Statistical Analysis Plan

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 3.0, 16 May 2024

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.

STATISTICAL ANALYSIS PLAN

Study Number: TAK-079-1004

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Phase: 2

Version: Amendment 3.0

Date: 16 May 2024

Prepared by: [redacted]

Based on:

Protocol Version and Date:

Amendment 5, 28 April 2022

REVISION HISTORY

Version	Date	Primary Rationale for Revision
Original version	05-APR-2021	Not applicable
Amendment 1.0	29-AUG-2022	Protocol amendment
Amendment 2.0	01-DEC-2023	To clarify statistical methods as outlined in Section 9.1
Amendment 3.0	16-MAY-2024	To address feedback from interim analysis and dry-run review of the tables, listings and figures

Table of Contents

LIST OF IN-TEXT TABLES

ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
BMI	body mass index
CI	confidence interval
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
ECG	electrocardiogram
eCRF	electronic case report form
EW	extension week
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
[redacted]	[redacted]
[redacted]	[redacted]
ITP	immune thrombocytopenia
[redacted]	[redacted]
LFP	long-term follow-up period
MAV	markedly abnormal values
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effects model for repeated measures
NK	natural killer
OLE	open label extension
PB	plasmablast
[redacted]	[redacted]
[redacted]	[redacted]
PRO	Patient Reported Outcomes
PT	preferred term (MedDRA)
PTE	pre-treatment event
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SFP	safety follow-up period

SOC	System Organ Class
SRC	Safety Review Committee
TEAE	treatment-emergent adverse event
WHO	World Health Organization

1.0 OBJECTIVES AND ENDPOINTS

1.1 Study Objectives

1.1.1 Primary Objective

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

1.1.2 Secondary Objective

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

1.1.3 [redacted]

1.2 Endpoints

1.2.1 Primary Endpoint

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

1.2.2 Secondary Endpoints

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

1. Number and *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,* without premature

discontinuation from the study drug *and without any other previous rescue therapy.*

2. Number and *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*, without premature discontinuation from the study drug *and without any other previous rescue therapy.*
3. Number and *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*, without premature discontinuation from the study drug *and without any other previous rescue therapy.*
4. Number and *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*, without premature discontinuation from the study drug *and without any other previous rescue therapy.*

1.2.3 [redacted]

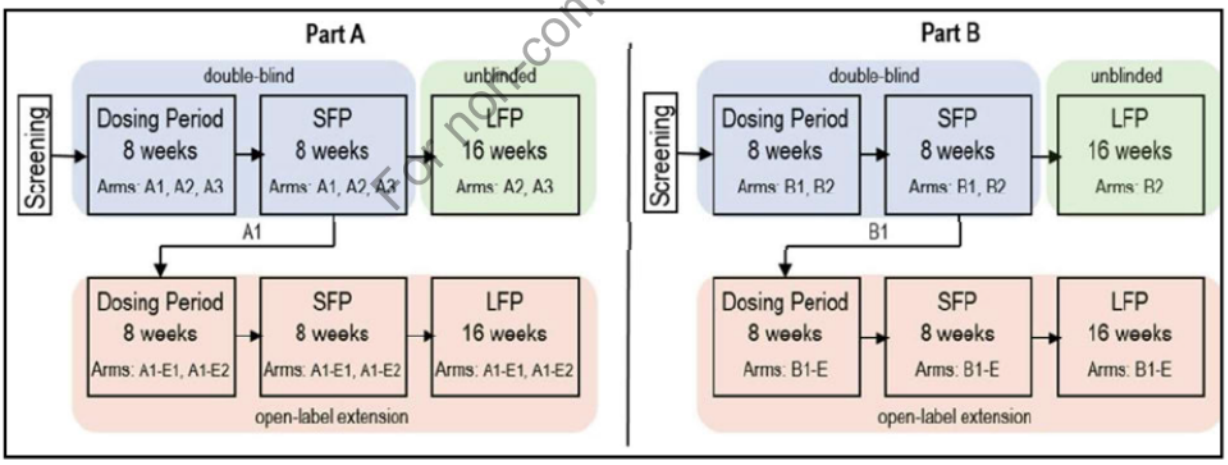
2.0 STUDY DESIGN

2.1 Overview of Study Design

This study is organized in 2 parts (see Protocol 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 are unblinded to allow for placebo patients to participate in an OLE for access to study drug while patients who were given TAK-079 continue to a long-term follow-up period (LFP) for continued observation of safety and efficacy. Following an interim analysis of safety and efficacy, an optional Part B may be triggered that enrolls patients at a to be determined dose of TAK-079 or placebo, in a design that is otherwise identical to Part A (see study schematics, Protocol Figure 6.a, Protocol Figure 6.b, and Protocol Figure 6.c, and Protocol Section 13.2 for further details on the planned interim analysis).

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 Protocol Section 8.1.3. Additional assessments and evaluations may be performed as deemed necessary by local institutional practices and the primary investigator.

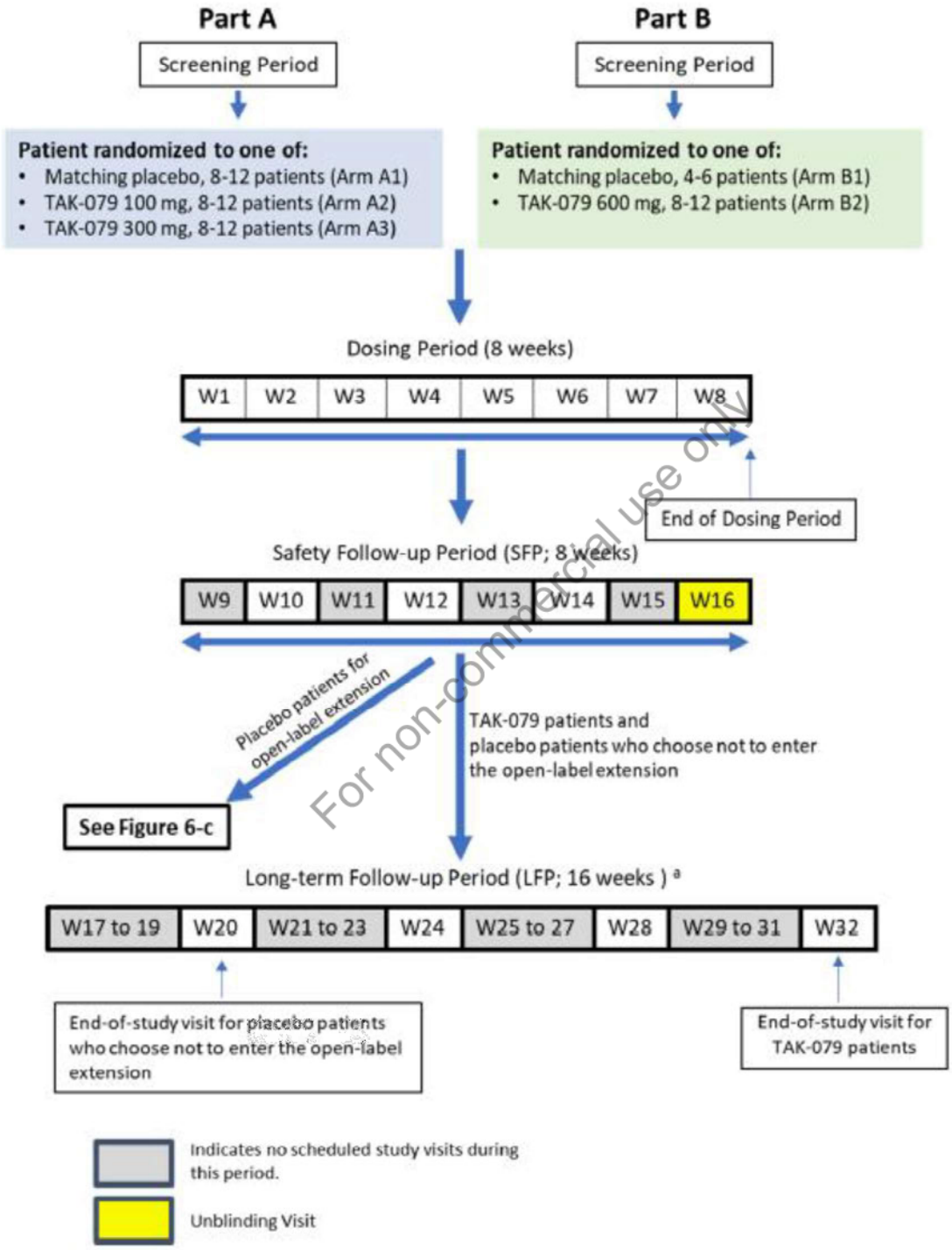
2.2 Protocol Figure 6.a Study Schema: Overview



LFP: long-term follow-up period; SFP: safety follow-up period.

See Protocol Sections 6.1.1 and 6.1.2 for definitions of the study arms.

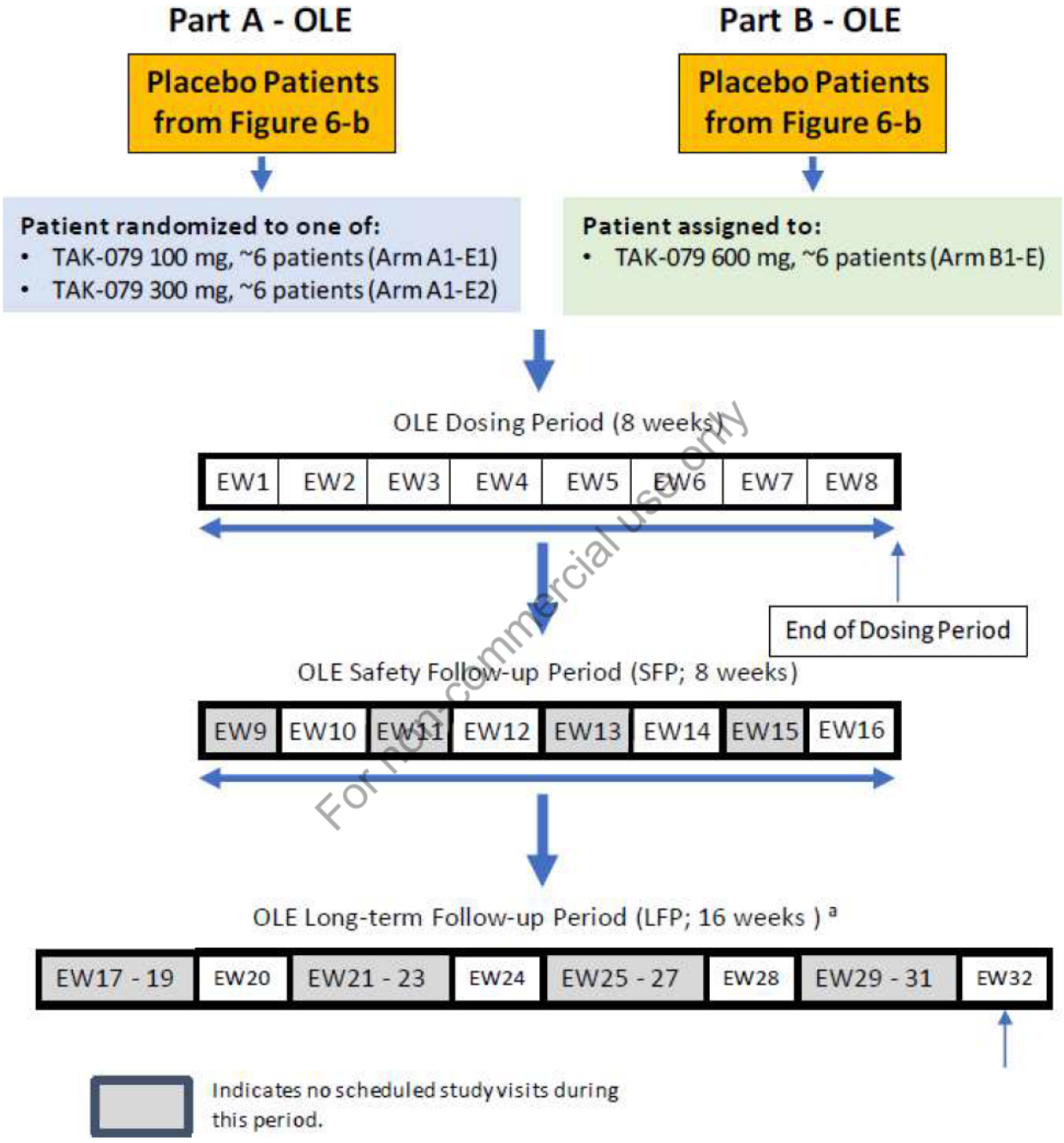
2.3 Protocol Figure 6.b Study Schematic: Part A and B, Main Study



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.

2.4 Protocol 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.

2.5 Part A Overview

After screening, at least 24 up to 36 eligible patients will be randomized in a double-blind 1:1:1 ratio to 1 of the following groups (see Protocol Figure 2.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 - 12patients).*
- ***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 Protocol 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 protocol *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 protocol *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.*

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 specified in Protocol Section 6.1.1.1 continue to be met.

The first dosing day in OLE-A (on Extension Week 1, [EW1], see Schedule of Events [SOE] in protocol *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* Protocol *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).

2.6 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 protocol *Section 6.1.2 for more details).* In addition, there will be a limited review of unblinded efficacy data related to the secondary efficacy endpoints by an independent Safety Review Committee (SRC). 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 (TAK079 at 600 mg sq weekly), (2) advance enrollment to Part B at a dose level lower than the Part B protocol-defined level, (3) continue or expand enrollment in Part A, or (4) enact early termination of the study.

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 Protocol *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).* This is the protocol-define dose level and will be replaced by the final SRC recommended dose level.

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. Placebo patients who opt not to participate in the OLE-B will end the study at the Week 20 visit.

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 Protocol *Section 6.1.1.1). The first dosing day in OLE-B (on EW1, see SOE in* Protocol *Appendix B) is to occur approximately less than 4 weeks after the Week 16 visit. In the OLE-B, patients will be offered (see Protocol 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).

2.7 Interim Analyses

One unblinded safety review with a limited assessment of efficacy *and one interim analysis will be conducted before the final database lock of this study.*

Unblinded Safety Review: *An unblinded safety review* by an independent safety review committee *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). Limited assessment of efficacy will also be performed at the unblinded safety review. The primary study team will remain blinded to treatment assignment.

***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* by the primary study team *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.*

2.8 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 regions.

2.9 Duration of Study

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.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

No tests of statistical hypotheses are planned.

3.2 Multiplicity Adjustment

No multiplicity adjustments are planned.

4.0 SAMPLE-SIZE DETERMINATION

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 in a ratio 1:2 to treatment groups (matching placebo or TAK-079 600 mg).

5.0 ANALYSIS SETS

The analysis sets will be defined in the main study phase and will include the following:

5.1 Enrolled Set

Subjects who are randomized.

5.2 Full Analysis Set

Subjects who are randomized and received at least 1 dose of study drug.

5.3 Safety Analysis Set

Subjects who received at least 1 dose of study drug.

5.4 [redacted]

[redacted]

5.5 [redacted]

[redacted]

5.6 [redacted]

[redacted]

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

6.1.1 General Principles

Continuous data will be summarized using number of patients (N), mean, standard deviation (SD), median, minimum, and maximum, where appropriate. Where indicated, the coefficient of variation (%CV) and geometric mean may also be included in the summary of continuous data. [redacted] For non-PK data, arithmetic means, geometric means, and medians will be presented to 1 more decimal place than the recorded data, and SDs will be presented to 2 more decimal places than the recorded data, where appropriate.

Categorical data will be summarized using the number and percent of patients for each category, where appropriate. Percentages will be reported to 1 decimal place.

Confidence intervals (CIs) will be 2-sided at the 95% level and will be presented to the same number of decimal places as the corresponding summary statistic (mean or percentage).

Summaries will be presented by study part and treatment group (placebo [Part A, Part B, combined], TAK-079 100 mg, TAK-079 300 mg, TAK-079 600 mg) and by visit where applicable. An additional "TAK-079 Combined" category combining the TAK-079 100 mg, 300 mg, and 600 mg treatment groups may be displayed in selected summaries.

The OLE phase will be summarized separately from the main study. In addition, descriptive summaries of pooled data from the OLE phase and the main study may be presented.

6.1.2 Longitudinal Modeling of Change from Baseline

For selected efficacy endpoints, a mixed effects model for repeated measures (MMRM) will be used to analyze differences in change from baseline between each TAK-079 arm and placebo at each scheduled post baseline visit up to Week 16 of the main study. The analysis for each endpoint described in Section 6.5.2 and Section 6.5.3 will indicate whether an MMRM analysis is planned.

- ***Statistical model.*** The MMRM analysis will only use data up to the Week 16 visit of the main study, and the model will include treatment, visit, and treatment-by-visit interaction terms as the factors and adjusted by baseline value and baseline-by-visit interaction. The Kenward-Roger method for calculating denominator degrees of freedom will be used. The unstructured covariance will be used as the default structure for the model. If there are convergence issues, a first order autoregressive covariance structure will be used.
- ***Intercurrent events and missing data.*** If a subject receives rescue therapy or prematurely discontinues from study drug, any assessments obtained thereafter will be excluded from the MMRM analysis. In addition, any assessments obtained within 4 weeks after a permitted dosing-period rescue treatment will be excluded from the MMRM analysis. This approach allows estimation of the treatment effect under the hypothetical situation in which the dosing schedule is adhered to without use of rescue therapy or other permitted rescue treatments. Based on the missing at random assumption, the MMRM analysis will be performed using observed case data only. A secondary MMRM analysis will also be performed as described above, with the additional rule that any assessments obtained within 4 weeks after any administration of systemic corticosteroids given at doses of >20 mg prednisone (or equivalent, ie, methylprednisolone, dexamethasone, prednisolone, cortisone, hydrocortisone, steroids) will be excluded from the data for analysis.
- ***Summaries.*** The MMRM estimated mean change from baseline along with standard error and CI, will be summarized for each visit by treatment group. Estimated differences of means between each TAK-079 arm and the placebo arm as well as standard errors and CIs for the differences will be provided. Observed values and change from baseline at all scheduled post baseline visits will be summarized separately for the main study and the OLE phase. The MMRM estimated mean change from baseline and standard error at each scheduled visit will be plotted by treatment group. The observed mean change from baseline will also beplotted.

6.1.3 Analysis of Binary Efficacy Endpoints

Binary endpoints will be presented using counts and percentages by treatment group. The percentage and corresponding Clopper-Pearson CI will be summarized by treatment group. The difference in percentage between each TAK-079 arm and the placebo arm as well as the Miettinen-Nurminen CI will be summarized. The corresponding p-value based on Barnard's test will be provided for the comparisons between TAK-079 arms and placebo.

6.1.4 Handling of Treatment Misallocations

For analyses of safety, efficacy, [redacted], patients will be analyzed according to actual treatment received.

6.2 Disposition of Subjects

Screen failures will be summarized, including number of subjects, demographics, and primary reason for failed screening.

Additional summaries and listings, based on the enrolled set, will include:

- Summary of disposition in the main study and open-label extension period in terms of subjects who completed dosing with the investigational study drug, subjects who prematurely discontinued from investigational study drug, primary reason for discontinuation from investigational study drug, subjects who prematurely discontinued from the study, and subjects who completed the study, as well as primary reason for discontinuation from study.
- Listing of subject disposition including date of first dose, date of last dose, duration of treatment, the reason for premature discontinuation of investigational study drug, and the reason for premature discontinuation of study.
- Summary of number of subjects in each analysis set.
- Summary by country and site.
- Summary and listing of significant protocol deviations.
- Listing of deviations from inclusion/exclusion criteria.
- Listing of protocol deviations related to COVID-19, including visits impacted by COVID-19.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographic Characteristics

Demographic characteristics will be summarized and listed using the safety analysis set. Variables to be presented include age, sex, country, ethnicity, and race.

6.3.2 Baseline Characteristics

Baseline characteristics will be summarized and listed using the safety analysis set. Variables to be presented include:

- Weight, height, body mass index (BMI) and female reproductive system status.
- ITP disease history
- Prior medications related to ITP as recorded in the eCRF as described in Section 9.2.5.

All medical history data related to study disease will be included in listings. Medications will be coded using the World Health Organization (WHO) Drug Dictionary.

6.3.3 Medical History

Medical history refers to significant conditions or diseases that stopped at or prior to informed consent or are ongoing at informed consent. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 23.0 or higher) and will be summarized using System Organ Class (SOC) and MedDRA preferred term (PT). The table will be sorted in alphabetical order by SOC. Within a SOC, PTs are sorted in decreasing frequency based on the total number of subjects. The number and percentage of subjects with any significant medical history will be summarized for each SOC and PT. The denominator used for calculating the percentages will be the total number of subjects included in each treatment group. For the tables, if a subject reports the same PT multiple times, then that PT will be counted only once for that subject. Similarly, if a subject reports multiple conditions within the same SOC, then that SOC will be counted only once for that subject. All medical history data will be presented in listings. Summaries and listings will use the safety analysis set.

Medical history related to ITP will be presented as part of baseline characteristics.

6.4 Concomitant Medications and Procedures

Medications used by patients and therapeutic procedures completed by patients, from 28 days before the first dose of study medication (TAK-079 or placebo) through the end of the subject's participation in the study as recorded in the eCRF, are referred to as concomitant medications and concomitant procedures and will be summarized and listed using the safety analysis set. For subjects who participate in the OLE phase of the study, concomitant medications and procedures occurring after reconsenting to participation in the OLE will be included in summaries for the OLE phase. Medications will be coded using the WHO Drug Dictionary.

Missing or partial dates will not be imputed. Conservatively, a medication or procedure will be classified as concomitant if the available information about the end date is insufficient to determine whether it occurred during the reporting period.

A separate summary for COVID-19 related medications and procedures may be provided.

6.5 Efficacy Analysis

The full analysis set will be used for analyses of efficacy endpoints.

6.5.1 Primary Endpoint Analysis

Not applicable, as the study has no primary efficacy endpoints.

6.5.2 Secondary Endpoints Analysis

The secondary endpoints are the following 4 types of binary responses, as defined in Section 1.2.2. These will be evaluated at Week 16 and Week 32.

1. Platelet response
2. Complete platelet response
3. Clinically meaningful platelet response
4. Hemostatic platelet response

Each of the 4 types of responses requires specific platelet counts expressed numerically, as defined in Section 1.2.2, to be attained on at least 2 visits where none of the following occurred:

- The subject received rescue therapy at any time prior to the visit.
- The subject received a dosing-period permitted rescue treatment within 4 weeks prior to the visit.
- The subject prematurely discontinued from study drug prior to the visit.
- The platelet count is missing at the visit.

The number and percentage of subjects attaining each type of response by Week 16 in the main study will be summarized by treatment group. Binary analyses will be performed following the methods specified in Section 6.1.3. CIs for percentages will be presented. Differences in percentages at Week 16 and CIs for the differences between each TAK-079 arm and placebo combined will be presented for the main study. In addition, for TAK-079 subjects in the main study, the number and percentage of subjects attaining each type of response by Week 32 will be presented along with CIs for the percentages. For subjects in the OLE, the number and percentage of subjects attaining each type of response by Week 16 and by Week 32 will be presented along with CIs for the percentages. As a supportive analysis for the secondary endpoints, MMRM analyses of change from baseline in platelet counts to Week 16 will be performed following the methods specified Section 6.1.2.

If an unexpected difference between Part A and Part B Placebo is observed, additional analyses may be performed based on Part A and Part B, separately.

6.5.3 [redacted]

6.5.3.1 [redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

Table 1 [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

6.5.3.2 [redacted]

6.5.3.3 [redacted]

[redacted]

[redacted]

6.5.3.4 [redacted]

[redacted]

[redacted]

[redacted]

6.5.3.5 [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

6.5.3.6 [redacted]

[redacted]

6.5.3.7 [redacted]

[redacted]

[redacted]

6.5.4 Subgroup Analyses

Subgroup analyses are not planned.

6.6 Safety Analysis

Safety will be evaluated by the frequency of TEAEs, severity and types of TEAEs, and by changes from baseline in vital signs, weight, and clinical laboratory results using the safety analysis set.

Exposure to investigational study drug will be tabulated.

To assess the impact of contingency measures taken on safety results of participating patients during the COVID-19 pandemic, the alternative method(s) of safety assessments (e.g., laboratory evaluations, vital signs, and/or ECG) due to COVID-19 may be listed or summarized if data permits.

6.6.1 Adverse Events

All pretreatment events (PTEs) and AEs will be coded by SOC and PT using MedDRA (version 23.0 or later) and will be listed for patients in the safety analysis set. AE intensity is determined by the CTCAE scale version 4.03.

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.

A treatment-emergent adverse event (TEAE) is defined as an AE having a start date and time equal to or later than the start date and time of the first dose of study drug. If the start date of the AE equals the start date of the first treatment and either the start time of the AE or the start time of the treatment is missing, then the AE will count as a TEAE. AEs with partially missing onset dates will be counted as TEAEs if the month (if available) and the year are equal to or later than the month and year of the date of first dose. AEs with a completely missing start date will be counted as TEAEs.

For subjects in OLE, TEAEs will be summarized separately for the main study and the OLE. The following summaries for TEAEs will be presented by treatment group for the dosing, SFP, and LFP period. Dosing, SFP, and LFP period TEAEs are defined in Section 9.2.6:

- Overall TEAEs including summaries of any TEAE, any TEAEs related to study drug, any serious TEAEs, any serious TEAEs related to study drug, any Grade 3

or higher TEAE, any Grade 3 or higher TEAE related to study drug, any ISR TEAE, any IRR TEAE, death due to TEAE, hospitalizations due to TEAE, and discontinuation from study drug due to TEAE. ISRs and IRRs are assessed by the investigators and recorded in the eCRF.

- TEAEs by SOC and PT.
- TEAEs for potential risks by SOC and PT.
- TEAEs by maximum toxicity grade, SOC, and PT.
- TEAEs by relationship to study drug (i.e., causality), SOC, and PT.
- TEAEs considered related to the study drug by SOC and PT.
- TEAEs leading to discontinuation of study drug by SOC and PT.
- Serious TEAEs by SOC and PT.
- Most frequent (occurring in ≥ 10% of the total) TEAEs by SOC and PT.

Treatment-emergent adverse events for [redacted]. The preferred terms from MedDRA (version 23.0 or later) Standardized MedDRA Queries (SMQ) will be used to identify an SMQ defined potential risk. [redacted] TEAEs of potential risks will be summarized separately by SMQ and PT. The sorting rules that follow will also apply to the SMQs.

SOCs will be sorted in descending order of total number of subjects with the SOC among all the treatment groups. Within an SOC, adverse events will be sorted in descending order of total number of subjects with the preferred term among all the treatment groups.

In the high-level adverse event summary tables, TEAEs will be summarized regardless of severity and relationship to study drug. Within each subject, multiple reports of events that map to a common MedDRA preferred term will be counted only once.

At the adverse event level, the summary tables will present the number of subjects reporting each of these MedDRA events, i.e., the number of subjects reporting 1 or more events that map to the given MedDRA preferred term.

At the SOC level, the summary tables will present the number of subjects reporting 1 or more events that map to the given SOC. That is, the number of subjects reported at the SOC

level will be less than or equal to the sum of the subject counts across all adverse events within that SOC.

For the summary of TEAEs by SOC, PT, and maximum toxicity, if a subject experiences more than 1 episode of a particular coded adverse event, the subject will be counted only once by the maximum severity of the episode (preferred term). Similarly, if a subject has more than 1 adverse event within a SOC, the subject will be counted only once by the maximum severity in that SOC. Missing toxicity grades will be imputed as grade 3 (severe).

AEs with missing causal relationship will be classified as related to study drug.

All AEs will be listed by treatment, subject identifier and onset date of the AE. The listing will contain: subject identifier, age, sex, race, AE (preferred term and reported term), relationship to study drug, onset date, end date or whether the event was ongoing, duration, severity, action taken concerning study drug, the outcome, and whether the adverse event was an SAE.

Special listings for SAEs, IRRs, ISRs, TEAEs leading to discontinuation of investigational study drug, and TEAEs leading to death will also be presented. ISRs and IRRs are assessed by the investigators and recorded in the eCRF.

AEs with start dates that are completely or partially missing will be imputed as follows:

- If month and year are known but day is missing
  - If month and year are the same as month and year of first dose date, then first dose date will be used.
  - If month and year are later than first dose date, then first day of the month will be used.
- If year is known but day and month are missing
  - If year equals year of first dose date, then first dose date will be used.
  - If year is greater than year of first dose date, then 1st of January of the year will be used.
- If all are missing, then the first dose date will be used.

After imputation, if the stop dates are complete, all imputed dates are checked against the stop dates to ensure that start dates do not occur after stop dates. If an imputed start date occurs after the stop date, then change the imputed start date to be the same as the stop date. When the start date and the stop date are both incomplete for a subject, the start date will be imputed first.

Adverse events with stop dates that are completely or partially missing will be imputed as follows:

- If "ongoing" is checked, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be used.

- If year is known, but day and month are missing
  - If the year is equal to or less than the year of last dose, then 31st of December will be used.
  - If the year is greater than the year of last dose, then 1st of January will be used.
- If all are missing, then 31st of December of the year of last dose will be used.

If a subject dies, then use death date for AE stop date. After imputation, all imputed dates are checked against start dates to ensure that stop dates do not occur before start dates. If an imputed stop date occurs prior to the start date, then change the imputed stop date to be the same as the start date.

To assess of the impact of COVID-19 on the safety of participating subjects, a listing of COVID- 19 related TEAEs will be provided.

6.6.2 Clinical Laboratory Evaluations

All laboratory values will be converted to standardized SI units and summarized in tables and listings by treatment groups. If a lab value is reported using a non-numeric qualifier (e.g., less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

The following summaries for laboratory test results will be presented by treatment group:

- Actual value and change from baseline values at each scheduled assessment.
- Shift tables for the change from Baseline to each post-baseline time point will be presented. For these tables, each subject will be categorized as low, normal, or high for the baseline value, and low, normal, or high for each post-baseline time point, according to the local laboratory reference ranges. The number of subjects as well as percentages in each of the combinations of shifts will be presented.
- Markedly abnormal values (MAVs) as defined by the criteria in Section 9.4 will be summarized by treatment group. The number and percentage of subjects with MAVs observed post-baseline in each of the applicable laboratory parameters will be presented.

All clinical laboratory data will be presented in SI units in data listings.

6.6.3 Vital Signs

The actual values and changes from baseline of vital sign parameters and weight at each scheduled visit will be summarized by treatment group. Vital sign values will also be presented in listings.

Post-dose vital sign MAVs as defined in Section 9.4 will be tabulated. If a subject has a post- dose MAV for a particular vital sign parameter, all visits for that subject for that parameter will be listed. The number and percentage of subjects with at least 1 post-dose markedly abnormal vital signs measurement will be summarized. The mapping of the

subjects who meet the MAV criteria will be listed as a table. All observations, including ones at unscheduled visits, will be included in the MAV evaluation and summaries if MAV criteria are satisfied.

6.6.4 12-Lead ECGs

ECG variables at scheduled visits and their changes from baseline will be summarized by treatment group. A shift table for the investigator's ECG interpretation will provide the number and percentage of subjects in each of the appropriate categories (Normal; Abnormal, Not Clinically Significant; Abnormal, Clinically Significant) at the scheduled visit relative to the baseline status. All ECG results will be presented in listings.

6.6.5 Pregnancy Test

Clinical laboratory sample collection and results for pregnancy tests will be presented in a separate listing.

6.6.6 Extent of Exposure and Compliance

The total number of doses taken, and the total amount of doses taken will be summarized descriptively by treatment group, separately for the main study and TAK-079 administration in the OLE period for previous placebo subjects.

Treatment compliance will be summarized in terms of the percent of scheduled doses received, defined for each subject as: [(Actual total number of doses taken) ÷ (Planed number of doses taken)] *100.

The date and time of each dose for each subject will be reported in a data listing.

The impact of the COVID-19 on exposure and compliance will be summarized in terms of the percent of scheduled doses missed for each subject due to each of the following reason:

- Subject diagnosed with COVID-19
- Subject discretion due to COVID-19
- Travel restrictions due to COVID-19
- Investigative site accessibility (site closure, site visit restrictions, or site staff unavailability) due to COVID-19

All COVID-19 impacts on dose administration are included in the COVID-19 impact listing.

6.7 [redacted]

6.7.1 [redacted]

[redacted]

[redacted]

6.7.2 [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

6.8 [redacted]

[redacted]

Table 2 [redacted]

6.9 Interim Analyses

One unblinded safety review with a limited efficacy review and one interim analysis will be conducted before the final database lock of this study as described in Section 2.7.

7.0 REFERENCES

Not applicable.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

The protocol stated that Fisher's exact test may be used for binary endpoint analysis where appropriate. Fisher's exact test was not included in this Statistical Analysis Plan. Barnard's test will be used for binary endpoint analysis instead.

9.0 APPENDIX

9.1 Changes from the Previous Version of the SAP

Changes made from previous version of the SAP that have an impact on the planned statistical analysis methods are described in Table **3** below. In addition, there were textual changes purely to improve the flow, organization, and clarity. As these represent cosmetic changes with no impact to the planned statistical analyses, they are not included in the table below.

Table 3 Changes from the Previous Version of the SAP

SAP Section	Change	Rationale for Change
6.6.1 Adverse Events	Update the search strategy for the TEAEs for potential risk	For additional clarity on selecting terms for potential risk
6.7 [redacted]	[redacted]	[redacted]
6.8 [redacted]	[redacted]	[redacted]
9.2.5 Prior ITP Medications	Update the list based on the Standard Medication Names recorded for the study	For completeness in assigning each standard medication name into a category
9.2.6 TEAEs Occurring during Dosing and SFP Period, LFP period	Update the definition of AEs in the Main Study who entered the OLE Phase	For additional clarity on the reporting of AEs on the tables and listings
9.4 Criteria for Identification of Markedly Abnormal Values	Update the high abnormal limit for total bilirubin and lactate dehydrogenase	For additional guidance on defining the MAV

9.2 Data Handling Conventions

9.2.1 Definition of Baseline

The baseline of the main study is defined as the last available scheduled assessment prior to the first dose of study drug.

The baseline for the OLE phase is defined as the last available scheduled assessment prior to the first dose of study drug during the OLE.

If a scheduled visit is not available, the last assessment prior to the first dose of the study drug will be used.

9.2.2 Definition of Study Days

Study Day 1 is defined as the day on which a patient is administered their first dose of the study drug. Other study days are defined relative to Study Day 1 with Day 1 being Study

Day 1 and Day -1 being the day prior to Study Day 1. Study days prior to the first dose of study drug will be calculated as: [date of interest – date of first dose of study drug]. Study days on or after the first dose of study drug will be calculated as: [date of interest – date of first dose of study drug + 1].

Similarly, OLE Study Day 1 is defined as the day on which a subject is administered their first dose of study drug in the OLE phase, and other OLE study days are defined relative to OLE Study Day 1.

9.2.3 Definition of Analysis Visits

Visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF). The detailed study visit windows can be found in Protocol Appendix A and Appendix B. Summaries and analyses by visit will use the nominal week associated with each visit as recorded on the eCRF.

9.2.4 Rescue Therapies and Permitted Rescue Treatment

Rescue therapies will be reviewed by clinicians prior to the database lock to confirm both rescue therapies and dosing-permitted rescue treatments. Dosing-permitted rescue treatments are specific rescue treatments given once during the dosing period that were allowed per protocol and did not require the discontinuation of study treatment. These will be classified into the three allowed categories: platelet transfusion, a single dose of IVIg up to 1 g/kg, or an additional 20 mg of prednisone (or equivalent) per day for up to 7 days.

An initial review will occur prior to database freeze prior to Part B unblinding (for data up to Week 16) and after the Part B unblinding (for LFP and OLE data) both for the interim analysis, and again periodically to review new data entries until database lock.

9.2.5 Prior ITP Medications

Prior ITP medications are further classified according to the categories in Table 4. All prior ITP medications will be reviewed by clinicians prior to database lock and classified. In the summary table, the number and percentages of subjects in each prior ITP medication category, as well as the number and percentage of subjects receiving each prior ITP medication will be summarized by treatment group.

In addition, prior ITP medications that are on-going at the subject's enrollment and either ended during the study or administered through the end of the subject's participation in the study. The number and percentages of subjects in each ITP medication category, as well as the number and percentage of subjects receiving each ITP medication will be summarized by treatment group.

Table 4 Prior ITP Medications and Category

MEDICATION CATEGORY	STANDARDIZED MEDICATION NAME
Immunosuppressants	AZATHIOPRINE CICLOSPORIN METHOTREXATE

	MYCOPHENOLATE MOFETIL MYCOPHENOLIC ACID TACROLIMUS CYCLOPHOSPHAMIDE VINBLASTINE VINCRISTINE VINDESINE
Corticosteroids	METHYLPREDNISOLONE CORTISONE DEXAMETHASONE PREDNISOLONE PREDNISONE HYDROCORTISONE STEROIDS
Thrombopoietin Receptor Agonists	ROMIPLOSTIM ELTROMBOPAG AVATROMBOPAG HETROMBOPAG OLAMINE HETROMBOPAG
Rituximab	RITUXIMAB
Fostamatinib	FOSTAMATINIB
IVIG	IMMUNOGLOBULINS NOS ANTI-D IMMUNOGLOBULIN
Immunostimulants	INTERFERON ALFA-2B OPRELVEKIN
Other ITP	ALEMTUZUMAB DANAZOL DAPSONE COLCHICINE ANTITHYMOCYTE IMMUNOGLOBULIN OTHER ("TRIAMCINOLONE", "HMPL 523", "TRETINOIN", "AGRIMONIA PILOSA;FORSYTHIA SUSPENSA;GLYCYRRHIZA SPP.;INDIGO;PAEONIA X SUFFRUTICOSA", "BLINDED THERAPY", "TRANEXAMIC ACID", "RILZABRUTINIB" "INVESTIGATIONAL DRUG")

9.2.6 TEAEs Occurring during Dosing and SFP Period, LFP period

The following will apply for both main study and OLE phases:

- TEAEs occurring during Dosing and SFP period are defined as TEAEs with a start date on or before the date of Week 16 visit date. For placebo subjects entering the OLE phase, the SFP period includes TEAEs occurring prior to the OLE treatment start date.

- TEAEs occurring during LFP period are defined as TEAEs with a start date after the date of Week 16 visit date.

9.3 Analysis Software

All statistical analyses will be conducted using SAS® Version 9.4 or higher.

9.4 Criteria for Identification of Markedly Abnormal Values

Hematology

Parameter	Low Abnormal	High Abnormal
Hemoglobin	<80 g/L	>1.2 × ULN
Hematocrit	<24 %	>1.2 × ULN
WBC	<1.5 × 10^9/L	>1.5 × ULN
Platelet count	<50 × 10^9/L	>600 × 10^9/L
Total lymphocyte count	<0.5 × 10^9/L	>1.5 × ULN
Neutrophils	<1 × 10^9/L	>8 × 10^9/L

LLN=lower limit of normal, ULN=upper limit of normal, WBC=white blood cell.

Serum Chemistry

Parameter	Low Abnormal	High Abnormal
ALT	--	>3 × ULN
AST	--	>3 × ULN
Alkaline phosphatase	--	>3 × ULN
Total bilirubin	--	>34.2 µmol/L and >2 x ULN
ALT and total bilirubin	--	ALT>3 × ULN and TB>2 × ULN
AST and total bilirubin		AST>3 × ULN and TB>2 × ULN
Albumin	<25 g/L	--
Creatinine	--	>177 µmol/L
Glucose	<2.8 mmol/L	>19.4 mmol/L
Chloride	<75 mmol/L	>126 mmol/L
Sodium	<130 mmol/L	>150 mmol/L
Potassium	<3.0 mmol/L	>6.0 mmol/L
Blood urea nitrogen	--	>10.7 mmol/L
Calcium	<1.75 mmol/L	>2.88 mmol/L
Carbon dioxide	<19 mmol/L	>29 mmol/L
Lactate dehydrogenase	<105 U/L	>333 U/L

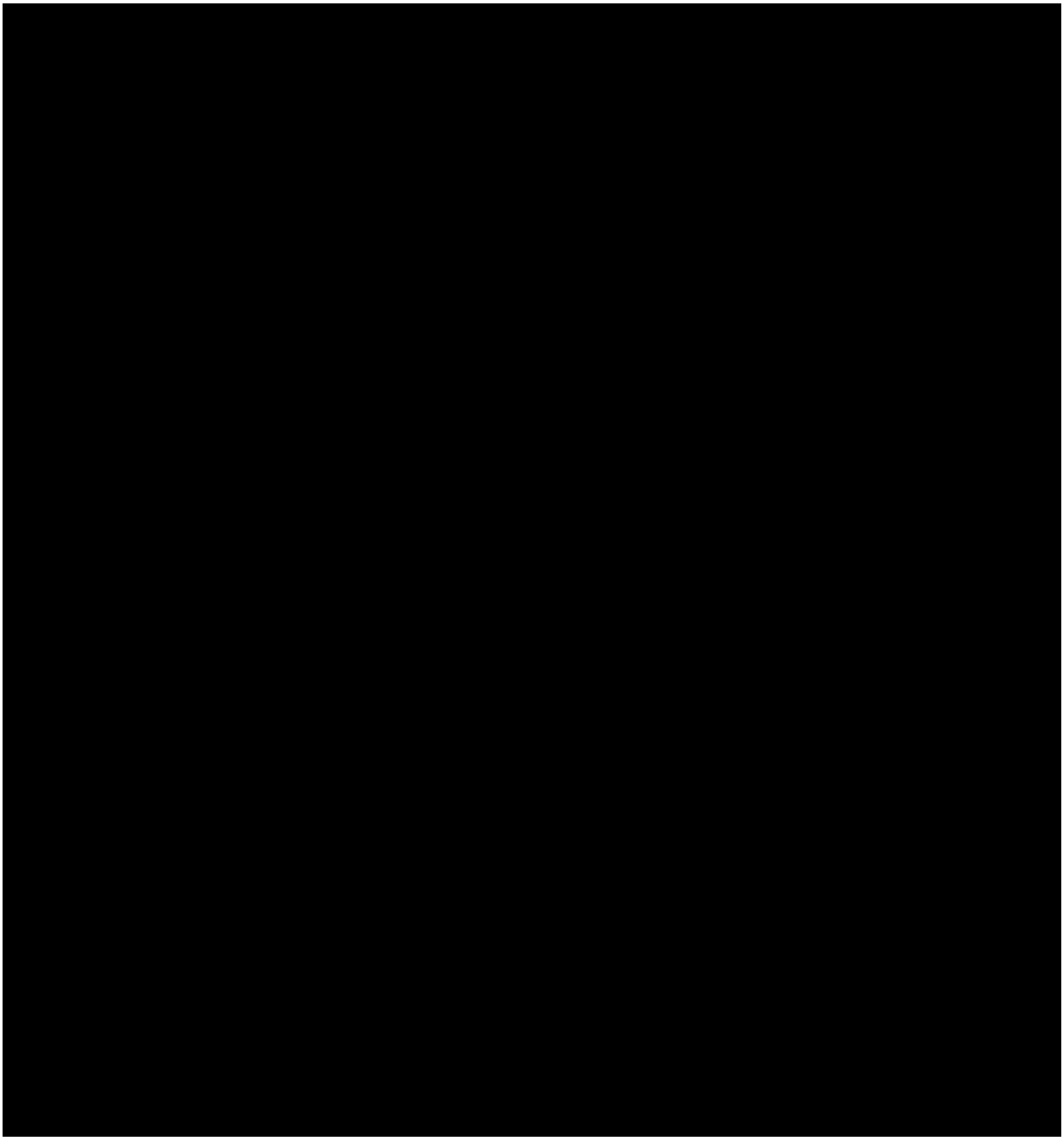
ALT=alanine aminotransferase, AST=aspartate aminotransferase, LLN=lower limit of normal, ULN=upper limit of normal. TB=total bilirubin.

Vital Signs

Parameter	Unit	Low Abnormal	High Abnormal
Pulse	bpm	<50	>120
Systolic blood pressure	mm Hg	<85	>180
Diastolic blood pressure	mm Hg	<50	>110
Body temperature	°C	<35.6	>37.7

9.5 [redacted]

[redacted]



STATISTICAL ANALYSIS PLAN APPROVAL FORM

Drug: TAK-079	Protocol Number: TAK-079-1004
Protocol Name:	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
Statistical Analysis Plan (SAP) Version Number: Amendment 3.0	Date: 16-MAY-2024

I confirm the final SAP for above noted study and approve the content for submission to the SAP approval team.

Biostatistics Author	[redacted], PhD Biostatistician, Statistics Statistics and Quantitative Sciences
	Print Name and Title
	DocuSigned by: [redacted] 17-May-2024 | 05:19:39 JST
	Signature and Date (DD/MM/YYYY)

Statistical Analysis Plan Approval by SAP Approval Team Members
I approve the final SAP for the above study as it pertains to my area of expertise.
Note: An approver may delegate the review and approval of this document to an appropriately qualified and clearly identified (by name and title) designee.

SAP Signatory	[redacted], MS [redacted], Statistics Statistics and Quantitative Sciences
	Print Name and Title
	DocuSigned by: [redacted] 16-May-2024 | 16:22:49 EDT
	Signature and Date (DD/MM/YYYY)