Clinical Study Protocol

NCT Number: NCT04278924

Title: A Phase 2, Randomized, Double-blind, Placebo-Controlled Study to Evaluate Safety, Tolerability, and Efficacy of TAK-079 in Patients With Persistent/Chronic Primary Immune Thrombocytopenia

Study Number: TAK-079-1004

Document Version and Date: Amendment 5.0, 28 April 2022

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

PROTOCOL

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Safety, Tolerability, and Efficacy of TAK-079 in Patients With Persistent/Chronic Primary Immune Thrombocytopenia

Sponsor: Takeda Development Center Americas, Inc.
95 Hayden Avenue,
Lexington, MA 02421 USA

Study Number: TAK-079-1004

EudraCT Number: 2019-004103-12

Compound: TAK-079

Date: 28 April 2022 **Amendment Number**: 5

Amendment History

Date	Amendment Number	Type	Region
28 April 2022	Amendment 5	Substantial	Global
05 May 2021	Amendment 4	Substantial	Global
18 December 2020	Amendment 3	Substantial	Global
7 October 2020	Amendment 2	Substantial	Global
26 December 2019	Amendment 1	Nonsubstantial	Global
06 November 2019	Initial protocol	Not applicable	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event (SAE) and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints.

Takeda Development Center–sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each patient.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

The names and contact information for the medical monitor and responsible medical officer are in the study manual.

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 (R2) Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

[redacted], MD, MSc, PhD, MPH Date
[redacted], Rare Diseases

[redacted], PhD Date
[redacted], Biostatistics
Statistical and Quantitative Sciences

[redacted], PhD (or designee) Date
[redacted]
Quantitative Clinical Pharmacology

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure (IB), prescribing information, 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 subject/patients in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH, E6 (R2) GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.0 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Appendix E).

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

1.3 Protocol Amendment 5 Summary of Changes

Protocol Amendment 5 Summary and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 5. The primary reason for this amendment is to update the number of patients enrolled in each study part, to modify the prophylactic drug coadministration, to clarify the criteria for opening study Part B, [redacted].

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

Change Number	Protocol Amendment 5 Summary of Changes Since the Last Version of the Approved Protocol		
	Sections Affected by Change	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Section 2.0 STUDY SUMMARY Section 4.2.1 Rationale for Dosing Regimen Section 6.1.1 Part A Overview Section 6.1.3 Part B Overview Figure 6.b Study Schematic: Part A and B, Main Study Section 6.2 Number of Patients Table 8.a Dosing Regimens Section 13.3 Determination of Sample Size	Defined the minimum number of patients enrolled in each treatment arm in both Part A and Part B.	Number of patients changed to expedite safety review of Part A.
2.	Section 4.2.1 Rationale for Dosing Regimen	Added a note to indicate that the information reflects the data used to support the dosing rationale included in the original protocol (dated 06 November 2019).	Edited to indicate the data from which the dose justification for this protocol were based.
3.	Section 4.2.1 Rationale for Dosing Regimen Section 8.7.2 [redacted]	Deleted references to the current TAK-079 investigator's brochure (IB).	As the dose justification section was written based on data that has since been updated, the references to the current TAK-079 IB are removed.

Change Number	Protocol Amendment 5 Summary of Changes Since the Last Version of the Approved Protocol Sections Affected by Change	Description of Each Change and Rationale	
	Location	***Description***	***Rationale***
4.	Section 4.3 Benefits and Risks Assessment	Added a statement directing the reader to always refer to the latest version of the TAK-079 IB for the overall benefit/risk assessment and the most accurate and current information regarding pharmacokinetics, efficacy, and safety of TAK-079.	Reminder for investigators to reference the IB for the latest data for TAK-079.
5.	Section 5.2.2 Secondary Endpoints	Clarified wording around secondary efficacy endpoints.	Clarification of nomenclature.
6.	Section 5.2.3 [redacted]	[redacted]	[redacted]
7.	Section 2.0 STUDY SUMMARY Figure 6.b Study Schematic: Part A and B, Main Study Figure 6.c Schematic for the OLE Periods Section 9.4.4 Medical History Section 9.4.5 Concomitant Medications and Procedures Section 10.2 Procedures for Recording and Reporting AEs and SAEs Section 10.3 Monitoring of AEs and Period of Observation Section 13.1.7 Safety Analysis Appendix A Part A and B Main Study Schedule of Events Appendix B Schedule of Events: OLE-A and OLE-B	Added that COVID-19 infection and vaccination prior to the study should be recorded as part of medical history, that COVID-19 vaccination and COVID-19 treatments received during the study through LFP will be recorded as concomitant medications, and that COVID-19 infection and COVID-19 vaccination AEs will be collected through the LFP regardless of causality.	Ensure that accurate COVID-19 information is completely captured.

Change Number	Protocol Amendment 5 Summary of Changes Since the Last Version of the Approved Protocol		
	Sections Affected by Change	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
8.	Section 2.0 STUDY SUMMARY Section 4.2.1 Rationale for Dosing Regimen Section 6.1 Overview of Study Design Section 6.1.2 Assessment and Criteria for Opening Part B Enrollment (New section) Section 6.1.3 Part B Overview Section 13.2 Interim Analyses	Added information discussing the criteria for assessment of unblinded safety data for a minimum of 24 evaluable Part A patients in order to determine whether enrollment in Part B will be opened; discussed the internal Safety Review Committee that will be responsible for analysis of the unblinded data. Updated information about the interim analysis of data from Parts A and B accordingly.	Clarified the procedures to be undertaken to determine if Part B of the study will proceed.
9.	Section 2.0 STUDY SUMMARY Section 6.2 Number of Patients	Updated the total number of patients in the study overall (36 to 54), total number of study sites (50), and location of the study sites (North America, Europe, and Asia-Pacific).	Number of sites and locations expanded to recruit patients from more areas. Subjects from the Asia-Pacific region will be included in Part B to collect ethnicity-specific information. Number of patients decreased due to enrollment rates and patient availability.
10.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Updated exclusion criterion 10 to also exclude patients with significant ocular medical conditions; updated exclusion criterion 12 to also exclude patients in vaccine studies; adjusted exclusion criterion 13 to clarify timing; clarified exclusion criterion 17 for identification of patients with hepatitis B or C.	Ensure investigators exclude patients with significant ocular conditions and patients participating in any vaccine studies. Provide clarification for investigators on the timeline for inclusion of patients with localized herpes simplex infections. Provide clarification regarding the tests used to identify patients with hepatitis B or C.

Change Number	Protocol Amendment 5 Summary of Changes Since the Last Version of the Approved Protocol Sections Affected by Change *Location*	Description of Each Change and Rationale *Description*	*Rationale*
11.	Section 8.2 Prophylactic Coadministration Regimen (New section) Section 8.2.1 Prophylactic Coadministration Regimen for First Study Drug Dosing Events (Main Study and OLE) (New section) Section 8.2.2 Prophylactic Coadministration Regimen for Study Drug Dosing Events Subsequent to First Dosing Events (New section) Table 8.b Prophylactic Coadministration Regimen for First Study Drug Dosing Events (New table) Table 8.c Prophylactic Coadministration Regimen for Study Drug Dosing Events Other Than First Dosing Events (New table) Section 8.2.3 Postdose Medication Section 8.2.4 Additional Considerations for Patients with Respiratory Complications (New section heading) Section 8.7.1 [redacted] Section 8.7.2.1 [redacted] Section 9.5.4 OLE Dosing Period (EW1 to EW8) Appendix A Part A and B Main Study Schedule of Events, edited footnote z Appendix B Schedule of Events: OLE-A and OLE-B, edited footnote p	Modified prophylactic coadministration regimens for each dose of TAK-079 and indicated that adjustments to this regimen may be communicated to the site, if needed, based on emerging data; updated relevant sections throughout the protocol.	Prevent possible [redacted] and provide option for updating guidance based on emerging data.
12.	Section 8.7.1 [redacted]	[redacted]	[redacted]

Change Number	Protocol Amendment 5 Summary of Changes Since the Last Version of the Approved Protocol Sections Affected by Change	Description of Each Change and Rationale	
	Location	*Description*	*Rationale*
13.	Section 8.7.1.1 [redacted]	[redacted]	[redacted]
14.	Table 8.f Summary of Subsequent Dosing Criteria Section 8.7.2.1 [redacted] Section 9.4.15 [redacted] Appendix A [redacted] Appendix B Schedule of Events: OLE-A and OLE-B, edited footnote m	[redacted]	[redacted]
15.	Section 8.7.2.1 [redacted]	[redacted]	[redacted]
16.	Section 9.4.1.1 [redacted] Section 9.4.14 [redacted] Appendix A [redacted] Appendix B Schedule of Events: OLE-A and OLE-B, including new footnote o	[redacted]	[redacted]

Change Number	Protocol Amendment 5 Summary of Changes Since the Last Version of the Approved Protocol Sections Affected by Change	Description of Each Change and Rationale	
	Location	***Description***	***Rationale***
17.	Section 9.4.4 Medical History Appendix A Part A and B Main Study Schedule of Events, added footnote h	Added that a complete medical history should include ocular medical history or ophthalmic clinical symptoms (including allergic reactions) and that if an eye exam has been conducted within the previous year, a copy of the records from that exam should be provided to the site as source documentation if possible	Ensure that medical history related to ocular events is not overlooked.
18.	Section 9.4.13.1 Primary Specimen Collection Table 9.b Primary Specimen Collection Section 9.4.15.1 [redacted] Section 9.4.15.2 [redacted] Section 9.4.15.3 [redacted] Section 9.4.15.4 [redacted] Section 9.4.15.5 [redacted] Appendix A [redacted] Appendix B [redacted] Appendix J [redacted]	[redacted]	[redacted]
19.	Section 9.4.18 [redacted] Appendix A [redacted] Appendix B [redacted]	[redacted]	[redacted]
20.	Section 11.0 STUDY-SPECIFIC COMMITTEES	Added that an internal safety review will be conducted by an internal independent SRC prior to initiation of Part B and as needed.	Clarification of the criteria for opening Part B.

Change Number	Protocol Amendment 5 Summary of Changes Since the Last Version of the Approved Protocol Sections Affected by Change	Description of Each Change and Rationale	
	Location	***Description***	***Rationale***
21.	Section 2.0 STUDY SUMMARY Section 13.1.3 Efficacy Analysis	Added that the number and percentage of subjects attaining each type of response will be summarized by treatment group	Clarification to specify statistical analysis parameters.
22.	Section 13.1.5 [redacted]	[redacted]	[redacted]
23.	Section 2.0 STUDY SUMMARY Section 13.3 Determination of Sample Size	Reworded section and bolded text stating that the study is exploratory and not powered to address any predefined hypothesis.	Clarification that the study is not powered to address any predefined hypotheses.
24.	Section 6.1 Overview of Study Design	Removed the statement that evaluation of intermediate doses and expansion of existing dose level may be permitted after discussion between the sponsor and investigators.	Clarification that this process is not planned.
25.	Section 8.2 Prophylactic Coadministration Regimen	Added the option for the sponsor to provide medications for prophylactic coadministration if they cannot be obtained by the clinical site.	Allow flexibility based on differences in regional drug availability or local regulations.
26.	Section 8.7.1.1 [redacted]	[redacted]	[redacted]
27.	Table 9.b Primary Specimen Collection	Added HBsAg to the primary specimen collection table.	Reflect assessment mentioned in the exclusion criterion for identification of patients with hepatitis.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	**Compound:** TAK-079
Title of Protocol: A Phase 2, Randomized, Double-blind, Placebo-Controlled Study to Evaluate Safety, Tolerability, and Efficacy of TAK-079 in Patients With Persistent/Chronic Primary Immune Thrombocytopenia	**EudraCT No.:** 2019-004103-12
Study Number: TAK-079-1004	**Phase:** 2

Study Design:

This is a randomized double-blind, placebo-controlled, phase 2 study designed to assess the safety, tolerability, and efficacy of TAK-079 in patients with persistent/chronic primary immune thrombocytopenia (ITP). This study is organized in 2 parts, Part A and Part B.

Part A

In Part A, patients are randomized to 1 of 3 study arms (including placebo) for a double-blind 8-week dosing period and 8-week blinded safety follow-up period (SFP).

- Arm A1: Matching placebo added to stable background therapy (n = 8 - 12 patients)
- Arm A2: TAK-079 100 mg added to stable background therapy (n = 8 - 12 patients).
- Arm A3: TAK-079 300 mg added to stable background therapy (n = 8 - 12 patients)

Safety assessments, including safety laboratory tests, will be performed each week before subsequent dosing. Patients may have study drug (TAK-079 or matching placebo) doses modified (eg, withheld or delayed) for safety reasons. Platelet levels will be assessed on Day 3 of Week 1 (2 days after the first dose) and on each weekly visit, before administration of the subsequent doses.

After an 8-week dosing period, patients will be followed for an 8-week blinded SFP. At the completion of SFP, study dosing will be unblinded and patients who were dosed with TAK-079, will continue to a 16-week long-term follow-up period (LFP) for continued observation of safety and efficacy. Those patients previously randomized to placebo will have the option to continue on to LFP or continue on to the open-label extension (OLE) phase.

Part A Open-label Extension

Additional laboratory evaluations and assessments will be performed at the Week 16 visit to ensure that the OLE eligibility criteria are met for those patients continuing on to OLE. The first dosing day in Part A open-label extension (OLE-A) phase (on Extension Week 1 [EW1]) is to occur less than 4 weeks after the Week 16 visit.

In OLE-A, patients will be randomly assigned to 1 of the following study arms:

- Arm A1-E1: TAK-079 100 mg added to stable, standard background therapy.
- Arm A1-E2: TAK-079 300 mg added to stable, standard background therapy.

Patients in Arms A1-E1 and A1-E2 will proceed through the 8-month protocol in an open-label fashion (2 months of open-label dosing, 2 months of open-label SFP, and 4 months of LFP).

Part B

Part B enrollment will not be initiated until a decision to continue on to Part B is determined based on an unblinded safety data review after a minimum of 24 patients (8 patients per arm) exit the dosing period with a minimum of 4 study doses.

In Part B, a minimum of 12 and up to approximately 18 eligible patients will be randomized after screening in a double-blind 1:2 ratio to 1 of the following treatment groups:

- Arm B1: Matching placebo added to stable, standard background therapy (n = 4 - 6).

- Arm B2: TAK-079 600 mg added to stable, standard background therapy (n = 8 - 12).

Similar to Part A, safety assessments, including safety laboratory tests, will be performed each week before subsequent dosing. Patients may have study drug (TAK-079 or matching placebo) doses modified (eg, withheld or delayed) for safety reasons. Platelet levels will be assessed on Day 3 of Week 1 (2 days after the first dose) and on each weekly visit, before administration of the subsequent doses.

After an 8-week dosing period, patients will be followed for an 8-week blinded SFP. At the completion of SFP, study dosing will be unblinded and patients who were dosed TAK-079, will continue to a 16-week LFP for continued observation of safety and efficacy. Those patients previously randomized to placebo will have the option to continue on to LFP or continue on to the OLE.

Part B Open-label Extension

Additional laboratory evaluations and assessments will be performed at the Week 16 visit (at the end of Part B) to ensure all OLE eligibility criteria are met for those patients continuing on to OLE. The first dosing day in Part B open-label extension (OLE-B) phase (on EW1) is to occur less than 4 weeks after the Week 16 visit.

In OLE-B, patients will be assigned to TAK-079 600 mg added to stable, standard background therapy (Arm B1-E).

Patients in Arms B1-E will proceed through the 8-month protocol in an open-label fashion (2 months of open-label dosing, 2 months of open-label SFP, and 4 months of LFP).

Note: At any point in the study, patients may receive rescue therapy, defined as additional dosing of concomitant medications, administered in accordance with institutional practices or the physician's best medical judgment, to control and manage ITP. Patients who receive rescue therapy during the dosing period will stop study treatment and enter the SFP, unless the patient is administered a specific dosing period–permitted rescue treatment as defined in Section 8.2.5. Additional assessments and evaluations may be performed as deemed necessary by local institutional practices and the primary investigator.

Primary Objectives:

The primary objective is to evaluate the safety and tolerability of TAK-079 in patients with persistent/chronic primary ITP.

Secondary Objectives:

The secondary objective is to assess the effects of TAK-079 on platelet counts in patients with persistent/chronic primary ITP.

Patient Population: Patients ≥18 years of age with persistent/chronic primary ITP.

Number of Patients:

Part A: at least 24 and up to 36 patients, randomized as follows:

- Matching placebo [a]: 8 - 12 patients
- TAK-079 100 mg [a]: 8 - 12 patients.
- TAK-079 300 mg [a]: 8 - 12 patients

Part B: at least 12 and up to 18 patients randomized as follows:

- Matching placebo [a]: 4 - 6 patients
- TAK-079 600 mg [a]: 8 - 12 patients.

[a] To be dosed in combination with principal investigator–directed ITP standard background therapy.

Number of Sites:

Approximately 50 study sites in North America, Europe, and Asia-Pacific.

Dose Level(s):	**Route of Administration:**
Part A: Matching placebo [a] TAK-079 100 mg [a] TAK-079 300 mg [a] **OLE-A:** TAK-079 100 mg [a] TAK-079 300 mg [a] **Part B:** Matching placebo [a] TAK-079 600 mg [a] **OLE-B:** TAK-079 600 mg [a] [a] To be dosed in combination with principal investigator–directed ITP standard background therapy.	TAK-079/matching placebo will be administered through subcutaneous injections.
Duration of Treatment: Once weekly for 8 weeks. For those eligible placebo patients choosing to continue to an OLE, there is also 8 weeks of dosing.	**Period of Evaluation:** Main dosing period (Part A and Part B): 8 weeks SFP: 8 weeks LFP: 16 weeks

Main Criteria for Inclusion:

1. Age 18 years or older and able and willing to comply with study procedures.
2. Diagnosed with ITP that has persisted for ≥3 months, diagnosed in accordance to The American Society of Hematology 2011 Evidence-based Practice Guideline for Immune Thrombocytopenia or the International Consensus Report on The Investigation and Management of Primary Immune Thrombocytopenia as locally applicable.
3. Has a mean platelet count of <30,000/μL (and individually ≤35,000/μL) on at least 2 measurements at least 1 week apart during screening.
4. Diagnosis of ITP supported by a prior response to an ITP therapy (other than a thrombopoietin receptor agonist) that achieved a platelet count of ≥50,000/μL.
5. If receiving standard background treatment for ITP, treatment should be stable in dose and frequency for at least 4 weeks before dosing.
   a) Permitted standard background treatments may include: 1 oral corticosteroid; ±1 immunosuppressant from the following list: azathioprine, danazol, dapsone, cyclosporine, mycophenolate mofetil, mycophenolate sodium; ±1 thrombopoietin receptor agonist (romiplostim, eltrombopag, avatrombopag); ± fostamatinib. Corticosteroids, including dexamethasone, must be given as oral, daily or every-other-day therapy as opposed to pulse therapy.
   b) The dose of any permitted standard background therapy must be expected to remain stable through the study, unless dose reduction is required due to toxicities.
6. Female patients of childbearing potential are required to have a negative pregnancy test. Both female patients of childbearing potential and male patients must practice an effective, reliable, and approved contraceptive regimen during the study and [redacted], whichever is longer, after discontinuation of treatment.
7. Voluntary written consent must be given before performance of any study-related procedure that is not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

Main Criteria for Exclusion:

1. Use of anticoagulants or any drug with antiplatelet effect (such as aspirin) within 3 weeks before screening.
2. History of any thrombotic or embolic event within 12 months before screening.
3. History of splenectomy within 3 months before screening.
4. Use of intravenous immunoglobulin (IVIg), subcutaneous immunoglobulin or anti-D immunoglobulin treatment within 4 weeks of screening, or an expectation that any therapy besides the patient's standard background therapies may be used for treatment of thrombocytopenia (eg, a rescue therapy) between screening and dosing.
5. Diagnosed with chronic obstructive pulmonary disease (COPD) or asthma, and a prebronchodilatory forced expiratory volume in 1 second (FEV_1) <50% of predicted normal.

   Note: FEV_1 testing is required for patients suspected of having COPD or asthma.
6. Use of rituximab or any monoclonal antibody for immunomodulation within 4 months before first dosing.

   Note: Patients with prior exposure to rituximab must have CD19 counts within the normal range at screening.
7. Use of immunosuppressants (such as cyclophosphamide, vincristine) other than permitted oral immunosuppressants within 6 months before first dosing.
8. Diagnosed with myelodysplastic syndrome.
9. Has received a live vaccine within 4 weeks before screening or has any live vaccine planned during the study.
10. Currently experiencing any medical condition that, in the opinion of the investigator, might interfere with the patient's participation in the study (such as significant ocular, cardiovascular, pulmonary, hematologic, gastrointestinal, endocrinologic, hepatic, renal, neurologic, malignancy, or infectious disease), that poses an added risk for the patient, or could confound the assessment of the patient.
11. Pregnancy or lactation during screening period or on Day 1 before first dose of study drug.
12. Participation in any other investigational drug study (including vaccine study) or exposure to other investigational agent within 4 weeks or 5 half-lives, whichever is longer, before Day 1.
13. Has 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. A mild, localized herpes simplex infection within 12 weeks before study treatment is initiated is allowed, as long as the lesion has resolved without systemic therapy before Day 1.

[redacted]

15. Has a positive T-cell interferon-γ release assay (TIGRA) (results through QuantiFERON TB Gold test or T-Spot/Elispot) at the screening visit, 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:
       – Has a negative PPD skin test (defined as <5 mm induration).
       – Is at 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).
16. Has a serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
17. Has hepatitis B (a positive test result for hepatitis B surface antigen [HBsAg], or hepatitis B core antibody [anti-Hbc]), or Hepatitis C (positive HCV RNA), or HIV antibody/antigen, at screening.
    However, an individual who has a known history of chronic hepatitis C and has been treated and fully cured of the

disease, confirmed with a negative hepatitis C virus RNA polymerase chain reaction test at screening, is not excluded on the basis of positive hepatitis C antibody alone.

18. Has a history of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in the TAK-079/placebo formulation.

Main Criteria for Evaluation and Analyses:

The primary endpoint is the percentage of patients with treatment-emergent adverse events (TEAEs) including Grade 3 or higher events, serious adverse events, and adverse events (AEs) leading to TAK-079 discontinuation.

The secondary efficacy endpoints assess the effects of TAK-079 administration on the changes in platelet count, through the following 4 endpoints:

1. **Percentage of patients with a platelet response.** Platelet response is defined as a platelet count ≥50,000/μL and ≥20,000/μL above baseline on at least 2 visits without a dosing period–permitted rescue treatment in the previous 4 weeks and without any other previous rescue therapy.
2. **The percentage of patients with a complete platelet response.** Complete platelet response is defined as a platelet count ≥100,000/μL on at least 2 visits without a dosing period–permitted rescue treatment in the previous 4 weeks and without any other previous rescue therapy.
3. **The percentage of patients with a clinically meaningful platelet response.** A clinically meaningful platelet response is defined as a platelet count ≥20,000/μL above baseline on at least 2 visits without a dosing period–permitted rescue treatment in the previous 4 weeks and without any other previous rescue therapy.
4. **The percentage of patients with a hemostatic platelet response.** A hemostatic platelet response is defined for patients with a baseline platelet count of <15,000/μL who achieve a platelet count of ≥30,000/μL and ≥20,000/μL above baseline on at least 2 visits without a dosing period–permitted rescue treatment in the previous 4 weeks and without any other previous rescue therapy.

Statistical Considerations:

Safety analysis: The safety analysis will include all patients who have received at least 1 dose of study drug.

Safety will be evaluated by the frequency of AEs, severity and types of AEs, and by changes from baseline in patients' vital signs, weight, and clinical laboratory results using the safety analysis set. Exposure to study drug and reasons for discontinuation will be tabulated.

AEs that occur after administration of the first dose of TAK-079 or placebo and through the end of the SFP will be tabulated and followed until resolution.

Related AEs and coronavirus disease 2019 (COVID-19)-related AEs that occur during the LFP will also be summarized.

AEs will be tabulated according to the latest version of Medical Dictionary for Regulatory Activities, and data will be summarized using Preferred Term and primary System Organ Class. All safety analyses will be performed using the safety analysis set.

Efficacy Analysis:

Efficacy endpoints will be summarized by descriptive statistics and presented by treatment group as well as by study Part. Where appropriate, efficacy endpoints may be analyzed with the following methods:

- The number and percentage of subjects attaining each type of response will be summarized by treatment group. Binary responder endpoints will be analyzed using a Fisher exact test.
- Change from baseline endpoints measured repeatedly over time will be analyzed using a mixed-model repeated-measures analysis, which includes treatment, visit, and (treatment × visit) interaction terms as the factors, with baseline values as covariates.

All tests of treatment effects will be conducted at a 2-sided α level of 0.05, and 95% CIs for the differences in proportions and least squares means will be provided. No inferential hypothesis was tested in these endpoints, so CIs and p-values are not adjusted for multiplicity.

Interim Analyses

One unblinded safety review and one interim analysis will be conducted before the final database lock of this study.

Unblinded Safety Review: An unblinded safety review will take place once a minimum of 24 evaluable patients are available for analysis in Part A. For the purposes of this unblinded safety review, an evaluable patient is defined as a patient who exits the dosing period in Part A having received a minimum of 4 study doses, regardless of the reason for exit (eg, completion of Part A dosing period, early discontinuation, study drug discontinuation). This unblinded safety review will include all unblinded safety data from all patients from Part A available at the data-cut (data up to the Week 16 visit).

Interim Analysis: After all patients in Part B (Arms B1 and B2) complete the blinded SFP (complete the Week 16 visit), an unblinded interim analysis with Part A and Part B data will take place to evaluate safety and efficacy. If it is deemed not appropriate to continue onto Part B after the unblinded safety review, then this interim analysis will not be conducted.

Sample Size Justification:

This study is exploratory and not powered to address any predefined hypothesis.

Part A: At least 24 and up to 36 patients will be randomized in a ratio of 1:1:1 to treatment groups (TAK-079 100 mg, TAK-079 300 mg, or matching placebo).

Part B: At least 12 and up to 18 patients will be randomized 1:2 to treatment groups (matching placebo or TAK-079 600 mg).

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the clinical supplier list in the study manual. The identified vendors will perform specific study-related activities either in full or in partnership with the sponsor.

3.2 List of Abbreviations

[redacted]	[redacted]
AE	adverse event
anti-D	anti-D immunoglobulin
AUC	area under the concentration-time curve
CFR	Code for Federal Regulations
C_{max}	maximum observed concentration
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CrCl	creatinine clearance
CRO	contract research organization
CRS	cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	electronic clinical report form
DSMB	data safety monitoring board
ECG	electrocardiogram
EDC	electronic data capture
EW	extension week
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
hCG	human chorionic gonadotropin
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
Ig	immunoglobulin
IRB	institutional review board
[redacted]	[redacted]
ISR	injection site reaction
ITP	primary immune thrombocytopenia
[redacted]	[redacted]
IV	intravenous
IVIg	intravenous immunoglobulin
IXRS	interactive voice/web response system
LFP	long-term follow-up period
LLN	lower limit of normal
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities

MHRA	Medicines and Healthcare products Regulatory Agency
NK	natural killer
NOAEL	no-observed-adverse-effect level
OLE	open-label extension
OLE-A, B	Part A, B open-label extension
PCR	polymerase chain reaction
[redacted]	[redacted]
PMDA	Pharmaceuticals and Medical Devices Agency of Japan
PPD	purified protein derivative
PTE	pretreatment event
QW	once weekly
RBC	red blood cell
RRMM	relapsed/refractory multiple myeloma
SAE	serious adverse event
SC	subcutaneous
SFP	safety follow-up period
SLE	systemic lupus erythematosus
[redacted]	[redacted]
SUSAR	serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TIGRA	T-cell interferon-γ release assay
TNF-α	tumor necrosis factor-alpha
TPO-RA	thrombopoietin receptor agonist
UK	United Kingdom
ULN	upper limit of normal
US	United States

3.3 Corporate Identification

Takeda	Takeda Development Center Americas, Inc.

4.0 INTRODUCTION

4.1 Background

Primary immune thrombocytopenia (ITP) is a rare autoimmune disease characterized by autoantibody-mediated destruction of platelets. The annual incidence of ITP is approximately 1 to 5 per 100,000 adults and prevalence in the United States (US) is 8 per 100,000 children and 12 per 100,000 adults (Terrell et al. 2012). The main clinical manifestation of ITP is thrombocytopenia (platelet count <100,000/µL) with normal platelet morphology in the absence of other hematologic findings (such as abnormalities in the coagulation cascade, appearance of schistocytes or abnormal leukocytes). While many patients may be asymptomatic, thrombocytopenia causes bleeding in most patients. Bleeding may manifest in a spectrum of petechiae, nonpalpable purpura, epistaxis, and severe hemorrhage. The greatest risk of severe bleeding occurs when the platelet count drops below 10,000 to 20,000/µL. Finally, fatigue and associated reduced quality of life are common features of ITP; however, the mechanisms of these effects are not well-understood (Hill and Newland 2015; McMillan et al. 2008; Newton et al. 2011).

ITP is caused by autoantibodies directed against platelet surface glycoproteins on platelets or megakaryocytes. Production of autoantibodies involves both autoreactive CD4-positive T helper cells and splenic macrophages as antigen-presenting cells (Chong 2009; Kuwana et al. 2009; Patel et al. 2008; Sukati et al. 2007). Autoantibodies against glycoproteins Ib/IX, Ia/IIa, IV, and V have been described, and epitope spreading is known to occur (Cines and Blanchette 2002). The presence of multiple antibodies against different epitopes may predict more severe disease. Platelets coated with autoantibodies are cleared by macrophages in the spleen and liver.

Treatment for ITP is divided into first-line and second-line treatments (Provan et al. 2010). First-line treatments include corticosteroids, intravenous immunoglobulin (IVIg) and anti-D immunoglobulin (anti-D). These agents generally work by decreasing platelet destruction. Second-line therapies include immunosuppressants that function to decrease the production of autoantibodies. Medical therapy includes azathioprine, cyclophosphamide, cyclosporin A, danazol, dapsone, mycophenolate mofetil, and rituximab. These drugs are limited by variable efficacy, toxicities, and transient response. Other forms of therapy are splenectomy and the use of thrombopoietin receptor agonists (TPO-RAs). Splenectomy, although highly efficacious, is associated with a high complication rate (Kojouri et al. 2004), and in many practice settings is deferred because of the surgical risk and patient and physician preference.

TPO-RAs (romiplostim, eltrombopag, and avatrombopag), which increase platelet production by stimulation of megakaryocytes, are also highly efficacious, but often require chronic treatment and are associated with an increase in bone marrow reticulin formation, which has been described for both romiplostim and eltrombopag (Bussel et al. 2009; Kuter et al. 2008) while abnormalities in liver function tests have been observed in 11% of patients on eltrombopag (Cheng et al. 2011). Eltrombopag has a boxed warning for severe and potentially life-threatening hepatotoxicity. Additionally, wide swings in the platelet count can be seen with TPO-RAs, with platelet counts reaching the 700,000 to 1 million/µL range. Fostamatinib, a tyrosine kinase inhibitor which

reduces phagocytosis of autoantibody-coated platelets, is a therapy of modest effect reserved for refractory patients who fail second-line therapies (Bussel et al. 2018).

Approximately 20% of patients do not respond to the therapeutic approaches listed above (Provan et al. 2010). There is a need for a novel therapy in ITP which could provide deeper and sustained responses with a favorable safety profile to help achieve a hemostatic platelet count and improve patients' quality of life.

4.2 Rationale for the Proposed Study

TAK-079 is a fully human anti-CD38 immunoglobulin (Ig) G1 monoclonal antibody (mAb), which depletes cells expressing high levels of target by apoptosis, antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and antibody-dependent cellular phagocytosis. CD38 is a cell surface molecule that is expressed at high levels on short- and long-lived plasma cells, plasmablasts and natural killer (NK) cells, and is induced on activated B- and T-cells. Depletion of plasma cells and plasmablasts would lead to a reduction in the levels of immunoglobulins (Ig) and pathogenic autoantibodies, thereby reducing the autoantibody-mediated destruction of platelets and improving the platelet count.

TAK-079 is therefore being proposed as a potential treatment for ITP in adult patients.

TAK-079 is in early-stage clinical development for the treatment of hematologic malignancies and autoimmune diseases. The clinical development plan is based on a comprehensive review of the available nonclinical and clinical data with TAK-079 and other anti-CD38 monoclonal antibodies, and the ongoing investigation of the biology of several possible indications. TAK-079 has been evaluated in a thorough, comprehensive nonclinical safety program comprising single- and repeat-dose toxicology studies in cynomolgus monkeys of up to 13 weeks in duration. In these studies, TAK-079 has demonstrated an acceptable safety profile and dose-dependent pharmacodynamic effects consistent with the mode of action, supporting continuing clinical development (see Module 2.6.2 and TAK-079 Investigator's Brochure [IB]).

4.2.1 Rationale for Dosing Regimen

This study is organized in 2 parts (Part A and an optional Part B, each consisting of the main study and open-label extension [OLE] phases, see Section 6.0, Figure 6.a, Figure 6.b, and Figure 6.c for details). In Part A of this study, doses of 100 and 300 mg of TAK-079 or matching placebo will be administered by subcutaneous (SC) injection in a double-blinded study design. Each study arm will enroll at least 8 and up to 12 patients (for a total of 24 to 36 patients across 3 dosing arms of Part A). The study drug or matching placebo is administered once weekly (QW) during the 8-week dosing period, for a maximum 8 study doses. After a minimum of 24 patients (8 patients per arm) exit the Part A dosing period with a minimum of 4 study doses, an unblinded safety data review will be performed (see Section 6.1.2 for details) to decide whether to move forward with study Part B. Part A enrollment will end once Part B enrollment is initiated. Part B consists of a dosing cohort of TAK-079 600 mg and a placebo arm. A total of 12 - 18 patients will be enrolled and randomized, with a ratio of 2:1, into the TAK-079 600 mg and the placebo arm. Similar to Part A, patients in Part B will receive study drug by SC injection in a double-blinded manner QW during the 8-week

dosing period, for a maximum 8 study doses. Within each study part (Part A and B), an OLE phase will be available for all placebo patients who wish to obtain access to active study drug following the completion of the main study dosing period and a 2-month safety follow-up period (SFP). Please note the information presented below reflects the data used to support the dosing rationale included in the original protocol (dated 06 November 2019).

The criteria for selecting the doses and schedule of TAK-079 for treating patients with ITP was based upon identifying previously well-tolerated doses that demonstrated pertinent pharmacodynamic activity. The clinical experience to date has demonstrated that TAK-079 is safe and well tolerated in 3 different populations (ie, healthy subjects, patients with relapsed/refractory multiple myeloma [RRMM], and patients with systemic lupus erythematosus [SLE]) and across a broad range of doses (up to 1200 mg), vascular concentrations and exposures.

In healthy subjects in Study TAK-079_101, single SC doses of TAK-079 up to 0.6 mg/kg (fixed dose equivalent of approximately 45 mg) were well tolerated, adverse events (AEs) were mild to moderate in intensity, with most of the AEs being mild. There were no serious AEs (SAEs) or deaths reported in the study, and no AEs led to either study or visit discontinuation. No remarkable findings for laboratory tests, electrocardiograms (ECGs), vital signs, or physical examinations were reported that were related to the administration of TAK-079 (see TAK-079 IB).

In the ongoing study in RRMM, 33 patients in total have been enrolled across 5 dose-escalation cohorts (4 patients in 45 mg; 3 patients in 135 mg; 12 patients in 300 mg; 12 patients in 600 mg and 2 patients in 1200 mg). A maximum duration of exposure is 12 cycles as of September 2019, for a patient in each of the 135 mg and 300 mg cohorts, respectively. The maximum tolerated dose has not been identified and no dose-limiting toxicities have been reported. At the IB data-cut off (20 March 2019), the safety profile was comparable for all tested doses (45 mg [n = 4], 135 mg [n = 3], 300 mg [n = 6] and 600 mg [n = 6]. No patients have experienced dose-limiting toxicities, injection site reactions (ISRs), or systemic infusion reactions. No drug-related SAEs, AEs that led to study discontinuation, or on-study deaths, have been reported. As of June 2019, with additional enrollment to the 300 mg and 600 mg dose cohorts, TAK-079 continues to be safe and well tolerated, and no new safety concerns have been identified. The most commonly reported (at least 20% of all patients) treatment-emergent AEs (TEAEs) by Preferred Term regardless of causality at doses up to 600 mg include anemia, decreased appetite, fatigue, headache, hypertension, and insomnia. All AEs have been scored according to the Common Terminology Criteria for Adverse Events (CTCAE) scale as Grade 1 or 2 other than 2 events that were reported as drug-related Grade 3 events (decreased neutrophil count and anemia [in 1 patient each]), both of which were transient.

In the ongoing study in SLE, 8 patients have been enrolled and treated with 45 mg TAK-079 or placebo (in a blinded manner). As of the IB data cutoff (N = 3 patients) from March 2019, 1 patient has reported 2 TEAEs: nausea and headache (both events Grade 1). No infusion reactions, cytokine release syndrome (CRS) or ISRs have been reported.

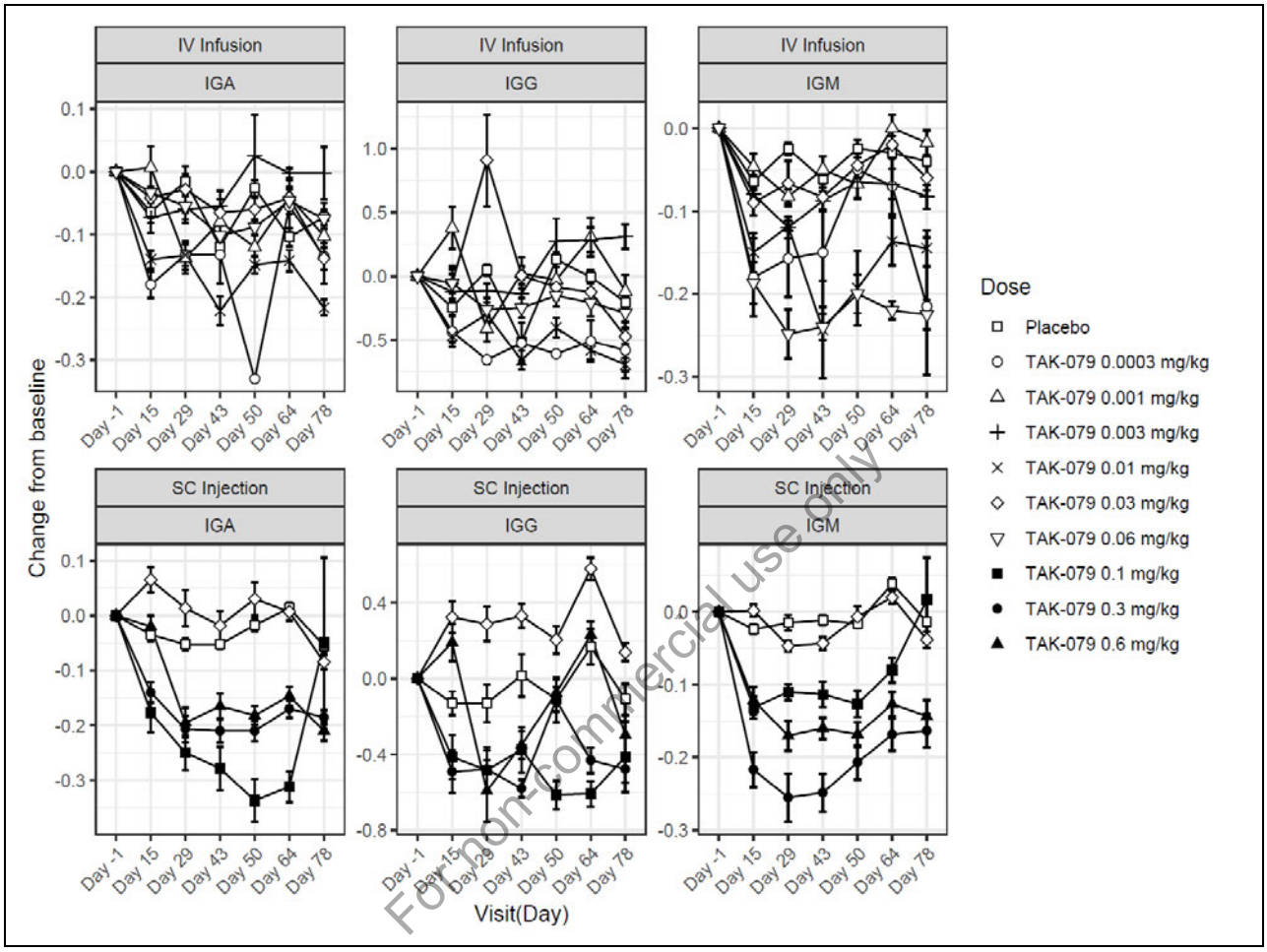
Three AEs were observed in the repeat-dose, 3-month, Good Laboratory Practice (GLP)-compliant toxicology studies in pharmacologically-responsive monkeys. These adverse effects were dose-dependent thrombocytopenia, anemia, and/or leukopenia (associated with infection only at nontolerated doses). Thrombocytopenia set the nonclinical

no-observed-adverse-effect level (NOAEL) at a dose of 0.3 mg/kg, which corresponded to a maximum observed concentration (C_{max}) of 8.1 µg/mL and an area under the concentration-time curve (AUC) of 28.88 d*µg/mL. Drug-related thrombocytopenia, anemia, and leukopenia have not been observed in clinical studies to date, despite the current dosing regimens exceeding the associated nonclinical doses, concentrations, and exposures up to a maximum clinical dose of 600 mg (maximum individual concentration of 235 µg/mL and AUC of 698.1 d*µg/mL; note, data for 1200 mg cohort is not yet available).

To further investigate the potential for anemia and thrombocytopenia in humans, a series of in vitro studies were performed. TAK-079 bound to CD38 on 11% to 17% of human platelets in platelet-rich plasma (1:8 platelet-rich plasma dilution, n = 2 healthy donors) with intensity 57% to 70% that of isotype control antibody at concentrations of 20 µg/mL in vitro (TKD-BCS-00327-R1 Amendment 1) (monkey platelets were not assessed due to technical limitations). Also, TAK-079 bound to CD38 on healthy human red blood cells (RBCs) (~10 to 51%, n = 5) and monkey RBCs (up to 19%, n = 1) with low intensity at concentrations 0.1 to 100 µg/mL in vitro (TKD-BCS-00064-R1-Report and TKD-BCS-00327-R1 Amendment 1) and did not induce hemolysis ≤20 µg/mL, or hemagglutination ≤1000 µg/mL in vitro, the highest concentrations tested (TKD-BCS-00327-R1 Amendment 1). TAK-079 also bound to human and monkey megakaryocyte and erythroid progenitors but did not induce direct cytotoxicity in these cells (TKD-BCS-00315-R1 and TKD-BCS-00407-R1). Lastly, TAK-079 bound to subsets of human and monkey leukocytes and depleted cells that express high densities of CD38 (eg, plasma cells, plasmablasts, and NK cells) (TAK-079-10010, TAK-079-10166, and TAK-079-1501). Importantly, despite binding activity observed in vitro, drug-related anemia or thrombocytopenia have not been observed in clinical studies to date.

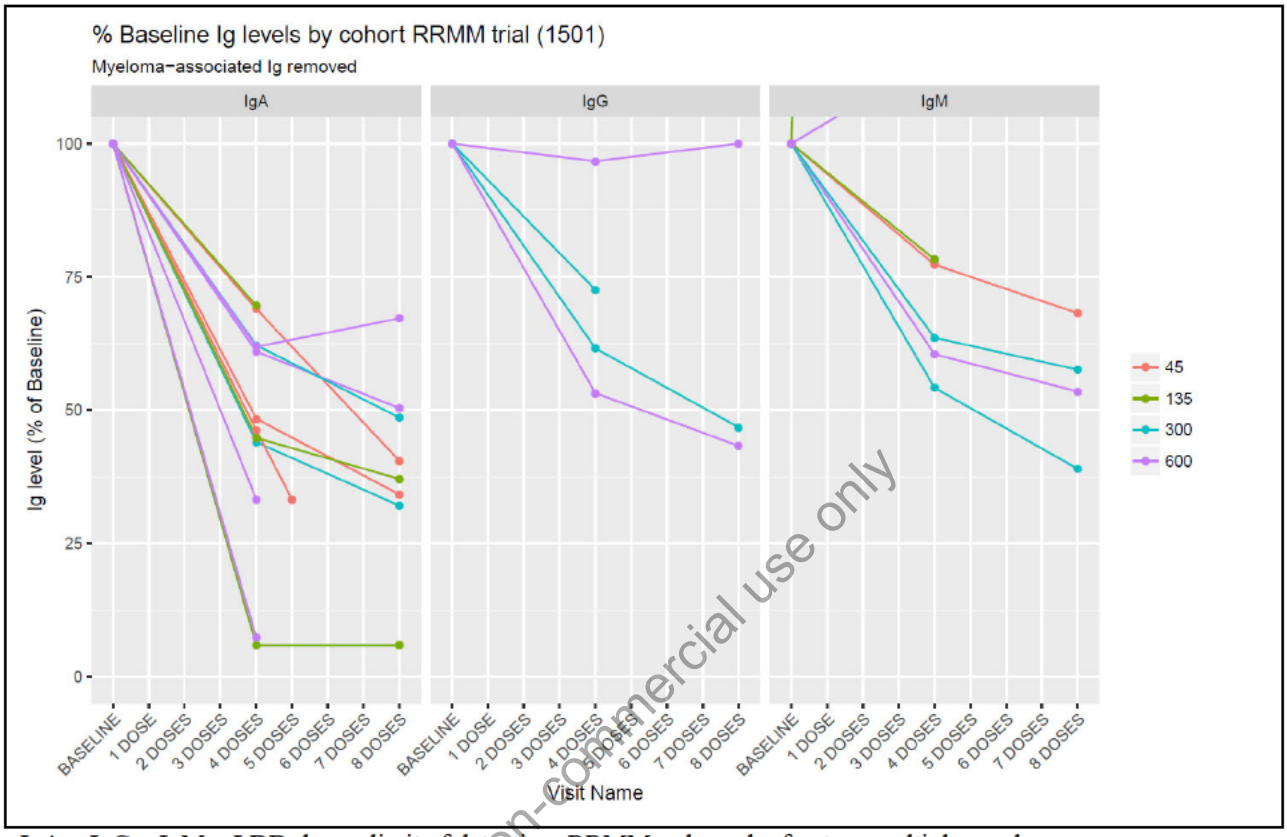
[redacted] A single SC dose of TAK-079 at 0.1, 0.3, or 0.6 mg/kg to healthy subjects in Study TAK-079_101 reduced serum mean IgA levels by 20% to 30%; IgG levels by 40% to 60%; and, IgM by 10% to 25% (Figure 4.a). Similarly, weekly dosing of patients with RRMM in Study TAK-079-1501 with 45, 135, 300, or 600 mg generally reduced serum IgA to 30% to 95%, IgG to 5% to 60%, and IgM to 0% to 50% of baseline levels (Figure 4.b).

Figure 4.a Change in Serum Baseline of Total IgA, IgG, and IgM in Healthy Subjects



Ig: immunoglobulin; IV: intravenous(ly); SC: subcutaneous(ly); SEM: standard error of measurement.
Serum samples obtained following a single administration of TAK-079 or placebo, administered either as 0.003 to 0.06 mg/kg IV or 0.03 to 0.6 mg/kg as an SC injection.
Symbols represent the mean change for the cohort and error bars represent the SEM.

Figure 4.b Serum Levels of Total IgA, IgG, and IgM in Patients With RRMM



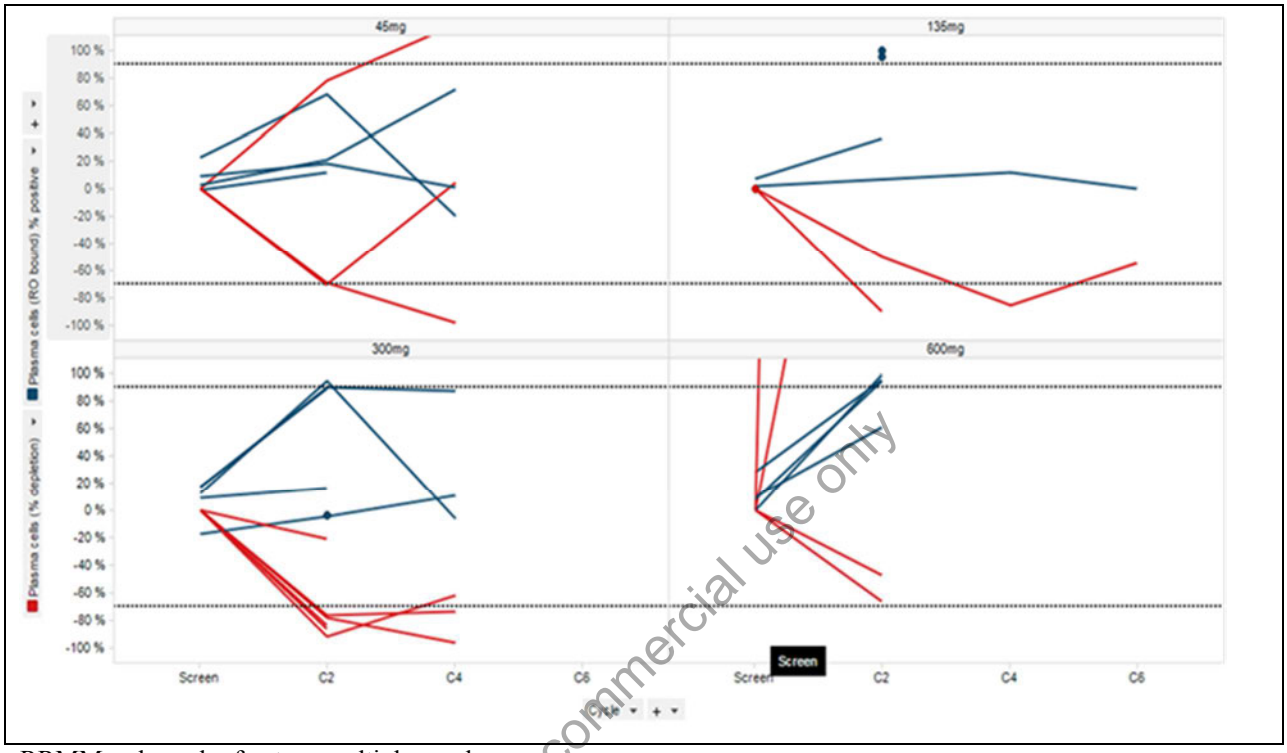
IgA: ; IgG: ; IgM: ; LDD: lower limit of detection; RRMM: relapsed refractory multiple myeloma.
Serum immunoglobulin levels (represented as percent of baseline value for IgA, IgG, or IgM) for each patient obtained after TAK-079 subcutaneous dosing (45, 135, 300, or 600 mg) 1 week after the indicated number of doses. The myeloma-associated immunoglobulin is not shown. Immunoglobulin profiles whose baseline values were already low (within 10% of the LLD of the assay) and subsequently dropped below the LLD are not shown.

[redacted] Importantly, the local production of autoantibodies in the bone marrow may inhibit platelet production by sequestering nearby megakaryocytes and newly-formed platelets, which can compound the thrombocytopenia caused by peripheral platelet destruction. The desired 80% sustained reduction in nonmalignant bone marrow plasma cells was best seen at ≥300 mg of TAK-079, with some effect seen at 135 mg and a weaker but positive effect seen at 45 mg (Figure 4.c). On the basis of these data, 2 doses (100 and 300 mg) were chosen for Part A of the study. The 100 mg dose was chosen as an intermediary dose between 45 and 135 mg, while the 300 mg dose was chosen as the lowest dose [redacted]. These doses also allow for a safety margin against 600 mg, which, as of the data cutoff of 20 March 2019, is the highest dose

tested in humans to date for which safety data are available. Although all doses tested thus far have not revealed any safety concerns (no SAEs or discontinuations attributed to study drug), the 600 mg dose (evaluated in Part B) will not be evaluated until an unblinded safety review is conducted once a minimum of 24 patients exit the dosing period having received a minimum of 4 doses of study drug in Part A (see Section 6.1.2 for details).

The dosing schedule in Study TAK-079-1004 was estimated on the basis of the desired effect of [redacted] In the absence of data characterizing TAK-079 activity [redacted]. In patients with RRMM, a ~50% reduction in IgG was observed after 8 weekly doses of TAK-079 (in the 300 mg and 600 mg cohorts, Figure 4.b). On the basis of these data, a schedule of 8 weekly doses was selected for the present study, with weekly monitoring of clinical laboratory values (complete blood count, [redacted]; see Table 8.f, Appendix A, and Appendix B for details and timings of these assessments) to ensure the safety of this approach. Following the 8-week dosing period, a 6-month follow-up is planned for the continued monitoring of safety laboratory test results and for evaluating the durability of any clinical benefit. Additionally, information will be obtained on [redacted] the reconstitution kinetics of IgG and autoantibody levels in patients with ITP to facilitate modeling for revised dosing regimens in subsequent studies. On the basis of the duration of reduction in IgG after a single exposure to TAK-079 in healthy subjects, 8 weekly doses as an inductive approach could be sufficient to provide long-term, durable efficacy in patients with ITP (as opposed to chronic dosing).

Figure 4.c Pharmacodynamic Effects of TAK-079 on Plasma Cells in Bone Marrow Aspirate Samples From Patients With RRMM



RRMM: relapsed refractory multiple myeloma.

Target occupancy (blue lines, percent of CD38 bound by TAK-079) and levels of plasma cells (red line, percent change from baseline level) in bone marrow aspirates from patients before treatment (screen), and then after 4 doses (Cycle 2), 12 doses (Cycle 4), and 14 doses (Cycle 6), at doses of TAK-079 at 45, 135, 300, or 600 mg dosed weekly for 8 weeks; followed by biweekly for 8 weeks; then monthly until disease progression. Target occupancy and plasma cell levels were quantified by flow cytometry and the data represent individual patients.

Case reports exist of successfully treating antibody-driven diseases with anti-CD38 therapy using the same dose and schedule as in patients with myeloma (daratumumab 16 mg/mL for ≥6 weekly doses), despite the absence of overall elevations in target plasma cells. For example, daratumumab was used to treat a patient with pure red cell aplasia (and otherwise normal bone marrow) from persistent anti-RBC antibodies following an ABO-mismatched allogenic bone marrow transplant for myelodysplastic syndrome (Chapuy et al. 2018). Similarly, daratumumab at the myeloma dose was used successfully in a pediatric patient with anti-RBC antibodies following bone marrow transplantation (Tolbert 2016). Lastly, a case of antibody-mediated rejection following renal transplantation for postinfectious membranoproliferative glomerulonephritis was treated successfully with 7 weekly doses of myeloma-dose of daratumumab following failure of bortezomib and rituximab therapy in a patient with a normal bone marrow (less than 1% plasma cells) and concurrently treated with tacrolimus and prednisone (Anand et al. 2017). No specific safety concerns of daratumumab therapy were reported. Together, these case reports indicate that the myeloma-dose of anti-CD38 therapy was safe and effective in patients without myeloma who

did not have any plasma cell tumor burden, had normal if not hypocellular bone marrow, and who had a critical need for removal of plasma cells secreting pathogenic antibodies.

In conclusion, the collective safety, tolerability, [redacted] profiles of TAK-079 in dose-escalation studies in healthy subjects and patients with RRMM supported the initial doses in Part A and dose escalation in Part B, as well as the dosing frequency and duration.

4.3 Benefits and Risks Assessment

Always refer to the latest version of the TAK-079 IB for the overall benefit/risk assessment and the most accurate and current information regarding pharmacokinetics, efficacy, and safety of TAK-079.

Because TAK-079 has not yet been tested in patients with ITP, the overall clinical benefits and risks of TAK-079 in treating patients with ITP have not been fully determined.

Potential benefits of TAK-079 in patients with ITP are based on nonclinical and clinical data presented in Section 4.2, "Rationale for the Proposed Study." TAK-079 has been shown to reduce autoantibodies in an in vitro study of long-lived plasma cells from lupus patients, reduce inflammation in a monkey collagen-induced arthritis model, and reduce total immunoglobulin levels (a surrogate marker for autoantibodies) in a clinical study of healthy subjects and a clinical study of patients with RRMM. It is therefore hypothesized that TAK-079 can reduce the levels of pathogenic autoantibodies in patients with ITP, thereby treating the thrombocytopenia caused by the autoantibody-mediated clearance of platelets.

Risks of TAK-079 are based on clinical and nonclinical data presented in Section 4.2.1, "Rationale for Dosing Schedule" and the intrinsic pharmacology of TAK-079 discussed in Section 8.7, "Management of Clinical Events." [redacted] Patients will be monitored closely for AEs in clinical studies with TAK-079.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective is to evaluate the safety and tolerability of TAK-079 in patients with persistent/chronic primary ITP.

5.1.2 Secondary Objective

The secondary objective is to assess the effects of TAK-079 administration on platelet counts in patients with persistent/chronic primary ITP.

5.1.3 [redacted]

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoint is the percentage of patients with TEAEs including Grade 3 or higher events, SAEs, and AEs leading to TAK-079 discontinuation.

5.2.2 Secondary Endpoints

The secondary efficacy endpoints assess the effects of TAK-079 administration on the changes in platelet count, through the following 4 endpoints:

1. The percentage of patients with a platelet response. Platelet response is defined as a platelet count ≥50,000/μL and ≥20,000/μL above baseline on at least 2 visits without a dosing period–permitted rescue treatment in the previous 4 weeks and without any other previous rescue therapy.
2. The percentage of patients with a complete platelet response. Complete platelet response is defined as a platelet count ≥100,000/μL on at least 2 visits without a dosing period–permitted rescue treatment in the previous 4 weeks and without any other previous rescue therapy.
3. The percentage of patients with a clinically meaningful platelet response. A clinically meaningful platelet response is defined as a platelet count ≥20,000/μL above baseline on at least 2 visits without a dosing period–permitted rescue treatment in the previous 4 weeks and without any other previous rescue therapy.
4. The percentage of patients with a hemostatic platelet response. A hemostatic platelet response is defined for patients with a baseline platelet count of <15,000/μL who achieve a platelet count of ≥30,000/μL and ≥20,000/μL above baseline on at least 2 visits without a dosing

period–permitted rescue treatment in the previous 4 weeks and without any other previous rescue therapy.

5.2.3 [redacted]

[redacted]

6.0 STUDY DESIGN

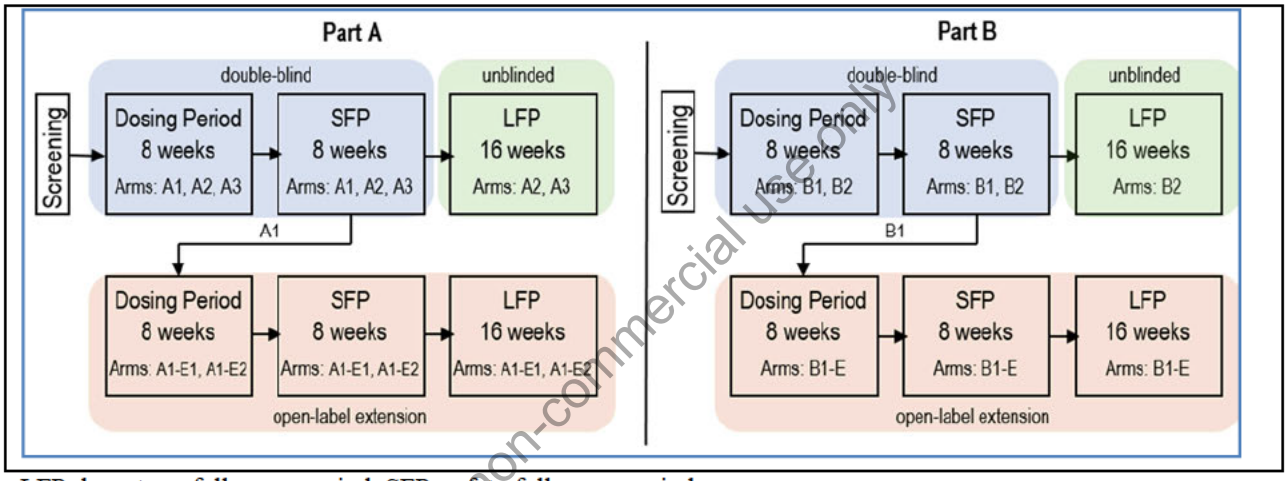
6.1 Overview of Study Design

This is a randomized double-blind, placebo-controlled, phase 2 study designed to assess the safety, tolerability, and efficacy of TAK-079 in patients with persistent/chronic primary ITP. This study is organized in 2 parts (see Figure 6.a): In Part A, patients are randomized to 1 of 3 study arms (including placebo) for a double-blind 8-week dosing period and 8-week SFP. After the SFP, patients will be unblinded to allow for placebo patients to participate in an OLE for access to TAK-079 while patients who were given TAK-079 continue to a long-term follow-up period (LFP) for continued observation of safety and efficacy. An unblinded safety review will take place once a minimum of 24 evaluable patients are available for analysis in Part A to decide whether to open enrollment into Part B (see Section 6.1.2 for more details). Following this unblinded safety analysis, an optional Part B may be triggered that enrolls patients at a higher dose of TAK-079 or placebo, in a design that is otherwise identical to Part A (see study schematics, Figure 6.a, Figure 6.b, and Figure 6.c). After all patients in Part B (Arms B1 and B2) complete the Week 16 visit, an

unblinded interim analysis with Part A and Part B data will take place to evaluate the preliminary safety and efficacy.

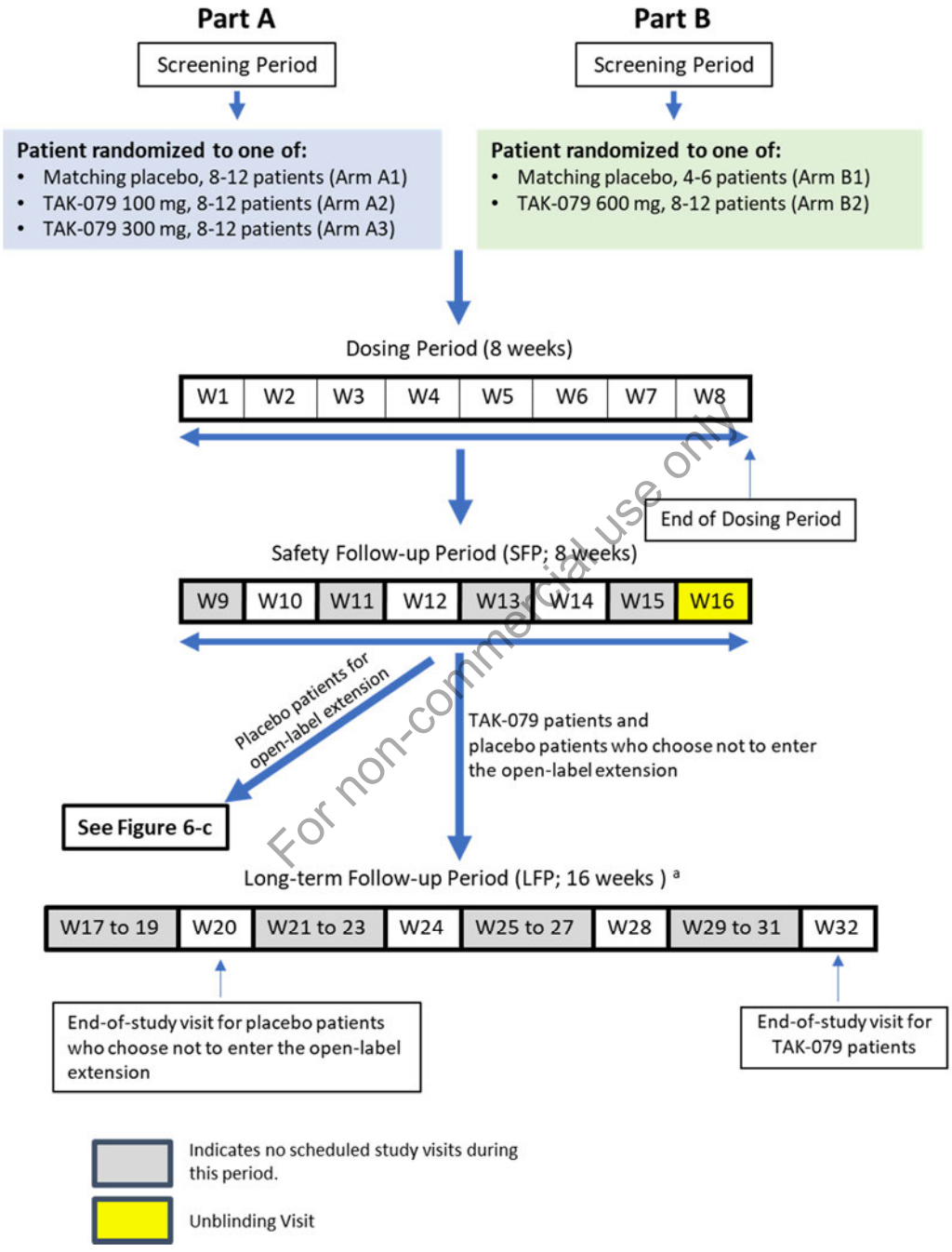
At any point in the study, patients may receive rescue therapy, defined as additional dosing of concomitant medications, administered in accordance with institutional practices or the physician's best medical judgment, to control and manage ITP. Patients who receive rescue therapy during the dosing period will stop study treatment and enter the SFP, unless the patient is administered a dosing period–permitted rescue treatment as defined in Section 8.2.5. Additional assessments and evaluations may be performed as deemed necessary by local institutional practices and the primary investigator.

Figure 6.a Study Schema: Overview



LFP: long-term follow-up period; SFP: safety follow-up period.
See Sections 6.1.1 and 6.1.2 for definitions of the study arms.

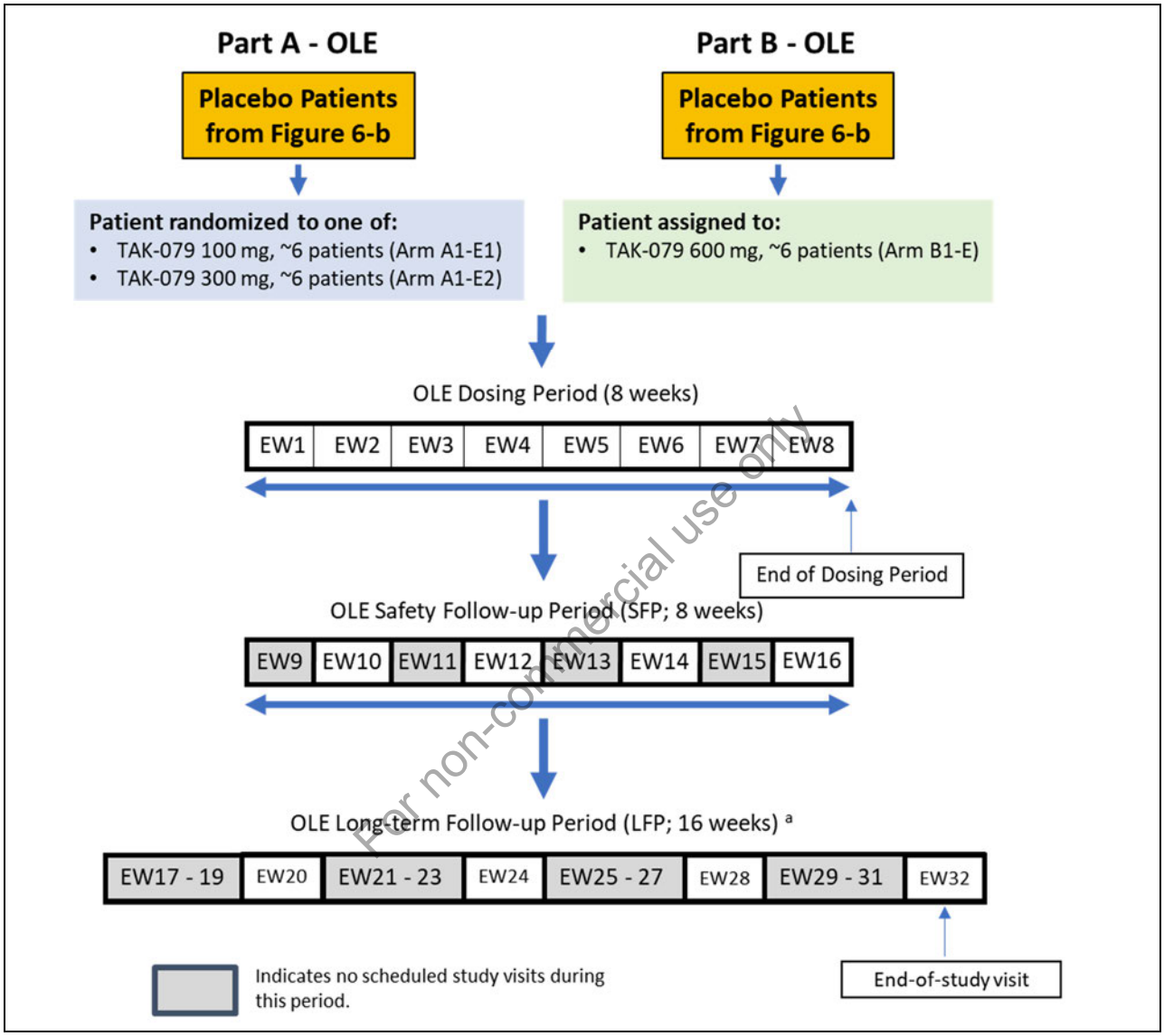
Figure 6.b Study Schematic: Part A and B, Main Study



AE: adverse event; COVID-19: coronavirus disease 2019; LFP: long-term follow-up period; SFP: safety follow-up period; W: week.

[a] Unresolved AEs as of Week 16 and related AEs/serious AEs with onset after SFP will be collected through the LFP. COVID-19 infection and COVID-19 vaccination-related AEs will be collected through the LFP regardless of causality.

Figure 6.c Schematic for the OLE Periods



AE: adverse event; COVID-19: coronavirus disease 2019; EW: extension week; LFP: long-term follow-up period; OLE: open-label extension; SFP: safety follow-up period.

[a] Unresolved AEs as of Week 16 and related AEs/serious AEs with onset after SFP will be collected through the LFP. COVID-19 infection and COVID-19 vaccination-related AEs will be collected through the LFP regardless of causality.

6.1.1 Part A Overview

After screening, at least 24 and up to 36 eligible patients will be randomized in a double-blind 1:1:1 ratio to 1 of the following groups (see Figure 6.b):

- **Arm A1:** Matching placebo added to stable background therapy (n = 8 - 12 patients).

- **Arm A2:** TAK-079 100 mg added to stable background therapy (n = 8 - 12 patients).
- **Arm A3:** TAK-079 300 mg added to stable background therapy (n = 8 - 12 patients).

TAK-079 or matching placebo will be administered via SC injection QW for 8 weeks (see Section 8.1 for more details). Safety assessments, including safety laboratory tests, will be performed each week before subsequent dosing. Patients may have study drug (TAK-079 or matching placebo) doses modified (eg, withheld or delayed) for safety reasons (see further details on dose modification/stopping criteria in Section 8.5). Platelet levels will be assessed on Day 3 of Week 1 (2 days after the first dose) and on each weekly visit, before administration of the subsequent doses.

After completing the 8-week dosing period, patients will enter a blinded SFP, completing safety and laboratory assessments every 2 weeks for 2 months.

At the completion of SFP (Week 16 visit), patients will be unblinded.

Patients who were dosed with TAK-079 (Arms A2 and A3) will be followed monthly for 4 months in an LFP to check platelet counts and to monitor for any ongoing drug-related AEs at the end of the SFP. Patients who were dosed with matching placebo (Arm A1) will be eligible for the Part A open-label extension (OLE-A) phase (see Section 6.1.1.1) for access to study drug. Placebo patients who opt not to participate in the OLE-A will end the study at the Week 20 visit of the LFP.

6.1.1.1 Part A Open-label Extension Phase

For patients who obtained placebo in Part A and who wish to continue in the OLE-A for access to study drug, laboratory evaluations will be obtained at the Week 16 visit (at the end of Part A) to ensure inclusion/exclusion criteria continue to be met as follows:

OLE Inclusion Criteria:

1. Platelet count at Week 16 or later of less than 50,000/μL and continued need for additional medical treatment in the opinion of the investigator.
2. For female patients of childbearing potential, a continued negative urine pregnancy test.
3. Meets all continued dosing criteria as in Table 8.f.
4. Continues to meet criteria for background concomitant medications as defined as follows: 1 oral corticosteroid (as daily or every-other-day therapy); ±1 immunosuppressant from the following list: azathioprine, danazol, dapsone, cyclosporine, mycophenolate mofetil, mycophenolate sodium; ±1 TPO-RA (romiplostim, eltrombopag, avatrombopag); ±fostamatinib. Background therapy should be stable for 4 weeks before the first day of dosing in the OLE.

OLE Exclusion Criteria:

1. Experiencing any medical condition that, in the opinion of the investigator, might interfere with the patient's participation in the study (such as significant cardiovascular, pulmonary, hematologic, gastrointestinal, endocrinologic, hepatic, renal, neurologic, malignancy, or infectious disease), that poses an added risk for the patient, or could confound the assessment of the patient.
2. Use of any rescue therapy in the 2 weeks preceding the first day of dosing in the OLE.
3. Has had an opportunistic infection since 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. A mild, localized herpes simplex infection is allowed, as long as the lesion has resolved without systemic therapy prior to the first day of dosing in the OLE.

The first dosing day in OLE-A (on Extension Week 1 [EW1]; see Schedule of Events [SOE] in Appendix B) is to occur less than 4 weeks after the Week 16 visit. In OLE-A, patients will be randomly assigned to 1 of the following study arms (see Figure 6.c):

- **Arm A1-E1:** TAK-079 100 mg added to stable, standard background therapy.
- **Arm A1-E2:** TAK-079 300 mg added to stable, standard background therapy.

Patients in Arms A1-E1 and A1-E2 will proceed through the 8-month protocol in an open-label fashion (2 months open-label dosing, 2 months open-label SFP, 4 months LFP).

6.1.2 Assessment and Criteria for Opening Part B Enrollment

An unblinded safety review will take place once a minimum of 24 evaluable patients are available for analysis in Part A. For the purposes of this unblinded safety review, an evaluable patient is defined as a patient who exits the dosing period in Part A having received a minimum of 4 study doses, regardless of the reason for exit (eg, completion of Part A dosing period, early discontinuation, study drug discontinuation). This unblinded safety review will include all unblinded safety data from all patients from Part A available at the data-cut (data up to the Week 16 visit). The purpose of the safety review is to inform the decision of whether to open enrollment to Part B, and based on the unblinded safety review the study may: (1) advance enrollment to Part B at the protocol-defined dose level, (2) advance enrollment to Part B at a lower dose level than the Part B protocol-defined level, (3) continue or expand enrollment in Part A, or (4) enact early termination of the study. Enrollment into Part A will end once Part B enrollment begins.

An internal, independent Safety Review Committee (SRC) will be established to review unblinded study safety data. The SRC may also review unblinded efficacy data from all patients from Part A available at the data-cut. The decision to advance to Part B will be based on the unblinded study safety data.

Members of the SRC will be separated from the clinical study team upon receiving unblinded data and until after all patients enrolled in Part A complete the blinded portion of the study and are individually unblinded. During the time of SRC review, enrollment into Part A may be kept open.

Details of the SRC membership, responsibilities, and safety review criteria will be presented in the SRC Charter.

6.1.3 Part B Overview

Once at least 24 patients in Part A (8 patients in each arm) have received at least 4 study doses, an unblinded safety review with all unblinded safety data available at the data-cut (data up to the Week 16 visit) across all Part A patients will be conducted by the Safety Review Committee to decide whether to open enrollment into Part B (see Section 6.1.2 for more details). In Part B, a minimum of 12 and up to 18 eligible patients will be randomized after screening in a double-blind 1:2 ratio to 1 of the following groups (see Figure 6.b):

- **Arm B1:** Matching placebo added to stable, standard background therapy (n = 4 - 6).
- **Arm B2:** TAK-079 600 mg added to stable, standard background therapy (n = 8 - 12).

The Schedule of Events/visits will continue as in Part A.

As in Part A, patients will be unblinded at the end of the SFP (Week 16 visit). Patients who were dosed with TAK-079 (Arm B2) will be followed monthly for 4 months in the LFP. Patients dosed with matching placebo (Arm B1) will be eligible for Part B open-label extension (OLE-B) phase for access to study drug (see Section 6.1.3.1). Placebo patients who opt not to participate in the OLE-B will end the study at the Week 20 visit.

6.1.3.1 Part B Open-label Extension Phase

For patients who obtained placebo in Part B who wish to continue in the OLE-B for access to study drug, laboratory evaluations will be obtained at the Week 16 visit (at the end of Part B) to ensure satisfaction of the OLE inclusion/exclusion criteria (as outlined in Section 6.1.1.1). The first dosing day in OLE-B (on EW1; see SOE in Appendix B) is to occur approximately less than 4 weeks after the Week 16 visit. In the OLE-B, patients will be offered (see Figure 6.c):

- **Arm B1-E:** TAK-079 600 mg added to stable, standard background therapy.

Patients in Arm B1-E will proceed through the 8-month protocol in an open-label fashion (2 months open-label dosing, 2 months open-label SFP, 4 months LFP).

6.2 Number of Patients

Approximately 36 to 54 patients with persistent/chronic primary ITP (ie, approximately 24 - 36 patients in Part A and 12 – 18 patients in Part B) will be randomized from approximately 50 study sites in the North America, Europe, and Asia-Pacific.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients randomized in Part A or Part B to TAK-079 will be treated for a maximum of 8 weeks and will be followed for an 8-week blinded SFP, and a 16-week unblinded LFP. Maximum total study participation will last 8 months from the initial day of study dosing.

Patients randomized to 8-week placebo dosing during either Part A or Part B, will have the option to continue on to their respective OLE phases (OLE-A or OLE-B) during which they will complete a maximum of 8 weeks of dosing with TAK-079, 8 weeks of SFP, and 16 weeks of LFP for a maximum total study participation of 13 months (including 4 weeks of interim time before the start of the OLE) from the initial day of the first dosing period. Patients who received placebo in either Part A or Part B who do not continue to an OLE will end the study at Week 20 in the LFP, for a maximum study participation of 5 months.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The analyses for the clinical study report will be conducted after all patients randomized in the study have completed the end-of-study visit (ie, Week 32 for TAK-079 patients, Week 20 for placebo patients who chose not to enter the OLE, or EW32 for placebo patients who participated in the OLE), as shown in Appendix A and Appendix B.

6.3.3 Time Frames for Primary and Secondary Endpoints to Support Disclosures

Refer to Section 15.4 for disclosure information for all primary and secondary endpoints.

6.3.4 Total Study Duration

It is anticipated that this study will end after all randomized patients have attended the end-of-study visit (ie, Week 32 for TAK-079 patients, Week 20 for placebo patients who chose not to enter the OLE or EW32 for placebo patients who participated in the OLE) as shown in Appendix A and Appendix B. It is expected that the full duration of the study will last for approximately 36 months (including the OLE), should Part B be activated, and 24 months if Part B is not activated.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

Each patient must meet all the following inclusion criteria to be to be randomized to treatment:

1. Age 18 years or older and able and willing to comply with study procedures.
2. Diagnosed with ITP that has persisted for ≥3 months, diagnosed in accordance to The American Society of Hematology 2011 Evidence-based Practice Guideline for Immune Thrombocytopenia (Neunert et al. 2011) or the International Consensus Report on The

Investigation and Management of Primary Immune Thrombocytopenia (Provan et al. 2010) as locally applicable.

3. Has a mean platelet count of <30,000/μL (and individually ≤35,000/μL) on at least 2 measurements at least 1 week apart during screening.
4. Diagnosis of ITP supported by a prior response to an ITP therapy (other than a TPO-RA) that achieved a platelet count of ≥50,000/μL.
5. If receiving standard background treatment for ITP, treatment should be stable in dose and frequency for at least 4 weeks before dosing.
   a) Permitted standard background treatments may include: 1 oral corticosteroid; ±1 immunosuppressant from the following list: azathioprine, danazol, dapsone, cyclosporine, mycophenolate mofetil, mycophenolate sodium; ±1 TPO-RA (romiplostim, eltrombopag, avatrombopag); ± fostamatinib. Corticosteroids, including dexamethasone, must be given as oral, daily or every-other-day therapy as opposed to pulse therapy.
   b) The dose of any permitted standard background therapy must be expected to remain stable through the study, unless dose reduction is required because of toxicities.
6. Female patients of childbearing potential are required to have a negative pregnancy test. Both female patients of childbearing potential and male patients must practice an effective, reliable, and approved contraceptive regimen during the study and [redacted], whichever is longer, after discontinuation of treatment (see Section 8.6.1).
7. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be randomized to treatment.

1. Use of anticoagulants or any drug with antiplatelet effect (such as aspirin) within 3 weeks before screening.
2. History of any thrombotic or embolic event within 12 months before screening.
3. History of splenectomy within 3 months before screening.
4. Use of IVIg, subcutaneous immunoglobulin or anti-D immunoglobulin treatment within 4 weeks of screening, or an expectation that any therapy besides the patient's standard background therapies may be used for treatment of thrombocytopenia (eg, a rescue therapy) between screening and dosing.
5. Diagnosed with chronic obstructive pulmonary disease (COPD) or asthma, and a prebronchodilatory forced expiratory volume in 1 second (FEV_1) <50% of predicted normal.

   Note: FEV_1 testing is required for patients suspected of having COPD or asthma.
6. Use of rituximab or any mAb for immunomodulation within 4 months before first dosing.

Note: Patients with prior exposure to rituximab must have CD19 counts within the normal range at screening.

7. Use of immunosuppressants (such as cyclophosphamide, vincristine) other than permitted oral immunosuppressants within 6 months before first dosing.
8. Diagnosed with myelodysplastic syndrome.
9. Has received a live vaccine within 4 weeks before screening or has any live vaccine planned during the study.
10. Currently experiencing any medical condition that, in the opinion of the investigator, might interfere with the patient's participation in the study (such as significant ocular, cardiovascular, pulmonary, hematologic, gastrointestinal, endocrinologic, hepatic, renal, neurologic, malignancy, or infectious disease), that poses an added risk for the patient, or could confound the assessment of the patient.
11. Pregnancy or lactation during screening period or on Day 1 before first dose of study drug.
12. Participation in any other investigational drug study (including vaccine study) or exposure to other investigational agent within 4 weeks or 5 half-lives, whichever is longer, before Day 1.
13. Has had an opportunistic infection ≤12 weeks before initial study dosing or is currently undergoing treatment for a chronic opportunistic infection, such as TB, pneumocystis pneumonia, cytomegalovirus, herpes simplex virus, herpes zoster, or atypical mycobacteria. A mild, localized herpes simplex infection within 12 weeks before study treatment is initiated is allowed, as long as the lesion has resolved without systemic therapy before Day 1.

[redacted]

15. Has a positive T-cell interferon-γ release assay (TIGRA) (results through QuantiFERON TB Gold test or T-Spot/Elispot) at the screening visit, 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:

- Has a negative PPD skin test (defined as <5 mm induration).
- Is at 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).

16. Has a serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
17. Has hepatitis B (a positive test result for hepatitis B surface antigen [HBsAg], or hepatitis B core antibody [anti-Hbc]), or Hepatitis C (positive HCV RNA), or HIV antibody/antigen, at screening.

    However, an individual who has a known history of chronic hepatitis C and has been treated and fully cured of the disease, confirmed with a negative hepatitis C virus RNA polymerase chain reaction test at screening, is not excluded on the basis of positive hepatitis C antibody alone.
18. Has a history of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in the TAK-079/placebo formulation.

8.0 STUDY DRUG

8.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

After completion of all screening assessments and procedures and confirmation of eligibility, patients will report to the study site on study Day 1 to begin dosing of TAK-079 or placebo in accordance to their randomized assigned treatment. Before TAK-079/placebo administration, patients will receive premedication as listed in Section 8.2.1 and will complete safety assessments as outlined in Table 8.f and Appendix A. Both the patient and physician will be blinded to treatment.

Patients will receive study drug via SC injection, QW, for 8 weeks as outlined in Table 8.a and the SOE in Appendix A. As study treatment will generally require multiple SC injections to administer the full dose, the Week 1 dose (and the dose on EW1 of the OLE; see Section 9.5.4 and Appendix B) will be administered by giving each SC injection 30 minutes apart until the full scheduled dose has been administered. On all other drug administration days, if the patient did not have a clinically significant infusion reaction per the investigator, the SC injections can be given at the same time without a waiting period.

Investigators will evaluate patients before each dose for the parameters outlined in Table 8.f. For the first dose in the main study or the OLE, laboratory assessments in Table 8.f may be evaluated using results obtained at screening or the Week 16 visit, respectively. Otherwise, laboratory results

should be obtained on the day before or the day of dosing. In instances where clinical parameters do not meet criteria for continued dosing, the study drug must be temporarily withheld until parameters meet dosing levels, or discontinued, as outlined in Table 8.f or in accordance with the principal investigator's judgment. Dosing of TAK-079/placebo may not otherwise be reduced or escalated for any given patient.

Note:

- If study dosing is held for 2 consecutive doses because of safety concerns or conditions outlined in Table 8.f, the patient will be discontinued from study dosing and will advance to the SFP.
- If 2 or more patients discontinue study dosing on the basis of the dose discontinuation criteria in Table 8.f, the Takeda clinician or designee will review available safety data to determine if adjustments to the treatment plan should be made.

Excluded and permitted medications are summarized in Table 8.d and Table 8.e, respectively. Rescue therapy information is outlined in Section 8.2.5.

Table 8.a Dosing Regimens

Dosing Arms	N	TAK-079 Dose Once Weekly for 8 Doses
Part A	**24 - 36 patients**	
ARM A1	8 - 12	Matching placebo
ARM A2	8 - 12	100 mg
ARM A3	8 - 12	300 mg
Part A open-label extension	**8 - 12 patients from Arm A1**	
ARM A1-E1	~4 - 6	100 mg
ARM A1-E2	~4 - 6	300 mg
Part B	**12 - 18 patients**	
ARM B1	4 - 6	Matching placebo
ARM B2	8 - 12	600 mg
Part B open-label extension	**4 - 6 patients from Arm B1**	
ARM B1-E1	~4 - 6	600 mg

8.2 Prophylactic Coadministration Regimen

Pre- and postdose prophylactic medications will be administered for prevention of [redacted]. An equivalent medication can substitute for an individual medication listed below. In case of safety concerns of any of these medications for an individual patient, a potential alternative regimen may be used upon approval from the sponsor. The clinical site is responsible for sourcing treatments administered pre- or post-TAK-079/placebo administration. In the event that a protocol-required medication for prophylactic coadministration is not able to be obtained by a

clinical site due to regional drug availability or local regulations, the medication may be supplied by the sponsor.

On the basis of emerging safety data, the sponsor may adjust pre- and postdose medication regimen to ensure patient safety. If modifications are needed, investigators will be notified via written communication of any required modifications to the pre-and postdose medication regimen.

8.2.1 Prophylactic Coadministration Regimen for First Study Drug Dosing Events (Main Study and OLE)

For the first dosing event in the main study (W1 Day 1) and the OLE (EW1 Day 1), the regimen outlined in Table 8.b should be followed for the prevention of a possible [redacted] Considering the timing of the risk of [redacted] after study drug dosing, this will ensure that therapeutic levels of prophylactic medications are present at the time of expected maximum exposure of study drug.

Table 8.b Prophylactic Coadministration Regimen for First Study Drug Dosing Events

Medication	[redacted]		
[redacted]	X	None	None
	X	X	X
	X	X	X
	None	X	X
[redacted]			

8.2.2 Prophylactic Coadministration Regimen for Study Drug Dosing Events Subsequent to First Dosing Events

On each dosing day **other than** W1 Day 1 or EW1 Day 1, patients are to be premedicated with [redacted] 1 to 3 hours before mezagitamab administration as outlined in Table 8.c.

Table 8.c Prophylactic Coadministration Regimen for Study Drug Dosing Events Other Than First Dosing Events

Medication	Dosing Days Other Than First Dosing Events[a]
[redacted]	X
[redacted]	X

8.2.3 Postdose Medication

[redacted]

If clinically indicated and in consultation with and approval from the medical monitor or Takeda medical director, [redacted]

8.2.4 Additional Considerations for Patients with Respiratory Complications

Patients with a higher risk of respiratory complications (eg, patients with a history of COPD and patients with asthma) may be administered the following premedications and postmedications, before or after each subsequent study dose at the investigator's discretion and after consultation with the medical monitor and sponsor, when possible):

- Antihistamines: oral cetirizine (10 mg) and oral famotidine (20 mg).
- Leukotriene-receptor antagonist: oral montelukast (10 mg).
- In addition, these patients may be administered the following medications to control their asthma or COPD:
  - A short-acting ß2-adrenergic receptor agonist, such as salbutamol (albuterol) aerosol for patients with asthma or COPD.
  - 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 investigator should consult with the medical monitor and sponsor regarding care and treatment of all high-risk patients.

On the basis of emerging data, the Takeda physician/designee may modify treatments administered pre- or post–TAK-079/placebo injection to ensure patient safety.

8.2.5 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 ITP conditions.

Rescue medications may include, but are not limited to, high-dose corticosteroids, IVIg, and increasing or adding background therapies. Rescue therapy given during the dosing period generally will result in the discontinuation from study dosing and advancement to the SFP.

However, one of the following dosing period–permitted rescue treatments is allowed as a bridge therapy for safety reasons (especially at the beginning of the study), since it may take several weeks before TAK-079 begins to have an effect on platelet levels:

[redacted]

Rescue with one of the above will allow patients to continue treatment with study drug and not be discontinued from the dosing period. Since these dosing period–permitted rescue therapies are typically expected to have a duration of effect of 4 weeks or less, a long-term effect on platelet levels is not anticipated. A second rescue treatment, however, will result in dosing period discontinuation.

8.3 Excluded Concomitant Medications and Procedures

Excluded concomitant medications are summarized in Table 8.d.

Table 8.d Excluded Concomitant Medications

Category or Agent	Exclusion Criteria (Exclusion Criteria Must Be Upheld Throughout Study Participation, in Addition to the Time Points Indicated Below)
Anticoagulants (to include any medicinal agent with antiplatelet effects)	Restricted from ≤3 weeks before obtaining screening laboratory samples, as outlined in Appendix A.
Intravenous or subcutaneous immunoglobulins or anti-D immunoglobulins	Restricted from ≤4 weeks before obtaining screening laboratory samples, as outlined in Appendix A. IVIg may be given as part of a single, dosing period–permitted rescue treatment as described in Section 8.2.5
Rituximab or any monoclonal antibody for immunomodulation not otherwise specified	Restricted within 4 months before first dosing. Note: Patients with prior rituximab exposure must have CD19 counts within normal range at the time of screening visit.
Immunosuppressants (eg, cyclophosphamide, vincristine)	Unless otherwise stated, restricted from ≤6 months before dosing, as outlined in Appendix A. Note: See Table 8.e for permitted oral immunosuppressants.
Live vaccinations	Restricted from ≤4 weeks before obtaining screening laboratory samples, as outlined in Appendix A.

8.4 Permitted Concomitant Medication

Stable dosing of concomitant background therapy, based on standard background treatment for ITP, is permitted throughout study participation, if the therapy regimen has remained stable in dose and frequency for ≥4 weeks before initiating study dosing. The dose of any permitted standard background therapy must be expected to remain stable through the study, unless dose reduction is required because of toxicities. Permitted standard background treatments may include 1 oral corticosteroid; ±1 permitted oral immunosuppressant from the following list: azathioprine, danazol, dapsone, cyclosporine, mycophenolate mofetil, mycophenolate sodium; ±1 TPO-RA (romiplostim, eltrombopag, avatrombopag); ±fostamatinib (see Table 8.e).

Table 8.e Permitted Concomitant Medications

Medications	Criteria (Criteria Are to Be Maintained Throughout the Study)
Immunosuppressants Azathioprine Danazol Dapsone Cyclosporine Mycophenolate mofetil Mycophenolate sodium	Therapy must be stable in dose and frequency for at least 4 weeks before dosing.
Oral corticosteroids	Therapy must be stable in dose and frequency for at least 4 weeks before dosing. Oral corticosteroids may be given as part of a dosing period rescue treatment as described in Section 8.2.5.
Thrombopoietin receptor agonist(s) (eg, romiplostim, eltrombopag, avatrombopag)	Therapy must be stable in dose and frequency for at least 4 weeks before dosing.
Fostamatinib	Therapy must be stable in dose and frequency for at least 4 weeks before dosing.

8.5 Study Stopping Rules

Takeda clinicians/designee will provide ongoing safety oversight and surveillance throughout the entire study. As such, TAK-079 clinicians/designee are to receive and trend all reported SAEs and conduct a review of all safety data periodically throughout the study (see Section 6.1.2). On the basis of outcomes of the Takeda safety reviews and in accordance with predefined criteria, decisions about the dosing regimen and/or study conduct are to be made and implemented.

8.5.1 Assessment and Criteria for Terminating Patient Dosing

Investigators will evaluate patients before each dose for the parameters outlined in Table 8.f. In instances where clinical parameters do not meet criteria for continued dosing, study drug dosing must be temporarily withheld until parameters meet dosing levels, or discontinued.

Patients whose clinical parameters meet dose discontinuation criteria, as outlined in Table 8.f, are to be permanently discontinued from study dosing and will advance to the SFP, completing all associated assessments listed in the SOE table in Appendix A (or Appendix B, if during the OLE).

In addition, patients should be permanently discontinued from study dosing 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 receives rescue medication that is not a dosing period–permitted treatment as described in Section 8.2.5.
- If study dosing is held for 2 consecutive doses because of safety concerns or conditions outlined in Table 8.f.
- The patient chooses to withdraw from study dosing.
- The patient has a confirmed pregnancy.

NOTE: If 2 or more patients discontinue study drug dosing on the basis of the dose discontinuation criteria in Table 8.f, the Takeda clinician/designee will review available safety data to determine if adjustments to the treatment plan should be made.

Immunoglobulin levels may be reduced with TAK-079; therefore, quantitative immunoglobulin levels (IgG, IgA, and IgM) will be evaluated during the dosing period at a central laboratory. If any of these are >50% below the lower limit of normal (LLN), the investigator should manage as clinically appropriate on the basis of signs and symptoms the patient is experiencing. If IgG levels are below the LLN and the patient is experiencing a severe infection, IVIg may be administered, per physician discretion according to standard practice. If IVIg is given as a rescue treatment as described in Section 8.2.5, the patient may continue with dosing of the study drug; otherwise, the patient will be discontinued from the dosing period of the study and enter the SFP.

Table 8.f Summary of Subsequent Dosing Criteria

8.6 Precautions and Restrictions

Patients will be closely monitored before all TAK-079/placebo administrations [redacted] 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 (see Section 9.4.8), and additional postdose medications for those with a history of asthma or COPD may be considered, as outlined in Section 8.2.3.

On each dosing day, it is recommended that patients should not drive, operate dangerous tools or machinery, or engage in any other potentially hazardous activity that requires full alertness and coordination if they experience sedation from any premedication listed in Section 8.2.1.

Patients are to be instructed to limit the use of alcohol while enrolled in this study.

8.6.1 Pregnancy, Lactation, and Contraception

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

TAK-079 has not been administered to women who are pregnant or lactating. No reproductive or developmental toxicity studies have been performed for TAK-079 to date; hence, the effects of TAK-079 on fertility and the developing fetus are not known at this time. There were no TAK-079–related findings (organ weight changes or microscopic findings) noted in the reproductive tract (cervix, epididymis, ovary, oviduct, testis, and vagina) of sexually immature male and female monkeys after administration for up to 13 weeks. Women of childbearing potential may be enrolled in clinical studies with appropriate precautions to prevent pregnancy.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception at the same time (Table 8.g), from the time of signing of the informed consent form (ICF) through [redacted]*, whichever is longer, after discontinuation of treatment, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient (periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception). Female and male condoms should not be used together.

Table 8.g Highly Effective and Other Effective Methods of Contraception for Female Patients

Highly Effective Methods	Other Effective Methods (Barrier Methods)
IUD	Latex or nonlatex condom with or without a spermicidal agent
Hormonal (oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants)	Diaphragm with spermicide; cervical cap with a spermicide; sponge with a spermicide

IUD: intrauterine device.
It is recommended to combine a highly effective method with a barrier method. If one of the highly effective methods cannot be used, using 2 barrier methods at the same time is recommended.

Male patients, even if surgically sterilized (ie, status postvasectomy), must agree to 1 of the following:

- Agree to practice effective barrier contraception (Table 8.h) during the entire study dosing period and through [redacted]*, whichever is longer, after discontinuation of treatment, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.

Table 8.h Highly Effective and Other Effective Methods of Contraception for Male Patients

Highly Effective Methods	Other Effective Methods (Barrier Methods)
Vasectomy	Latex or nonlatex condom with or without a spermicidal agent Diaphragm with spermicide; cervical cap with spermicide; sponge with spermicide

It is recommended to combine the highly effective method with a barrier method. If the highly effective method cannot be used, using 2 barrier methods at the same time is recommended.

* Note that the half-life of TAK-079 has not yet been determined. On the basis of conservative information in the literature regarding the half-life of IgG1 as well as other IgG1 human monoclonal antibodies (Mankarious et al. 1988; Suzuki et al. 2010) a conservative time frame to continue contraception would be [redacted].

8.6.2 Drug Interactions

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

8.6.3 Interference With Serological Testing

Anti-CD38 monoclonal antibodies have been reported to bind to CD38 on 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 (Darzalex (daratumumab) injection 2019; Regan and Markowitz 2016). It is possible TAK-079 may affect the results of these blood tests. [redacted] Patients should be advised to keep these results in case future transfusions are needed.

8.6.3.1 Crossmatching for Blood Transfusions While on Study

Should a patient require a blood transfusion, the transfusion service should be informed that the patient is on anti-CD38 therapy, to prevent delays in obtaining RBCs. Recommendations for crossmatching, including the use of dithiothreitol-treated cells, or by providing antigen-matched RBC units, or by using uncrossmatched ABO/RhD-compatible blood (in the event of an emergency), have been reported elsewhere, including the Advancing Transfusion and Cellular Therapies Worldwide Bulletin #16-02, available online (Regan and Markowitz 2016; Rituxan (rituximab) injection for intravenous use 2019).

8.7 Management of Clinical Events

8.7.1 [redacted]

[redacted]

[redacted]

8.7.1.1 [redacted]

[redacted]

[redacted]

8.7.2 [redacted]

[redacted]

[redacted]

8.7.2.1 [redacted]

[redacted]

[redacted]

8.7.3 [redacted]

[redacted]

8.7.4 [redacted]

[redacted]

8.7.5 [redacted]

[redacted]

8.7.6 [redacted]

[redacted]

[redacted]

8.7.7 Overdose

As outlined in Section 10.1.2, an overdose is defined as a known deliberate or accidental administration of investigational drug, to or by the study patient, at a dose above that which was assigned to that individual patient according to the study protocol.

To date, there is no experience with overdose of TAK-079. If an overdose does occur, as defined in Section 10.1.2, close monitoring and supportive treatment, as medically required, are recommended. Events of overdose, with or without an associated AE, should be promptly reported to the study medical monitor and will be entered into the electronic clinical report forms (eCRFs) as an AE.

8.8 Description of Investigational Agents

8.8.1 Study Drug: TAK-079

TAK-079 is a full-length, human IgG1 mAb directed against human CD38. The antibody is composed of 2 light chains of the lambda subclass and 2 heavy chains linked together by 2 disulfide bridges.

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). 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.

8.8.1.1 Preparation, Reconstitution, and Dispensation

Refer to the Pharmacy Manual for detailed instructions regarding the preparation of TAK-079 study supply.

TAK-079 is a mAb and caution should be exercised when handling TAK-079 as with other biologics.

8.8.1.2 Packaging and Labeling

Supplies of TAK-079 are labeled according to the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practices and include any locally required statements.

8.8.1.3 Storage, Handling, and Accountability

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. The investigator or designee must confirm that appropriate temperature conditions

have been maintained for all TAK-079 received and that any discrepancies are reported and resolved before use.

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, the investigator or designee should acknowledge the receipt of the shipment by signing the bottom half of the packing list and faxing per instructions provided on the form. If there are any discrepancies between the packing list and 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. The sponsor must be notified immediately of any temperature excursions and shipping and handling or storage discrepancies.

All clinical study material must be kept in an appropriate, limited access, secure location until used, destroyed, or returned to the sponsor or designee. TAK-079 must be stored according to the manufacturer's stipulation, as specified on the label (see the Pharmacy Manual for additional information). 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 will be counted and reconciled at the site before being returned to Takeda or designee or being destroyed.

The investigator or designee must ensure that the study medication 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 delivery to the site, site inventory, use by each patient, and return to the sponsor or designee.

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.

8.8.2 Clinical Study Drug Blinding

The assignment of study patients to 1 of 3 study arms in Part A or 1 or 2 study arms in Part B is maintained through a blinded randomization schedule, available in instances of medical emergencies to the principal investigator. Otherwise, site staff will remain blinded through Week 16 of the study, as described in Section 6.1. Details on maintaining the study blind, and unblinding procedures, are outlined in Section 8.8.4.

8.8.3 Randomized 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.

8.8.4 Clinical Study Blind Maintenance/Unblinding Procedure

- 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 are 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 clinician or designee (in accordance to contact information and procedures outlined in the relevant study documentation).
  - A decision to break the blind must be reached by the Takeda clinician and the investigator. The investigator, or designee, may break the blind through the IXRS independent of the Takeda clinician 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 for emergency reasons, the patient will be discontinued from further study drug administration in this study.

8.8.5 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 investigator must maintain 100% accountability for all study medication (TAK-079) 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 will be disposed of, retained, or returned to the sponsor or designee, as directed by the sponsor or designee. The investigator must maintain a current inventory (drug accountability log) of all sponsor-supplied study medication delivered to the site, inventory at the site, and patients' use records. This log must accurately reflect the drug accountability of the study medication at all times. The following information will be recorded at a minimum: 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 the person receiving the study medication. The log should include all required information as a separate entry for each patient to whom study medication is dispensed.

Before site closure or at appropriate intervals, a representative from the sponsor or its designee will perform clinical study material accountability and reconciliation before clinical study materials are returned to the sponsor or its designee or destroyed at the site, as applicable. The investigator will retain the original documentation regarding clinical study material accountability, return, and/or destruction, and copies will be sent to the sponsor or designee.

Further guidance and information are provided in the Pharmacy Manual.

9.0 STUDY CONDUCT

This study will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and ICH guidelines.

9.1 Study Personnel and Organizations

Contact information for the project clinician, central laboratory(ies), coordinating investigator(s), the interactive response technology provider, and CRO team may be found in the Study Manual. The list of investigators is available in the sponsor's investigator database.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of

the recruitment strategy, they will be reviewed by the institutional review board (IRB)/ independent ethics committee (IEC).

9.3 Treatment Group Assignments

Patients will be randomly assigned to the treatment arms as outlined in Table 8.a (1:1:1 ratio of placebo, TAK-079 100 mg, TAK-079 300 mg in Part A and 1:2 ratio of placebo, TAK-079 600 mg in Part B) at the completion of study screening and before dosing on study Day 1, in accordance with the randomization schedule as generated by the sponsor or designee. Randomization information is stored in a secured area, accessible only by authorized personnel, and necessary site staff in instances of emergency unblinding.

9.4 Study Procedures

Refer to the SOE (Appendix A and Appendix B) for timing of assessments. Additional details are provided as necessary in the sections that follow.

The screening period for this study is 28 days (Day -28 to Day -1). Assessments and procedures should be performed on schedule, within the time frame and window allowance in Appendix A and Appendix B. Further time allowance for most study procedures and assessments is acceptable in extenuating circumstances (ie, holidays, vacations and other administrative reasons) on approval by the medical monitor or delegate; however, these time extensions **should not deviate more than 7 days** from the scheduled procedural time.

9.4.1 Informed Consent

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. Written informed consent for participation for study extension phases (OLE-A and OLE-B) and confirmation of consent to participate in the OLE phases of the study, must be obtained before conducting assessments and procedures specifically to determine OLE eligibility, with participation contingent on meeting all relevant eligibility criteria.

9.4.1.1 [redacted]

[redacted]

9.4.2 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. Eligibility must be reconfirmed for those eligible patients agreeing to remain on study for study extension phases (OLE-A and OLE-B). Eligibility for OLE entry is reconfirmed at the Week 16 visit (see Section 9.5.1).

Principal investigators must provide the Takeda clinician/study medical monitor a summary of key eligibility criteria for review so eligibility can be verified before randomizing each patient.

9.4.3 Patient Demographics

Patient demographic characteristics will be collected at screening and will include age, sex, race, and ethnicity (optional depending on country).

9.4.4 Medical History

A complete medical history is compiled for each patient during the screening period and includes assessment and documentation of prior medical history, comorbidities, and concomitant treatments. This includes assessments of current ITP signs and symptoms, as evaluated and scored by disease activity tools, and previous and current ITP therapies. The complete medical history should include history of eye disease or ophthalmic clinical symptoms (including allergic reactions). If an eye exam has been conducted within the previous year, a copy of the records from the exam should be provided to the site as source documentation. Coronavirus disease 2019 (COVID-19) infection and vaccination prior to the study should be recorded as part of medical history.

9.4.5 Concomitant Medications and Procedures

Concomitant medications, blood products, and procedures from within 28 days before the first dose of TAK-079 through the end of SFP will be recorded in the eCRF.

Trade name and international nonproprietary name (if available), indication, and start and end dates of the administered medication are to be recorded. Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF (see Sections 8.3 and 8.4 for a list of excluded and permitted concomitant medications).

COVID-19 vaccination and COVID-19 treatments received during the study through LFP will be recorded as concomitant medications.

9.4.5.1 Background ITP Therapy

Eligible patients must have protocol-compliant ITP background therapy in accordance to criteria outlined in Table 8.d and Table 8.e. Once randomized into the study, patients will remain on protocol-compliant background therapy, as managed by their principal investigator, in accordance with local institutional practices, throughout study participation. Patients should remain on their stable dose of standard background therapy throughout the study unless dose reduction is required due to toxicities. Permitted standard background treatments may include 1 oral corticosteroid; ±1 oral immunosuppressant from the following list: azathioprine, danazol, dapsone, cyclosporine, mycophenolate mofetil, mycophenolate sodium; ±1 TPO-RA (romiplostim, eltrombopag, avatrombopag); ±fostamatinib. Background ITP therapy at the time of screening and throughout study participation will be recorded in the eCRF.

9.4.6 Physical Examination

A complete physical examination as well as a symptom-directed physical examination with assessments for ITP signs and symptoms will be completed in accordance with standard of care at the times specified in the SOE (see Appendix A and Appendix B). Women of childbearing potential should be asked about their menstrual history at each visit. A serum pregnancy test should be conducted for delayed menses (see Section 9.4.10).

9.4.7 Patient Height and Weight

Height will be measured during screening only (within 28 days before the first dose of TAK-079).

Weight will be measured during screening and during Weeks 10, 16, and 32 as outlined in Appendix A and EW10, EW16, and EW32, as outlined in Appendix B.

9.4.8 Vital Signs

Vital signs (body temperature, respiratory rate, heart rate, and blood pressure) will be evaluated at visits specified in Appendix A and Appendix B, and recorded both on the source documentation and in the eCRF. In addition, vital signs should be assessed at any time it is clinically warranted [redacted] As indicated in Appendix A and Appendix B, vital signs are to be assessed before each study dose [redacted].

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

9.4.9 12-Lead ECG

A single 12-lead ECG is to be performed at the screening visit (for assessment of eligibility) and at Weeks 10 and 16 of the SFP in both the main study and OLE (as outlined in Appendix A and Appendix B), and will be read locally. Additional ECGs may be done per investigator discretion.

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

NOTE: Any ECG finding that is judged by the investigator as clinically significant (except at the screening visit) is considered an AE; as such, clinically significant findings are to be recorded on the source documentation and in the eCRF, and the patient should undergo continued monitoring as described in Section 10.1.2.

9.4.10 Pregnancy Test

A serum pregnancy (human chorionic gonadotropin [hCG]) test will be completed for female patients of childbearing potential; this test will be performed at screening, during the SFP (ie, Weeks 10 and 16), and during the LFP (Week 32); results must be negative for the patient to be randomized and to continue in the study. Likewise in the OLE, serum pregnancy tests will be performed at EW10, EW16, and EW32.

A urine pregnancy test will be completed for all female patients of childbearing potential before the first dose of TAK-079/placebo and at Week 5 of the dosing period. In the OLE, a urine pregnancy test will be completed on EW1 before the first dose of TAK-079 and at EW5 of the OLE dosing period. If the subject reports delayed menses, a serum pregnancy test should be completed and a negative result obtained before dosing with the study drug.

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.

9.4.10.1 Definition of Women of Childbearing Potential

A woman of childbearing potential is a sexually mature woman who:

- Has not undergone a hysterectomy or bilateral oophorectomy, or
- Is not postmenopausal. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

9.4.10.2 Timing of Pregnancy Testing

Women of childbearing potential must have pregnancy testing completed in accordance with the timing outlined as follows:

- *Before Initial Study Dosing*:
  - Screening period: a negative **serum** pregnancy test (hCG <5 mIU/mL).
  - Baseline (either Day 1 before initial study dosing, or 1 day before study dosing): 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*:
  - At Week 5 (and EW5), before dosing (**urine** pregnancy test).
  - During SFP and LFP, as outlined in Appendix A and Appendix B (**serum** pregnancy test).
  - 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.

9.4.11 AEs

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in Appendix A and Appendix B. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of AEs and SAEs.

9.4.12 Clinical Laboratory Evaluations

Hematology and serum chemistry will be performed locally, with reference ranges provided in the electronic data capture (EDC) system. Clinical laboratory evaluations will be performed according to the SOE in Appendix A and Appendix B throughout the study.

Instructions for handling and shipping clinical laboratory samples are provided in the study laboratory manual.

9.4.12.1 Clinical Chemistry and Hematology

Blood samples for analysis of the clinical chemistry and hematology parameters shown in Table 9.a will be obtained as specified in the SOE (see Appendix A and Appendix B).

9.4.12.2 Blood Type Assessment and Serologic Testing

As stated in Section 8.6.3, it is possible that TAK-079 may affect blood bank serologic testing. Recommendations for avoiding problems with blood transfusions for patients treated with anti-CD38 antibodies are detailed in Section 8.6.3 (Lancman et al. 2018; Regan and Markowitz 2016).

[redacted]

Table 9.a Clinical Chemistry and Hematology Evaluations

Hematology	Serum Chemistry	
Hematocrit	Albumin	Chloride
Hemoglobin	Alkaline phosphatase	Glucose
Leukocytes with differential	Alanine aminotransferase	Lactate dehydrogenase
Total lymphocyte count [a]	Aspartate aminotransferase	Potassium
Neutrophils [a]	Bilirubin (total)	Sodium
Platelet (count)	Blood urea nitrogen	
International normalization ratio	Calcium	
Partial thromboplastin time	Carbon dioxide	
Coombs test (both direct and indirect)	Creatinine	
Serum pregnancy test		

[a] Total lymphocyte count and absolute neutrophil count are resulted as part of the leukocyte differential and will be specifically recorded in electronic data capture.

9.4.13 [redacted]

[redacted]

9.4.13.1 Primary Specimen Collection

Primary specimen collection is shown in Table 9.b. [redacted]

Table 9.b Primary Specimen Collection

Specimen Name in Schedule of Procedures	Primary Specimen	Description of Intended Use	Sample Collection
Blood type assessment	Blood	RBC antigen typing	Mandatory [a]
[redacted]			
Serum sample for HCV, HIV, and HBV antibodies and HBsAg	Serum	Study eligibility (Viral antibody measurements)	Mandatory
Blood sample for HCV RNA PCR	Blood	Study eligibility (HCV RNA)	Mandatory [c]

HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; PCR: polymerase chain reaction; [redacted]; RBC: red blood cell(s).

Note: [redacted]

[a] [redacted]

[c] To be performed only for patients who have received curative treatment for prior chronic HCV infection.

9.4.14 [redacted]

[redacted]

9.4.15 [redacted]

[redacted]

9.4.15.1 [redacted]

[redacted]

9.4.15.2 [redacted]

[redacted]

9.4.15.3 [redacted]

[redacted]

9.4.15.4 [redacted]

[redacted]

9.4.15.5 [redacted]

[redacted]

9.4.16 [redacted]

[redacted]

[redacted]

9.4.17 [redacted]

[redacted]

9.4.18 [redacted]

[redacted]

9.5 Special Study Visit Days/Periods

9.5.1 Study Week 16

The Week 16 visit is the final visit of the SFP. During this study visit, patients will be unblinded.

Patients who were in a TAK-079 group will obtain a panel of safety laboratory assessments as outlined in Appendix A and advance to the LFP. Any clinical parameters below the level in Table 8.f for continued dosing, including ongoing drug-related AEs, should be monitored during the LFP until the parameters/AEs are resolved, return to baseline, or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Patients who were in the placebo group will be given the option for participation in the OLE. Patients interested in advancing to the OLE will obtain an additional set of screening laboratory assessments as outlined in Section 6.1.1 and Appendix A to reconfirm their eligibility for study participation. After confirmation of continued study eligibility as outlined in Section 6.1.1, those patients consenting to participate in OLE will continue on to EW1, for their first day of OLE dosing (see Appendix B for the SOE of the OLE).

Patients who decide not to continue into an OLE will have a final set of safety labs obtained as for patients given TAK-079 and return on Week 20 for an end-of-study visit.

9.5.2 Study Week 20

Patients who were randomized to placebo and decide not to enter the OLE will complete their end-of-study visit during Week 20. Samples for laboratory assessments will not be obtained for these patients.

For patients who were randomized to TAK-079, the Week 20 visit is the first visit of the LFP.

9.5.3 Study Week 32

For patients who were randomized to TAK-079, the Week 32 visit is the end-of-study visit.

9.5.4 OLE Dosing Period (EW1 to EW8)

For patients who were randomized to placebo in the main study (Part A or B) who advance to the OLE based on their preference and reconfirmation of their eligibility, the EW1 visit is the first day of open-label dosing of TAK-079. This visit is to occur <4 weeks after the unblinding visit (Week

16 of the main study SFP). As in the main study, the OLE dosing period will last for 8 weeks (see Appendix B for details).

As the administration of full dose will generally require multiple SC injections, the EW1 dose will be administered by giving each SC injection 30 minutes apart until the full scheduled dose has been administered. On all other drug administration days after EW1, if the patient did not have a clinically significant infusion reaction per the investigator, the SC injections can be given at the same time without a waiting period.

[redacted]

For subsequent doses, premedication is required for all patients, postdose medication is only to be administered as clinically indicated.

9.5.5 EW16

The EW16 visit is the final visit of the OLE-SFP. Patients will obtain a panel of safety labs as outlined in Appendix B and advance to the LFP. Any clinical parameters below the level in Table 8.f for continued dosing, including ongoing drug-related AEs, should be monitored during the LFP until the parameters/AEs are resolved, return to baseline, or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

9.5.6 EW32

The EW32 visit is the end-of-study visit for patients in the OLE.

9.6 End of Safety Follow-up Assessments

End of SFP clinical parameters, as outlined in Table 9.c, will be assessed at Week 16 and EW16 of the SFP in the main study and in the OLE, respectively (see SOE in Appendix A and Appendix B, respectively). If clinical presentation and parameters do not meet the end of SFP criteria, and are deemed by the principal investigator as study related, the study-related parameters not meeting end-of-study criteria will continue to be assessed in the LFP until they normalize or return to baseline.

Table 9.c Clinical Parameters for End of Safety Follow-up Period

Safety Parameter Laboratory Investigations	End-of-Study Criteria	Continuation to Long-term Follow-up
Neutrophils	≥LLN or ≥study baseline levels or low levels that are not directly related to dosing of investigational product.	<LLN and <study baseline levels that is directly related to dosing of investigational product.
Total lymphocyte count		
Hgb		
IgG, IgA, and IgM levels		
Events of clinical interest [a]		

[redacted]

; CTCAE: Common Terminology Criteria for Adverse Events; Hgb: hemoglobin; Ig: immunoglobulin; [redacted]; LLN: lower limit of normal.

[redacted].

9.7 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed study treatment once they have completed the 8-week dosing period of the main study.

9.8 Completion of Study (for Individual Patients)

A patient will be considered to have completed the study once they have completed the dosing period and at completion of the following, as relevant:

- The Week 20 end-of-study visit of the LFP, for patients originally randomized to placebo who chose not to enter an OLE.
- The Week 32 end-of-study visit of the LFP, for patients originally randomized to TAK-079.
- The EW32 visit of the OLE LFP, for patients originally randomized to placebo who participated in the OLE, completing the dosing period, SFP, and LFP of the OLE.

9.9 Discontinuation of Treatment With Study Drug and Patient Replacement

Study drug must be permanently discontinued for patients meeting any of the following criteria:

- Withdrawal by patient.
- Pregnancy.

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

- AE/SAE.
- Protocol deviation.
- Symptomatic deterioration.
- Unsatisfactory therapeutic response.
- Study terminated by sponsor.
- Withdrawal by patient.
- Lost to follow-up.
- Other.

Once study drug has been discontinued, all study procedures outlined for the end-of-treatment visit will be completed as specified in the SOE (see Appendix A). and Appendix B). The primary reason for study drug discontinuation will be recorded on the eCRF.

In addition, study drug should also be discontinued if the patient meets the criteria outlined in Section 8.5.1.

Patients who discontinue/withdraw prematurely from study drug dosing for reasons other than safety may be replaced at the discretion of the sponsor.

9.10 Withdrawal of Patients From Study

A patient may be withdrawn from the study for any of the following reasons:

- Death.
- Study terminated by sponsor.
- Withdrawal by patient.
- Lost to follow-up.
- Other.

The consequence of a patient withdrawing consent from further treatment and follow-up is that no new information will be collected from the withdrawn patient and added to the existing data or any database. However, every effort will be made to follow all patients for safety. Data collected during patient consent, however, must be included in the database.

9.11 Study Compliance

TAK-079 will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

9.12 COVID-19–Related Procedural Changes

The following information provides guidance regarding changes to the study procedures that could be implemented for study participants or study sites affected by the COVID-19 public health emergency. This guidance takes references from the US Food and Drug Administration (FDA) Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency - Guidance for Industry, Investigators, and Institutional Review Boards, March 2020, updated 04 December 2020, and the EMA Guidance on the Management of Clinical Trials During the COVID 19 (Coronavirus) Pandemic, Version 3 (28 April 2020).

As the COVID-19 pandemic may peak in different regions at different times and restrictions implemented by local laws and recommendations may vary, any decision on procedural changes should be made on a case-by-case basis by the principal investigator in consultation with the study team and the medical team as needed, while maintaining patient safety and confidentiality as the priority.

Procedural changes due to COVID-19 may include the following:

- Informed Consent Procedure: If necessary, informed consent from a potential or current trial participant may be obtained via electronic informed consent capabilities, or an electronic face-to-face consent interview when these individuals are unable to travel to the site.
- During the COVID-19 public health emergency, remote visits may be conducted by phone (eg, collection of AEs and safety monitoring), video conferencing (Telehealth with the physician or Telemedicine or other platform acceptable to the physician and patient) or site staff visiting the participant's residence. Local visits and Telemedicine must comply with national and local laws and regulations. The type of alternative visit must be recorded on the eCRF. The investigator may use their judgment to determine the appropriateness of a remote visit as an alternative visit in advance (for example, if no significant issues arise that may necessitate a hands-on physical exam).
- "Remote visits" via virtual communications may be performed as a safety check on the patient's well-being.
- For home healthcare visits, collection of clinical laboratory samples (blood specimen collection or other diagnostic tests) may be performed by the investigator, qualified site staff or qualified home healthcare provider who can visit the trial participant's residence. These may be obtained the day before a scheduled visit (see Appendix A and Appendix B).
- ECG procedures: For home healthcare visits, ECGs may be performed by a qualified health care professional who is authorized/certified to perform such tests routinely.
- Patient visits at screening (except for the second platelet count determination), Week 1, Week 2, Week 3, Week 4, Week 10, Week 16, Week 20 (only for placebo patients not advancing to the OLE), and Week 32 of the main study and EW1, EW2, EW3, EW4, EW10, EW16, and EW32 of the OLE must be done with the patient present at the investigative site. Other visits may be conducted at the clinic or by optional home healthcare visits (or a hybrid of Telehealth/Telemedicine with home healthcare) to extend flexibility to patients during

COVID-19 public health emergency. Home healthcare visits will be documented in the study records and eCRF.

- For dosing visits at home, the investigator or qualified site staff must evaluate the patient either remotely or at the patient's residence prior to dose administration. A patient should have previously received 3 to 4 doses of study drug at the clinic site unless otherwise approved by the sponsor. Safety parameters for dosing decisions (Table 8.f) must be evaluated as in a regular in-clinic visit. Dose administration must be performed by a qualified healthcare provider.
- Safety labs (eg, complete blood count, chemistry, liver function tests) may be obtained at a clinic local to the patient's home with sponsor approval.
- Deviations from the protocol-specified procedures will be recorded as related to COVID-19.
- Patients who discontinued from screening or run-in period due to COVID-19–related factors but were otherwise qualified to participate in the trial may be rescreened if the sponsor's clinician agrees.
- Missed or delayed clinic visits or subject withdrawals due to COVID-19 must be recorded on the eCRF.
- Withdrawal: If a patient chooses to withdraw from study participation due to personal concerns related to the COVID-19 pandemic (other than a COVID-19–related AE), this should be specified as the reason for patient withdrawal in the eCRF.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event (PTE) is any untoward medical occurrence in a patient who has signed informed consent 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.

10.1.2 AE Definition

AE means any untoward medical occurrence in a patient administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product.

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a preexisting condition. (Intermittent events for preexisting 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, that is, 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 retest 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.
- 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.

Preexisting conditions:

- A preexisting condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as a PTE or AE. A baseline evaluation (eg, laboratory test, ECG, x-ray) should NOT be recorded as a PTE unless related to a study procedure. However, if the patient 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 patient has a preexisting 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 patient has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), 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 patient 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 patient 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 informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) because of worsening of the preexisting condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the patient's medical condition should not be recorded as AEs but should be documented in the patient'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 patient, at a dose above that which is assigned to that individual patient according to the study protocol.
- All cases of overdose (with or without associated AEs) are to be documented on the Overdose page of the eCRF to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on the AE CRF(s) according to Section 10.5.
- SAEs of overdose should be reported according to the procedure outlined in Section 10.2.
- If an overdose does occur, close monitoring and supportive treatment as medically required.

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

1. Results in **death**.

2. Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
3. Requires inpatient **hospitalization or prolongation of an existing hospitalization**.
4. Results in **persistent or significant disability or incapacity**.
5. Is a **congenital anomaly/birth defect**.
6. Is a **medically important event** that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the patient to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

Note: Some clinical centers may only be able to provide certain dosing period–permitted rescue therapies (eg, IVIg) via inpatient hospitalization. Therefore, the hospital admission itself (in an otherwise clinically stable patient) specifically for access and administration of rescue therapy does not count automatically as an SAE, unless there are other circumstances that fulfill SAE criteria.

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner. An inpatient hospitalization specifically for the access and administration of rescue therapy for thrombocytopenia, as described in Section 8.2.5, in an otherwise clinically stable patient is not considered a fulfillment of criterion 2, above.

Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4) because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as a single comprehensive event.

Regardless of causality, SAEs must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event. This will be done by transmitting an EDC SAE report. If transmission of an EDC SAE report is not feasible within 24 hours, then a facsimile of the completed Takeda paper-based SAE form should be sent (please see fax numbers below). In case of fax, site personnel need to confirm successful transmission of all pages and include an email address on the fax cover sheet so that an acknowledgment of receipt can be returned via e mail within 1 business day. Email submission of SAE forms with an attachment in portable document format should only be used in the case where fax is not possible and EDC is not feasible within 24 hours of receiving the event. In case of email, site personnel need to confirm successful transmission by awaiting an acknowledgment of the receipt via email within 1 business day. If SAEs are reported via fax or by email, EDC must be updated as soon as possible with the appropriate information.

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
Rest of World fax#: +1-202-315-3560

Email: takedaoncocases@cognizant.com

If information not available at the time of the first report becomes available at a later date, then the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation 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 followed up 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.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the study are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug administration.

Severity (toxicity grade) for each AE, including any laboratory abnormality, will be determined using the National Cancer Institute CTCAE, Version 4.03, effective 14 June 2010. The criteria are provided in the study manual.

Relationship of the event to study drug administration (ie, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: Is there a reasonable possibility that the AE is associated with the study drug?

COVID-19 vaccination-related AEs will be confirmed by the investigator and flagged in the AE eCRF form.

10.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the signing of informed consent through the SFP and recorded in the eCRF. AEs ongoing at the Week 16 visit of the SFP should be monitored through the LFP until they are resolved, return to baseline, or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). Study-drug related AEs/SAEs with onset after the SFP will be collected through the LFP.
- SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of informed consent through the SFP and recorded in the eCRF. After this period, during the LFP, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).
- COVID-19 infection and COVID-19 vaccination-related AEs will be recorded from the signing of informed consent through LFP regardless of causality.

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10.5 Procedures for Reporting (Including Overdose)

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on the AE eCRF. SAEs of overdose should be reported according to the procedure outlined in Section 10.2.

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

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs and 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, SUSARs will be submitted to the regulatory authorities as expedited reports 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 product's administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

In accordance with Takeda standard operating procedures, each clinical study is evaluated to determine whether a data safety monitoring board (DSMB) should be convened. Applicable regulation and guidance (including the guidance set forth by the US FDA as described in the Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees, fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf, Accessed 24 July 2019) are used to evaluate each study 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.

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. However, the decision to convene a DSMB could be made at any time during the conduct of Study TAK-079-1004.

Although a formal DSMB will not be formed, internal reviews of available safety information by an internal independent SRC will be conducted prior to initiation of Part B and as needed. Key safety data will be reviewed and evaluated by sponsor representatives for possible study conduct recommendation(s). The sponsor representatives will make decisions regarding dosing and/or scheduling, which will be discussed with investigators for decision for alignment.

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 eCRFs

Completed eCRFs are required for each patient that signs an ICF.

The sponsor or its designee will supply investigative sites with access to eCRFs and 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, CRO partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

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 designee) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs 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 the change.

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

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor (or designee) will be permitted to review the patient'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.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 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 ICFs, patient authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copies of eCRFs including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the sponsor (or designees). Any source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the patient's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) 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 Section 4.9.5 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 for record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan 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.

13.1.1 Analysis Sets

- **Full analysis set**: All enrolled patients. In efficacy analyses, only patients with both baseline and at least 1 valid postbaseline value will be included.
- **Safety analysis set**: Patients who have received at least 1 dose of study drug.
- [redacted]
- [redacted]
- [redacted]

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Patient demographic and baseline characteristics will be summarized descriptively. Variables to be analyzed include sex, age, race, medical history, prior medications/therapies, ECG findings and other parameters as appropriate. For continuous variables, descriptive statistics (number, mean, SD, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented as needed.

13.1.3 Efficacy Analysis

Efficacy is not the primary endpoint for this study. Secondary efficacy measures will include the measures outlined in Section 5.2.2. [redacted]

Efficacy endpoints will be summarized by descriptive statistics and presented by treatment group as well as by study Part. Where appropriate, efficacy endpoints may be analyzed with the following methods:

- The number and percentage of subjects attaining each type of response will be summarized by treatment group. Binary responder endpoints will be analyzed using a Fisher exact test.
- Change from baseline endpoints measured repeatedly over time will be analyzed using a mixed-model repeated-measures analysis, which includes treatment, visit, and (treatment × visit) interaction terms as the factors, with baseline values as covariates.

All tests of treatment effects will be conducted at a 2-sided α level of 0.05, and 95% CIs for the differences in proportions and least squares means will be provided. No inferential hypothesis was tested in these endpoints, so CIs and p-values are not adjusted for multiplicity.

All efficacy analyses will be performed using the full analysis set.

13.1.4 [redacted]

[redacted]

13.1.5 [redacted]

[redacted]

13.1.6 [redacted]

[redacted]

13.1.7 Safety Analysis

Safety will be evaluated by the frequency of AEs, severity and types of AEs, and by changes from baseline in patients' vital signs, weight, and clinical laboratory results using the safety analysis set. Exposure to study drug and reasons for discontinuation will be tabulated.

AEs that occur after administration of the first dose of TAK-079 and through to the end of the SFP will be tabulated and followed until resolution.

Related AEs and COVID-19-related AEs that occur after administration of the first dose of TAK-079 and through LFP will be summarized. AEs will be tabulated according to the MedDRA, and data will be summarized using Preferred Term and primary System Organ Class. All safety analyses will be performed using the safety analysis population.

13.2 Interim Analyses

One unblinded safety review and one interim analysis will be conducted before the final database lock of this study.

Unblinded Safety Review: An unblinded safety review will take place once a minimum of 24 evaluable patients are available for analysis in Part A. For the purposes of this unblinded safety review, an evaluable patient is defined as a patient who exits the dosing period in Part A having received a minimum of 4 study doses, regardless of the reason for exit (eg, completion of Part A dosing period, early discontinuation, study drug discontinuation). This unblinded safety review will include all unblinded safety data from all patients from Part A available at the data-cut (data up to the Week 16 visit). For additional information, see Section 6.1.2.

Interim Analysis: After all patients in Part B (Arms B1 and B2) complete the blinded SFP (complete the Week 16 visit), an unblinded interim analysis with Part A and Part B data will take place to evaluate safety and efficacy. If it is deemed not appropriate to continue onto Part B after the unblinded safety review, then this interim analysis will not be conducted.

13.3 Determination of Sample Size

This study is exploratory and not powered to address any predefined hypothesis.

In Part A, at least 24 and up to approximately 36 patients will be randomized in a ratio of 1:1:1 to treatment groups (TAK-079 100 mg, TAK-079 300 mg, or matching placebo).

In Part B, a minimum of 12 and up to approximately 18 patients will be randomized 1:2 to treatment groups (matching placebo or TAK-079 600 mg).

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 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 institution guarantee access to source documents by the sponsor or its designee (ie, CRO) and by the IRB or IEC.

In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches such as remote source data verification or telephone contact may be used to ensure data quality and integrity and maintain patient safety. Alternative monitoring approaches should be used only where allowed by applicable local regulations and permitted by the IRB/IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized) including, but not limited to, the investigator's binder, study medication, patient medical records, informed consent documentation, documentation of patient authorization to use personal health information (if separate from the ICFs), 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.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study 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.

The site should document all protocol deviations in the patient's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or IEC, as required). 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 the primary study assessment.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

14.3 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 US FDA, the United Kingdom [UK] Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, 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 E. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 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 because of privacy and conflict of interest concerns should instead provide a Federalwide Assurance number or comparable number assigned by the US 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 IB, a copy of the ICF, and, if applicable, patient recruitment materials and 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 patient informed consent 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 its exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from the competent authority to begin the trial. Until the site receives 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 designee).

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

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent 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, and 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. If the subject is not capable of rendering adequate written informed consent, 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 to participate in the study. If the subject, or the subject's legally acceptable representative, determines that 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 a ballpoint pen with either blue or black ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and before the subject enters 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 informed consent 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 ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 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 be linked to the sponsor's clinical study database or documentation only 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 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, US FDA, UK MHRA, Japan PMDA), 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 15.2).

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

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 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.

15.4.2 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 interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined by Takeda policy/standards. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed, Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants in finding a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods preferred by callers requesting trial information. Once subjects 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 Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov, clinicaltrialsregister.eu, and other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda policy/standards, applicable laws, and/or regulations.

15.4.4 Data Sharing

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which may be unrelated to the study drug or the patient's disease. The data provided to external researchers will not include information that identifies patients personally.

15.5 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 clinical study subjects. Refer to the clinical 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.

16.0 REFERENCES

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Appendix A Part A and B Main Study Schedule of Events

[redacted]

Study Procedures [a]		Dosing Period									SFP				LFP			
Period	Screening	Length: 8 weeks																
Week [b]	Day -28 to -1	W1	W1 D3	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 10	W 12	W 14	W 16 [c]	W 20 [d]	W 24	W 28	W 32
Window		±2 days									±2 days				±2 days			
Informed consent [e]	X													X [f]				
Eligibility criteria [g]	X													X [f]				
Demographics	X																	
Complete medical history, including prior therapy [h]	X																	
Complete physical examination	X													X				X
Symptom-directed physical examination [i, j]		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	
12-lead ECG [a, k]	X										X			X				
[redacted]																		
Vital signs [j, m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Investigator predosing criteria assessment [j]				X	X	X	X	X	X	X								
Height (cm)	X																	
Weight (kg)	X										X			X				X

Appendix A Part A and B Main Study Schedule of Events

[redacted]

Study Procedures [a]	Screening	Dosing Period									SFP				LFP			
Period		Length: 8 weeks																
Week [b]	Day -28 to -1	W1	W1 D3	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 10	W 12	W 14	W 16 [c]	W 20 [d]	W 24	W 28	W 32
Window		±2 days									±2 days				±2 days			
Laboratory Assessments																		
Blood type assessment [n]	X																	
Serum pregnancy test [k]	X										X			X				X
Urine pregnancy test [j, o]		X					X											
Hematology [p, j, k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation test [q]	X																	
Clinical chemistry [j, k, p]	X						X			X				X	X	X	X	X
Direct/indirect Coombs [j, k]		X					X				X							
TIGRA	X																	

[redacted]

Appendix A Part A and B Main Study Schedule of Events

[redacted]

Study Procedures [a]		Dosing Period									SFP				LFP			
Period	Screening	Length: 8 weeks																
Week [b]	Day -28 to -1	W1	W1 D3	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 10	W 12	W 14	W 16 [c]	W 20 [d]	W 24	W 28	W 32
Window		±2 days									±2 days				±2 days			
[redacted]																		
Serum sample for HBV, HCV, and HIV antibodies	X																	
Blood sample for HCV RNA PCR test [y]	X																	
[redacted]																		

Appendix A Part A and B Main Study Schedule of Events

[redacted]

Study Procedures [a]		Dosing Period									SFP				LFP			
Period	Screening	Length: 8 weeks																
Week [b]	Day -28 to -1	W1	W1 D3	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 10	W 12	W 14	W 16 [c]	W 20 [d]	W 24	W 28	W 32
Window		±2 days									±2 days				±2 days			
Study Therapy Administration																		
Premedication dosing [j, z]		X		X	X	X	X	X	X	X								
TAK-079/placebo, SC [aa]		X		X	X	X	X	X	X	X								
Postmedication dosing [z]		X																
AE reporting [bb]	New onset recorded from the signing of the ICF through the SFP; SAEs collected from the signing of the ICF through the SFP; related AEs/SAEs with onset after SFP collected through the LFP; COVID-19 infection and COVID-19 vaccine-related AEs/SAEs collected from the signing of the ICF through the LFP regardless of causality.																	
Concomitant medications/ procedures monitoring	Recorded from signing of the ICF through SFP														Recorded only for concomitant medications/procedures related to underlying disease and related to COVID-19.			

AE: adverse event; CRS: cytokine release syndrome; D: day; ECG: electrocardiogram; HBV: hepatitis B virus; HCV: hepatitis C virus; ICF: informed consent form; Ig: immunoglobulin; ITP: immune thrombocytopenia; [redacted]; LFP: long-term follow-up period; OLE: open-label extension; OLE-A: Part A open-label extension; OLE-B: Part B open-label extension; [redacted] SAE: serious adverse event; SC: subcutaneous(ly); SFP: safety follow-up period; TIGRA: T-cell interferon-γ release assay; W: week.

[a] Patients may undergo additional laboratory 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.

[b] Patient visits at screening, Weeks 1-4, 10, 16, 20 (only for placebo patients not advancing to the OLE), and Week 32 must be done with the patient present at the investigative site. Other visits may be conducted at the clinic or by optional home healthcare visits (or a hybrid of Telehealth/Telemedicine with home healthcare)

Appendix A Part A and B Main Study Schedule of Events

[redacted]

Study Procedures [a]		Dosing Period									SFP				LFP			
Period	Screening	Length: 8 weeks																
Week [b]	Day -28 to -1	W1	W1 D3	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 10	W 12	W 14	W 16 [c]	W 20 [d]	W 24	W 28	W 32
Window		±2 days									±2 days				±2 days			

to extend flexibility to patients during COVID-19 public health emergency. Home healthcare visits will be documented in the study records and eCRF.

[c] Patients will be unblinded at Week 16. Clinical parameters below the levels in Table 8.f for continued dosing, including ongoing drug-related AEs, at Week 16, should be monitored until the parameters/AEs are resolved, returned to baseline, or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

[d] End-of-study visit for patients who had received placebo dosing and are not continuing on to OLE. Laboratory assessments will not be performed on these patients during this visit. For patients who are randomized to TAK-079, Week 20 visit is the first visit of LFP, and indicated laboratory assessments should be completed.

[e] Informed consent must be documented before initiating any screening procedures associated with the study, and if applicable, confirmation of consent to participate in the OLE phases of the study must be obtained before conducting assessments and procedures specifically for the determination of OLE eligibility.

[f] To be assessed only for patients continuing on to the OLE phase of the study.

[g] Screening period is 28 days (ie, Day -28 to Day -1). Confirmation of patient eligibility by a Takeda project clinician or designee is required before enrollment. See protocol for additional time allowance for extenuating circumstances, to include but not limited to need for screening retesting, as granted on approval of Takeda or sponsor designee. Specific eligibility criteria of patients agreeing to participate in study extension phases (OLE-A and OLE-B), evaluated at Week 16 (see Section 9.5.1), is provided in Section 6.1.1.1.

[h] A complete medical history is compiled during the screening period. This includes assessments of current ITP signs and symptoms. This also includes history of eye disease or ophthalmic clinical symptoms (including allergic reactions). See Section 9.4.4.

[i] Physical examinations are to be symptom- and ITP disease–directed with significant clinical findings noted as AEs. In LFP, needed only if there were ongoing drug-related AEs at the Week 16 assessment. Women of childbearing potential should be asked about their menstrual history at each visit. A serum pregnancy test should be conducted for delayed menses (see Section 9.4.10).

[j] To be performed before TAK-079/placebo administration.

[k] The assessment may be performed on the day before the day of the indicated visit (except at the screening visit). [redacted]

Appendix A Part A and B Main Study Schedule of Events

[redacted]

Study Procedures [a]		Dosing Period									SFP				LFP			
Period	Screening	Length: 8 weeks																
Week [b]	Day -28 to -1	W1	W1 D3	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 10	W 12	W 14	W 16 [c]	W 20 [d]	W 24	W 28	W 32
Window		±2 days									±2 days				±2 days			

[m] Vital signs (temperature, blood pressure, respiratory rate, and heart rate) are measured before all study drug administration [redacted]. In addition, vital signs should be assessed at any time it is clinically warranted. As per the investigator's judgment, if there are no concerns raised by the patient's clinical status and symptoms, or the symptom-directed physical, vital signs measurements are not required to be collected at the Week 12 and 14 visits during the COVID-19 pandemic.

[n] Assessment to include ABO/Rh typing [redacted]. See Sections 8.6.3 and 9.4.12.2 for details.

[o] The results of urine pregnancy will be completed for female patients of childbearing potential before dosing (see Section 9.4.10). The assessment may be performed on the day before the indicated visit. If the subject reports delayed menses, a serum pregnancy test should be completed and a negative result obtained before dosing with the study drug (see Section 9.4.10). Serum pregnancy testing may be used in place of urine pregnancy testing with prior permission from the sponsor.

[p] Hematology and chemistry laboratory samples will be collected locally. Local laboratory evaluations may be done more frequently at the investigator's discretion (ie, for acute management of treatment-emergent AEs) and may be used for dosing decisions. At least one additional hematology sample is to be collected at least 1 week after the screening visit for eligibility.

[q] To include international normalized ratio and partial thromboplastin time.

[redacted]

Appendix A Part A and B Main Study Schedule of Events

[redacted]

Study Procedures [a]		Dosing Period									SFP				LFP			
Period	Screening	Length: 8 weeks																
Week [b]	Day -28 to -1	W1	W1 D3	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 10	W 12	W 14	W 16 [c]	W 20 [d]	W 24	W 28	W 32
Window		±2 days									±2 days				±2 days			

[redacted]

[y] Blood sample is only drawn for patients who have received curative treatment for prior chronic HCV infection.

[z] Premedication and postmedication administration as outlined in Sections 8.2.1 and 8.2.3.

[aa] Time and anatomical site should be recorded for each injection. [redacted]

[bb] Assessments for AEs are to include a symptomatic examination per standard medical practices.

Appendix B Schedule of Events: OLE-A and OLE-B

[redacted]

Study Procedures [a]	OLE Dosing Period									SFP				LFP			
Period	Length: 8 weeks																
Week [b]	EW 1	EW1 D3	EW 2	EW 3	EW 4	EW 5	EW 6	EW 7	EW 8	EW 10	EW 12	EW 14	EW 16 [c]	EW 20	EW 24	EW 28	EW 32
Window	±2 days									±2 days				±2 days			
Complete physical examination													X				X
Symptom-directed physical examination [c, d]	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	
12-lead ECG [e]										X			X				
[redacted]																	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X				
Investigator predosing criteria assessment [d]	X		X	X	X	X	X	X	X								
Weight (kg)										X			X				X
Laboratory Assessments																	
Serum pregnancy test [e]										X			X				X
Urine pregnancy test [e, h]	X					X											
Hematology [d, e, i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical chemistry [d, e, i]						X			X				X	X	X	X	X

Appendix B Schedule of Events: OLE-A and OLE-B

[redacted]

Study Procedures [a]	OLE Dosing Period									SFP				LFP			
Period	Length: 8 weeks																
Week [b]	EW 1	EW1 D3	EW 2	EW 3	EW 4	EW 5	EW 6	EW 7	EW 8	EW 10	EW 12	EW 14	EW 16 [c]	EW 20	EW 24	EW 28	EW 32
Window	±2 days									±2 days				±2 days			
Direct/indirect Coombs [d, e]						X				X							

[redacted]

Appendix B Schedule of Events: OLE-A and OLE-B

[redacted]

Study Procedures [a]	OLE Dosing Period									SFP				LFP			
Period	Length: 8 weeks																
Week [b]	EW 1	EW1 D3	EW 2	EW 3	EW 4	EW 5	EW 6	EW 7	EW 8	EW 10	EW 12	EW 14	EW 16 [c]	EW 20	EW 24	EW 28	EW 32
Window	±2 days									±2 days				±2 days			
[redacted]																	
Study Therapy Administration																	
Premedication dosing [d, q]	X		X	X	X	X	X	X	X								
TAK-079, SC [p]	X		X	X	X	X	X	X	X								
Postmedication dosing [q]	X																
AE reporting [r]	New onset recorded from the signing of the ICF through the SFP; SAEs collected from the signing of the ICF through the SFP; related AEs/SAEs with onset after SFP collected through the LFP; COVID-19 infection and COVID-19 vaccine-related AEs/SAEs collected from the signing of the ICF through the LFP regardless of causality.																
Concomitant medications/ procedures monitoring	Recorded only for concomitant medications/procedures related to underlying disease and related to COVID-19.																

AE: adverse event; CRS: cytokine release syndrome; D: day; ECG: electrocardiogram; EW: extension week; ICF: informed consent form; Ig: immunoglobulin; ITP: immune thrombocytopenia; [redacted]; LFP: long-term follow-up period; OLE: open-label extension; OLE-A: Part A open-label extension phase; OLE-B: Part B open-label extension phase; [redacted] SAE: serious adverse event; SC: subcutaneous(ly); SFP: safety follow-up period.

[a] Patients may undergo additional laboratory assessment and observations as necessary based on the principal investigator's best medical judgment, and as

Appendix B Schedule of Events: OLE-A and OLE-B

[redacted]

Study Procedures [a]	OLE Dosing Period									SFP				LFP			
Period	Length: 8 weeks																
Week [b]	EW 1	EW1 D3	EW 2	EW 3	EW 4	EW 5	EW 6	EW 7	EW 8	EW 10	EW 12	EW 14	EW 16 [c]	EW 20	EW 24	EW 28	EW 32
Window	±2 days									±2 days				±2 days			

warranted by exhibited clinical signs or symptoms at each study clinic visit.

[b] Patient visits at EW1, EW2, EW3, EW4, EW10, EW16, and EW32 of the OLE must be done with the patient present at the investigative site. Other visits may be conducted at the clinic or by optional home healthcare visits (or a hybrid of Telehealth/Telemedicine with home healthcare) to extend flexibility to patients during COVID-19 public health emergency. Home healthcare visits will be documented in the study records and eCRF.

[c] Physical examinations are to be symptom- and ITP disease–directed with significant clinical findings noted as AEs. In LFP, needed only if there were ongoing drug-related AEs at the EW16 assessment (see Section 9.4.6). Women of childbearing potential should be asked about their menstrual history at each visit. A serum pregnancy test should be conducted for delayed menses (see Section 9.4.10).

[d] To be performed before TAK-079 administration.

[e] The assessment may be performed on the day before the day of the indicated visit. [redacted]

[g] Vital signs (temperature, blood pressure, respiratory rate, and heart rate) are measured before all TAK-079 administration [redacted]. In addition, vital signs should be assessed at any time it is clinically warranted. As per the investigator's judgment, if there are no concerns raised by the patient's clinical status and symptoms, or the symptom-directed physical, vital signs measurements are not required to be collected at the Week 12 and 14 visits during the COVID-19 pandemic.

[h] The results of urine pregnancy will be completed for female patients of childbearing potential before dosing (see Section 9.4.10). The assessment may be performed on the day before the indicated visit. A serum pregnancy test should be performed if the patient's menstrual period is delayed (see Section 9.4.10). Serum pregnancy testing may be used in place of urine pregnancy testing with prior permission from the sponsor.

[i] Hematology and chemistry laboratory samples will be collected locally. Local laboratory evaluations may be done more frequently at the investigator's discretion (ie, for acute management of treatment-emergent AEs) and may be used for dosing decisions.

[redacted]

Appendix B Schedule of Events: OLE-A and OLE-B

[redacted]

Study Procedures [a]	OLE Dosing Period									SFP				LFP			
Period	Length: 8 weeks																
Week [b]	EW 1	EW1 D3	EW 2	EW 3	EW 4	EW 5	EW 6	EW 7	EW 8	EW 10	EW 12	EW 14	EW 16 [c]	EW 20	EW 24	EW 28	EW 32
Window	±2 days									±2 days				±2 days			

[redacted]

[p] Time and anatomical site should be recorded for each injection.

[redacted]

[q] Premedication and postmedication as outlined in Sections 8.2.1 and 8.2.3.

[r] Assessments for AEs are to include a symptomatic examination per standard medical practices.

Appendix C [redacted]

[redacted]

Appendix D [redacted]

[redacted]

Appendix E 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 who 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 Code for Federal Regulations (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 subjects. 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, laboratory results, etc, 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.

Appendix F Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the investigator, including his or her name, address, and other identifying personal information. In addition, the investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the UK, US, 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.

The 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 the 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 study registries, databases, and websites.

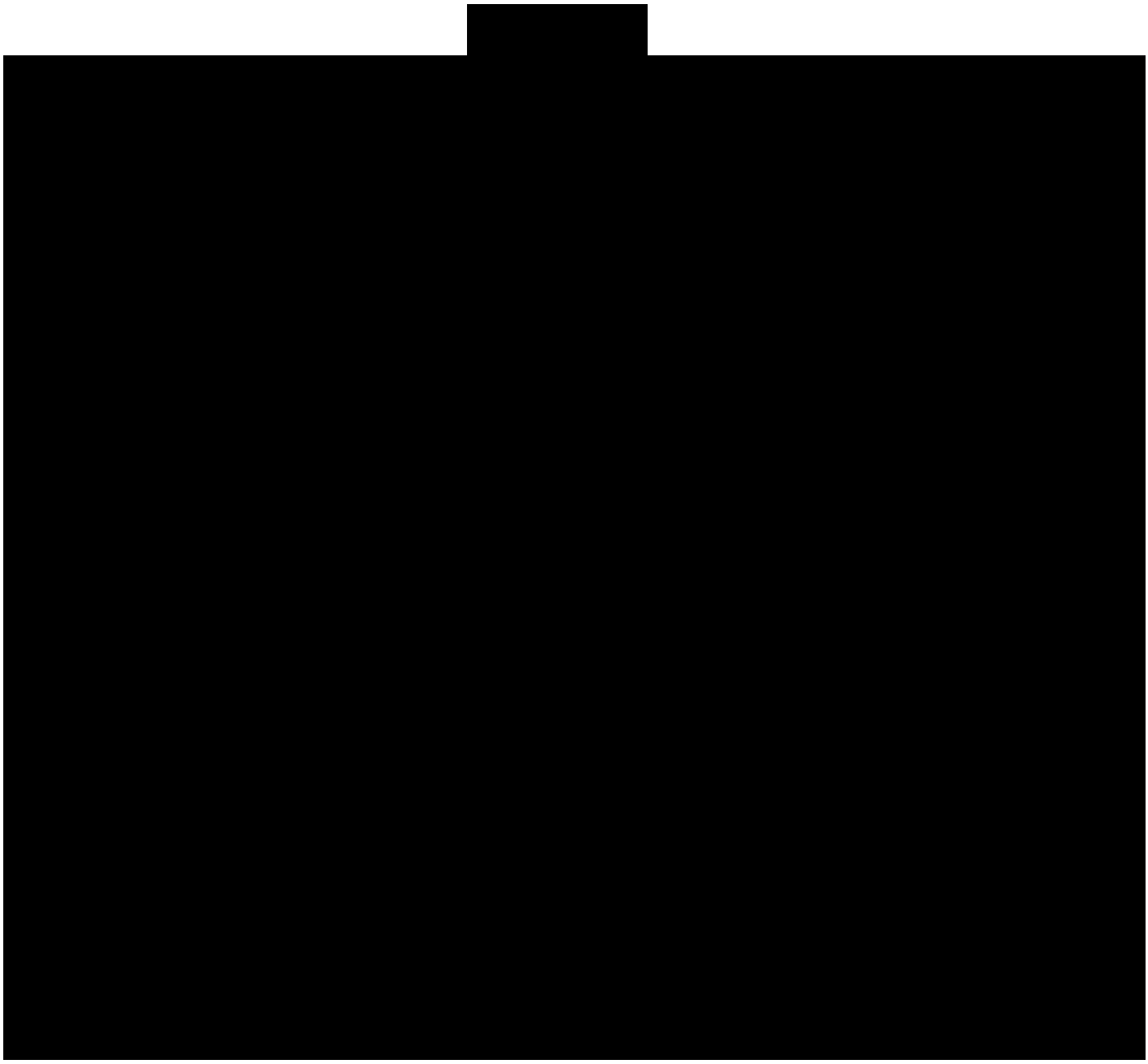
The investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in the investigator's own country.

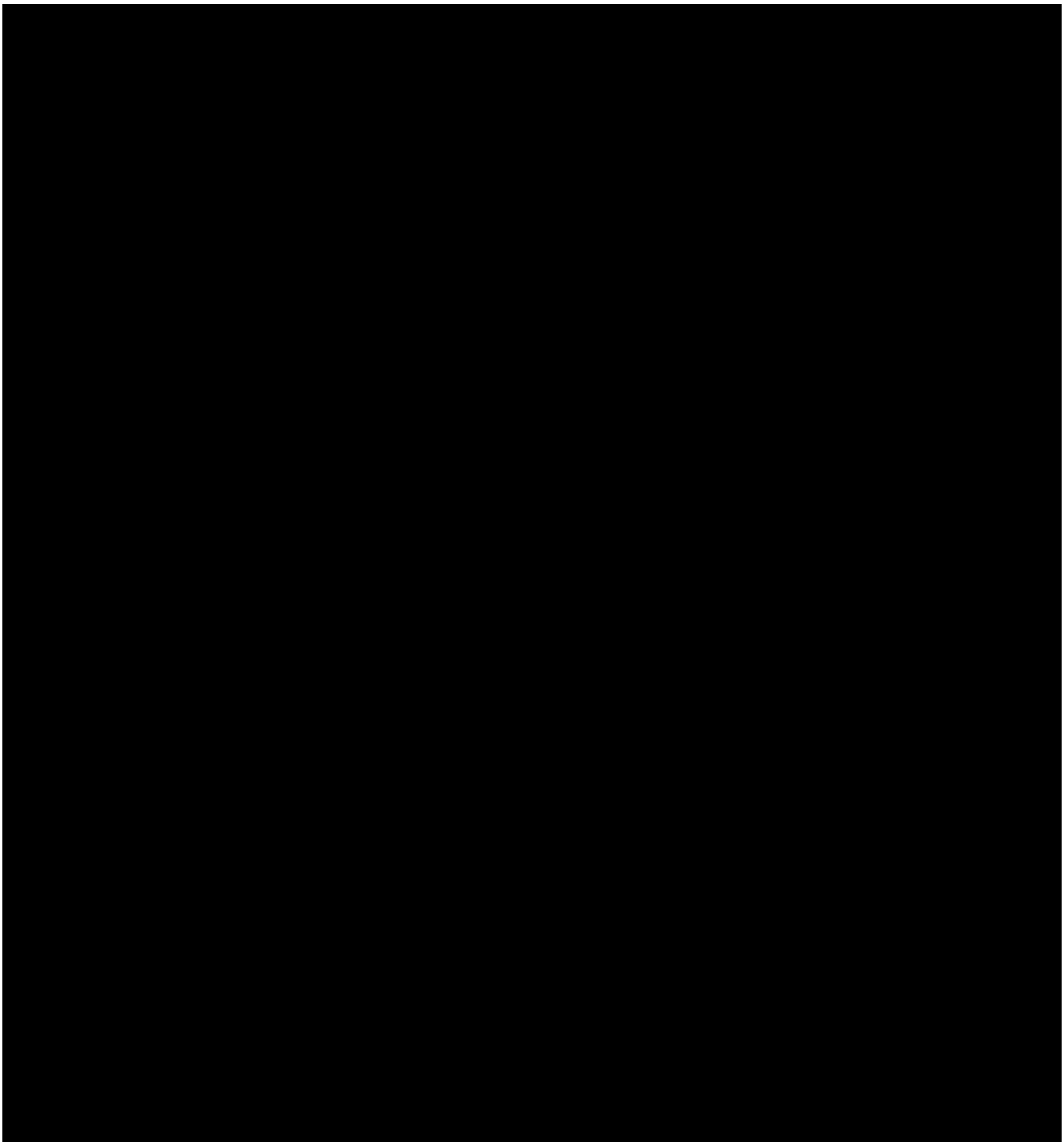
The investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

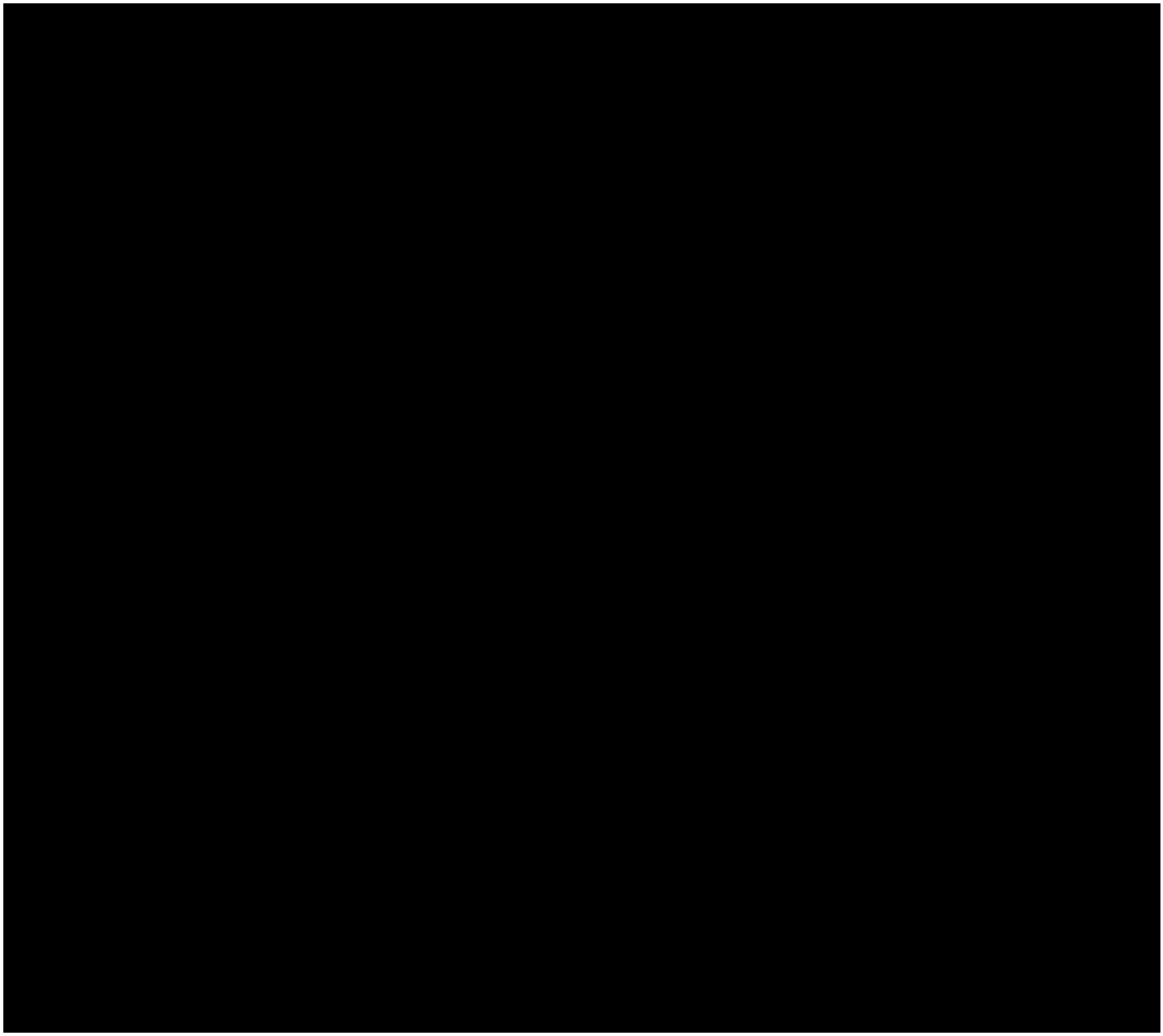
Appendix G [redacted]

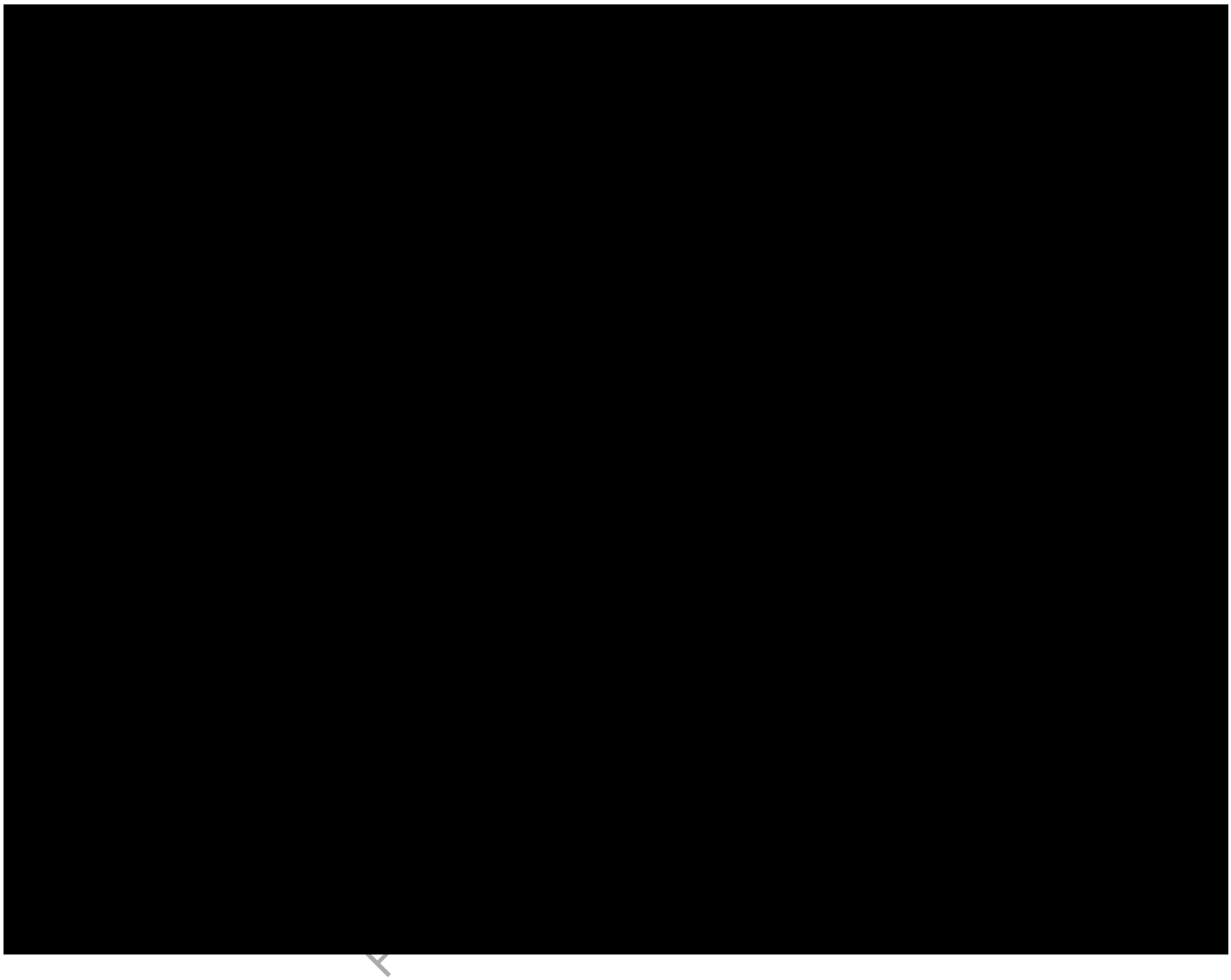
[redacted]

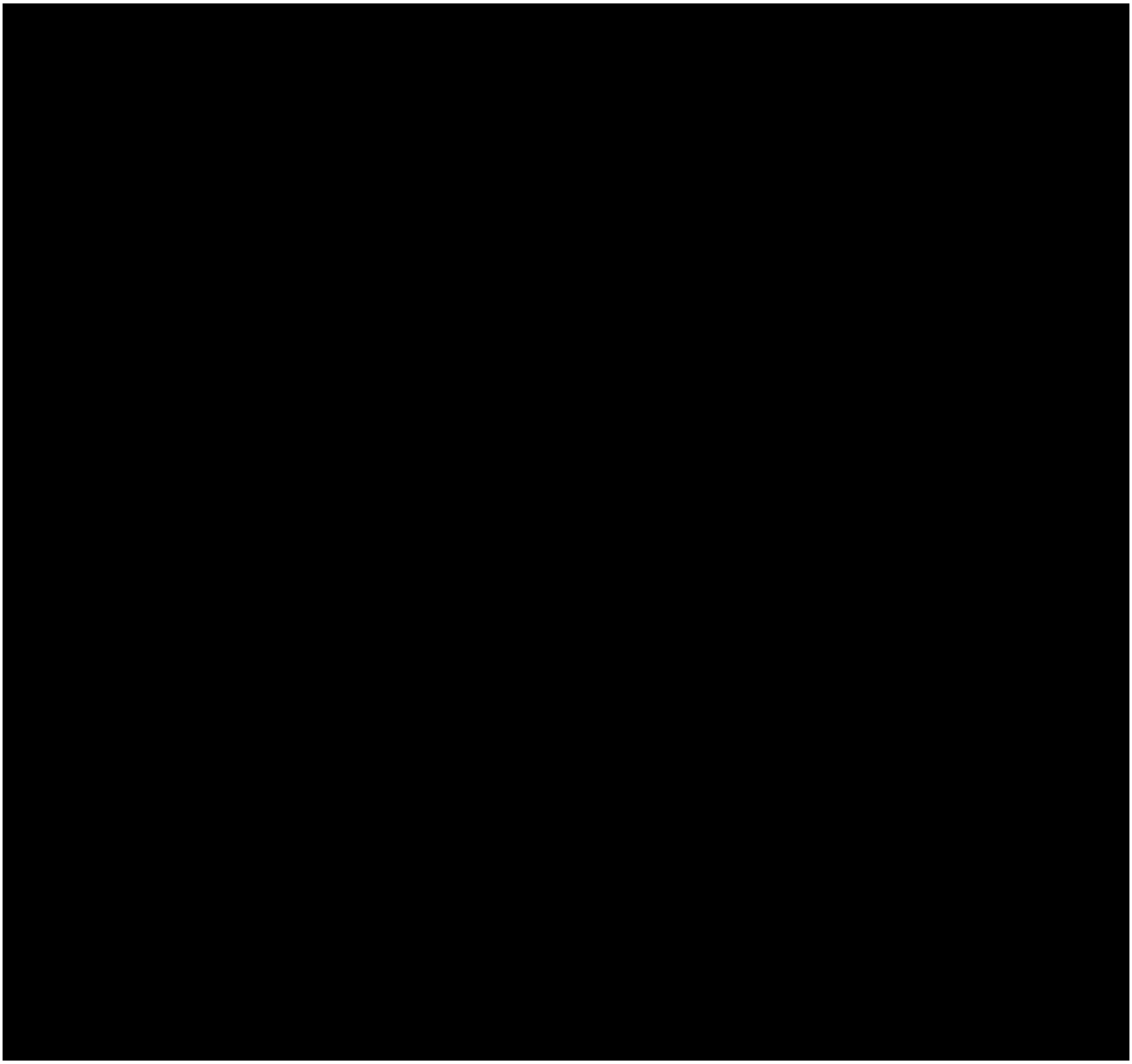
Appendix H [redacted]











Appendix I Protocol History

Date	Amendment Number	Type	Region
28 April 2022	Amendment 5	Substantial	Global
05 May 2021	Amendment 4	Substantial	Global
18 December 2020	Amendment 3	Substantial	Global
7 October 2020	Amendment 2	Substantial	Global
26 December 2019	Amendment 1	Nonsubstantial	Global
06 November 2019	Initial protocol	Not applicable	Global

Protocol Amendment 4 and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 4. The primary reason for this amendment is to change the legal entity name for the sponsor to Takeda Development Center Americas, Inc. Other changes are outlined in the table below.

Change Number	Protocol Amendment 4 Summary of Changes Since the Last Version of the Approved Protocol		
	Sections Affected by Change	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1	Title Page 2.0 STUDY SUMMARY	Changed legal entity name for the sponsor from Millennium Pharmaceuticals, Inc (MPI), 40 Lansdowne Street, Cambridge, MA 02139 to: Takeda Development Center Americas, Inc, 95 Hayden Avenue, Lexington, MA 02421, USA.	New legal entity name for sponsor.
2	3.3 Corporate Identification	Changed corporate identification from Millennium Pharmaceuticals, Inc. a wholly owned subsidiary of Takeda to read: Takeda, Takeda Development Center Americas, Inc.	New legal entity name for sponsor.
3	6.2 Number of Patients	Changed US, Canada to North America	To be consistent with Synopsis.
4	Table 8.c Permitted Concomitant Medications	Table header for second column changed from "Criteria Are to Be Maintained from Screening to Completion of Study Dosing Phase" to read: "Criteria Are to Be Maintained Throughout the Study"	Correction.
5	10.1.3 SAE Definition	Under 6. Is a MEDICALLY IMPORTANT EVENT: Removed "Includes any event or synonym described in the Takeda Medically Significant AE List (see Table 10.a)." Removed Table 10.a	To be consistent with updated protocol template.

Protocol Amendment 3 and Rationale

The primary reason for Amendment 3 was to revise the timing of sample collection for the ITP bleeding scores and the procedure for occult blood samples. Other changes are outlined in the table below.

Protocol Amendment 3		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 1.2 Approval	Change name of Biostatics approver from [redacted]	To update study personnel.
Section 2.0 STUDY SUMMARY Section 6.2 Number of Patients	Increase number of sites from approximately 30 to approximately 33.	To mitigate the delayed enrollment caused by coronavirus disease 2019 (COVID-19).
Section 9.4 Study Procedures Section 9.4.4 Medical History Section 9.4.5 Concomitant Medications and Procedures Section 9.4.7 Patient Height and Weight Appendix A Part A and B Main Study Schedule of Events	Increase the length of the screening period from 21 days to 28 days.	To lengthen the screening period by 1 week due to COVID-related shipping delays.
Section 8.1.2 Postdose Medication Section 9.5.4 OLE Dosing Period (EW1 to EW8)	Modify timing of medication following the first dose of study drug from: "Considering the timing of the greatest pharmacologic effect of TAK-079, postdose medication should be given after the first dose and 1 day after the first dose of study drug." to read: Considering the timing of [redacted] risk after TAK-079 dosing, [redacted]"	To clarify the rationale and provide more detailed guidance on the administration of postdose medication.
Appendix A, Part A and B Main Study Schedule of Events, footnote x Appendix B Schedule of Events: OLE-A and OLE-B, footnote p.	Text added: [redacted] Postdose medication may be given with subsequent doses if clinically indicated and under the discretion of the principal investigator (see Section 8.1.2)."	To provide more detailed guidance on the administration of postdose medication.

Protocol Amendment 3		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 9.4.6 Physical Examination Appendix A Part A and B Main Study Schedule of Events, footnote h Appendix B Schedule of Events: OLE-A and OLE-B, footnote c.	The following sentence has been added: "Women of childbearing potential should be asked about their menstrual history at each visit. A serum pregnancy test should be conducted for delayed menses (see Section 9.4.10)."	To ensure a woman is not pregnant before study drug administration.
Section 9.4.8 Vital Signs Appendix A Part A and B Main Study Schedule of Events, footnote l Appendix B Schedule of Events: OLE-A and OLE-B, footnote g	A window of ±10 minutes has been added [redacted].	To provide a 10 minute window for obtaining vital signs after administration of study drug In addition, footnote "l" in Appendix A was revised to remove unclear wording about which vital signs are to be taken during the visits.
Section 9.4.10 Pregnancy Test Appendix A Part A and B Main Study Schedule of Events, Urine pregnancy test, footnote n Appendix B Schedule of Events: OLE-A and OLE-B, Urine pregnancy test, footnote h	The following sentence has been added: "If the subject reports delayed menses, a serum pregnancy test should be completed and a negative result obtained before dosing with the study drug." Text added to Appendix A (footnote n) and Appendix B (footnote h): A serum pregnancy test should be performed if the patient's menstrual period is delayed (see Section 9.4.10).	To ensure a woman is not pregnant before the first dose of study drug administration and at Week 5 of the dosing period in the main study (double-blind study) and at extension week (EW) 1 before the first dose of study drug and at EW5 in the open-label extension dosing period.
Section 9.4.10.1 Definition of Women of Childbearing Potential	Removed: "Has not been naturally postmenopausal (amenorrhea after cancer therapy does not rule out childbearing potential) for at least 24 consecutive months, ie, has had menses at any time in the preceding 24 consecutive months." Clarified the definition of postmenopausal.	To remove confusing wording from template language that does not apply to this protocol.

Protocol Amendment 3		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 9.4.17 [redacted] Appendix A [redacted] Appendix B [redacted]	[redacted]	[redacted]
Appendix A [redacted]	[redacted]	[redacted]
Section 9.12 COVID-19–Related Procedural Changes	Date of Food and Drug Administration (FDA) guidance on COVID 19 changed from 02 July 2020 to 4 December 2020.	To reference date of most recent FDA guidance on COVID-19.
	6th bullet: Weeks 4 and 10 of the main study and EW4 and EW10 of the open-label extension (OLE) study added to visits that must be conducted with the patient present at the investigative site.	To increase the number of required visits at the investigative sites to align with administration of the [redacted] to ensure optimal safety monitoring.

Protocol Amendment 3		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Appendix A, Part A and B Main Study Schedule of Events, footnote b	Footnote b added to row labeled "Week": "Patient visits at screening, Weeks 1-4, Week 10, Week 16, Week 20 (only for placebo patients not advancing to the OLE), and Week 32 must be done with the patient present at the investigative site. Other visits may be conducted at the clinic or by optional home healthcare visits (or a hybrid of Telehealth/Telemedicine with home healthcare) to extend flexibility to patients during COVID-19 public health emergency. Home healthcare visits will be documented in the study records and eCRF."	To clarify which visits must be conducted with patient present and which visits may be conducted in the clinic or by optional home healthcare visits.
Appendix B Schedule of Events: OLE-A and OLE-B, footnote b.	Footnote b added to row labeled "Week": "Patient visits at EW1, EW2, EW3, EW4, EW10, EW16, and EW32 of the OLE must be done with the patient present at the investigative site. Other visits may be conducted at the clinic or by optional home healthcare visits (or a hybrid of Telehealth/Telemedicine with home healthcare) to extend flexibility to patients during COVID-19 public health emergency. Home healthcare visits will be documented in the study records and eCRF."	To clarify which visits must be conducted with patient present and which visits may be conducted in the clinic or by optional home healthcare visits.
Appendix I Protocol History	Changes in Amendment 2 added.	Added according to template guidelines.

Protocol Amendment 2 and Rationale

The primary reasons for Amendment 2 were to:

- Provide clarifications regarding inclusion/exclusion criteria for platelet counts and prior high-dose pulse steroid therapy. These changes will provide for a more efficient screening process while continuing to ensure inclusion of patients with stable platelet counts below 30,000/μL.
- Allow patients to receive predefined rescue therapies during the dosing period without automatic discontinuation from study drug dosing and advancement to the safety follow-up period (SFP). As it may take several weeks for TAK-079 to increase platelet counts, this change enables investigators to provide a limited bridge therapy for safety purposes.
- Clarify the eligibility criteria for the open-label extension (OLE)-A and OLE-B and enhance access to the OLE for placebo patients who receive rescue therapies during the study.
- Address feedback from a health authority by providing a specific protocol section on the risks and benefits of TAK-079, and by specifying the allowable contraception methods.
- Add contingency plans for the COVID-19 pandemic by incorporating flexibility for study participants, investigators, and study-site monitors while continuing to maintain patient safety and study integrity as per local site regulations.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study were included for clarification and administrative purposes only.

Protocol Amendment 2		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 2.0 Study Summary Section 5.2.2 Secondary Endpoints	Changed definition of platelet response to exclude counts for patients who received a nonpermitted rescue therapy and counts from patients who had received a rescue therapy in the previous 4 weeks.	Evaluation of the secondary endpoints 4 weeks after a dosing period–permitted rescue treatment is allowed since the duration of effect is typically less than 4 weeks. Any other rescue therapy prevents further evaluation of the secondary endpoints.

Protocol Amendment 2		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 2.0 Study Summary Section 6.1 Overview of Study Design Section 8.1.3 Rescue Therapy Table 8.c Permitted Concomitant Medications	Added provision for dosing to proceed if rescue therapy is given as a [redacted] Clarified that platelet count should be censored for 4 weeks thereafter. If patient needs more than 1 rescue treatment or other form of rescue treatment, then study drug dosing should be discontinued and the patient should advance to the SFP.	Allows for certain types of rescue therapy to be given without requiring discontinuation from study dosing. This is a bridge therapy for safety reasons (especially at the beginning of the study), since the effect of TAK-079 on platelet levels may not have an onset for several weeks. Typically, dosing period–permitted rescue therapies have a duration of effect of less than 4 weeks without a long-term effect on platelet levels.
Section 2.0 Study Summary Section 6.1.1.1 Part A Open-label Extension Phase Section 6.1.2.1 Part B Open-label Extension Phase Section 8.4.1 Assessment and Criteria for Terminating Patient Dosing	Defined eligibility for the OLE.	Clarification of eligibility.
Section 2.0 Study Summary Section 7.1 Inclusion Criteria	#3 Inclusion Criterion: Changed from: "Presents with a mean platelet count of <30,000/µL for the 4 weeks before the first study dose. The mean platelet count is based on at least 2 platelet counts within 4 weeks of dosing, including the value obtained at screening. No individual platelet count >35,000/µL during these times is allowed." to read: "Has a mean platelet <30,000/µL (and individually ≤35,000/µL) on at least 2 measurements obtained at least 1 week apart."	Reduced time that patients are required to have platelets <30,000/µL to at least 1 week for safety reasons. The shorter duration allows for patients to be enrolled without principal investigator-directed changes in background therapy before Day 1. After Day 1, the amended protocol allows for permitted forms of rescue therapy without discontinuation from study drug dosing.
Section 2.0 Study Summary Section 7.1 Inclusion Criteria	#4 Inclusion Criterion: Revised to add diagnosis of immune thrombocytopenia (ITP) supported by a response to a prior ITP therapy that achieved a platelet count of ≥50,000/µL (other than thrombopoietin receptor agonists [TPO-RAs]).	Reworded for clarity. Additionally, removed TPO-RAs as a diagnostic treatment for this criterion since this class of medications can result in platelet increases in many disease states and not just ITP.

Protocol Amendment 2		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 2.0 Study Summary Section 7.1 Inclusion Criteria Table 8.c Permitted Concomitant Medications	#5 Inclusion Criterion: Removed text that restricted high-dose pulse steroid therapy 14 days before dosing and clarified that every-other-day dosing of oral corticosteroid therapy is allowed.	High-dose pulse steroid therapy may confound platelet counts for longer than 14 days and is not consistent with the dosing period–permitted rescue therapies. Also clarifies that stable background therapy with daily or every-other-day corticosteroids is allowed, as the intent was not to exclude this group of patients.
Section 2.0 Study Summary Section 7.2 Exclusion Criteria	#4 Exclusion Criterion: Revised to exclude patients if there is an expectation that any rescue therapy may be needed between screening and dosing.	Clarifies that a patient's platelet count should be stable enough that the need for a rescue therapy is not expected before dosing.
Section 2.0 Study Summary Section 7.2 Exclusion Criteria Section 8.2 Excluded Concomitant Medications and Procedures	#9 Exclusion Criterion: Revised vaccination restriction to live vaccines only.	Patients who receive TAK-079 or any other immunosuppressive drug, such as corticosteroids, may be placed at increased risk of infection from a live vaccine. This risk is not present with inactive vaccines. It is recommended to continue with vaccinations with inactive vaccines as these may confer protective benefit.
Section 2.0 Study Summary Section 7.2 Exclusion Criteria Appendix B Schedule of Events: OLE-A and OLE-B	#13 Exclusion Criterion: Definition updated to clarify parameters for patients with herpes simplex infection.	Most local herpes lesions are benign and do not require any specific systemic treatment; infections of this type that have resolved do not pose any risk to the patient with study drug treatment.
Section 2.0 Study Summary Section 7.2 Exclusion Criteria Appendix B Schedule of Events: OLE-A and OLE-B	#17 Exclusion Criterion: Revised to allow patients cured of hepatitis C.	Patients who have been fully cured of hepatitis C are no longer at risk of worsening of infection by immunosuppressive agents. Additionally, the hepatitis B core Ab test is used to exclude patients with possible latent/occult hepatitis B to prevent the theoretical possibility of reactivation.
Section 2.0 Study Summary Section 13.1.3 Efficacy Analysis	Specified how different types of secondary efficacy endpoints (binary vs continuous) will be analyzed.	Clarifies statistical analyses.

Protocol Amendment 2		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 13.1.4 [redacted]	[redacted]	[redacted]
Section 2.0 Study Summary Section 13.3 Determination of Sample Size	Amended the sample size justification to remove the statement describing a power calculation for the secondary efficacy endpoints.	Further clarifies that this study is an exploratory study and not powered to test any predefined statistical hypothesis at a formal α level. Statistical tests will be not be inferential and will not be adjusted for multiplicity.
Section 4.3 Benefits and Risks Assessment	New section added summarizing the risks and benefits.	Added in response to a health authority request.
Section 5.2.3 [redacted]	[redacted]	[redacted]
Section 8.1 Study Drug Administration	Added clarifying statements that first dose assessments detailed in Table 8.d may be satisfied by screening or Week 16 labs.	Clarifies that, on Day 1 of the main study or the OLE, these laboratory studies would have been recently obtained in the absence of recently administered study drug. For other doses, the window is expanded to allow obtaining labs the day before (rather than restricted to 24 hours before the study visit) for flexibility in obtaining laboratory results, especially in light of operational complexities due to COVID-19.
Section 8.2 Excluded Concomitant Medications and Procedures	Table 8.b: Corrected restriction of concomitant use of immunosuppressants; should be 6 months from dosing, not 4 months from screening.	Fixes an error in Table 8.b so that the table is consistent with exclusion criterion #7.
Section 8.2 Excluded Concomitant Medications and Procedures	Table 8.b: Error in table corrected to match with Exclusion criterion #6 that says rituximab is restricted within 4 months before first dosing.	Correction of an error in Table 8.b.
Section 8.4.1 Assessment and Criteria for Terminating Patient Dosing	Table 8.d: Revised dosing criteria for total lymphocyte count. Continue Dosing: $\geq 500/mm^3$ or $\geq 90\%$ of the baseline level. Dose Hold: $<500/mm^3$ and $< 90\%$ of the baseline level.	Allows for minor fluctuations in the cell counts for patients on background therapy who may also have low baseline values. This criterion is based on emerging information from ongoing clinical studies with TAK-079.

Protocol Amendment 2		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 8.5.1 Pregnancy, Lactation and Contraception	Added contraception method recommendations as given in the informed consent form.	Added in response to a request from a health authority.
Section 8.6.1.1 [redacted]	First sentence: [redacted] . [redacted]	Correct typo. [redacted]
Table 8.d Summary of Subsequent Dosing Criteria	Table 8.d: Revised wording: [redacted]	Make dosing criteria for [redacted]
Section 9.4.10 Pregnancy Test Appendix A and Appendix B	Added serum pregnancy test at Week 32 and Extension Week 32.	Added at the estimated end of systemic exposure to TAK-079 (>150 days after the last dose), in accordance with recommendations from the Clinical Trial Facilitation Group.

Protocol Amendment 2		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 9.4.10.2 Appendix A Part A and B Main Study Schedule of Events	Footnote x added: Assessments may be performed on the day before the indicated visit (except at the screening visit).	Clarification.
Section 9.4.13.1 Primary Specimen Collection Appendix A Part A and B Main Study Schedule of Events Appendix B Schedule of Events: OLE-A and OLE-B	Table 9.b: [redacted]	[redacted]
Section 9.4.13.1 Primary Specimen Collection Appendix A Part A and B Main Study Schedule of Events	Table 9.b: Added: Blood sample for hepatitis C virus (HCV), RNA, and polymerase chain reaction (PCR).	For patients with prior HCV infection who have been cured of disease, addition of this test confirms the resolution of infection.
Section 9.6 End of Safety Follow-up Assessments, Table 9.c Clinical Parameters for End of Safety Follow-up Period	Table 9.c: Revised wording: Neutrophils, total lymphocyte count, and Hgb End-of-Study Criteria: ≥lower limit of normal (LLN) or ≥study baseline levels or low levels that are not directly related to dosing of investigational product. Continuation to Long-term Follow-up: <LLN and <study baseline levels that is directly related to dosing of investigational product. [redacted]	Clarify the end-of-study criteria and long-term follow-up parameters by correcting errors and unclear wording.

Protocol Amendment 2		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
	[redacted]	
Section 9.6 End of Safety Follow-up Assessments, Table 9.c Clinical Parameters for End of Safety Follow-up Period *continued*		
Section 9.12 COVID-19–Related Procedural Changes Appendix A Part A and B Main Study Schedule of Events Appendix B Schedule of Events OLE-A and OLE-B	Added contingency plans for the COVID-19 pandemic ongoing during the clinical study. Appendix A Footnote h (added text): As per the investigator's judgment, if there are no concerns raised by the symptom-directed physical, vital signs measurements will not be required to be collected at the Week 12 and 14 visits during the COVID-19 pandemic. Appendix B Footnote c (added text): same as above for Appendix A.	New section to mitigate the impact of the COVID-19 pandemic to ensure the rights, safety, and well-being of patients, the safety of clinical trial staff, maintain compliance with Good Clinical Practice, maintain study integrity, and patient privacy.
Section 10.1.3 SAE Definition	Added clarification that inpatient stay for rescue therapy does not automatically count as an serious adverse event (SAE).	Some clinical centers may only be able to provide certain dosing period–permitted rescue therapies (eg, IVIg) via inpatient hospitalization. Therefore, the hospital admission itself (in an otherwise clinically stable patient) specifically for access and administration of rescue therapy does not count automatically as an SAE, unless there are other circumstances that fulfill SAE criteria.
Section 10.2 Procedures for Recording and Reporting AEs and SAEs	Updated SAE reporting procedure and global fax number.	New Takeda process for reporting SAEs, which now includes an acknowledgment of receipt of the SAE report to be sent back to sites within 1 business day from Cognizant, the SAE reporting contact. Additional contact information for global access (fax number) was added.
Section 14.1 Study-Site Monitoring Visits	Text added to address alternative monitoring approaches if needed due to the COVID-19 pandemic.	Takeda guidelines for conducting study-site monitoring visits due to COVID-19 pandemic.

Protocol Amendment 2		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Appendix A Part A and B Main Study Schedule of Events	Footnote a added to "Study Procedures" allowing patients to undergo additional laboratory assessment and observations as necessary based on the principal investigator's best medical judgment.	Clarification.
Appendix A Part A and B Main Study Schedule of Events	Footnote i: Revised to note ABO/Rh typing [redacted] is performed at the central laboratory.	Clarification.
Appendix A Part A and B Main Study Schedule of Events Appendix B Schedule of Events OLE-A and OLE-B	Footnote j (Appendix A) and Footnote d (Appendix B): Added statement to allow sites to use serum pregnancy testing instead of urine pregnancy testing.	Clarify that the intent of the protocol is not to exclude use of more accurate serum pregnancy tests if this is logistically feasible for a site.
Appendix A Part A and B Main Study Schedule of Events	Footnote k: Added statement that an additional hematology sample is to be collected at least 1 week after the screening visit for eligibility.	Added to reflect the modified inclusion criteria #3 requiring at least 2 measurements of the platelet count at least 1 week apart.
Appendix B Schedule of Events OLE-A and OLE-B	Footnote o added: The assessment may be performed on the day before the indicated visit.	Clarification.

Protocol Amendment 1 and Rationale

This document describes the changes to the protocol incorporating Amendment 01. The primary reason for this amendment is to address United States (US) Food and Drug Administration (FDA) feedback on the primary immune thrombocytopenia (ITP) Investigational New Drug (IND).This feedback indicated that all patients should have either phenotype or genotype testing prior to study drug treatment with no exceptions. This is because there is a potential that TAK-079 may affect blood bank serologic testing should a patient require a red blood cell (RBC) transfusion. While the informed consent form specified that this test is required for all patients, the language in the protocol was inconsistent with this. This amendment revises the protocol language to accurately reflect that the RBC phenotype or genotype assessment is required for study participation.

- Extended RBC antigen typing (assessed by phenotyping or genotyping) is required before initiation of study dosing.
- Correction of FEV_1 to be defined as forced expiratory volume in 1 second; previously erroneously defined as forced expiratory volume in 1 minute.
- Correction of Appendix B Schedule of Events: OLE-A and OLE-B; indicating postmedication dosing is to be conducted during EW1, previously it was erroneously indicated to be performed during EW1D3.

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

Appendix J [redacted]

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Pharmacology Approval	02-May-2022 12:53 UTC
[redacted]	Biostatistics Approval	02-May-2022 13:24 UTC
[redacted]	Clinical Approval	02-May-2022 15:16 UTC