This is the translated version of the Statistical Analysis Plan written in Japanese.

Statistical Analysis Plan

Study title:	Phase 3 Clinical Study of R788 in Patients with Chronic Idiopathic Thrombocytopenic Purpura
Protocol number:	R788-1301
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1. Objectives

The purpose of this statistical analysis plan is to provide details of the analyses described in "14. Statistical Analysis" of the protocol (Version: 1.0).

2. Analysis Sets

When the full analysis set (FAS) is used for analysis, the analysis will be performed based on the treatment groups to which the subjects have been assigned. When the safety set (SS) or pharmacokinetic analysis set (PKS) is used for analysis, the analysis will be performed based on the actual treatment received by the subjects.

1) FAS
Subject population which excludes subjects who deviated GCP, who did not receive any study drug, who discontinued prior to Period I, who was ineligible to the major inclusion/exclusion criteria, and who could not obtain any of the primary endpoint data.

2) SS
Subject population which excludes subjects who deviated GCP, who did not receive any study drug, and who discontinued prior to Period I.

3) PKS
Set of subjects excluding subjects who have no plasma drug concentration data at all from subjects in the SS

The correspondence between analysis variables and analysis sets is shown in Table 2-1.

Table 2-1 Analysis Variables and Analysis Sets

Variables evaluated	Variables analyzed	Analysis set
Demographics and other baseline characteristics	Subject demographics	SS
	Other	SS
Treatment compliance	All variables	SS
Efficacy	All variables	FAS
Safety	All variables	SS
Pharmacokinetics	All variables	PKS

3. Analysis Group

Unless otherwise specified, the analysis will be performed on the following subjects and data. For FAS analysis, "treated subjects" will be handled as "randomized subjects."

1) Evaluation in Period I

- R788 group: Period I data of subjects who received R788 in Period I
- Placebo group: Period I data of subjects who received placebo in Period I

2) Evaluation during long-term treatment of R788

- R788 group: The analysis will be performed on the following subjects and data:
  - Period I data of subjects who received R788 in Period I
  - Period II data of subjects who received R788 in Period I, completed treatment with R788 in Period I and transitioned to Period II (subjects on long-term treatment of R788)

3) Evaluation in Period II

- R788-R788 group: Period II data of subjects who received R788 in Period I and early transitioned to Period II after discontinuing Period I
- P-R788 group: Period II data of subjects who received placebo in Period I and transitioned to Period II

4) Evaluation in non-dosing period

- R788 group: Non-dosing period data of subjects who transitioned to the non-dosing period (subjects who transitioned from Period II to Period III without non-dosing period are excluded).

5) Evaluation in Period III

- R788 group: Period III data of subjects who transitioned to Period III

6) Evaluation in R788 treatment period

- R788 group: The analysis will be performed on the following subjects and data:
  - Data from Period I, Period II, and Period III of subjects who received R788 in Period I
  - Data from Period II and Period III of subjects who received placebo in Period I and transitioned to Period II

7) Evaluation in the entire study period

- R788-R788 group: Data from Period I, Period II, non-dosing period, and Period III of subjects who received R788 in Period I
- P-R788 group: Data from Period I, Period II, non-dosing period, and Period III of subjects who received placebo in Period I

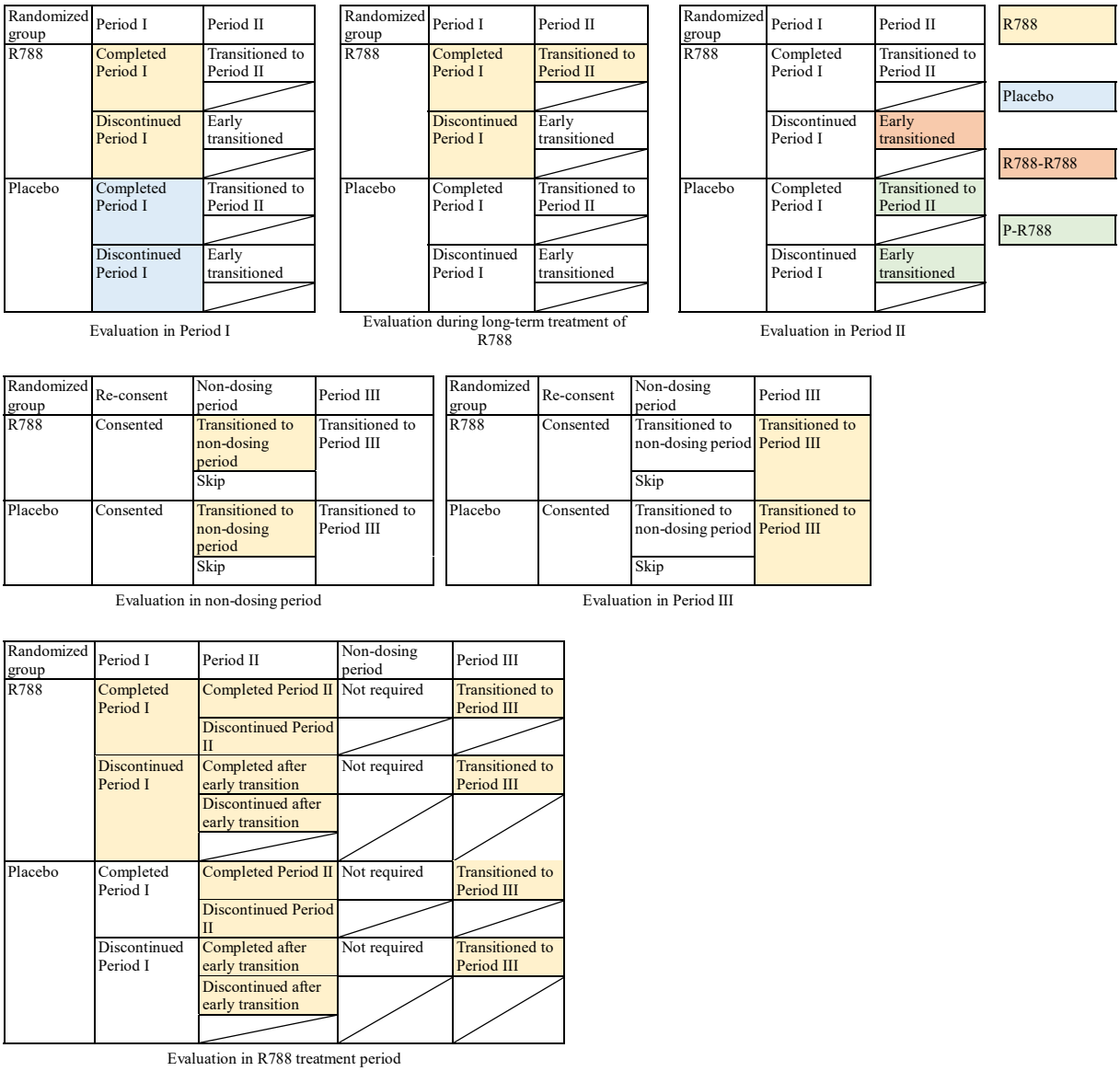

Figure 3-1 Analyzed subjects and data for each evaluation

4. General Principles of Statistical Analysis

- Statistical tests will be performed using a two-sided significance level of 5%.
- Summary statistics will include the number of subjects, mean, standard deviation, minimum, median, maximum, and quartiles.
- Unless otherwise specified, data will be summarized for each analysis group, each period, and each analysis visit.
- For confidence intervals (CIs) of proportions, Clopper-Pearson exact two-sided 95% CIs will be presented for each group, and Chan-Zhang exact two-sided 95% CIs will be presented for between-group differences.

5. Data Handling

5.1 Number of Digits to be Reported for Calculated Values

1) P values and statistics
Values will be rounded down to the third decimal place. Exceptionally, P values less than 0.001 will be reported as "P < 0.001" or "< 0.001."

2) Mean, standard deviation, geometric mean, adjusted mean, estimate of difference, and confidence interval
Values will be rounded off to one digit after the last place of the significant digits of the data.

3) Minimum, median, maximum, and quartiles
Values will be presented by the significant digits of the data.

4) Proportion, estimate and CI of incidence, and geometric coefficient of variation (CV)
Values will be rounded off to the first decimal place.

5.2 Reporting of Prior ITP Medications, Concomitant Medications, and Rescue Medications

Prior ITP medications, concomitant medications, and rescue medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) Global and reported with the following categories and Standardized Medication Names.

- Prior ITP medication categories: Corticosteroids, Rituximab, Thrombopoietin Receptor Agonists, Intravenous Immunoglobulins, Immunosuppressants, and Other
- Concomitant medication categories: ATC Level 3 Class Code
- Rescue medication categories: Platelet Transfusion, Intravenous Immunoglobulins, Intravenous Methylprednisolone, Oral Dexamethasone, Oral Prednisolone, and Other.

5.3 Reporting of Complications, Adverse Events, and Adverse Drug Reactions

Primary System Organ Classes (SOCs) and Preferred Terms (PTs) will be reported according to Medical Dictionary for Regulatory Activities (MedDRA).

For adverse events (AEs) of interest, event categories will be presented instead of primary SOCs. Subcategories will be set and reported for gastrointestinal complaints among AEs of interest. Category-based data summarization will also include subcategory-based summarization.

AEs for which more than one action was taken with the study drug will be reported with the highest level of action taken (discontinuation > dose reduction > interruption).

The definition of AEs of interest is shown in Table 5.3-1.

Table 5.3-1 Adverse Events of Interest

AEs of interest (category)	Applicable PT (PT code)
Bleeding events	Conjunctival haemorrhage (10010719), Epistaxis (10015090), Haemorrhage subcutaneous (10018999), Menorrhagia (10027313), Mouth haemorrhage (10028024), Purpura (10037549), Contusion (10050584), Procedural haemorrhage (10071229)
Gastrointestinal complaints	AEs that fall under the following subcategories:
Nausea	Nausea (10028813)
Vomiting	Vomiting (10047700)
Non-infectious diarrhea SMQ	Diarrhoea (10012735)
Abdominal pain	Abdominal discomfort (10000059), Abdominal pain (10000081), Abdominal pain upper (10000087)
Infection	Cellulitis (10007882), Cystitis (10011781), Diarrhoea infectious (10012742), Diverticulitis (10013538), Gastroenteritis (10017888), Gingivitis (10018292), Herpes zoster (10019974), Nasopharyngitis (10028810), Otitis media (10033078), Paronychia (10034016), Periodontitis (10034539), Pulpitis dental (10037464), Urinary tract infection (10046571), Viral infection (10047461), Tinea infection (10060889), COVID-19 (10084268)
Hypertension SMQ	Blood pressure increased (10005750), Hypertension (10020772)
Neutropenia	Neutropenia (10029354), Neutrophil count decreased (10029366)
Drug related hepatic disorders SMQ	Alanine aminotransferase increased (10001551), Aspartate aminotransferase increased (10003481), Autoimmune hepatitis (10003827), Blood bilirubin increased (10005364), Hepatic cyst (10019646), Hepatic function abnormal (10019670), Hepatic steatosis (10019708), Liver function test abnormal (10024690), Hepatic enzyme increased (10060795), Liver function test increased (10077692)
Thrombosis, embolism, and thromboembolism	Not applicable

5.4 Handling of Drug Concentration Data

Measurements below the limit of quantification (LOQ) for the plasma R406 concentration will be handled as 0 (LOQ: 2.5 ng/mL). Plasma R406 concentration data collected during interruption of R788 will be excluded from the analysis. When calculating the geometric mean and geometric CV, if the measured value before logarithmic transformation is 0, it will be handled as missing.

5.5 Handling of Laboratory and Immunoglobulin Test Data

Values below the LOQ in laboratory and immunoglobulin tests will be handled as the LOQ.

5.5.1 Handling of platelet count data

Any platelet count data obtained within 4 weeks (28 days) after the use of a rescue medication will be handled as missing in the efficacy evaluation.

In the analysis of the primary endpoint, missing data will be imputed except for data from subjects who discontinued due to an AE or lack of efficacy or those who used a rescue medication between Week 10 and Week 24. For details, see "11.1.1 Analysis methods for the primary endpoint."

5.6 Handling of Quality of Life Assessment (SF-36) Data

The following scores calculated based on the Japanese Version of MOS 36-Item Short-Form

Health Survey Version 2 (SF-36v2) Scoring Program[1)] will be included in the evaluation.

- Norm-based scoring (NBS)
  - Bodily pain
  - General health
  - Mental health
  - Physical functioning
  - Role emotional
  - Role physical
  - Social functioning
  - Vitality
- Three component summary scores
  - Mental component summary
  - Physical component summary
  - Role/social component summary

5.7 Handling of ITP Bleeding Score

The following variables calculated from 9 anatomical sites (Skin [PE], Oral [PE], Epistasis, Gastrointestinal, Urinary, Gynecological, Pulmonary, Intracranial haemorrhage, and Subconjunctival haemorrhage) will be included in the evaluation:

- Average score
  Defined as the mean of 9 sites at each time point. Handled as missing if there is a missing score for any of the sites.
- Total score
  Defined as the sum of 9 sites at each time point. Handled as missing if there is a missing score for any of the sites.
- Maximum score
  Defined as the maximum of 9 sites at each time point. Handled as missing if there is a missing score for any of the sites.
- Post-dose mean of average scores
  Defined as the mean of average scores after study drug administration in each period.

5.8 Handling of Blood Pressure Data

At analysis visits where blood pressure is measured multiple times, the mean blood pressure value will be used for evaluation.

5.9 Analysis Visits

Unless otherwise specified, each analysis variable will be evaluated at the following time points.

- Data obtained outside the time window of analysis visits and data from unscheduled visits

will be excluded from summarization at each time point.

- For analyses of each treatment period, test data obtained outside the range of "the day of the last dose plus the specified number of days" will be excluded from the analysis. The specified number of days is 3 days for Period I and 7 days for Periods II and III.
- The last observed visit (LOV) other than the non-dosing period is defined as the last scheduled visit or the discontinuation visit, whichever is later, performed within the range of "the day of the last dose plus the specified number of days" for each period. The specified number of days is 3 days for Period I and 7 days for Periods II and III.
- The LOV in the non-dosing period is defined as the data for the latest test among all tests performed up to the last day of the non-dosing period.
- For all variables, Day 1 of Period I will be used as a baseline and only changes at time points after Day 1 of each period will be evaluated.
- In the non-dosing period, change from the start of the non-dosing period will be evaluated in addition to the change from Period I Day 1. Time points after Day 1 of the non-dosing period will be evaluated.

1) Evaluation in Period I

Table 5.9-1 Analysis Visits in Period I

Variables evaluated	Analysis visit
Platelets	Screening A, B, Day 1, Week 2 to 24 (every 2 weeks)
Treatment dose	Day 1, Week 2 to 24 (every 2 weeks)
QOL assessment (SF-36)	Day 1, Week 4, 12, 24
ITP Bleeding Score	Screening A, Day 1, Week 2 to 24 (every 2 weeks), LOV
ECOG Performance Status	Screening A, Day 1, Week 4 to 24 (every 4 weeks), LOV
Hematology (excluding platelets)	Screening A, B, Day 1, Week 2 to 24 (every 2 weeks), LOV
Serum chemistry	Screening A, Day 1, Week 2 to 24 (every 2 weeks), LOV
Urinalysis	Screening A, Day 1, Week 4 to 24 (every 4 weeks), LOV
Immunoglobulin test	Screening A, Day 1, Week 24, LOV
Vital signs	Screening A, B, Day 1, Week 2 to 24 (every 2 weeks), LOV
Plasma drug concentration	Pre-study drug administration: Week 2, 6; Post-study drug administration: Week 2 to 24 (every 2 weeks)

Table 5.9-2 Time Windows for Each Analysis Visit in Period I

Analysis visit	Target study day[a)]	Lower limit	Upper limit
Screening A	−28	−31	−25
Screening B	−14	−17	−11
Day 1	1	1	1
Week 2 to 24	$7 \times x + 1$[b)]	Target study day −3	Target study day +3

a) The first day of study drug administration in Period I is defined as Day 1, and the day before the first day of study drug administration as Day −1.
b) x: Number of weeks

2) Evaluation during long-term treatment of R788

Table 5.9-3 Analysis visits during long-term treatment of R788

Variables evaluated	Analysis visit
Platelets	Screening A, B, Day 1, Week 2 to 24 (every 2 weeks), Week 28 to 52 (every 4 weeks)
Treatment dose	Day 1, Week 2 to 24 (every 2 weeks), Week 28 to 52 (every 4 weeks)
QOL assessment (SF-36)	Day 1, Week 4, 12, 24, 52
ITP Bleeding Score	Screening A, Day 1, Week 2 to 24 (every 2 weeks), Week 28 to 52 (every 4 weeks), LOV
ECOG Performance Status	Screening A, Day 1, Week 4 to 52 (every 4 weeks), LOV
Hematology (excluding platelets)	Screening A, B, Day 1, Week 2 to 24 (every 2 weeks), Week 28 to 52 (every 4 weeks), LOV
Serum chemistry	Screening A, Day 1, Week 2 to 24 (every 2 weeks), Week 28 to 52 (every 4 weeks), LOV
Urinalysis	Screening A, Day 1, Week 4 to 24 (every 4 weeks), Week 28 to 52 (every 12 weeks), LOV
Immunoglobulin test	Screening A, Day 1, Week 24, Week 52, LOV
Vital signs	Screening A, B, Day 1, Week 2 to 24 (every 2 weeks), Week 28 to 52 (every 4 weeks), LOV

Table 5.9-4 Time Windows for Each Analysis Visit during Long-term Treatment of R788

Analysis visit	Target study day[a)]	Lower limit	Upper limit
Screening A	−28	−31	−25
Screening B	−14	−17	−11
Day 1	1	1	1
Week 2 to 24	7 × x + 1[b)]	Target study day −3	Target study day +3
Week 28 to 52	7 × x + 1[b)]	Target study day −7	Target study day +7

a) The first day of study drug administration in Period I is defined as Day 1, and the day before the first day of study drug administration as Day −1.
b) x: Number of weeks

3) Evaluation in Period II

The following data will be used as Week 24 to 52 data:

- Data from Week 24 to 52 of subjects who received placebo in Period I, completed Period I, and transitioned to Period II.
- Data from early transition Day 1 to early transition Week 28 of subjects who discontinued Period I and early transitioned to Period II.

Table 5.9-5 Analysis Visits in Period II

Variables evaluated	Analysis visit
Platelets	Week 24 to 52 (every 4 weeks)
Treatment dose	Week 24 to 52 (every 4 weeks)
QOL assessment (SF-36)	Week 24, Week 52
ITP Bleeding Score	Week 24 to 52 (every 4 weeks), LOV
ECOG Performance Status	Week 24 to 52 (every 4 weeks), LOV
Hematology (excluding platelets)	Week 24 to 52 (every 4 weeks), LOV
Serum chemistry	Week 24 to 52 (every 4 weeks), LOV
Urinalysis	Week 24, Week 28 to 52 (every 12 weeks), LOV
Immunoglobulin test	Week 24, Week 52, LOV
Vital signs	Week 24 to 52 (every 4 weeks), LOV

Table 5.9-6 Time Windows for Each Analysis Visit in Period II (for those who completed Period I)

Analysis visit	Target study day[a)]	Lower limit	Upper limit
Week 24 to 52 (every 4 weeks)	$7 \times x + 1$[b)]	Target study day −7	Target study day +7

a) The first day of study drug administration in Period I is defined as Day 1, and the day before the first day of study drug administration as Day −1.
b) x: Number of weeks

Table 5.9-7 Time Windows for Each Analysis Visit in Period II (for those who early transitioned)

Analysis visit	Target study day[a)]	Lower limit	Upper limit
Week 24	1	−1	1
Week 28 to 52 (every 4 weeks)	$7 \times (x-24) + 1$[b)]	Target study day −7	Target study day +7

a) The first day of study drug administration in Period II is defined as Day 1 and the day before the first day of study drug administration as Day −1.
b) x: Number of weeks

4) Evaluation in non-dosing period

Day 1 of the non-dosing period is defined as Week 52 of Period II for subjects who completed Period I, and as early transition Week 28 for subjects who early transitioned to Period II. Day 1 of Period III is defined as Week 4 of the non-dosing period.

Table 5.9-8 Analysis Visits in Non-Dosing Period

Variables evaluated	Analysis visit
Platelets	Day 1, Week 2, Week 4, LOV
ITP Bleeding Score	Day 1, Week 2, Week 4, LOV
QOL assessment (SF-36)	Day 1, Week 2, Week 4, LOV
ITP Bleeding Score	Day 1, Week 2, Week 4, LOV
ECOG Performance Status	Day 1, Week 2, Week 4, LOV
Hematology (excluding platelets)	Day 1, Week 2, Week 4, LOV
Serum chemistry	Day 1, Week 2, Week 4, LOV
Urinalysis	Day 1, Week 2, Week 4, LOV
Immunoglobulin test	Day 1, Week 2, Week 4, LOV
Vital signs	Day 1, Week 2, Week 4, LOV

Table 5.9-9 Time Windows for Each Analysis Visit in Non-Dosing Period

Analysis visit	Target study day[a)]	Lower limit	Upper limit
Day 1	1	1	1
Week 2, Week 4	$7 \times x + 1$[b)]	Target study day −3	Target study day +3

a) Day 1 is defined as the day of Week 52 visit for subjects who completed Period I and the day of Week 28 visit for those who early transitioned to Period II.
b) x: Number of weeks

5) Evaluation in Period III

Day 1 is the first visit in Period III.

Table 5.9-10 Analysis Visits in Period III

Variables evaluated	Analysis visit
Platelets	Day 1, Week 8 (every 8 weeks thereafter)
Treatment dose	Week 8 (every 8 weeks thereafter)
ITP Bleeding Score	Day 1, Week 8 (every 8 weeks thereafter)
ECOG Performance Status	Day 1, Week 8 (every 8 weeks thereafter)
Hematology (excluding platelets)	Day 1, Week 8 (every 8 weeks thereafter)
Serum chemistry	Day 1, Week 8 (every 8 weeks thereafter)
Urinalysis	Day 1, Week 8 (every 8 weeks thereafter)
Vital signs	Day 1, Week 8 (every 8 weeks thereafter)

Table 5.9-11 Time Windows for Each Analysis Visit in Period III

Analysis visit	Target study day[a)]	Lower limit	Upper limit
Day 1	1	1	1
Week 8 (every 8 weeks thereafter)	$7 \times x + 1$[b)]	Target study day −14	Target study day +14

a) The first visit in Period III is defined as Day 1, and the day before the first visit as Day −1.
b) x: Number of weeks

6) Evaluation in R788 treatment period

Day 1 of the R788 treatment period is defined as the first day of study drug administration in Period I for subjects who received R788 in Period I, and as the first day of study drug administration in Period II for those who received placebo in Period I and transitioned to Period II. No analysis visit-specific analysis will be performed for evaluation in the R788 treatment period.

7) Evaluation in the entire study period

Day 1 is defined as the first day of study drug administration in Period I. No analysis visit-specific analysis will be performed for evaluation in the entire study period.

6. Statistical/Analytical Issues

6.1 Adjustments for Covariates

Analyses adjusted for covariates will not be performed.

6.2 Handling of Dropouts and Missing Data

When data to be used for analysis are missing, they will be handled as missing, and no statistical imputation will be performed, excluding the variables listed in "5 Data Handling" and below. Last observation carried forward (LOCF) imputation will be applied to the primary endpoint. For details, see "11.1 Primary Endpoint."

6.3 Interim Analyses and Data Monitoring

6.3.1 Timing of analysis

1) First data cutoff

After all subjects have completed Period I, the following data collected by the first data cut-off date will be analyzed for Period I, long-term treatment of R788, R788 treatment period, and the

entire study period.

- Period I data of all subjects
- Period II data of subjects who completed Period II
- Follow-up data of subjects who completed the follow-up period

2) Second data cutoff

After all subjects have completed the non-dosing period, all data collected by the second data cut-off date will be analyzed for Period I, long-term treatment of R788, Period II, non-dosing period, Period III, R788 treatment period, and the entire study period.

6.4 Multicenter Studies

No site-specific analysis will be performed because the per site sample size is not large enough.

6.5 Multiple Comparison/Multiplicity

6.5.1 Multiplicity for multiple analyses and multiple analysis visits

The primary endpoint is defined as stable platelet response based on platelet counts from Week 14 to Week 24 in Period I, and other variables, and time points will be used for reference only. Therefore, multiplicity adjustment for multiple analysis visits will not be performed.

6.5.2 Multiplicity among multiple evaluations

Stable platelet response is set as the primary endpoint and other variables will be used for reference only. Therefore, multiplicity adjustment among multiple variables will not be performed.

6.5.3 Multiplicity for multiple analysis sets

Not applicable because only the FAS, SS, and PKS will be used for the analysis of efficacy, safety, and pharmacokinetics, respectively.

6.6 Use of an "Efficacy Subset" of Subjects

Not applicable because only the FAS will be used for efficacy analysis.

6.7 Active-Control Studies Intended to Show Non-inferiority

Not applicable.

6.8 Subgroup Analyses

Efficacy will be analyzed for each line of therapy and by stable platelet response. For details, see "11.3 Subgroup Analysis of Efficacy." No subgroup analysis of safety will be performed.

7. Definition of Derived Data

Each variable will be calculated based on the following definitions.

- The following drugs are considered as prior ITP medications:

  - Drugs collected as prior ITP medications
  - Drugs collected as permitted concomitant ITP medications that were used prior to study drug administration

- Number of unique prior ITP medications (categories)
  Defined as the number of categories of prior ITP medications used. For example, if 3 corticosteroids and rituximab are used, the number of prior ITP medications (categories) will be 2.

- Number of unique prior ITP medications (drugs)
  Defined as the number of prior ITP medications used. For example, if eltrombopag olamine and romiplostim are used, the number of prior ITP medications will be 2.

- Line of therapy
  Prior ITP medications will be classified into the following line of therapy categories. The line of therapy will be the number obtained by adding 1 to the number of categories (excluding "Other"). For category "Other," the number of generic names of the relevant medications will be added to the line number. If splenectomy was performed, add 1 to the line number. However, if prior ITP medications only include steroid ("Corticosteroids" or "Danazol") and/or "Intravenous Immunoglobulins" and splenectomy has not been performed, the line of therapy will be 2 instead of 3.
  - Line of therapy categories: Thrombopoietin Receptor Agonists, Corticosteroids, Intravenous Immunoglobulins, Rituximab, Immunosuppressant, Danazol, Chemotherapy, Other.

- Duration of exposure
  - Period I: Day of last administration in Period I − Day of first administration in Period I + 1
  - Long-term treatment of R788
    - For subjects who discontinued Period I: Day of last administration in Period I − Day of first administration in Period I + 1
    - For subjects who completed Period I and transitioned to Period II: Day of last administration in Period II − Day of first administration in Period I + 1
  - Period II: Day of last administration in Period II − Day of first administration in Period II + 1
  - Non-dosing period: End day of the non-dosing period − Start day of the non-dosing period + 1
  - Period III: Day of last administration in Period III − Day of first administration in Period III + 1
  - R788 treatment period: Day of last administration of R788 − Day of first administration of R788 + 1 − (End day of the non-dosing period − Start day of the non-dosing period)

- Elapsed time after administration = Time of blood sampling − Time of study drug administration

- Treatment compliance = Total number of administered tablets / Number of prescribed tablets × 100

- Number of prescribed tablets
  Defined as the sum of the products of the number of tablets prescribed per day and the duration of treatment. However, if dose interruption due to an AE or any other reasons occurs during a period other than the non-dosing period, the dose prescribed immediately before the dose interruption will be applied.

- Treatment dose at each analysis visit
  Defined as the dose at the time of measurement of platelet count. For Day 1 of Period I, Week 24 of Period II, and Day 1 of Period III, the initial doses for each period will be used. If the study drug is interrupted on the relevant day, the dose will be categorized as interruption. Analysis visits after treatment discontinuation will be excluded from the analysis.

- Average daily dose
  Defined as the weighted average of treatment dose, with the duration of exposure at each dose as the weighting factor. Dose interruption will be handled as 0 mg dose.

- Duration of platelet response = End day of response − Start day of response + 1
  The start day of response is defined as the first day after the start of study treatment in each period on which a platelet count of ≥ 50000/μL for at least 28 consecutive days without the use of rescue medications was achieved. The end day of response is defined as the day of use of a rescue medication or the first day of the period in which the platelet count fell below 50000/μL for at least 28 consecutive days, whichever is earlier. For subjects who discontinue or complete each period with the platelet count maintained at ≥ 50000/μL, the last measurement day in each period is defined as the end day of response. The calculation of the duration of platelet response includes analysis visits outside the acceptable time window and unscheduled visits.

- Sustained stable platelet response
  Subjects who achieve a platelet count of ≥ 50000/μL within 12 weeks after the start of study treatment and maintain it for the subsequent 12 weeks will be considered as responders. Maintenance of the platelet count for the subsequent 12 weeks is defined as platelet response for at least 12 weeks (85 days). All subjects not assessed as responders due to discontinuation or missing data will be considered as non-responders.

8. Disposition of Subjects

8.1 Analysis Sets

Applicable period: Period I

For all randomized subjects, the number and percentage of subjects included in or excluded from the analysis sets listed in Table 8.1-1 will be presented. Differences between groups will be analyzed using Fisher's exact test.

Table 8.1-1 Category

Analysis set	Category
FAS	Included, Excluded
SS	Included, Excluded
PKS	Included, Excluded

8.2 Discontinuation and Reasons for Discontinuation

Applicable period: Period I, long-term treatment of R788, Period II, Period III, and R788 treatment period

The number and percentage of subjects who discontinued the study will be presented. In Period I, differences between groups will be analyzed using Fisher's exact test. Subjects who are ongoing in the applicable period at the time of data cut-off will be categorized as "Ongoing."

Reasons for discontinuation will be classified into the following categories, and the number and percentage of subjects will be presented.

Evaluation during long-term treatment of R788 includes whether there were discontinuations after transition to Period II and their reasons. For evaluation in Period II, the number of subjects who completed Period I or early transitioned to Period II will also be presented.

- Adverse events: Withdrawal due to Withdrawal Criteria (withdrawal in individual subjects) 1) "Adverse Events"
- Lack of efficacy: Withdrawal due to Withdrawal Criteria (withdrawal in individual subjects) 2) "Lack of Efficacy (inadequate response)"
- Withdrawal by subject: Withdrawal due to Withdrawal Criteria (withdrawal in individual subjects) 3) "Subject's voluntary request for withdrawal from the study"
- Significant deviation: Withdrawal due to Withdrawal Criteria (withdrawal in individual subjects) 4) "Significant deviation from the protocol during the study period"
- Other: When the reason for discontinuation does not correspond to "adverse event," "lack of efficacy," "withdrawal by subject" or "significant deviation" in this category.

9. Demographics and Other Baseline Characteristics

9.1 Subject Demographics

Applicable period: Period I, R788 treatment period

The variables to be analyzed are listed below. The pooled analysis of R788 and placebo groups will be performed only for Period I. For both Period I and the R788 treatment period, data from Day 1 of Period I will be used for analysis.

- Nominal scale variables
  - Sex: Male, female
  - Splenectomy: Yes, no
  - Prior ITP medications: Corticosteroids, rituximab, thrombopoietin receptor agonists, intravenous immunoglobulins, immunosuppressants, other
- Ordinal scale variables
  - Age: < 65 years, ≥ 65 years
  - Time since ITP diagnosis: < 3 years, ≥ 3 years
  - Time since splenectomy: < 6 months, ≥ 6 months

- Number of unique prior ITP medications (categories): 1, 2, 3, ≥ 4
- Number of unique prior ITP medications (drugs): 1, 2, 3, 4, 5, ≥ 6
- Line of therapy: 2, ≥ 3
- Platelet count: < 15000, 15000 ≤ < 30000, 30000 ≤ < 35000, ≥ 35000/μL

- Continuous variables: Age, height, weight, body mass index (BMI), time since ITP diagnosis (years), time since splenectomy (months), number of unique prior ITP medications (categories), number of unique prior ITP medications (drugs), line of therapy, platelet count

The numbers and percentages of subjects will be presented for nominal and ordinal scale variables, and summary statistics for continuous variables.

Subjects who have not undergone splenectomy will be excluded from the evaluation of time since splenectomy.

9.2 Complications and Medical History

Applicable period: Period I
The numbers and percentages of subjects will be presented for the entire population and by primary SOC and PT.

9.3 Prior ITP medications

Applicable period: Period I
For medications used for the treatment of ITP before study drug administration, the numbers and percentages of subjects who used such drugs will be presented.

9.4 Concomitant Medications Used for Complications

Applicable period: Period I, long-term treatment of R788, Period II, and non-dosing period
For medications used to treat complications after study drug administration, the numbers and percentages of subjects who used such drugs will be presented.

10. Treatment compliance

10.1 Duration of Exposure

Applicable period: Period I, long-term treatment of R788, Period II, non-dosing period, Period III, and R788 treatment period
Summary statistics will be presented. For the non-dosing period, the duration of dose interruption will be presented.

10.2 Distribution of Duration of Exposure

Applicable period: Period I, long-term treatment of R788, Period II, non-dosing period, Period III, and R788 treatment period
The variables to be analyzed are as follows:

- Duration of treatment (Period I): <4, 4≤ <8, 8≤ <12, ≥12 weeks
- Duration of treatment (long-term treatment of R788): <4, 4≤ <8, 8≤ <12, 12≤ <24, ≥24 weeks

- Duration of treatment (Period II): <4, 4≤ <8, 8≤ <12, 12≤ <24, ≥24 weeks
- Duration of dose interruption (non-dosing period): <4, ≥4 weeks
- Duration of treatment (Period III): <24, 24≤ <48, 48≤ <72, ≥72 weeks
- Duration of treatment (R788 treatment period): <4, 4≤ <8, 8≤ <12, 12≤ <24, 24≤ <52, ≥52 weeks

The numbers and percentages of subjects will be presented. The duration of dose interruption will be presented for the non-dosing period.

10.3 Treatment Compliance

Applicable period: Period I, long-term treatment of R788, Period II, Period III
Summary statistics will be presented. The evaluation in Period III will be conducted at study completion only.

10.4 Daily Dose

Applicable period: Period I, long-term treatment of R788, Period II, Period III

- Dose: 100, 150, 200, and 300 mg/day, withdrawal

The numbers and percentages of subjects treated with each dose level will be presented.

10.5 Average Daily Dose

Applicable period: Period I, long-term treatment of R788, Period II, Period III, and R788 treatment period
Summary statistics will be presented.

10.6 ITP Concomitant Medications

Applicable period: Period I, long-term treatment of R788, Period II, non-dosing period, Period III, and R788 treatment period
For medications used to treat ITP after study drug administration (excluding rescue medications), the numbers and percentages of subjects who used such drugs will be presented.

10.7 Rescue Medications

Evaluation will be made for all rescue medications and for each indication (increased platelet, other).

10.7.1 Use of rescue medications

Applicable period: Period I, long-term treatment of R788, Period II, non-dosing period, Period III, and R788 treatment period
For rescue medications used after study drug administration, the numbers and percentages of subjects who used such medications will be presented.

10.7.2 Frequency of rescue medication use

Applicable period: Period I, long-term treatment of R788, Period II

The number and percentage of subjects by the frequency of rescue medication use will be presented. The type of rescue medications will not be considered.

10.7.3 Use of rescue medications (in each period)

Applicable period: Period I, long-term treatment of R788, Period II
The numbers and percentages of subjects who used rescue medications after study drug administration will be presented every 2 weeks for Period I and every 4 weeks for Period II. Subjects who used rescue medications across two or more periods will be considered to have used those medications throughout all applicable periods.

11. Efficacy

11.1 Primary Endpoint

Applicable period: Period I
The primary efficacy endpoint in this study is the achievement rate of stable platelet response. The analysis of the primary endpoint will be based on data from Period I.
Stable platelet response: Subjects who achieve a platelet count of ≥ 50000/μL at 4 or more of the 6 visits from Weeks 14 to 24 will be considered as responders, and the percentage of responders will be evaluated.
Whether a subject has achieved stable platelet response will be evaluated according to the following rules:

- Subjects who discontinued due to an AE or lack of efficacy and those who used rescue medications between Week 10 and Week 24 will be considered as non-responders.
- Missing data in subjects other than those listed above will be imputed by LOCF until Week 24, and whether stable platelet response has been achieved will be determined based on the imputed data.

11.1.1 Analysis methods for the primary endpoint

The number and percentage of subjects achieving stable platelet response and their two-sided 95% CIs will be presented. The difference in the achievement rate between groups and its two-sided 95% CI will be calculated. The superiority of the R788 group to the placebo group will be evaluated using Fisher's exact test.

11.2 Secondary Endpoints

11.2.1 Evaluation in Period I

Applicable period: Period I

11.2.1.1 Achievement rates for platelet count-related endpoints

The variables to be analyzed are as follows:

- Achievement rate of a platelet count of ≥ 50000/μL at Weeks 12 and 24
- Achievement rate of a platelet count of ≥ 30000/μL and change from the baseline in platelet count of ≥ 20000/μL at Weeks 12 and 24 (for subjects with a baseline platelet count of < 15000/μL)

- Achievement rate of overall response (subjects who achieve a platelet count of ≥ 50000/μL at 1 or more of the 6 visits from Weeks 2 to 12 will be considered as responders, and the percentage of responders will be evaluated)

The number and percentage of responders and their two-sided 95% CIs will be presented. The difference in the achievement rate between groups and its two-sided 95% CI will be presented. All subjects who are not assessed as responders due to discontinuation or missing data will be considered as non-responders.

11.2.1.2 Number of scheduled visits with platelet ≥ 50000/μL

The variables to be analyzed are as follows:

- Number of visits with a platelet count of ≥ 50000/μL among 6 visits from Week 2 to Week 12
- Number of visits with a platelet count of ≥ 50000/μL among 12 visits from Week 2 to Week 24

The numbers and percentages of subjects will be presented.

11.2.1.3 Duration of platelet response

Summary statistics will be presented.

11.2.1.4 Summary statistics of platelet count

The variables to be analyzed are as follows:

- Platelet count
- Change from baseline in platelet count

Summary statistics will be presented. Additionally, medians and quartiles will be presented graphically.

11.2.1.5 Distribution of platelet count

The variables to be analyzed are as follows:

- Platelet count: < 15000, 15000 ≤ < 30000, 30000 ≤ < 50000, ≥ 50000/μL
- Change from baseline in platelet count: < 20000, ≥ 20000/μL

The numbers and percentages of subjects will be presented.

11.2.1.6 Individual plots of platelet count

Individual plots and a swimmer plot will be presented for the change in platelet count in each subject. The swimmer plot will show the duration of exposure, as well as the number of days until the following events:

- Maintenance start: The start day of platelet response
- Maintenance end: The end day of platelet response
- Continued response: The end day of the evaluation period when the platelet response is ongoing at the end of the evaluation period.

11.2.1.7 Summary statistics of quality of life assessment (SF-36)

Summary statistics will be presented.

11.2.2 Evaluation during long-term treatment of R788

Applicable period: Long-term treatment of R788

11.2.2.1 Achievement rates for platelet count-related endpoints

The variables to be analyzed are as follows:

- Achievement rate of a platelet count of ≥ 50000/μL at Weeks 12, 24, 36, 48, and 52
- Achievement rate of a platelet count of ≥ 30000/μL and change from the baseline in platelet count of ≥ 20000/μL at Weeks 12, 24, 36, 48, and 52 (for subjects with a baseline platelet count of < 15000/μL)

Achievement rates and their two-sided 95% CIs will be presented. All subjects who are not assessed as responders due to discontinuation or missing data will be considered as non-responders.

11.2.2.2 Duration of platelet response

Summary statistics will be presented.

11.2.2.3 Summary statistics of platelet count

The variables to be analyzed are as follows:

- Platelet count
- Change from baseline in platelet count

Summary statistics will be presented. Additionally, medians and quartiles will be presented graphically.

11.2.2.4 Distribution of platelet count

The variables to be analyzed are as follows:

- Platelet count: < 15000, 15000 ≤ < 30000, 30000 ≤ < 50000, ≥ 50000/μL
- Change from baseline in platelet count: < 20000, ≥ 20000/μL

The numbers and percentages of subjects will be presented.

11.2.2.5 Individual plots of platelet count

Individual plots and a swimmer plot will be presented for the change in platelet count in each subject. The dates to be displayed in the figures are as described in "11.2.1.6 Individual plots of platelet count."

11.2.2.6 Summary statistics of quality of life assessment (SF-36)

Summary statistics will be presented.

11.2.3 Evaluation in Period II

Applicable period: Period II

11.2.3.1 Achievement rate of platelet response in Periods I and II (sustained stable platelet response)

This analysis includes data from Periods I and II of subjects who received placebo in Period I and transitioned to Period II.
The achievement rate of sustained stable platelet response in each period and their two-sided 95% CIs will be presented. The difference in the achievement rate between Periods I and II and its two-sided 95% CI will be presented. A CI (normal approximation) based on the standard error of the difference in the rate will be calculated. McNemar test will be used to analyze the difference in the achievement rate between Periods I and II.

11.2.3.2 Achievement rates for platelet count-related endpoints

The variables to be analyzed are as follows:

- Achievement rate of a platelet count of ≥ 50000/μL at Weeks 36, 48, and 52
- Achievement rate of a platelet count of ≥ 30000/μL and change from the baseline in platelet count of ≥ 20000/μL at Weeks 36, 48, and 52 (for subjects with a baseline platelet count of < 15000/μL)

Achievement rates and their two-sided 95% CIs will be presented. The difference in the achievement rate between groups and its two-sided 95% CI will be presented. All subjects not assessed as responders due to discontinuation or missing data will be considered as non-responders.

11.2.3.3 Duration of platelet response

Summary statistics will be presented.

11.2.3.4 Summary statistics of platelet count

The variables to be analyzed are as follows:

- Platelet count
- Change from baseline in platelet count

Summary statistics will be presented. Additionally, medians and quartiles will be presented graphically.

11.2.3.5 Distribution of platelet count

The variables to be analyzed are as follows:

- Platelet count: < 15000, 15000 ≤ < 30000, 30000 ≤ < 50000, ≥ 50000/μL
- Change from baseline in platelet count: < 20000, ≥ 20000/μL

The numbers and percentages of subjects will be presented.

11.2.3.6 Individual plots of platelet count

Individual plots and a swimmer plot will be presented for the change in platelet count in each subject. The dates to be displayed in the figures are as described in "11.2.1.6 Individual plots of platelet count."

11.2.3.7 Summary statistics of quality of life assessment (SF-36)

Summary statistics will be presented.

11.2.4 Evaluation in the non-dosing period

Applicable period: Non-dosing period

11.2.4.1 Summary statistics of platelet count

The variables to be analyzed are as follows:

- Platelet count
- Change from baseline in platelet count
- Change in platelet count from the start of the non-dosing period

Summary statistics will be presented.

11.2.4.2 Distribution of platelet count

The variables to be analyzed are as follows:

- Platelet count: < 15000, $15000 \leq < 30000$, $30000 \leq < 50000$, ≥ 50000/μL
- Change from baseline in platelet count: < 20000, ≥ 20000/μL

The numbers and percentages of subjects will be presented.

11.2.4.3 Individual plots of platelet count

Individual plots will be presented for the change in platelet count in each subject.

The number of days will be shown on the horizontal axis. The platelet count in unscheduled measurements and after the use of rescue medication will also be displayed.

11.2.4.4 Decrease in platelet count after dose interruption

The variables to be analyzed are as follows:

- Platelet count of <10000/μL with a decrease from baseline of ≥ 10000/μL

The number and percentage of subjects who met the conditions of the analysis variables during the non-dosing period will be presented.

11.2.4.5 Summary statistics of quality of life assessment (SF-36)

Summary statistics will be presented.

11.2.5 Evaluation in Period III

Applicable period: Period III

11.2.5.1 Summary statistics of platelet count

The variables to be analyzed are as follows:

- Platelet count
- Change from baseline in platelet count

Summary statistics will be presented.

11.2.5.2 Distribution of platelet count

The variables to be analyzed are as follows:

- Platelet count: < 15000, $15000 \leq < 30000$, $30000 \leq < 50000$, $\geq 50000/\mu L$
- Change from baseline in platelet count: < 20000, $\geq 20000/\mu L$

The numbers and percentages of subjects will be presented.

11.2.5.3 Individual plots of platelet count

Individual plots will be presented for the change in platelet count in each subject.

11.2.6 Evaluation in R788 treatment period

Applicable period: R788 treatment period

11.2.6.1 Platelet response rate

The variables to be analyzed are as follows:

- Platelet count: $\geq 50000/\mu L$

The number and percentage of subjects achieving a platelet count of $\geq 50000/\mu L$ at least one analysis visit between the day of first administration of R788 and Week 52 of Period II will be presented.

11.2.6.2 Duration of platelet response

Summary statistics will be presented. The non-dosing period will be included in the evaluation of the duration of platelet response. This assessment will be performed for the R788 group, R788-R788 group, and P-R788 group.

11.2.6.3 Individual plots of platelet count

A swimmer plot will be presented for the platelet count. Items to be presented graphically are as shown in "11.2.1.6 Individual plots of platelet count." The non-dosing period will be included in the duration of exposure. This assessment will be performed for the R788-R788 group and P-R788 group.

11.2.7 Evaluation in the entire study period

Applicable period: Entire study period excluding follow-up

11.2.7.1 Individual plots of platelet count

Individual plots will be presented for the change in platelet count in each subject. The horizontal axis represents the number of days from the first day of study drug administration in Period I. The plot will include all platelet count measurements obtained between the start of the screening period and the end or discontinuation of the study, including unscheduled measurements and measurements affected by rescue medications. In addition, the dose of R788, times of use of rescue medications, and types and doses of permitted concomitant ITP medications will be presented.

11.3 Subgroup Analysis of Efficacy

1) The analyses described in "11.2.6.1 Platelet response rate" will be performed for each line of therapy (2nd line, 3rd line or later).
2) At the first data cut-off, the analyses described in "11.2.2.1 Achievement rates for platelet count-related endpoints" will be performed, excluding subjects who are still in Period II.
3) Summary statistic of platelet count in "11.2.1.4 Summary statistics of platelet count" will be presented for responders and non-responders in stable platelet response. Additionally, medians and quartiles will be presented graphically for responders and non-responders in the R788 group, and for the placebo group.
4) For the data in Period I, the median platelet count after the administration of the investigational product will be calculated for each subject, and the summary statistics will be presented for the R788 group, for responders and non-responders in stable platelet response in the R788 group, and for the placebo group.

12. Safety

12.1 Adverse Events and Adverse Drug Reactions

Applicable period: Period I, long-term treatment of R788, Period II, non-dosing period, Period III, and R788 treatment period
The following analyses will be performed. For evaluation in the R788 treatment period, AEs and adverse drug reactions (ADRs) that occurred after administration of R788 will be included in the analysis.

12.1.1 Incidence rates of adverse events and adverse drug reactions

The number of events, number of subjects with events, and incidence rates of events with two-sided 95% CIs will be presented. For Period I, the difference in incidence rates between groups and their two-sided 95% CIs will be presented.

12.1.2 Incidence of adverse events and adverse drug reactions (summary)

The variables to be analyzed are as follows:

- AEs and ADRs

- AEs and ADRs leading to death
- Serious AEs and ADRs excluding deaths
- AEs and ADRs leading to study drug withdrawal
- AEs and ADRs leading to dose reduction
- AEs and ADRs leading to dose interruption
- AEs and ADRs of interest

The number of events, number of subjects with events, and incidence rates of events will be presented.

12.1.3 Occurrence of adverse events and adverse drug reactions

The variables to be analyzed are as follows:

- AEs and ADRs
- AEs and ADRs leading to study drug withdrawal
- AEs and ADRs leading to dose reduction
- AEs and ADRs leading to dose interruption
- Serious AEs and ADRs
- AEs and ADRs of interest
- AEs and ADRs of interest leading to study drug withdrawal
- AEs and ADRs of interest leading to dose reduction
- AEs and ADRs of interest leading to dose interruption
- Serious AEs and ADRs of interest

The number of events, number of subjects with events, and incidence rates of events will be presented overall and by primary SOC and PT. For AEs and ADRs of interest, event categories will be presented instead of primary SOCs.

12.1.4 Severity of adverse events and adverse drug reactions

The variables to be analyzed are as follows:

- AEs and ADRs
- AEs and ADRs of interest

The number of events by severity will be presented overall and by primary SOC and PT.
The number of subjects with events and incidence rates by severity will be presented overall and by primary SOC and PT. For multiple events of the same category occurring in a single subject, only the event with the highest severity will be considered in the calculation of the number of subjects with events and incidence rates.
For AEs and ADRs of interest, event categories will be presented instead of primary SOCs.

12.1.5 Early occurrence of adverse events and adverse drug reactions

Applicable period: Period I, R788 treatment period
The variables to be analyzed are as follows:

- AEs and ADRs occurring up to Week 4 (Day 29)
- AEs and ADRs of interest occurring up to Week 4 (Day 29)
- AEs and ADRs occurring up to Week 12 (Day 85)
- AEs and ADRs of interest occurring up to Week 12 (Day 85)

The number of events, number of subjects with events, and incidence rates of events will be presented overall and by primary SOC and PT.
For AEs and ADRs of interest, event categories will be presented instead of primary SOCs.

12.1.6 Timing of occurrence of adverse events and adverse drug reactions

Applicable period: R788 treatment period
The variables to be analyzed are as follows:

- AEs and ADRs
- AEs and ADRs of interest

The categories of timing of onset are shown as follows.

- ≤12, 12< ≤24, 24< ≤36, 36< ≤48, 48< ≤72, 72< weeks, follow-up period

For each category of timing of onset, the number of events, number of subjects with events, and incidence rates of events will be presented overall and by primary SOC and PT. The denominator for the calculation of incidence of the events occurring in the follow-up period will be the subjects who received R788, excluding the ongoing subjects.

For AEs and ADRs of interest, the event categories will be presented instead of primary SOCs.

If the same event occurred multiple times, analysis will also be conducted to include only the events of initial onset. In such cases, the first occurrence of the event within each category of timing of onset will be analyzed overall and by primary SOC and category of AEs of interest as well.

12.1.7 Occurrence of adverse events and adverse drug reactions by dose at onset

Applicable period: R788 treatment period

The variables to be analyzed are as follows:

- AEs and ADRs
- AEs and ADRs of interest

For each dose at onset, the number of events, number of subjects with events, and incidence rates of events will be presented overall and by primary SOC and PT. Events occurring during drug interruption will be excluded from the analysis. The denominator for the incidence will be the subjects who received the applicable dose at least once. For AEs and ADRs of interest, event categories will be presented instead of primary SOCs.

12.2 ITP Bleeding Score

Applicable period: Period I, long-term treatment of R788, Period II, non-dosing period, and Period III
The variables to be analyzed are as follows:

- Average score
- Total score
- Maximum score
- Post-dose mean of average scores (Period I, Period II)

Summary statistics will be presented for the average score, total score, and post-dose mean of average scores. For maximum score, the numbers and percentages of subjects will be presented.

12.3 ECOG Performance Status

Applicable period: Period I, long-term treatment of R788, Period II, non-dosing period, Period III
The numbers and percentages of subjects with each score will be presented.

12.4 Laboratory and Immunoglobulin Tests

Applicable period: Period I, long-term treatment of R788, Period II
The variables to be analyzed are listed below.

- Laboratory tests (quantitative variables)
  Hematology: Platelets, red blood cells, white blood cells, hemoglobin, hematocrit, neutrophils, eosinophils, basophils, lymphocytes, monocytes, reticulocyte ratio, MCHC, MCH, MCV
  Serum chemistry: Sodium, potassium, chloride, calcium, phosphorus, BUN, creatinine, A/G ratio, blood glucose, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma glutamyl transferase (gamma-GTP), total bilirubin, direct bilirubin, indirect bilirubin
  Urinalysis: Specific gravity, pH
- Laboratory tests (qualitative variables)
  Urinalysis: Glucose, ketone bodies, occult blood, protein, nitrite, bilirubin, urobilinogen, white blood cells
- Immunoglobulin test
  Immunoglobulin M (IgM), immunoglobulin G (IgG), immunoglobulin A (IgA)

12.4.1 Summary statistics of laboratory tests (quantitative variables) and immunoglobulin tests

Applicable period:
Laboratory tests (quantitative variables); Period I, long-term treatment of R788, Period II, non-dosing period, Period III
Immunoglobulin test; Period I, long-term treatment of R788, Period II, non-dosing period

The variables to be analyzed are as follows:

- Laboratory tests (quantitative variables) and immunoglobulin tests
- Changes from baseline in laboratory tests (quantitative variables) and immunoglobulin tests

Summary statistics will be presented.

12.4.2 Scatter plots of laboratory tests (quantitative variables) and immunoglobulin tests

Scatter plots of quantitative variables before and after treatment will be presented.
Applicable analysis visits: Baseline, LOV

12.4.3 Distribution of laboratory tests (qualitative variables)

Applicable period:Period I, long-term treatment of R788, Period II, non-dosing period, Period III

The numbers and percentages of subjects will be presented.

12.4.4 Shift tables of laboratory and immunoglobulin tests

For measurements obtained before and after administration, the number and percentages of subjects with low, normal, or high values will be presented.
Applicable analysis visit: Baseline, LOV

12.4.5 Distribution of post-baseline extrema of laboratory tests

The variables to be analyzed are as follows: ULN stands for the upper limit of normal.

- ALT (post-baseline maximum): > 3 × ULN, > 5 × ULN, > 10 × ULN
- AST (post-baseline maximum): > 3 × ULN, > 5 × ULN, > 10 × ULN
- ALP (post-baseline maximum): > 1.5 × ULN
- Total bilirubin (post-baseline maximum): > 2 × ULN
- Neutrophils (post-baseline minimum): < 500, 500 ≤ < 1000, 1000 ≤ < 1500, ≥ 1500/μL

The numbers and percentages of subjects will be presented.

12.5 Vital Signs

Applicable period: Period I, long-term treatment of R788, Period II
The variables to be analyzed are as follows:

- Systolic blood pressure, diastolic blood pressure, pulse rate, body temperature

12.5.1 Vital signs

Applicable period:Period I, long-term treatment of R788, Period II, non-dosing period, Period III

The variables to be analyzed are as follows:

- Measured value
- Change from baseline in measured values

Summary statistics will be presented.

12.5.2 Scatter plots of vital signs

Scatter plots of measured values before and after treatment will be presented.
Applicable analysis visits: Baseline, LOV

12.5.3 Distribution of blood pressure

The variables to be analyzed are as follows:

- Systolic blood pressure (post-baseline maximum): < 120, $120 \leq < 140$, $140 \leq < 160$, $160 \leq < 180$, ≥ 180 mmHg
- Diastolic blood pressure (post-baseline maximum): < 80, $80 \leq < 90$, $90 \leq < 100$, $100 \leq < 110$, ≥ 110 mmHg

The numbers and percentages of subjects will be presented.

12.5.4 Distribution of post-baseline extrema of blood pressure

The variables to be analyzed are as follows:

- Systolic and diastolic blood pressure: Systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg
- Systolic and diastolic blood pressure: Systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg

The number and percentage of subjects will be presented for the number of post-baseline scheduled visits with blood pressure values within the above ranges.

12.6 Listing of Safety Data

The lists of the following events will be prepared. If no applicable event is observed, the corresponding table will not be prepared.

- Deaths
- Serious AEs excluding deaths
- AEs leading to study drug withdrawal
- AEs leading to dose reduction
- AEs leading to dose interruption
- AEs of interest
- Abnormal laboratory values for each subject

13. Pharmacokinetics

Applicable period: Period I

13.1 Plasma drug concentration

This analysis will include subjects who received R788 in Period I.

13.1.1 Plasma Concentration

Summary statistics, geometric means, and geometric CVs of plasma R406 concentration will be presented for each of the following groups based on the R788 dose immediately before pharmacokinetic sampling. At evaluation time point 1, the analysis will be performed separately before and after study drug administration on pharmacokinetic sampling days. At evaluation time point 2, the analysis will be performed on pooled data from before and after study drug administration on pharmacokinetic sampling days. In addition, for post-dose plasma concentration data at evaluation time point 1, measured values and their geometric means will be presented graphically.
R788 dose groups: Twice daily (BID), 100 mg BID, 150 mg BID

Table 13.1.1-1 Evaluation time point 1

Applicable weeks	Applicable time point	Time window (time elapsed since study drug administration immediately before pharmacokinetic sampling)
Weeks 2 and 6	Pre-dose	—
Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24	Post-dose	—
	≤ 4 hr post-dose	≤ 4 hr
	> 4 hr post-dose	> 4 hr

Table 13.1.1-2 Evaluation time point 2

Applicable weeks	Applicable time point	Time window (time elapsed since study drug administration immediately before pharmacokinetic sampling)
Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24	0 hr post-dose	0 ≤ < 0.5 hr
	1 hr post-dose	0.5 ≤ < 1.5 hr
	2 hr post-dose	1.5 ≤ < 3 hr
	4 hr post-dose	3 ≤ < 5 hr
	6 hr post-dose	5 ≤ and < 7 hr
	8 hr post-dose	7 ≤ and < 10 hr
	12 hr post-dose	10 ≤ < 14 hr
	14 hr post-dose	≥ 14 hr

13.1.2 Individual plots of plasma concentrations

The time course of plasma concentration and R788 dose will be presented for each subject. Plasma concentrations measured during R788 interruption will also be plotted.

13.1.3 Scatter plots of plasma concentrations

Scatter plots of plasma concentrations and time after R788 administration immediately before pharmacokinetic sampling will be presented for each of the following groups based on the R788 dose immediately before pharmacokinetic sampling.
R788 dose groups: 100 mg BID, 150 mg BID

14. Software Used for Analysis

Analyses will be performed using SAS System Release 9.4 for Windows (SAS Institute Inc.). Other statistical software will also be used as appropriate.

15. Tables, Figures and Listing Shells

The tables, figures and listing (TFL) shells will be provided separately.

16. Changes from the Protocol

16.1 Changes in Statistical Analysis Plan Version 1.0

1) In "3 Analysis Group," the "period I data of subjects who discontinued R788 treatment in Period I" were added to the evaluation during long-term treatment of R788.

   Reason: The purpose of this analysis was to evaluate the efficacy and safety of R788 from the start to the end of treatment with the product. Therefore, it was considered appropriate to include subjects who discontinued Period I in the analysis.

2) In "3 Analysis Group," evaluation in the entire study period was added.

   Reason: To evaluate platelet response throughout the entire period after study entry.

3) In "5.9 Analysis Visits," the baseline for change calculation was defined as Day 1 of Period I for all periods.

   Reason: In the protocol, the baseline was defined as Day 1 of each period. However, it was considered appropriate to use the value not affected by study drug administration as the baseline value.

4) In "6.3.1 Timing of analysis," the scope of data to be cutoff was changed, and variables to be analyzed were clarified.

   Reason: To include Period II data in the first data cutoff and the non-dosing period data in the second data cutoff. In addition, variables to be analyzed at the time of cutoff were clarified.

5) Evaluation of line of therapy-related variables was added to "9.1 Subject Demographics," and evaluation of achievement rate of platelet-related endpoints was added to "11.2.6.1 Platelet response rate" and "11.3 Subgroup Analysis of Efficacy."

   Reason: To evaluate the effect of line of therapy on efficacy, as evaluated in the paper of foreign studies.

6) In "7 Definition of Derived Data," the definition of the start day of platelet response was changed to "the first day after the start of study treatment in each period on which a platelet count of ≥ 50000/μL for at least 28 consecutive days without the use of rescue medications was achieved."

   Reason: To evaluate stable maintenance of platelet count.

7) In "11.1 Primary Endpoint," sensitivity analysis of the primary endpoint planned in the protocol was deleted.

   Reason: A blind review confirmed that no subject would need imputation of missing

platelet count data for the evaluation of stable platelet response. It was thus decided not to perform sensitivity analysis because no imputation would be performed.

8) In 12.4.5 Distribution of post-baseline extrema of laboratory tests, the analysis categories were changed for ALT and AST. In addition, evaluations of ALP, total bilirubin, and neutrophils were added.

   Reason: The above evaluations were added for comparison with safety evaluations in foreign studies.

9) In "12.5.3 Distribution of blood pressure," the analysis categories were changed for systolic and diastolic blood pressure.

   Reason: The above changes were made to allow for comparison with safety evaluations in foreign studies.

16.2 Changes in Statistical Analysis Plan Version 2.0

1) In "8.2 Discontinuation and Reasons for Discontinuation," the "Ongoing" category was added.

   Reason: To clarify the number of ongoing subjects at the time of data cutoff.

2) In "11.2.7.1 Individual plots of platelet count," the statement was changed to include permitted concomitant ITP medications used outside the treatment period in the figure.

   Reason: To allow permitted concomitant ITP medications discontinued during the screening period to appear on the figure.

3) In "11.3 Subgroup Analysis of Efficacy," the analysis of "11.2.2.1 Achievement rates for platelet count-related endpoints" excluding ongoing subjects was added.

   Reason: To perform the analysis after excluding subjects who are still on long-term treatment at the time of data cutoff.

4) In "13.1.1 Plasma Concentration," the statement on evaluation time point 2 was changed to include pre-dose data obtained on pharmacokinetic sampling days in the analysis.

   Reason: To align the analysis with "13.1.3 Scatter plots of plasma concentrations."

16.3 Changes in Statistical Analysis Plan Version 3.0

1) In "5.3 Reporting of Complications, Adverse Events, and Adverse Drug Reactions," PTs applicable to AEs of interest were changed.

   Reason: To add applicable events at the time of the second data cutoff.

2) In "5.5.1 Handling of platelet count data," platelets to be regarded as missing after the use of rescue medication were corrected.

   Reason: Corrected to clarify the scope of assessment on platelet count after the use of rescue medication.

3) In "5.9 Analysis Visits," LOV in the non-dosing period and change from the start of the non-dosing period were added.

   Reason: Since the non-dosing period only includes a small number of scheduled evaluation

time points and includes many unscheduled measurements, evaluation at LOV that includes unscheduled measurements was added to enable a more appropriate evaluation. In addition, change from the start of the non-dosing period was added to assess the change in platelet count after dose interruption.

4) In "6.3.1 Timing of analysis," descriptions regarding the details of analysis conducted at the second data cutoff were corrected. Also, in "10.3 Treatment Compliance," description regarding implementation at study completion only was added.

   Reason: Corrected the descriptions to clarify the details of analysis at the second data cutoff. Since the number of tablets administered in Period III cannot be finalized at cutoff, the evaluation of treatment compliance rate was set to be performed at study completion only.

5) In "10.2 Distribution of Duration of Exposure," evaluation of the duration of dose interruption in the non-dosing period was added.

   Reason: Added to evaluate the early termination of the non-dosing period.

6) In "11.2.4.1 Summary statistics of platelet count," evaluation on the change from the start of the non-dosing period was added.

   Reason: Added to evaluate the change in platelet count after transitioning to the non-dosing period.

7) In "11.2.4.3 Individual plots of platelet count," unscheduled measurements and measurements after the use of rescue medication were included in evaluation.

   Reason: Since the non-dosing period only includes a small number of scheduled evaluation time points and includes many unscheduled measurements, evaluation at LOV that includes unscheduled measurements was added to enable a more appropriate evaluation. In addition, measurements after the use of rescue medication were presented graphically as there is a limited number of measurements on platelet count during the non-dosing period.

8) In "11.2.4.4 Decrease in platelet count after dose interruption," evaluation of the decrease in platelet count during the non-dosing period was added.

   Reason: Added to evaluate the impact of dose interruption on platelet count.

9) In "11.2.6.2 Duration of platelet response," evaluation of the duration of maintenance in R788 treatment period was added. In "11.2.6.3 Individual plots of platelet count," a swimmer plot in R788 treatment period was added.

   Reason: Added for evaluation including the platelet response from Period III onwards.

10) In "6.8 Subgroup Analyses" and "11.3 Subgroup Analysis of Efficacy," evaluation of platelet count for responders and non-responders in stable platelet response was added.

    Reason: Evaluation methods in the research papers on overseas studies and integrated analysis were added for the detailed evaluation of differences in platelet response between responders and non-responders for stable platelet response.

11) In "12.1.6 Timing of occurrence of adverse events and adverse drug reactions," categories of the timing of onset were corrected. In addition, evaluation on the initial onset of AEs and ADRs in the multiple occurrences of the same event was added.

Reason: Period III was previously classified in an independent category; however, it was decided that categorized by the number of days from the day of first administration of R788, combined with the events that occurred in other periods. Also, this was added to evaluate the duration to the initial onset of AEs and ADRs.

12) In "12.1.7 Occurrence of adverse events and adverse drug reactions by dose at onset," evaluation of the AEs and ADRs by dose at onset was added.

Reason: Added to evaluate the impact of the dose on the onset of AEs and ADRs.

13) Evaluation of the non-dosing period was added to "11.2.4.5 Summary statistics of quality of life assessment (SF-36)"and immunoglobulin tests in "12.4.1 Summary statistics of laboratory tests (quantitative variables) and immunoglobulin tests." In addition, applicable evaluation time points were added in "5.9 Analysis Visits."

Reason: Added as a certain number of evaluable subjects is expected even in the non-dosing period.

14) Evaluation of the non-dosing period and Period III was added to the "12.3 ECOG Performance Status," laboratory tests in "12.4.1 Summary statistics of laboratory tests (quantitative variables) and immunoglobulin tests," "12.4.3 Distribution of laboratory tests (qualitative variables)," and "12.5.1 Vital signs." In addition, applicable evaluation time points were added in "5.9 Analysis Visits."

Reason: Added as a certain number of evaluable subjects is expected even in the non-dosing period and Period III.

17. Revision History of the Statistical Analysis Plan

Version	Date of preparation/revision:	Author	Description
1.0	December 2, 2021	[redacted]	Preparation of the first version
2.0	December 16, 2021		Preparation of the 2nd version
3.0	June 24, 2022		Preparation of the 3rd version

18. References

1) Qualitest Co., Ltd. "Japanese Version of SF-36v2® Scoring Program [Web version]" https://www.qualitest.jp/manual/scrong-prog.html, (cited on May 27, 2021).