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

Protocol

Title of study:	A Phase 3 Study in Patients with Chronic Idiopathic Thrombocytopenic Purpura in R788
Protocol No.:	R788-1301
Version:	1.0
Date of preparation/revision:	August 28, 2019
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NCT number:	NCT04132050

Protocol Synopsis

Title of study:
A Phase III Study in Patients with Chronic Idiopathic Thrombocytopenic Purpura in R788
(Protocol No.: R788-1301)

Study phase:
Phase III

Study objectives:

1. Primary objective
   To investigate the increase in platelet count in patients with chronic idiopathic thrombocytopenic purpura (ITP) after oral administration of R788 for 24 weeks in a placebo-controlled, double-blind manner (Period I).
2. Secondary objectives
   1) To evaluate the following efficacy of R788 in patients with chronic ITP
      - Maintenance of platelet count during long-term treatment with R788
      - Increase in platelet count during Period II for patients who received placebo in Period I
      - Improving of quality of life (QOL)
   2) To investigate the safety of R788 in patients with chronic ITP
   3) To investigate the pharmacokinetics of R788 in patients with chronic ITP (Period I).
3. Exploratory objective
   To investigate the time course of platelet count in patients with chronic ITP during interruption of R788 (Non-dosing (ND) period)

Endpoints:

1. Primary endpoint
   Achievement of stable platelet response (subjects who achieve a platelet count of ≥ 50000/μL on at least 4 of the 6 visits from Weeks 14 to 24 are considered as a responder and the percentage of responders will be evaluated)

2. Secondary endpoints
   1) Achievement rate of a platelet count of ≥ 50000/μL at the specified evaluation time point
   2) Achievement rate of a platelet count of ≥ 30000/μL at the specified evaluation time points and platelet count increase at least 20000/μL above baseline (for subjects with a baseline platelet count of < 15000/μL)
   3) Achievement rate of overall response (subjects who achieve a platelet count of ≥ 50000/μL during at least 1 of the 6 visits from Weeks 2 to 12 are considered as a responder and the percentage of responders will be evaluated)
   4) Number of times when a platelet count of ≥ 50000/μL in the 6 visits from Weeks 2 to 12
   5) Number of times when a platelet count of ≥ 50000/μL in the 12 visits from Weeks 2 to 24
   6) Duration of maintained platelet count since first achievement of a platelet count ≥ 50000/μL after administration of the study drug
   7) Percentage of subjects who maintained platelet count for 12 weeks since achievement of a platelet count ≥ 50000/μL within 12 weeks after administration of the study drug in Periods I and II (only for subjects who transition to Period II after being treated with placebo in Period I)
   8) Summary statistics of platelet count
   9) Distribution of platelet count
   10) Individual courses in platelet count
   11) QOL assessment (Short form 36 [SF-36])

3. Safety endpoints
   1) Incidence of adverse events and adverse drug reactions
   2) Laboratory tests (hematology, serum chemistry, and urinalysis)
   3) Immunoglobulin test
   4) ITP Bleeding Score
   5) Eastern Cooperative Oncology Group (ECOG) Performance Status
   6) Vital signs
   7) 12-lead electrocardiogram (ECG)

4. Pharmacokinetic endpoints
   Plasma concentration of R406 (active substance)

Subjects:
Patients with chronic ITP who meet all of the following inclusion criteria and do not meet any of the exclusion criteria are eligible.

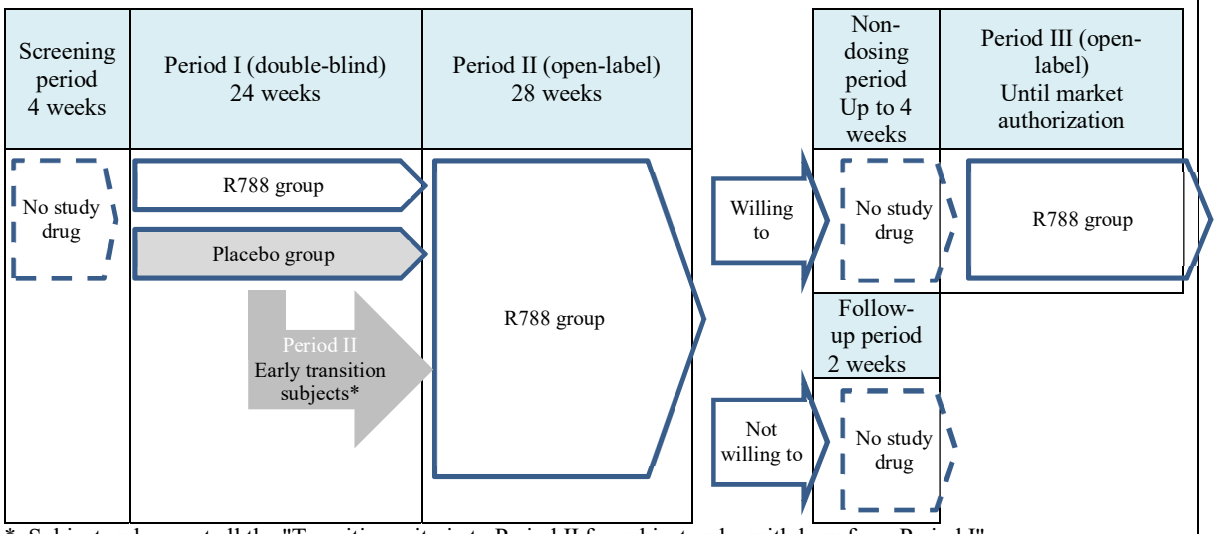
1. Inclusion criteria
   1) Japanese patients (defined as Japanese whose all relatives within the second degree are Japanese) who give written informed consent to participate in the study
   2) Patients at least 20 years of age (at the time of informed consent)
   3) Patients diagnosed with ITP according to the ITP diagnostic criteria (revised in 1990) by the Study Group on Idiopathic Hematopoietic Disorders of the Ministry of Health, Labour and Welfare at least 6 months before acquisition of consent
   4) Patients with a platelet count average of < 30000/μL at Screen A, Screen B, and Day 1. Each platelet count should not exceed 35000/μL.
   5) Patients who have used and failed or who were intolerant at least 1 of the following typical regimen for the treatment of ITP before informed consent
      - Corticosteroids
      - Thrombopoietin (TPO) receptor agonists (eltrombopag olamine or romiplostim)
      - Rituximab
      - Intravenous immunoglobulin
   6) Patients with ECOG performance status of 0 or 1 at Screening A and Day 1
   7) Patients who do not use treatment for ITP or patients whose concurrent treatment may consist of either corticosteroids (equivalent to 10 mg/day prednisolone or less), azathioprine, or danazol. The dose of the concurrent medication must have been stable for at least 2 weeks prior to Day 1 and must be expected to remain stable throughout Period I.
   8) Patients who can discontinue or have already discontinued the following ITP drugs for at least the following periods prior to Day 1, if applicable
      - Cyclosporine or mycophenolate mofetil: 2 weeks
      - Eltrombopag olamine: 2 weeks
      - Romiplostim: 3 weeks
      - Alkylating agent: 8 weeks
      - Rituximab or other anti-CD20 monoclonal antibodies: 24 weeks
   9) Patients who are negative for *H. pylori* or who have completed *H. pylori* eradication therapy

2. Exclusion criteria
   1) Patients with thrombocytopenia associated with other diseases (eg, lymphoma, chronic lymphocytic leukemia, viral infection, autoimmune disease, thyroid disease, human immunodeficiency virus, hepatitis, or myelodysplasia), induced or alloimmune thrombocytopenia, antiphospholipid antibody syndrome, or liver cirrhosis
   2) Patients who are suspected cyclic thrombocytopenia
   3) Patients with autoimmune hemolytic anemia
   4) Patients with a history of or active clinically significant, respiratory, gastrointestinal (pancreatitis), renal, hepatic, neurological, psychiatric, musculoskeletal, genitourinary, dermatological, or other disorders that could affect the conduct of the study or the absorption, distribution, metabolism, or excretion of the study drug
   5) Patients complicated with any major cardiovascular event including but not limited to myocardial infarction, unstable angina, cerebrovascular accident, pulmonary embolism, or New York Heart Association Class III or IV heart failure, or with a history of such events within 6 months prior to Day 1
   6) Patients with systolic blood pressure ≥ 140 mmHg or diastolic blood pressure of ≥ 90 mmHg at Screening A, Screening B, or Day 1 whether or not the subject is receiving anti-hypertensive treatment
   7) Patients with conditions with increased thrombus formation, such as factor V Leiden mutation, active protein C resistance, congenital antithrombin III deficiency, and lupus anticoagulant, or patients complicated with coagulopathy, such as arterial or venous thromboembolism, or history of coagulopathy within 6 months prior to Screening A
   8) Patients who cannot discontinue anticoagulants at least 30 days prior to Screening A because of a history of venous thromboembolism at least 6 months prior to Screening A, or patients with a D-dimer assay result out of the normal range at Screening A in spite of the discontinuance of anticoagulants at least 30 days prior to Screening A

9) Patients with an ITP Bleeding Score of Grade 2 at any site at Screen A or Day 1
10) Patients with 1 or more of the following laboratory abnormalities at Screening A, Screening B, or Day 1:
    - White blood cell count < 2500/μL
    - Neutrophil count < 1500/μL
    - Lymphocyte count < 750/μL
    - Hemoglobin < 10 g/dL
11) Patients with 1 or more of the following laboratory abnormalities at Screening A:
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 × the upper limit of normal (ULN)
    - Total bilirubin > 2.0 mg/dL
    - Estimated glomerular filtration rate (eGFR) < 30 mL/min
12) Patients with significant infection, acute infection such as influenza, or active inflammatory response during the screening period
13) Patients with acute gastrointestinal symptoms (eg, nausea, vomiting, diarrhea, or abdominal pain) during the screening period
14) Patients with increased the dose of, or added, prescription drugs within the 2 weeks prior to Day 1. Except for prescription drugs for which the investigator has determined that the assessment of efficacy and safety of the study drug is not affected.
15) Patients who tested positive or the lower limit of quantitation for at least 1 of the following immunological tests at Screening A
    - Human immunodeficiency virus (HIV) antigen
    - HIV antibodies
    - Hepatitis B surface (HBs) antigen
    - Anti-HBs (excluding HBs antibody monopositive cases due to hepatitis B (HB) vaccination or hepatitis B virus (HBV) DNA levels below the lower limit of quantification)
    - Anti-hepatitis B core (HBc) (unless HBV DNA levels are below the lower limit of quantification)
    - Hepatitis C virus (HCV) RNA quantification
16) Patients who has received any transfusion or blood products between 2 weeks prior to Screening A and Day 1
17) Patients who have used at least 1 of the following drugs during the screening period
    - Platelet transfusion
    - Intravenous immunoglobulin
    - Intravenous methylprednisolone
    - Oral dexamethasone (unless equivalent to 10 mg/day prednisolone or less)
    - Oral prednisolone (unless dosage is 10 mg/day or less)
18) Patients with allergy or sensitivity to any of the components of the study drug
19) Patients who underwent splenectomy within 12 weeks prior to Day 1
20) Patients who has had major surgery within 4 weeks prior to Day 1 or has a surgical wound that is not fully healed.
21) Patients who are scheduled to undergo surgery for whom use of rescue therapy is planned from the time of informed consent to the end of the follow-up period.
22) Patients with malignancy or a history of malignancy within 5 years before obtaining informed consent.
23) Patients with a history of severe drug hypersensitivity.
24) Patients with concomitant or past history of alcoholism.
25) Patients with concomitant or past history of drug abuse (defined as illicit drug use).
26) Patients with psychiatric disorders, such as depression, schizophrenia, or dementia.
27) Pregnant patients, breast-feeding patients, patients who wish to become pregnant during the period from informed consent to 30 days after the last dose of the study drug, or women who are not willing to use appropriate methods of contraception.
28) Patients who have received other study drugs within 12 weeks before acquisition of consent.
29) Other patients whom the investigator judges to be inappropriate for the study.

Study design:
A placebo-controlled, multicenter, randomized, double-blind, parallel-group study (Period I) and a multicenter, open-label study (Periods II and III).

Structure of the study:
1) Screening period
   Screening period is defined as 4 weeks from Screening A to before the administration of the study drug on Day 1.
2) Period I
   Period I is defined as 24 weeks from after the administration of the study drug on Day 1 to Week 24.
3) Period II
   - The day at the beginning of study drug administration in Period II is Week 24 for subjects who complete Period I. Period II is defined as 28 weeks from Weeks 24 to 52.
   - The day at the beginning of study drug administration in Period II is early transition (ET) Day 1 for early transition subjects (subjects who meet all the "Transition criteria to Period II for subjects who withdraw from Period I"). Period II is defined as 28 weeks from ET Day 1 to ET Week 28.
4) Non-dosing period
   Non-dosing period is defined as maximum 4 weeks from Week 52 or ET Week 28 to Day 1 of Period III.
5) Period III
   Period III is defined as the period from Day 1 of Period III to the date of marketing approval of R788.
6) Follow-up period
   - Follow-up period is defined as 2 weeks from Week 52 or ET Week 28 to the tests at the end of the follow-up period for subjects who complete Period II and are not willing to participate in the Non-dosing period and Period III.
   - Follow-up period is defined as 2 weeks from the Withdrawal Visit to the tests at the end of the follow-up period for subjects who withdraw from Period I and do not transition to Period II, those who withdraw from Period II, and those who withdraw from Period III.
   - Follow-up period is defined as the period until 2 weeks after Week 52 or ET Week 28 for subjects who withdraw from the Non-dosing period before ND Week 2.
   - No follow-up period is established for subjects who withdraw from the Non-dosing period at ND Week 2 or later or subjects who continue Period III until the date of marketing approval of R788.



*: Subjects who meet all the "Transition criteria to Period II for subjects who withdraw from Period I"

Figure 1 Structure of Study

Transition:
1) Transition to Period II
   The following subjects transition to Period II.
   - Subjects who completed Period I
   - Early transition subjects (subjects who meet all the "Transition criteria to Period II for subjects who withdraw from Period I")

2) Transition criteria to Period II for subjects who withdraw from Period I
   (1) Subjects who meet any of the following criteria and withdraw from Period I due to "2) Lack of efficacy (inadequate response)" in "Withdrawal criteria (withdrawal in individual subjects)"
   - Subjects with a platelet count of ≥ 15000/μL on Day 1:
     a) Platelet count of < 50000/μL after Week 12 despite the increased dose to 150 mg *bid* for more than 4 weeks.
     b) Platelet count of < 50000/μL after Week 12 because of the inability to increase the dose to 150 mg *bid* due to possible poor tolerability.
   - Subjects with platelet count of < 15000/μL on Day 1:
     a) Platelet count increase of < 20000/μL from Day 1 after Week 12 despite the increased dose to 150 mg *bid* for more than 4 weeks.
     b) Platelet count increase of < 20000/μL from Day 1 after Week 12 because of the inability to increase the dose to 150 mg *bid* due to possible poor tolerability.

   (2) Subjects with systolic blood pressure of < 140 mmHg and diastolic blood pressure of < 90 mmHg on ET Day 1 whether or not the subject is receiving antihypertensive treatment
   (3) Subjects without the following laboratory abnormalities on ET Day 1:
   - White blood cell count < 2000/μL
   - Neutrophil count < 1000/μL
   - Lymphocyte count < 750/μL
   - Hemoglobin < 10 g/dL

   (4) Subjects without the following laboratory abnormalities on the last laboratory test before ET Day 1
   - ALT or AST > 1.5 × ULN
   - Total bilirubin > 1.5 × ULN
   - eGFR < 30 mL/min

   (5) Subjects who do not have significant infection, an acute infection such as influenza, or inflammatory process on ET Day 1.
   (6) Subjects who have not received blood or blood products within the 2 weeks prior to ET Day 1 (intravenous immunoglobulin or platelet transfusion are allowed if used for rescue therapy).
3) Transition to Non-dosing period
   Subjects who provide written informed consent to participate in the Non-dosing period and Period III transition to the Non-dosing period. However, subjects with platelet count of < 50000/μL at Week 52 or at ET Week 28 may skip the Non-dosing period and transition to Period III at the discretion of the investigator.
4) Transition to Period III
   The following subjects transition to Period III.
   - Subjects who completed the Non-dosing period
   - Subjects receiving any rescue therapy during the Non-dosing period
   - Subjects who have platelet count of < 50000/μL during the Non-dosing period and need to transition to Period III before completing the Non-dosing period, as judged by the investigator

Study drugs:

Test drug

1) Product Code: R788
2) International nonproprietary name (INN): fostamatinib
3) Content and dosage formulation:
   R788 100 mg Tablets: orange-colored round film-coated tablets containing 100 mg of fostamatinib per tablet
   R788 150 mg Tablets: orange-colored oval film-coated tablets containing 150 mg of fostamatinib per tablet
4) Storage: Store in a tightly closed container at room temperature.

Control drug

1) Content and dosage formulation:
   R788 100 mg Tablets placebo: orange-colored round film-coated tablets containing 0 mg of fostamatinib per tablet
   R788 150 mg Tablets placebo: orange-colored oval film-coated tablets containing 0 mg of fostamatinib per tablet
   R788 100 mg Tablets cannot be distinguished from R788 100 mg Tablets placebo. R788 150 mg Tablets cannot be distinguished from R788 150 mg Tablets placebo.

2) Storage: Store in a tight container at room temperature.

Dose and administration method:

1) Screening period
   No study drug is administered.
2) Period I
   R788 or the matching placebo is administered orally for 24 weeks. The initial dose should be 100 mg *bid* and the dose should be adjusted during Period I in accordance with "Dosing adjustments." Morning and evening doses should be at least 8 hours apart and should be taken at approximately the same time each day, with or without food during Period I.
3) Period II
   R788 is orally administered for 28 weeks.
   (1) Subjects who completed Period I
   The study drug for Period I is continued until the visit at Week 24 and the study drug for Period II is initiated after the visit at Week 24 (if study drug in Period II is initiated as twice daily, subjects who took the study drug for Period I in the morning on the day of the visit start the study drug for Period II from the evening of the same day). The dose and administration at the start of the study drug for Period II is as follows.
   - If platelet count at Week 24 is ≥ 50000/μL, study drug in Period II is initiated with the last dose and administration in Period I
   - If platelet count at Week 24 is < 50000/μL and last dose and administration in Period I is 150 mg *bid,* study drug in Period II is initiated with 100 mg *bid*
   - If platelet count at Week 24 is < 50000/μL and last dose and administration in Period I is 100 mg *qd*, 150 mg *qd*, or 100 mg *bid,* study drug in Period II is initiated with the last dose and administration in Period I

   (2) Early transition subjects
   The study drug for Period II is initiated after the visit on ET Day 1 (if study drug in Period II is initiated as twice daily, subjects who took the study drug for Period I in the morning on the day of the visit start the study drug for Period II from the evening of the same day). The dose and administration at the start of the study drug for Period II is as follows.
   - If the last dose and administration in Period I is 100 mg *bid* or 150 mg *bid,* study drug in Period II is initiated with 100 mg *bid*
   - If the last dose and administration in Period I is 100 mg *qd* or 150 mg *qd*, study drug in Period II is initiated with the last dose and administration in Period I

   The dose should be adjusted during Period II in accordance with "Dosing adjustments." Morning and evening doses should be at least 8 hours apart and should be taken at approximately the same time each day, with or without food during the Period II.
4) Non-dosing period
   No study drug is administered.
5) Period III
   The study drug is administered orally until market authorization of R788 in Japan. The study drug for Period III is initiated with the last dose and administration of study drug in Period II and is started after the visit on Day 1 of Period III. The dose should be adjusted during Period III in accordance with "Dose adjustments." Morning and evening doses should be at least 8 hours apart and should be taken at approximately the same time each day, with or without food during the Period III.
6) Follow-up period
   No study drug is administered.

Dosing adjustments

1) Dose escalation for subjects not responding
   (1) Period I
   If the platelet count at Week 4 or after is below 50000/μL and the study drug has been well tolerated, the dose of study drug should be increased from 100 mg *bid* to 150 mg *bid* at the discretion of the investigator.
   (2) Period II
   - Subjects who completed Period I:
     If the platelet count after the study drug for Period II is initiated remains below 50000/μL and the

study drug has been well tolerated, the dose of study drug should be increased from 100 mg *bid* to 150 mg *bid* at the discretion of the investigator.

- Early transition subjects:
  If the platelet count at ET Week 4 or after is below 50000/μL and the study drug has been well tolerated, the dose of study drug should be increased from 100 mg *bid* to 150 mg *bid* at the discretion of the investigator.

(3) Period III
If the platelet count is below 50000/μL and the study drug has been well tolerated, the dose of study drug should be increased from 100 mg *bid* to 150 mg *bid* at the discretion of the investigator.

2) Dose adjustment due to adverse events
If the following adverse events or abnormal results of laboratory tests, abnormal findings, and abnormal symptoms associated with adverse events are observed and any of the dose adjustment criteria is met, the dose of the study drug should be adjusted.

- Increases in ALT, AST, or bilirubin
- Neutrophil count decreased
- Onset of diarrhea
- Increase in blood pressure

Additionally, if any other severe or serious adverse events with a potential relationship to the study drug are observed, the dose of the study drug should be adjusted at the discretion of the investigator.

If adverse events or abnormal results of laboratory tests, abnormal findings, and abnormal symptoms associated with adverse events which result in dose reduction of study drug recover, the dose of study drug can be re-escalated by 1 dose level in accordance with Table 1 based on the investigator's decision.
If adverse events or abnormal results of laboratory tests, abnormal findings, and abnormal symptoms associated with adverse events which leads to interruption of study drug recover, the study drug is restarted at 1 lower dose level than that before the interruption. After resuming the study drug, the dose of study drug can be re-escalated by 1 dose level in accordance with Table 1 based on the investigator's decision.

Table 1 Dosing Adjustments

Dose reduction				Dose before dose escalation/reduction	Dose escalation		
Dose level −4	Dose level −3	Dose level −2	Dose level −1		Dose level +1	Dose level +2	Dose level +3
Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*	—	—	—
—	Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*	—	—
—	—	Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*	—
—	—	—	Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*

3) Dose adjustment due to excessive elevation of platelet count
(1) Period I
If excessive platelet count increase is observed, the investigator should respond in accordance with Table 2. The doses/regimens of allowed ITP therapies (corticosteroids, azathioprine, or danazol) should not be changed. If platelet count is above 250000/μL even after the dose of the study drug is adjusted, the dose of allowed ITP therapy is reduced according to "Allowed ITP therapies".

Table 2 Actions Taken with the Study Drug for Excessive Elevation of Platelet Count in Period I

	Action
1) Platelet counts > 250000/μL	• Reduce the dose of the study drug by 1 dose level until the platelet count falls to ≤ 250000/μL. • Monitor platelet count until platelet count falls to < 200000/μL (the frequency of additional measurements will be determined by the investigator). • If the excessive elevation of platelet count is improved, the dose of study

	drug can be re-escalated by 1 dose level based on the investigator's decision.
2) Platelet counts > 150000/μL and ≤ 250000/μL	• Continue the study drug at full dose. • Monitor the platelet count until stable to assure it does not exceed 250000/μL (the frequency of additional measurements will be determined by the investigator).

(2) Periods II and III
If excessive platelet count increase is observed, the investigator should respond in accordance with "Allowed ITP therapies". If platelet count is above 250000/μL even after the dose of allowed ITP therapy is adjusted, reduce the dose of the study drug by 1 dose level until the platelet count falls to ≤ 250000/μL (see Table 1) and measure the platelet count until it falls to < 200000/μL. If the excessive elevation of platelet count is improved, the dose of study drug can be re-escalated by 1 dose level based on the investigator's decision.

Concomitant therapies:

1) Concomitant therapies
Drugs for various symptoms with ITP and drugs used at the start of the screening period for complications should not change the doses/regimens as much as possible until the end of the follow-up period or market authorization. It is acceptable to change the doses/regimens of concomitant medications for safety, such as the occurrence of adverse events.

2) Prohibited concomitant medications
The concomitant use of the medications listed in Table 3 is prohibited from 2 weeks before Day 1 to the end of the follow-up period or market authorization.

Table 3 Prohibited Concomitant Medications

Classification	Principal drugs
1) Strong cytochrome P450 (CYP) 3A4 inhibitors	Itraconazole, indinavir sulfate ethanol adduct, clarithromycin, cobicistat, diltiazem hydrochloride, nelfinavir mesilate, voriconazole, ritonavir containing preparation
2) Study drugs other than R788	Any study drugs other than R788

3) Prohibited ITP concomitant medications
The concomitant use of the medications listed in Table 4 is prohibited from the period specified in "Washout" before Day 1 (Table 8) to the end of the follow-up period or market authorization.

Table 4 Prohibited ITP concomitant medications

Classification	Principal drugs
ITP medications other than the allowed ITP therapies or ITP medications specified as rescue therapies	Cyclosporine, mycophenolate mofetil, eltrombopag olamine, romiplostim, rituximab or other anti CD20 monoclonal antibodies, alkylating agents

4) Restricted medications
Medications listed in Table 5 should be administered with attention to subject safety from 2 weeks before Day 1 to the end of the follow-up period or market authorization.

Table 5 Restricted Medications

Classification	Principal drugs
1) Moderate CYP3A4 inhibitors	Atazanavir sulfate, aprepitant, amiodarone hydrochloride, istradefylline, imatinib mesylate, erythromycin, crizotinib, cyclosporine, ciprofloxacin hydrochloride, cimetidine, tofisopam, fluconazole, fluvoxamine maleate, verapamil hydrochloride, fosamprenavir calcium hydrate, fosfluconazole, miconazole
2) CYP3A4 inducers	Etravirine, efavirenz, enzalutamide, carbamazepine, St. John's wort, nevirapine, barbiturates, phenytoin, bosentan hydrate, mitotane, modafinil, rifabutin, rifampicin, rufinamide
3) P-glycoprotein (P-gp) substrates	Digoxin
4) Hydroxymethylglutaryl (HMG)-CoA reductase inhibitors	Simvastatin, rosuvastatin, atorvastatin, pitavastatin

5) Allowed ITP therapies
(1) Screening period and Period I

Subjects are allowed to use only one of the specific therapies for ITP: corticosteroids (equivalent to 10 mg/day prednisolone or less), azathioprine, or danazol, throughout the screening period and Period I. Dosage of these allowed ITP therapies should not be changed from at least 2 weeks before Day 1 to any of the following visit. Tapering of the allowed ITP therapies will not be permitted, even if platelet count exceeds 50000/μL. New treatments allowed for ITP should not be added from at least 2 weeks before Day 1.

- Withdrawal Visit (subjects who withdraw from Period I and do not transition to Period II)
- ET Day 1 (subjects who withdraw from Period I and transition to Period II)
- Week 24 (except for the above)

However, if platelet count is above 250000/μL even after the dose of the study drug is adjusted in accordance with "Dose adjustment due to excessive elevation of platelet count" (Table 2), reduce the dose of the allowed ITP therapy until the platelet count falls to ≤ 250000/μL and measure the platelet count until it falls to < 200000/μL.

(2) Period II

The same drug as in Period I can be used as ITP therapy in Period II with the same doses/regimens as in Period I. Consideration can be given to tapering the dose of allowed ITP therapy in subjects whose platelet count is stable at ≥ 50000/μL during Period II (including the start of Period II) at the discretion of the investigator. New treatments for ITP should not be added. If excessive platelet count increase is observed during Period II (including the start of Period II), the investigator should respond in accordance with Table 6.

(3) Non-dosing period

The same drug as in Period II can be used as ITP therapy in Non-dosing period with the same doses/regimens as used at the end of Period II. Doses/regimens of these allowed ITP therapies should not be changed until any of the following visit. New treatments for ITP should not be added. If excessive platelet count increase is observed during Non-dosing period, the investigator should respond in accordance with Table 6.

- Period III Day 1 (subjects who transition to Period III)
- Withdrawal Visit (subjects who withdraw from the Non-dosing period)

(4) Period III

The same drug as in Non-dosing period can be used as ITP therapy in Period III with the same doses/regimens as used at the end of Non-dosing period. Consideration can be given to tapering the dose of allowed ITP therapy in subjects whose platelet count is stable at ≥ 50000/μL during Period III (including the start of Period III) at the discretion of the investigator. New treatments for ITP should not be added. If excessive platelet count increase is observed during Period III (including the start of Period III), the investigator should respond in accordance with Table 6.

(5) Follow-up period

Doses/regimens of the allowed ITP therapy at the completion of Period II or at the Withdrawal Visit should not be changed during the follow-up period. New treatments for ITP should not be added. However, if excessive platelet count increase is observed, the investigator should respond in accordance with Table 6.

Table 6 Actions Taken for Allowed ITP Therapy for Excessive Elevation of Platelet Count

	Action
1) Platelet counts > 250000/μL	• Reduce the dose of the allowed ITP therapy. • Monitor platelet count until platelet count falls to < 200000/μL (the frequency of additional measurements will be determined by the investigator). • If the excessive elevation of platelet count is improved, the dose of allowed ITP therapies can be re-escalated based on the investigator's decision.
2) Platelet counts > 150000/μL and ≤ 250000/μL	• Leave the dose of the allowed ITP therapy unchanged. • Monitor the platelet count until stable to assure it does not exceed 250000/μL (the frequency of additional measurements will be determined by the investigator).

6) Rescue therapy

Rescue therapy may be used at the discretion of the investigator from the start of the study drug in Period I to the end of the follow-up period or market authorization for subjects who meet any one or both of the

following conditions.

- Platelet count < 50000/μL and at immediate risk of bleeding or with clinically significant bleeding or wet purpura.
- Platelet count < 50000/μL and requires urgent or emergent surgery.

The drugs listed in Table 7 can be used for rescue therapy. The investigator should determine the dose and administration of rescue therapy with reference to Table 7.

Table 7 Rescue Therapy

Drug	Doses/regimens
Platelet transfusion	10 to 20 units/dose
Intravenous immunoglobulin	400 mg/kg/day for 5 consecutive days
Intravenous methylprednisolone	1 g/day for 3 consecutive days
Oral dexamethasone	Up to 40 mg/day for 1 to 2 days
Oral prednisolone	Up to 1 mg/kg/day for 1 to 3 days

7) Washout

Prior to start of the study drug administration in Period I, the use of all ITP medications except the allowed ITP therapies are prohibited during the specific period as shown in Table 8.

Table 8 Washout Period

Drug	Prohibited period prior to study drug administration
Cyclosporine or mycophenolate mofetil	2 weeks
Eltrombopag olamine	2 weeks
Romiplostim	3 weeks
Alkylating agents	8 weeks
Rituximab or other anti-CD20 monoclonal antibodies	24 weeks

Study assessments/procedures and time points:

See the study schedule table.

Number of subjects

Twenty-four subjects (16 in the Period I R788 group and 8 in the Period I placebo group)

Study Schedule Table for Period I

	Informed consent	Screening period		Period I													Withdrawal	Follow-up period
	—	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	—	The end of follow-up
	—	Screening A	Screening B	Day 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12 [a]	Week 14 [a]	Week 16 [a]	Week 18 [a]	Week 20 [a]	Week 22 [a]	Week 24	—	2 weeks after Withdrawal Visit
Allowance (days)	—	−31 to −25	−17 to −11	1	12 to 18	26 to 32	40 to 46	54 to 60	68 to 74	82 to 88	96 to 102	110 to 116	124 to 130	138 to 144	152 to 158	166 to 172	—	±7
Informed consent	●[b]																	
Inclusion/exclusion	●	●		●														
Demographics		●	●	●														
Registration	First	Second		Third						← Early transition to Period II allowed →								
Study drug dispensed				●[c]	←					●[d]						●		
Study drug compliance					●	●	●	●	●	●	●	●	●	●	●	●	●	
ITP Bleeding Score		●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
ECOG Performance Status		●		●		●		●		●		●		●		●	●	●
Height and weight				●														
12-lead ECG[e]		●														●	●	●
Vital signs		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Hematology		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Serum chemistry		●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Urinalysis		●		●		●		●		●		●		●		●	●	●
D-dimer assay[f]		●																
Prothrombin time-international normalized ratio/activated partial thromboplastin time (PT-INR/APTT)		●		●														
Immunoglobulin test		●		●												●	●	●
Immunological test		●																
Pregnancy test[g]		●								●						●	●	●
Pharmacokinetics (before administration of the study drug)					●[h]		●[h]										●[j]	
Pharmacokinetics (after administration of the study drug)					●[h]	●[i]	●[h]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]		
SF-36[k]				●		●				●						●	●	●
Adverse events	←																	→
Concomitant meds	←																	→

a) If the subject withdraws from Period I and transition to Period II, in principle, the study procedures on ET Day 1 will be performed on the same day as the last visit in Period I. When the study procedures on ET Day 1 are performed on the same day as the last visit for Period I, the procedures overlapping on ET Day 1 with the last visit of Period I may be omitted when the procedures on ET Day 1 are performed. If the procedures on ET Day 1 cannot be performed on the same day as the last visit of Period I, all procedures on ET Day 1 must be performed within 1 week from the last visit of Period I. All procedures on ET Day 1 should be performed on the same day.
b) Written informed consent must be obtained before starting Screening A (before performing any test specified in this study) or washout of ITP drugs, whichever comes earlier.
c) The dose of 100 mg of the study drug is administered at study institutions and this must be the only administration of the study drug on Day 1, irrespective of the time of administration.
d) The need of dispensing the study drug is decided, considering the number of tablets to be taken before the next visit.
e) In principle, the 12-lead ECG is taken before vital signs, laboratory tests, immunoglobulin test, immunological test (Screening A only), pregnancy test (women of childbearing potential only), and pharmacokinetics (only at Week 24 and at the Withdrawal Visit).
f) D-dimer assay is performed if the patient has a history of venous thromboembolism more than 6 months prior to Screening A.
g) Pregnancy testing should be performed for all female subjects of childbearing potential no matter with or without contraception.
h) In principle, the subject should visit the hospital in the morning without administration of the study drug for the morning and blood sample is collected. Study drug is administered at the study site and blood sample is collected again 1 to 4 hours after taking the study drug.
i) In principle, the study drug is administered in the morning 1 to 4 hours before blood sampling and blood sample is collected during morning at the study institution.
j) The time of the last study drug administration before blood sampling to the date of blood sampling are not specified.
k) SF-36 assessment is performed prior to other procedures and assessments. However, when all procedures on ET Day 1 are performed on the same day as the last visit of Period I, SF-36 assessments are performed prior to other procedures and assessments on ET Day 1.

Study Schedule for Period II (for subjects who completed Period I)

	Period I	Period II							Withdrawal	Follow-up period
	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19	Visit 20	Visit 21	Visit 22	—	The end of follow-up
	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52	—	Week 52 or 2 weeks after Withdrawal Visit[a)]
Allowance (days)	166 to 172	190 to 204	218 to 232	246 to 260	274 to 288	302 to 316	330 to 344	358 to 372	—	±7
Informed consent								●[b)]		
Registration	●									
Study drug dispensed	●	●	●	●	●	●	●			
Study drug compliance	●	●	●	●	●	●	●	●	●	
ITP Bleeding Score	●	●	●	●	●	●	●	●	●	●
ECOG Performance Status	●	●	●	●	●	●	●	●	●	●
12-lead ECG[c)]	●							●	●	●
Vital signs	●	●	●	●	●	●	●	●	●	●
Hematology	●	●	●	●	●	●	●	●	●	●
Serum chemistry	●	●	●	●	●	●	●	●	●	●
Urinalysis	●	●			●			●	●	●
Immunoglobulin test	●							●	●	●
Pregnancy test[d)]	●				●			●	●	●
Pharmacokinetics	●[e)]									
SF-36[f)]	●							●	●	●
Adverse events	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷
Concomitant meds	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷

a) The tests at the end of the follow-up period are not performed for subjects who want to participate in the Non-dosing period and Period III and provide written informed consent.
b) Written informed consent is obtained from subjects who want to participate in the Non-dosing period and Period III.
c) In principle, the 12-lead ECG is taken before vital signs, laboratory tests, immunoglobulin test, pregnancy test (women of childbearing potential only), and pharmacokinetics (Week 24 only).
d) Pregnancy testing should be performed for all female subjects of childbearing potential no matter with or without contraception.
e) In principle, study drug is administered in the morning 1 to 4 hours before blood sampling and blood sample is collected during morning at the study institution.
f) SF-36 assessment is performed prior to other procedures and assessments.

Study Schedule for Period II (for early transition subjects)

	Period I	Period II							Withdrawal	Follow-up period
	ET Visit 1	ET Visit 2	ET Visit 3	ET Visit 4	ET Visit 5	ET Visit 6	ET Visit 7	ET Visit 8	—	The end of follow-up
	ET Day 1 [a)]	ET Week 4	ET Week 8	ET Week 12	ET Week 16	ET Week 20	ET Week 24	ET Week 28	—	ET Week 28 or 2 weeks after Withdrawal Visit[b)]
Allowance (days)	1	22 to 36	50 to 64	78 to 92	106 to 120	134 to 148	162 to 176	190 to 204	—	±7
Informed consent								●[c)]		
Inclusion/exclusion	●									
Registration	●									
Study drug dispensed	●	●	●	●	●	●	●			
Study drug compliance	●	●	●	●	●	●	●	●	●	
ITP Bleeding Score	●	●	●	●	●	●	●	●	●	●
ECOG Performance Status	●	●	●	●	●	●	●	●	●	●
12-lead ECG[d)]	●							●	●	●
Vital signs	●	●	●	●	●	●	●	●	●	●
Hematology	●	●	●	●	●	●	●	●	●	●
Serum chemistry	●	●	●	●	●	●	●	●	●	●
Urinalysis	●	●			●			●	●	●
Immunoglobulin test	●							●	●	●
Pregnancy test[e)]	●				●			●	●	●
SF-36[f)]	●							●	●	●
Adverse events	←	—	—	—	—	—	—	—	—	→
Concomitant meds	←	—	—	—	—	—	—	—	—	→

a) If the subject withdraws from Period I and transition to Period II, in principle, the study procedures on ET Day 1 will be performed on the same day as the last visit in Period I. When the study procedures on ET Day 1 are performed on the same day as the last visit for Period I, the procedures overlapping on ET Day 1 with the last visit of Period I may be omitted when the procedures on ET Day 1 are performed. If the procedures on ET Day 1 cannot be performed on the same day as the last visit of Period I, all procedures on ET Day 1 must be performed within 1 week from the last visit of Period I. All procedures are performed on the same day.

b) The tests at the end of the follow-up period are not performed for subjects who want to participate in the Non-dosing period and Period III and provide written informed consent.

c) Written informed consent is obtained from subjects who want to participate in the Non-dosing period and Period III.

d) In principle, the 12-lead ECG is taken before vital signs, laboratory tests, immunoglobulin test, and pregnancy test (women of childbearing potential only).

e) Pregnancy testing should be performed for all female subjects of childbearing potential no matter with or without contraception.

f) SF-36 assessment is performed prior to other procedures and assessments. However, when all procedures on ET Day 1 are performed on the same day as the last visit of Period I, SF-36 assessments are performed prior to other procedures and assessments on ET Day 1.

Study Schedule for Non-dosing Period and Period III

	Period II	Non-dosing period[a)]		Period III	Withdrawal[b)]	Follow-up period
	Visit 22 or ET Visit 8	Non-dosing period Visit 1	Period III Visit 1	Period III Visit 2 to market authorization	—	The end of follow-up
	Week 52 or ET Week 28	Non-dosing period Week 2 [c)]	Period III Day 1 [d)]	From Period III Week 8	—	2 weeks after Withdrawal Visit[e)]
Allowance (days)	1	12 to 18	26 to 32	Period III Every 8 weeks ± 14 from Day 1	—	±7
Informed consent	●[f)]					
Study drug dispensed			●	●		
Study drug compliance	●			●	●	
ITP Bleeding Score	●	●	●	●	●	●
ECOG Performance Status	●	●	●	●	●	●
12-lead ECG[g)]	●	●	●			
Vital signs	●	●	●	●	●	●
Hematology	●	●	●	●	●	●
Serum chemistry	●	●	●	●	●	●
Urinalysis	●	●	●	●	●	●
Immunoglobulin test	●	●	●			
Pregnancy test[h)]	●	●	●	●	●	●
SF-36[i)]	●	●	●			
Adverse events	⟷	⟷	⟷	⟷	⟷	⟷
Concomitant Meds[j)]	⟷	⟷	⟷	⟷	⟷	⟷

a) Subjects with platelet count of < 50000/μL at Week 52 or at ET Week 28 may skip the Non-dosing period and transition to Period III at the discretion of the investigator. The study procedures for Day 1 of Period III are immediately performed irrespective of the allowance of visit for subjects who transition from the Non-dosing period to Period III before completing the Non-dosing period.

b) The tests on the Withdrawal Visit are not performed for subjects who withdraw from the Non-dosing period.

c) The study procedures for ND Week 2 are not performed for subjects who skip the Non-dosing period and transition to Period III, or transition from the Non-dosing period to Period III before performing the study procedures for ND Week 2.

d) When the study procedures on Day 1 of Period III are performed on the same day as those for ND Week 2, the procedures overlapping on Day 1 of Period III with ND Week 2 may be omitted when the procedures on Day 1 of Period III are performed. The study procedures for Day 1 of Period III are omitted for subjects who skip the Non-dosing period and transition to Period III.

e) The tests at the end of the follow-up period are performed at Week 52 or 2 weeks after ET Week 28 for subjects who withdraw from the Non-dosing period before ND Week 2. The tests at the end of the follow-up period are not performed for subjects who withdraw from the Non-dosing period at ND Week 2 or later.

f) Written informed consent is obtained from subjects who want to participate in the Non-dosing period and Period III.

g) In principle, the 12-lead ECG is taken before vital signs, laboratory tests, immunoglobulin test, and pregnancy test (women of childbearing potential only).

h) Pregnancy testing should be performed for all female subjects of childbearing potential no matter with or without contraception.

i) SF-36 assessment is performed prior to other procedures and assessments.

j) Only the use of ITP drugs is checked during Period III or later.

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List of Abbreviations and Terms

Abbreviation or term	Description
AIHA	Autoimmune hemolytic anemia
ATP	Adenosine triphosphate
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from zero (0) hours to infinity (∞)
AUC_{0-t}	Area under the plasma concentration-time curve from zero (0) hours to last quantifiable concentration
AUC_{ss}	Area under the plasma concentration-time curve during any dosing interval at steady state
AUC_{τ}	Area under the plasma concentration-time curve from zero to the end of the dosing interval
BCR	B-cell receptor
^{14}C	Carbon-14 labeled
C_{max}	Maximum plasma concentration
$C_{max, ss}$	Maximum plasma concentration at steady state
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
ECOG	Eastern Cooperative Oncology Group
GCP	Good Clinical Practice
HCG	Human chorionic gonadotropin
H. pylori	*Helicobacter pylori*
ICH	The International Council for Harmonization of Technical Requirements for Pharmaceuticals for human use
ITP	Idiopathic thrombocytopenic purpura
LC-MS/MS	Liquid chromatography-tandem mass spectrometer
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
P-gp	P-glycoprotein
PT-INT/APTT	Prothrombin time-international normalized ratio/activated partial thromboplastin time
PT	Preferred term
RA	Rheumatoid arthritis
Rac	Accumulation ratio
SF-36	Short form 36
SOC	System organ class
SYK	Spleen tyrosine kinase
TPO	Thrombopoietin
$t_{1/2}$	Terminal elimination half-life
$t_{1/2, ss}$	Terminal elimination half-life at steady state
t_{max}	Time to reach maximum plasma concentration
$t_{max, ss}$	Time to reach maximum plasma concentration at steady state
UGT	UDP-glucuronosyltransferase

1. History and Background of Study Plan

1.1 Idiopathic Thrombocytopenic Purpura

ITP is an autoimmune disorder characterized by the development of antibodies to platelet membrane proteins and binding of them to platelets or megakaryocyte, which enhances platelet destruction in reticuloendothelial cells in the spleen and suppresses platelet production in bone marrow, thereby causing thrombocytopenia.[1)] Although patients with ITP develop thrombocytopenia, they often have normal or increased numbers of megakaryocytes, which are the precursors cells of platelets in the bone marrow.[1)] Therefore, ITP is thought to be the main condition in which thrombocytopenia results from increased destruction of platelets rather than inhibition of platelet production, but the etiology of ITP remains unknown and the mechanism of antibody production has not been determined.[1)]

The clinical symptom of ITP show various hemorrhagic manifestations on the skin and mucous membrane mainly as the purpura.[2)] A platelet count of < 10000/μL is associated with an increased risk of serious bleeding episodes.[2)] Severe mucosal bleeding may be fatal because it may lead to gastrointestinal bleeding or intracranial hemorrhage.[3)] In Japan, ITP has been specified as a designated intractable disease by the "Act on Medical Care for Patients with Intractable Diseases" (Act No. 50, 2014). The health administration report from the Ministry of Health, Labour and Welfare in 2017 showed that there were 17618 patients who had a certificate for receiving specific medical expenses (for the designated intractable disease).[4)] The annual incidence of newly diagnosed patients in Japan was reported to be 2.4 per 100000 people.[2)]

1.2 Treatment of ITP

Based on the scientific verification by accumulated therapeutic experience of ITP and long-term follow-up of its clinical course, not all thrombocytopenia in patients with ITP needs to be treated, and this therapeutic concept is getting consensus internationally.[5)] It is revealed that platelet count recovered spontaneously in 5% to 10% of untreated patients with ITP, and that ITP patients with a platelet count of ≥ 30000/μL were not greatly different from the general population in life prognosis. It has been shown that the non-treatment follow-up is not necessarily a negative factor for ITP patients with a platelet count of ≥ 30000/μL from the perspective of long-term prognosis considering both death by ITP-induced hemorrhage and death by adverse drug reactions.[5)] Based on this view, the therapeutic goal for ITP is not to restore platelet count to a normal level, but to maintain platelet count at a level at which serious bleeding can be prevented (platelet count ≥ 30000/μL, or ≥ 50000/μL if possible).[6)]

The Japanese ITP treatment reference guide in 2012[5)] recommends that, after definite diagnosis is made, patients with ITP should be subjected to the examination for *Helicobacter pylori* (*H. pylori*) infection, and that positive patients should be treated with eradication therapy. Drug therapy is initiated to patients at risk of bleeding who had no platelet response to eradication therapy or who are negative for *H. pylori* infection. As the first line therapy, corticosteroids are used to suppress an excessive immune response and prevent peripheral platelet destruction. A splenectomy is considered as the second-line therapy to prevent platelet destruction as with corticosteroids in patients responding poorly to the first-line therapy or in patients who cannot tolerate the first-line therapy. In addition to immunosuppressive agents such as azathioprine and rituximab, TPO receptor agonists that stimulate platelet production in the bone marrow are widely used as the third line treatment.

The first-line corticosteroid therapy has increased platelet count to ≥ 30000/μL in approximately 80% of patients and to ≥ 100000/μL in approximately 50% of them.[5)] However, corticosteroids need dose reduction because their long-term use may cause adverse drug reactions. Therefore, ITP often recurs during dose reduction even in responders. Splenectomy is considered when the maintenance dose of steroids is high.[3),5)]

The second-line splenectomy provides platelet responses for approximately 80% of patients who received it. However, because of the recurrence in approximately 20% of them, approximately 60% have permanent platelet response.[5)] Although splenectomy is a highly effective treatment, earlier studies have reported postoperative complications, such as portal vein thrombosis, reduced protection against *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* by splenectomy, risk of serious post-splenectomy infection,[5)] and increased frequency of sepsis and thrombosis.[7)] Splenectomy was performed in approximately 0.7% (715) of ITP patients requiring treatment in 10 years from 2005 to 2014. The rate of patients undergoing splenectomy has shown a gradually decrease in recent years.[7)]

As third-line TPO receptor agonists, romiplostim (Romiplate® Subcutaneous Injection), which is an injection preparation, and eltrombopag olamine (Revolade® Tablets), which is an oral preparation, have been used in Japan. TPO receptor agonists bind to TPO receptors, which are factors stimulating megakaryocyte growth and platelet production, to accelerate megakaryocytic maturation, thereby stimulating platelet production. Although they have an effect to increase platelets in patients with refractory chronic ITP, they have been reported to result in treatment discontinuance by adverse events in approximately one third of patients[8)] and eventually lead to the loss of therapeutic effect in approximately 30% of responders.[9)] Furthermore, it was reported that, given their mechanism of action, they cannot cure ITP and require long-term use as symptomatic therapy, and that they caused adverse drug reactions, including increased reticulin fibers in the bone marrow, serious thrombosis, and reduction in platelet count below the baseline level, leading to exacerbated bleeding tendency after discontinuation.[5)]

Rituximab, an anti-CD 20 monoclonal antibody, was approved for insurance coverage for chronic ITP in June 2017 in response to the requests for approval of unapproved and off-label drugs with high medical need. In the Japanese clinical study of rituximab, the percentage of patients achieving the primary endpoint of a platelet count at Week 24 of ≥ 50000/μL was 30.8% (two-sided 95% confidence interval, 14.3% to 51.8%). Although it was lower than the predetermined threshold (20%, lower limit of the 95% confidence interval), it shows that the drug has a certain level of efficacy.[10)] The mean duration of response to rituximab is 10.5 months, showing a long-term sustained effect, but relapse has been reported to occur in 10.5% of patients.[5)] The investigation of the safety of rituximab has reported that it reactivated the hepatitis B virus and only infrequently caused progressive multifocal leukoencephalopathy, and it is therefore recommended that the drug be used carefully.[11)]

In summary, in the early phase of ITP treatment, the administration of high-dose corticosteroids and splenectomy have been performed to suppress the destruction of platelets in the periphery, and rituximab or TPO receptor agonists and others have been used in patients with insufficient response. However, based on the abundant evidence on efficacy, TPO receptor agonists are now widely used to promote platelet production. Under these circumstances, a new drug that inhibits the increased destruction of platelets, the main pathology of ITP, and is positioned as a radical therapy is expected.

1.3 Development History of R788

R788 (nonproprietary name: fostamatinib) is a prodrug product of an orally available small-molecule tyrosine kinase inhibitor developed by Rigel Pharmaceuticals, Inc. (hereinafter referred to as Rigel) in the United States. R788 is metabolized to its active substance, R406, through the cleavage of the phosphate group by alkaline phosphatase in the apical brush border membrane of gastrointestinal cells. R406 inhibits splenic tyrosine kinase (SYK), one of the tyrosine kinases involved in Fcγ receptor activation and B-cell receptor signaling, thereby inhibiting platelet phagocytosis and destruction by macrophages. The effect of R406 on B cells may also inhibit antiplatelet antibody production.

For the overseas development of R788, Rigel obtained the approval for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment in April 2018 and launched it in May 2018 in the United States. In Europe, the application for marketing approval for the same indication was received in October 2018 and approval review is ongoing. Rigel is currently developing the product for the indication of autoimmune hemolytic anemia (AIHA) in Europe and the United States. In addition, R788 was designated as an orphan drug for ITP in 2015 and for AIHA in 2018 in the United States.

Outside of Japan, 28 Phase I clinical studies (including 2 studies in Japanese patients), 1 Phase II clinical study in ITP patients, and 3 Phase III clinical studies in ITP patients have been conducted. In addition to these clinical studies, R788 was once developed for indications other than ITP and AIHA. The safety data from at least 4600 patients are available, including Japanese patients with rheumatoid arthritis (RA).

This study is planned to investigate the efficacy, safety, and pharmacokinetics of the oral administration of R788 for 24 weeks and the safety and efficacy of the long-term administration of R788 in Japanese patients with chronic ITP.

1.3.1 Nonclinical studies

1.3.1.1 Primary pharmacodynamics

The key aspects of the pharmacology are summarized below.

- R406 inhibited Fcε receptor-dependent human mast cell degranulation and release of lipid and cytokine mediators of inflammation.
- R406 showed a reversible adenosine triphosphate (ATP) competitive inhibition of SYK.
- R406 specifically inhibited phosphorylation of of the SYK substrate linker of activated T-cells and downstream molecules of SYK activity.
- R406 inhibited Fcγ receptor-dependent human mast cell, macrophage, and neutrophil responses.
- R406 inhibited B-cell receptor (BCR) mediated responses in primary human B cells.
- R788 treatment mitigated clearance of platelets and red blood cells in murine models of immune autoantibody-mediated thrombocytopenia and AIHA.

1.3.1.2 Secondary pharmacodynamics

R406 was highly selective in biochemical assays of 326 molecular targets across various

enzymes, receptors, and transporters. The most potent activity was as an antagonist of human adenosine A3 receptors. R406 was profiled in broad kinase panels utilizing different biochemical assays indicating a range of potential activities, some of which have been confirmed or identified by relevant cell-based assays. Using cell-based assays, R406 inhibits the kinase activity of RET proto-oncogene, vascular endothelial growth factor receptor-2, FMS-related tyrosine kinase 3, Janus kinase 1/3, and KIT proto-oncogene receptor tyrosine kinase within 5-fold of R406 activity against the SYK assay.

1.3.1.3 Safety pharmacology

R406 was well tolerated in safety pharmacology studies (considering the central nervous system [CNS], respiratory system, and cardiovascular system). Mild behavioral abnormality (e.g., hypoactivity) were observed at 50 mg/kg of R406 in the rat CNS study, and a slight reduction in heart rate at 50 mg/kg and a trend towards increased blood pressure were observed at 50 mg/kg in the monkey cardiovascular study. Data from anesthetized rat studies suggested that R788-induced increase in blood pressure elevation from increased vascular resistance. Data from other investigative studies suggested that impaired vasorelaxation due to inhibition of vascular endothelial growth factor-induced endothelial nitric oxide release may contribute to this effect. In conscious telemetered rats, there was a direct relationship between plasma concentrations of R406 and increased blood pressure. Increased blood pressure persisted throughout the 28-day treatment period and blood pressure returned to the baseline level after treatment discontinuation. Increased blood pressure was resolved with standard antihypertensive drugs including nifedipine (calcium antagonist), atenolol (β-blocker), and captopril (angiotensin-converting enzyme inhibitor).

1.3.1.4 Pharmacokinetics

1) Absorption

   The results from *in vivo* pharmacokinetic studies showed that there is negligible systemic or portal exposure to R788 following oral administration. *In vivo* conversion of R788 to R406 is rapid, extensive and most likely to be catalyzed by intestinal alkaline phosphatases. R406 bioavailability from R788 dosing ranged from approximately 40 to 80% in various species. Consistent with the high bioavailability, approximately 73% of the radioactivity was recovered in urine and bile following oral ^{14}C-R788 dosing to monkeys. Oral absolute bioavailability for R788 in humans was 55%.

2) Distribution

   R406 was highly bound to plasma proteins in mice (98.6%), rats (97.9%), rabbits (99.5%), monkeys (98.5%), and humans (98.3%). ^{14}C-R406 had a mean binding to purified human serum albumin of 96.3% over the concentration range of 100 to 4000 ng/mL. It showed a mean binding to purified alpha 1-acid glycoprotein of 75.5% over the same concentration range. In *in vitro* studies, ^{14}C-R406 was distributed preferentially into not monocytes but red blood cells (2.6-fold). The volume of distribution of R406 was approximately 0.3 to 1.2 L/kg in all the animal species, suggesting extravascular distribution of R406. A quantitative whole body autoradiography study in rats showed that, with the exception of the CNS, drug-derived radioactivity was widely distributed to tissues of pigmented and albino rats 4 hours after oral dosing of 20 mg/kg of ^{14}C-R788. For most tissues, the maximum concentrations were observed at 1 hour post-dose. Radioactivity levels in the

majority of tissues were below the quantitation limit at 24 hours; however, the eyes (uveal tract), the liver, and the contents of the small intestine had low levels of radioactivity at 168 hours post-dose.

3) Metabolism

Purified bovine alkaline phosphatase and human intestinal microsomes rapidly converted R788 to R406. The major metabolite formed in hepatic microsomes from humans and all animal species was para-*O*-demethylated R406 (R529). CYP3A4 was identified as the human CYP450 isoform primarily involved in this biotransformation. Direct N-glucuronidation of R406, primarily mediated by UDP-glucuronosyltransferase (UGT) 1A9 in humans, was also observed *in vitro*. The major metabolites in plasma from all species were glucuronide and sulfate conjugates of R529.

4) Excretion

Clearance of R406 averaged 16.9, 13.4, 73.5, and 1.99 mL/min/kg in rats, monkeys, mice, and rabbits, respectively, and the terminal half-life averaged 1.51, 3.09, 0.58, and 3.41 hours, respectively. Mass balance studies were performed in rats using ^{14}C-R406 and in mice, monkeys, rabbits, and humans with ^{14}C-R788. In all species, fecal elimination of drug-related material was the primary route of excretion (80% to 84% of the dose). Urinary excretion was highest in humans (19.3% of the dose) and ranged from 3% to 10% of the dose in all other species.

1.3.1.5 Toxicology

Toxicology studies in rats and monkeys (doses: ≤ 100 mg/kg/day of R788) for 4 to 26 weeks and 4 to 39 weeks, respectively, identified lymphohematopoietic and liver function test abnormalities (mild and fully reversible), and reproductive and/or developmental liabilities in rats and rabbits. Consistent with bone growth plate effects in rats in the general toxicity study, similar findings were observed in the carcinogenicity studies in rat and mouse and the 1-month juvenile study in rabbits (doses: 12.5 to 50 mg/kg/day). A related finding of odontodysplasia was also observed in the rat 2-year carcinogenicity study. There were no adverse effects on any male reproductive parameters in rats at doses up to 40 mg/kg/day.

There was no evidence for mutagenic or clastogenic effects in genotoxicity studies, nor carcinogenic potential in mouse and rat carcinogenicity studies. R788 promoted no remarkable adverse effects on host response in murine immunological host resistance models (*Streptococcus*, *Listeria*, and Influenza viruses).

1.3.2 Clinical studies

Outside of Japan, 28 Phase I clinical studies (including 2 studies for Japanese), 1 Phase II clinical study in ITP patients, and 3 Phase III clinical studies in ITP patients have been conducted. In addition to these clinical studies, clinical studies for indications other than ITP, such as AIHA and RA, have been conducted.

1.3.2.1 Phase I study in healthy White and Japanese subjects after single and multiple ascending doses (D4300-007)

The pharmacokinetics and safety of R788 (parent compound) and R406 (major active metabolite) were evaluated in 12 healthy White subjects with R788 150 mg, each 6 healthy

Japanese subjects with R788 50, 100, or 200 mg, and 12 healthy Japanese subjects with R788 150 mg, respectively, administered orally in a single dose in a fasted state (Day 1 of the study drug administration), followed by repeated oral administration in a fasted state for 7 days (Day 2–3 of the study drug administration: untreated, Day 4–9 of the study drug administration: *bid* [50, 100, and 200 mg groups] or *qd* [150 mg group], and Day 10 of the study drug administration: *qd*). Two subjects (50, 100, and 200 mg groups) or four subjects (150 mg group) in each treatment group received placebo. There were no major differences in the pharmacokinetics of R406 between Japanese and White subjects, and the pharmacokinetics in Japanese and White subjects were considered similar.

Table 1.3.2.1-1 Plasma Pharmacokinetic Parameters of R406 (Single Dose)

Treatment group	C_{max} (ng/mL)	t_{max} a) (hr)	$AUC_{0-\infty}$ (ng·hr/mL)	AUC_{0-t} (ng·hr/mL)	AUC_{τ} b) (ng·hr/mL)	$t_{1/2}$ (hr)
50 mg Japanese	163 (36.5)	3 (1, 4)	2170 (14.9)	2090 (15.7)	1080 (29.8)	15.2 (22.2)
100 mg Japanese	338 (39.8)	3 (1.5, 6)	4150 (33)	3960 (30.4)	2080 (24.9)	15.9 (40.3)
150 mg Japanese	626 (39)	1.5 (1, 4)	5870 (27.6)	5730 (27.1)	4500 (31.6)	12.6 (34.9)
150 mg White	431 (47.7)	1.5 (0.5, 4)	4620 (32.8)	4480 (32.9)	3400 (34.1)	12.7 (42.8)
200 mg Japanese	395 (38.8)	1.5 (1, 4)	4430 c) (32.1)	4300 c) (32.8)	2260 (44.9)	14.8 c) (9.56)

Data show the geometric mean (geometric CV%) of 6 subjects (50, 100, and 200 mg) or 12 subjects (150 mg).
a) Median (min, max), b) AUC_{0-12} (*bid*) or AUC_{0-24} (*qd*), c) 5 subjects

Table 1.3.2.1-2 Plasma Pharmacokinetic Parameters of R406 (7-day Repeated Dose, Steady State)

Treatment group	$C_{max, ss}$ (ng/mL)	$t_{max, ss}$ a) (hr)	AUC_{0-t} (ng· hr/mL)	AUC_{ss} (ng· hr/mL)	$t_{1/2, ss}$ (hr)	$Rac_{(Cmax)}$ b)	$Rac_{(AUC)}$ c)
50 mg Japanese	340 (16.7)	2 (1.5, 4)	4900 (16.9)	2570 (12.5)	16.5 (19.8)	2.09 (38)	2.39 (35.4)
100 mg Japanese	615 (31.1)	2 (1.5, 4)	8930 (44.8)	4610 (31)	16 (35.1)	1.82 (36.7)	2.22 (18.1)
150 mg Japanese	643 (37)	4 (1, 6)	7480 (34.7)	5900 (33.5)	14.3 (30.6)	1.01 (38.4)	1.26 (25.3)
150 mg White	520 (45.2)	2 (1, 4)	6670 (46.8)	4980 (37.9)	12.7 (45.4)	1.21 (59.4)	1.46 (39.6)
200 mg Japanese	1730 (20.4)	1.5 (1, 4)	26500 (33.5)	14100 (19.4)	12.3 (17.5)	4.51 (48.9)	6.55 (52.1)

Data show the geometric means (geometric CV%) of 5 subjects (200 mg), 6 subjects (50 and 100 mg), 11 subjects (150 mg, Japanese), or 12 subjects (150 mg, White).
a) Median (min, max), b) $Rac_{(Cmax)}$ ($C_{max, ss}$ of 7-day repeated dose /C_{max} of single dose), c) $Rac_{(AUC)}$ (AUC_{ss} over 7-day repeated dose /AUC_{τ} of single dose)

There were no serious adverse events or withdrawals due to adverse events. No major differences in incidence of adverse events or adverse drug reactions were observed between Japanese and White subjects.

1.3.2.2 Overseas Phase III clinical studies (C788-047 and C788-048 studies) and overseas long-term extension study (C788-049 study) in patients with ITP

The overseas Phase III clinical studies in patients with ITP included 2 double-blind, randomized, placebo-controlled studies (C788-047 and C788-048 studies) and 1 open-label, long-term extension study (C788-049 study) in patients with persistent/chronic ITP were conducted. The C788-047 and C788-048 studies were identically designed clinical studies to evaluate the efficacy and safety of R788 administered for 24 weeks as compared to placebo in patients with persistent/chronic ITP. Subjects who discontinued the study after Week 12 based on the platelet count criteria were able to enter the C788-049 study (when the baseline platelet count was < 15000/μL), as with the subjects who completed 24 weeks of treatment in the C788-047 or C788-048 study.

The analysis of the primary efficacy endpoint of the C788-047 and C788-048 studies showed that the achievement rate of stable platelet response in subjects treated with R788 (18%) was consistent between the studies. The difference from the placebo group was statistically significant in the C788-047 study, while no significant difference was observed in the C788-048 study in which there was one responder in the placebo group.

In the C788-049 study, the achievement rate of stable response in subjects randomized to placebo in the C788-047 or C788-048 study was compared with the achievement rate of stable response in these patients after the treatment with R788 (predetermined within-subject and between-study comparison). The stable response was met when the platelet count was increased to ≥ 50000/μL within 12 weeks after the start of treatment and increased platelet count was maintained for the subsequent 12 weeks. A total of 44 subjects who were randomized to the placebo group enrolled to the C788-049 study; one subject was a responder in the C788-048 study and the other 43 were non-responders. One subject met the criteria for stable response during the treatment with placebo in the C788-048 study, while 10 of these 44 subjects (22.7%) met the criteria for stable response in the C788-049 study, indicating a consistent response rate as compared to the subjects treated with R788 in the C788-047 and C788-048 studies.

1.4 Summary of Expected Adverse Drug Reactions and Benefits

1.4.1 Expected adverse drug reactions

The integrated safety analysis of 2 overseas Phase III clinical studies (C788-047 and C788-048 studies) in 150 patients with persistent/chronic ITP (102 in the R788 group and 48 in the placebo group) showed that adverse events occurred in 83.3% (85/102) of the R788 group and 75.0% (36/48) of the placebo group. Common adverse events with an incidence of ≥ 5% in the R788 group included diarrhea, hypertension, and nausea (Table 1.4.1-1).

Treatment-related adverse events occurred in 58.8% (60/102) of the R788 group and 27.1% (13/48) of the placebo group. Common treatment-related adverse events with an incidence of ≥ 5% in the R788 group included diarrhea in 26.5% (27/102), hypertension in 15.7% (16/102), nausea in 14.7% (15/102), ALT increased in 9.8% (10/102), dizziness in 8.8% (9/102), and AST increased in 6.7% (7/102).

Serious adverse events occurred in 12.7% (13/102) in the R788 group and 20.8% (10/102) in the placebo group. Treatment-related serious adverse event occurred in 3.9% (4/102) in the R788 group (febrile neutropenia, diarrhea, pneumonia, and hypertensive crisis) and 2.1% (1/48)

in the placebo group (menorrhagia). Serious bleeding-related adverse events were reported in 4.9% (5/102) in the R788 group and 10.4% (5/48) in the placebo group.

The integrated safety analysis of the C788-047, C788-048, and C788-049 studies showed that the occurrence of adverse events was comparable between the C788-047 and C788-048 studies and C788-049 study, and that there were no new safety-related trends during extended treatment.

Table 1.4.1-1 Incidence of Common Adverse Events (≥ 5%) in C788-047 and C788-048 Studies

	R788 (N = 102)				Placebo (N = 48)			
Adverse events	Mild %	Moderate %	Severe %	Total %	Mild %	Moderate %	Severe %	Total %
Diarrhea[a)]	21	10	1	31	13	2	0	15
Hypertension[b)]	17	9	2	28	10	0	2	13
Nausea	16	3	0	19	8	0	0	8
Dizziness	8	2	1	11	6	2	0	8
ALT increased	5	6	0	11	0	0	0	0
AST increased	5	4	0	9	0	0	0	0
Respiratory infection[c)]	7	4	0	11	6	0	0	6
Rash[d)]	8	1	0	9	2	0	0	2
Abdominal pain[e)]	5	1	0	6	2	0	0	2
Fatigue	4	2	0	6	0	2	0	2
Chest pain	2	3	1	6	2	0	0	2
Neutropenia[f)]	3	2	1	6	0	0	0	0

a) Includes diarrhea and frequent bowel movements.
b) Includes hypertension, blood pressure increased, diastolic blood pressure abnormal, and diastolic blood pressure increased.
c) Includes upper respiratory tract infection, respiratory tract infection, lower respiratory tract infection, and viral upper respiratory tract infection.
d) Includes rash, rash erythematous and rash macular.
e) Includes abdominal pain and abdominal pain upper.
f) Includes neutropenia and neutrophil count decreased.

1.4.2 Expected benefits

The efficacy of R788 including increased platelet count was confirmed in the overseas Phase III clinical studies in patients with persistent/chronic ITP (C788-047 and C788-048 studies). R788 is expected to increase platelet count in patients with chronic ITP in this study.

2. Title of Study and Study Phase

2.1 Title of Study

A Phase III Study in Patients with Chronic Idiopathic Thrombocytopenic Purpura in R788

2.2 Study Phase

Phase III

3. Objective

3.1 Primary Objective

To investigate the increase in platelet count in patients with chronic ITP after oral administration of R788 for 24 weeks in a placebo-controlled, double-blind manner (Period I).

3.2 Secondary Objectives

1) To evaluate the efficacy of R788 in patients with chronic ITP for the following points:
    - Maintenance of platelet count during long-term treatment with R788
    - Increase in platelet count during Period II for patients who received placebo in Period I
    - Improving of QOL
2) To investigate the safety of R788 in patients with chronic ITP
3) To investigate the pharmacokinetics of R788 in patients with chronic ITP (Period I).

3.3 Exploratory Objective

To investigate the time course of platelet count in patients with chronic ITP during interruption of R788 (Non-dosing period)

4. Endpoints

4.1 Efficacy Endpoints

4.1.1 Efficacy endpoints

4.1.1.1 Primary endpoint

Achievement rate of stable platelet response (subjects who achieve a platelet count of ≥ 50000/μL on at least 4 of the 6 visits from Weeks 14 to 24 are considered as a responder and the percentage of responders will be evaluated)

4.1.1.2 Secondary efficacy endpoints

1) Achievement rate of a platelet count of ≥ 50000/μL at the specified evaluation time point
2) Achievement rate of a platelet count of ≥ 30000/μL at the specified evaluation time points and platelet count increase at least 20000/μL above baseline (for subjects with a baseline platelet count of < 15000/μL)
3) Achievement rate of overall response (subjects who achieve a platelet count of ≥ 50000/μL during at least 1 of the 6 visits from Weeks 2 to 12 are considered as a responder and the percentage of responders will be evaluated)
4) Number of times when a platelet count of ≥ 50000/μL in the 6 visits from Weeks 2 to 12
5) Number of times when a platelet count of ≥ 50000/μL in the 12 visits from Weeks 2 to 24

6) Duration of maintained platelet count since first achievement of a platelet count ≥ 50000/μL after administration of the study drug

7) Percentage of subjects who maintained platelet count for 12 weeks since achievement of a platelet count ≥ 50000/μL within 12 weeks after administration of the study drug in Periods I and II (only for subjects who transition to Period II after being treated with placebo in Period I)

8) Summary statistics of platelet count

9) Distribution of platelet count

10) Individual courses in platelet count

11) QOL assessment (SF-36)

4.1.2 Rationale for efficacy endpoints

1) Primary endpoint

The achievement rate of stable platelet response was the primary endpoint used in the overseas Phase III clinical studies (C788-047 and C788-048 studies). The primary endpoint in the overseas Phase III clinical studies was set to allow the evaluation of the persistence of efficacy and ensure the feasibility of visits by subjects, with reference to the endpoints used for clinical studies of TPO receptor agonists. The endpoint was set by considering the background of the endpoint in the overseas Phase III clinical studies and comparing Japanese and non-Japanese clinical study results.

2) Secondary efficacy endpoints

The endpoints of 1), 2), and 6) to 11) were set to allow the comparison of Japanese and non-Japanese clinical study results because they were evaluated in the overseas Phase III clinical studies (C788-047 and C788-048 studies) or the overseas long-term extension study (C788-049 study). The endpoint of 3) was set as a clinically significant evaluation indicator for evaluating the effect to increase platelet count during the early treatment stage (Weeks 2 to 12) because it was evaluated in the analysis after unblinding in the overseas Phase III clinical studies (C788-047 and C788-048 studies) and correlated with the reduced incidence of bleeding-related adverse events and reduced use of rescue therapy.[12)] The endpoints of 4) and 5) were set as secondary endpoints to evaluate the frequency of the effect to increase platelet count during the early treatment stage and Period I, respectively.

4.2 Safety Endpoints

4.2.1 Safety endpoints

1) Incidence of adverse events and adverse drug reactions

2) Laboratory tests (hematology, serum chemistry, and urinalysis)

3) Immunoglobulin test

4) ITP Bleeding Score

5) ECOG Performance Status

6) Vital signs
7) 12-lead ECG

4.2.2 Rationale for safety endpoints

In addition to general safety endpoints, an immunoglobulin test was set, considering the action mechanism of R788. The ITP Bleeding Score was also set as a safety endpoint, considering the characteristics of the target disease.

4.3 Pharmacokinetic endpoint

4.3.1 Pharmacokinetic endpoint

Plasma concentration of R406 (active substance)

4.3.2 Rationale for pharmacokinetic endpoint

The pharmacokinetic endpoint was set to evaluate pharmacokinetics and the relationship between pharmacokinetics and efficacy or safety during the extended treatment with R788 in Japanese patients with chronic ITP.

5. Subjects

Patients with chronic ITP who meet all the following inclusion criteria and do not meet any of the exclusion criteria are eligible.

5.1 Inclusion Criteria

5.1.1 Inclusion criteria

1) Japanese patients (defined as Japanese whose all relatives within the second degree are Japanese) who give written informed consent to participate in the study
2) Patients at least 20 years of age (at the time of informed consent)
3) Patients diagnosed with ITP according to the ITP diagnostic criteria (revised in 1990)[1)] by the Study Group on Idiopathic Hematopoietic Disorders of the Ministry of Health, Labour and Welfare at least 6 months before acquisition of consent
4) Patients with a platelet count average of < 30000/μL at Screen A, Screen B, and Day 1. Each platelet count should not exceed 35000/μL.
5) Patients who have used and failed or who were intolerant at least 1 of the following typical regimen for the treatment of ITP before informed consent
    - Corticosteroids
    - TPO receptor agonists (eltrombopag olamine or romiplostim)
    - Rituximab
    - Intravenous immunoglobulin
6) Patients with ECOG performance status of 0 or 1 at Screening A and Day 1

7) Patients who do not use treatment for ITP or patients whose concurrent treatment may consist of either corticosteroids (equivalent to 10 mg/day prednisolone or less), azathioprine, or danazol. The dose of the concurrent medication must have been stable for at least 2 weeks prior to Day 1 and must be expected to remain stable throughout Period I.

8) Patients who can discontinue or have already discontinued the following ITP drugs for at least the following periods prior to Day 1, if applicable

- Cyclosporine or mycophenolate mofetil: 2 weeks
- Eltrombopag olamine: 2 weeks
- Romiplostim: 3 weeks
- Alkylating agent: 8 weeks
- Rituximab or other anti-CD20 monoclonal antibodies: 24 weeks

9) Patients who are negative for *H. pylori* or who have completed *H. pylori* eradication therapy

5.1.2 Rationale for inclusion criteria

1) This criterion was set according to the ethical principles based on the Declaration of Helsinki and Good Clinical Practice (GCP).

2) This criterion was set to specify the age at which the informed consent of the subject alone was legally valid.

3) This criterion was set to include patients with chronic ITP.

4) This criterion was set with reference to the treatment goal in the "Reference Guide for Management of Adult Idiopathic Thrombocytopenic Purpura (ITP) 2012 Version."

5) This criterion was set to include patients who did not respond adequately to standard ITP drugs or for whom standard ITP drugs were not considered tolerated.

6) This criterion was set to ensure the safety of subjects.

7), 8) These criteria were set to appropriately evaluate the efficacy of R788.

9) This criterion was set with reference to the "Flow of Adult ITP Treatment" in the "Reference Guide for Management of Adult Idiopathic Thrombocytopenic Purpura (ITP) 2012 Version."

5.2 Exclusion Criteria

5.2.1 Exclusion criteria

1) Patients with thrombocytopenia associated with other diseases (eg, lymphoma, chronic lymphocytic leukemia, viral infection, autoimmune disease, thyroid disease, human immunodeficiency virus, hepatitis, or myelodysplasia), induced or alloimmune thrombocytopenia, antiphospholipid antibody syndrome, or liver cirrhosis

2) Patients who are suspected cyclic thrombocytopenia

3) Patients with autoimmune hemolytic anemia

4) Patients with a history of or active clinically significant, respiratory, gastrointestinal

(pancreatitis), renal, hepatic, neurological, psychiatric, musculoskeletal, genitourinary, dermatological, or other disorders that could affect the conduct of the study or the absorption, distribution, metabolism, or excretion of the study drug

5) Patients complicated with any major cardiovascular event including but not limited to myocardial infarction, unstable angina, cerebrovascular accident, pulmonary embolism, or New York Heart Association Class III or IV heart failure, or with a history of such events within 6 months prior to Day 1

6) Patients with systolic blood pressure ≥ 140 mmHg or diastolic blood pressure of ≥ 90 mmHg at Screening A, Screening B, or Day 1 whether or not the subject is receiving anti-hypertensive treatment

7) Patients with conditions with increased thrombus formation, such as factor V Leiden mutation, active protein C resistance, congenital antithrombin III deficiency, and lupus anticoagulant, or patients complicated with coagulopathy, such as arterial or venous thromboembolism, or history of coagulopathy within 6 months prior to Screening A

8) Patients who cannot discontinue anticoagulants at least 30 days prior to Screening A because of a history of venous thromboembolism at least 6 months prior to Screening A, or patients with a D-dimer assay result out of the normal range at Screening A in spite of the discontinuance of anticoagulants at least 30 days prior to Screening A.

9) Patients with an ITP Bleeding Score of Grade 2 at any site at Screen A or Day 1

10) Patients with 1 or more of the following laboratory abnormalities at Screening A, Screening B, or Day 1:

    - White blood cell count < 2500/μL
    - Neutrophil count < 1500/μL
    - Lymphocyte count < 750/μL
    - Hemoglobin < 10 g/dL

11) Patients with 1 or more of the following laboratory abnormalities at Screening A:

    - ALT or AST > 1.5 × ULN
    - Total bilirubin > 2.0 mg/dL
    - eGFR < 30 mL/min

12) Patients with significant infection, acute infection such as influenza, or active inflammatory response during the screening period

13) Patients with acute gastrointestinal symptoms (eg, nausea, vomiting, diarrhea, or abdominal pain) during the screening period

14) Patients with increased the dose of, or added, prescription drugs within the 2 weeks prior to Day 1. Except for prescription drugs for which the investigator has determined that the assessment of efficacy and safety of the study drug is not affected.

15) Patients who tested positive or the lower limit of quantitation for at least 1 of the following immunological tests at Screening A

    - HIV antigen

- HIV antibodies
- HBs antigen
- Anti-HBs (excluding HBs antibody monopositive cases due to HB vaccination or HBV DNA levels below the lower limit of quantification)
- Anti-HBc (unless HBV DNA levels are below the lower limit of quantification)
- HCV RNA quantification

16) Patients who has received any transfusion or blood products between 2 weeks prior to Screening A and Day 1
17) Patients who have used at least 1 of the following drugs during the screening period
    - Platelet transfusion
    - Intravenous immunoglobulin
    - Intravenous methylprednisolone
    - Oral dexamethasone (unless equivalent to 10 mg/day prednisolone or less)
    - Oral prednisolone (unless dosage is 10 mg/day or less)
18) Patients with allergy or sensitivity to any of the components of the study drug
19) Patients who underwent splenectomy within 12 weeks prior to Day 1
20) Patients who has had major surgery within 4 weeks prior to Day 1 or has a surgical wound that is not fully healed.
21) Patients who are scheduled to undergo surgery for whom use of rescue therapy is planned from the time of informed consent to the end of the follow-up period.
22) Patients with malignancy or a history of malignancy within 5 years before obtaining informed consent.
23) Patients with a history of severe drug hypersensitivity.
24) Patients with concomitant or past history of alcoholism.
25) Patients with concomitant or past history of drug abuse (defined as illicit drug use).
26) Patients with psychiatric disorders, such as depression, schizophrenia, or dementia.
27) Pregnant patients, breast-feeding patients, patients who wish to become pregnant during the period from informed consent to 30 days after the last dose of the study drug, or women who are not willing to use appropriate methods of contraception.
28) Patients who have received other study drugs within 12 weeks before acquisition of consent.
29) Other patients whom the investigator judges to be inappropriate for the study.

5.2.2 **Rationale for exclusion criteria**

1) to 3) These criteria were set to exclude patients ineligible for the study.

4), 14), 16), 17), 19)	These criteria were set to exclude the matters that might affect the efficacy evaluation of R788.
5) to 13), 15), 18), 20) to 25), 28)	These criteria were set to ensure the safety of subjects.
26)	This criterion was set to eliminate the effect on the efficacy evaluation of R788 and compliance with the protocol.
27)	Animal studies have reported that R788 has embryofetal toxicity and migrates into breast milk. This criterion was set to avoid the administration of R788 in pregnant or lactating patients.

5.3 Withdrawal in Individual Subjects

5.3.1 Withdrawal criteria (withdrawal in individual subjects)

1) Adverse events
   - If the investigator judges that the adverse event requires withdrawal from the study.
   - If the subject does not wish to continue the study due to the adverse event.

2) Lack of efficacy (inadequate response)
   - If the investigator determines that there is an unacceptable risk for the subject to continue due to lack of efficacy of the study drug. The lack of efficacy of the study drug will be determined with reference to the following.

   (1) Period I
   - Subjects with a platelet count of ≥ 15000/μL on Day 1:
     a) Platelet count of < 50000/μL after Week 12 despite the increased dose to 150 mg *bid* for more than 4 weeks.
     b) Platelet count of < 50000/μL after Week 12 because of the inability to increase the dose to 150 mg *bid* due to possible poor tolerability.
   - Subjects with platelet count of < 15000/μL on Day 1:
     a) Platelet count increase of < 20000/μL from Day 1 after Week 12 despite the increased dose to 150 mg *bid* for more than 4 weeks.
     b) Platelet count increase of < 20000/μL from Day 1 after Week 12 because of the inability to increase the dose to 150 mg *bid* due to possible poor tolerability.
   - Requirement for rescue therapy from Week 10 to platelet test at Week 24.

   (2) Periods II and III
   - Subjects who complete Period I:
     a) Platelet count remains < 50000/μL despite the increase dose to 150 mg *bid* for more than 4 weeks after the start of the study treatment in Period I.

b) Platelet count remains < 50000/μL because of the inability to increase the dose to 150 mg *bid* due to possible poor tolerability.

- Subjects who meet all the "8.3.1 Transition criteria to Period II for subjects who withdraw from " (hereinafter referred to as early transition subjects):

a) Platelet count remains < 50000/μL after ET Week 12 despite the treatment with 150 mg *bid* for at least 4 weeks after the start of the study treatment in Period II.

b) Platelet count remains at < 50000/μL after ET Week 12 because of the inability to increase the dose to 150 mg *bid* after the start of the study treatment in Period II due to possible poor tolerability.

However, the study drug may be continued in both subjects who complete Period I and early transition subjects if the investigator judges that tangible clinical benefit from the use of study drug is evident, with reference to the following a) to c).

a) If the platelet count is obviously increased (eg, if the platelet count increases 20000/μL or more from Day 1 and the platelet count is 30000/μL or more)

b) Reduction in bleeding events

c) Reduction in rescue therapy

3) Subjects' voluntary request to discontinue the study (discontinuation due to adverse events is classified as 1) and discontinuation due to lack of efficacy is classified as 2)).

4) Significant protocol deviations during the study period

- If GCP violations are found
- If it is found that the subject of the protocol, inclusion criteria, or exclusion criteria are not met after case registration
- If the investigator judges that the subject does not comply with the protocol and causes health damage to the subject due to continuation of the study

5) Pregnancy

6) Termination of the entire study

7) Discontinuation of the study at the study institution in question

8) Unobservable or loss to follow-up

- If the subject cannot be contacted and the continuation of the study becomes impossible

9) In addition, if the investigator judges that discontinuation of the study is necessary (the reason is recorded in the Case Report Form [CRF] in detail)

5.3.2 Actions to be taken against withdrawal in individual subjects

When any subject meets the criteria specified in "5.3.1 Withdrawal criteria (withdrawal in individual subjects)" during the study period, the investigator will immediately decide to withdraw the subject from the study. The test items specified for the Withdrawal Visit will be measured and evaluated and the date and reason for withdrawal will be recorded in the CRF.

The date when withdrawal is decided by the investigator is considered as the date of withdrawal.

When any subject withdraws from the study due to the onset of an adverse event, the investigator will immediately take appropriate measures and follow the subject as specified in "10.15.9 Follow-up."

5.3.3 Investigation of subjects who do not visit study institutions

When any subject becomes unable to visit the study institution on the scheduled date, the investigator or clinical research coordinator will immediately investigate the reason and subsequent process.

6. Consent of Subjects

6.1 Time to Collect Informed Consent

Written informed consent must be obtained before starting Screening A (before performing any test specified in this study) or washout of ITP drugs, whichever comes earlier. Written informed consent will be obtained again at Week 52 or ET Week 28 for subjects who want to participate in the Non-dosing period and Period III.

6.2 Collection of Consent

The investigator will prepare the patient information leaflet and informed consent form with reference to the materials and information provided by the sponsor for preparing the patient information leaflet (eg, reference samples of patient information and consent forms) and will submit them to Institutional Review Board (IRB) for approval.

The investigator will select subjects suitable for the objective of the study from ethical and scientific perspectives. Patients who are unable to consent will be excluded from the subjects. Adequate attention should be paid to the voluntary participation of subjects when they may be unfairly disadvantaged by not participating in the study.

The investigator will provide the candidates with sufficient explanation about the study using the patient information leaflet before enrolling them in the study. The investigator will give each candidate an opportunity to ask questions, fully answer the questions, and confirm that he/she fully understands the explanation before collecting his/her written informed consent (consent form) to voluntarily participate in the study. The investigator who gives the explanation will enter the date and affix his/her name and seal or sign it. The subject enters the date and signs it. The clinical research coordinator who gives a supplementary explanation will also enter the date and affix his/her name and seal or sign it, if applicable.

The investigator will hand the patient information leaflet and a copy of the consent form to each subject and retain the original consent form at the study institution.

7. Study Drugs

7.1 Test and Control Drugs

7.1.1 Test drug

1) Product Code: R788
2) INN: fostamatinib
3) Content and dosage formulation:
    - R788 100 mg Tablets: orange-colored round film-coated tablets containing 100 mg of fostamatinib per tablet
    - R788 150 mg Tablets: orange-colored oval film-coated tablets containing 150 mg of fostamatinib per tablet
4) Storage: Store in a tightly closed container at room temperature.

7.1.2 Control drug

1) Content and dosage formulation:
    - R788 100 mg Tablets placebo: orange-colored round film-coated tablets containing 0 mg of fostamatinib per tablet
    - R788 150 mg Tablets placebo: orange-colored oval film-coated tablets containing 0 mg of fostamatinib per tablet

    R788 100 mg Tablets cannot be distinguished from R788 100 mg Tablets placebo. R788 150 mg Tablets cannot be distinguished from R788 150 mg Tablets placebo.
2) Storage: Store in a tight container at room temperature.

7.1.3 Rationale for the control drug

With reference to the "Choice of Control Groups and Related Issues in Clinical Trials" (PMSB/ELD Notification No. 136 dated February 27, 2001), placebo was selected as the control drug to control all potential effects (natural history of the disease, expectations of the subject or physician, effects of participation in the study, use of other treatments, and subjective elements of assessment) other than the pharmacological action of the test drug on actual or apparent disease progression.

7.2 Packaging Form of Study Drugs

Sixty tablets will be filled per bottle for R788 100 mg Tablets or placebo for R788 100 mg Tablets and R788 150 mg Tablets or placebo for R788 150 mg Tablets.

7.3 Labeling

The details of labeling are specified in the procedure specified elsewhere.

7.4 Drug Accountability

The study drug administrator will appropriately control and store the study drugs in accordance with the written procedure specified elsewhere.

8. Study Method

8.1 Study Design

A placebo-controlled, multicenter, randomized, double-blind, parallel-group study (Period I) and a multicenter, open-label study (Periods II and III).

8.2 Structure of the Study

1) Screening period

   Screening period is defined as 4 weeks from Screening A to before the administration of the study drug on Day 1.

2) Period I

   Period I is defined as 24 weeks from after the administration of the study drug on Day 1 to Week 24.

3) Period II

   - The day at the beginning of study drug administration in Period II is Week 24 for subjects who complete Period I. Period II is defined as 28 weeks from Weeks 24 to 52.
   - The day at the beginning of study drug administration in Period II is ET Day 1 for early transition subjects. Period II is defined as 28 weeks from ET Day 1 to ET Week 28.

4) Non-dosing period

   Non-dosing period is defined as maximum 4 weeks from Week 52 or ET Week 28 to Day 1 of Period III.

5) Period III

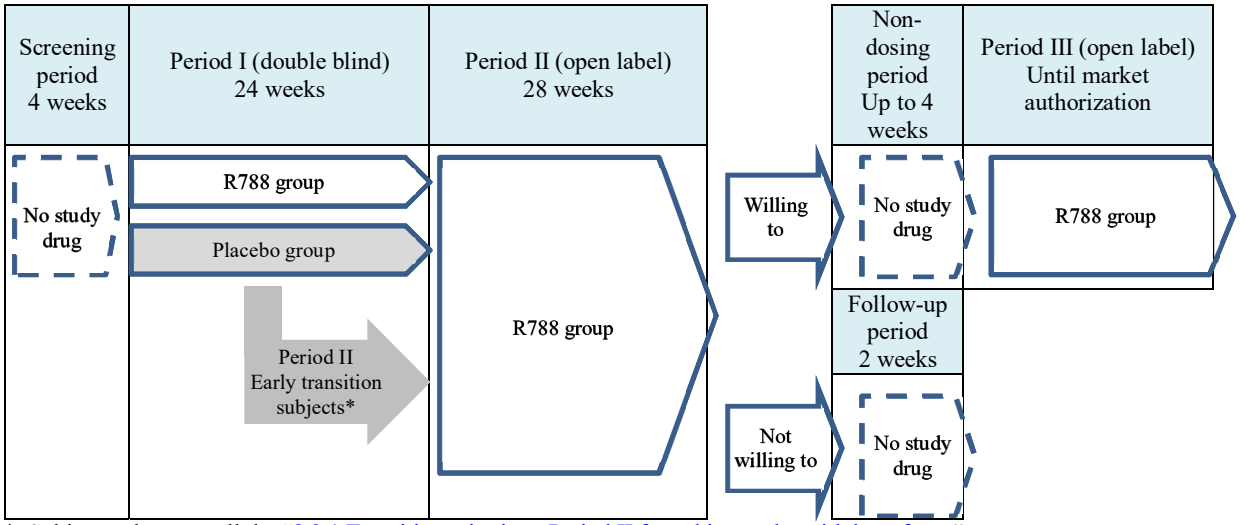
   Period III is defined as the period from Day 1 of Period III to the date of marketing approval of R788.

6) Follow-up period

   - Follow-up period is defined as 2 weeks from Week 52 or ET Week 28 to the tests at the end of the follow-up period for subjects who complete Period II and are not willing to participate in the Non-dosing period and Period III.
   - Follow-up period is defined as 2 weeks from the Withdrawal Visit to the tests at the end of the follow-up period for subjects who withdraw from Period I and do not transition to Period II, those who withdraw from Period II, and those who withdraw from Period III.
   - Follow-up period is defined as the period until 2 weeks after Week 52 or ET Week

28 for subjects who withdraw from the Non-dosing period before ND Week 2.

- No follow-up period is established for subjects who withdraw from the Non-dosing period at ND Week 2 or later or subjects who continue Period III until the date of marketing approval of R788.



*: Subjects who meet all the "8.3.1 Transition criteria to Period II for subjects who withdraw from "

Figure 8.2-1 Structure of Study

8.3 Transition to Period II

The following subjects transition to Period II.

- Subjects who completed Period I
- Early transition subjects (subjects who meet all the "8.3.1 Transition criteria to Period II for subjects who withdraw from ")

8.3.1 Transition criteria to Period II for subjects who withdraw from Period I

1) Subjects who meet any of the following criteria and withdraw from Period I due to "2) Lack of efficacy (inadequate response)" in "5.3.1 Withdrawal criteria (withdrawal in individual subjects)"

   - Subjects with a platelet count of ≥ 15000/μL on Day 1:
     a) Platelet count of < 50000/μL after Week 12 despite the increased dose to 150 mg *bid* for more than 4 weeks.
     b) Platelet count of < 50000/μL after Week 12 because of the inability to increase the dose to 150 mg *bid* due to possible poor tolerability.
   - Subjects with platelet count of < 15000/μL on Day 1:
     a) Platelet count increase of < 20000/μL from Day 1 after Week 12 despite the increased dose to 150 mg *bid* for more than 4 weeks.
     b) Platelet count increase of < 20000/μL from Day 1 after Week 12 because of

the inability to increase the dose to 150 mg *bid* due to possible poor tolerability.

2) Subjects with systolic blood pressure of < 140 mmHg and diastolic blood pressure of < 90 mmHg on ET Day 1 whether or not the subject is receiving antihypertensive treatment

3) Subjects without the following laboratory abnormalities on ET Day 1:

- White blood cell count < 2000/μL
- Neutrophil count < 1000/μL
- Lymphocyte count < 750/μL
- Hemoglobin < 10 g/dL

4) Subjects without the following laboratory abnormalities on the last laboratory test before ET Day 1

- ALT or AST > 1.5 × ULN
- Total bilirubin > 1.5 × ULN
- eGFR < 30 mL/min

5) Subjects who do not have significant infection, an acute infection such as influenza, or inflammatory process on ET Day 1.

6) Subjects who have not received blood or blood products within the 2 weeks prior to ET Day 1 (intravenous immunoglobulin or platelet transfusion are allowed if used for rescue therapy).

8.3.2 **Rationale for transition criteria to Period II for subjects who withdraw from Period I**

1) This criterion was set to include subjects who withdraw from Period I due to lack of efficacy.

2) to 5) These criteria were set to ensure the safety of subjects.

6) This criterion was set to exclude the matters that might affect the efficacy evaluation of R788.

8.4 Transition to Non-dosing Period

Subjects who provide written informed consent to participate in the Non-dosing period and Period III transition to the Non-dosing period. However, subjects with platelet count of < 50000/μL at Week 52 or at ET Week 28 may skip the Non-dosing period and transition to Period III at the discretion of the investigator.

8.5 Transition to Period III

The following subjects transition to Period III.

- Subjects who completed the Non-dosing period

- Subjects receiving any rescue therapy during the Non-dosing period
- Subjects who have platelet count of < 50000/μL during the Non-dosing period and need to transition to Period III before completing the Non-dosing period, as judged by the investigator

8.6 Dose and Administration

8.6.1 Dose and administration

Dose and administration method are shown in Figure 8.6.1-1 and Figure 8.6.1-2.

1) Screening period

No study drug is administered.

2) Period I

R788 or matching placebo is administered orally for 24 weeks. On Day 1, 100 mg of the study drug will be administered at the study institution. This must be the only administration of the study drug on Day 1, irrespective of the time of administration. The study drug will be administered twice daily beginning on the next day and the dose will be adjusted according to "8.6.2 Dose adjustment" during Period I. Morning and evening doses should be at least 8 hours apart and should be taken at approximately the same time each day, with or without food during Period I. In principle, subjects will visit the study institution in the morning without taking the study drug and take the study drug at the study institution in the morning to measure drug concentration at Weeks 2 and 6. In principle, subjects will take the study drug at 1 to 4 hours before visiting the study institution in the morning at Week 4 and Weeks 8 to 24.

3) Period II

R788 is orally administered for 28 weeks.

(1) Subjects who completed Period I
The study drug for Period I is continued until the visit at Week 24 and the study drug for Period II is initiated after the visit at Week 24 (if study drug in Period II is initiated as twice daily, subjects who took the study drug for Period I in the morning on the day of the visit start the study drug for Period II from the evening of the same day). The dose and administration at the start of the study drug for Period II is as follows.

- If platelet count at Week 24 is ≥ 50000/μL, study drug in Period II is initiated with the last dose and administration in Period I.
- If platelet count at Week 24 is < 50000/μL and last dose and administration in Period I is 150 mg *bid*, study drug in Period II is initiated with 100 mg *bid*.
- If platelet count at Week 24 is < 50000/μL and last dose and administration in Period I is 100 mg *qd*, 150 mg *qd*, or 100 mg *bid*, study drug in Period II is initiated with the last dose and administration in Period I.

(2) Early transition subjects
The study drug for Period II is initiated after the visit on ET Day 1 (if study drug in Period II is initiated as twice daily, subjects who took the study drug for Period I in the

morning on the day of the visit start the study drug for Period II from the evening of the same day). The dose and administration at the start of the study drug for Period II is as follows.

- If the last dose and administration in Period I is 100 mg *bid* or 150 mg *bid*, study drug in Period II is initiated with 100 mg *bid*.
- If the last dose and administration in Period I is 100 mg *qd* or 150 mg *qd*, study drug in Period II is initiated with the last dose and administration in Period I.

The dose should be adjusted during Period II in accordance with "8.6.2 Dose adjustment." Morning and evening doses should be at least 8 hours apart and should be taken at approximately the same time each day, with or without food during the Period II.

4) Non-dosing period

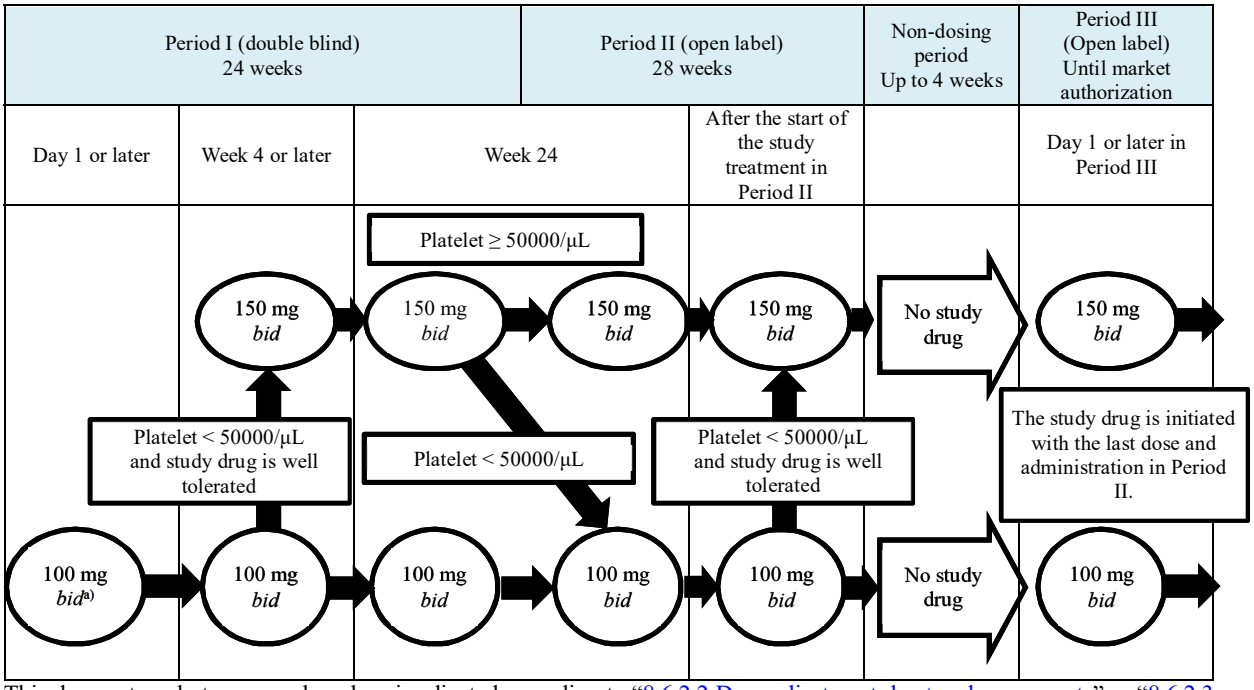
No study drug is administered.

5) Period III

The study drug is administered orally until market authorization of R788 in Japan. The study drug for Period III is initiated with the last dose and administration of study drug in Period II and is started after the visit on Day 1 of Period III. The dose should be adjusted during Period III in accordance with "8.6.2 Dose adjustment." Morning and evening doses should be at least 8 hours apart and should be taken at approximately the same time each day, with or without food during the Period III.

6) Follow-up period

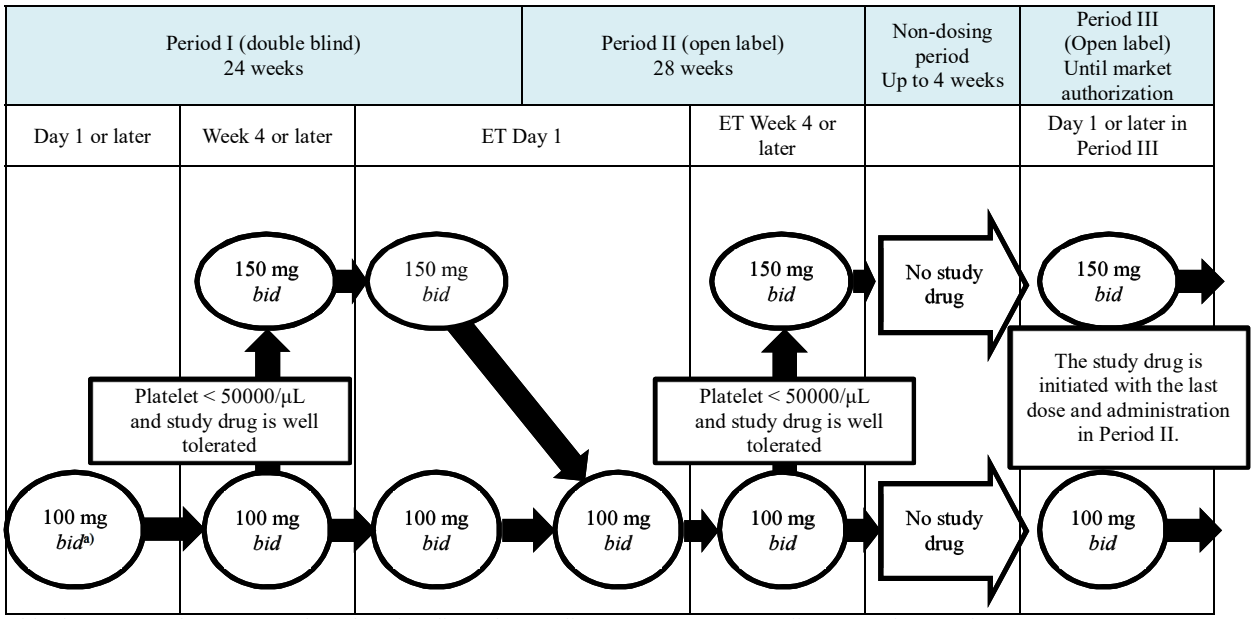
No study drug is administered.



This does not apply to cases when dose is adjusted according to "8.6.2.2 Dose adjustment due to adverse events" or "8.6.2.3 Dose adjustment due to excessive elevation of platelet count."

a) The dose of 100 mg of the study drug is administered at study institutions and this must be the only administration of the study drug on Day 1, irrespective of the time of administration.

Figure 8.6.1-1 Dose and Administration Method for Subjects Who Complete Period I



This does not apply to cases when dose is adjusted according to "8.6.2.2 Dose adjustment due to adverse events" or "8.6.2.3 Dose adjustment due to excessive elevation of platelet count."

a) The dose of 100 mg of the study drug is administered at study sites and this must be the only administration of the study drug on Day 1, irrespective of the time of administration.

Figure 8.6.1-2 Dose and Administration Method for Early Transition Subjects

8.6.2 Dose adjustment

8.6.2.1 Dose escalation for subjects not responding

1) Period I

   If the platelet count at Week 4 or after is below 50000/μL and the study drug has been well tolerated, the dose of study drug should be increased from 100 mg *bid* to 150 mg *bid* at the discretion of the investigator. Subjects whose dose is escalated should continue to be monitored carefully for adverse events.

2) Period II

   (1) Subjects who completed Period I:
   If the platelet count after the study drug for Period II is initiated remains below 50000/μL and the study drug has been well tolerated, the dose of study drug should be increased from 100 mg *bid* to 150 mg *bid* at the discretion of the investigator. Subjects whose dose is escalated should continue to be monitored carefully for adverse events.

   (2) Early transition subjects:
   If the platelet count at ET Week 4 or after is below 50000/μL and the study drug has been well tolerated, the dose of study drug should be increased from 100 mg *bid* to 150 mg *bid* at the discretion of the investigator. Subjects whose dose is escalated should continue to be monitored carefully for adverse events.

3) Period III

   If the platelet count is below 50000/μL and the study drug has been well tolerated, the dose of study drug should be increased from 100 mg *bid* to 150 mg *bid* at the discretion of the investigator. Subjects whose dose is escalated should continue to be monitored carefully for adverse events.

8.6.2.2 Dose adjustment due to adverse events

The dose of the study drug will be adjusted according to the applicable appendices if the following adverse events or abnormal results of laboratory tests, abnormal findings, and abnormal symptoms associated with adverse events are observed.

- Increases in ALT, AST, or bilirubin (see Appendix 3)
- Neutrophil count decreased (see Appendix 4)
- Onset of diarrhea (see Appendix 5)
- Increase in blood pressure (see Appendix 6)

Additionally, if any other severe or serious adverse events with a potential relationship to the study drug are observed, the dose of the study drug should be adjusted at the discretion of the investigator.

If adverse events or abnormal results of laboratory tests, abnormal findings, and abnormal symptoms associated with adverse events which result in dose reduction of study drug recover, the dose of study drug can be re-escalated by 1 dose level in accordance with Table 8.6.2.2-1 based on the investigator's decision.

If adverse events or abnormal results of laboratory tests, abnormal findings, and abnormal symptoms associated with adverse events which leads to interruption of study drug recover, the study drug is restarted at 1 lower dose level than that before the interruption. After restarting the study drug, the dose of study drug can be re-escalated by 1 dose level in accordance with Table 8.6.2.2-1 based on the investigator's decision. The study drug will be restarted at 100 mg *qd* when the dose regimen before interruption is 100 mg *qd*. For "2) Recurrence of neutrophil count of < 1000/μL" in "Appendix 4 Management of Neutrophil Count Decreased" or "3) Recurrence of Grade 3 or 4 diarrhea" in "Appendix 5 Management of Diarrhea," study drug is restarted at 2 lower dose level after the adverse event or laboratory test abnormality, abnormal finding, or symptom associated with the adverse event is recovered. However, the study drug will be restarted at 100 mg *qd* when the dose before interruption is 100 mg *qd* or 150 mg *qd*. The study drug will be administered in the morning when it is administered once daily.

Table 8.6.2.2-1 Dose Adjustment

Dose reduction				Dose before dose increase/ reduction	Dose escalation		
Dose level −4	Dose level −3	Dose level −2	Dose level −1		Dose level +1	Dose level +2	Dose level +3
Interruption	100 mg *qd*	150 mg qd	100 mg *bid*	150 mg *bid*	—	—	—
—	Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*	—	—
—	—	Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*	—
—	—	—	Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*

8.6.2.3 Dose adjustment due to excessive elevation of platelet count

1) Period I

If excessive platelet count increase is observed, the investigator should respond in accordance with Table 8.6.2.3-1. The doses/regimens of allowed ITP therapies (corticosteroids, azathioprine, or danazol) should not be changed. If platelet count is above 250000/μL even after the dose of the study drug is adjusted, the dose of allowed ITP therapy is reduced according to "8.7.7 Allowed ITP therapies".

Table 8.6.2.3-1 Actions Taken with the Study Drug for Excessive Elevation of Platelet Count in Period I

	Actions
1) Platelet counts > 250000/μL	• Reduce the dose of the study drug by 1 dose level until the platelet count falls to ≤ 250000/μL. • Monitor platelet count until platelet count falls to < 200000/μL (the frequency of additional measurements will be determined by the investigator). • If the excessive elevation of platelet count is improved, the dose of study drug can be re-escalated by 1 dose level based on the investigator's decision.
2) Platelet counts > 150000/μL and ≤ 250000/μL	• Continue the study drug at full dose. • Monitor the platelet count until stable to assure it does not exceed 250000/μL (the frequency of additional measurements will be determined by the investigator).

2) Periods II and III

If excessive platelet count increase is observed, the investigator should respond in accordance with "8.7.7 Allowed ITP therapies." If platelet count is above 250000/μL even after the dose of allowed ITP therapy is adjusted, reduce the dose of the study drug by 1 dose level until the platelet count falls to ≤ 250000/μL (see Table 8.6.2.2-1) and measure the platelet count until it falls to < 200000/μL (the frequency of additional measurements will be determined by the investigator). If the excessive elevation of platelet count is improved, the dose of study drug can be re-escalated by 1 dose level based on the investigator's decision.

8.6.3 Rationale for dose

In an overseas Phase II clinical study (D4300-022 study) in which R788 was administered in 18 patients with ITP in a dose ascending manner from a starting dose of 75, 100, 125, or 150 mg *bid* with monitoring of safety and efficacy, increase of platelet count was mainly observed at 100, 125, or 150 mg *bid*.

In the overseas Phase III clinical studies in 150 patients with persistent or chronic ITP (C788-047 and C788-048 studies), R788 or placebo was administered for 24 weeks at a starting dose of 100 mg *bid*, which was allowed to increase to 150 mg *bid* when platelet count was < 50000/μL at Week 4 or later. The integrated analysis of the 2 studies showed that the primary endpoint, or the "achievement rate of platelet count of ≥ 50000/μL at 4 or more of the 6 visits between Weeks 14 and 24 (stable platelet response)" was 17.8% (18/101) in the R788 group and 2.0% (1/49) in the placebo group, indicating a significantly higher achievement in the R788 group (P = 0.0003, Fisher's exact test). In the overseas Phase III clinical studies (C788-047 and C788-048 studies), serious bleeding-related adverse events occurred in 5.0% (5/101) of the R788 group and 10.2% (5/49) of the placebo group and moderate to severe bleeding-related adverse events occurred in 9.9% (10/101) and 16.3% (8/49), respectively. These results indicate that R788 given at 100 to 150 mg *bid* provided ITP patients with an effect to increase platelet count and concomitantly reduce bleeding symptoms.

Phase I clinical studies in Japanese and White healthy adults (D4300-007 and D4300-032 studies) have been conducted so far. The single oral administration of 150 mg of R788 followed by the repeated oral administration with qd for 7 days showed no major differences in the pharmacokinetics of the active substance, R406, between Japanese and White subjects, suggesting similar pharmacokinetics between Japanese and White subjects.

Given the similar pharmacokinetics of R406 between Japanese and non-Japanese subjects and similar exposure-response relationship of R788 between Japanese and non-Japanese subjects based on the lack of report of ethnic difference in the onset of SYK inhibited by R406, the starting dose of R788 was set at 100 mg *bid* and an increase in dose to 150 mg *bid* was allowed when a platelet count of < 50000/μL was observed and R788 was well tolerated at Week 4 or later after the start of treatment, as in the overseas Phase III clinical studies (C788-047 and C788-048 studies) in which the efficacy of R788 was verified.

8.7 Concomitant Medications

Drugs for various symptoms with ITP and drugs used at the start of the screening period for complications should not change the doses/regimens as much as possible until the end of the follow-up period or market authorization. It is acceptable to change the doses/regimens of concomitant medications for safety, such as the occurrence of adverse events.

8.7.1 Prohibited concomitant medications

The concomitant use of the medications listed in Table 8.7.1-1 is prohibited from 2 weeks before Day 1 to the end of the follow-up period or market authorization.

Table 8.7.1-1 Prohibited Concomitant Medications

Classification	Principal drugs
1) Strong CYP3A4 inhibitors	Itraconazole, indinavir sulfate ethanol adduct, clarithromycin, cobicistat, diltiazem hydrochloride, nelfinavir mesilate, voriconazole, ritonavir containing preparation
2) Study drugs other than R788	Any study drugs other than R788

8.7.2 Rationale for prohibited concomitant medications

1) This criterion was set considering the possible drug interaction with R788 because the concurrent administration with a strong CYP3A4 inhibitor increases the exposure to R406 by about 2.0-fold, which may affect the safety of subjects.
2) This criterion was set to assure subject safety because the safety of study drugs under development has not been established and their interactions with R788 are unknown.

8.7.3 Prohibited ITP concomitant medications

The concomitant use of the medications listed in Table 8.7.3-1 is prohibited from the period specified in "8.7.9 Washout" before Day 1 to the end of the follow-up period or market authorization.

Table 8.7.3-1 Prohibited ITP concomitant medications

Classification	Principal drugs
ITP medications other than the allowed ITP therapies or ITP medications specified as rescue therapies	Cyclosporine, mycophenolate mofetil, eltrombopag olamine, romiplostim, rituximab or other anti CD20 monoclonal antibodies, alkylating agents

8.7.4 Rationale for prohibited ITP concomitant medications

These criteria were set to exclude the matters that might affect the efficacy evaluation of R788.

8.7.5 Restricted concomitant medications

Medications listed in Table 8.7.5-1 should be administered with attention to subject safety from 2 weeks before Day 1 to the end of the follow-up period or market authorization.

Table 8.7.5-1 Restricted concomitant medications

Classification	Principal drugs	Precautions for co-administration
1) Moderate CYP3A4 inhibitors	Atazanavir sulfate, aprepitant, amiodarone hydrochloride, istradefylline, imatinib mesylate, erythromycin, crizotinib, cyclosporine, ciprofloxacin hydrochloride, cimetidine, tofisopam, fluconazole, fluvoxamine maleate, verapamil hydrochloride, fosamprenavir calcium hydrate, fosfluconazole, miconazole	Concomitant use with a moderate CYP3A4 inhibitor increases the exposure to R406 by approximately 1.4-fold, which may affect the safety of subjects. The investigator will decide whether or not to use it concomitantly, taking into account the necessity of treatment.
2) CYP3A4 inducers	Etravirine, efavirenz, enzalutamide, carbamazepine, St. John's wort, nevirapine, barbiturates, phenytoin, bosentan hydrate, mitotane, modafinil, rifabutin, rifampicin, rufinamide	Concomitant use with a CYP3A4 inducer reduces the exposure to R406 by approximately 0.25-fold, which may be below the therapeutic range of R406. The investigator will decide whether or not to use it concomitantly, taking into account the necessity of treatment.
3) P-gp substrates	Digoxin	Concomitant use with R788 increases the exposure to digoxin by approximately 1.4-fold, which may affect the safety of subjects. Since the dose reduction of digoxin may be required in subjects who need to take digoxin or who are taking digoxin, the investigator should carefully monitor adverse events.
4) HMG-CoA reductase inhibitors	Simvastatin, rosuvastatin, atorvastatin, pitavastatin	Concomitant use with R788 increases the exposure to HMG-CoA reductase inhibitors by approximately 1.6 to 2.0-folds, which may affect the safety of subjects. Since the dose reduction of HMG-CoA reductase inhibitors may be required in subjects taking HMG-CoA reductase inhibitors, the investigator should carefully monitor adverse events such as lipid reactions or myositis.

8.7.6 Rationale for restricted concomitant medications

1) to 4) These restricted medications were selected, considering the possible interactions with R788.

8.7.7 Allowed ITP therapies

1) Screening period and Period I

Subjects are allowed to use only one of the specific therapies for ITP: corticosteroids (equivalent to 10 mg/day prednisolone or less), azathioprine, or danazol, throughout the screening period and Period I. Dosage of these allowed ITP therapies should not be changed from at least 2 weeks before Day 1 to any of the following visit. Tapering of the allowed ITP therapies will not be permitted, even if platelet count exceeds 50000/μL. New treatments allowed for ITP should not be added from at least 2 weeks before Day 1.

- Withdrawal Visit (subjects who withdraw from Period I and do not transition to Period II)

- ET Day 1 (subjects who withdraw from Period I and transition to Period II)
- Week 24 (except for the above)

If platelet count is above 250000/μL even after the dose of study drug is adjusted in accordance with "8.6.2.3 Dose adjustment due to excessive elevation of platelet count," reduce the dose of allowed ITP therapy until the platelet count falls to ≤ 250000/μL and measure the platelet count until it falls to < 200000/μL (the frequency of additional measurements will be determined by the investigator).

2) Period II

The same drug as in Period I can be used as ITP therapy in Period II with the same doses/regimens as in Period I. Consideration can be given to tapering the dose of allowed ITP therapy in subjects whose platelet count is stable at ≥ 50000/μL during Period II (including the start of Period II) at the discretion of the investigator. New treatments for ITP should not be added. If excessive platelet count increase is observed during Period II (including the start of Period II), the investigator should respond in accordance with Table 8.7.7-1.

3) Non-dosing period

The same drug as in Period II can be used as ITP therapy in Non-dosing period with the same doses/regimens as used at the end of Period II. Doses/regimens of these allowed ITP therapies should not be changed until any of the following visit. New treatments for ITP should not be added. If excessive platelet count increase is observed during Non-dosing period, the investigator should respond in accordance with Table 8.7.7-1.

- Period III Day 1 (subjects who transition to Period III)
- Withdrawal Visit (subjects who withdraw from the Non-dosing period)

4) Period III

The same drug as in Non-dosing period can be used as ITP therapy in Period III with the same doses/regimens as used at the end of Non-dosing period. Consideration can be given to tapering the dose of allowed ITP therapy in subjects whose platelet count is stable at ≥ 50000/μL during Period III (including the start of Period III) at the discretion of the investigator. New treatments for ITP should not be added. If excessive platelet count increase is observed during Period III (including the start of Period III), the investigator should respond in accordance with Table 8.7.7-1.

5) Follow-up period

Doses/regimens of the allowed ITP therapy at the completion of Period II or at the Withdrawal Visit should not be changed during the follow-up period. New treatments for ITP should not be added. However, if excessive platelet count increase is observed, the investigator should respond in accordance with Table 8.7.7-1.

Table 8.7.7-1 Actions Taken for Allowed ITP Therapy for Excessive Elevation of Platelet Count

	Action
1) Platelet counts > 250000/μL	• Reduce the dose of the allowed ITP therapy. • Monitor platelet count until platelet count falls to < 200000/μL (the frequency of additional measurements will be determined by the investigator). • If the excessive elevation of platelet count is improved, the dose of allowed ITP therapies can be re escalated based on the investigator's decision.
2) Platelet counts > 150000/μL and ≤ 250000/μL	• Leave the dose of the allowed ITP therapy unchanged. • Monitor the platelet count until stable to assure it does not exceed 250000/μL (the frequency of additional measurements will be determined by the investigator).

8.7.8 Rescue therapy

Rescue therapy may be used at the discretion of the investigator from the start of the study drug in Period I to the end of the follow-up period or market authorization for subjects who meet any one or both of the following conditions.

- Platelet count < 50000/μL and at immediate risk of bleeding or with clinically significant bleeding or wet purpura.
- Platelet count < 50000/μL and requires urgent or emergent surgery.

The drugs listed in Table 8.7.8-1 can be used for rescue therapy. The investigator should determine the dose and administration of rescue therapy with reference to Table 8.7.8-1.

Table 8.7.8-1 Rescue Therapy

Drug	Doses/regimens
Platelet transfusion	10 to 20 units/dose
Intravenous immunoglobulin	400 mg/kg/day for 5 consecutive days
Intravenous methylprednisolone	1 g/day for 3 consecutive days
Oral dexamethasone	Up to 40 mg/day for 1 to 2 days
Oral prednisolone	Up to 1 mg/kg/day for 1 to 3 days

8.7.9 Washout

Prior to start of the study drug administration in Period I, the use of all ITP medications except the allowed ITP therapies are prohibited during the specific period as shown in Table 8.7.9-1.

Table 8.7.9-1 Washout Period

Drug	Prohibited period prior to study drug administration
Cyclosporine or mycophenolate mofetil	2 weeks
Eltrombopag olamine	2 weeks
Romiplostim	3 weeks
Alkylating agents	8 weeks
Rituximab or other anti-CD20 monoclonal antibody	24 weeks

8.8 Randomization and Blinding

8.8.1 Allocation of study drugs

The responsible person for study drug allocation prepares the randomization code list for Period I, with the ratio of R788 to placebo being 2:1.

8.8.2 Preparation of emergency key code

The person responsible for study drug allocation will prepare an emergency key code so that the study drug can be identified immediately in an emergency.

8.8.3 Storage of the study drug assignment table and emergency key code

The person responsible for study drug assignment will seal the study drug assignment table and emergency key code and retain them until unblinding according to the written procedure specified elsewhere.

8.8.4 Registration

8.8.4.1 First registration

The investigator will confirm the eligibility of each subject who provides informed consent at the time of collection, fill in the first registration form, and promptly perform the procedure to enroll him/her.

The Subject Registry Center will notify the investigator of whether to accept the first registration or not. The completed first registration form and first registration confirmation form from the Subject Registry Center will be stored at the study institution.

8.8.4.2 Second registration

The investigator will confirm the eligibility of each subject at Screening A, fill in the second registration form, and promptly perform the procedure to enroll him/her.

The Subject Registry Center will notify the investigator of whether to accept the second registration or not. The completed second registration form and second registration confirmation form obtained from the Subject Registry Center will be stored at the study institution. In addition, the investigator will inform the Subject Registry Center of the reason subjects who were considered eligible at the first registration were not considered eligible at the second registration.

8.8.4.3 Third registration

The investigator will make the last confirmation of eligibility of each subject on Day 1, fill in the third registration form, and promptly perform the procedure to register the subject.

The Subject Registry Center will notify the investigator of whether to accept the third registration or not. The completed third registration form and third registration confirmation form obtained from the Subject Registry Center will be stored at the study institution. In addition, the investigator will inform the Subject Registry Center of the reason subjects who

were considered eligible at the second registration were not considered eligible at the third registration.

8.8.4.4 Randomization

The Subject Registry Center will randomly assign each subject considered eligible at the third registration to either of the treatment groups based on the study drug assignment table according to the dynamic allocation method using platelet count (</≥ 15000/μL) as a stratification factor, and inform the investigator of the number of the study drug to be administered to the subject using the drug number confirmation form. The drug number confirmation form obtained from the Subject Registry Center will be retained at the study institution.

8.8.4.5 Enrollment for transition to Period II

The investigator will fill in the Period II transition enrollment form for each subject who completes Period I at Week 24 and promptly perform the procedure to enroll the subject. The completed Period II transition enrollment form and Period II transition enrollment confirmation form obtained from the Subject Registry Center will be stored at the study institution.

In addition, the investigator will examine each subject who withdraws from Period I due to "2) Lack of efficacy (inadequate response)" in "5.3.1 Withdrawal criteria (withdrawal in individual subjects)" for the eligibility for the transition to Period II (see "8.3.1 Transition criteria to Period II for subjects who withdraw from ") on ET Day 1 and then fill in the Period II transition enrollment form to promptly enroll the subject. The Subject Registry Center will notify the investigator of whether to accept the subject for the Period II transition enrollment. The completed Period II transition enrollment form and Period II transition enrollment confirmation form obtained from the Subject Registry Center will be stored at the study site.

8.8.5 Emergency key code breaking

When it is necessary to immediately know the identity of the study drug in an emergency, the emergency key code of the drug number in question will be opened in accordance with the following unblinding procedure.

1) In an emergency, the investigator should promptly provide appropriate treatment to the subject, check the subject's health status, and report it to the sponsor. The investigator should request the sponsor to break the emergency key code when it is considered necessary to secure the subject's safety.
2) The sponsor will open the emergency key code of the drug number in question according to the procedure specified elsewhere and report the result to the investigator when the sponsor is requested to open it by the investigator or when the sponsor decides it necessary to open it.
3) The investigator will prepare the CRF and "Record of earlier than scheduled unblinding of study drug assignment code" for the subject with the drug number and submit them to the sponsor.

8.8.6 Unblinding

The person responsible for study drug assignment will unblind the study drug assignment table after confirming that the blindness of the study was maintained until the data on all enrolled subjects in Period I were fixed.

8.9 Number of Subjects

8.9.1 Number of subjects

Twenty-four subjects (16 in the Period I R788 group and 8 in the Period I placebo group)

8.9.2 Rationale for the number of subjects

It is expected that only a limited number of patients will be included in the study because ITP is rare and because patients with ITP are included in the study when they poorly responded to at least 1 of the standard therapies for ITP or when at least 1 of the standard therapies were not tolerated. Therefore, the number of subjects was set at 24 (16 in the Period I R788 group and 8 in the Period I placebo group), considering availability of subjects.

Achievement rate of stable platelet response, which is the primary endpoint of this study, was 0.0% (0/25) and 4.2% (1/24) in the placebo groups and 17.6% (9/51) and 18.0% (9/50) in the R788 group in the overseas Phase III clinical studies (C788-047 and C788-048 studies), respectively. In the target sample size of 24 patients (16 in the Period I R788 group and 8 in the Period I placebo group), assuming that the primary endpoint is 17.8% in the R788 group and 2.0% in the placebo group, the likelihood that the point estimate would be exceed in the R788 group compared with the placebo group is calculated as 89% by performing 100000 simulations of the Simon selection design.

9. Guidance to and Management of Subjects

The investigator will fully explain the significance and objectives of this study to subjects and give guidance to subjects and manage them particularly for the following points.

1) Subjects should immediately inform the investigator and follow his/her instructions when they experience increased bowel movements, diarrhea, or other physical abnormalities.
2) Subjects should properly take the study drug according to the instructions from the investigator and should not discontinue the study drug or change its dose on their own judgment.
3) Morning and evening doses will be given at an interval of at least 8 hours and at approximately the same time of the day irrespective of diet.
4) Subjects should visit the study institution after taking the morning dose of the study drug. Subjects should try to visit the study institution at the same time of the day during the study period. However, at Week 2 and 6, subjects should visit the study institution in the morning without taking the morning dose and take it at the study institution. At Week 4 and Weeks 8 to 24, subjects should take the morning dose of the study drug 1 to 4 hours before the blood sampling and visit the study institution in the morning.
5) Subjects should take the morning dose of the study drug when the dose regimen is changed to once daily because of dose reduction.

6) Subjects should not talk with other subjects about the intake of the study drug (eg, taste and color).

7) Subjects should bring all the study drugs given, including empty bottles, at each study visit. Subjects should report the reason to the investigator, clinical research coordinator, or study drug administrator when they fail to bring all of the study drugs given. Subjects should bring the bottle(s) to the next visit and should not take the study drug from the bottle(s) when they failed to bring it.

8) Subjects should quickly inform the investigator, clinical research coordinator of any loss of study drug bottles and receive the shortage from the investigator.

9) Subjects should accurately complete the dosing diary every day by themselves. Subject should bring the dosing diary with them at each visit. Subjects should bring the dosing diary at the next visit if they leave the dose diary at home.

10) Subjects should take all the prescribed drugs other than the study drug, including the allowed ITP drug, as directed.

11) Subjects should not take the study drug with grapefruit or food and beverages containing grapefruit.

12) Subjects should visit the study institution as scheduled. Subjects should inform the study institution if they cannot visit the institution as scheduled.

13) Subjects should report the drugs they are currently taking to the investigator before participating in the study. Subjects should consult the investigator when they are prescribed new drugs by other departments or medical institutions or when they use OTC drugs. Subjects should immediately inform the investigator when they use such drugs without consulting the investigator.

14) Subjects should inform the investigator in advance when they visit other departments or medical institutions, and report their participation in the clinical study to the physicians in other departments or medical institutions. Subjects should report their participation in this clinical study to physicians in other departments or medical institutions when they visit them in an emergency. They should immediately report their visit to other medical institutions and drugs prescribed to the investigator.

15) Subjects should report any physical abnormality they experience after completing the study to the investigator.

16) Female subjects of childbearing potential must avoid sexual intercourse or use appropriate contraception from the time of informed consent to 30 days after the last dose of the study drug. Subjects should immediately inform the investigator if they suspect that they have become pregnant from informed consent to 30 days after the last dose of the study drug.

17) Subjects should use appropriate, highly effective contraception methods, such as the combination of the barrier method (condom or diaphragm) and another method (eg, spermicides, oral contraceptives, or intrauterine devices) or sterilization of the subject or his/her partner.

18) Subjects should not disclose any information related to this study, such as materials used for the study, adverse events that occurred during the study period, tests/examinations performed, and personal impression about the study drug on the Internet (eg, Facebook, Twitter, and blogs) or on media (eg, newspapers, magazines, or advertisements).

10. Study Assessments and Procedures

The investigator will perform investigations, observations, tests/examinations, and evaluations according to the study schedule and investigation/observation/test/examination procedures.

10.1 Demographics

The following information should be investigated as subject's background and should be recorded in CRF.

1) Date of informed consent
2) Month and year of birth, sex, race
3) The disease affecting at the time of obtaining consent form, or medical history of autoimmune diseases including autoimmune hemolytic anemia, together with the disease name(s)
4) Information regarding the inclusion and exclusion criteria
5) Onset date of ITP
6) Prior medication for ITP, treatment period, and reason for discontinuation
7) Received splenectomy or not. If yes, time of splenectomy
8) Any treatment for ITP and treatment period (excluding splenectomy)
9) Need of pregnancy test

10.2 Administration State

The investigator or a clinical research coordinator will check the compliance of administration (amount of dose, drug number, starting day of dosing, completion day of dosing, and number of tablets administered) and record these information in the CRF. When the investigators change the amount of dose, the reason for the change and the compliance of administration after the change (amount of dose after the change, drug number, starting day of dosing, completion day of dosing, and number of tablets administered) will be checked and recorded on the CRF.

10.2.1 Dosing diary

The investigator or clinical research coordinator will instruct subjects on how to complete the dosing diary. Subjects will record the study drug taken and time it was taken in the dosing diary every day. The time that the study drug was taken will be recorded in the dosing diary only during Period I but not during Periods II and III.

10.3 Concomitant Medications

10.3.1 Concomitant medications

For all drugs (including over-the-counter drugs) used during the study period from the time of obtaining informed consent to the tests at the end of the follow-up period, the status of use (name of the drug, route of administration, duration of administration, and reason for use) will be recorded on the CRF. The equivalent information on the drugs used in Period III (including over-the-counter drugs) will not be recorded in the CRF.

10.3.2 ITP treatment

For all the ITP drugs (including prohibited concomitant ITP drugs, allowed ITP drugs, and rescue therapy) used during the study period from the time of obtaining informed consent to the tests at the end of the follow-up period or market authorization, the status of use (name of the drug, route of administration, dosage, duration of administration, and reason for use) will be recorded on the CRF.

10.4 Efficacy Endpoints

10.4.1 SF 36

Health related QOL will be assessed by subjects themselves using SF-36 v2 Japanese version. SF-36 assessment is performed before any other procedures and evaluations. Assessment date and results will be recorded in the CRF.

10.5 Laboratory Tests

10.5.1 Hematology

The following laboratory tests will be measured in the laboratory in each study institution. The standard range of each parameter, blood sample collection date and time, and test results will be recorded on the CRF. As a general rule, the laboratory parameters should be measured by the same devices for the same subject throughout the study period.

Platelet count, red blood cell count, white blood cell count, hemoglobin, hematocrit, differential white blood count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), neutrophil count, eosinophil count, basophil count, lymphocyte count, monocyte count, reticulocyte ratio, MCHC, MCH, and MCV

10.5.2 Serum chemistry

The following laboratory test parameters will be measured in the designated central laboratory. The presence or absence of sample collection will be recorded on the CRF. When additional laboratory tests are performed at the laboratory in the study institution, the standard range, blood sample collection date and time, and tests results will be recorded on the CRF.

Sodium, potassium, chlorine, calcium, phosphorus, BUN, creatinine*, A/G ratio, blood glucose, total protein, albumin, ALT, AST, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), γ-glutamyltransferase (γ-GTP), total bilirubin, direct bilirubin, and indirect bilirubin

*The eGFR will be calculated using the following formula. Age at the date of informed consent should be used for calculation.
For male, eGFR (mL/min/1.73 m^2) = 194 × serum $creatinine^{-1.094}$ × $Age^{-0.287}$
For female, eGFR (mL/min/1.73 m^2) = 194 × serum $creatinine^{-1.094}$ × $Age^{-0.287}$ × 0.739

10.5.3 Urinalysis

The following laboratory test parameters will be measured in the designated central laboratory. The presence or absence of sample collection will be recorded on the CRF.

Glucose, ketone bodies, occult blood, proteins, nitrites, bilirubin, specific gravity, pH, urobilinogen, and white blood cells

10.5.4 D-dimer

A D-dimer assay will be performed at the designated central laboratory for subjects with a history of venous thromboembolism > 6 months before Screening A. D-dimer assay should be performed only after resolution of the venous thromboembolism and after all anticoagulants have been discontinued for at least 30 days. The presence or absence of sample collection will be recorded on the CRF.

10.5.5 PT-INR/APTT

PT-INR/APTT will be measured at the designated central laboratory. The presence or absence of sample collection will be recorded on the CRF.

10.6 Immunoglobulin Test

Serum immunoglobulin levels (immunoglobulins M, G, and A) will be measured in the designated central laboratory. The presence or absence of sample collection will be recorded on the CRF.

10.7 Immunological Test

The following immunology test items will be measured in the designated central laboratory. The presence or absence of sample collection will be recorded on the CRF.

HIV antigen, HIV antibody, HBs antigen, HBs antibody, HBV DNA assay, HBc antibody, HCV RNA assay

10.8 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator will evaluate the condition of subjects using the ECOG Performance Status Japanese translation (see Appendix 1). Assessment date and results will be recorded in the CRF.

10.9 Vital Signs

Systolic and diastolic blood pressure, pulse rate, and body temperature (axillary) are measured after the subject rests (approximately for 3 minutes) in the sitting position. The measurement date, time, and results of systolic and diastolic blood pressure will be recorded on the CRF. The measurement date and results of pulse rate and body temperature (axillary) will be recorded on the CRF. If the initial blood pressure on each specified visit is > 130 mmHg systolic or > 80 mmHg diastolic, the blood pressure should be taken 2 additional times at least 5 minutes apart, and date, time and results for all 3 measurements will be recorded on the CRF. When the systolic and diastolic blood pressure is measured 3 times, the mean value of the 3 measurements will be used to make a decision for "5.2 Exclusion Criteria," "8.3.1 Transition criteria to Period II for subjects who withdraw from ," and "8.6.2.2 Dose adjustment due to adverse events." As a general rule, the laboratory parameters should be measured by the same devices for the same subject throughout the study period.

10.10 Height and Weight

Height and weight will be measured. The measurement date and results will be recorded on the CRF.

10.11 12-lead ECG

Twelve-lead ECG will be measured after subject rests (approximately for 5 minutes) in the supine position, and the measurement date and investigator's assessment will be recorded on the CRF. As a general rule, the 12-lead ECG should be measured by the same devices for the same subject throughout the study period. In principle, the 12-lead ECG is taken before the vital signs, laboratory tests, immunoglobulin test, immunological test, pregnancy test (women of childbearing potential only), and pharmacokinetics.

10.12 Pregnancy Test

Pregnancy test (serum human chorionic gonadotropin [HCG]) will be performed in women of childbearing potential (women who have not had their uteri or bilateral ovaries removed and had their last menstrual within 1 year) in the designated central laboratory. The presence or absence of sampling and pregnancy will be recorded in the CRF.

10.13 ITP Bleeding Score

The investigator will evaluate the bleeding score of subjects using the ITP Bleeding Scale (see Appendix 2). In principle, the same investigator should evaluate the same subjects. Assessment date and results will be recorded in the CRF.

10.14 Pharmacokinetics

The plasma concentration of R406 (active substance) will be measured. Plasma R406 concentrations will be measured by the liquid chromatography-tandem mass spectrometer (LC-MS/MS) method in the designated pharmacokinetic measurement laboratory (the detailed procedure of pharmacokinetic measurement is specified in the separate pharmacokinetic protocol). The date and time of the administration of the study drug from 2 days before to the day of blood sampling for the pharmacokinetic examination and the date and time of blood sampling on the day of the pharmacokinetic examination will be recorded in the CRF.

10.15 Adverse Events

An adverse event is defined as any untoward or unintended sign, symptom, aggravation of a complication, or disease that occurs in a subject, irrespective of the causal relationship with the study drug. The worsening of an efficacy variable is not considered to be an adverse event.

10.15.1 Collection of adverse events

The following information on each adverse event will be recorded in the CRF: name of the adverse event, date of onset, date of resolution (when the outcome is recovered/resolved, recovered/resolved with sequelae, or death), severity, dose at onset, seriousness assessment, action taken on the study drug, other actions taken, outcome, and causal relationship with the study drug. For adverse events that occur from the collection of informed consent to before the start of study treatment, the name of the adverse event and seriousness assessment will be recorded in the CRF.

10.15.1.1 Adverse event collection period

AEs will be collected from the collection of informed consent to the end of the follow-up period

or market authorization.

10.15.1.2 Inquiry about adverse events

The investigator should give sufficient consideration not to affect the voluntary reporting by subjects when conducting interviews with subjects. Specifically, the investigator should ask a general question, such as "Has anything happened since the last visit?"

10.15.1.3 Considerations for recording adverse events

1) When a diagnosis is determined from the signs and/or symptoms, the diagnosis will be recorded as an adverse event. Abnormal laboratory test values, abnormal findings, and symptoms associated with the adverse event will not be considered as an adverse event.
2) When a diagnosis is not determined from signs and/or symptoms, abnormal laboratory test values, abnormal findings, and symptoms will be handled as adverse events.
3) Abnormal laboratory test values and abnormal findings will be handled as an adverse event when they are clinically relevant variations or changes, as judged by the investigator. A clinically relevant variation or change is defined as a variation or change that requires medical intervention or treatment or is out of the normal physiological variation for the subject, as judged by the investigator.
4) Abnormal laboratory test values or abnormal findings observed at the start of the screening period should not be handled as an adverse event.
5) Diseases, symptoms, and findings present before the informed consent should not be handled as an adverse event.
6) Any worsening of a complication, existing symptom, or finding should be handled as an adverse event. Worsening of a complication, existing symptom, or finding is defined as an increase in the frequency or severity of a seasonal or intermittent symptom or finding when the investigator considers that the relevant disease, symptom, or finding before study participation has worsened more than expected.
7) Any adverse event that occurs from the collection of informed consent to before the start of the study treatment and worsens after the start of the study treatment is considered as a new adverse event.
8) Any surgery or procedure scheduled before the collection of informed consent is not handled as an adverse event.
9) Elective surgeries or procedures that have no impact on disease (eg, dental implant surgery, cosmetic surgery, or suture removal after skin suture at the subject's request) are not handled as an adverse event. However, any clinically relevant finding or symptom caused by such a surgery/procedure should be handled as an adverse event.
10) Events considered as a worsening within the range expected for the target disease are not handled as an adverse event.

10.15.2 Onset date of adverse events

- Date when the subject or investigator noticed the sign or symptom
- Date when the subject or investigator noticed the aggravation of the complication, existing

symptom, or finding

- Date of diagnosis confirmed even if the time of onset can be estimated for asymptomatic diseases
- For abnormal laboratory test values and abnormal findings, the date of examination from which a clinically relevant variation or change is obtained, as judged by the investigator

10.15.3 Severity of adverse events

The severity of adverse events will be evaluated with a 3-rank scale according to Table 10.15.3-1. The most severe rank will be recorded for adverse events that vary in severity.

Table 10.15.3-1 Severity of Adverse Events

Severity	Decision criteria
Mild	Events that do not interfere with activities of daily living,[a)] or slightly interfere with them but do not require particular treatment, or require simple treatment
Moderate	Events that interfere with activities of daily living[a)] and require treatment
Severe	Events that make activities of daily living[a)] almost impossible or requiring systemic treatment

a) For example, sleeping, moving, working, going out, eating, exercise, and bathing

10.15.4 Serious adverse events

Any adverse event that meets any of the following criteria will be handled as a serious adverse event for all adverse events, including those that occur from the collection of informed consent to before the start of the study treatment. If any serious adverse event occurs, its symptom or laboratory test parameter and the reason for judging it as serious will be recorded in the CRF.

1) Death
2) Life Threatening
3) Initial or Prolonged Hospitalization
4) Persistent or Significant Disability/Incapacity
5) Congenital Anomaly or Birth Defect
6) Other Medically Important Event

Other Medically Important Event is defined as cases that do not immediately threaten life or lead to hospitalization, but may expose patients to danger, or cases associated with medical events that require treatment or procedure to prevent the outcomes listed in the above 1) to 5).

10.15.5 Adverse events of special interest

The following adverse events are considered as an adverse event of special interest (regardless of seriousness). The details of adverse events of special interest are specified in the Statistical Analysis Plan.

1) Bleeding-related adverse events
2) Gastrointestinal disorders
3) Infection
4) Hypertension

5) Neutropenia

6) Hepatic dysfunction

7) Thrombosis, embolism, and thromboembolism

10.15.6 Actions taken with the study drug

Actions taken with the study drug are defined in Table 10.15.6-1.

Table 10.15.6-1 Actions Taken with the Study Drug

Action	Definition
Drug withdrawn	Discontinuation of the study treatment due to the adverse event in question, including the discontinuation requested by the subject
Drug interrupted	Interruption of the study drug due to the adverse event in question, including the interruption requested by the subject
Dose Reduced	Dose reduction of the study drug due to the adverse event in question, including the dose reduction requested by the subject Inability to increase the dose of the study drug due to the adverse event in question in subjects who meet the dose increase criteria
Dose not changed	Study treatment continued without taking any action to the study drug
Unknown	Actions taken to the study drug cannot be determined
Not applicable	The administration of the study drug is completed or discontinued before the onset of the adverse event in question

10.15.7 Outcome of the adverse event

The outcome of adverse events will be assessed according to Table 10.15.7-1.

Table 10.15.7-1 Outcome of the Adverse Event

Outcome	Decision criteria
Recovered/Resolved	Resolution of or recovery from symptoms, normalization of test values, or recovery to the baseline level
Recovering/Resolving	Reduction or improving tendency of the severity of symptoms or abnormal values
Not Recovered/Not Resolved	Almost no change or exacerbation in symptoms or abnormal values
Recovered/Resolved with Sequelae	Dysfunction derived from symptoms or abnormal values and interfering with activities of daily living
Fatal	Death related to symptoms/abnormal values *This outcome should not be chosen for death not related to symptoms or abnormal values.
Unknown	Inability to follow the outcome despite every possible effort to follow symptoms and abnormal values

10.15.8 Causal relationship between adverse events and the study drug

The causal relationship of adverse events with the study drug will be assessed on a 2-point scale according to Table 10.15.8-1, considering the condition of subjects, complications, medical history, concomitant drugs, and temporal relationship with the onset. Of adverse events that develop after the start of the study treatment, those evaluated as “Yes” for the causal relationship with the study drug are considered to be an adverse drug reaction.

For adverse events secondary to another adverse event, the causal relationship with the study drug should be evaluated for each adverse event independently.

Table 10.15.8-1 Causal Relationship between Adverse Events and the Study Drug

Relationship to study treatment	Decision criteria
Related	An adverse event is considered to have a causal relationship with the study drug because, for example, the onset of the adverse event can be easily explained from the condition of the subject, complications, medical history, concomitant drugs, or temporal relationship with the onset of the adverse event.
Not related	An adverse event does not meet the above decision criteria for the causal relationship with the study drug because it meets any of the following criteria. • The adverse event is clearly attributable to a factor other than the study drug. • There is no temporal correlation between the onset/resolution of the adverse event and administration of the study drug and there is a long interval between them. • The occurrence of the adverse event is considered incidental (eg, the same event has been frequently observed since before the study and the adverse event that occurred during the study is considered to be one of them). • There are possible factors other than the study drug, such as the medical history/condition of the subject or other concomitant drugs/measures, treatment, and meals.

10.15.9 Follow-up

Among serious adverse events that occur from the collection of the informed consent to before the start of the study treatment and adverse events that occur after the start of the study treatment, those for which symptoms are not resolved or improved to the level before onset by the end of the follow-up period as judged by the investigator will be followed. Follow-up will be terminated in either of the following cases.

1) The event is improved or resolved, as judged by the investigator.

2) The event no longer requires additional follow-up, as judged by the investigator.

10.16 Evaluation of Diarrhea

When diarrhea occurs as an adverse event, the grade of diarrhea according to Common Terminology Criteria for Adverse Events (CTCAE) Ver. 5.0 (see Appendix 5), duration of onset by grade, and actions taken with the study drug will be recorded in the CRF to confirm the appropriateness of dose adjustment of the study drug.

11. Schedule of Study Assessments and Procedures

The investigator and clinical research coordinator will perform the specified study assessments and procedures according to the study schedule and "10 Study Assessments and Procedures."

11.1 Collection of Informed Consent

- Written informed consent
- Inclusion/exclusion criteria
- First registration

11.2 Screening Period

11.2.1 Visit 1 (Screening A)

- Demographics
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- 12-lead ECG[a)]
- Vital signs
- Laboratory tests (hematology, serum chemistry, urinalysis, D-dimer assay,[b)] PT-INR/APTT)
- Immunoglobulin test
- Immunological test
- Pregnancy test (women of childbearing potential only)
- Inclusion/exclusion criteria
- Second registration

a) In principle, the 12-lead ECG is taken before vital signs, laboratory tests, immunoglobulin test, immunological test, and pregnancy test (women of childbearing potential only).
b) D-dimer assay is performed if the patient has a history of venous thromboembolism more than 6 months prior to Screening A.

11.2.2 Visit 2 (Screening B)

- Demographics
- Adverse events/concomitant medications
- Vital signs
- Laboratory test (Hematology)

11.3 Period I

11.3.1 Visit 3 (Day 1)

- QOL evaluation (SF-36)[a)]
- Demographics
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- Height and weight

- Vital signs
- Laboratory tests (hematology, serum chemistry, urinalysis, and PT-INR/APTT)
- Immunoglobulin test
- Inclusion/exclusion criteria
- Third registration
- Study drug dispensed (Period I)
- Administration of study drug

a) The QOL evaluation (SF-36) is performed before other procedures and evaluations.

11.3.2 Visit 4 (Week 2)

In principle, subjects should visit the study institution in the morning without taking the morning dose of the study drug.

- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- Vital signs
- Laboratory tests (hematology and serum chemistry)
- Pharmacokinetics (before study drug administration)
- Study drug dispensed (Period I)[a)]
- Administration of study drug
- Pharmacokinetics (1 to 4 hours after study drug administration)

a) The need of dispensing the study drug is decided, considering the number of tablets to be taken before the next visit.

11.3.3 Visit 5 (Week 4)

In principle, subjects should take the morning dose of the study drug 1 to 4 hours before blood sampling and then visit the study institution in the morning.

- QOL evaluation (SF-36)[a)]
- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- Vital signs
- Laboratory tests (hematology, serum chemistry, and urinalysis)
- Pharmacokinetics (1 to 4 hours after study drug administration)

- Study drug dispensed (Period I)[b)]

a) The QOL evaluation (SF-36) is performed before other procedures and evaluations.
b) The need of dispensing the study drug is decided, considering the number of tablets to be taken before the next visit.

11.3.4 Visit 6 (Week 6)

In principle, subjects should visit the study institution in the morning without taking the morning dose of the study drug.

- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- Vital signs
- Laboratory tests (hematology and serum chemistry)
- Pharmacokinetics (before study drug administration)
- Study drug dispensed (Period I)[a)]
- Administration of study drug
- Pharmacokinetics (1 to 4 hours after study drug administration)

a) The need of dispensing the study drug is decided, considering the number of tablets to be taken before the next visit.

11.3.5 Visit 7 (Week 8)

In principle, subjects should take the morning dose of the study drug 1 to 4 hours before blood sampling and then visit the study institution in the morning.

- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- Vital signs
- Laboratory tests (hematology, serum chemistry, and urinalysis)
- Pharmacokinetics (1 to 4 hours after study drug administration)
- Study drug dispensed (Period I)[a)]

a) The need of dispensing the study drug is decided, considering the number of tablets to be taken before the next visit.

11.3.6 Visit 8 (Week 10)

In principle, subjects should take the morning dose of the study drug 1 to 4 hours before blood sampling and then visit the study institution in the morning.

- Study drug compliance
- ITP Bleeding Score

- Adverse events/concomitant medications
- Vital signs
- Laboratory tests (hematology and serum chemistry)
- Pharmacokinetics (1 to 4 hours after study drug administration)
- Study drug dispensed (Period I)[a)]

a) The need of dispensing the study drug is decided, considering the number of tablets to be taken before the next visit.

11.3.7 Visit 9 (Week 12)

In principle, subjects should take the morning dose of the study drug 1 to 4 hours before blood sampling and then visit the study institution in the morning.

- QOL evaluation (SF-36)[a)]
- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- Vital signs
- Laboratory tests (hematology, serum chemistry, and urinalysis)
- Pregnancy test (women of childbearing potential only)
- Pharmacokinetics (1 to 4 hours after study drug administration)
- Study drug dispensed (Period I)[b)]

a) The QOL evaluation (SF-36) is performed before other procedures and evaluations.
b) The need of dispensing the study drug is decided, considering the number of tablets to be taken before the next visit.

11.3.8 Visit 10 (Week 14)

In principle, subjects should take the morning dose of the study drug 1 to 4 hours before blood sampling and then visit the study institution in the morning.

- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- Vital signs
- Laboratory tests (hematology and serum chemistry)
- Pharmacokinetics (1 to 4 hours after study drug administration)
- Study drug dispensed (Period I)[a)]

a) The need of dispensing the study drug is decided, considering the number of tablets to be taken before the next visit.

11.3.9 Visit 11 (Week 16)

In principle, subjects should take the morning dose of the study drug 1 to 4 hours before blood sampling and then visit the study institution in the morning.

- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- Vital signs
- Laboratory tests (hematology, serum chemistry, and urinalysis)
- Pharmacokinetics (1 to 4 hours after study drug administration)
- Study drug dispensed (Period I)[a)]

a) The need of dispensing the study drug is decided, considering the number of tablets to be taken before the next visit.

11.3.10 Visit 12 (Week 18)

In principle, subjects should take the morning dose of the study drug 1 to 4 hours before blood sampling and then visit the study institution in the morning.

- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- Vital signs
- Laboratory tests (hematology and serum chemistry)
- Pharmacokinetics (1 to 4 hours after study drug administration)
- Study drug dispensed (Period I)[a)]

a) The need of dispensing the study drug is decided, considering the number of tablets to be taken before the next visit.

11.3.11 Visit 13 (Week 20)

In principle, subjects should take the morning dose of the study drug 1 to 4 hours before blood sampling and then visit the study institution in the morning.

- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- Vital signs
- Laboratory tests (hematology, serum chemistry, and urinalysis)

- Pharmacokinetics (1 to 4 hours after study drug administration)
- Study drug dispensed (Period I)[a)]

a) The need of dispensing the study drug is decided, considering the number of tablets to be taken before the next visit.

11.3.12 Visit 14 (Week 22)

In principle, subjects should take the morning dose of the study drug 1 to 4 hours before blood sampling and then visit the study institution in the morning.

- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- Vital signs
- Laboratory tests (hematology and serum chemistry)
- Pharmacokinetics (1 to 4 hours after study drug administration)
- Study drug dispensed (Period I)[a)]

a) The need of dispensing the study drug is decided, considering the number of tablets to be taken before the next visit.

11.3.13 Visit 15 (Week 24)

In principle, subjects should take the morning dose of the study drug 1 to 4 hours before blood sampling and then visit the study institution in the morning.

- QOL evaluation (SF-36)[a)]
- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- 12-lead ECG[b)]
- Vital signs
- Laboratory tests (hematology, serum chemistry, and urinalysis)
- Immunoglobulin test
- Pregnancy test (women of childbearing potential only)
- Pharmacokinetics (1 to 4 hours after study drug administration)
- Enrollment for Transition to Period II
- Study drug dispensed (Period II)

a) The QOL evaluation (SF-36) is performed before other procedures and evaluations.
b) In principle, the 12-lead ECG is taken before the vital signs, laboratory tests, immunoglobulin test, pregnancy test (women of childbearing potential only), and pharmacokinetics.

11.4 Period II (Subjects Who Completed Period I)

11.4.1 Visit 16 (Week 28)

- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- Vital signs
- Laboratory tests (hematology, serum chemistry, and urinalysis)
- Study drug dispensed (Period II)

11.4.2 Visit 17 (Week 32) and Visit 18 (Week 36)

- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- Vital signs
- Laboratory tests (hematology and serum chemistry)
- Study drug dispensed (Period II)

11.4.3 Visit 19 (Week 40)

- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- Vital signs
- Laboratory tests (hematology, serum chemistry, and urinalysis)
- Pregnancy test (women of childbearing potential only)
- Study drug dispensed (Period II)

11.4.4 Visit 20 (Week 44) and Visit 21 (Week 48)

- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status

- Vital signs
- Laboratory tests (hematology and serum chemistry)
- Study drug dispensed (Period II)

11.4.5 Visit 22 (Week 52)

- QOL evaluation (SF-36)[a)]
- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- 12-lead ECG[b)]
- Vital signs
- Laboratory tests (hematology, serum chemistry, and urinalysis)
- Immunoglobulin test
- Pregnancy test (women of childbearing potential only)
- Written informed consent (only for subjects who want to participate in the Non-dosing period and Period III)

a) The QOL evaluation (SF-36) is performed before other procedures and evaluations.
b) In principle, the 12-lead ECG is taken before vital signs, laboratory tests, immunoglobulin test, and pregnancy test (women of childbearing potential only).

11.5 Period II (Early Transition Subjects)

11.5.1 ET Visit 1 (ET Day 1)

If the subject withdraws from Period I and transition to Period II, in principle, the study procedures on ET Day 1 will be performed on the same day as the last visit in Period I. When the study procedures on ET Day 1 are performed on the same day as the last visit for Period I, the procedures overlapping on ET Day 1 with the last visit of Period I may be omitted when the procedures on ET Day 1 are performed. If the procedures on ET Day 1 cannot be performed on the same day as the last visit of Period I, all procedures on ET Day 1 must be performed within 1 week from the last visit of Period I. All procedures on ET Day 1 should be performed on the same day.

- QOL evaluation (SF-36)[a)]
- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- 12-lead ECG[b)]

- Vital signs
- Laboratory tests (hematology, serum chemistry, and urinalysis)
- Immunoglobulin test
- Pregnancy test (women of childbearing potential only)
- Inclusion/exclusion criteria
- Enrollment for Transition to Period II
- Study drug dispensed (Period II)

a) The QOL evaluation (SF-36) is performed prior to other procedures and assessments on ET Day 1.
b) In principle, the 12-lead ECG is taken before vital signs, laboratory tests, immunoglobulin test, and pregnancy test (women of childbearing potential only).

11.5.2 ET Visit 2 (ET Week 4)

- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- Vital signs
- Laboratory tests (hematology, serum chemistry, and urinalysis)
- Study drug dispensed (Period II)

11.5.3 ET Visit 3 (ET Week 8) and ET Visit 4 (ET Week 12)

- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- Vital signs
- Laboratory tests (hematology and serum chemistry)
- Study drug dispensed (Period II)

11.5.4 ET Visit 5 (ET Week 16)

- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- Vital signs

- Laboratory tests (hematology, serum chemistry, and urinalysis)
- Pregnancy test (women of childbearing potential only)
- Study drug dispensed (Period II)

11.5.5 ET Visit 6 (ET Week 20) and ET Visit 7 (ET Week 24)

- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- Vital signs
- Laboratory tests (hematology and serum chemistry)
- Study drug dispensed (Period II)

11.5.6 ET Visit 8 (ET Week 28)

- QOL evaluation (SF-36)[a)]
- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- 12-lead ECG[b)]
- Vital signs
- Laboratory tests (hematology, serum chemistry, and urinalysis)
- Immunoglobulin test
- Pregnancy test (women of childbearing potential only)
- Written informed consent (only for subjects who want to participate in the Non-dosing period and Period III)

a) The QOL evaluation (SF-36) is performed before other procedures and evaluations.
b) In principle, the 12-lead ECG is taken before vital signs, laboratory tests, immunoglobulin test, and pregnancy test (women of childbearing potential only).

11.6 Non-dosing Period

11.6.1 ND Visit 1 (ND Week 2)

The study procedures for ND Week 2 are not performed for subjects who skip the Non-dosing period and transition to Period III, or transition from the Non-dosing period to Period III before performing the study procedures for ND Week 2.

- QOL evaluation (SF-36)[a)]

- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- 12-lead ECG[b)]
- Vital signs
- Laboratory tests (hematology, serum chemistry, and urinalysis)
- Immunoglobulin test
- Pregnancy test (women of childbearing potential only)

a) The QOL evaluation (SF-36) is performed before other procedures and evaluations.
b) In principle, the 12-lead ECG is taken before vital signs, laboratory tests, immunoglobulin test, and pregnancy test (women of childbearing potential only).

11.7 Period III

11.7.1 Period III Visit 1 (Period III Day 1)

The study procedures for Period III Day 1 are not performed for subjects who skip the Non-dosing period and transition to Period III. The study procedures for Period III Day 1 will be immediately performed irrespective of the allowance of visit for subjects who transition from the Non-dosing period to Period III before completing the Non-dosing period. When the study procedures on Period III Day 1 are performed on the same day as hose for ND Week 2, the procedures overlapping on Period III Day 1 with ND Week 2 may be omitted when the procedures on Period III Day 1 are performed.

- QOL evaluation (SF-36)[a)]
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- 12-lead ECG[b)]
- Vital signs
- Laboratory tests (hematology, serum chemistry, and urinalysis)
- Immunoglobulin test
- Pregnancy test (women of childbearing potential only)
- Study drug dispensed (Period III)

a) The QOL evaluation (SF-36) is performed before other procedures and evaluations.
b) In principle, the 12-lead ECG is taken before vital signs, laboratory tests, immunoglobulin test, and pregnancy test (women of childbearing potential only).

11.7.2 Period III Visit 2 (Period III Visit 2)

After Period III Week 8, subjects will visit the study institution every 8 weeks to undergo the

same study procedures as those at Period III Week 8.

- Study drug compliance
- ITP Bleeding Score
- Adverse events and use of ITP concomitant medications
- ECOG Performance Status
- Vital signs
- Laboratory tests (hematology, serum chemistry, and urinalysis)
- Pregnancy test (women of childbearing potential only)
- Study drug dispensed (Period III)

11.8 At Withdrawal

11.8.1 Withdrawal Visit

Subjects will undergo the Withdrawal Visit when they withdraw from Period I and do not transition to Period II, when they withdraw from Period II, or when they withdraw from Period III. Early transition subjects will not undergo the Withdrawal Visit. When the tests/examinations and evaluations on ET Day 1 do not meet "8.3.1 Transition criteria to Period II for subjects who withdraw from ," the tests/examinations and evaluations on ET Day 1 will be considered as those for Withdrawal Visit. Subjects who withdraw from the Non-dosing period will not undergo the Withdrawal Visit.

- QOL evaluation (SF-36)[a)]
- Study drug compliance
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- 12-lead ECG[b)]
- Vital signs
- Laboratory tests (hematology, serum chemistry, and urinalysis)
- Immunoglobulin test[c)]
- Pregnancy test (women of childbearing potential only)
- Pharmacokinetics[d)]

a) The QOL evaluation should be performed only for subjects who withdraw from Period I and do not transition to Period II or subjects who withdraw from Period II. If the QOL evaluation is performed, it should be performed before the other tests/examinations and evaluations.
b) The 12-lead ECG should be performed only for subjects who withdraw from Period I and do not transition to Period II or subjects who withdraw from Period II. In principle, the 12-lead ECG is taken before vital signs, laboratory tests, immunoglobulin test, immunological test, pregnancy test (women of childbearing potential only), and pharmacokinetics.
c) The Immunoglobulin test should be performed only for subjects who withdraw from Period I and do not transition to Period II or subjects who withdraw from Period II.
d) Pharmacokinetics should be examined only for subjects who withdraw from Period I and do not transition to Period II. The

time of the last study drug administration before blood sampling to the date of blood sampling are not specified.

11.9 Follow-up Period

11.9.1 Test at the end of the follow-up period

Subjects will undergo the test at the end of the follow-up period when they withdraw from Period I and do not transition to Period II, when they withdraw from Period II, when they complete Period II and do not want to participate in the Non-dosing period and Period III, when they withdraw from the Non-dosing period before ND Week 2, or when they withdraw from Period III. The tests at the end of the follow-up period are not performed for subjects who withdraw from the Non-dosing period at ND Week 2 or later.

- QOL evaluation (SF-36)[a)]
- ITP Bleeding Score
- Adverse events/concomitant medications
- ECOG Performance Status
- 12-lead ECG[b)]
- Vital signs
- Laboratory tests (hematology, serum chemistry, and urinalysis)
- Immunoglobulin test[c)]
- Pregnancy test (women of childbearing potential only)

a) Subjects should undergo the QOL evaluation only at the end of the follow-up period when they withdraw from Period I and do not transition to Period II, when they withdraw from Period II, or when they complete Period II and do not want to participate in the Non-dosing period and Period III. If the QOL evaluation is performed, it should be performed before the other tests/examinations and evaluations.
b) Subjects should undergo the 12-lead ECG only at the end of the follow-up period when they withdraw from Period I and do not transition to Period II, when they withdraw from Period II, or when they complete Period II and do not want to participate in the Non-dosing period and Period III. If the 12-lead ECG is taken, it should be taken, in principle, before the vital signs, laboratory tests, immunoglobulin test, and pregnancy test (women of childbearing potential only).
c) Subjects should undergo the immunoglobulin test only at the end of the follow-up period when they withdraw from Period I and do not transition to Period II, when they withdraw from Period II, or when they complete Period II and do not want to participate in the Non-dosing period.

12. Security of Study

12.1 Management of Adverse Events

When an adverse event occurs during the study period, the investigator will provide appropriate treatment to ensure the safety of the subject. The investigator will follow the adverse event according to "10.15.9 Follow-up" if it meets the criteria specified in the section.

12.2 Management of Serious Adverse Events

12.2.1 Measures to be taken against serious adverse events

When any serious adverse event specified in "10.15.4 Serious adverse events" occurs, the investigator will provide appropriate emergency measures to improve the health of the subject.

12.2.2 Handling of serious adverse events

The investigator will notify the person in charge of monitoring within 24 hours after he/she learns of the occurrence of the serious adverse event, and will submit the designated document within 3 days.

The principal investigator will promptly report the serious adverse event to the head of the study institution according to the applicable procedure of the study institution.

12.3 Management of Pregnant Women

When any female subject is found or suspected to be pregnant during the period from the start of the study drug administration to 30 days after the end of the study drug administration, the investigator should promptly discontinue the study treatment for the subject. Additionally, when the investigator becomes aware of any information suggesting pregnancy, he/she will promptly report it to the sponsor. Furthermore, the investigator will follow the course of pregnancy until delivery and the offspring up to about 1.5 years after birth and notify the sponsor of the information obtained. However, the follow-up is not necessary for subjects who are found to belong to the placebo group and do not transition to Period II.

12.4 Management of Abnormal Liver Function Test Values

The investigator will submit the designated form provided by the sponsor to the sponsor within 5 days after learning that all the following criteria are met at the same time. When the investigator determines the event as serious adverse event, the investigator will take actions according to "12.2 Management of Serious Adverse Events" and does not need to submit the specified form to the sponsor.

1) Increase in AST or ALT to ≥ 3 × ULN
2) Increase in total bilirubin to ≥ 2 × ULN

12.5 Collection and Provision of Safety Information

12.5.1 Collection of new safety information

The sponsor will continuously collect and evaluate information that may adversely affect the safety of subjects, affect the conduct of the study, or change the approval of the IRB for continuation of the study.

12.5.2 Provision of new safety information

The sponsor will promptly notify in writing all the principal investigators, heads of the study institutions, and IRBs (via the head of each study institution) involved in the study of any new information on the safety of the study drug that has to be reported to the investigators. The sponsor may notify the IRBs at the same time only for the notifications related to Article 20, Paragraphs 2 and 3 of GCP if the sponsor, IRBs, and heads of the study institutions have agreed to it.

When the investigator thinks that the information may affect the willingness of subjects to continue the study, the investigator will immediately inform subjects of the information and confirm their intention to continue the study. At the same time, the investigator will record in

writing (in the medical records) that the information was provided to subjects, and that their intention to continue the study was confirmed. If the principal investigator obtains information indicating the need to revise the informed consent form, the principal investigator will promptly revise it based on the information and obtain prior approval from the IRB. The investigator will explain the study to the subjects participating in the study again using the revised informed consent form and obtain the written informed consent to continue participation in the study from the subjects. In principle, no new subjects will be enrolled in the study until the revision of the informed consent form is approved. However, new subjects may be enrolled if the sponsor and the principal investigator decide that it is not necessary to change, discontinue, or suspend the study. In that case, the original informed consent form will be used and new safety information that may affect subjects' willingness to continue the study will be provided and that fact will be recorded. The consent to participate in the study will be obtained again using the revised informed consent form approved by the IRB.

13. Discontinuation/suspension of Study

13.1 Discontinuation/suspension of Part of the Study or the Entire Study

If an event that meets any of the discontinuation criteria occurs during the study period, the sponsor or the principal investigator will determine the handling of the event in consideration of discontinuation/suspension of part of the study or the entire study.

13.2 Discontinuation Criteria (Discontinuation/suspension of Part of the Study or the Entire Study)

1) The continuation of the study is considered difficult based on new safety information (including the onset of a serious adverse event).
2) The sponsor, study institution, or the principal investigator commits a serious violation of GCP, protocol, or contract, which interferes with the appropriate continuation of the study.
3) The continuation of the study is considered difficult due to the change in the study system (eg, transfer of the principal investigator)
4) The continuation of the study is considered inappropriate based on the new information obtained or change in the study environment during the study.

13.3 Procedure for Discontinuation/suspension

The following procedure should be taken to discontinue or suspend the study.

1) When the sponsor discontinues or suspends part of the study or the entire study, the sponsor will promptly notify the head of each study institution of the fact and detailed reason in writing.
2) When the principal investigator discontinues or suspends the study, the principal investigator will promptly report the fact and reason to the head of the study institution in writing.
3) When the head of each study institution receives the notification of the discontinuation/suspension of part of the study or the entire study from the sponsor, the

head of each study institution will immediately notify the principal investigator and IRB of the fact in writing and then report the reason for discontinuation/suspension in writing. When the head of the study institution receives the notification from the principal investigator, the head of the study institution will immediately notify the sponsor and IRB of the fact in writing and then report the reason for discontinuation/suspension in writing.

When the principal investigator receives the notification of the discontinuation/suspension of the study, the principal investigator will promptly inform the subjects with the study drug administration of the fact and take appropriate follow-up measures.

14. Statistical Analysis

Data analysis will be performed by the associate statistician as directed by the statistical analysis manager. The main analysis methods are as specified below. The detailed analyses methods will be specified in the statistical analysis plan to be prepared separately before the data from Period I are locked. Any necessary analysis other than the pre-specified analyses will be performed using an appropriate method at the discretion of the statistical analysis manager. SAS 9.4 or later will be used as the analysis software.

Inclusion/exclusion of subjects in analysis sets and handling of data will be determined before data lock in Period I.

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 quartile. Unless otherwise specified, data will be tabulated for each analysis group, each period, and each time point.

The time points of analysis are shown in this chapter. The time window of each time point will be specified separately.

14.1 Analysis Sets

Analysis will be performed based on the assigned treatment when the full analysis set (FAS) is used as the analysis set. Analysis will be performed based on the actual treatment when the safety set (SS) and pharmacokinetic analysis set (PKS) are used as an analysis set.

- 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.
- SS: Subject population which excludes subjects who deviated GCP, who did not receive any study drug, and who discontinued prior to Period I.
- PKS: Set of subjects excluding subjects who have no plasma drug concentration data at all from subjects in the SS

14.2 Analysis Group

1) Evaluation in Period I
    - R788 group: Subjects who receive R788 in Period I
    - Placebo group: Subjects who receive placebo in Period I

2) Evaluation of long-term treatment of R788
   - R788 group: Subjects who complete the treatment with R788 in Period I and then transition to Period II (subjects who receive the long-term continuous treatment with R788)
3) Evaluation in Period II
   - R788 group in Period I: Early transition subjects after completing the treatment with R788 in Period I
   - Placebo group in Period I: Subjects who transition to Period II after the treatment with placebo in Period I
4) Evaluation in the Non-dosing period
   - R788 group: Subjects who transition to the Non-dosing period
5) Evaluation in Period III
   - R788 group: Subjects who receive R788 in Period III
6) Evaluation in the R788 treatment period
   - R788 group: Subjects of R788 group in Period I and subjects who transition to Period II/III

14.3 Disposition of Subjects

The number and percentage of subjects will be presented for the inclusion or exclusion of subjects in/from the analysis sets in Period I and the presence or absence of withdrawal in each period. The difference between groups in Period I will be evaluated using Fisher's exact test.

14.4 Demographic and Other Baseline Characteristics

For the major demographic characteristics of Period I, summary statistics or number and percentage of subjects will be presented both overall and by treatment groups, depending on data characteristics.

14.5 Efficacy

FAS will be used as the efficacy analysis set.

14.5.1 Primary endpoint

The primary efficacy endpoint in this study is the achievement rate of stable platelet response. The primary endpoint will be analyzed using data from Period I.

Achievement rate of 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 are considered to be a responder and the percentage of responders will be evaluated.

The following procedures should be taken to evaluate the achievement rate of stable platelet response.

- Subject who withdrawn from the study due to “adverse event” or “lack of efficacy” or

subject receiving rescue therapy from Week 10 to Week 24 will be considered non-responders.

- For missing data in subjects other than those listed above, data will be imputed using last observation carried forward (LOCF) method until Week 24 and the achievement rate of stable platelet response will be analyzed based on imputed data.

14.5.1.1 Analysis method for primary endpoint

The achievement rate of stable platelet response with two-sided 95% exact confidence interval (Clopper-Pearson) will be presented. The difference in the achievement rate between the groups with two-sided 95% exact confidence interval will be calculated. The superiority of the R788 group to the placebo group will be evaluated using the Fisher's exact test. The significance level is two-sided 5%.

14.5.1.2 Sensitivity analysis of primary endpoint

The robustness of the primary endpoint will be evaluated by a sensitivity analysis using multiple imputation as shown below.

First, non-monotone missing data will be imputed using MI procedure with MCMC options. This imputation is based on platelet count from Week 2 to 24 as covariate. Then, monotone missing data will be imputed based on the chained equation method. This imputation will be performed by MI procedure with MONOTONE REG options. The imputed data sets will be analyzed for stable platelet response using a logistic regression model by treatment, and the results will be summarized using PROC MIANALYZE.

14.5.2 Secondary efficacy endpoints

14.5.2.1 Evaluation in Period I

The following analyses will be performed for the R788 and placebo treatment groups in Period I. Baseline is defined as Day 1 in Period I.

1) Achievement rate of platelet count

   The achievement rate with two-sided 95% exact confidence interval (Clopper-Pearson) will be presented for the following endpoints. The difference in the achievement rate between the groups and its two-sided 95% exact confidence interval will be presented. Any subject not evaluated as a responder will be regarded as a non-responder.

   - Achievement rate of a platelet count of at least 50000/μL at Weeks 12 and 24
   - Achievement rate of a platelet count increase at least 20000/μL above baseline and ≥ 30000/μL at Week 12 and 24 (for subjects with baseline platelet count < 15000/μL)
   - Achievement rate of overall response (subjects who achieve a platelet count of ≥ 50000/μL at least 1 of the 6 visits from Weeks 2 to 12 are defined as a responder and the percentage of responders will be evaluated)

2) Number of times of achieving platelet count

   Frequency distributions will be presented for the following endpoints.

- Number of times a platelet count ≥ 50000/μL in the 6 visits between Week 2 to Week 12
- Number of times a platelet count of ≥ 50000/μL in the 12 visits from Weeks 2 to 24

3) Duration of stable platelet response

   Summary statistics will be presented for the duration of the stable platelet response since the first achievement of a platelet count of ≥ 50000/μL after administration of the study drug.

4) Summary statistics will be presented for the measured value of platelet count and change from the baseline.

5) Frequency distributions of platelet count will be presented.

6) The time course of platelet count in individual subjects will be presented.

7) The summary statistics of the QOL evaluation (SF-36) will be presented.

14.5.2.2 Evaluation of long-term treatment of R788

The data from subjects who receive the long-term continuous treatment with R788 in Periods I and II will be analyzed as follows. Baseline is measurements at Day 1 in Period I.

1) Achievement rate of platelet count

   The achievement rate with two-sided 95% exact confidence interval (Clopper-Pearson) will be presented for the following endpoints. Any subject not evaluated as a responder will be regarded as a non-responder.

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

2) Duration of stable platelet response

   Summary statistics will be presented for the duration of the stable platelet response since the first achievement of a platelet count of ≥ 50000/μL after administration of the study drug.

3) Summary statistics will be presented for the measured value of platelet count and change from the baseline.

4) Frequency distributions of platelet count will be presented.

5) The time course of platelet count in individual subjects will be presented.

6) The summary statistics of the QOL evaluation (SF-36) will be presented.

14.5.2.3 Evaluation in Period II

The data in Periods I and II from subjects who receive placebo in Period I and transition to Period II will be analyzed as described in 1). The data in Period II from early transition subjects after completing the treatment with R788 in Period I and those who receive placebo in Period I

and transition to Period II will be analyzed by groups, as specified in 2) to 7). The periods from Weeks 24 to 52 and from ET Day 1 to ET Week 28 will be hereinafter expressed as Day 1 to Week 28 of Period II and Day 1 of Period II will be considered as the baseline of Period II.

1) Achievement rate of maintenance of platelet count in Periods I and II

   Considering the subjects who achieve a platelet count of ≥ 50000/μL within 12 weeks after the start of study treatment in Periods I and II and maintain it for 12 weeks as a responder, the achievement rate with two-sided 95% exact confidence interval (Clopper-Pearson) will be presented. The difference in the achievement rate between Periods I and II and its two-sided 95% exact confidence interval will be presented. McNemar test will be used to evaluate the difference in the achievement rate between Periods I and II.

2) Achievement rate of platelet count

   The achievement rate with two-sided 95% exact confidence interval (Clopper-Pearson) will be presented for the following endpoints. Any subject not evaluated as a responder will be regarded as a non-responder.

   - Achievement rate of platelet count of ≥ 50000/μL at Weeks 12, 24, and 28 in Period II
   - Achievement rate of a platelet count increase at least 20000/μL above baseline and ≥ 30000/μL at Weeks 12, 24, and 28 in Period II (for subjects with a baseline platelet count of < 15000/μL)

3) Duration of stable platelet response

   Summary statistics will be presented for the duration of stable platelet response from the first achievement of a platelet count of ≥ 50000/μL after administration of the study drug in Period II.

4) Summary statistics will be presented for the measured value of platelet count and change from the baseline.

5) Frequency distributions of platelet count will be presented.

6) The time course of platelet count in individual subjects will be presented.

7) The summary statistics of the QOL evaluation (SF-36) will be presented.

14.5.2.4 Evaluation in the Non-dosing period

Data during the Non-dosing period from subjects who transition to the Non-dosing period are included. Week 52 and ET Week 28 are considered as Day 1 of the Non-dosing period, which is regarded as the baseline.

1) Summary statistics will be presented for the measured value of platelet count and change from the baseline.

2) Frequency distributions of platelet count will be presented.

3) The time course of platelet count in individual subjects will be presented.

14.5.2.5 Evaluation in Period III

Data during Period III from subjects who transition to Period III will be included. Day 1 of

Period III will be regarded as the baseline.

1) Summary statistics will be presented for the measured value of platelet count and change from the baseline.
2) Frequency distributions of platelet count will be presented.
3) The time course of platelet count in individual subjects will be presented.

14.6 Safety

SS will be used as the safety analysis set. Safety will be analyzed by the analysis groups and Day 1 of each period will be considered as the baseline. Day 1 of Period I will be considered as the baseline for the evaluation of the long-term administration of R788. In addition, the analysis for the Non-dosing period and Period III will be performed only for "14.6.1 Adverse events and adverse drug reactions" and "14.6.2 ITP Bleeding Score", and the analysis for R788 treatment period will be performed only for "14.6.1 Adverse events and adverse drug reactions."

14.6.1 Adverse events and adverse drug reactions

The data on adverse events and adverse drug reactions will be analyzed as follows. Adverse events and adverse drug reactions that occur after the dosing of R788 will be analyzed in the evaluation of the R788 treatment period.

1) Incidence rate of adverse events and adverse drug reactions

   The number of events, number of subjects with events, and incidence rate with two-sided 95% exact confidence interval (Clopper-Pearson) will be presented for adverse events and adverse drug reactions. The difference in incidence rate between the groups and its two-sided 95% exact confidence interval will be presented.

2) Incidence of adverse events and adverse drug reactions (major events)

   The number of events, number of subjects with events, and incidence rate will be presented for the overall adverse events and adverse drug reactions, events leading to death, serious events excluding death, events leading to discontinuation, events leading to interruption, events leading to dose reduction, and events of special interest.

3) Adverse events and adverse drug reactions

   The number of events, number of subjects with events, and incidence rate will be presented for the overall adverse events and adverse drug reactions, primary System organ classes (SOCs) and Preferred terms (PTs). The same analysis will be performed for adverse events and adverse drug reactions of special interest.

4) Severity of adverse events and adverse drug reactions

   The number of events by severity will be presented for the overall adverse events and adverse drug reactions, primary SOCs and PTs. The same analysis will be performed for adverse events and adverse drug reactions of special interest.

14.6.2 ITP Bleeding Score

1) Summary statistics will be presented for the mean and total scores of the anatomical sites (9 sites except Skin [Hx] and Oral [Hx]) and distribution of the maximum score will be presented.

14.6.3 ECOG performance status

1) The frequency distribution of scores will be presented.

14.6.4 Vital signs

1) For vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, and body temperature), the summary statistics of measured values and changes from the baseline will be presented. Scatter plot of measured values before and after administration will be presented.
2) The maximum systolic blood pressure after the dosing of the study treatment in each period will be categorized into < 140 mmHg, ≥ 140 mmHg to < 160 mmHg, ≥ 160 mmHg to < 180 mmHg, and ≥ 180 mmHg and frequency distribution will be shown.
3) The maximum diastolic blood pressure after the dosing of the study treatment in each period will be categorized into < 90 mmHg, ≥ 90 mmHg to < 100 mmHg, ≥ 100 mmHg to < 110 mmHg, and ≥ 110 mmHg, and frequency distribution will be shown.
4) For systolic and diastolic blood pressure, frequency distribution of the number of times of systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg after the dosing of the study treatment in each period will be shown. The number of times of systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg will also be presented in the same manner.

14.6.5 Laboratory and immunoglobulin tests

1) Summary statistics will be presented for quantitative values and changes from the baseline. Scatter plot of measured values before and after administration will be presented.
2) The number and percentage of subjects will be presented for qualitative parameters.
3) Shift tables before and after administration will be presented.
4) The maximum ALT or AST value after the start of the study treatment in each period will be categorized into $\leq 3 \times$ ULN, $\geq 3 \times$ ULN to $< 5 \times$ ULN, $\geq 5 \times$ ULN to $< 10 \times$ ULN, and $\geq 10 \times$ ULN, and frequency distribution will be presented.

14.7 Pharmacokinetics

PKS will be used as the pharmacokinetic analysis set.

14.7.1 Plasma drug concentration

1) Summary statistics of the plasma concentrations of R406 (active metabolite) will be presented.

14.8 Timing of Analysis

The statistical analysis will be performed with the data in Period I when the data in Period I are locked. The data until the date of data cutoff will be analyzed after all subjects complete Period II.

15. Agreement on and Amendment to the Protocol

15.1 Agreement on the Protocol

The principal investigator must write his or her name and seal or sign, and date the protocol or an alternative document in order to prove that the principal investigator has agreed to the contents of the protocol and agreed to comply with the protocol.

15.2 Amendment to the Protocol

The sponsor must revise the protocol, where necessary, when the sponsor becomes aware of important information to ensure the quality, efficacy, and safety of the study drug or to conduct the study proper manner. When the protocol is revised and even when the protocol is revised by the order of the head of the study institutions based on the opinion from the IRB, the sponsor must obtain agreement with the principal investigator.

The investigator should not implement any deviation from or change to the protocol without prior documented agreement between the principal investigator and the sponsor, and prior review and documented approval from the IRB of an amendment, except where necessary for medical emergency such as to eliminate an immediate hazard(s) to subjects, or when the change involves only administrative aspects of the study.

15.3 Protocol Deviations

If a deviation from or change to the protocol is implemented to eliminate an immediate hazard(s) to subjects or for other medical emergency prior to obtaining approval, the principal investigator must, as soon as possible, submit the deviation or change with its reason(s) and, if appropriate, the proposed protocol amendment to the sponsor, the head of the study institution, and to the IRB via the head of the study institution for approval. The principal investigator also should obtain approval from the head of the study institution, as well as a documented agreement with the sponsor via the head of the study institution. In addition, the investigator should document all deviations from the protocol.

16. Direct access to Source Documents

16.1 Source Documents

A “source documents” is defined as a document, data, and record to create a document such as a CRF. Specifically, that is a necessary record to allow reconstruction of the course of events and evaluation of the study, including the informed consent form, medical records, test/examination data, and a history of the study drug administration. The study institution should consult with the sponsor to identify source documents.

16.2 Direct Access

The head of the study institution and the principal investigator should accept monitoring and audit by the sponsor, and investigations by the IRB and regulatory authorities of Japan and other countries, and make available for direct access the source documents.

The sponsor should confirm that each subject has consented in written to allow the direct access to his or her source clinical records at the time of such monitoring, audit, or investigations by the IRB and regulatory authorities of Japan and other countries.

16.3 Consistency of a Case Report From with the Source Documents

The sponsor should check the CRF from created by principal investigator against the study-related documents such as source documents and confirm that both are accurate.

The CRF should be consistent with the source documents. If any discrepancy is found, the principal investigator should create a document to explain the reason(s) and submit to the sponsor. The study institution should retain a copy of the document.

17. Quality Control and Assurance for the Study

The sponsor will implement quality control and assurance for the study in accordance with the standard operating procedures. The sponsor's auditor should assess whether or not this study is being conducted in compliance with the GCP, the protocol and the operating procedures independently, separating from the routine monitoring and quality control functions in the study.

18. Ethics

18.1 Compliance with GCP

This study will be conducted in accordance with Article 14 (3) and Article 80 (2) of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices and any other relevant standards for clinical studies of drug, which have been specified by the Minister of Health, Labour and Welfare, “Ministerial Ordinance on Good Clinical Practice for Drugs” that was established as the standards stipulated by the ministerial ordinance, and the protocol consistent with the ethical principles that have their origin in the latest Declaration of Helsinki.

18.2 Subject Confidentiality Considerations

The head of the study institution should take necessary measures to ensure the subject's confidentiality. The confidentiality of records related to subjects (e.g., CRFs) must be protected using subject identification codes, and the subject's right should be fully taken into account. The monitor, the auditor, the IRB, and regulatory authorities must maintain subject information as confidential when they access the source documents.

18.3 Compensation to Subjects

1) In the event of study-related health damages in a subject, the study institution must provide treatment and take any other necessary procedures.

2) Regarding the study-related health damages, if the subject claims compensation or indemnification to the study institution or there is such a possibility, the study institution must immediately notify the sponsor and strive to resolve the problem together.
3) The sponsor must compensate the study-related health damages in accordance with the compensation regulations set by the sponsor.
4) In the event of study-related health damages for which indemnity liability arises later, the compensation should be made at the liable person's own risk and expense.
5) The sponsor must purchase insurance for compensation or indemnification described above.

19. Data Handling and Records Retention

19.1 Case Report from Creation and Submission

In this study, clinical study data including investigations, observations, tests and evaluations will be electronically collected and recorded, creating the subject's CRFs. The investigator should create the CRF for each subject who provided informed consent, and the principal investigator will confirm the all record. Data on platelet count, rescue therapy, compliance with the study drug, vital signs (systolic and diastolic blood pressure), diarrhea and neutrophil count should be recorded in the CRFs generally within 3 days (excluding Saturday, Sunday, and holidays) after the data become available. For subjects who do not enter the Period I, demographics (excluding those related to the inclusion/exclusion criteria), tests/examinations and evaluations performed during the screening period, adverse events, and study discontinuation will be collected and recorded. For the creation method of CRF, the separate documented procedure is to be followed.

19.2 External Data

If the results measured at external laboratories are obtained as electronic data, the data should be obtained directly from external laboratories. For the method and timing of the data creation, the written procedure established at the external laboratory should to be followed.

19.3 Records Retention

19.3.1 Study institution

The head of the study institution must retain all documents and records associated with this study until the sponsor notifies the study institution that such documents and records are no longer needed. The head of the study institution or the records retention manager must take measures to avoid any loss or destroying these records during retention and to provide them upon request.

The principal investigator must retain all documents associated with the conduct of the study in accordance with the instructions from the head of the study institution.

19.3.2 Institutional Review Board

The founder of the IRB must retain all documents and records associated with this study until the sponsor notifies the founder that such documents and records are no longer needed. These

records should be readily available to be provided upon request from the regulatory authorities.

19.3.3 Sponsor notifications

The sponsor will notify the head of the study institution as well as the founder of the IRB via the head of the study institution when the retained documents and records associated with the study by the head of the study institution and the founder of the IRB are no longer needed.

20. Payment

Regarding payments to subjects, the study institution and the sponsor will have a prior discussion and obtain approval from the IRB. When approval is obtained, payments should be based on the documents relating to payment to subjects.

21. Publication Policy

Unpublished data in this protocol is proprietary information of the sponsor and must not be disclosed to third parties without prior documented agreement with the sponsor. External disclosure of whole or part of the results from this study in the academic conference or journals requires prior approval from the sponsor.

22. Study Organization

This study will be planned and conducted by the organization described in a separate addendum. Revisions of the addendum should be managed separately from this protocol.

23. Protocol Revision History

Prepared on August 28, 2019. Version: 1.0

24. References

1) Japan Intractable Diseases Information Center Certification Criteria for Idiopathic Thrombocytopenic Purpura (homepage on the Internet). (cited on April 19, 2018) Available from http://www.nanbyou.or.jp/upload_files/File/063-201704-kijyun.pdf

2) Fujimura K. Idiopathic Thrombocytopenic Purpura. *The Journal of the Japanese Society of Internal Medicine*. 2009;98(7):1619-26

3) Kuwana M. Idiopathic Thrombocytopenic Purpura. *Japanese Journal of Thrombosis and Hemostasis*. 2008;19(2):199-201

4) Ministry of Health, Labour and Welfare, Report on Public Health Administration and Services (as of the end of 2017)

5) Fujimura K, Miyagawa Y, and Kurata Y, et al. Reference Guide for the Management of Adult Idiopathic Thrombocytopenic Purpura (ITP) 2012 Version. *The Japanese Journal of Clinical Hematology*. 53(4):433-42

6) Tomiyama Y. Current topics in primary immune thrombocytopenia. *The Japanese Journal of Clinical Hematology*. 2017;58(5):537-41

7) Annual Report of Research Study Team for Intractable Disease (Blood Coagulation Abnormalities), the Ministry of Health, Labour, and Welfare. 2017 General Assigned Study Report

8) Depre F, Aboud N, Ringel F, et al. Thrombopoietin Receptor Agonists Are Often Ineffective in Immune Thrombocytopenia and/or Cause Adverse Reactions: Results from One Hand. *Transfus Med Hemother* 2016;43:375-9

9) Carpenedo M, Cantoni S, Coccini V, et al. Response loss and development of neutralizing antibodies during long-term treatment with romiplostim in patients with immune thrombocytopenia: a case series. *European Journal of Haematology*. 2016;97(1):101-3

10) Miyakawa Y, Katsutani S, Yano T, et al. Efficacy and safety of rituximab in Japanese patients with relapsed chronic immune thrombocytopenia refractory to conventional therapy. *Int J Hematol* 2015;102(6):654-61

11) Tomiyama Y. Rituximab Therapy for Autoimmune Thrombocytopenic Purpura. *Hematology*. 2012;65(6):832-7

12) Bussel J, Arnold D, Grossbard E, et al. Fostamatinib for the Treatment of Adult Persistent and Chronic Immune Thrombocytopenia: Results of Two Phase 3, Randomized, Placebo-Controlled Trials. *Am J Hematol.* 2018;93:921-30

Appendix 1 Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

Score	Definition
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Source:
Common Toxicity Criteria, Version 2.0 Publish Date April 30, 1999
National Cancer Institute（https://ctep.cancer.gov/）

Appendix 2 Immune Thrombocytopenic Purpura Bleeding Scale

Site	Bleeding score		
	0	1	2
Skin (Physical Examination [PE])	None	1–5 bruises and/or scattered petechiae	> 5 bruises with size > 2 cm and/or diffuse petechiae
Oral (PE)	None	1 blood blister or > 5 petechiae or gum bleeding that clears easily with rinsing	Multiple blood blisters and/or gum bleeding
Skin (Hx)	None	1–5 bruises and/or scattered petechiae	> 5 bruises with size > 2 cm and/or diffuse petechiae
Oral (Hx)	None	1 blood blister or > 5 petechiae and/or gum bleeding < 5 min	Multiple blood blisters and/or gum bleeding > 5 min
Epistasis	None	Blood when blowing nose and/or epistaxis < 5 min (per episode)	Bleeding > 5 min (per episode)
Gastrointestinal (GI)	None	Occult blood	Gross blood
Urinary (U)	None	Microscopic (+ve dipstick)	Macroscopic
Gynecological (GYN)	None (normal period)	Spotting not at time of normal period	Bleeding > spotting not at time of period or very heavy period
Pulmonary	None	N/A	Yes
Intracranial haemorrhage	None	N/A	Yes
Subconjunctival haemorrhage	None	Yes	N/A

Source:
Page LK, Psaila B, Provan D, et al. The immune thrombocytopenic purpura (ITP) bleeding score: assessment of bleeding in patients with ITP. British journal of haematology. 2007;138(2):245-8.

Appendix 3 Management of Increases in AST, ALT, or Bilirubin

Liver enzyme abnormities or associated symptoms should be managed by adjusting the dose of the study drug or performing additional tests/examinations according to the following instructions. Additional tests/examinations may be performed at the study institution. The investigator should inform the sponsor of the onset of liver function test abnormality specified in "12.4 Management of Abnormal Liver Function Test Values" by the due date specified in "12.4 Management of Abnormal Liver Function Test Values."

R788 is an inhibitor of UGT1A1, the enzyme responsible for the glucuronidation of bilirubin; occasionally an isolated increase in total and unconjugated (indirect) bilirubin may be observed. Study drug should not be interrupted for an isolated increase in total and unconjugated (indirect) bilirubin.

1) In the case that subjects meet a), b) and c)

   a) ALT or AST ≥ 3 × ULN

   b) Total bilirubin > 2 × ULN

   c) ALP < 2 × ULN

   (1) Interrupt the study drug and consider withdrawing the subject from the study due to suspected drug-induced liver injury.

   (2) The investigator will follow the subject until liver function test results and clinical symptoms and findings return to normal or the level of Day 1, or as long as medically indicated.

   (3) The investigator will investigate the etiology of the event and perform diagnostic examinations.

2) In the case that subjects meet a) or b) and have nausea, vomiting, abdominal pain

   a) ALT or AST ≥ 3 × ULN

   b) Total bilirubin > 2 × ULN

   (1) Study drug administration should be interrupted.

   (2) Liver function tests, including bilirubin and alkaline phosphatase should be repeated until ALT/AST or total bilirubin returns to < 1.5 × ULN (the frequency of repeat tests is decided by the investigator).

   (3) When the ALT/AST or total bilirubin returns to < 1.5 × ULN, the study drug may be restarted at 1 lower dose level.

   (4) The recurrence of the condition of 2) should be managed in the same manner.

3) In the case that subject meet a) or b) and subject is asymptomatic

   a) ALT or AST ≥ 3 × ULN

   b) Total bilirubin > 2 × ULN

(1) Repeat liver function tests immediately, including ALP.

(2) If repeat testing shows an increase in ALT/AST or total bilirubin and the ALT/AST value exceeds 5 × ULN, immediately interrupt study drug administration.

(3) Liver function tests including ALP will be repeated until ALT, AST, or total bilirubin returns to < 1.5 × ULN (the frequency of repeat tests is decided by the investigator).

(4) When the ALT/AST or total bilirubin returns to < 1.5 × ULN, the study drug may be restarted at 1 lower dose level.

(5) The recurrence of the condition of 3) should be managed in the same manner.

Dose Adjustment

Dose reduction				Dose before dose increase/ reduction	Dose escalation		
Dose level −4	Dose level −3	Dose level −2	Dose level −1		Dose level +1	Dose level +2	Dose level +3
Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*	—	—	—
—	Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*	—	—
—	—	Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*	—
—	—	—	Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*

References:
FDA. Guidance for Industry: Drug-induced liver injury: premarketing clinical evaluation. In: FDA,CDER,CBER.http://www.fda.gov/downloads/drugs/guidancecomplianceregulatory information/guidances/ucm174090.pdf: issued July 2009.

Appendix 4 Management of Neutrophil Count Decreased

Neutrophil count decreased should be managed by adjusting the dose of the study drug or performing additional tests/examinations according to the following instructions.

1) Neutrophil count decreased to < 1000/μL
   (1) Repeat neutrophil count measurement immediately.
   (2) If repeat testing confirms that neutrophil count is < 1000/μL, immediately interrupt study drug administration and repeat the measurement of neutrophil count (the frequency of additional measurements will be determined by the investigator).
   (3) When neutrophil count recovers to > 1500/μL, restart study drug at 1 lower dose level.

2) Recurrence of neutrophil count of < 1000/μL
   (1) Repeat neutrophil count measurement immediately.
   (2) If repeat testing confirms that neutrophil count is < 1000/μL, immediately interrupt study drug administration and repeat the measurement of neutrophil count (the frequency of additional measurements will be determined by the investigator).
   (3) When neutrophil count recovered to > 1500/μL, restart study drug at 2 lower dose level from the dose level at which the "1) Neutrophil count decreased to < 1000/μL" occurred.

Dose Adjustment

Dose reduction				Dose before dose increase/ reduction	Dose escalation		
Dose level −4	Dose level −3	Dose level −2	Dose level −1		Dose level +1	Dose level +2	Dose level +3
Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*	—	—	—
—	Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*	—	—
—	—	Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*	—
—	—	—	Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*

Appendix 5 Management of Diarrhea

Subjects should be made aware that they may experience diarrhea and instructed to contact the clinical site if they experience diarrhea. If diarrhea is observed, the investigator decide grade of diarrhea according to CTCAE v 5.0 (see the table below) and adjust the dose of study drug or perform additional tests in accordance with the following instructions.

Grade of Diarrhea (CTCAE v 5.0)

Grade	Decision criteria
Grade 1	• Increase of < 4 stools per day over baseline • Mild increase in ostomy output compared to baseline
Grade 2	• Increase of 4 to 6 stools per day over baseline • Moderate increase in ostomy output compared to baseline • Limiting instrumental activities of daily living
Grade 3	• Increase of ≥ 7 stools per day over baseline • Hospitalization indicated • Severe increase in ostomy output compared to baseline • Limiting self care activities of daily living
Grade 4	• Life-threatening consequences; urgent intervention indicated
Grade 5	• Death

Source:
Quoted from Common Terminology Criteria for Adverse Events v 5.0
National Cancer Institute (https://ctep.cancer.gov/)

1) Grade 1 or 2 diarrhea

(1) Study drug may be continued. Diarrhea should be managed until resolution of symptom in reference to the following items.

- Discontinue all laxatives.
- Subjects should be instructed to drink 8 to 10 glasses of water or clear fluids per day.
- Subjects should be encouraged to make dietary changes including elimination of dairy products and eating smaller but more frequent meals.
- Consider stool sample for microbiologic evaluation and antibiotics if subject is neutropenic.
- Grade 1, consider initiating treatment with loperamide according to the regimen below. Grade 2, initiate treatment with loperamide according to the regimen below.
  a) Up to 2 mg loperamide initial dose.
  b) If loose stool persists, the dose of loperamide will be adjusted and administration will be continued.

(2) Subjects with persistent diarrhea (> 48 hours) should be monitored carefully for dehydration and electrolyte imbalance.

(3) Manage the recurrence of 1) in the same manner.

2) Grade 3 or 4 diarrhea

(1) Study drug administration should be interrupted. Diarrhea should be managed until resolution of symptoms in reference to the following items.

- Initiate aggressive fluid replacement to treat potential dehydration.
- Consider stool sample for microbiologic evaluation and antibiotics if subject is neutropenic.
- Begin treatment with loperamide and continue treatment until the diarrhea has been resolved.
  a) Up to 2 mg loperamide initial dose.
  b) If loose stool persists, the dose of loperamide will be adjusted and administration will be continued.

(2) When diarrhea improves to ≤ Grade 1, restart study drug at 1 lower dose level.

3) Recurrence of Grade 3 or 4 diarrhea

(1) Study drug administration should be interrupted. Diarrhea should be managed until resolution of symptoms in reference to the following items.

- Initiate aggressive fluid replacement to treat potential dehydration.
- Consider stool sample for microbiologic evaluation and antibiotics if subject is neutropenic.
- Begin treatment with loperamide and continue treatment until the diarrhea has been resolved.
  a) Up to 2 mg loperamide initial dose.
  b) If loose stool persists, the dose of loperamide will be adjusted and administration will be continued.

(2) When diarrhea improves to ≤ Grade 1, restart study drug at 2 lower dose level from that at the onset of "2) Grade 3 or 4 diarrhea."

Dose Adjustment

Dose reduction				Dose before dose increase/ reduction	Dose escalation		
Dose level −4	Dose level −3	Dose level −2	Dose level −1		Dose level +1	Dose level +2	Dose level +3
Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*	—	—	—
—	Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*	—	—
—	—	Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*	—
—	—	—	Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*

References:

Yang JC, Reguart N, Barinoff J, et al. Diarrhea associated with afatinib: an oral ErbB family blocker. Expert review of anticancer therapy. 2013;13(6):729-36.

Appendix 6 Management of Increased Blood Pressure

Increases in blood pressure have proven to be amenable to treatment, generally without a requirement for study drug interruption. Subjects with elevated blood pressure should receive prompt treatment. Blood pressure for all subjects should be kept systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg; for subjects with increased cardiovascular risk, diabetes or renal insufficiency consideration should be given to maintaining systolic blood pressure < 130 mmHg and diastolic blood pressure < 80 mmHg.

In previous overseas clinical studies evaluating R788, the following antihypertensive agents have been proven effective in managing blood pressure:

- Calcium channel blockers
- Angiotensin converting enzyme inhibitors
- Angiotensin receptor blockers
- β blockers

If antihypertensive therapy does not control systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg, the investigator adjust the dose of study drug or perform additional tests in accordance with the following instructions.

1) Immediately interrupt the study drug when the subject meets either or both of the following criteria.

   - The subject becomes symptomatic due to blood pressure elevation.
   - The blood pressure cannot be brought under control despite best efforts at blood pressure management.

2) If systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg at any time after the start of study treatment:
   (1) Study drug administration should be interrupted.
   (2) Initiate antihypertensive medication or increase the dose of the existing antihypertensive drug, if any.
   (3) Instruct the subject to visit the study institution within 1 week to measure blood pressure.
   (4) Increase the dose of the antihypertensive drug until systolic blood pressure is controlled at < 140 mmHg and diastolic blood pressure at < 90 mmHg.
   (5) Restart study drug at 1 lower dose level when systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg.
   (6) If systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg again despite antihypertensive treatment, interrupt study drug.

3) If systolic blood pressure ≥ 160 mmHg and < 180 mmHg or diastolic blood pressure ≥ 100 mmHg and < 110 mmHg at any visit after the start of the study treatment:

(1) Continue study drug at assigned dose level.

(2) Initiate antihypertensive medication or increase the dose of the existing antihypertensive drug, if any.

(3) Instruct the subject to visit the study institution within 2 weeks to measure blood pressure. If the result of measurement still shows systolic blood pressure ≥ 160 mmHg and < 180 mmHg or diastolic blood pressure ≥ 100 mmHg and ≥ 110 mmHg despite aggressive antihypertensive treatment, interrupt study drug.

(4) Increase the dose of the antihypertensive drug until systolic blood pressure is controlled at < 140 mmHg and diastolic blood pressure at < 90 mmHg.

(5) Restart study drug at 1 lower dose level when systolic blood pressure is controlled at < 140 mmHg and diastolic blood pressure at < 90 mmHg.

4) If systolic blood pressure ≥ 140 mmHg but less than 160 mmHg or diastolic blood pressure ≥ 90 mmHg but less than 100 mmHg at any visit after the start of study treatment:

(1) Continue study drug at assigned dose level.

(2) Instruct the subject to visit the study institution within 2 weeks to measure blood pressure.

(3) If systolic blood pressure remains above ≥ 140 mmHg or diastolic blood pressure remains ≥ 90 mmHg after 2 weeks, initiate or increase antihypertensive therapy.

(4) Instruct the subject to visit the study institution once every 2 weeks to measure blood concentration until systolic blood pressure is controlled at < 140 mmHg and diastolic blood pressure at < 90 mmHg.

(5) If systolic blood pressure remains ≥ 140 mmHg or diastolic blood pressure remains ≥ 90 mmHg for more than 8 weeks, despite appropriate antihypertensive therapy, reduce dose of study drug at 1 lower dose level.

Dose Adjustment

Dose reduction				Dose before dose increase/ reduction	Dose escalation		
Dose level −4	Dose level −3	Dose level −2	Dose level −1		Dose level +1	Dose level +2	Dose level +3
Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*	—	—	—
—	Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*	—	—
—	—	Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*	—
—	—	—	Interruption	100 mg *qd*	150 mg *qd*	100 mg *bid*	150 mg *bid*

References:

Maitland ML, Bakris GL, Black HR, et al. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. Journal of the National Cancer Institute. 2010;102(9):596-604.