CLINICAL STUDY PROTOCOL

NCT Number: NCT03724916

Study Title: A Phase 1b Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of TAK-079 in Combination With Standard Background Therapy in Patients With Moderate to Severe Systemic Lupus Erythematosus

Study Number: TAK-079-2001

Protocol Amendment and Date:

Version 1.0 : 10 March 2019

TAKEDA PHARMACEUTICALS

PROTOCOL

A Phase 1b Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of TAK-079 in Combination With Standard Background Therapy in Patients With Moderate to Severe Systemic Lupus Erythematosus

Study Identifier: TAK-079-2001

Compound: TAK-079

Date: 19 February 2019

Version/Amendment Number: 01

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1.0 STUDY SUMMARY

Name of Sponsor: Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited	**Compound:** TAK-079
Study Identifier: TAK-079-2001	**Phase:** 1b
Protocol Title: A Phase 1b Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of TAK-079 in Combination With Standard Background Therapy in Patients With Moderate to Severe Systemic Lupus Erythematosus	

Background:

Systemic lupus erythematosus (SLE) is a heterogenous autoimmune disease characterized by dysregulation of T and B lineage cells, as well as other components of the innate immune system. A hallmark of the disease is the production of pathogenic autoantibodies to double-stranded DNA (dsDNA), phospholipids, blood cells, and other targets. Tissue damage in SLE is caused primarily by these pathogenic autoantibodies through immune complex deposition with Fc- and complement-mediated inflammation, as well as through direct antibody-target interactions.

The therapeutic agents that are used for treatment of SLE have demonstrated limited success in targeting autoantibody production. Short-lived plasmablasts (PB), plasma cells (ie, terminally differentiated B cells), and long-lived plasma cells produce the characteristic pathogenic autoantibodies and are therefore critically involved in SLE pathogenesis.

CD38 is a type II glycoprotein that is highly and uniformly expressed on antibody-producing PBs and plasma cells, making it a potential target for treatment of SLE. TAK-079 is a fully human IgG1 mAb that binds with high affinity to CD38. The available nonclinical and clinical data demonstrate an acceptable safety profile and encouraging pharmacodynamic (PD) effects in reducing target cells expressing CD38. Therefore, TAK-079 is proposed to be investigated for potential treatment of adult patients with moderate to severe SLE.

Trial Design:

This multicenter, phase 1b study is designed to further elucidate the proof of mechanism and potential biologic activity of TAK-079 in a study population with moderate to severe SLE. The study design allows for the evaluation of the safety and biologic activity of TAK-079 or matching placebo in combination with stable SLE background therapy.

Sequentially enrolling, dose-escalating cohorts will allow for the evaluation of TAK-079 dosing in a step-wise, double-blinded design, thereby providing for both an intracohort and cross-cohort analysis of active TAK-079 and matching placebo. The dosing regimen will consist of a single subcutaneous (SC) injection, of either TAK-079 or matching placebo, to be administered every 21 days (ie, 3 weeks) over the course of a 12-week dosing period, for a maximum 4 study doses, in combination with a stable principal investigator–directed background therapy for SLE. After the 12-week dosing period, patients will continue on study for a 12-week postdose safety follow-up period, allowing for continued observation and assessment of safety and sustainability of biologic activity. Patients whose protocol-defined safety parameters do not return to adequate protocol-defined rebound levels by the end of the safety follow-up period will progress to a long-term follow-up period for continued monitoring. These continued safety observation periods provide optimal oversight and assessment of any ongoing study-related sequela.

Takeda clinicians/designees will provide ongoing safety oversight and surveillance throughout the study dosing period. As such, TAK-079 clinicians/designee will receive and trend all reported adverse events (AEs) and serious adverse events (SAEs), and a blinded review of all safety data will be conducted periodically throughout the study. Based on the outcomes of the Takeda safety reviews and in accordance with predefined criteria, decisions about the dosing regimen for current cohorts will be implemented.

As such, before each study dose, principal investigators will provide the medical monitor with a summary of assessment outcomes associated with the dosing criteria for review and approval. In instances where clinical parameters do not meet dosing criteria, study dosing will be temporarily withheld until parameters meet protocol-defined dosing levels.

An assessment of safety trends and potential risks associated within and across dosing cohorts will be conducted near the completion of each cohort. Based on these findings, and in alignment with protocol-defined dose determination

and cohort dose-escalation stoppage criteria, the study may: (1) advance enrollment to the next cohort at the next protocol-defined dose level, (2) advance enrollment in the next cohort at a reduced intermediate dose level, (3) expand enrollment at the current dose level, or (4) enact early termination of the study.

Study Primary Objective:

The primary objective of this study is to evaluate the safety and tolerability of TAK-079 in comparison with matching placebo, administered once every 3 weeks over a 12-week dosing period in patients with active SLE who are receiving stable background therapy for SLE.

Secondary Objectives:

The secondary objective of this study is to assess the pharmacokinetics (PK), PD, and immunogenicity of TAK-079 administration over a 12-week dosing period.

Study Subject Population: The study population is limited to patients with SLE who exhibit moderate to severe disease with persistent disease activity, who have not responded adequately to standard SLE background therapy treatment, and have not recently had an acute flare that was moderate to severe in nature.

Planned Number of Subjects: 24 subjects	**Planned Number of Sites:** 20 sites
Dose Levels by 3 Sequentially Enrolling Cohorts Cohort A: (n = 6) TAK-079 dosed 45 mg Cohort B: (n = 6) TAK-079 dosed 90 mg Cohort C: (n = 6) TAK-079 dosed 135 mg Each cohort will enroll an additional 2 patients randomized to matching placebo	**Route of Administration:** Subcutaneous injection
Duration of Treatment: Dosing period: 12 weeks	**Planned Trial Duration:** Total study participation: 24 to 36 weeks (approximately 6 to 9 months) Total study duration: 18 to 24 months

Main Criteria for Inclusion:

To be eligible for study participation, patients must:

1. Be aged 18 to 75 years at the time of signing the study informed consent.
2. Meet either the 2012 Systemic Lupus International Collaborating Clinics criteria or the American College of Rheumatology criteria for SLE diagnosis.
3. Have a Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score ≥6.
4. Be positive for anti-dsDNA antibodies and/or antiextractable nuclear antigens antibodies.

Main Criteria for Exclusion:

The following criteria will deem the patient ineligible for study participation:

1. An opportunistic infection ≤12 weeks before initial study dosing or is currently undergoing treatment for a chronic opportunistic infection, such as tuberculosis, pneumocystis pneumonia, cytomegalovirus, herpes simplex virus, herpes zoster, or atypical mycobacteria.
2. An acute or chronic infection requiring hospitalization ≤30 days before the screening visit and/or administration of parenteral (intravenous [IV] or intramuscular) antibacterial, antiviral, antifungal, or antiparasitic agents ≤30 days before the screening visit.
3. Drug-induced SLE and any other rheumatologic or autoimmune disease (excluding secondary Sjögren syndrome, and mixed connective tissue disease).
4. Active neuropsychiatric SLE (eg, new or worsening impaired level of consciousness; psychosis; delirium or confusional state; grand mal seizure [including status epilepticus]; aseptic meningitis, ascending or transverse myelitis; chorea, cerebellar, ataxia, or demyelinating syndromes) that has required therapeutic intervention ≤60 days before initial study dosing.

5. Protocol-defined active glomerulonephritis with concurrent acute renal flare or with documented acute renal flare in the previous 3 months that has required lupus nephritis induction therapy.
6. A positive hepatitis B surface antigen or hepatitis C antibody, or HIV antibody/antigen.
7. Concurrent medical condition that, in the opinion of the investigator, could confound interpretation of results or affect the patient's ability to fully participate in the study.
8. Laboratory test values outside of the limits for the tests specifically defined in the protocol.
9. Concomitant medications that do not meet the protocol criteria (with regard to excluded and dose-limited medications).

Main Criteria for Evaluation and Analyses:

The primary endpoints of this study will evaluate the safety and tolerability of TAK-079 to include the incidence, type, and grade of AEs, as well as the percentage of patients with ≥1 AE leading to study treatment discontinuation.

The secondary endpoints will be assessed through evaluation of the following parameters:

1. PK evaluations of TAK-079.
2. PD evaluations of TAK-079.
3. Assessment of immunogenicity of TAK-079.

Statistical Considerations:

The safety analysis set will consist of all patients who are enrolled and received at least 1 dose of study drug. All pretreatment events (PTEs) and treatment-emergent adverse events (TEAEs) will be coded by system of organ class and preferred term using the Medical Dictionary for Regulatory Activities. TEAEs with an onset occurring during the dosing period and safety follow-up periods will be listed and included in the summary tables. Summary tables will include TEAEs and drug-related AEs, the relationship of AEs to study drug (related vs not-related), grade, and severity of AEs. AEs leading to study drug discontinuation and SAEs will be listed.

Sample Size Justification:

This study is not statistically powered for any hypothesis testing. The sample size for each study cohort are considered to be sufficient to fulfill the study objectives of the evaluation of safety, tolerability, and pharmacokinetics of each cohort.

[redacted]

1.1 Protocol Amendment 01 Summary of Changes

Rationale for Amendment 01

This document describes the changes to the protocol incorporating Amendment 01. The primary reason for the amendment is to adjust T-cell laboratory levels for dosing criteria to better take into consideration the clinical setting for patients with SLE on background therapy, the patient's baseline value, and the quantification of important changes from baseline as safety endpoints.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

For specific descriptions of the text changes and where the changes are located see Appendix H.

Changes in Amendment 01

1. Clarification that the assessment of systemic lupus erythematosus antibodies (Ab) is expected at baseline.
2. Clarification that no dosing criteria assessments are to be conducted as part of screening.
3. Removal of redundant RNA sampling schedule in Table 3.a.
4. Addition of a one-day window (+/- 1 day) for visits: HV7, HV8 and HV9, has been added for consistency with other visits.
5. Removal of details for urine sample collection.
6. Clarification of T-cell safety parameters as they pertain to dosing criteria. This clarification takes into consideration the natural history of SLE on background therapy, the patient's T-cell baseline values, as well as changes from baseline that would warrant the continuation or holding of a dose of TAK-079.
7. Changes to dosing criteria in the event of infusion related reaction, to better align actions with the appropriate grading criteria. Grade 2 or higher reactions still require dose discontinuation.
8. Clarification of dosing criteria in the event of hypersensitivity-related events, to better align with the CTCAE criteria for allergic reactions, as originally intended. Any symptom of an anaphylactic reaction continues to require TAK-079 discontinuation.
9. Clarification that Common Terminology Criteria for Adverse Events version 4.03 must be used in the study.
10. Clarification of excluded and dose limited concomitant medications.
11. The addition of a protocol subsection to provide clarification regarding potential interference with serological testing.
12. Clarifications made regarding the management of hypersensitivity reactions to better align with the CTCAE criteria for allergic reactions, as originally intended.
13. Removal of any reference to an unblinded pharmacist.

[redacted]

14. Clarification that ECGs are to be read locally, to include readings of triplicate electrocardiograms for safety assessments. Otherwise, triplicate ECGs will be submitted for subsequent central reading at a future time.
15. Clarification of Coombs testing to be analyzed by local labs; with further clarification that all other laboratory tests, unless otherwise noted, should be submitted for central analysis.
16. Adjustments to pregnancy test methodology during screening and just prior to the first dose of TAK-079, though 2 negative pregnancy tests are still needed prior to dosing. Details about the duration of continued contraception after the last dose of study medication have been added.
17. Removal of British Isles Lupus Assessment Group assessments and all associated trainings and site/study activities.
18. Clarification that the statistical analysis plan will be prepared before database lock.

[redacted]

2.0 STUDY SCHEMATIC

Figure 2.a TAK-079-2001 Study Cohort Reviews

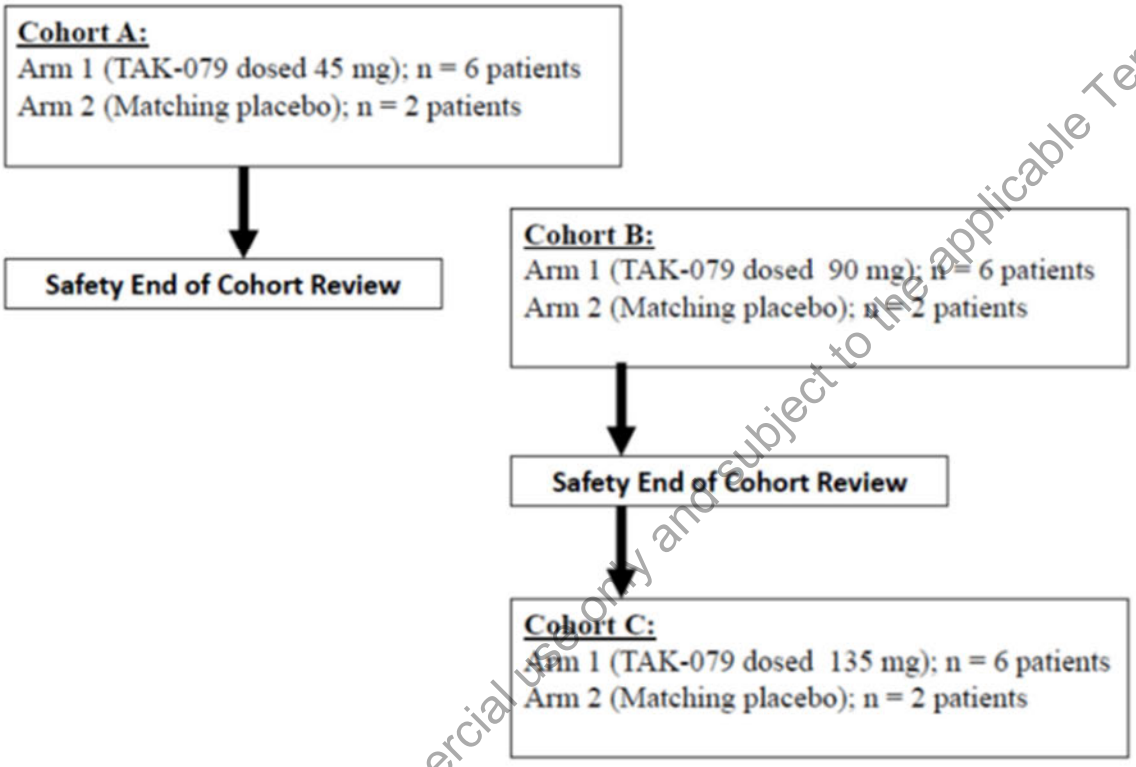
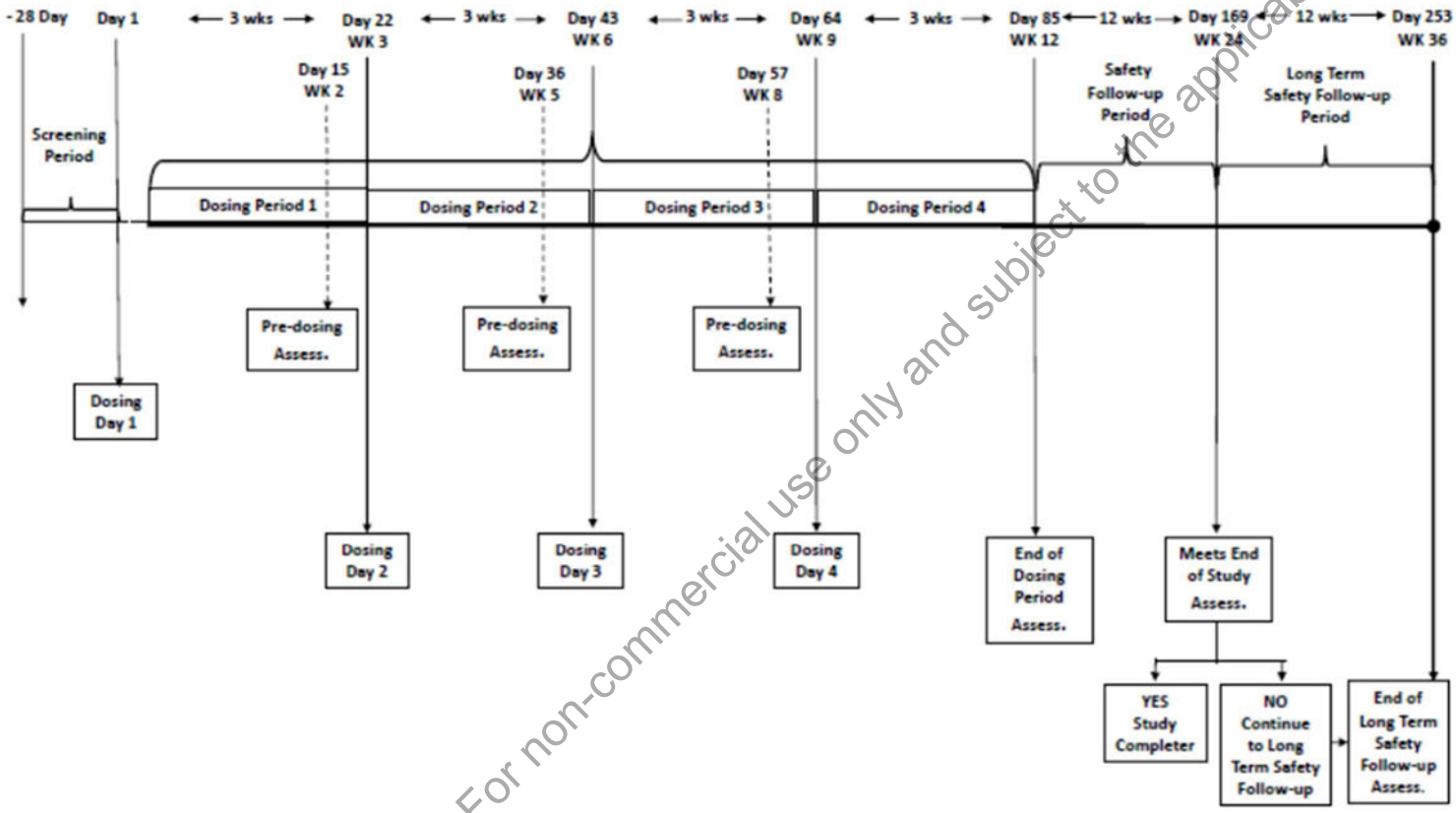


Figure 2.b TAK-079-2001 Study Schematic



3.0 SCHEDULE OF STUDY PROCEDURES

Table 3.a Schedule of Study Events: Dosing Period

Study Procedures	Screening	Period 1					Period 2					Period 3			Period 4			End-of-Dosing Visit [a]
		Dosing V1	HV1	HV2	HV3	Pre-dose V1	Dosing V2	HV4	HV5	HV6	Pre-dose V2	Dosing V3	HV7	Pre-dose V3	Dosing V4	HV8	HV9	
Study day (window) [b]	-28 to -1	D1	D2 (+1 d)	D5 (+1 d)	D8 (±1 d)	D15 (±1 d)	D22	D23 (+1 d)	D26 (+1 d)	D29 (±1 d)	D36 (±1 d)	D43	D50 (±1 d)	D57 (±1 d)	D64	D71 (±1 d)	D78 (±1 d)	D85 (±1 d)
Informed consent	X																	
Inclusion and exclusion criteria	X																	
Medical history including SLE	X																	
[redacted]																		
Physical examination [e]	X	X [d]					X [d]					X [d]			X [d]			X
Vital signs [f]	X	X					X					X			X			X
Dosing criteria assessment		X [d]				X	X [d]				X	X [d]		X	X [d]			
Concomitant medications	Recorded ≤28 days before the first dose of TAK-079, through completion of final study safety visit (ie, final safety follow-up visit, or when applicable, the final long-term safety follow-up visit).																	
AE assessment [g]	(Serious) AEs (to include pretreatment, and related and unrelated treatment-emergent events) are to be recorded from the time of signing the ICF through to completion of the final study safety visit (ie, final safety follow-up visit, or when applicable, the final long-term safety follow-up visit).																	
Study day (window) [b]	-28 to -1	D1	D2 (+1 d)	D5 (+1 d)	D8 (±1 d)	D15 (±1 d)	D22	D23 (+1 d)	D26 (+1 d)	D29 (±1 d)	D36 (±1 d	D43	D50	D57 (±1 d	D64	D71	D78	D85 (±1 d)
Dosing																		
Premedication dosing [h]		X [d]					X [d]					X [d]			X [d]			
TAK-079 dosing [i]		X					X					X			X			

[redacted]

Table 3.a Schedule of Study Events: Dosing Period

Study Procedures	Screening	Period 1					Period 2					Period 3			Period 4			End-of-Dosing Visit [a]
		Dosing V1	HV1	HV2	HV3	Pre-dose V1	Dosing V2	HV4	HV5	HV6	Pre-dose V2	Dosing V3	HV7	Pre-dose V3	Dosing V4	HV8	HV9	
Laboratory Assessments (NOTE: See Table 3.c for additional laboratory draws)																		
Pregnancy test [j]	X	X [d]					X [d]					X [d]			X [d]			X
Hematology	X					X					X			X				X
Chemistries	X					X					X			X				X
Urinalysis [k]	X	X [d]				X	X [d]				X	X [d]		X	X [d]			X
Immune profiling	X					X					X			X				X
[redacted]																		
Cytokine markers [m]		X [d]					X [d]					X [d]			X [d]			X
SLE Ab [n]	X	X [d]					X [d]					X [d]			X [d]			X
Quantitative IgA/IgM/IgG	X					X					X			X				X
Immuno-genicity assessments (to include ADA)		X [d]					X [d]					X [d]			X [d]			X

Abbreviations: Ab, antibody; ADA, antidrug antibodies; AE, adverse event; [redacted] CRS, cytokine-release syndrome; D, study day; [redacted]; HV, home visit; ICF, informed consent form; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; IRB, institutional review board; SLE, systemic lupus erythematosus; [redacted].

[a] After completing Week 12 of study dosing, patients will continue in the study for a 12-week safety follow-up period as outlined in Table 3.b.

[b] See Section 9.0 for additional time allowance for extenuating circumstances, as granted on approval of medical monitor or designee.

[redacted]

To be performed before dose administration.

[e] Physical examinations are to be symptom- and SLE disease–directed with significant clinical findings noted as AEs.

[f] Vital signs, including temperature, pulse, respiratory rate, and blood pressure, are to be assessed before each study dose and 4 hours after dosing, as part of postinjection assessments; vital signs should also be assessed at any time it is clinically warranted, either during clinic or home study visits (ie, in instances where the patient exhibits signs or symptoms of injection reaction, CRS, or hypersensitivity reactions). See Section 9.2.5 for further details.

[g] Assessments for AEs are to include a symptomatic examination of the patient's current disease state, conditions, and treatments (see Section 10.0).

[h] Premedication dosing and dosages are outlined in Section 6.2.1.

[i] The time and the anatomical site of injection are to be recorded for each study dose; patients should be closely monitored in the clinic for at least 4 hours after each dose; before discharge all patient must receive information on signs and symptoms of anaphylactic reactions and CRS.

[redacted]

Table 3.a Schedule of Study Events: Dosing Period

Study Procedures	Screen-ing	Period 1					Period 2					Period 3			Period 4			End-of-Dosing Visit [a]
		Dosing V1	HV1	HV2	HV3	Pre-dose V1	Dosing V2	HV4	HV5	HV6	Pre-dose V2	Dosing V3	HV7	Pre-dose V3	Dosing V4	HV8	HV9	

[j] Pregnancy testing details are provided in Section 9.2.9 and Appendix A. Additional testing must be assessed if the patient's menstrual period is delayed, or if the IRB requests.

[k] Urinalysis, including [redacted] nitrates, will be performed by central laboratory 1 week before dosing; additional protein and nitrate assessments are to be performed by local laboratory (ie, dipstick) on study dosing days, before dosing; abnormal findings by local laboratory assessment must be confirmed by central laboratory evaluation. Further detail is provided in Section 9.2.8.3.

[redacted]

[m] Additional samples of cytokine markers are to be drawn if CRS is suspected; additional PK [redacted] sampling may be requested

[n] SLE antibodies include, but are not limited to, antiphospholipid, [redacted] antibodies.

[redacted]

Table 3.b Schedule of Study Events: Safety Follow-up and Long-term Safety Follow-up Periods

	Safety Follow-up Period			Long-Term Safety Follow-up Period [a]		
	Safety V1	Safety V2	Safety/ Early End-of-Study Visit [a] V3	Long-term Safety V1	Long-term Safety V2	Long-term End-of-Study Visit V3
Study Week	Week 16	Week 20	Week 24	Week 28	Week 32	Week36
[redacted]						
Concomitant medications	Recorded ≤28 days before the first dose of TAK-079 through completion of final study safety visit (ie, final safety follow-up visit, or if applicable, at the final long-term safety follow-up visit)					
AE assessment [c]	(Serious) AEs (includes pretreatment, and related and unrelated treatment-emergent events) are to be recorded from the signing of the ICF through completion of final study safety visit (ie, final safety follow-up visit, or if applicable, the final long-term safety follow-up visit)					
Laboratory Assessments						
Pregnancy test [d]			X			
Hematology	X	X	X			
Chemistries	X	X	X			
Urinalysis [e]	X	X	X			

Abbreviations: AE, adverse event; [redacted]; HV, home visit; ICF, informed consent form; IRB, institutional review board; SLE, systemic lupus erythematosus; V, visit; [redacted]

[a] Clinical parameters that do not meet the end of study criteria, as outlined in Table 9.c, and are deemed by the principal investigator as study related, will continue to be assessed no less than every 4 weeks until resolution, as outlined in Section 9.4.

[redacted]

AE assessments are to include a symptomatic examination of the patient's current disease state, conditions, and treatments.

[d] Pregnancy testing details are provided in Section 9.2.9 and Appendix A for critical details. Additional testing must be assessed if menstrual period is delayed, or at IRB request.

[e] Urinalysis, including [redacted] nitrates, will be performed by central laboratory; additional protein and nitrate assessments are to be performed on each clinic visit; abnormal findings by local laboratory assessment must be confirmed by central laboratory evaluation. Further detail is provided in Section 9.2.8.3.

[redacted]

Table 3.c Pharmacokinetic, CD38, TBNK Samples, and ECG Times by Visit

Visit	Study Day	Specialty Laboratory Sample Times				ECG Assessments [a]
		TBNK	CD38	RNA	PK [c]	
Screening	**NA**					X
Dosing Visit 1	**D1**	X [b]	X [b]	X [b]	**All 3 visit timepoints as follows:** • Any time point before dosing • 2 hr (±1 hr) after dosing • 5 hr (±1 hr) after dosing	• X [b] • Pre-dose • 5 hr after dosing (prior to PK draw)
HV1	**D2**	X	X	X	33 hr (±9 hr) after dosing	X
HV2	**D5**	X	X	X	108 hr (±12 hr) after dosing	X
HV3	**D8**				168 hr (±24 hr) after dosing	
Predose Visit 1	**D15**	X	X	X	Any time during visit	
Dosing Visit 2	**D22**	X [b]	X [b]	X [b]	**All 3 visit timepoints as follows:** • Any time point before dosing • 2 hr (±1 hr) after dosing • 5 hr (±1 hr) after dosing	X [b]
HV4	**D23**	X	X	X	33 hr (±9 hr) after dosing	X
HV5	**D26**	X	X	X	108 hr (±12 hr) after dosing	
HV6	**D29**				Any time during visit	
Predose Visit 2	**D36**	X	X	X	Any time during visit	
Dosing Visit 3	**D43**	X [b]	X [b]	X [b]	**Both visit timepoints as follows:** • Any time point before dosing • 5 hr (±1 hr) after dosing	X [b]
HV7	**D50**	X	X	X	Any time during visit	X
Predose Visit 3	**D57**	X	X	X	Any time during visit	
Dosing	**D64**	X [b]	X [b]	X [b]	**Both visit timepoints as follows:**	X [b]

[redacted]

Table 3.c Pharmacokinetic, CD38, TBNK Samples, and ECG Times by Visit

Visit Visit 4	Study Day	Specialty Laboratory Sample Times				ECG Assessments [a]
		TBNK	CD38	RNA	PK [c] • Any time point before dosing • 5 hr (±1 hr) after dosing	
HV8	D71	X	X	X	Any time during visit	X
HV9	D78				Any time during visit	
End-of-dosing visit	D85	X	X	X	Any time during visit	X
End-of–safety follow-up visit	Week 24					X

Abbreviations: D, day; ECG, electrocardiogram; HV, home visit; NA, not applicable; PK, pharmacokinetic; TBNK, T, B, and NK cells.
[a] ECGs must be obtained just before PK sampling when scheduled on the same study days; as part of study screening and at the end of safety follow-up visit, a single ECG must be obtained and assessed (read locally); during study-treatment, triplicate 12-lead ECGs should be obtained, (read locally), with a copy submitted centrally for future analysis. (see Section 9.2.6).
[b] To be performed before study dosing.
[c] Additional PK draws may be requested by the MM.

[redacted]

4.0 INTRODUCTION

4.1 Background

Systemic lupus erythematosus (SLE) is a serious condition that has defied efforts to develop effective therapies, leaving a significant unmet medical need for patients with moderate to severe disease. During the past several decades, more than 30 promising, strategically targeted biologics have entered early development for the treatment of lupus; however, only belimumab has successfully completed a phase 3 program to obtain regulatory approvals worldwide [1]. These failures, which may be partially attributed to heterogeneity in the pathophysiology of SLE, indicate the need for the development of more effective targeted therapeutics.

SLE is a heterogenous autoimmune disease characterized by dysregulation of T and B lineage cells, as well as other components of the innate immune system. A hallmark of the disease is the production of pathogenic autoantibodies to double-stranded DNA (dsDNA), phospholipids, blood cells, and other targets. Tissue damage in SLE is caused primarily by these pathogenic autoantibodies through immune complex deposition with Fc- and complement-mediated inflammation, as well as through direct antibody-target interactions [2]. Virtually any organ or system in the body can be affected by SLE [3,4].

The clinical course of SLE is episodic, with flares of disease activity that lead to increased disability and organ damage over time. For moderate to severe cases, the current standard of care includes off-label therapies, including immunosuppressants (azathioprine, cyclophosphamide, and mycophenolate mofetil), high-dose steroids, and intravenous (IV) immunoglobulin for cytopenia.

The therapeutic agents that are used for treatment of SLE have demonstrated limited success in targeting autoantibody production. Short-lived plasmablasts (PB), plasma cells (ie, terminally differentiated B cells), and long-lived plasma cells produce the characteristic pathogenic autoantibodies and are therefore critically involved in SLE pathogenesis.

Studies have shown an increased number of PBs in the blood of patients with active SLE [3]. Rituximab (anti-CD20) and belimumab (anti-BLys) target B cells, interrupting the release of newly generated PBs from memory B cells that are depleted by the drugs and thereby reducing autoantibody production to some degree [4]. However, PBs and long-lived plasma cells are not susceptible to these therapies [5-7]. Similarly, the available broadly acting immunosuppressant agents (eg, azathioprine, cyclophosphamide, and mycophenolate mofetil) and high-dose steroids do not specifically target plasma cells and PBs, and their utility is further limited because of tolerability issues.

CD38 is a type II glycoprotein that is highly and uniformly expressed on antibody-producing PBs and plasma cells [8], making it a potential target for treatment of SLE. In an ex vivo study of CD38 expression on various immune cells in peripheral blood mononuclear cells from patients with SLE, the highest CD38 expression was observed on plasma cells and PBs, followed by natural killer (NK) cells, plasmacytoid dendritic cells, a regulatory T cell subpopulation, and naïve T cells [9].

The significantly higher CD38 expression on PCs and PBs compared with other immune cells suggests the potential for selectively depleting these cells with an anti-CD38 antibody. Consistent

with this hypothesis, daratumumab, a commercially available CD38 antibody licensed for treatment of multiple myeloma, effectively depleted plasma cells and PBs in peripheral blood mononuclear cells from patients with SLE in a dose-dependent manner in vitro [9].

Other studies have confirmed that the levels of CD38-expressing PBs are increased in patients with SLE. A study that transcriptionally profiled blood samples from 158 pediatric SLE patients identified 13 distinct signatures (ie, phenotypes) of lupus, out of which the PB signature with elevated expression of CD38 and increased levels of anti-dsDNA, antibodies was most strongly positively correlated with disease activity [10]. These findings were supported by a study of immunophenotyping of 143 patients with SLE [11] and are consistent with previous studies in patients with SLE treated with rituximab that showed a positive correlation between disease progression and the level of CD38-expressing PBs that are not susceptible to the anti-CD20 antibody [12].

Thus, the level of unmet need in SLE remains high, and therapies with novel mechanisms of action are needed to provide improved efficacy in reducing disease activity, to help decrease use of corticosteroids, and to improve quality of life for patients with SLE. Specifically, targeted therapies that deplete PBs and plasma cells could be of important therapeutic benefit for patients with SLE.

4.2 Rationale for Proposed Study

TAK-079 is, a fully human IgG1 monoclonal antibody (mAb) that binds with high affinity to CD38. The available nonclinical and clinical data demonstrate an acceptable safety profile and encouraging pharmacodynamic (PD) effects in reducing target cells expressing CD38. Therefore, TAK-079 is being proposed as a potential treatment for moderate to severe SLE in adult patients.

Preclinical studies showed that TAK-079 depletes the CD38-expressing target cells by means of antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity (TAK-079-10012). In in vitro experiments, the addition to TAK-079 to blood or bone marrow samples taken from patients with lupus was shown to deplete 80% of plasma cell populations, including short-lived plasma cells ($CD19^+$ plasma cells) and long-lived plasma cells ($CD19^-$ plasma cells). Additionally, the number of cells producing autoantigen-specific antibodies was dramatically reduced, including VH4-34 9G4+ antibodies (70% reduction), anti-Ro antibody (70% reduction), and anti-dsDNA antibody (80% reduction) [13].

In vivo, the efficiency of depletion of each cell type correlated with the levels of CD38 expression and exposure of TAK-079 in healthy cynomolgus monkeys (TAK-079-10015, TAK-079-10018, TAK-079-10019). Furthermore, TAK-079 demonstrated anti-inflammatory and disease-modifying activity in a monkey model of collagen-induced arthritis (CIA) that mirrors clinical aspects of human rheumatoid arthritis (RA) (TAK-079-10032). TAK-079 treatment prevented or reduced joint inflammation and subsequent joint, bone, and cartilage damage with efficacy comparable to high-dose dexamethasone but with better tolerability (as measured by changes in body weight). This efficacy correlated with the reduction of B, NK, and T cells in peripheral blood.

To date, TAK-079 has been evaluated in a single escalating-dose study of healthy subjects (n = 74; TAK-079-101). In that study, TAK-079 administration resulted in dose-dependent, reversible reduction of blood cell subsets that express CD38, including NK cells, PBs, B cells, and T cells. TAK-079 was well tolerated, with no unexpected and unwanted clinical or hematologic effects identified.

In conclusion, the available nonclinical and clinical data demonstrate an acceptable safety profile, and encouraging PD effects in reducing target cells expressing CD38. These findings suggest that TAK-079 may have the potential to address the unmet needs of SLE.

The primary objective of the TAK-079 SLE development program is to investigate the utility of TAK-079 as a disease-modifying therapy in SLE. This phase 1b double-blind, placebo-controlled, multicenter study will evaluate the safety, tolerability, pharmacokinetics (PK), and PD of TAK-079 in patients with moderate to severe SLE by comparing active TAK-079 with matching placebo in combination with standard background therapy for SLE.

4.3 Rationale for Study Design, Dose, and Endpoints

4.3.1 Rationale of Study Design

This phase 1b study is designed to further understand the proof of mechanism and potential biologic activity of TAK-079 in a study population with specific, measurable clinical manifestations of SLE. The study design allows for patients to continue their SLE background therapy, managed under the care of their physician, while evaluating the benefit-risk of TAK-079 as an investigational add-on therapy.

Sequentially enrolling the double-blind cohorts allows for the evaluation of TAK-079 dosing in a step-wise, double-blinded design, thereby providing for both an intracohort and cross-cohort analysis of active TAK-079 and matching placebo (see Figure 2.a).

Takeda clinicians conduct reviews of adverse events (AEs), serious adverse events (SAEs), and related clinical parameters to ensure consistency with an acceptable benefit-risk ratio throughout the study. At the patient level, safety and tolerability are closely monitored for each patient at the completion of each dose and before the next subsequent dose to ensure clinical dosing criteria are met before each subsequent administration of TAK-079 or matching placebo. Further, safety is assessed at the end of treatment in each cohort, which allows for decisions regarding enrollment in subsequent cohorts. A 12-week post-dose safety follow-up period allows for continued observation and assessment of safety and sustainability of biologic activity. Patients whose safety parameters do not return to adequate protocol-defined rebound levels by the end of the safety follow-up period may progress to a long-term follow-up period for continued monitoring (Table 3.b, Table 6.b). These continued safety observation periods provide optimal oversight and assessment of any ongoing study-related sequela.

4.3.2 Rationale for Selected Patient Population

As outlined in inclusion criteria (Section 7.1), the study population is limited to patients with SLE who exhibit moderate to severe disease with persistent disease activity and who have not

responded adequately to standard SLE background therapy treatment but have not recently had an acute flare that was moderate to severe in nature. All patients must be positive for anti-dsDNA antibodies and/or antiextractable nuclear antigens (anti-ENA) antibodies.

Based on findings from the first-in-human (FIH) study (TAK-079-101), most subjects will have detectable expression of CD38. The level of CD38 expression (quantified in molecules of equivalent soluble fluorochrome [MESF]) on PB cells was evaluated from samples obtained at screening in the TAK-079-101 study in healthy subjects. A total of 129 evaluable subjects were analyzed for expression of CD38, of whom 100% had detectable levels of CD38. The level of CD38 expression in these healthy subjects ranged approximately 5-fold from 693,474 MESF units to 3,531,222 MESF units, with a mean of 1,747,840 MESF units. The lowest CD38 expression was approximately 7-fold higher than background, indicating that healthy subjects express high levels of CD38 on the surface of peripheral blood PBs (Supplemental Study Report, Baseline CD38 Expression in Healthy Subjects from the TAK-079-101 Study, is available on request).

4.3.3 Rationale for Dose

The study dosing regimen consists of a single subcutaneous (SC) injection of either TAK-079 or matching placebo, administered every 21 days (ie, 3 weeks) over the course of a 12-week dosing period for a maximum of 4 study doses, in combination with a principal investigator–directed background therapy for SLE.

The selection of doses and the frequency of administration of TAK-079 are based on a comprehensive review and analysis of data derived from the following: (1) dosing of healthy subjects with TAK-079 (Study TAK-079-101); (2) nonclinical repeat TAK-079 dosing studies (TAK-079-10015, TAK-079-1018, and TAK-079-10019) in cynomolgus monkeys; and (3) data derived from repeat dosing of daratumumab (Darzalex), a related anti-CD38 cytolytic antibody that is licensed for treatment in multiple myeloma [11].

The starting dose of 45 mg for the initial dosing cohort (ie, Cohort A) is selected based on the favorable safety profile and PD target effect (ie, a sustained reduction of PBs) observed after a 0.6 mg/kg dose was administered to healthy subjects (Study TAK-079-101). A single SC dose of 0.6 mg/kg TAK-079 reduced the level of PBs in peripheral blood >90% and NK cells >80% without comparable reductions in monocytes and B and T cells. Levels of PBs and NK cells recovered to 50% of baseline levels 21 days after administration, on average. At this dose, there were no SAEs, on-study deaths, or AEs that led to study discontinuation. No remarkable findings for laboratory tests, electrocardiogram (ECGs), vital signs, or physical examinations were reported that were related to TAK-079 administration. Two subsequent dosing cohorts are planned at doses of 90 mg (2-fold increase from the first dose cohort) and 135 mg (a 50% increase from the previous cohort). Because patients with lupus generally exhibit higher levels of PBs expressing CD38 than those seen in healthy study subjects, higher doses may be needed to achieve comparable PD effects; subjects should be carefully monitored to maintain a balance of benefit-risk (refer to the dose-modeling overview shown in Figure 4, provided in Appendix G).

[redacted]

4.3.4 Rationale for Endpoints

4.3.4.1 Primary Endpoint

The primary endpoint of the TAK-079-2001 SLE study is the incidence, type, and grade (based on the CTCAE [Common Terminology Criteria for Adverse Events] category, version 4.03) of all reported AEs and SAEs, regardless of causality. The percentage of study patients with ≥1 AE leading to discontinuation of investigational study medication is also included in this evaluation. This endpoint supports the study objective, to evaluate the safety and TAK-079, in addition to the principal investigator–directed background SLE therapy in patients with moderate to severe SLE.

4.3.4.2 Secondary Endpoints

Secondary endpoints include the evaluation of PK, PD, immunogenicity of TAK-079, and the incidence of human antihuman antibodies in the study population, to be evaluated at baseline and at Weeks 16 and 28.

4.3.4.3 Exploratory Endpoints

[redacted]

4.4 Benefit-Risk Profile

Because of the limited clinical exposure of TAK-079, the overall clinical benefits and risks of TAK-079 have not been fully determined.

Minimal clinical efficacy data are available to date; the only completed study with TAK-079 is the study in healthy subjects. There is one ongoing clinical study with TAK-079 in patients with relapsed/refractory multiple myeloma (RRMM), the recruitment for this study started in May 2018. As of July 2018, three patients have been enrolled in the first cohort receiving the 45 mg dose. No dose-limiting toxicities have been reported in 2 of 2 evaluable patients (evaluable because they have completed the 4 weekly doses in Cycle 1). One patient is still receiving therapy in Cycle 1. No patient has reported an infusion reaction or cytokine release syndrome (CRS). Further, there have not been any infections, injection site reactions (ISRs), or clinically significant changes in hematologic parameters as of this date. One patient has reported Grade 1 fatigue related to TAK-079; no AEs have been reported in the second and third patients. Myeloma response data are available for 2 of the 3 patients. Both evaluable patients have shown evidence of reduction in their disease (1 minimal response and 1 stable disease per International Myeloma Working Group

[redacted]

criteria). Preliminary data show antimyeloma activity with minimal toxicity at a dose of 45 mg after 4 weekly doses.

The expected potential benefits of TAK-079 in patients with SLE are based on the observed non-clinical and clinical PD effects, as described in detail in the investigator's brochure. Quite relevant to this study, the therapeutic efficacy of TAK-079 was demonstrated in a monkey collagen-induced arthritis model, which mirrors clinical aspects of human RA. TAK-079 treatment reduced joint inflammation and subsequent joint, bone, and cartilage damage. It had comparable efficacy to the steroid dexamethasone, as evidenced by reduction of arthritis scores and faster reduction of C-reactive protein levels. This efficacy correlated with the reduction of B, NK, and T cells in peripheral blood. Furthermore, TAK-079 was better tolerated than dexamethasone; no weight loss was observed in animals treated with TAK-079, in contrast to those treated with dexamethasone (TAK-079-10032).

In the FIH study (TAK-079-101), a single dose of TAK-079 IV or SC treatment resulted in the transient, dose-dependent, reversible reduction of blood cell subsets that express CD38, including NK cells, PBs, B cells, and T cells. Although the duration of PB depletion was relatively short-lived (up to 15 days in SC cohorts) after a single administration at low doses, this study demonstrated that PBs are particularly sensitive to TAK-079 as would be expected, based on the target of this mAb and the high expression of CD38 on PBs.

In conclusion, considering the efficacy signals following administration of TAK-079 in a monkey collagen-induced arthritis model, and the promising PD effects following TAK-079 administration observed in both in vitro and in vivo studies, as well as in the FIH study in healthy subjects, further investigation of TAK-079 as a potential treatment for SLE is warranted. Patients with SLE have a PB (CD38-expressing) phenotype, therefore an agent such as TAK-079 that specifically targets CD38-expressing cells may have potential benefit for patients with SLE.

Possible AEs are based on the intrinsic pharmacology of TAK-079, reports from other biologic agents, the nonclinical data to date, and the limited data from Study TAK-079-101 in healthy human subjects. Risks of TAK-079 may include, but are not limited to, the following: ISRs, CRS, changes in hematologic parameters, and infections. Patients will be monitored closely for these and other potential side effects in accordance to the assessments and procedures outlined in this protocol (see Sections 6.4, 6.5, and 9.0). Further details on TAK-079 risks can be found in the TAK-079 Investigator's Brochure.

In the FIH trial (Study TAK-079-101), single doses of TAK-079 ranging from 0.0003 to 0.06 mg/kg given by IV infusion and 0.03 to 0.6 mg/kg given by SC injection were well tolerated. AEs were mild to moderate in intensity, with most AEs being mild. There were no SAEs or deaths reported in the study, and no AEs led to either study or visit discontinuation. No remarkable findings for laboratory tests, ECGs, vital signs, or physical examinations were reported that were related to TAK-079 treatment (TAK-079-101 CSR).

Mild, transient CRS was observed in subjects who were administered higher TAK-079 doses, mostly in the 2 cohorts receiving higher intravenous doses. Common symptoms included fever, headache, dizziness, and orthostatic hypotension. Incidences of CRS coincided with moderate

cytokine increases and occurred in the same cohorts that significant and rapid lymphocyte depletion occurred, suggesting that the symptoms associated with CRS could have been caused by lymphocyte depletion rather than activation. These data are consistent with findings from nonclinical studies that showed that TAK-079 is a cell-depleting antibody and did not elicit cytokine release from viable leukocytes. Relative to the intravenously dosed study groups, the subcutaneously dosed study groups had fewer subjects who experienced CRS, and there were minimal cytokine level increases despite subjects receiving TAK-079 at doses 10-fold higher than the intravenously dosed study groups. This could be the result of differences in the kinetics of the drug. However, SC administration effectively depleted PB for a longer duration than seen with IV administration, suggesting SC administration is a suitable route of administration for future clinical development. In addition, only mild, transient ISRs were observed after SC injections, most of which resolved within 7 days. The ISRs have an inverse dose-effect relationship, as 5 out of 6 subjects administered the lowest SC dose had ISRs, whereas only one subject had a mild ISR in each of the 2 highest dose cohorts.

4.5 Benefits and Risks Conclusions

Because of the limited clinical exposure of TAK-079, the overall clinical benefits and risks of TAK-079 have not been fully determined.

Risks of TAK-079 may include, but are not limited to, the following: ISRs, CRS, hypersensitivity reactions, changes in hematologic parameters, and infections. These AEs are based on the intrinsic pharmacology of TAK-079, reports from other biologic agents, the nonclinical data to date, and the limited data from Study TAK-079-101 in healthy human subjects. Patients will be monitored closely for these AEs in clinical studies with TAK-079.

Potential benefits of TAK-079 in patients with SLE are based on nonclinical and clinical PD effects. Patients with SLE have a PB (CD38-expressing) phenotype; therefore, an agent such as TAK 079 that specifically targets CD38-expressing cells may have potential benefit for patients with SLE.

[redacted]

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of TAK-079 in comparison with matching placebo, administered once every 3 weeks over a 12-week dosing period in patients with active SLE who are receiving stable background therapy for SLE.

5.1.2 Secondary Objective

The secondary objective of the study is to assess the PK, PD, and immunogenicity of TAK-079 administration over a 12-week dosing period.

5.1.3 Exploratory Objectives

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoints of this study will evaluate the safety and tolerability of TAK-079 to include the incidence, type, and grade of AEs, as well as the percentage of patients with ≥1 AE leading to study treatment discontinuation.

5.2.2 Secondary Endpoints

The secondary endpoints will include:

1. Pharmacokinetic evaluations of TAK-079.
2. Pharmacodynamics evaluations of TAK-079.
3. Immunogenicity assessments of TAK-079.

5.2.3 Exploratory Endpoints

[redacted]

[redacted]

[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

This phase 1b double-blind, placebo-controlled, multicenter study will evaluate the safety, PK, and PD of TAK-079 in a study population receiving standard principal investigator–directed background therapy for moderate to severe SLE.

6.1 Study Design

The study will compare active TAK-079 with matching placebo in combination with a background SLE standard treatment, across 3 sequentially enrolling cohorts in a double-blinded study design. A 3:1 randomization, within each cohort, will assign each patient to: (1) TAK-079 administered as a single SC injection every 3 weeks for 12 weeks (total of 4 doses); or, (2) matching placebo given in same route and schedule (see Figure 2.a). Each cohort will enroll 8 patients; 6 patients will be randomized to TAK-079 dosing and 2 patients to TAK-079 matching placebo. After each dosing day, patients will return for postdose assessments as outlined in Table 3.a and Table 3.b.

Following completion of the 12-week dosing period, patients will return for an additional 12-week safety follow-up period, completing safety visits every 4 weeks and ending this postdosing study period with a safety visit on Week 24. Based on clinical assessments at this visit, patients may complete the study or may advance to the long-term safety follow-up period, for an additional on-study 12-week safety monitoring period (based on end-of-study criteria outlined in Table 9.c), during which time the end of study parameters not met and deemed by the principal investigator as study related, will continue to be assessed and followed as outlined in Section 9.4.

6.2 Study Drug

Study drug is to be administered only to eligible patients under the supervision of the principal investigator or identified subinvestigator(s). Patients will be dosed TAK-079 or matching placebo in accordance to their assigned study cohort every 3 weeks, as outlined in Table 6.a. All protocol-specific criteria for administration of study drug must be met and documented before drug administration (see Table 6.b. During the study, dosing of TAK-079 may be temporarily held or discontinued, based on the dosing criteria outlined in Table 6.b or in accordance to the principal investigator's judgment. Dosing of TAK-079 may not otherwise be reduced or escalated for any given patient (study dosing by cohort, will be assessed and sequentially increased, as outlined in Figure 2.a).

Concomitant medication, to include acceptable criteria for principal investigator-directed SLE background medications, are provided in Section 9.2.3. Rescue therapy information is outlined in Section 6.2.4.

In accordance with timings and criteria outlined in Section 6.3.1 key safety data will be reviewed and evaluated by Takeda clinicians/designees, who will review the safety of all treated patients and make decisions regarding dose escalation. In addition, changes to the dose-escalation scheme or dose schedule (dosing interval) may be considered. All decisions will be documented in writing. Any decision to modify the dose-escalation scheme and schedule (with the exception of testing intermediate dose levels, or expanding a dose level) will be communicated to institutional review

boards (IRBs). The investigators will also be informed in writing of the more conservative approach. The protocol will be considered for amendment accordingly.

Table 6.a TAK-079 Dosing by Study Cohort

	Study Dosing Arms			
	TAK-079 [a]		Matching Placebo [a]	
Cohort	Patients (n)	Dose (mg)	Patients (n)	Dose (mg)
Cohort A	6	45	2	NA
Cohort B	6	90	2	NA
Cohort C	6	135	2	NA

Abbreviations: NA, not applicable.
[a] Patients will receive TAK-079 or matching placebo through SC administration every 21 days (ie, 3 weeks) over the course of 12 weeks, for 4 total doses.

6.2.1 Premedication

On each dosing day, 1 to 3 hours before TAK-079 administration, patients are to be premedicated with a regimen consistent with, but not limited to, the following:

1. Antipyretic: oral acetaminophen (650 to 1000 mg).
2. Antihistamine: oral or IV diphenhydramine (25 to 50 mg, or equivalent).

The clinical site is responsible for sourcing premedications outlined in the protocol.

6.2.2 Post-dose Medications

Patients may receive low-dose methylprednisolone (<20 mg) for the prevention of delayed injection-related reaction, as clinically indicated, and under the discretion of the principal investigator.

NOTE: Patients with a higher risk of respiratory complications (eg, patients with a history of chronic obstructive pulmonary disease [COPD] and patients with asthma) may be administered the following, after each study dose (at the investigator's discretion):

a) An antihistamine (diphenhydramine or equivalent) on the first and second days after study dosing.
b) A short-acting β2-adrenergic receptor agonist, such as salbutamol (albuterol) aerosol.
c) Control medications for lung disease, such as the following:
   - Inhaled corticosteroids with or without long-acting β2 adrenergic receptor agonists for patients with asthma.
   - Long-acting bronchodilators, such as tiotropium or salmeterol with or without inhaled corticosteroids, for patients with COPD.

The clinical site is responsible for sourcing treatments administered pre- or post-TAK-079 injection, as outlined in the protocol.

Based on emerging data, the Takeda physician/designee may enhance treatments administered pre- or post-TAK-079 injection to ensure patient safety.

6.2.3 TAK-079 and Matching Placebo Administration

The strength of the TAK-079 drug product for SC use in this study is 100 mg TAK-079 in 1 mL (100 mg/mL).

After patients have received premedication treatment, the TAK-079 dose or matching placebo will be administered with a syringe as SC injections up to a maximum volume of 2 mL, such that the full schedule dose has been administered. The time and anatomical site of SC injection must be recorded for each dose, with the site of injection rotated for each dose (injection sites of the abdomen, thighs, arms, and upper buttock area are acceptable). Refer to the pharmacy manual for detailed instructions regarding preparation of TAK-079 and matching placebo dose.

6.2.4 Rescue Therapy

Rescue therapy is defined as additional dosing of concomitant medications in accordance with institutional practices or the physician's best medical judgment to control and manage underlying SLE conditions. Protocol-restricted and dose-limited concomitant medications are outlined in Table 7.a and Table 7.b (Note: Concomitant dosing of cyclophosphamide is restricted during study enrollment).

Patients should remain on their stable dose of immunosuppressive and corticosteroid therapies throughout the study (as aligned with protocol requirements in Table 7.a and Table 7.b).

- Decreases in the dose of immunosuppressants, due to toxicity, are allowed at the discretion of the investigator.
- Increasing, adding, or changing background immunosuppressive, or adding a medication not otherwise within protocol limits, as deemed necessary by the principal investigator to treat manifestations of SLE, must result in discontinuation of the patient from study dosing and advancement to safety follow-up; these patients will be categorized as study nonresponders.

NOTE: Patients who require an increase in corticosteroid dose above 0.5 mg/kg/d (or 40 mg/d of prednisone) or equivalent, for control of SLE activity, or management of a new SLE flare during the study, are to be discontinued from study drug. The prednisone dosage or equivalent may be increased to a dose that is less than or equal to 0.5 mg/kg/d or 40 mg/d, whichever is lower. However, dosing should be tapered to the preflare level or 20 mg/d, whichever is greater, within 4 weeks or less. If tapering is not possible AND a higher dose is needed to treat SLE manifestations, the patient must be discontinued from study drug and advanced to safety follow-up, and be designated a study nonresponder.

6.3 Study Stopping Rules

Takeda clinicians/designee will provide ongoing safety oversight and surveillance throughout the study dosing period and safety follow-up periods. As such, TAK-079 clinicians are to receive and trend all reported SAEs and conduct a review of all safety data periodically throughout the study. Based on outcomes of the Takeda safety reviews and in accordance with predefined criteria, decisions about the dosing regimen are to be made and implemented.

6.3.1 Assessment and Criteria for Terminating Patient Dosing

Before each study dose, principal investigators provide the medical monitor (MM) with a summary of assessment outcomes associated with the dosing criteria, for review and approval. In instances where clinical parameters do not meet dosing criteria, study dosing must be temporarily withheld until parameters meet dosing levels or discontinued, as outlined in Table 6.b. As such, patients should return for re-evaluation of dosing criteria every 3 weeks until completion of Week 12 of the dosing period, at which time the patient begins the safety follow-up period.

In addition, study drug must be permanently discontinued, and patients must advance to the safety follow-up period of the study, if any of the following is experienced:

- An AE or other medical condition in which the principal investigator deems it is not in the best interest of the patient to continue study dosing.
- The patient chooses to withdrawal from study dosing.
- The patient has a confirmed pregnancy.

NOTE: If two or more patients discontinue study drug dosing based on the dose discontinuation criteria in Table 6.b, the Takeda clinician/designee will review available safety data, to determine if adjustments to the treatment plan should be made. In such instances, discontinued patients will need to be unblinded to assess relatedness to the study drug. The unblinding process is outlined in Section 8.1.5.

[redacted]

Table 6.b Summary of Dosing Criteria

Safety Parameter	Dosing Criteria		
	Continue Dosing	**Dose Hold [a]**	**Dose Discontinuation [b]**
Laboratory Investigations			
Neutrophils	ANC ≥1500/mm^3	Total neutrophils ≥Grade 2 [c] ANC <1500/mm^3	
Platelets	Thrombocytopenia ≤Grade 2 Platelets ≥50,000/mm^3	Thrombocytopenia ≥Grade 3 [c] Platelets <50,000/mm^3	
T cells	T cells ≥500 cells/uL NOTE: Dosing may continue in instances of T cells < 500 cells/uL if CD3+ cell count is ≥ 70% of the baseline level	CD3+ cells count <500 cells/uL **and** is < 70% of baseline CD3+ cell count level.	
Hgb	≥8 g/dL	<8 g/dL	
IgG, IgA, IgM levels	>50% LLN	≤50% LLN	
Events of Clinical Interest			
TAK-079–related infusion reaction (to include systemic signs and symptoms related to CRS [d]) **NOTE**: IRR is classified in accordance to the NCI CTCAE criteria, version 4.03. CRS is classified in accordance to the parameters outlined in Appendix B and Appendix C.	≤Grade 1 with symptomatic treatment allowed in accordance with Appendix C. NOTE: Dosing may resume after symptoms have resolved [f].		≥Grade 2 IRR **or** CRS [f] leading to moderate clinical symptoms based on a global assessment of symptoms
Hypersensitivity (allergic reaction or anaphylaxis) [e]	≤Grade 2 In accordance with NCI CTCAE, version 4.03 grading for allergic reactions which respond promptly to symptomatic measures		≥Grade 3 [c] In accordance with NCI CTCAE (version 4.03) grading for allergic reaction **or** any signs or symptoms of an anaphylactic reaction [14]
Systemic infection		Grade 2 [c] Hold dosing until the infection is resolved	≥Grade 3[c] **or** infections requiring hospitalization

Abbreviations: ANC, absolute neutrophil count; CRS, cytokine release syndrome; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; Hgb, hemoglobin; IRR, infusion-related reaction; LLN, lower limit of normal.

[a] Patients whose clinical parameters meet dose-hold criteria, will not receive their next scheduled cohort dose (ie, TAK-079 or matching placebo), and instead return for the next scheduled dose-criteria assessment for reassessment and evaluation of the subsequent dosing.

[b] Patients whose clinical parameters meet dose discontinuation criteria are to be permanently discontinued from study dosing (ie, TAK-079 or matching placebo); patients are to then

advance to the safety follow-up period of the study, completing all associated assessments, while continuing to receive standard background therapy for SLE, in accordance to principal investigator's discretion and local institutional practices.

[c] Laboratory grading, allergic reactions, and infection grading is based on NCI CTCAE v4.03.

[d] A full cytokine panel is to be obtained for any suspected events, at any grade, of CRS; refer to Section 6.5.2 for further information and suggested management of CRS.

[e] See Section 6.5.1 for further information regarding study-related hypersensitivity reactions.

[f] See Appendix B and Appendix C for further details on the grading and clinical signs and symptoms of CRS.

[redacted]

6.3.2 Assessment and Criteria for Terminating Cohort Advancement

A cohort analysis, assessing for safety trends and potential risks associated within and across dosing cohorts will be conducted near the completion of each cohort. The Takeda clinicians/designee will take into consideration all SAEs and AEs of severe intensity medically considered related to study drug in dose escalation decisions. Analysis for each cohort will be initiated at the time the seventh patient within each study cohort completes all follow-up assessments and procedures associated with their second study dose. Decisions regarding cohort advancement will be made once the cohort completes full enrollment, incorporating full assessment of safety parameters of all patients in the cohort.

Based on these findings, and in alignment with protocol-defined dose hold and dose discontinuation criteria, the study may: (1) advance enrollment to the next cohort at the next protocol-defined dose level, (2) advance enrollment in the next cohort at a reduced intermediate dose level, (3) expand enrollment at the current dose level, or (4) enact early termination of the study.

6.4 Precautions and Restrictions

Patients should be closely monitored both before and for at least 4 hours after each dose, with additional assessment and observations as necessary based on the principal investigator's best medical judgment, and as warranted by exhibited clinical signs or symptoms at each study clinic visit. Postdose monitoring should include vital sign assessments as outlined in Section 9.2.5, and additional postdose medications for those with a history of asthma or COPD, as outlined in Section 6.2.2.

6.4.1 Pregnancy and Lactation

TAK-079 has not been administered to women who are pregnant or lactating. Dedicated fertility and embryo-fetal development toxicology studies have not been conducted with TAK-079. However, there were no TAK-079–related changes in organ weights or microscopic findings noted in the male and female reproductive tract of monkeys following administration for up to 13 weeks. Women of child-bearing potential may be enrolled in clinical trials with appropriate precautions to prevent pregnancy (additional details in Section 9.2.9).

TAK-079 should not be administered to women who are pregnant or breastfeeding.

6.4.2 Drug Interactions

Nonclinical drug interaction studies have not been conducted with TAK-079. However, as a fully human IgG1 mAb, the risk of drug-drug interactions is low.

6.4.3 Interference with Serological Testing

Anti-CD38 monoclonal antibodies have been reported to bind to CD38 on red blood cells (RBCs) and results in a positive indirect coombs test, which may persist for up to 6 months. The determination of a patient's ABO and Rh blood type are not impacted, but the RBC binding may

mask detection of antibodies to minor antigens in the patient's serum [14,15]. It is possible TAK-079 may affect the results of these blood tests, this is being evaluated. Until those tests are known, it is recommended that baseline type and serological screening be established before starting TAK-079. Patients should keep these results in case future transfusions are needed. Blood transfusion centers should also be informed of this interference with serological testing as necessary.

6.5 Management of Events of Clinical Interest

6.5.1 Hypersensitivity Reactions: Infusion and Injection Site Reactions

Since infusion reactions and other antibody-mediated hypersensitivity reactions have been reported with other biologic agents, similar AEs may be seen with TAK-079. Infusion reactions are potentially dose-limiting AEs, not uncommonly associated with IV administration of biologic agents, but are less frequently associated with SC injection of these therapies [16-19].

Symptoms of hypersensitivity may range from mild skin rash to more severe reactions, wheezing, hypotension, poor perfusion, respiratory arrest, and rarely death. Nonanaphylactic clinical hypersensitivity typically occurs within the first hour; however, delayed responses have been reported in literature. Symptoms of anaphylaxis, a potentially life-threatening condition, range from swelling, angioedema, bronchospasm, respiratory distress, and shock [20]. Hypersensitivity reactions in the literature often occur within a few hours following drug intake. Based on outcomes from studies with daratumumab, patients with pre-existing COPD or asthma may be at particular risk for such respiratory complications as bronchospasm should an infusion reaction event occur. Therefore, patients whose forced expiratory volume in 1 second (FEV_1) is <50% of predicted normal will be excluded from study participation (see Section 7.2) [21]. Eligible patients with a history of COPD may require additional postdose medications to manage respiratory complications (see Section 6.2.2) [18].

To date, subjects administered TAK-079 have not exhibited anaphylactic symptoms. In the clinical study of healthy subjects (TAK-079-101), an infusion-related reaction (IRR) was defined as a treatment-emergent adverse event (TEAE) occurring within 2 hours of the start of an infusion; there were no IRRs in this study as no allergic or cytokine release reactions were observed within this time period.

In this study:

- Patients with a history of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in the TAK-079 formulation are not eligible for this study and therefore will not be exposed to TAK-079.
- Premedication before each study dose, to prevent infusion reactions, is mandatory for all patients (as described in Section 6.2.1); postdose medication can be administered at the investigator's discretion.

[redacted]

- Patients who are treated with TAK-079 will be carefully monitored in the clinic for 4 hours after dosing, and any AE will be managed in accordance with available guidelines or institutional standards of care [22,23].

NOTE: Additional blood pressure (BP) measure should be assessed at any time the patient complains of symptoms consistent with an infusion reaction. If the patient experiences hypotension (with or without symptoms), intensive blood pressure monitoring according to local practice should be instituted. The patient should not be released from the site until blood pressure has returned to Grade 1 or baseline for at least 1 hour.

6.5.1.1 Management Recommendations for Hypersensitivity Reactions

Patients in clinical trials receiving TAK-079 are to be carefully monitored for signs and symptoms of ISRs, with appropriate medical management of these events. Depending on the severity of the reaction, management may include discontinuation of SC administration of TAK-079 and/or the administration of appropriate medical therapy.

Recommendations for the management of hypersensitivity reactions [22], are as follows:

Grade 1

a) Study Management:

- If the full dose of TAK-079 has not yet been administered, hold dosing until symptoms resolve, at which time the remainder of TAK-079 dose may be administered.

b) Patient Support:

- Monitor closely until resolution of symptoms.

Grade 2

a) Study Management:

- If the full dose of TAK-079 has not yet been administered, hold dosing until symptoms resolve, at which time the remainder of TAK-079 dose may be administered.

b) Patient Support:

- Administer appropriate symptomatic and prophylactic medical care; consider post-injection medications as outlined in Section 6.2.2.
- For allergic reaction, provide symptomatic treatment (e.g. antihistimines, nonsteroidal anti-inflammatory drugs, narcotics, epinephrine) as medically appropriate and consider post-infection medications (as per Section 6.2.2).

[redacted]

Grade 3 or Greater (symptomatic bronchospasm with or without urticaria, angioedema, hypotension).

a) **Study Management**:

- Patients are to discontinue study dosing and advance to the safety follow-up period of the study.

b) **Patient Support**:

- Provide symptomatic treatment, including epinephrine, until symptoms resolve.
- Consider hospitalization as appropriate.

Local injection site abnormalities have not been observed in monkey and rat nonclinical studies after SC and/or IV administration of TAK-079. In the clinical study of healthy subjects (TAK-079-101), mild injection site AEs were reported; most were Grade 1 and included primarily erythema or tenderness. All injection reactions resolved within a few days.

6.5.2 Cytokine Release Syndrome

CRS represents an important infusion reaction often associated with the use of monoclonal antibodies used in anti-inflammatory and antitumor therapies. Onset of CRS may occur early in therapy, often after the first infusion of the drug due to a high level of activation of the immune system and engagement and proliferation of T cells that can result in increased cytokine release.

Nonclinical studies have shown that TAK-079 has no agonist activity, suggesting that TAK-079 is unlikely to cause cytokine release due to cell activation. There were no TAK-079–related increases in cytokines at 0.1 mg/kg. At ≥0.3 mg/kg, dose-related increases (up to 29.5-fold for any individual monkey) in tumor necrosis factor alpha (TNF-α) were observed 30 minutes after the first dose of TAK-079. These increases were considered small compared with elevations observed during a cytokine storm event, were not accompanied by changes in other cytokines, and did not translate into clinical manifestation of an IRR. Increases in serum TNF-α may be related to TAK-079–mediated lyses of CD38+ lymphocytes.

In the FIH study, conducted in healthy subjects, rarely observed symptoms consistent with mild CRS were reported, particularly at higher doses; dose adjustment or interruption was not required.

The CRS hallmark is fever. CRS also presents with rash, urticaria, headache, chills, fatigue, nausea, and/or vomiting. [16,17]. Severe CRS is characterized by severe dyspnea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. The acute respiratory failure may be accompanied by such events as pulmonary interstitial infiltration or edema visible on a chest x-ray. The syndrome frequently manifests within 1 or 2 hours of initiating the first infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumor infiltration may be at greater risk of poor outcome and should be treated with increased caution [16]. On the basis of outcomes from studies of the anti-CD38 mAb daratumumab, patients with pre-existing COPD or asthma may be at particular risk for respiratory complications, such as bronchospasm, should an infusion reaction or CRS event occur [21].

[redacted]

Therefore, if the patient's FEV_1 is <50% of predicted normal, they will be excluded from study participation (see Section 7.2). Eligible patients with a history of COPD may require additional postinfusion medications to manage respiratory complications [18](see Section 6.2.2)

6.5.2.1 Management Recommendations for CRS

Premedication before each study dose, to prevent infusion reaction, is mandatory for all patients as described in Section 6.2.1. Poststudy dosing medication, to be administered at the investigator's discretion, is described in Section 6.2.2.

Immediate clinical assessment and management of symptoms is key to symptom management. In the anti-CD38 literature, IRRs are almost always reported with the first dose [18,24], therefore especially for the first dose, patients will be monitored in the clinic for at least 4 hours after dosing. Medical symptomatic treatment according to guidelines or institutional standard of care is recommended [17]. Before discharge from the clinic, all patients will receive information about possible signs and symptoms of anaphylactic reactions and CRS to monitor at home. Further, patients should receive information about what to do if emergency care is needed (see Appendix B and Appendix C tables for further details on clinical signs and symptoms associated with CRS and the CRS grading system [17]).

If a patient is exhibiting signs or symptoms possibly assessed as a CRS by the investigator, a blood draw should be performed for central evaluation that could include, but not limited to, immune markers and cytokine markers. Additional guidance for study management and patient support for CRS, by grade is as follows:

Grade 1 (defined as fever, constitutional symptoms)

a) **Study Management:** Hold study dosing until symptoms resolve; resume dose of TAK-079 at same dose level after symptom resolution.

b) **Patient Support:** Provide vigilant supportive symptomatic treatment, which may include antipyretics, analgesics, and antihistamines (see Appendix C).

Grade 2 (defined as hypotension, hypoxia, organ toxicity)

a) **Study Management:** Discontinue study dosing and advance to safety follow-up period.

b) **Patient Support:** Provide vigilant supportive symptomatic treatment, which may include antipyretics, analgesics, antihistamines, with or without tocilizumab.

Grade 3 (defined as hypotension, hypoxia, and severe organ toxicity)

a) **Study Management:** Discontinue study dosing and advance to safety follow-up period.

b) **Patient Support:** Provide vigilant supportive care, including but not limited to tocilizumab, antipyretics, analgesics, and antihistamines, as medically indicated [17].

6.5.3 Hematologic Effects

Reductions in platelets, lymphocytes, and red blood cells (RBCs) occurred in nonclinical studies in some animals administered doses of TAK-079 higher than the no-observed-adverse-effect level

[redacted]

(NOAEL) of 0.3 mg/kg. In the FIH study, no decreases were seen in RBCs or platelets, despite observations of reductions in these cell counts in monkey toxicology studies after repeated dosing at higher dose levels (≥ 1 mg/kg).

Patients will be monitored closely, including testing of hematology parameters throughout this clinical study as described in Section 9.2.8 and Table 9.a and outlined in Table 3.a and Table 3.b. In instances where clinical parameters do not meet dosing criteria, study dosing must be temporarily or permanently withheld as outlined in Table 6.b. Medical interventions may be administered according to institutional guidelines.

6.5.4 Infections

In a Good Laboratory Practice (GLP)-compliant 13-week toxicology study, bacterial and/or viral infection, secondary to immune suppression, was observed in cynomolgus monkeys at IV doses of 3, 30, and 80 mg/kg administered once every 2 weeks. The NOAEL dose of 0.3 mg/kg, administered IV once every week, was not associated with infections. In the FIH study, mild infections, specifically nasopharyngitis, was reported.

Patients will be monitored for any signs and symptoms of infections throughout this clinical study (see Table 3.a, Table 3.b, and Table 6.b). In instances where clinical parameters do not meet dosing criteria, study dosing must be temporarily or permanently withheld as outlined in Table 6.b. Management of infections according to standard medical care is recommended.

6.5.5 Antidrug Antibody Interactions

Antidrug antibody (ADA) responses were detected in most monkeys in the single-dose PK studies and the 4-week (non-GLP) and 13-week (GLP) toxicology studies. Stronger positive ADA responses were generally associated with lower serum concentrations of TAK-079, and this was especially notable in the 13-week repeat-dose toxicity studies and at lower doses. In the single-dose healthy subject study (TAK-079-101), 5 of 54 TAK-079–treated subjects were positive for ADA (3 subjects with transient ADA and 2 subjects with persistent ADA). Of these, one subject was treated in the 0.06 mg IV cohort and the remaining 4 subjects were treated with 0.03 mg/kg (2 subjects), 0.1 mg/kg (1 subject), or 0.6 mg/kg (1 subject) SC TAK-079. Immunogenicity was not associated with clinically significant AEs, even in the 2 subjects with persistent immunogenicity.

6.5.6 Overdose

As outlined in Section 10.2, an overdose is defined as a known deliberate or accidental administration of investigational drug, to or by the study subject, at a dose above that which was assigned to that individual subject (ie, patient) according to the study protocol.

To date, there is no experience with overdose. If an overdose does occur, as defined in Section 10.2, close monitoring and supportive treatment, as medically required, are recommended. Events of overdose, with or without an associated adverse event, should be promptly reported to the study MM and will be entered into the electronic case report forms (eCRFs) as an AE.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

The study population is limited to patients diagnosed with SLE who meet all eligibility criteria outlined in Sections 7.1 and 7.2.

7.1 Inclusion Criteria

Patients eligible for enrollment in the study must meet the following criteria:

1. The patient understands and agrees to study participation by providing a signed and dated written informed consent form (ICF) and any required privacy authorization before the initiation of any study procedures (as applicable, the patient's legally acceptable representative may provide written ICF in accordance to local and regional regulatory requirements) **and**, in the opinion of the investigator, is capable of complying with protocol requirements.
2. The patient is aged 18 to 75 years, at the time of signing the study ICF.
3. The patient been diagnosed with SLE as defined by either the 2012 Systemic Lupus International Collaborating Clinics or the American College of Rheumatology diagnostic criteria.
4. The patient has a SLEDAI-2K score ≥6.
5. The patient is positive for anti-dsDNA antibodies and/or anti-ENA antibodies.
6. The patient is receiving current concomitant medication that is consistent with medication restrictions and limitations outlined in Table 7.a and Table 7.b and, in the best medical judgment of the principal investigator, the patient is considered likely to be able to maintain dosages consistent with protocol limitations throughout the study dosing period, unless precluded by toxicity or the need for protocol-defined rescue therapy.
7. The patient meets and/or agrees to the following birth control requirements:

   a) Men:

   - Sterile, **or** if nonsterile, agrees to (1) remain abstinent **or** (2) use an appropriate method of contraception, including a condom with spermicide, from study drug administration on the first day of the first dose until 90 days or 5 half-lives of study drug, whichever is longer, after the last dose of study drug administration (see Appendix A). No restrictions are required for a vasectomized male patient provided the patient is at least 1 year postbilateral vasectomy procedure before study drug administration on first day of the first dose. A male patient whose vasectomy procedure was performed less than 4 months before study drug administration on the first day of the first dose must follow the same restrictions as a nonvasectomized man. Appropriate documentation of surgical procedure should be provided.
   - Agrees to not donate sperm from study drug administration on the first day of the first dose, until 90 days or 5 half-lives of study drug, whichever is longer, after the last dose of study drug administration (see Appendix A)

b) Women:

- Women of child-bearing potential:
  - Female patients who are of child-bearing potential must agree to remain abstinent or use double barrier contraception, consisting of protocol-defined, medically acceptable methods (eg, implants, injectables, oral contraceptives, intrauterine devices). Contraception must be used from the time of signing the ICF through 90 days or 5 half-lives of study drug, whichever is longer, after the last dose of study drug administration (see Appendix A).
- Women with no child-bearing potential will be defined as meeting at least one of the following criteria:
  - Postmenopausal (defined as 12 months of spontaneous amenorrhea in women with serum follicle-stimulating hormone [FSH] levels >40 mIU/mL). Appropriate documentation of FSH levels is required.
  - Surgically sterile by hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.
  - Had a tubal ligation with appropriate documentation of surgical procedure.
  - Has a congenital condition resulting in no uterus.

7.2 Exclusion Criteria

Patients meeting any of the following criteria are not eligible for study enrollment:

1. The patient has participated in another investigational study within 4 weeks or 5 half-lives of study drug, whichever is the longer, before the screening visit (the 4-week window is derived from the date of the last study procedure, and/or AE related to the study procedure in the previous study, to the screening visit of the current study).
2. The patient has a positive pregnancy test.
3. The patient is currently lactating/nursing or plans to nurse during the study (to include during the 12-week safety follow-up period of the study).
4. The patient has a history of chronic alcohol or drug abuse ≤12 months before the screening visit.
5. The patient has a history of a malignant disease (except for successfully treated basal cell carcinoma, squamous cell carcinoma, or cervical carcinoma in situ) ≤5 years before the screening visit.
6. Patients has COPD or asthma with a FEV_1 <50% of predicted normal.

   Note: FEV_1 testing is required for patients suspected of having COPD or asthma.
7. The patient has had a major surgery and/or donated or lost ≥1 unit of blood (approximately 500 mL) in ≤4 weeks before the screening visit.

[redacted]

8. The patient had an opportunistic infection ≤12 weeks before initial study dosing **or** is currently undergoing treatment for a chronic opportunistic infection, such as tuberculosis (TB), pneumocystis pneumonia, cytomegalovirus, herpes simplex virus, herpes zoster, or atypical mycobacteria.
9. The patient currently has, or recently had, an acute or chronic infection requiring one or more of the following interventions:
   - Hospitalization ≤30 days before the screening visit.
   - Administered parenteral (IV or intramuscular) antibacterial, antiviral, antifungal, or antiparasitic agents ≤30 days before the screening visit.
10. The patient has a positive T-cell interferon-γ release assay (TIGRA) (resulted through Quanti FERON TB Gold test or T-Spot/Elispot) at the screening visit (to be analyzed by local laboratory), noting the following:
    a) A purified protein derivative (PPD) skin test may be used as a replacement, if TIGRA testing is not available.
    b) Patients with an indeterminate TIGRA result must meet the following criteria:
       - Negative PPD skin test (defined as <5 mm induration).
       - Low risk of acquiring TB (eg, avoids close contact with TB positive individual[s]), and/or chest x-ray ≤6 months before the screening visit that is consistent with no evidence of latent or active TB).
11. The patient has drug-induced SLE or any other rheumatologic or autoimmune disease (excluding secondary Sjögren syndrome or mixed connective tissue disease).
12. The patient required therapeutic intervention ≤60 days before initial study dosing for active neuropsychiatric SLE, as demonstrated by, but not limited to, the following:
    a) New or worsening impaired level of consciousness.
    b) Psychosis.
    c) Delirium or confusional state.
    d) Grand mal seizure (including status epilepticus).
    e) Aseptic meningitis.
    f) Ascending or transverse myelitis.
    g) Chorea, cerebellar ataxia, or demyelinating syndromes.
13. The patient has an active glomerulonephritis (ie, a concurrent acute renal flare or documented acute renal flare in the previous 3 months that required lupus nephritis induction therapy) that meets at least one of the following criteria:
    a) Proteinuria (protein >3000 mg/24 hr).

b) Urine protein-to-creatinine ratio of >300 mg/mmol.

c) An estimated glomerular filtration rate (GFR) <30 mL/min/1.73m2 (as calculated by the Modification of Diet in Renal Disease [MDRD] formula [see Section 9.2.8.2]).

14. The patient has at least one of the following laboratory test values:

a) Alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal (ULN).

b) Total bilirubin >1.5 times ULN (Note: Patients with a confirmed diagnosis of Gilbert syndrome that is documented in the patient's medical record are not excluded based on this criterion).

c) Platelets <75,000/mm3.

d) Neutrophils <1500/mm3.

e) Hemoglobin <8 g/dL.

f) IgG less than lower limit of normal (LLN).

15. The patient has a positive test result for hepatitis B surface antigen or hepatitis C antibody, or HIV antibody/antigen, at screening.

16. The patient has a concurrent medical condition that, in the opinion of the investigator, could confound interpretation of results or affect the patient's ability to fully participate in the study.

17. The patient has a history of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in the TAK-079 formulation.

[redacted]

7.3 Excluded and Dose-Limited Medications

Excluded and dose-limited concomitant medications are provided in Table 7.a and Table 7.b.

Table 7.a Excluded Medications

Category or Agent	Exclusion Criteria (Exclusion Criteria Must Be Upheld Throughout Study Participation, in Addition to the Timepoints Indicated Below) [a]
Belimumab, abatacept, or tocilizumab	≤3 months before the screening visit
Cyclophosphamide	Restricted from ≤12 weeks before initiation of on-study dosing
Immunosuppressant regimen	To include calcineurin-inhibitors (eg, systemic cyclosporine and tacrolimus), leflunomide, to be excluded throughout study participation. Must be discontinued at least 3 months before screening visit.
Live vaccines	**All vaccines**: Maintain restrictions as follows and throughout study participation, until 12 weeks following the last dose of study dosing **Live vaccines**: 90 days before initial dosing on study Day 1 **Inactivated vaccines**: 30 days before initial dosing on study Day 1
Rituximab or other cell depleting biological agents	≤6 months before the screening visit
Alemtuzumab	No previous or concurrent dosing while on study

Abbreviation: AE, adverse event.
[a] Exceptions to excluded medications may be allowed for treatment of adverse events, after discussion and agreement between the sponsor and principal investigator.

Table 7.b Dose-Limited Concomitant Medications

Medications	Dosing Criteria (Criteria Are to Be Maintained From Screening to Completion of Study Dosing Phase)
Immunosuppressants [a]	• Generally, agents must be dosed for at least 12 weeks before screening, with stable dosing for at least 8 weeks before the first dose of TAK-079 or matching placebo. • Regimens consisting of < 2 agents while on study (not applicable to topical agents; see dose restrictions outlined in Table 7.a).
• Azathioprine	1 to 2 mg/kg/d
• Mycophenolate mofetil	1 to 2 g/d
• Methotrexate	7.5 to 25 mg/wk.
Corticosteroid [a]	Stable dosing equivalent to ≤20 mg/day of oral prednisone maintained for ≥28 days prior to the first dose of TAK-079 or matching placebo.
Antimalarials	Stable dosing maintained for ≥28 days and is likely to maintain the current dose throughout the dosing period, as determined by the principal investigator.

[a] Dose limitations not applicable to topical agents.

7.4 Criteria for Discontinuation or Withdrawal of a Patient

Laboratory findings in which TAK-079 dosing should be temporarily held, or permanently discontinued, are outlined in Table 6.b. Patients exhibiting these or other clinical findings for which the principal investigator considers that continued TAK-079 dosing may place the patient at undue risk, should be immediately held from further TAK-079 dosing and continue to be followed for safety. In such instances, TAK-079 may be resumed under consultation with the study MM and in accordance to protocol-defined dosing criteria.

Treatment with study drug may be discontinued permanently for any of the following reasons:

- AE and/or SAE.
- Withdrawal by subject.
- Protocol violation.
- Study terminated by sponsor.
- Lost to follow-up.
- Other.

Once study drug has been discontinued, all study procedures outlined for follow up will be completed as specified in the schedule of events (SOE) (see Table 3.b). Patients withdrawing from study treatment will be asked if they will permit follow-up assessment or not. If the patient completely withdraws consent, no further follow-up assessments can be completed. The primary reason for study drug discontinuation will be recorded on the eCRF.

7.5 Procedures for Discontinuation or Withdrawal of a Patient

Patients withdrawing from study dosing should remain on study, completing all assessments and procedures associated with the 12-week safety follow-up period. If the principal investigator or patient determines it's in the patient's best interest to withdraw from the study, procedures and assessments associated with a final study visit, as outlined in Table 3.b, should be completed.

[redacted]

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

Refer to the pharmacy manual for detailed instructions regarding the storage and preparation of TAK-079 study supply.

8.1 Clinical Study Drug

TAK-079 is a recombinant human IgG1 mAb supplied as 100 mg TAK-079 in 1 mL (100 mg/mL) solution, to be administered as a single SC injection every 21 days (ie, 3 weeks) over the course of 12 weeks for 4 total doses as part of each study cohort.

TAK-079 drug product and matching placebo are supplied in aseptically filled, single-use, clear, type I, borosilicate glass vials with fluoropolymer-coated butyl rubber stoppers and aluminum crimp seals with flip-off caps.

8.1.1 Clinical Study Drug Labeling

Supplies of TAK-079 and matching placebo are labeled according to the current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practices (GCP) and Good Manufacturing Practices (GMP) and include any locally required statements.

8.1.2 Clinical Study Drug Inventory, and Storage

8.1.2.1 Receipt of Study Drug

The investigator is responsible for ensuring that deliveries of TAK-079 and other study materials from the sponsor are correctly received, recorded, and handled, and stored safely and properly in accordance with the Code of Federal Regulations (CFR) or national and local regulations, and used in accordance with this protocol.

During shipping, vials are to be protected from light and maintained within temperatures provided in the Pharmacy Manual. Each TAK-079 shipment includes a packing slip listing the contents of the shipment, and any applicable forms. The investigator or designee must confirm that appropriate temperature conditions have been maintained for all TAK-079 and matching placebo received and that any discrepancies are reported and resolved before use of TAK-079 or matching placebo.

Upon receipt of study medication, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, the medication is received within the labeled storage conditions, and is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by signing bottom half of the packing list and faxing per instructions provided on the form. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

[redacted]

The sponsor must be notified immediately of any temperature excursions, shipping and handling or storage discrepancies.

8.1.2.2 Storage of Study Drug

All clinical trial material must be kept in an appropriate, limited-access, secure location until used or returned to the sponsor or designee.

TAK-079 and matching placebo must be stored according to the manufacturer's stipulation, as specified on the label, and remain in the original container until dispensed. As such, TAK-079 drug product and matching placebo must be stored under conditions outlined in the pharmacy manual. A daily temperature log of the drug storage area must be maintained every day.

8.1.2.3 Study Drug Dispensing and Inventory

The principal investigator or designee must ensure that the study medication (ie, TAK-079 and matching placebo) is used in accordance with the approved protocol and is dispensed only to patients enrolled in the study. To document appropriate use of study medication (TAK-079), the investigator must maintain records of all study medication (1) delivered to the site, (2) maintained in site inventory, (3) dispensed/used by each patient, and (4) returned to the sponsor or designee.

Detailed dosage preparation instructions are provided in the directions for use section of the pharmacy manual. Complete receipt, inventory, accountability, reconciliation, and destruction records must be maintained for all used and unused study drug vials. Detailed instructions and the associated forms for these activities are in the pharmacy manual.

Drug supplies are to be counted and reconciled at the site before being returned to Takeda or designee or being destroyed.

The investigator will be notified of any expiry date or retest date extension of clinical study material during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired clinical study material for return to the sponsor or its designee.

Further guidance and information are provided in the pharmacy manual.

8.1.3 Clinical Study Drug Blinding

The assignment of study patients to one of two study arms, within each cohort, is maintained through a blinded randomization schedule, available, in instances of medical emergencies, to the principal investigator. Otherwise site staff, will remain blinded through the conduct of the study. Details on maintaining the study blind, and unblinding procedures are outlined in Section 8.1.5.

8.1.4 Randomization Code Creation and Storage

The randomization and medication schedule will be generated and maintained by an interactive voice/web response system (IXRS). All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.1.5 Clinical Trial Blind Maintenance/Unblinding Procedure

To maintain the integrity of the study, all study personnel, including the investigators, site personnel, the contract research organization medical monitor, study clinicians, and the sponsor, will be blinded to the treatment assignments during the treatment period. Treatment assignments will be obtained through the IXRS according to the procedures outlined in the study manual. Information regarding the treatment assignments will be kept securely at Takeda or designee, per its standard operating procedures.

- Records of the patient number, the date the study drug was dispensed, and the treatment assignment will be maintained by the study site.
- Emergency unblinding, if necessary, will be conducted via the IXRS. The following provides key factors to be considered regarding breaking the study blind:
  - If the treatment assignment must be revealed for the safety of the patient, to treat an AE, or to inform decisions for subsequent therapy, the investigator will contact the Takeda project clinician or designee (in accordance to contact information and procedures outlined in the study manual).
  - A decision to break the blind must be reached by the Takeda project clinician or designee and the investigator. The investigator, or designee, may break the blind through the IXRS independent of the Takeda project clinician or designee only if the investigator considers the situation to be an emergency and requires specific knowledge of the blinded study treatment to properly treat the AE/safety issue.
  - If the treatment of the AE/safety issue is anticipated to be the same regardless of study drug assignment, the blind should not be broken.
  - The event requiring breaking the blind must be documented in the eCRF, including the date the blind was broken.
  - After breaking the blind, the patient will be discontinued from further study drug administration in this study.

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

The investigator, institution, or head of the medical institution (where applicable) is responsible for TAK-079 accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

The principal investigator must maintain 100% accountability for all study medication (TAK-079 and matching placebo) received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date/retest date is provided to the investigator.
- Frequently verifying that actual inventory matches documented inventory.

- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

Empty, partially used, and unused TAK-079 are to be disposed of, retained, or returned to the sponsor or designee, as detailed in the pharmacy manual.

The investigator must maintain a current inventory (drug accountability log) of all sponsor-supplied study medication delivered to the site, the ongoing inventory at the site, and the patients' usage records. This log must accurately reflect the drug accountability of the study medication at all times. The following information, at minimum, will be recorded: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied medication, expiry/retest date, and amount dispensed, including the initials of the person dispensing and receiving the study medication. The log should include all required information as a separate entry for each patient to whom study medication is dispensed.

Further guidance and information are provided in the pharmacy manual.

[redacted]

9.0 STUDY PROCEDURES

Assessments and procedures should be performed on schedule, within the timeframe and window allowance in Table 3.a, Table 3.b, and Table 3.c. Further time allowance for most study procedures and assessments, except for PK draw times, are acceptable in extenuating circumstances (ie, holidays, vacations, and other administrative reasons) on approval by the MM or delegate; however, these time extensions **should not deviate more than 7 days** from the scheduled procedural time.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

9.1.2 Assignment of Randomization Numbers

At the time of randomization, after completion of all screening assessments and procedures and confirmation of eligibility, patients are assigned a 4-digit randomization sequence number. Randomization numbers are generated by the sponsor or designee. Randomized schedules are available to the unblinded study statistician.

9.1.3 Study Drug Assignment

Patients are randomly assigned in a 3:1 ratio to one of the two study arms as outlined in Figure 2.a at the completion of study screening and before dosing on study Day 1, in accordance to the randomization schedule as generated by the sponsor or designee. Randomization information is stored in a secured area, accessible only by authorized personnel, to include the unblinded study statistician, and necessary site staff in instances of emergency un-blinding (as outlined in Section 8.1.5).

9.2 Clinical Procedures and Assessments

9.2.1 Inclusion and Exclusion

Eligibility criteria and associated screening study assessments must be confirmed during the screening period, after a patient has signed the ICF, and before receiving study drug.

Principle investigators must provide the study MM a summary of key eligibility criteria for review so eligibility can be verified before enrolling each patient.

9.2.2 Medical History and Demography

A complete medical history is compiled for each patient during the screening period (ie, ≤28 days before study Day 1) and includes assessment and documentation of prior medical history, comorbidities and concomitant treatments. This includes assessments of current SLE signs,

symptoms, morbidities, as evaluated and scored by disease activity tools and previous and current SLE therapies (see Section 9.3.4).

Demographics will include the date of birth, race, ethnicity, and sex of the patient during screening.

9.2.3 Concomitant Medications and Procedures

Concomitant medications, blood products, and procedures will be recorded from the first dose of TAK-079 or matching placebo, through the end of the safety follow-up period (ie, end of safety follow-up visit in Week 24 or, when applicable, end of long-term safety follow-up visit in Week 36). Trade name and international nonproprietary name (if available), indication, and start and end dates of the administered medication are to be recorded.

9.2.3.1 Background SLE Therapy

Eligible patients will have received SLE background therapy for ≥12 weeks (with stable dosing ≥8 weeks), before screening. Once enrolled into the study, patients will remain on background therapy, as managed by their principal investigator, in accordance with local institutional practices, and in alignment with the study protocol, throughout study participation. Background SLE therapy ongoing at the time of screening will be recorded in the eCRF, as will any changes to this therapy.

9.2.4 Physical Examination

A symptom-directed physical examination with assessments for SLE signs and symptoms will be completed in accordance with standard of care at the times specified in the SOE (see Table 3.a and Table 3.b).

9.2.5 Vital Signs

Vital signs include body temperature, pulse, respiratory rate (RR), and BP. These are to be evaluated at visits specified in the SOE Table 3.a and Table 3.b and recorded both on the source documentation and in the eCRF. In addition, vital signs should also be assessed at any time it is clinically warranted, either in the clinic or home visit setting (ie, patient exhibits signs or symptoms of injection reaction, CRS, or hypersensitivity reactions). As indicated in these tables, vital signs are to be assessed before each study dose and 4 hours after dosing, as part of postdose assessments.

Pulse and BP should be assessed in similar positions at each study assessment.

Clinically significant values, as determined by the principal investigator, must be documented as an AE and closely monitored for follow-up.

NOTE: Additional vital signs to include BP measures should be assessed at any time the patient reports symptoms consistent with an infusion reaction. If the patient experiences hypotension (with or without symptoms), intensive BP monitoring according to local practice should be

instituted. The patient should not be released from the study site until BP values have returned to Grade 1 or baseline for at least 1 hour.

9.2.6 12-Lead Electrocardiogram

Each ECG recording should be performed according to standard institutional practice.

All study ECGs, to include triplicate ECGs, are interpreted by a qualified person (ie, read locally). Further, triplicate 12-lead ECGs are recorded electronically and are to be submitted to a central vendor for storage and for future analysis.

ECGs with clinically significant findings, as judged by the investigator, are to be considered a TEAE; (except for ECGs obtained as part of the screening) visit which would be considered part of medical history). Clinically significant findings are to be recorded on the source documentation and in the eCRF, and undergo continued monitoring as described in Section 10.2.5

A single 12-lead ECG is to be collected at the screening visit (for assessment of eligibility) and at the end of safety follow-up visit.

Triplicate 12-lead ECGs, obtained before each study dose, are to be collected just before PK sampling, during timeframes outlined in Table 3.a and Table 3.b. Triplicate ECGs will be stored centrally for future analysis.

When the timing of the triplicate and single (safety) ECGs coincide, the site can use the triplicate ECG collection for the safety evaluation.

9.2.7 AE Monitoring

Monitoring of TEAEs, serious and nonserious, are to be conducted throughout the study as specified in the SOE (see Table 3.a and Table 3.b). Refer to Section 10.0 for details regarding definitions, documentation, and reporting of TEAEs and SAEs.

Dosing criteria assessment will be completed as per Table 6.b to ensure patients meet parameters before study dosing.

9.2.8 Laboratory Procedures and Assessments

Unless otherwise stated in the protocol, all laboratory samples, with exception to Coombs tests, are to be sent to the study central laboratory for analysis, under the conditions for handling and shipping as outlined in the study laboratory manual. Coombs test will be done locally.

9.2.8.1 Clinical Laboratory Tests

Clinical laboratory evaluations are obtained, handled, stored, and shipped to the designated central laboratory, in accordance to the laboratory manual. Clinical chemistry and hematologic assays are outlined Table 9.a and urinalysis assays are outlined in Table 9.b. Timings of these assessments should be in accordance to the study SOE (see Table 3.a and Table 3.b).

Table 9.a Clinical Chemistry and Hematology Assessments

Hematology	Serum Chemistry	
ANC	Albumin	CRP
Hematocrit	ALP	Glucose (nonfasting)
Hemoglobin	ALT	LDH
Platelet count	AST	Potassium
WBC count	Bilirubin (total)	Sodium
WBC with differential	BUN	Total protein
Coagulation panel	Calcium	Urate (uric acid)
Coombs test (both direct and indirect)	Chloride	Glomerular filtration rate
	CO2 (bicarbonate)	
	Creatinine	

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cell.

9.2.8.2 Glomerular Filtration Rate

The GFR should be calculated using the MDRD formula, as follows:

$$GFR = 175 \times (serum\ creatinine)^{-1.154} \times (age)^{-0.023}$$

- For female patients, multiply sum by 0.742.
- For African American patients, multiply sum by 1.212.

9.2.8.3 Urinalysis

A full urinalysis [redacted] will be conducted by the study central laboratory, as defined in Table 9.b, and are to be performed as part of the predosing assessment 1 week before each dosing day, and on each follow-up safety visit (see Table 3.a and Table 3.b) Subsequently, on each dosing day, before dosing, and on each safety follow-up visit, urine should be assessed for the presence of protein and nitrates as analyzed by the local laboratory (ie, dipstick analysis).

Any abnormal findings from the local laboratory urine [redacted] assessments should be followed by a confirming evaluation by the study central laboratory. The central laboratory will perform urine microscopy if the urinalysis is abnormal. Microscopy consists of RBC/high-power field, white blood cells (WBC)/high-power field, and casts.

Table 9.b Clinical Urinalysis Assessments

Urinalysis	
Bilirubin	pH
Glucose	Protein [redacted] [a]
Ketones	Specific gravity
Leukocytes	Turbidity and color
Nitrite [a]	Urobilinogen
Occult blood	

[a] Protein and nitrates are to be assessed as part of the full urinalysis, analyzed by the central laboratory 1 week before each dosing day. In addition, before dosing on study dosing days, protein and nitrates should be assessed by local laboratory (ie, dipstick). Abnormal findings by local laboratory assessment must be confirmed by full urinalysis by central laboratory. Further details on assessment timings are provided in Table 3.a and Table 3.b.

9.2.9 Pregnancy Test

All study pregnancy testing may be conducted at a designated local laboratory as determined and confirmed by the sponsor, with appropriate laboratory documentation provided in advance of study testing.

9.2.9.1 Definition of Women of Child-bearing Potential

A woman of child-bearing potential is a sexually mature woman who:

- Has not undergone a hysterectomy or bilateral oophorectomy; or,
- Has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out child-bearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

9.2.9.2 Timings of Pregnancy Testing

Women of child-bearing potential must have pregnancy testing completed in accordance to the timings outlined as follows:

- *Before Initial Study Dosing*:
  - Screening period: a negative **serum** pregnancy tests (human chorionic gonadotropin [hCG] <5 mIU/mL).
  - Baseline: (within 24 hours before the start of study drug) a negative urine pregnancy test with a sensitivity of at least 50 mIU/mL. If the urine test is indeterminate, a serum pregnancy test is mandatory.
- *During Study Enrollment*:
  - On each dosing day, before dosing; (**urine** pregnancy test).
  - End of dosing period, as outlined in Table 3.a (**serum** pregnancy test).
  - During safety follow-up period, as outlined in Table 3.b (**serum** pregnancy test).

[redacted]

- If a menstrual period is delayed (**serum** pregnancy test).
- Additional pregnancy tests to be conducted as requested by the IRB and/or as required by local regulations.

9.3 [redacted] Pharmacokinetic, and Pharmacodynamic Samples

Blood samples are collected by venipuncture or indwelling catheter at the time points detailed in the SOE (Table 3.a and Table 3.b) for the measurement of serum concentrations of TAK-079 [redacted] Samples will be tested at a central laboratory.

9.3.1 Pharmacokinetic Measurements

Serum samples for the measurement of concentrations of TAK-079 are collected at multiple time points as specified in the SOE (see Table 3.a).

The timing of samples may be modified during the study based on emerging PK data if a change in the sampling scheme is considered necessary to better characterize the PK profile of TAK-079. Additional PK samples may be requested if deemed necessary by the MM for specific events of clinical interest or adverse events.

Details regarding the preparation, handling, and shipping of the PK samples are provided in the study manual.

9.3.2 Immunogenicity Samples and assessments

Serum samples for the measurement of anti–TAK-079 antibody (antidrug antibody and ADA are exchangeable terminologies in this protocol) are collected at multiple time points as specified in the SOE (see Table 3.a).

The samples must be taken before each dosing. Details regarding the preparation, handling, and shipping of the immunogencity samples are provided in the study manual. Positive ADA screening samples will be further tested for true positivity and titer by the study central laboratory.

9.3.3 [redacted]

[redacted]

9.3.3.1 Immunogenicity Assessments

The immunogenicity samples will be screened for the potential ADA positive, which will be further verified for true positivity and titer. [redacted]

[redacted]

9.3.4 [redacted]

[redacted]

9.3.4.1 [redacted]

[redacted]

9.3.4.2 [redacted]

[redacted]

9.3.4.3 [redacted]

[redacted]

9.4 End-of-Study Assessments

End-of-study clinical parameters, as outlined in Table 9.c, are assessed on Week 24 (end of safety follow-up period). If clinical presentation and parameters do not meet the end-of-study criteria, and are deemed by the principal investigator as study-related, the patient is required to continue on-study, completing a 12-week long-term safety follow-up period, during which time study-related parameters not meeting end-of-study criteria will continue to be assessed.

[redacted]

Table 9.c End-of-Study Clinical Parameters

Safety Parameter Laboratory Investigations	End-of-Study Criteria	Continuation to Long-Term Follow-up
B cells	≥LLN or study baseline levels	≤LLN or study baseline levels that is directly related to dosing of investigational product.
Neutrophils		
Platelets		
T cells		
Hgb		
IgG, IgA, and IgM levels		
Events of clinical interest		
TAK-079–related infusion reaction (systemic signs and symptoms) to include CRS	≤Grade 1 [a]	≥Grade 2 reaction [a] CRS leading to moderate clinical symptoms based on a global assessment of symptoms, as classified by the CTCAE version 4.03 (symptoms to include but not be limited to headache, fever, chills/rigors, nausea, vomiting, diarrhea, arthralgia, myalgia, and hypotension)
Systemic infection		≥Grade 2 Dosing is to be held until the infection is resolved

Abbreviations: CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events (CTCAE); LLN, lower limit of normal.
[a] Grading based on Lee, 2014 [17].

10.0 ADVERSE EVENTS

10.1 Pretreatment Events

A pretreatment event (PTE) is defined as any untoward medical occurrence in a clinical investigation subject who has signed ICF form to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.2 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed ICF to participate in a study; it does not necessarily have to have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a preexisting condition (intermittent events for pre-existing conditions or underlying disease should not be considered PTEs or AEs).
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters maybe considered AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

[redacted]

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of ICF) is considered a concurrent medical history condition and should NOT be recorded as a PTE or AE. A baseline evaluation (eg, laboratory test, ECG, radiograph) should NOT be recorded as a PTE unless related to a study procedure. However, if the subject experiences a worsening or complication of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an PTE/AE if the episodes become more frequent, serious, or severe in nature, that is, investigators should ensure that the AE term recorded captures the change from baseline in the condition (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, RA), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent than that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of a PTE after the first administration of study medication, or a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the subject experiences a change in the severity of an AE that is not associated with a change in study medication, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled before signing of ICF are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

[redacted]

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.
- All cases of overdose (with or without associated AEs) are to be documented on an overdose page of the (e)CRF to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.
- SAEs of overdose should be reported according to the procedure outlined in Section 10.2.6.
- In the event of drug overdose, the subject should be treated symptomatically.
- If an overdose does occur, close monitoring and supportive treatment as medically required are recommended.

10.2.1 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent the preceding items 1 through 5.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
    - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

[redacted]

Table 10.a General List of Takeda Medically Significant AEs

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
	Acute liver failure
Torsade de pointes/ventricular fibrillation / ventricular tachycardia	Anaphylactic shock
	Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizures	Pulmonary fibrosis
Agranulocytosis	Confirmed or suspected endotoxin shock
Aplastic anemia	Confirmed or suspected transmission of infectious agent by a medicinal product
Toxic epidermal necrolysis/Stevens-Johnson syndrome	
	Neuroleptic malignant syndrome/malignant hyperthermia
	Spontaneous abortion/stillbirth and fetal death

AEs that fulfill 1 or more of the preceding serious criteria are to be considered SAEs and should be reported and followed in the same manner (see Section 10.2.1).

10.2.2 AEs of Clinical Interest

AEs of clinical interest are based on the mechanism of action of TAK-079, reports from other biologic agents, the nonclinical data to date, and the limited data from Study TAK-079-101 in healthy human subjects. These AEs may include, but are not limited to, the following: ISRs, CRS, hypersensitivity reactions, changes in hematologic parameters, and infections. Patients will be monitored closely for these AEs in clinical studies with TAK-079. Refer to Section 6.5 for a discussion of these events and recommendations on the Management of Events of Clinical Interest, and Section 6.2.1 for a description of the required premedications before TAK-079 dosing. Section 4.4 provides a summary of the overall benefit-risk profile.

10.2.3 Assigning Severity/Intensity of Adverse Events

The different categories of severity/intensity are:

Table 10.b AE Definitions for Severity/Intensity by Category

Mild	An AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	An AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
Severe	An AE that interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention.

Abbreviation: AE, adverse event.

10.2.4 Assigning Causality of Adverse Events

The relationship of each AE to study medication(s) will be assessed using the following categories:

Table 10.c AE Definitions for Causality

Related	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility (ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible).
Not related	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.2.5 Collection and Reporting of AEs, SAEs, and AEs of Clinical Interest

10.2.5.1 Collection Period

Collection of AEs (ie, AEs, SAEs, AEs of clinical interest, and abnormal liver function tests) will commence at the time the subject signs the ICF. AEs ongoing at EOT should be monitored until they are resolved, return to baseline, are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es), or 6 months after EOT has occurred, whichever comes first. For patients who withdraw before the administration of study medication, AEs will be followed until the subject discontinues study participation.

10.2.5.2 Reporting AEs

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Patients experiencing an SAE before the first exposure to investigational product must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline, or until there is a satisfactory explanation for the change. Nonserious AEs that begin before the first exposure to investigational product, related or unrelated to the study procedure, need not be monitored for the purposes of the protocol.

All patients experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and end date and time.

- Pattern of AE (frequency).
- Severity/intensity.
- Causality (investigator's opinion of the causal relationship between the event and administration of study drug[s]).
- Action taken with trial drug.
- Outcome of event.
- Seriousness.

10.2.5.3 Reporting SAEs

When an SAE occurs through the AE collection period, it should be reported according to the following procedure:

A Takeda SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed as follows:

SAE Reporting Contact Information
Cognizant
United States and Canada
Toll-free fax #: 1-800-963-6290
E-mail: takedaoncocases@cognizant.com

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of SAEs that begin before first administration of investigational product will follow the same procedure for SAEs occurring on treatment.

SAE Follow-up

If information is not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes

(eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be monitored until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.2.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected SAEs and any other applicable SAEs to regulatory authorities, investigators and IRBs or independent ethics committee (IECs), as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, Serious Unexpected Serious Adverse Reaction (SUSAR) reports will be submitted within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

10.3 Drug Safety Monitoring Board

In accordance with Takeda standard procedures, each clinical trial is evaluated to determine if a Drug Safety Monitoring Board (DSMB) should be convened. Applicable regulation and guidance are used to evaluate each trial in terms of potential confounding factors that complicate evaluation of the study safety and/or efficacy data, and potential risks of the study design or treatment to study participants [25]. A DSMB is not indicated at this time for this study given that Takeda's standards and processes, which include continuous review and evaluation of safety data reported from all participating sites through the conduct of the study, are appropriate for the ongoing monitoring of patient safety and data integrity. Additionally, as noted in detail in Section 6.3, Takeda clinicians/ designee conduct ongoing safety oversight at the patient and study level as well as review of safety of a full cohort in the dose escalation phase. However, taking into consideration the evolving benefit-risk profile of TAK-079, the decision to convene a DSMB could be taken at any time during the conduct of Study TAK-079-2001.

[redacted]

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

11.1.1 Analysis Sets

11.1.1.1 Safety Set

The safety analysis set will consist of all patients who are enrolled and received at least 1 dose of study drug. Patients in this analysis set will be used for demographic, baseline characteristics and safety summaries.

11.1.1.2 PK Set

The PK set will consist of all patients who receive study drug and have at least 1 measurable plasma concentration.

11.1.1.3 PD Set

The PD set will consist of all patients who receive study drug and have at least 1 postdose PD measurement.

11.1.1.4 Immunogenicity Set

Immunogenicity analysis (ADA positive, negative, and titer) will be summarized using descriptive statistics as applicable. [redacted]

11.1.2 Analysis of Demography and Other Baseline Characteristics

Descriptive statistics (N, mean, standard deviation [SD], median, minimum, and maximum) will be generated for continuous demographic variables and baseline characteristics variables (age, weight) for pooled placebo, each TAK-079 dose level, and TAK-079 overall. The number and percentage of patients in each class of the categorical demographic variables and baseline characteristics variables (gender, ethnicity, and race) will be tabulated for pooled placebo group, each TAK-079 dose level, and TAK-079 overall. Individual patient demographic and baseline characteristics data will be listed. Placebo data will be pooled across the cohorts. Demographic variables of screen failure patients and reasons for screen failures will be summarized overall for patients who are screened, but not enrolled in the study. Individual demographic characteristics, date of ICF, and reason for screen failure will be listed.

[redacted]

11.1.3 Immunogenicity Analysis

Immunogenicity analysis (ADA positive, negative, and titer) will be summarized using descriptive statistics as applicable (based on the SAP). [redacted]

11.1.4 Pharmacokinetic Analysis

Concentrations of TAK-079 in serum and whole blood will be summarized by TAK-079 dose level at each scheduled sampling time using descriptive statistics (N, arithmetic mean, SD, median minimum, maximum and percent coefficient of variation [%CV]). Individual plasma concentration data versus time will be presented in a data listing. PK parameters of TAK-079 will be summarized for each dose level using descriptive statistics. In addition, geometric mean will be computed for maximum observed concentration (C_{max}) and areas under the concentration-time curve (AUCs). Dose proportionality will be assessed graphically and using the power model. Plots of C_{max} and AUCs, as well as dose-normalized C_{max} and AUCs, versus doses will be generated.

Other analyses or methods may be used, if appropriate.

11.1.5 Pharmacodynamic Analysis

Individual results and change from baseline at different timepoints for placebo and each TAK-079 dose level will be calculated for various immune cell subsets including plasma cells, PBs, NK cells, B cells, T cells, monocytes, and total lymphocytes. CD38 expression and receptor occupancy for plasma cells, PBs, NK cells, B cells, T cells, and monocytes will also be evaluated. Cytokine measurements and change from baseline at different timepoints for placebo and each TAK-079 dose level may be calculated for each subject. Individual values and changes in the levels of autoantibodies, immunoglobulin [redacted] will be summarized.

[redacted]

11.1.6 Safety Analysis

For all safety summary tables stated under this section, the tables will be summarized by placebo, each TAK-079 dose level, and TAK-079 overall. Placebo data will be pooled across the dose levels.

11.1.6.1 AEs

All PTEs and TEAEs will be coded by SOC and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs with onset occurring through the safety follow-up period will be listed and included in the summary tables. The TEAEs will be summarized by SOC and PT. The following summary tables will be included in the report: summary of TEAEs and drug-related AEs, relationship of AEs to study drug (related vs not related), grade of AEs and

[redacted]

related AEs. AEs leading to study drug discontinuation and SAEs will be listed. Data listings will be provided for all AEs including PTE, TEAEs, AEs leading to study drug discontinuation, and SAEs.

11.1.6.2 Clinical Laboratory Evaluation

Individual results of laboratory tests from hematology, chemistry, and urinalysis that meet abnormal criteria to be defined in the SAP will be listed and summarized. Baseline, postdose, and change from baseline to postdose laboratory data will be summarized. All clinical laboratory data will be listed. Clinical significant laboratory results will be captured as AEs.

11.1.6.3 Vital Signs

Individual results of vital signs that meet abnormal criteria will be defined as an AE as per the principal investigator; to be defined in the SAP will be listed and summarized. Baseline, post-dose, and change from baseline in vital sign measurements will be summarized. All vital signs data will be provided in the data listings.

11.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

11.3 Determination of Sample Size

This study is not statistically powered for any hypothesis testing. The sample size of 6 active and 2 placebo patients for each of the 45 mg, 90 mg, and 135 mg dose groups (Cohorts A, B, and C, respectively) are considered to be sufficient to fulfill the study objectives of the evaluation of safety, tolerability, and PK of each cohort.

[redacted]

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and study site guarantee access to source documents by the sponsor or its designee contract research organization and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or the sponsor's designee (as long as blinding is not jeopardized), including but not limited to the investigator's binder, trial drug, patient medical records, ICF documentation, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to trial patients. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the patient, or confound interpretation of primary study assessment.

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare Products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

[redacted]

13.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects, patients) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix D. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for ICF and investigator responsibilities.

13.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federalwide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the investigator's brochure, a copy of the ICF form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject ICF must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives drug/notification no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by patients, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to patients must be approved by the IRB or IEC and sponsor.

13.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of the ICF as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and, if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written ICF, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study, and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject enters into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the ICF in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICF must be reviewed and signed by relevant patients or the relevant patient's legally acceptable representative in the same manner as the original informed consent. The date the

[redacted]

revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

13.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare Products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 13.2).

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

13.4 Publication, Disclosure, and Clinical Trial Registration Policy

13.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the clinical study site agreement. In the event of any discrepancy between the protocol and the clinical study site agreement, the clinical study site agreement will prevail.

[redacted]

13.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for American investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once patients receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to the sponsor providing this information to callers must provide the sponsor with a written notice requesting that their information not be listed on the registry site.

13.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

13.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study patients. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

[redacted]

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

Contact Type / Role	Contact
SAE and pregnancy reporting	Pharmacovigilance Takeda Development Center Americas, Inc. Fax: 224-554-1052

Abbreviation: SAE, serious adverse event.

14.1.2 Investigator Agreement

I confirm that I have read and that I understand this protocol, the investigator's brochure, package insert, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study patients in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.2.6 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator Appendix D.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix E of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

[redacted]

14.1.3 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the study-related responsibilities template. The vendors identified for specific study-related activities will perform these activities in full or in partnership with the sponsor.

[redacted]

15.0 LIST OF ABBREVIATIONS

ADA	antidrug antibody(ies)
AE	adverse events
AUC	area under the concentration-time curve
BP	blood pressure
CFR	Code of Federal Regulations
[redacted]	[redacted]
C_{max}	maximum observed concentration
COPD	chronic obstructive pulmonary disease
CRS	cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
%CV	percent coefficient of variation
dsDNA	double-stranded DNA
DSMB	drug safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form (refers to any media used to collect study data [ie, paper or electronic])
ENA	extractable nuclear antigens
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FIH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practices
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practices
hCG	human chorionic gonadotropin
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IRB	institutional review board
IRR	infusion-related reaction
ISR	injection site reaction
IV	intravenous
IXRS	interactive voice/web response system
LLN	lower limit of normal
mAb	monoclonal antibody
MESF	quantified in molecules of equivalent soluble fluorochrome
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities

MM	medical monitor
NK	natural killer
NOAEL	no observed adverse effect level
PB	plasmablast
PD	pharmacodynamic
PK	pharmacokinetics
PPD	purified protein derivative
PT	preferred term
PTE	pretreatment events
RA	rheumatoid arthritis
RBC	red blood cell
RR	respiratory rate
RRMM	relapsed/refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SLE	systemic lupus erythematosus
SLEDAI-2K	systemic Lupus Erythematosus Disease Activity Index 2000
SOE	schedule of events
TB	tuberculosis
TEAE	treatment-emergent adverse event
TIGRA	T-cell interferon-γ release assay
TNF-α	tumor necrosis factor-alpha
ULN	upper limit of normal
[redacted]	[redacted]
WBC	white blood cell

16.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the data management plan. AEs, medical history, and concurrent conditions will be coded using MedDRA. Drugs will be coded using the World Health Organization Drug Dictionary.

16.1 CRFs (Electronic and Paper)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After the lock of the clinical study database, any change of, modification of, or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs. The principal investigator must review the data change for completeness and accuracy, and must sign and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

16.2 Record Retention

The investigator agrees to keep the records stipulated in Section 16.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating patients, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source

documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 requires the investigator to retain essential documents specified in ICH E6 until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical study site agreement between the investigator and sponsor.

Refer to the clinical study site agreement for the sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

[redacted]

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18.0 APPENDICES

Appendix A Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 90 days or 5 half-lives after last dose of study drug, all male subjects who are sexually active with a female partner of child-bearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Women of child-bearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception found at the end of this Appendix. Note the half-life of TAK-079 has not yet been determined. Based on conservative information in the literature regarding the half-life of IgG1 immunoglobulins as well as other IgG1 human monoclonal antibodies [26,27] a conservative timeframe to continue contraception would be 150 days.

Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 90 days or 5 half-lives after last dose of study drug, female subjects of child-bearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective/effective method of contraception (from the list that follows). As the half-life of TAK-079 has not yet been determined, based on conservative information in the literature regarding the half-life of IgG1 immunoglobulins as well as other IgG1 human monoclonal antibodies [Mankarious et al 1088; Suzuki et al 2019], a conservative timeframe to continue contraception would be 150 days.

In addition, they must be advised not to donate ova during this period.

Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered to be of child-bearing potential (ie, fertile) following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and a high FSH concentration (>40 IU/L) before any study medication is administered. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

** Sterilized males should have undergone bilateral vasectomy at least 1 year before entering the study and able to provide documentation of the absence of sperm in the ejaculate or bilateral orchiectomy.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, the only acceptable methods of contraception are:
   - Nonhormonal methods:
     - Intrauterine device (IUD).
     - Bilateral tubal occlusion.
     - Vasectomized partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success).
     - True sexual abstinence, only if this is in line with the preferred and usual life style of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, and postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.
   - Hormonal methods: Hormonal contraception may be susceptible to interaction with the investigative compound, comparator, or concomitant medications, which may reduce the efficacy of the contraception method.
     - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom, or diaphragm) if for shorter duration until she has been on a contraceptive for 3 months;
       - Oral †.
       - Intravaginal † (eg, ring).
       - Transdermal †.
     - Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom, or diaphragm) until she has been on a contraceptive for 3 months;
       - Oral †.
       - Injectable.
       - Implantable.
2. Other effective methods of contraception (there may be a higher than 1% failure rate) are:
   - Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or creams PLUS male condom).

[redacted]

- Progestogen only hormonal contraception, where inhibition of ovulation is not the primary mode of action PLUS condom with or without spermicide.

3. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.
   - Sexual abstinence is NOT an acceptable method of contraception.
4. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, (and sperm donation) during the course of the study.
5. During the study, regular serum/or urine hCG pregnancy tests will be performed only for women of child-bearing potential, and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   a) Contraceptive requirements of the study
   b) Reasons for use of barrier methods (ie, condom) in males with pregnant partners
   c) Assessment of subject compliance through such questions as:
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?
      iii. Are your menses late (even in women with irregular or infrequent menstrual cycles, a pregnancy test must be performed if the answer is "yes")
      iv. Is there a chance you could be pregnant?
6. In addition, negative pregnancy results must be confirmed in female subjects of child-bearing potential, during the following timeframes:
   a) Screening and baseline:
      i. During screening; a negative **serum** pregnancy test (hCG < 5 mIU/mL).
      ii. Before first dose of investigational drug (within 24 hours); a negative **urine** pregnancy test (with sensitivity < 50 mIU/mL).

Note: Before administration of the first dose of investigational drug, the subject must confirm menses within the past month before dosing (ie, no delayed menses).

b) Study dosing period: urine screening
    i. Prior to each study dosing day.
c) At any time point during study enrollment: serum screening
    i. If a menstrual period is delayed.
    ii. On request by an IRB or if required by local regulations.

If any subject is found to be pregnant during the study, she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 90 days after the last dose should also be recorded following authorization from the subject's partner.

If the female subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received (blinded or unblinded, as applicable).

All pregnancies, including female partners of male subjects, in subjects on active study drug will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

[redacted]

Appendix B Clinical Signs and Symptoms of Cytokine Release Syndrome

Organ System	Symptoms
Constitutional	Fever with or without rigors, malaise, fatigue, anorexia, myalgias, arthalgias, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia with or without bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word-finding difficulty or frank aphasia, hallucinations, tremor, dysmetria, altered gait, seizures

Source: Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124(2):188-95.

Appendix C Grading System for Cytokine Release Syndrome

Grade	Toxicity
Grade 1	Symptoms are not life threatening and require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgias, malaise)
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement <40% or Hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥40% or Hypotension requiring high dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis
Grade 4	Life-threatening symptoms Requirements for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
Grade 5	Death

Source: Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124(2):188-95.
Grades 2 to 4 refer to the CTCAE v4.03 grading.

[redacted]

Appendix D Responsibilities of the Investigator

Clinical research studies sponsored by the Sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to patients. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, and laboratory results, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should

contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the Sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

[redacted]

Appendix E Investigator Consent to the Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

[redacted]

Appendix F Elements of the Subject's Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of patients involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written ICF, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's

legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
23. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:

    That personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;

    It is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer patients the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;

    That personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;

    That patients agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

    That the subject's identity will remain confidential in the event that study results are published.

24. Female patients of child-bearing potential (eg, nonsterilized, premenopausal female patients) who are sexually active must use highly effective contraception (as defined in the informed consent) from signing the informed consent through 90 days or 5 half-lives of study drug, whichever is longer, after the last dose of study drug. Regular pregnancy tests will be

performed throughout the study for all female patients of child-bearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.

25. Male patients must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for 90 days after the last dose of study drug. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

[redacted]

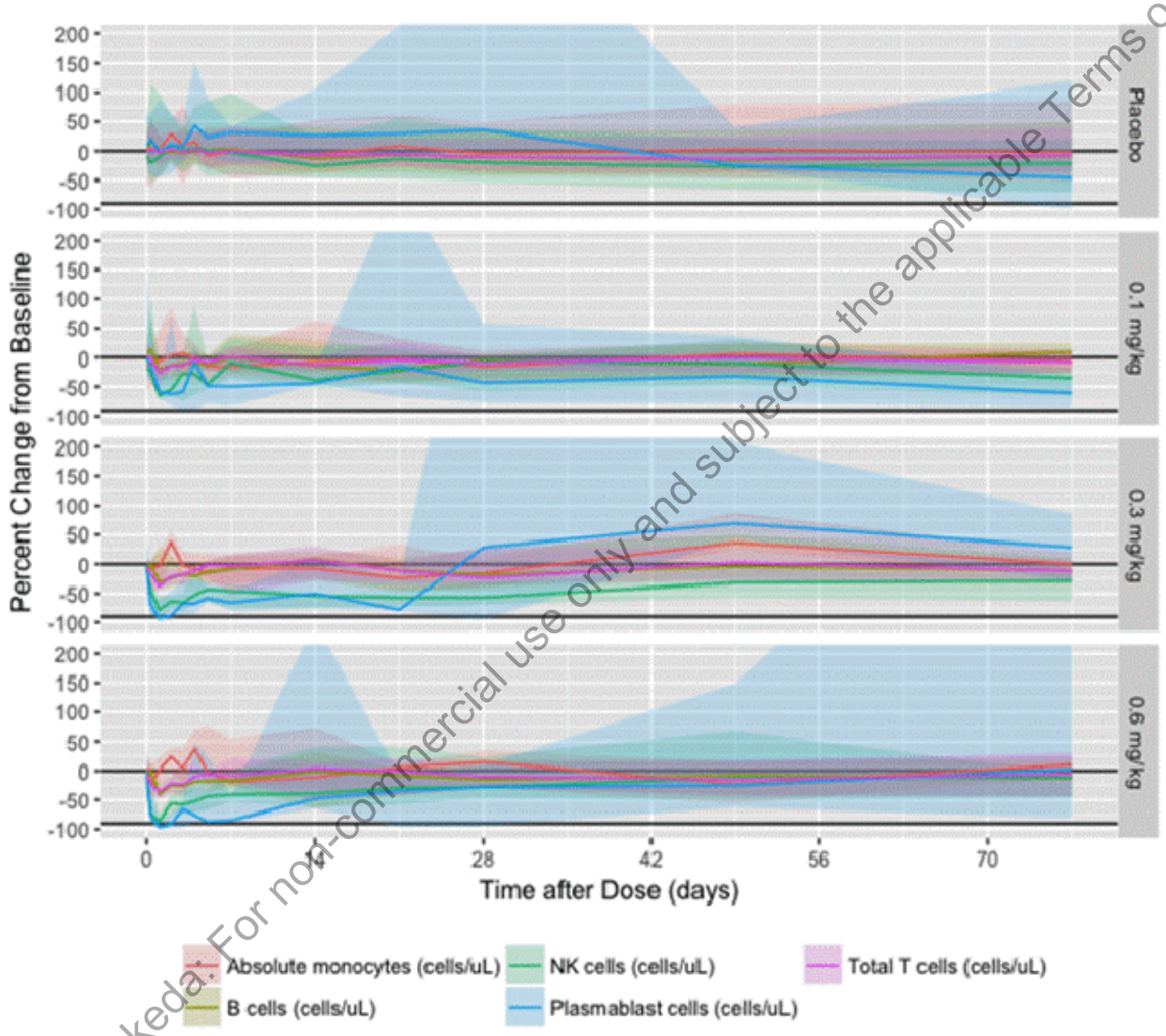
Appendix G Dose Modeling of TAK-079

The selection of doses and the frequency of administration of TAK-079 for the TAK-079-2001 study are based on the following: (1) a comprehensive review and analysis of data derived from the dosing of healthy subjects with TAK-079 (TAK-079-101); (2) repeat dosing of monkeys with TAK-079 (TAK-079-10015, TAK-079-1018, and TAK-079-10019); and, (3) data derived from repeat dosing of patients with multiple myeloma with daratumumab (Darzalex), a related anti-CD38 cytolytic antibody [11].

A semimechanistic population PK/PD model for TAK-079 with target-mediated drug disposition, incorporated the existing knowledge mentioned above. The model was subsequently used to conduct simulations of different doses to project human PK and estimate changes in PB, NK cells, B cells, and T cells (as outlined in Figure 1).

The 45 mg dose for the initial dosing cohort (ie, Cohort A) is selected based on the favorable safety profile and therapeutic target effect (ie, a sustained reduction of PBs) observed after a 0.6 mg/kg dose was administered to healthy subjects (Study TAK-079-101). A single SC dose of 0.6 mg/kg TAK-079 reduced the level of PBs in peripheral blood >90% and NK cells >80% without comparable reductions in monocytes and B and T cells. Levels of PBs and NK cells recovered to 50% of baseline levels 21 days after administration, on average (Figure 2). Two subsequent dosing cohorts are planned at doses of 90 mg (2-fold increase from the first dose cohort) and 135 mg (a 50% increase from the previous cohort), keeping in mind a balance of benefit-risk.

Figure 1 Levels of Plasmablasts, Monocytes, and B, T, and NK Cells in Peripheral Blood of Healthy Subjects After a Single Administration of Placebo or 0.6 mg/kg TAK-079 on Day 0

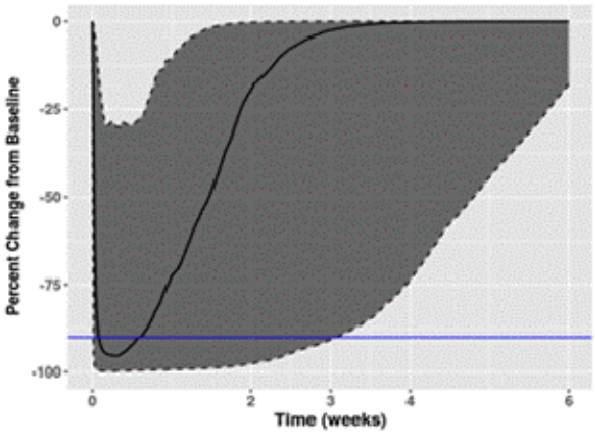


Source: TAK-079-101 Report
Abbreviation: NK, natural killer; SC, subcutaneous.
Graph indicates change of immuno-inflammatory cells following a single SC dose of 0.1 mg/kg, 0.3 mg/kg, or 0.6 mg/kg of TAK-079 or matching placebo; medians indicated by solid lines; 95% CI indicated by associated shading.

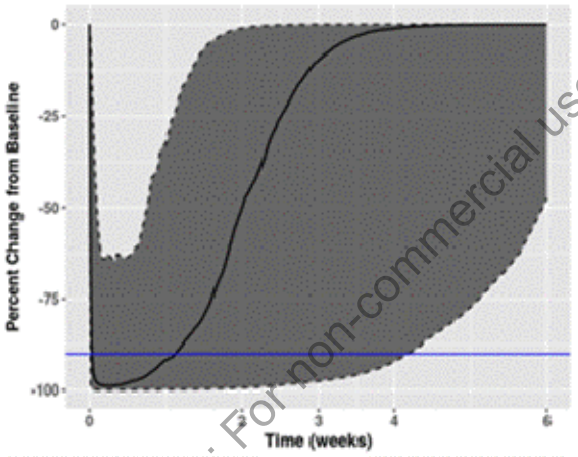
Figure 2 Summary of Dose Modeling Overview by Dose

Predicted plasmablast % change from baseline following a single TAK-079 SC dose of 45 mg, 90 mg, and 135 mg

A. Plasmablasts following 45 mg SC Dose [a]

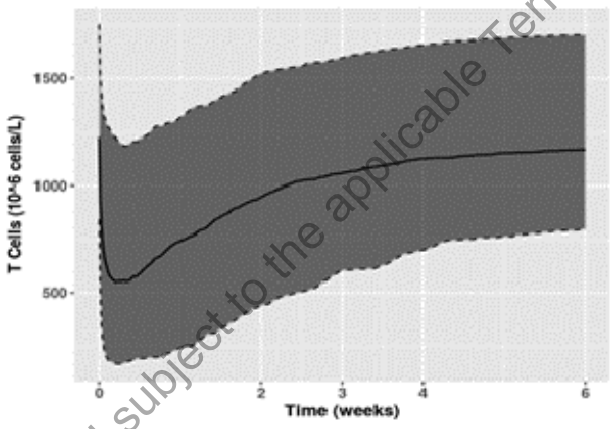


B. Plasmablasts following 90 mg SC dose [a]

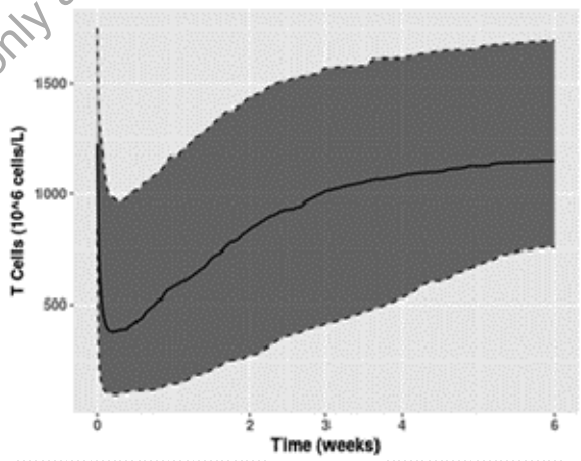


Predicted T-cell levels change from baseline following a single TAK-079 SC dose of 45 mg, 90 mg, and 135 mg

D. T cell levels following 45 mg SC dose [a]



E. T cell levels following 90 mg SC dose [a]

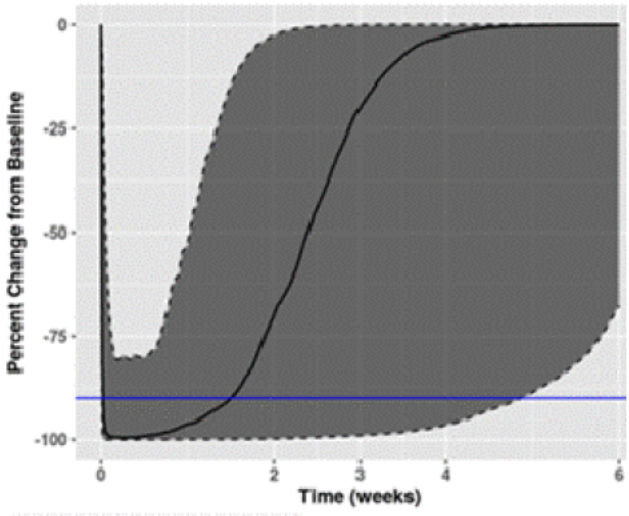


[redacted]

Figure 2 Summary of Dose Modeling Overview by Dose

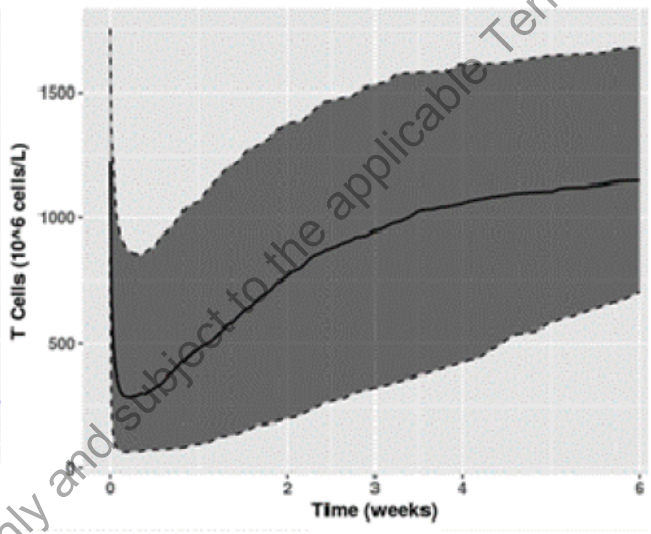
Predicted plasmablast % change from baseline following a single TAK-079 SC dose of 45 mg, 90 mg, and 135 mg

C. Plasmablasts following 135 mg SC dose [a]



Predicted T-cell levels change from baseline following a single TAK-079 SC dose of 45 mg, 90 mg, and 135 mg

F. T cell levels following 135 mg SC dose [a]



[redacted]

Appendix H Detailed Description of Amendment to Text

The primary sections of the protocol affected by the changes in Amendment 01 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Clarification that the assessment of systemic lupus erythematosus antibodies (Ab) is expected at baseline.

The primary change occurs in Table 3.a Schedule of Events	
Description of change:	In the row *SLE Ab*, in the cell spanning *Screening* column, X was added.

Rationale for Change: Table 3a in original protocol did not align with SLE Ab timings in original protocol.

Change 2: Clarification that no dosing criteria assessments are to be conducted as part of screening.

The primary change occurs in Table 3.a Schedule of Events	
Description of Change:	In the row *Dosing criteria assessment*, in the cell spanning *Screening* column, X was removed, with footnote o.

Rationale for Change: Table 3.a in original protocol did not align with dosing criteria assessment timings in original protocol.

Change 3: Removal of redundant RNA sampling schedule in Table 3.a.

The primary change occurs in Table 3.a Schedule of Events	
Description of Change:	The row *RNA*, was removed.

Rationale for Change: RNA assessment timings are adequately covered in other areas of the protocol, removal reduced redundancy, and improving protocol clarity.

Change 4: Addition of a one-day window (+/- 1 day) for visits: HV7, HV8 and HV9, has been added for consistency with other visits.

The primary change occurs in Table 3.a Schedule of Events	
Description of Change:	In the header cells for columns rows *HV7, HV8* and *HV9,* (+/- 1 day) has been added to each header cell.

Rationale for Change: All HV visits have a visit window allowance of +/- 1 day. Adding the +/- 1 day allowance for HV7, HV8, and HV9 in Table 3.a, provides the necessary consistency.

[redacted]

Change 5: Removal of details for urine sample collection.

The primary change occurs in Table 3.a Schedule of Events footnote k

Initial wording:	[k] Urinalysis, including [redacted] and nitrates, will be performed by central laboratory 1 week before dosing; additional protein and nitrate assessments are to be performed by local laboratory (ie, dipstick) on study dosing days, before dosing; abnormal findings by local laboratory assessment must be confirmed by central laboratory evaluation. Samples must be first morning urine collected by patients in specimen containers provided by the study site. Further detail is provided in Section 9.2.8.3.
Amended or new wording:	[k] Urinalysis, including [redacted] and nitrates, will be performed by central laboratory 1 week before dosing; additional protein and nitrate assessments are to be performed by local laboratory (ie, dipstick) on study dosing days, before dosing; abnormal findings by local laboratory assessment must be confirmed by central laboratory evaluation. ~~Samples must be first morning urine collected by patients in specimen containers provided by the study site.~~ Further detail is provided in Section 9.2.8.3.

Rationale for Change: Instructions within protocol are unnecessary as such details will be provided in site trainings and associated study documents for the site staff

Change 6: Clarification of T-cell safety parameters as they pertain to dosing criteria. This clarification takes into consideration the natural history of SLE on background therapy, the patient's T-cell baseline values, as well as changes from baseline that would warrant the continuation or holding of a dose of TAK-079.

The primary change occurs in Table 6.b Summary of Dosing Criteria

Initial wording:	• In the row *T-cells*, in the cell spanning *Continuing Dosing* column, original text read, "T cells ≥500 cells/uL" • In the row T-cells, in the cell spanning Dosing Hold column, original text read, "T cells <500 cells/uL"
Amended or new wording:	• In the row *T-cells*, in the cell spanning *Continuing Dosing* column, new text was added to existing text: "**NOTE: Dosing may continue in instances of T cells <500 cells/uL if CD3 + cell count is ≥70% of the baseline level"**. • In the row T-cells, in the cell spanning Dosing Hold column, text was amended: "**CD3+ cells count <500 cells/uL and is < 70% of baseline CD3+ cell count level**."

The following sections also contain this change: No other areas of the protocol are impacted by this change.

[redacted]

Rationale for Change: This clarification incorporates consideration of the natural history of SLE on background therapy, the patient's T-cell baseline values, as well as changes from baseline that would warrant the continuation or holding of a dose of TAK-079. This clarification now incorporates all available T-cell count information into the dosing decisions.

Change 7: Changes to dosing criteria in the event of infusion related reaction, to better align actions with the appropriate grading criteria. Grade 2 or higher reactions still require dose discontinuation.

The primary change occurs in Table 6.b Summary of Dosing Criteria

Initial wording:	In the row *TAK-079-related infusion reaction*, in the cell spanning *Continuing Dosing* column, original text read, "Grade 1".
Amended or new wording:	In the row *TAK-079-related infusion reaction*, in the cell spanning *Continuing Dosing* column, new text was added to existing text: "≥ Grade 1 with symptomatic treatment allowed in accordance with Appendix C. NOTE: Dosing may resume after symptoms have resolved [f]"

The following sections also contain this change: No other areas of the protocol are impacted by this change.

Rationale for Change: Added statement allows for alignment with referenced grading criteria.

Change 8: Clarification of dosing criteria in the event of hypersensitivity-related events, to better align with the CTCAE criteria for allergic reactions, as originally intended. Any symptom of an anaphylactic reaction continues to require TAK-079 discontinuation.

The primary change occurs in Table 6.b Summary of Dosing Criteria

Initial wording:	1. Under the column, *Laboratory Investigations*, original text in cell "Hypersensitivity",
Amended or new wording:	1. Under the column, *Laboratory Investigations*, new text added to cell "Hypersensitivity", is as follows "(allergic reaction or anaphylaxis)". 2. In the row *Hypersensitivity"*, in the cell spanning *Continuing Dosing* column, new text was added "≤Grade 2 In accordance with NCI CTCAE, version 4.03 grading for allergic reactions which respond promptly to symptomatic measures". 3. In the row *Hypersensitivity"*, in the cell spanning *Dose Hold* column, the following text was deleted, "~~Grade 1 as per NCI CTCAE grading for allergic reactions. Hold and reassess as per protocol timings for next dose~~" 4. In the row *Hypersensitivity"*, in the cell spanning *Dose Discontinuation* column, the text was amended as follows, " ≥Grade **3** [c] ~~2~~ **In accordance with** NCI CTCAE **(version 4.03)** grading for allergic reaction **or** any signs or symptoms of an anaphylactic reaction." 5. In the row *Hypersensitivity"*, in the cell spanning *Dose Discontinuation*

[redacted]

column, a citation to the following reference was added:

Regan DM, Markowitz MA. Mitigating the Anti-CD38 Interference with Serology Testing. Advancing Transfusion and Cellular Therapies World wide Association Bulletin #16-02 2016:1-4.

6. Footnote c, text was amended as follows: "Laboratory grading**, allergic reactions, and infection grading** is based on **NCI** CTCAE v~~3.0~~**4.03.**"

The following sections also contain this change: No other areas of the protocol are impacted by this change.

Rationale for Change: Changes were made to better align with the CTCAE criteria for allergic reactions as originally intended. No changes were made to anaphylactic reactions.

Change 9: Clarification that Common Terminology Criteria for Adverse Events version 4.03 must be used in the study.

The primary change occurs in Table 6.b Summary of Dosing Criteria.

Added text: NCI CTCAE, **version 4.03**

Rationale for Change: To ensure consistent use of NCI CTCAE version as intended.

Change 10: Clarification of excluded and dose limited concomitant medications

The primary change occurs in Section 7.3 in Table 7.a and Table 7.b.

Initial wording:

- Table 7.a Under the column, *Exclusion Criteria*, in cell spanning *Immunosuppressant regimen* original text was "To include calcineurin-inhibitors (eg, systemic cyclosporine and tacrolimus), leflunomide, to be excluded throughout study participation"
- Table 7.b Under the column *Dosing Criteria,* in the cell spanning *Immunosuppressants*, original text was "Regimens consisting of ≥ 2 agents while on study (not applicable to topical agents; see dose restrictions outlined in Table 7.a"
- Table 7.b Under the column *Dosing Criteria,* in the cell spanning *Corticosteriods*, original text was "Stable dosing equivalent to ≤20 mg/day of oral predisolone maintained for ≥28 days prior to the first dose of TAK-079 or matching placebo."

Amended or new wording:

- Table 7.a Under the column, *Exclusion Criteria*, in cell spanning *Immunosuppressant regimen* new text added to original text, "To include calcineurin-inhibitors (eg, systemic cyclosporine and tacrolimus), leflunomide, to be excluded throughout study participation. **Must be discontinued at least 3 months before screening visit.**"
- Table 7.b Under the column *Dosing Criteria,* in the cell spanning

Immunosuppressants, amended text is "Regimens consisting of <2 agents while on study (not applicable to topical agents; see dose restrictions outlined in Table 7.a"

- Table 7.b Under the column *Dosing Criteria,* in the cell spanning *Corticosteriods*, amended text is "Stable dosing equivalent to ≤20 mg/day of oral **prednisone** ~~predisolone~~ maintained for ≥28 days prior to the first dose of TAK-079 or matching placebo."

The following sections also contain this change: No other areas of the protocol are impacted by this change.

Rationale for Change: Statement regarding timeframe for discontinuation of immunosuppressants was added for consistency. Other changes were corrections of typographical errors in the original protocol.

Change 11: The addition of a protocol subsection to provide clarification regarding potential interference with serological testing.

The primary change occurs in Section 6.4

Added text: **6.4.3 Interference with Serological Testing**

Anti-CD38 monoclonal antibodies have been reported to bind to CD38 on red blood cells (RBCs) and results in a positive indirect coombs test, which may persist for up to 6 months. The determination of a patient's ABO and Rh blood type are not impacted, but the RBC binding may mask detection of antibodies to minor antigens in the patient's serum [14,15]. It is possible TAK-079 may affect the results of these blood tests, this is being evaluated. Until those tests are known, it is recommended that baseline type and serological screening be established before starting TAK-079. Patients should keep these results in case future transfusions are needed. Blood transfusion centers should also be informed of this interference with serological testing as necessary.

Rationale for Change: The impact that TAK-079 may have on minor antibodies is still to be determined through ongoing analysis. The newly added section provides clarity on this potential impact, and the importance of establishing baseline blood and serology levels at screening, as a precautionary safety measure should future transfusions be required while the patient is on study.

[redacted]

Change 12: Clarifications made regarding the management of hypersensitivity reactions to better align with the CTCAE criteria for allergic reactions, as originally intended.

The primary change occurs in Section 6.5.1.1

Initial wording:

Grade 1:

Study Management: Hold further TAK-079 dosing until symptoms resolve. Resume dose of TAK-079 at same dose level at the time of symptom resolution with appropriate prophylactic medical care.

Patient Support: Provide symptomatic treatment, to include epinephrine as needed.

Grade 2:

Study Management: Discontinue study dosing and advance to the safety follow-up period of the study.

Patient Support: For anaphylaxis, provide symptomatic treatment, to include epinephrine.

Grade 3 or Greater: (symptomatic bronchospasm with or without urticaria, angioedema, hypotension).

Study Management: Patients are to discontinue study dosing and advance to the safety follow-up period of the study.

Patient Support: Provide symptomatic treatment, including epinephrine, until symptoms resolve.

Local injection site abnormalities have not been observed in monkey and rat nonclinical studies after SC and/or IV administration of TAK-079. In the clinical study of healthy subjects (TAK-079-101), mild injection site AEs were reported; most were Grade 1 and included primarily erythema or tenderness. All injection reactions resolved within a few days.

Grade 3 or Greater: (symptomatic bronchospasm with or without urticaria, angioedema, hypotension).

Study Management: Patients are to discontinue study dosing and advance to the safety follow-up period of the study.

Patient Support: Provide symptomatic treatment, including epinephrine, until symptoms resolve.

Amended or new wording:

Grade 1

a) Study Management:

~~Hold further TAK-079 dosing until symptoms resolve. Resume dose of TAK-079 at same dose level at the time of symptom resolution with appropriate prophylactic medical care~~. **If the full dose of TAK-079 has not**

[redacted]

yet been administered, hold dosing until symptoms resolve, at which time the remainder of TAK-079 dose may be administered.

b) Patient Support

~~Provide symptomatic treatment, to include epinephrine as needed~~. **Monitor closely until resolution of symptoms.**

Grade 2

c) Study Management:

~~Discontinue study dosing and advance to the safety follow-up period of the study.~~ **If the full dose of TAK-079 has not yet been administered, hold dosing until symptoms resolve, at which time the remainder of TAK-079 dose may be administered.**

d) Patient Support

~~For anaphylaxis, provide symptomatic treatment, to include epinephrine.~~

- **Administer appropriate symptomatic and prophylactic medical care; consider post-injection medications as outlined in Section 6.2.2.**
- **For allergic reaction, provide symptomatic treatment (e.g. antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, epinephrine) as medically appropriate and consider post-infection medications (as per Section 6.2.2).**

Grade 3 or Greater: (symptomatic bronchospasm with or without urticaria, angioedema, hypotension).

a) Study Management:

- Patients are to discontinue study dosing and advance to the safety follow-up period of the study.

b) Patient Support:

- Provide symptomatic treatment, including epinephrine, until symptoms resolve.
- **Consider hospitalization as appropriate.**

The following sections also contain this change: No other areas of the protocol are impacted by this change.

Rationale for Change: Revised text provides clarification for appropriate symptom management to better align with appropriate toxicity grading criteria guidance, while providing patients the opportunity to continue study dosing if and when symptoms should resolve.

Change 13: Removal of any reference to an unblinded pharmacist.

The primary change occurs in Section 8.1.3

Initial wording:	The assignment of study patients to one of two study arms, within each cohort, is maintained through a blinded randomization schedule, available to the study site pharmacist, and in instances of medical emergencies, to the principal investigator. Details on maintaining the study blind, and unblinding procedures are outlined in Section 8.1.5.
Amended or new wording:	The assignment of study patients to one of two study arms, within each cohort, is maintained through a blinded randomization schedule, available~~, to the study site pharmacist, and~~ in instances of medical emergencies, to the principal investigator. **Otherwise site staff, will remain blinded through the conduct of the study**. Details on maintaining the study blind, and unblinding procedures are outlined in Section 8.1.5.

The following sections also contain this change: Section 8.1.5, Section 9.1.2, and Section 9.1.3

Rationale for Change: Pharmacist is not unblinded in this study

Change 14: Clarification that ECGs are to be read locally, to include readings of triplicate electrocardiograms for safety assessments. Otherwise, triplicate ECGs will be submitted for subsequent central reading at a future time.

The primary change occurs in Section 9.2.6

Initial wording:	A single 12-lead ECG is to be collected at the screening visit (for assessment of eligibility) and at the end of safety follow-up visit, and will be read locally. Triplicate 12-lead ECGs, obtained before each study dose, are to be collected just before PK sampling, during timeframes outlined in Table 3.a and Table 3.b. Triplicate ECGs will be read centrally. When the timing of the triplicate and single (safety) ECGs coincide, the site can use the triplicate ECG collection for the safety evaluation. Each ECG recording should be performed according to standard institutional practice. It is recommended that patients refrain from eating or limit themselves to bland food for 1 hour before dosing and for 1 hour before each scheduled triplicate ECG measurement. Each ECG is recorded electronically, interpreted by a qualified person, and transmitted to a central vendor for storage. NOTE: Any ECG finding that is judged by the investigator as clinically significant (except at the screening visit) is considered a TEAE; as such clinically significant findings are to be recorded on the source documentation and in the eCRF, and undergo continued monitoring as described in Section 10.2.5.

[redacted]

Amended or new wording:

Each ECG recording should be performed according to standard institutional practice.

All study ECGs, to include triplicate ECGs, are interpreted by a qualified person (ie, read locally). Further, triplicate 12-lead ECGs are recorded electronically and are to be submitted to a central vendor for storage and for future analysis.

ECGs with clinically significant findings, as judged by the investigator, are to be considered a TEAE; (except for ECGs obtained as part of the screening) visit which would be considered part of medical history). Clinically significant findings are to be recorded on the source documentation and in the eCRF, and undergo continued monitoring as described in Section 10.2.5

A single 12-lead ECG is to be collected at the screening visit (for assessment of eligibility) and at the end of safety follow-up visit~~, and will be read locally~~.

Triplicate 12-lead ECGs, obtained before each study dose, are to be collected just before PK sampling, during timeframes outlined in Table 3.a and Table 3.b. Triplicate ECGs will be ~~read~~ stored centrally for future analysis.

When the timing of the triplicate and single (safety) ECGs coincide, the site can use the triplicate ECG collection for the safety evaluation.

~~Each ECG recording should be performed according to standard institutional practice. It is recommended that patients refrain from eating or limit themselves to bland food for 1 hour before dosing and for 1 hour before each scheduled triplicate ECG measurement. Each ECG is recorded electronically, interpreted by a qualified person, and transmitted to a central vendor for storage.~~

~~NOTE: Any ECG finding that is judged by the investigator as clinically significant (except at the screening visit) is considered a TEAE; as such clinically significant findings are to be recorded on the source documentation and in the eCRF, and undergo continued monitoring as described in Section 10.2.5.~~

Rationale for Change: Additional text has been added to alleviate and avoid confusion regarding central reads, which will be conducted later in the study; and, to clarify that all ECG (both those obtain in single and triplicate) must be read locally.

[redacted]

Change 15: Clarification of Coombs testing to be analyzed by local labs; with further clarification that all other laboratory tests, unless otherwise noted, should be submitted for central analysis.

The primary change occurs in Section 9.2.8.

Initial wording:	Unless otherwise stated in the protocol, all laboratory samples are to be sent to the study central laboratory for analysis, under the conditions for handling and shipping as outlined in the study laboratory manual.
Amended or new wording:	Unless otherwise stated in the protocol, all laboratory samples, with exception to Coombs tests, are to be sent to the study central laboratory for analysis, under the conditions for handling and shipping as outlined in the study laboratory manual. Coombs test will be done locally.

The following sections also contain this change: No other areas of the protocol are impacted by this change.

Rationale for Change: Central lab vendor does not perform Coombs testing, so test needs to be completed by local lab.

Change 16: Adjustments to pregnancy test methodology during screening and just prior to the first dose of TAK-079, though 2 negative pregnancy tests are still needed prior to dosing. Details about the duration of continued contraception after the last dose of study medication have been added.

The primary change occurs in Section 9.2.9.2

Initial wording:

Women of child-bearing potential must have pregnancy testing completed in accordance to the timings outlined as follows:

- *Before Initial Study Dosing*: Two negative **serum** pregnancy tests (human chorionic gonadotropin [hCG] <5 mIU/mL) to include:
  - Screening period (within 10 to 14 days before the start of study drug).
  - Baseline (within 24 hours before the start of study drug).

Amended or new wording:

Women of child-bearing potential must have pregnancy testing completed in accordance to the timings outlined as follows:

- *Before Initial Study Dosing*: ~~Two~~
  - Screening period: a negative **serum** pregnancy tests (human chorionic gonadotropin [hCG] <5 mIU/mL) ~~to include:~~
  1. ~~Screening period (within 10 to 14 days before the start of study drug).~~
  - Baseline (within 24 hours before the start of study drug) a negative urine pregnancy test with a sensitivity of at least 50 mIU/mL. If the urine test is indeterminate, a serum pregnancy test is mandatory.

[redacted]

The following sections also contain this change: Table 3.a, footnote j and Appendix A

Rationale for Change:

Changes to Pregnancy Testing Criteria: To reduce the need for blood draws within study, while maintaining appropriate measures for pregnancy assessments.

Changes to Barrier Contraception After Last Dose On-Study: Change made to provide specific detail about suggested duration of contraception after last dose on study drug and rationale for the duration recommended.

Change 17: Removal of British Isles Lupus Assessment Group assessments and all associated trainings and site/study activities.

The primary change occurs in Section 9.3.4

Deleted Text

~~*9.3.4.2BILAG 2004 Index*~~

~~All investigative site personnel performing BILAG 2004 Index evaluations must be trained and certified before conducting study assessments.~~

~~The BILAG 2004 Index is a clinical measure of lupus disease activity reported in 9 body systems. The BILAG score is based on clinical presentations of present, new, worse, the same, or improving, in comparison to the previous assessment. General BILAG categories are as follows:~~

- ~~BILAG A: The presence of one or more serious features of lupus.~~
- ~~BILAG B: Moderate features of the disease.~~
- ~~BILAG C: Mild symptomatic features.~~
- ~~BILAG D: Prior activity with no current symptoms due to active lupus.~~
- ~~BILAG E: An organ that has never been involved.~~

The following sections also contain this change Footnotes to Table 3.a, Table 3.b, Section 4.3.4.3, Section 5.2.3.

Rationale for Change: Considering the primary objective of the study is safety and tolerability and not efficacy, and given the number of SLE assessment tools currently incorporated into the protocol, the BILAG assessment was determined to not be necessary and was removed.

[redacted]

Change 18: Clarification that the statistical analysis plan will be prepared before database lock.

The primary change occurs in Section 11.1

Deleted Text	A statistical analysis plan (SAP) will be prepared and finalized before ~~unblinding of patients' treatment and~~ before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

Rationale for Change: To provide clarification that the statistical analysis plan will be prepared before database lock.

[redacted]

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Nonclinical [redacted] Approval	08-Mar-2019 13:20 UTC
[redacted]	Biostatistics Approval	08-Mar-2019 15:57 UTC
[redacted]	Clinical Science Approval	08-Mar-2019 18:30 UTC
[redacted]	Clinical [redacted] Approval	10-Mar-2019 19:58 UTC