


**ORIGINAL ARTICLE**

# Safety, tolerability, pharmacokinetics and pharmacodynamics of the anti-CD38 cytolytic antibody TAK-079 in healthy subjects

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**Aims:** This investigation characterised tolerability, pharmacokinetics and pharmacodynamics of the anti-CD38 antibody TAK-079.

**Methods:** A randomised, double-blind, placebo-controlled trial of a single intravenous (i.v.) infusion or subcutaneous (s.c.) injection of TAK-079 at escalating doses in healthy subjects ( $n = 74$ ), who were followed for 92 days postexposure.

**Results:** TAK-079 was well tolerated. All adverse events were mild or moderate. There were no withdrawals, infusion, or injection site reactions over the tested i.v. and s.c. doses up to 0.06 and 0.6 mg kg<sup>-1</sup>, respectively. At higher doses, transient cytokine level increases, following i.v. administration, coincided with reduction in CD38-expressing cells; clinical symptoms included mild pyrexia, headache, and postural hypotension. Following an i.v. infusion of 0.06 mg kg<sup>-1</sup> TAK-079, maximum observed serum concentration ( $C_{max}$ ) was 100.4 (%CV: 52) ng mL<sup>-1</sup>, time to  $C_{max}$  was the end of infusion and natural killer (NK) cells were reduced 93.8 (±8.5) % from baseline levels. Following a s.c. injection of 0.6 mg kg<sup>-1</sup> TAK-079,  $C_{max}$  was 23.0 (%CV: 67) ng mL<sup>-1</sup> with time to  $C_{max}$  of 24 (range 7.98–96.02) hours, and plasmablasts were subsequently reduced 93.4 (±8.8) % from predose levels. Serum immunoglobulin (Ig)M, IgA and IgG levels were reduced by 15–60% and had not returned to baseline levels within 78 days after administration at ≥0.3 mg kg<sup>-1</sup> s.c. Reductions in NK cells at 0.6 mg kg<sup>-1</sup> s.c. were approximately 2–3 times more durable than at 0.06 mg kg<sup>-1</sup> i.v.

**Conclusions:** TAK-079 was well tolerated and s.c. administration elicited more durable reductions in plasmablasts and NK cells. This plasmacytolytic profile could be useful for treating disorders caused by plasma or NK cells, malignant counterparts, and/or pathogenic antibodies.

The authors confirm that the Principal Investigator for this paper was Annelize Koch, MB ChB, PAREXEL Int, Harrow, UK, and that she had direct clinical responsibility for patients.

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## KEYWORDS

anticancer drugs, monoclonal antibodies, pharmacokinetic–pharmacodynamic, phase I, rheumatology

## 1 | INTRODUCTION

The human cluster of differentiation 38 (CD38) antigen is expressed by subpopulations of leucocytes, with the highest densities occurring on plasma cells and plasmablasts, followed by natural killer (NK) cells, plasmacytoid dendritic cells, and activated B and T lymphocytes in healthy subjects and patients diagnosed with rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE).<sup>1</sup> Analysis of synovial tissue also revealed that CD38 is expressed at higher levels in RA and SLE patients than in other forms of arthritis.<sup>2,3</sup> Recent transcriptional profiling studies of patient blood have identified up to 13 distinct signatures (i.e. phenotypes) of SLE patients and concluded that disease activity correlated most positively with elevated levels of CD38-expressing (CD38+) plasmablasts.<sup>4,5</sup> Furthermore, the level of CD38+ plasmablasts in peripheral blood of adult SLE patients treated with rituximab and oral steroids was the best predictor of time to relapse and the duration of relapse-free survival.<sup>3</sup>

CD38 deficiency in mice has been associated with decreased levels of peripheral T regulatory and invariant NK T cells, defects in humoral B-cell responses,<sup>6,7</sup> dendritic cell trafficking,<sup>7</sup> and attenuation of collagen-induced arthritis.<sup>8,9</sup> Pharmacological reduction of plasma cells, plasmablasts, and anti-double stranded DNA in refractory SLE patients with bortezomib was associated with reduced disease activity and improvement in renal function.<sup>10</sup> Collectively, these data indicate that specifically reducing CD38+ plasma cells in RA or SLE patients could ameliorate disease activity.

CD38 is also expressed by haematological tumours including multiple myeloma (MM). Daratumumab is an immunoglobulin (Ig) G<sub>1λ</sub> monoclonal antibody (mAb) that binds to CD38 and eliminates myeloma cells by apoptosis, antibody-dependent cellular cytotoxicity, and complement-dependent cytotoxicity.<sup>11</sup> Intravenous (i.v.) infusion containing 1200 mg of daratumumab is approved for treatment newly diagnosed and refractory MM.<sup>11</sup> The most frequent dose-limiting adverse event (AE) is an infusion reaction, which occurs in approximately half of patients.<sup>11</sup>

TAK-079 is a fully human IgG<sub>1λ</sub> mAb that binds to CD38, allosterically inhibits enzymatic activity, induces apoptosis and cytolyses cells by antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.<sup>12</sup> The addition of TAK-079 to blood or bone marrow samples from patients with SLE reduced levels of plasma cells and autoantibodies.<sup>13</sup> TAK-079 selectively reduced NK cells and subpopulations of B and T lymphocytes in monkeys,<sup>14</sup> prevented the development of monkey collagen-induced arthritis when administered prophylactically, and inhibited progression when administered therapeutically.<sup>15</sup> Collectively, these data indicate that depleting CD38+ cells may be an effective strategy for treating autoimmune disease.

### What is already known about this subject

- Antibodies are produced by plasma cells and are pathogenic in several disorders.
- TAK-079 is a human monoclonal antibody, which decreases antibody production by depleting plasma cells.

### What this study adds

- The first tolerability, pharmacokinetic and pharmacodynamic profiles of the cytolytic anti-CD38 antibody in healthy subjects.
- The first characterisation of plasmablast depletion by an anti-CD38 antibody in human subjects.

### Clinical significance

- TAK-079 could be useful for treating disorders caused by pathogenic antibodies, plasma cells and/or natural killer cells.
- A subcutaneous route of administration may be more effective than an intravenous infusion.

The purpose of the current investigation was to characterise the tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of a single i.v. infusion or a single subcutaneous (s.c.) injection of TAK-079 in escalating dose cohorts of healthy subjects in a first-in-human clinical trial.

## 2 | METHODS

### 2.1 | Study design and objectives

This was a first-in-human Phase 1, randomised, double-blind, placebo-controlled, single-dose trial of TAK-079 in healthy adult subjects. The primary trial objective was to assess the safety and tolerability of single-escalating doses of TAK-079 after i.v. infusion or s.c. injection. Secondary objectives were to assess the PK and PD on blood cell populations and immunogenicity.

A total of 74 subjects were enrolled in this trial. After 2 screening visits, subjects were admitted at Day –2 prior to dosing for baseline

assessments. TAK-079 was administered on Day 1 via a 2-hour i.v. infusion at sequential ascending doses of 0.0003, 0.001, 0.003, 0.01, 0.03 or 0.06 mg kg<sup>-1</sup> in 6 cohorts or via s.c. injection at doses of 0.03, 0.1, 0.3 or 0.6 mg kg<sup>-1</sup> in another 4 cohorts (Figure 1). Dose selection was determined using a population PK model derived from preclinical pharmacology and toxicology studies, mechanistic *ex vivo/in vitro* investigations with human and animal cells, and PK/PD modelling of 8 studies in cynomolgus monkeys<sup>14</sup> and incorporated a 1000-fold safety factor to mitigate the potential risks of extensive cytolysis in healthy subjects. These investigations provided the essential information required for the selection of a safe starting dose and escalation based on the minimal anticipated biological effect level. At each dose level, 6–8 subjects were randomised to TAK-079 ( $n = 4$ –6) or matching placebo ( $n = 2$ ).

Sentinel dosing was used for each cohort with an initial 2 subjects receiving either TAK-079 or placebo (1:1). The 24-hour postdose safety and tolerability data from these 2 subjects was reviewed before the remaining subjects in each cohort were dosed. Participants were confined to an inpatient Clinical Pharmacology Unit until Day 8 followed up by weekly or bi-weekly follow-up visits, with the last planned clinic visit on Day 78 for general safety assessment and PK, PD and immunogenicity analysis. A final follow-up phone call occurred at Day 92.

Dose escalation was predominantly based on AE severity as graded using the Common Terminology Criteria for Adverse Events grading criteria. Dose escalation was to be stopped if at least 2 subjects in 1 cohort experienced cytokine release syndrome (CRS) leading to moderate clinical syndromes or moderate to severe administration

reactions. Given that TAK-079 was a cytolytic antibody in monkeys, no further dose escalation was allowed if clinically relevant reductions in total or subtypes of lymphocyte counts (nominally >50% reduction from the subject's lowest predose value and below the lower limit of normal reference ranges [NRRs]) were observed and were maintained for  $\geq 29$  days. The investigator and sponsor reviewed all blinded safety data for all participants at each dose level prior to proceeding to the next higher dose.

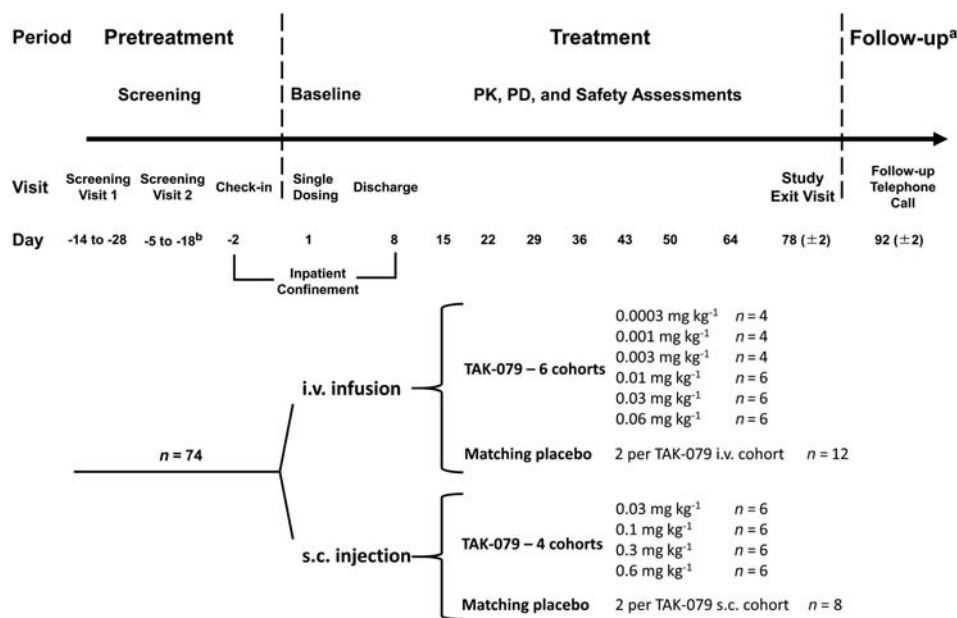
The trial was conducted in accordance with Good Clinical Practice guidelines at the Parexel International Phase 1 Clinical Pharmacology Unit located in Northwick Park Hospital, Harrow, UK. The protocol was reviewed and approved (approval number 16/LO/2067) by a local independent ethics committee, the London-Brent Research Ethics Committee (London, UK). All subjects signed the Informed Consent Form before initiation of any trial procedures.

## 2.2 | Study participants

Eligible participants were healthy, males or females (without child-bearing potential) between the ages of 18 and 55 years, weighing 50–100 kg, and with a body mass index of 18.5–30 kg m<sup>-2</sup>.

The flow cytometry-based counts of CD45+ lymphocytes, T cells, CD4+ T cells and B cells were required to be above the lower limit of NRRs and NK cell counts within the upper 50<sup>th</sup> percentile of the NRR given that CD38 is highly expressed on NK cells.

Participants were excluded if they met the exclusion criteria defined in the protocol, such as known immunodeficiency, elevated



**FIGURE 1** Clinical study design. <sup>a</sup>The follow-up visit occurred via telephone on Day 92 (±2) unless abnormal, clinically significant findings were observed at study exit. In these cases, subjects were brought back to the clinic for re-evaluation and necessary assessments (such as additional immunogenicity [ADA] and PK samples, as well as clinical laboratory tests) at the discretion of the investigator and sponsor, as unscheduled visits with a follow-up visit via telephone 14 days (±2) after the last unscheduled visit. <sup>b</sup>Screening visit 2 was to be at least 5 days after the screening visit 1 and at least 5 days before day 1. ADA = anti-drug antibodies; i.v. = intravenous; PD = pharmacodynamics; PK = pharmacokinetics; s.c. = subcutaneous

infection risk, history of malignancy or taking another investigational drug prior to the trial that could impact the effect of the investigational drug.

## 2.3 | Safety assessments

Routine safety parameters such as AEs, clinical laboratory parameters, physical examinations, electrocardiograms (ECGs), and vital signs were monitored at screening, before dosing, and throughout the confinement period and follow-up visits. Infusion reactions have been reported in clinical studies of other anti-CD38 antibodies administered to MM patients after i.v. infusion, for example, 48% of relapsed/refractory MM patients experienced infusion reactions with treated with 16 mg kg<sup>-1</sup> of daratumumab as a monotherapy.<sup>11</sup> Although *ex vivo* experiments showed no evidence of agonist activity by TAK-079 in human blood cells,<sup>12</sup> and infusion of TAK-079 did not induce observable findings suggestive of infusion reaction in non-clinical studies in monkeys, signs of infusion reaction or CRS (headache, fever, chills, hypotension, nausea and vomiting) were nonetheless closely monitored. Decreasing the rate of infusion and/or oral prophylactic premedications with paracetamol and antihistamines (anti-H1 and anti-H2) was allowed to minimise side effects, if needed. For the s.c. cohorts, signs of injection site reactions such as injection site pain, burning, redness, itching, swelling or induration were monitored. The safety set for analyses consisted of all subjects who were enrolled and received at least 1 dose of trial drug or placebo (after trial drug dosing started), including subjects who did not complete all scheduled trial visits. Subjects in this analysis set were used for demographic, baseline characteristics and safety summaries.

## 2.4 | PK, PD and immunogenicity

To measure serum TAK-079 concentrations, serial blood samples were collected prior to dosing and up to 168 hours postdose (Figure 1). Serum samples were analysed at 5 min; 1, 4, and 8 hours; and 2, 3, 4, 5, 6, 8 and 15 days after i.v. administration, and 1 and 8 hours and 2, 3, 4, 5, 6, 8, and 15 days after s.c. administration. Additional blood samples were collected at intermediate timepoints postdose or at early termination. Serum TAK-079 concentrations were determined using an enzyme-linked immunosorbent assay validated at ICON Laboratory Services, Inc (Whitesboro, NY, USA). TAK-079 concentrations were determined using a 4-parametric logistic curve fitting program with 1/y<sup>2</sup> weighting. The lower limit of quantification (LLOQ) of this method is 10 ng mL<sup>-1</sup>, and the limit of detection (LOD) was 1 ng mL<sup>-1</sup> in 100% human serum. The enzyme-linked immunosorbent assay method was validated in compliance with the subsections of the United States Code of Federal Regulations, Title 21: Part 58 (21 CFR 58, Food and Drug Administration Good Laboratory Practices for Nonclinical Laboratory Studies) and International Council for Harmonisation E (6) (ICH Guideline for Good Clinical Practice) that can be applied to bioanalysis of human clinical samples. All work was

**TABLE 1** Demographics and baseline characteristics of subjects receiving an intravenous infusion

	TAK-079 (mg kg <sup>-1</sup> )							Overall (n = 42)		
	Intravenous infusion	Pooled placebo (n = 12)	0.0003 (n = 4)	0.001 (n = 4)	0.003 (n = 4)	0.01 (n = 6)	0.03 (n = 6)		0.06 (n = 6)	TAK-079 Total (n = 30)
Age (y), mean (SD)		35.5 (10.61)	23.5 (3.42)	42.3 (12.12)	32.8 (10.72)	36.2 (9.52)	32.3 (5.92)	35.7 (11.60)	34.0 (10.01)	34.4 (10.08)
Sex, n (%)		12 (100)	4 (100)	4 (100)	4 (100)	6 (100)	6 (100)	6 (100)	30 (100)	42 (100)
Male		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Female		8 (67)	3 (75)	2 (50)	3 (75)	4 (67)	5 (83)	5 (83)	22 (73)	30 (71)
Race, n (%)		1 (8)	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	0 (0)	1 (33)	2 (5)
White		2 (17)	0 (0)	1 (25)	0 (0)	0 (0)	1 (17)	0 (0)	2 (7)	4 (9)
Black or African American		1 (8)	1 (25)	1 (25)	0 (0)	2 (33)	0 (0)	1 (17)	5 (17)	6 (14)
Asian		1 (8)	1 (25)	1 (25)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Multiracial		174.7 (9.17)	181.3 (6.90)	175.0 (8.04)	179.5 (10.91)	173.8 (1.47)	175.5 (7.97)	173.8 (7.03)	176.1 (7.17)	175.7 (7.70)
Height (cm), mean (SD)		73.98 (7.355)	80.63 (8.768)	76.68 (9.011)	72.10 (9.090)	75.45 (11.042)	69.12 (8.043)	71.32 (6.187)	73.76 (8.833)	73.83 (8.349)
Weight (kg), mean (SD)										

SD = standard deviation.

carried out according to the validation plan and Standard Operating Procedures of ICON Laboratory Services, Inc.

To assess the PD response of TAK-079, peripheral blood samples were collected at the screening visits; on Days -1, 1, 2 (s.c. only), 3 (s.c. only), 4 (i.v. only), 5 (s.c. only), 6, 8, 15, 22, 29, 50 and 78 postdose; or at early termination. The primary and secondary PD endpoints were plasmablasts (CD3-CD19 + CD38++CD27++) and NK cells (CD3-CD56 + CD16+), respectively. A flow cytometry assay was validated at LabCorp Clinical Trials (Brussels, Belgium) using a fit-for-purpose approach to measure plasmablasts from peripheral blood. Briefly, samples fixed-frozen in buffer were thawed, washed with phosphate buffered saline/1% bovine serum albumin and adjusted to a cell count between  $20 \times 10^6$  and  $40 \times 10^6$  with phosphate buffered saline/1% bovine serum albumin. Samples were incubated with human serum at ambient temperature and then CD38-fluorescein isothiocyanate (FITC) antibodies (Takeda Pharmaceuticals, clone TSF19, custom-conjugated to FITC by Southern Biotech), CD3-PE (BD Biosciences, Cat. #347347, RRID:AB\_400287), CD27-APC (BD Biosciences Cat. #558664, RRID:AB\_1645457), CD45-AF-700 (BioLegend Cat. #304023, RRID:AB\_493760), and CD19-V450 (BD Biosciences Cat. #560353, RRID:AB\_1645564) are added to the sample for 30 minutes at ambient temperature in the dark. After incubation, the cells were washed and resuspended in 1% paraformaldehyde. Approximately 1 000 000 total events were acquired on a BD FACSCanto II flow cytometer. NK cell counts were measured in peripheral blood using a 2-tube BD Trucount 4-color flow cytometry assay validated at LabCorp Clinical Trials (Brussels, Belgium). Samples were acquired on a FACSCalibur instrument (BD Biosciences). Data acquisition was set for 10,000 CD45+ lymphocytes, with a LLOQ of 0.5% and a LOD of 0.1%. Additional assessments included total white blood cell count and differential, total T cells (anti-CD3-FITC, BD Biosciences Cat. #340492, RRID:AB\_400471),  $T_{\text{helper}}$  subsets

(anti-CD4-APC; BD Biosciences Cat. #340491, RRID:AB\_400470),  $T_{\text{cytotoxic}}$  subsets (anti-CD8-PE; BD Biosciences Cat. #340491, RRID:AB\_400470), B cell counts (anti-CD19-APC; BD Biosciences Cat. #340492, RRID:AB\_400471), monocyte counts (anti-CD16-PE; BD Biosciences Cat. #340492, RRID:AB\_400471) and granulocyte counts.

A conventional electrochemiluminescent immunoassay was validated for the detection of anti-TAK-079 antibodies in human serum at ICON Laboratory Services, Inc. Briefly, samples (including positive controls and pooled negative control) were acidified and then neutralized with an equal volume of ruthenylated TAK-079 and biotinylated TAK-079 conjugates. Anti-TAK-079 antibodies bound to both the ruthenylated and biotinylated TAK-079 molecules and formed an antibody complex bridge, which were detected via binding to a streptavidin-coated mesoscale plate in the presence of a tripropylamine-containing read buffer in which ruthenium produces a chemiluminescent signal that is triggered when voltage is applied. The signal produced was proportional to the amount of anti-TAK-079 antibody present, and the LOD was determined to be  $57 \text{ ng mL}^{-1}$  in 100% human serum. All work carried out in this validation was conducted in accordance with applicable Good Laboratory Practices, as described in the 21 CFR 58, and with the Standard Operating Procedures of ICON Development Solutions.

## 2.5 | Data and statistical analysis

Continuous data were summarized using N, mean, SD, median, minimum and maximum, where appropriate. Where indicated, coefficient of variation and geometric mean were also included in the summary of continuous data. Categorical data were summarized using the number and percentage of subjects for each category, where appropriate.

**TABLE 2** Demographics and baseline characteristics of subjects receiving a subcutaneous injection

Subcutaneous injection	TAK-079 ( $\text{mg kg}^{-1}$ )					TAK-079 Total (n = 24)	Overall (n = 32)
	Pooled placebo (n = 8)	0.03 (n = 6)	0.1 (n = 6)	0.3 (n = 6)	0.6 (n = 6)		
Age (y),							
mean (SD)	34.9 (13.61)	36.7 (10.33)	31.0 (8.15)	40.8 (7.83)	27.7 (8.16)	34.0 (9.61)	34.3 (10.51)
Sex, n (%)							
Male	7 (87)	6 (100)	6 (100)	6 (100)	6 (100)	24 (100)	31 (97)
Female	1 (12)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)
Race, n (%)							
White	6 (75)	4 (67)	3 (50)	6 (100)	2 (33)	15 (63)	21 (66)
Black or African American	1 (12)	0 (0)	0 (0)	0 (0)	1 (17)	1 (4)	2 (6)
Asian	1 (12)	2 (33)	3 (50)	0 (0)	3 (50)	8 (33)	9 (28)
Height (cm),							
mean (SD)	177.8 (7.91)	176.8 (3.31)	181.2 (8.80)	177.8 (6.68)	172.3 (4.32)	177.0 (6.58)	177.2 (6.81)
Weight (kg),							
mean (SD)	78.5 (12.50)	79.7 (8.58)	75.1 (9.88)	79.7 (8.31)	71.2 (9.43)	76.4 (9.20)	76.9 (9.95)

SD = standard deviation.

**TABLE 3** Total TEAEs and AEs reported in 2 or more subjects receiving an i.v. infusion

Intravenous infusion	Pooled placebo (n = 12)	Pooled active (n = 30)	TAK-079 (mg kg <sup>-1</sup> ) number of subjects (%)					
			0.0003 (n = 4)	0.001 (n = 4)	0.003 (n = 4)	0.01 (n = 6)	0.03 (n = 6)	0.06 (n = 6)
Subjects with any TEAEs	11 (92)	27 (90)	3 (75)	3 (75)	3 (75)	6 (100)	6 (100)	6 (100)
Pyrexia	0 (0)	5 (17)	0 (0)	0 (0)	0 (0)	1 (17)	1 (17)	3 (50)
Chills	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (33)
Nasopharyngitis	2 (17)	3 (10)	0 (0)	1 (25)	0 (0)	0 (0)	0 (0)	2 (33)
Headache	4 (33)	11 (37)	0 (0)	0 (0)	1 (25)	2 (33)	3 (50)	5 (83)
Dizziness postural	0 (0)	6 (20)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16)	5 (83)
Somnolence	0 (0)	3 (10)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16)	2 (33)

A TEAE was defined as an AE that occurs or gets worse after receiving the first dose of trial drug and within 94 days after the last dose of trial drug. This table includes TEAEs of any intensity and any investigator-assessed causality. No serious AEs and no AEs of severe intensity were reported and no AEs led to discontinuation.

Subjects with 1 or more AEs within a treatment group and level of MedDRA term were counted only once in that level. Percentages are based on the number of subjects in the safety set per treatment. MedDRA (Version 18.0) was used for coding AEs.

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

**TABLE 4** Total TEAEs and AEs reported in two or more subjects receiving a subcutaneous injection

Subcutaneous injection	Pooled placebo (n = 8)	Pooled active (n = 24)	TAK-079 (mg kg <sup>-1</sup> ) number of subjects (%)			
			0.03 (n = 6)	0.1 (n = 6)	0.3 (n = 6)	0.6 (n = 6)
Subjects with any TEAEs	6 (75)	22 (92)	6 (100)	6 (100)	5 (83)	5 (83)
Injection site erythema	1 (13)	7 (30)	5 (83)	0 (0)	1 (17)	1 (17)
Injection site pain	0 (0)	6 (25)	3 (50)	3 (50)	0 (0)	0 (0)
Feeling hot	0 (0)	4 (17)	0 (0)	1 (17)	1 (17)	2 (33)
Nasopharyngitis	1 (13)	9 (37)	2 (33)	3 (50)	1 (17)	3 (50)
Headache	2 (25)	7 (29)	2 (33)	1 (17)	1 (17)	3 (50)
Oropharyngeal pain	1 (13)	3 (13)	0 (0)	2 (33)	0 (0)	1 (17)

<sup>a</sup>A TEAE was defined as an AE that occurs or gets worse after receiving the first dose of trial drug and within 94 days after the last dose of trial drug. This table includes TEAEs of any intensity and any investigator-assessed causality. No serious AEs and no AEs of severe intensity were reported and no AEs led to discontinuation.

<sup>b</sup>Subjects with 1 or more AEs within a treatment group and level of MedDRA term were counted only once in that level. Percentages are based on the number of subjects in the safety set per treatment. MedDRA (Version 18.0) was used for coding AEs.

<sup>c</sup>AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

**TABLE 5** Number and percentage of subjects with clinical CRS

Intravenous infusion	TAK-079 (mg kg <sup>-1</sup> ) number of subjects (%)						
	Pooled placebo (n = 12)	0.0003 (n = 4)	0.001 (n = 4)	0.003 (n = 4)	0.01 (n = 6)	0.03 (n = 6)	0.06 (n = 6)
CRS	0	0	0	0	0	1 (17)	6 (100)
Severity						Mild	All mild

Subcutaneous injection	TAK-079 (mg kg <sup>-1</sup> ) number of subjects (%)				
	Pooled placebo (n = 8)	0.03 (n = 6)	0.1 (n = 6)	0.3 (n = 6)	0.6 (n = 6)
CRS	0	0	0	1 (17)	2 (33)
Severity				Mild	All mild

CRS = cytokine release syndrome

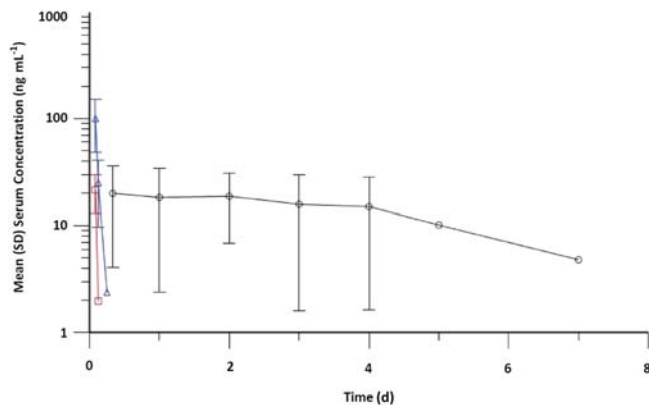
**TABLE 6** Summary pharmacokinetic parameters of TAK-079 following a single 2-hour intravenous infusion of TAK-079 at 0.03 and 0.06 mg kg<sup>-1</sup> or a single subcutaneous injection of TAK-079 at 0.6 mg kg<sup>-1</sup> to healthy subjects

Route	Dose	$t_{\max}$ (h; $n = 6$ )	$C_{\max}$ (ng mL <sup>-1</sup> ; $n = 6$ )	$AUC_{\text{last}}$ (ng day <sup>-1</sup> mL <sup>-1</sup> ; $n = 6$ )
Intravenous	0.03 mg kg <sup>-1</sup>	2.09 (2.07, 2.67)	21.4 (39)	NA
	0.06 mg kg <sup>-1</sup>	2.09 (2.07, 2.13)	100.4 (52)	NA
Subcutaneous	0.6 mg kg <sup>-1</sup>	23.87 (7.98, 96.02) <sup>13</sup>	23.0 (67)	90.4 (92)

$n = 5$ .

$C_{\max}$  and  $AUC_{\text{last}}$  values represent mean (coefficient of variance),  $t_{\max}$  values represent median (range).

$AUC_{\text{last}}$  = area under the serum concentration-time curve from time 0 to time of the last quantifiable concentration;  $C_{\max}$  = maximum observed serum concentration; NA = not applicable; PK = pharmacokinetics;  $t_{\max}$  = time to maximum serum concentration.

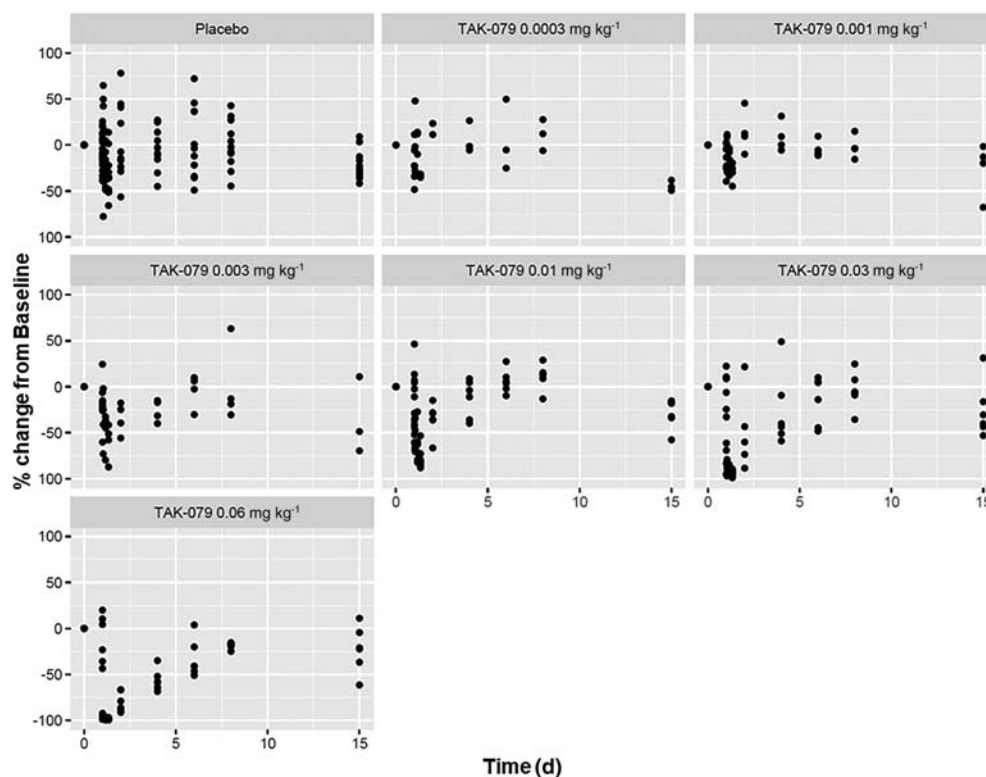


**FIGURE 2** Mean (standard deviation, SD) serum concentration time profiles of TAK-079 following a single 2-hour intravenous infusion of TAK-079 at 0.03 (squares) and 0.06 (triangles) mg kg<sup>-1</sup> or a single subcutaneous injection of TAK-079 at 0.6 mg kg<sup>-1</sup> (circles) to healthy subjects ( $n = 6$  per cohort)

There was no imputation of incomplete or missing data. Serum concentrations that were below the limit of quantification were treated as zero in summarizing of concentration values and deriving of PK parameters. Summary statistics and data analysis were conducted using SAS version 9.2 and R version 3.5.1. The data and statistical analysis comply with the recommendations on experimental design and analysis in pharmacology.<sup>16</sup>

## 2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY. TAK-079 does not exist as a discrete entry within this database.



**FIGURE 3** Percent change from baseline levels of natural killer cells in peripheral blood after a single 2-hour intravenous infusion of placebo or TAK-079 at 0.0003–0.06 mg kg<sup>-1</sup> intravenous into healthy subjects ( $n = 12$  for placebo pooled from each cohort;  $n = 6$  subjects receiving TAK-079 per cohort). Symbols represent the percent change from baseline levels of individual subjects at that timepoint

### 3 | RESULTS

#### 3.1 | Disposition and demographics of subjects

Seventy-four subjects were enrolled and received a single dose of TAK-079 ( $n = 54$ ) or placebo ( $n = 20$ ). Six i.v. cohorts receiving TAK-079 at doses of 0.0003, 0.001, 0.003, 0.01, 0.03 or 0.06  $\text{mg kg}^{-1}$  or matching placebo and 4 s.c. cohorts receiving TAK-079 at doses of 0.03, 0.1, 0.3 or 0.6  $\text{mg kg}^{-1}$  or matching placebo were monitored for 92 days; all completed the trial (Figure 1). Participants were all men except for 1 woman in the s.c. placebo group (Table 1 and Table 2). The trial population consisted of Caucasian ( $n = 51$ ), Asian ( $n = 13$ ), African ( $n = 4$ ) and multiracial ( $n = 6$ ) ethnicities. The median age (37.5 years, range 19–55 years) and median body mass index ( $24.5 \text{ kg m}^{-2}$  range 24–25  $\text{kg m}^{-2}$ ) were similar between i.v. cohorts and s.c. cohorts and between TAK-079- and placebo-treated groups.

#### 3.2 | Safety and tolerability

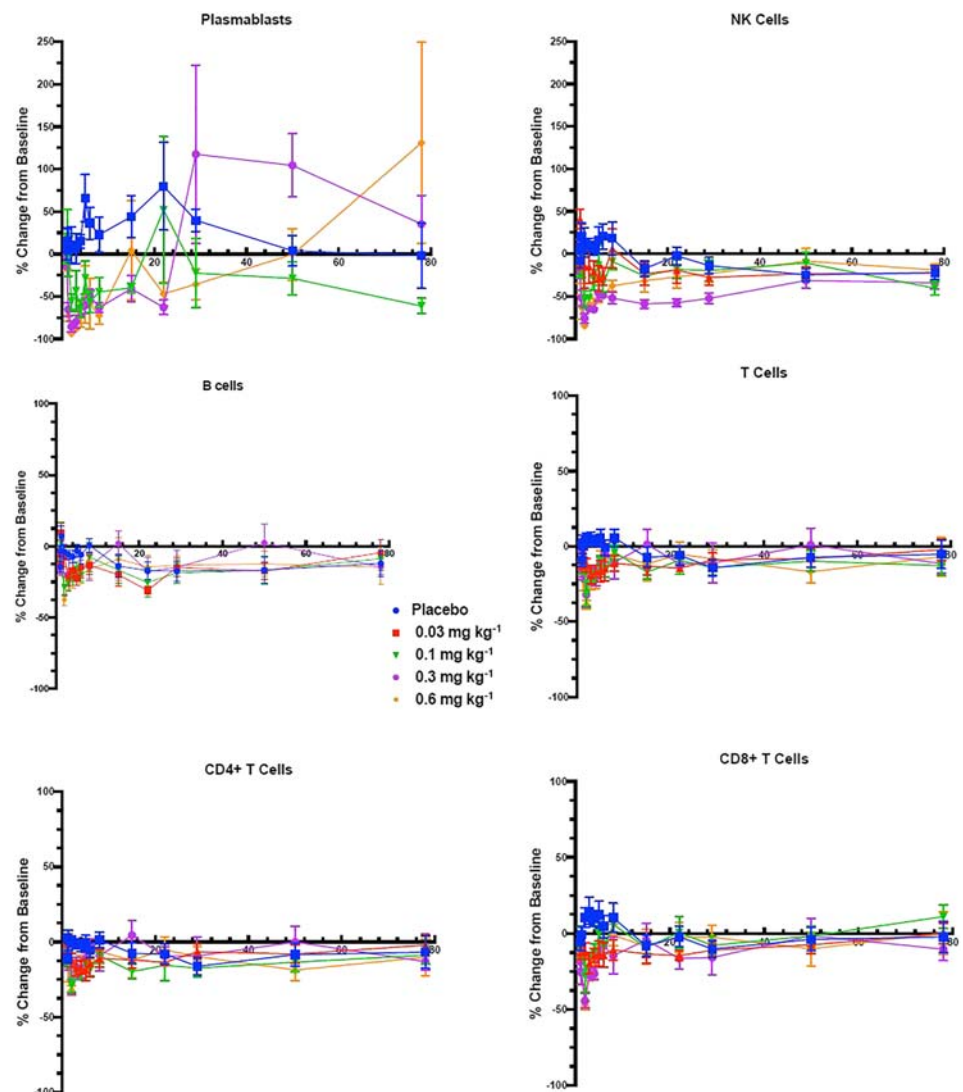
All doses of TAK-079 were well tolerated in this trial. The AEs were mild to moderate in intensity, with most being sporadic with no trend

of dose relationship (Table 3 and Table 4), except for headache, dizziness and chills, which were seen more frequently at the higher i.v. and s.c. TAK-079 dose groups, consistent with higher incidences of CRS (Table 5) in subjects receiving the higher doses (one subject and 6 subjects in the 0.03 and 0.06  $\text{mg kg}^{-1}$  i.v. groups, respectively; 1 subject and 2 subjects in the 0.3 and 0.6  $\text{mg kg}^{-1}$  s.c. groups, respectively). There were no serious AEs or deaths, and no AEs led to either trial or visit discontinuation (Table 3 and Table 4). Mild, transient injection site reactions were observed after s.c. injections, the majority of which resolved within 7 days. These reactions exhibited an inverse dose-effect relationship, as 5 of 6 subjects treated with lowest s.c. dose, and only 1 subject in each of the 2 highest dose cohorts had reactions. There were no infusion reactions, anaemia, thrombocytopenia, lymphopenia or remarkable findings for laboratory tests, ECGs, vital signs or physical examinations reported that were related to TAK-079 treatment.

#### 3.3 | The pharmacokinetics of TAK-079

Serum concentrations of TAK-079 were quantified in 30% of all PK sampling timepoints. The concentration of TAK-079 in subjects

**FIGURE 4** Percent change from baseline levels of plasmablasts, NK, B, total T cells,  $\text{CD4}^+$  T helper, and  $\text{CD8}^+$  cytotoxic subsets, monocytes and granulocytes in peripheral blood from healthy subjects after a single subcutaneous injection of placebo control or TAK-079 at 0.03 to 0.6  $\text{mg kg}^{-1}$  ( $n = 8$  for placebo pooled from each cohort,  $n = 6$  subjects receiving TAK-079 per cohort). Symbols represent the mean change for the cohort, and error bars represent the standard error of the mean. CD = cluster of differentiation; NK = natural killer (cell)





administered 0.0003–0.01 mg kg<sup>-1</sup> i.v. was below the LLOQ of the detection assay (i.e. 10 ng mL<sup>-1</sup>). Following i.v. infusion of 0.03 and 0.06 mg kg<sup>-1</sup> TAK-079, the mean maximum observed serum concentration ( $C_{\max}$ ) increased approximately 4.7-fold (Table 6 and Figure 2). Serum concentrations subsequently decreased to the LLOQ within 1 or 4 hours after end of infusion, and exposures could not be calculated accurately. Due to the limited TAK-079 serum concentrations (at 1–3 timepoints per subject) available from i.v. 0.03 and 0.06 mg kg<sup>-1</sup> cohorts, PK parameters other than time to maximum serum concentration ( $t_{\max}$ ) and  $C_{\max}$  could not be calculated accurately.

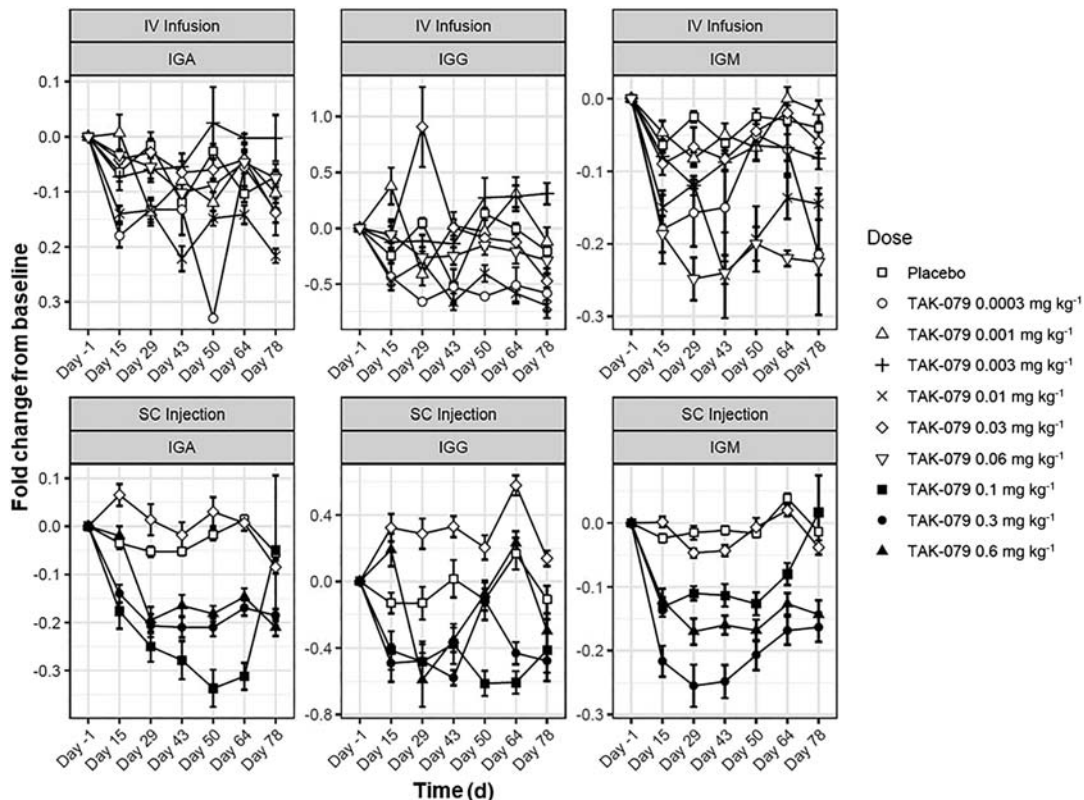
The concentration of TAK-079 in subjects administered 0.03–0.3 mg kg<sup>-1</sup> s.c. was below the LLOQ of the detection assay at all timepoints. Following a 0.6 mg kg<sup>-1</sup> TAK-079 s.c. injection, the mean  $C_{\max}$  of all 6 subjects (including 1 subject with serum concentrations below LLOQ) was 23.0 ng mL<sup>-1</sup> (67% CV; Table 6 and Figure 2), whereas the mean exposure of the 5 subjects above the LLOQ was 90.4 ng day<sup>-1</sup> mL<sup>-1</sup> (92% CV). Serum concentrations of TAK-079 subsequently decreased to the LLOQ by 3–14 days after injection (Figure 2).

### 3.4 | The PD of TAK-079

In the cohorts administered TAK-079 by i.v. infusion, dose-dependent reductions in NK cells in peripheral blood were observed in all

subjects dosed  $\geq 0.003$  mg kg<sup>-1</sup> as compared to a time-matched placebo control cohort (Figure 3). In each subject receiving a 0.06 mg kg<sup>-1</sup> infusion, the level of NK cells in peripheral blood was reduced 97–99% from baseline levels at 8 hours after the end of infusion (i.e. 10 hours after the initiation of infusion). An effective dose at 50% of maximum response ( $ED_{50}$ ) was 0.02 mg kg<sup>-1</sup> with an effective concentration at 50% of maximum response ( $EC_{50}$ ) of 0.01 mg mL<sup>-1</sup>, as estimated by linear regression. While the levels of NK cells were consistently reduced from baseline, the durations of recovery (e.g. to within –25% of baseline levels) were variable and generally related to dose; recovery to baseline levels for the 0.003, 0.01, 0.03 and 0.06 mg kg<sup>-1</sup> doses generally required 3–4, 4–5, 5–6 and 6–8 days, respectively (Figure 3). The variability observed in NK cell levels longitudinally may be caused by environmental, rather than technical, factors because variance is minimal after exposure to TAK-079 (e.g. reductions on Days 1 to 10 by 0.06 mg kg<sup>-1</sup> TAK-079 i.v.). Comparable reductions were not observed for red blood cells, platelets, granulocytes, total lymphocytes, B and T cells, helper T cells, or cytotoxic T cell subsets.

A novel assay that measures levels of plasmablasts was utilized during the latter half of the trial to monitor for potential effects on precursors of antibody-secreting cells. In the cohorts treated with TAK-079 by s.c. injection, dose-dependent reductions in plasmablasts in peripheral blood were observed at doses  $\geq 0.1$  mg kg<sup>-1</sup> as compared to a time-matched placebo control cohort (Figure 4). In all subjects



**FIGURE 5** Fold change from baseline levels of total IgA, IgG and IgM in serum from healthy subjects after a single infusion of placebo control ( $n = 12$ ) or TAK-079 at 0.003 ( $n = 4$ ) to 0.06 ( $n = 6$ ) mg kg<sup>-1</sup> IV, or injection of placebo control ( $n = 8$ ) or TAK-079 at 0.03 ( $n = 6$ ) to 0.6 ( $n = 6$ ) mg kg<sup>-1</sup>. SC symbols represent the mean change for the cohort, and error bars represent the standard error of the mean. IG = immunoglobulin; IV = intravenous; SC = subcutaneous

receiving a 0.6 mg kg<sup>-1</sup> injection, plasmablasts were reduced >90% from baseline levels (Figure 4). An ED<sub>50</sub> was 0.1 mg kg<sup>-1</sup> with an EC<sub>50</sub> of 0.01 mg ml<sup>-1</sup>, as estimated by linear regression. The reductions exhibited a *t*<sub>max</sub> of 48 hours and recovered to within -25% of baseline levels by 22-29, 22-29 and 29-50 days, for the 0.1, 0.3 and 0.6 mg kg<sup>-1</sup> doses, respectively (Figure 4).

A corresponding reduction in NK cells from peripheral blood were observed at doses ≥0.1 mg kg<sup>-1</sup> as compared to a time-matched placebo control cohort (Figure 4). The ED<sub>50</sub> was 0.1 mg kg<sup>-1</sup> with an estimated EC<sub>50</sub> of 0.01 mg ml<sup>-1</sup>. The NK cell reductions also exhibited a *t*<sub>max</sub> of 48 hours and recovered to within -25% of baseline levels by 4-5 and 15-22 days for the 0.1 and 0.6 mg kg<sup>-1</sup> doses, respectively (Figure 4). The NK cell reductions after s.c. administration (Figure 4) appear to be 2-3-fold more durable than those after i.v. administration (Figure 3). There were no sustained reductions in B and T cells, cytotoxic T cells, helper T cells, monocytes, granulocytes (Figure 4), total lymphocytes, platelets or red blood cells (data on file, Takeda Pharmaceuticals Incorporated).

The levels of total Igs were measured in serum samples to determine if TAK-079 affected tissue-resident plasma cells. While the overall levels of total Igs remained within the normal range for healthy subjects, injections of TAK-079 of ≥0.1 mg kg<sup>-1</sup> reduced total IgA, IgG and IgM levels in serum as compared to time-matched placebo controls, whereas these effects were less pronounced with i.v. doses (Figure 5). Igs generally returned to baseline levels within 78 days after dosing in subjects receiving 0.1 mg kg<sup>-1</sup> s.c., but not in those receiving 0.3 and 0.6 mg kg<sup>-1</sup> s.c. (Figure 5).

One subject in the 0.03 mg kg<sup>-1</sup> s.c. cohort exhibited a persistent (i.e. Days 15, 29 and 78), moderate titre (i.e. 1:160, 1:1280 and 1:320) of anti-TAK-079 antibody. The serum concentrations of TAK-079 in this subject were below LLOQ over the entire trial period, as were the TAK-079 levels in the anti-drug antibody-negative subjects in the same cohort; therefore, the potential impact of this anti-drug antibody could not be determined.

## 4 | DISCUSSION AND CONCLUSIONS

A therapeutic strategy for treating autoimmune diseases, such as RA and SLE, is to reduce the level of CD38+ leucocytes, based on several reports that demonstrate associations between levels of CD38 and disease activity<sup>1-4,10</sup> and the activity of TAK-079 in several translational models.<sup>13,14,17</sup> Therefore, the purpose of this investigation was to characterise the safety, tolerability, PK and PD of single i.v. infusion and s.c. injection of TAK-079 in healthy subjects and determine if clinical studies in autoimmune patients are warranted.

Dose selection was determined using a population PK model derived from preclinical pharmacology and toxicology studies, mechanistic *ex vivo/in vitro* investigations with human and animal cells, and PK/PD modelling of 8 studies in cynomolgus monkeys,<sup>14</sup> which incorporated a 1,000-fold safety factor to mitigate the potential risks of extensive cytolysis in healthy subjects who were not pretreated with an analgesic, antihistamine or steroid. All doses of TAK-079 were well

tolerated in this trial. AEs were mild to moderate in intensity with the majority being mild (Table 3 and Table 4). No remarkable findings for laboratory tests, ECGs, vital signs, or physical examinations were reported that were related to TAK-079 treatment. There were no infusion reactions, which is noteworthy, because 48% of relapsed/refractory MM patients experienced infusion reactions when treated with 16 mg kg<sup>-1</sup> of the anti-CD38 daratumumab i.v., as a monotherapy, despite prophylactic administration of analgesics, antihistamines and steroids.<sup>11</sup> Similarly, anaemia, thrombocytopenia, neutropenia and lymphopenia were not observed with TAK-079, while these AEs occur in approximately 45, 48, 60 and 72%, respectively, in relapsed/refractory MM patients infused with 16 mg kg<sup>-1</sup> of daratumumab i.v. as a monotherapy (Janssen Biotech 2015). It is unknown whether these potential differences in the incidence of infusion reaction, anaemia, thrombocytopenia, neutropenia and lymphopenia are attributable to differences between the mechanism of actions of these antibodies, or conversely to dosing, formulations, patient populations etc. A multiple-ascending, repeat-dose trial of TAK-079 monotherapy in a similar population of refractory MM patients is ongoing (NCT03439280) and could provide a better comparison.

CRS was observed in 7 subjects in the TAK-079 i.v. infusion group and in 3 subjects in the TAK-079 s.c. group (Table 5). Cases of CRS coincided with reductions in plasmablasts and NK cells (Figure 3 and Figure 4, respectively), and moderate increases in cytokines (e.g. tumour necrosis factor- $\alpha$ , - $\beta$  and interleukin (IL)-6; data on file, Takeda Pharmaceuticals Incorporated) and C-reactive protein in blood (data on file, Takeda Pharmaceuticals Incorporated). These data are consistent with studies in monkeys, illustrating that cell depletion coincided with an elevation in serum levels of tumour necrosis factor- $\alpha$ .<sup>14</sup> As compared to i.v. treatment groups, the s.c. treatment cohorts experienced a lower incidence of CRS and had minimal cytokine level increases at comparable concentrations of TAK-079 in peripheral blood (e.g. 0.03 mg kg<sup>-1</sup> i.v. vs 0.6 mg kg<sup>-1</sup> s.c.).

It was anticipated that serum concentrations and exposures of TAK-079 could not be determined for the starting dose in human subjects because interspecies scaling of the model-based PK parameters and simulations<sup>14</sup> predicted that *C*<sub>max</sub> (at the end of the 2-hour infusion) would be 0.0059  $\mu$ g mL<sup>-1</sup>, which was below the 0.010  $\mu$ g mL<sup>-1</sup> LLOQ of the PK assay. Nonetheless, human concentrations and exposures of TAK-079 were lower than those observed in monkeys at comparable doses. For example, the mean *C*<sub>max</sub> was 2.09 ng mL<sup>-1</sup> for the 0.06 mg kg<sup>-1</sup> i.v. cohort of human subjects (Table 6), whereas it was 1,850 ng mL<sup>-1</sup> after a single dose of 0.1 mg kg<sup>-1</sup> i.v. within a group of monkeys.<sup>14</sup> These differences may be explained by higher target-mediated drug disposition in human subjects because TAK-079 binds to monkey CD38 with lower affinity than human CD38, presumably due to an amino acid substitution in the epitope between these species. Consequently, a lower affinity of binding to monkey CD38 could result in a lower rate of clearance, causing a higher exposure of TAK-079 in monkeys as compared to human subjects.

Dose-normalized *C*<sub>max</sub> following a s.c. injection was substantially lower than that following a 2-hour i.v. infusion. After *C*<sub>max</sub> was

reached, serum concentrations decreased more slowly following a s.c. injection and were maintained above LLOQ longer than with an i.v. infusion. Due to the limited amount of serum concentration data, a formal assessment on the dose proportionality or s.c. bioavailability of TAK-079 in healthy subjects could not be conducted. Nonetheless,  $C_{\max}$  following i.v. infusion appeared to increase greater than dose proportionally (i.e. approximately 5-fold increase over a 2-fold increase in dose from 0.03 to 0.06 mg kg<sup>-1</sup>), consistent with a similar trend observed in monkeys dosed repeatedly with TAK-079<sup>14</sup> and with those published daratumumab trials, which is principally cleared by target-mediated elimination.<sup>18</sup> It is noteworthy that a multiple-ascending, repeat-dose trial of TAK-079 dosed at 45–1800 mg s.c. in refractory MM patients is ongoing (NCT03439280) and could provide further characterization of PK.

The PD response of healthy subjects to TAK-079 i.v. is the most potent example of NK cell depletion by an anti-CD38 mAb described to date. TAK-079 at 0.06 mg kg<sup>-1</sup> generated a mean  $C_{\max}$  of 0.1 µg mL<sup>-1</sup> (100.4 ng mL<sup>-1</sup>) and reduced peripheral blood NK cells in each healthy subject at least 90% lower than their baseline levels (Figure 3, Table 6). This extent of NK cell reduction was not achieved in relapsed/refractory MM patients infused with daratumumab up to 24 mg kg<sup>-1</sup> and with a mean  $C_{\max}$  of up to 573 µg mL<sup>-1</sup>.<sup>18,19</sup> It is unknown whether this difference in potencies results from differences in properties of the respective antibodies and/or the trial populations. A more definitive comparison could emerge from the PK and PD profile of TAK-079 in a similar population of relapsed/refractory myeloma patients (NCT03439280).

This is the first demonstration of cell reduction after s.c. injection of a cytolytic anti-CD38 antibody into human subjects. A 1 mL s.c. injection of 0.6 mg kg<sup>-1</sup> TAK-079 elicited maximal PD activity (e.g. >90% reduction of plasmablasts in each subject) in peripheral blood of healthy subjects (Figure 4). The corresponding EC<sub>90</sub> for plasmablast reduction was approximately 23.0 ng mL<sup>-1</sup>, whereas it was 100.4 ng mL<sup>-1</sup> for NK cell reduction (Figure 4). This potential difference in sensitivity may be related to the level of CD38 expression expressed by these populations; plasmablasts express approximately a 5-fold higher density of CD38 than NK cells.<sup>20</sup>

Total Ig levels were measured in serum because they are the primary mediator of plasma cells. A single s.c. dose of TAK-079 of ≥0.1 mg kg<sup>-1</sup> reduced total IgA, IgG and IgM levels in serum, whereas these effects were not as pronounced with i.v. doses (Figure 5). The mean  $C_{\max}$  of 0.6 mg kg<sup>-1</sup> TAK-079 s.c. was 23.0 ng mL<sup>-1</sup>, whereas it was 21.4 and 100.4 ng mL<sup>-1</sup> for 0.03 and 0.06 mg kg<sup>-1</sup> TAK-079 i.v., respectively (Table 6), suggesting that these reductions occur independently of  $C_{\max}$ . While IgA, IgG and IgM returned to baseline levels within 78 days after dosing in subjects receiving 0.1 mg kg<sup>-1</sup> s.c. (Figure 5), this was generally not observed in subjects receiving 0.3 and 0.6 mg kg<sup>-1</sup> s.c. These data illustrate that an acute exposure to TAK-079 may reduce levels of Igs for a relatively long duration. A similar effect was observed in SLE patients exposed for 2–4 doses of the proteasome inhibitor bortezomib; there were decreases in serum levels of IgM (34%), IgA (34%), and IgG (15%), which corresponded with reductions in anti-

double stranded DNA antibodies (60%), blood plasmablasts (54%), bone marrow plasma cells (50%) and disease activity scores.<sup>21</sup> In a majority of patients, anti-double stranded DNA antibodies remained below baseline levels 182 days following the last dose. Collectively, these data indicate that reducing the source of Igs (i.e. plasma cells) may elicit reductions of longer duration than other mechanisms of action, such as increased catabolism via **neonatal Fc receptor** antagonism (e.g. return to baseline approximately 57 days after last administration)<sup>22</sup> or physical removal via plasma exchange (e.g. return to baseline approximately 42 days after last procedure).<sup>23</sup>

In conclusion, a single dose of TAK-079 administered i.v. or s.c. was well tolerated by healthy subjects and selectively reduced plasmablasts, NK cells and Ig. This selective plasmacytolytic activity could be beneficial for treatment of a variety of haematological malignancies and/or immunologic disorders involving pathogenic plasma cells, antibodies, Ig and NK cells. If the potency of this effect translates to patients, then a relatively small volume (e.g. 2 mL) of TAK-079 might be self-administered using a device (e.g. auto-injection pen). Self-care could increase productivity (e.g. lost work) and reduce overall health care costs on a per patient basis by reducing the amount of infrastructure (e.g. transportation, health professionals, infusion clinics) required to administer the potential therapy.

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## COMPETING INTERESTS

Annelize Koch declared no conflict of interest. All other authors were employees and stockholders of Takeda Pharmaceuticals Incorporated while this investigation was conducted.

## CONTRIBUTORS

E.R.F. contributed to the experimental design, data analysis, and authoring of the manuscript. L.Z. contributed to the experimental design, clinical trial execution, data analysis, and authoring of the manuscript. A.K. was the Principal Investigator of the trial, had direct clinical responsibility for patients, and contributed to the authoring of the manuscript. G.S. contributed to the experimental design, clinical trial execution, data analysis, and authoring of the manuscript. J.E. contributed to the experimental design, clinical trial execution, data analysis, and authoring of the manuscript. G.C. contributed to the experimental design, data analysis, and authoring of the manuscript. G.L. contributed to data analysis and authoring of the manuscript. S.R. contributed to the experimental design and data analysis. J.L. contributed to the data analysis and authoring of the manuscript. L.M. contributed to the experimental design, clinical trial execution, data analysis, and authoring of the manuscript.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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