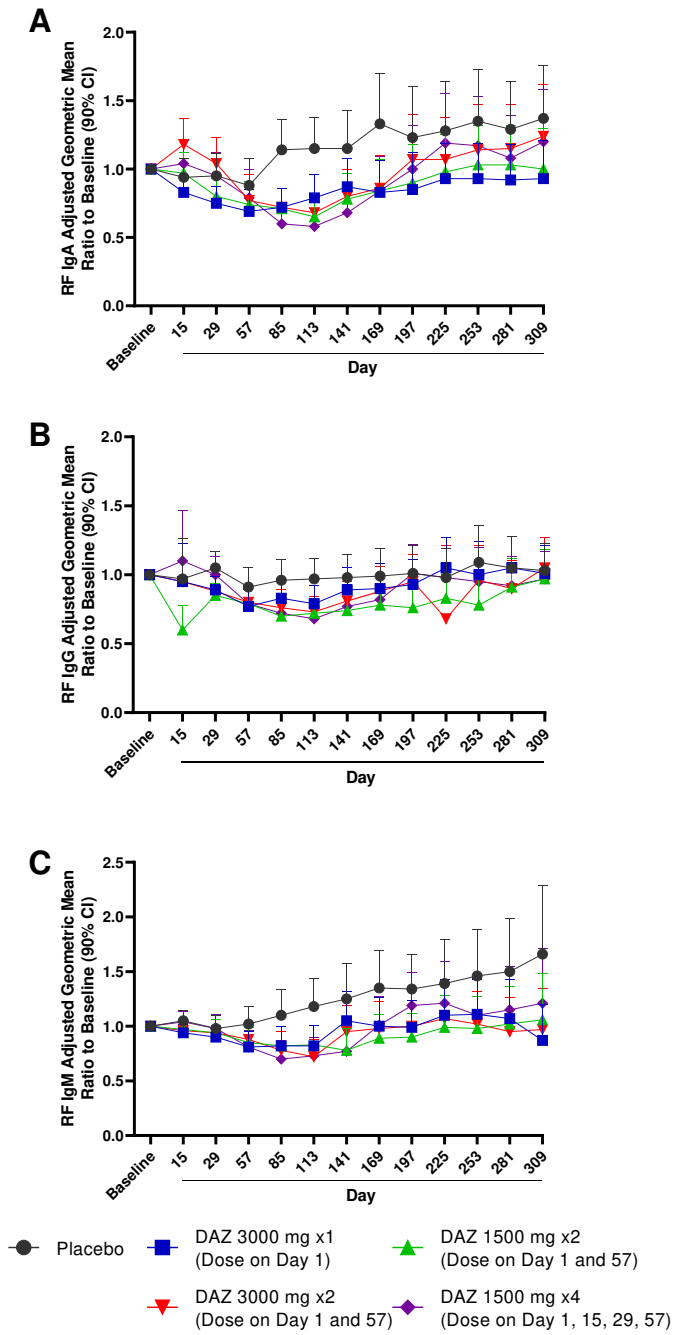
Supplemental Figure 3. Individual Pharmacokinetic Profiles by Anti-drug Antibody Status



All sample results were below the LLOQ for participants in the placebo group and are therefore not included in the figure. Values below the LLOQ (0.0500 µg/mL, as shown by dotted line) are plotted at half of LLOQ for illustrative purposes only.

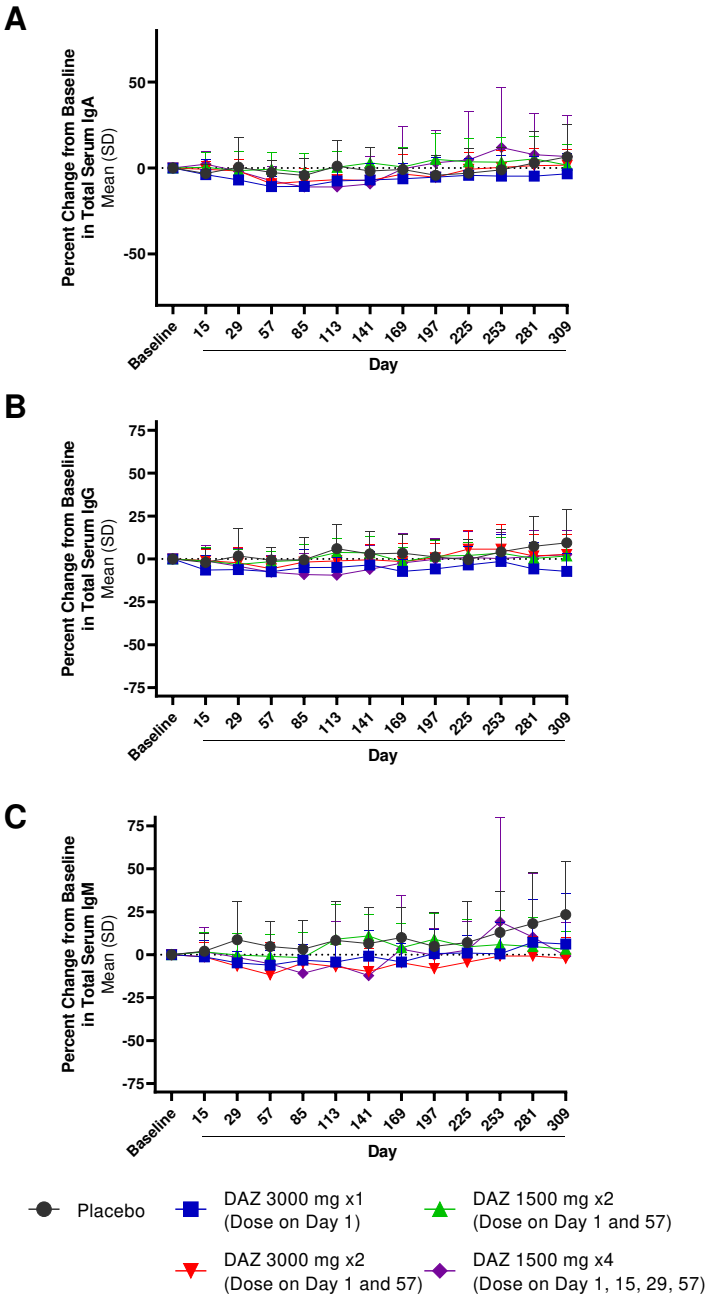
ADA, anti-drug antibodies; ADA Negative, ADA negative participant, titer < 60; ADA Positive, ADA positive subject with titer ≥ 60; LLOQ, lower limit of quantitation; PK, pharmacokinetic.

Supplemental Figure 4. Rheumatoid Factor Isotype Levels



Longitudinal data presented by study visit for RF (A) IgA, (B) IgG, and (C) IgM. CI, confidence interval; RF, rheumatoid factor.

Supplemental Figure 5. Serum Total IgG, IgA, and IgM



Longitudinal data presented by study visit for total serum (A) IgA, (B) IgG, and (C) IgM. CI, confidence interval; SD, standard deviation.

References

1. Karnell JL, Albulescu M, Drabic S, Wang L, Moate R, Baca M, et al. A CD40L-targeting protein reduces autoantibodies and improves disease activity in patients with autoimmunity. Sci Transl Med. 2019 Apr 24; 11(489).