NOVARTIS

Novartis Research and Development

ETB115/Eltrombopag/Promacta®/Revolade®

CETB115J2411 / NCT03524612

A phase II, open-label, prospective, single-arm, study to assess ability of eltrombopag to induce sustained remission in subjects with ITP who are refractory or relapsed after first-line steroids (TAPER)

Document type:	Amended Protocol Version
EUDRACT number:	2018-000452-18
Version number:	01 (Clean)
Clinical Trial Phase:	II
Release date:	06-Mar-2019

Clinical Trial Protocol Template Version 1.0 (01-Dec-2017)

[redacted]

Table of contents

[redacted]

[redacted]

[redacted]

List of tables

[redacted]

List of figures

[redacted]

List of abbreviations

aCL	Anticardiolipin
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
Anti-D	Immunoglobulin that recognizes and binds specifically to the erythrocyte D antigen used to treat ITP
aPTT	Activated Partial Thromboplastin Time
ASH	American Society of Hematology
AST	Aspartate Aminotransferase
β-HCG	β-Human Chorionic Gonadotropin
BPM	Beats per Minute
[redacted]	[redacted]
BUN	Blood Urea Nitrogen
CI	Confidence Interval
cITP	Chronic Immune Thrombocytopenia
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CR	Complete Response
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DILI	Drug-Induced-Liver Disease
EBV	Epstein Barr Virus
ECG	Electrocardiogram
eCRF	Electronic Case Report Forms
ECRS	Electronic Case Retrieval Sheet
EDC	Electronic Data Capture
FACIT	Functional Assessment of Chronic Illness Therapy
FACT	Functional Assessment of Cancer Therapy
FACT-Th6	Functional Assessment of Cancer Therapy – Thrombocytopenia 6-item version
FAS	Full Analysis Set
FDA	Food and Drug Administration
FUP	Follow-Up
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GP5	Bothered by side effects component of the FACT-G assessment
HbsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HD-DEX	High Dose Dexamethasone
HIV	Human Immunodeficiency Virus
HRQoL	Health-Related Quality of Life
HSV	Herpes Simplex Virus

IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
ITP	Immune Thrombocytopenia
IVIG	Intravenous Immunoglobulin
LC-MS/MS	Liquid Chromatography – Tandem Mass Spectroscopy
LFT	Liver Function Test
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantification
MCS	Mental Component Score
MedDRA	Medical Dictionary for Regulatory Activities
MR	Minor Response
OR	Overall Response
ORR	Overall Response Rate
[redacted]	[redacted]
PCS	Physical Component Score
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PR	Partial Response
PK	Pharmacokinetic(s)
PRO	Patient-Reported Outcomes
PT	Prothrombin Time
QD	Daily, Every Day
QoL	Quality of Life
QTcF	QT interval corrected by Fridericia's formula
R Value	ALT/ALP x ULN
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SD	Standard Deviation
SF-36	Short Form 36
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBIL	Total Bilirubin

[redacted]

TEAE	Treatment-Emergent Adverse Event
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
TPO-RA	Thrombopoietin Receptor Agonists
[redacted]	[redacted]
TSQM-9	Treatment Satisfaction Questionnaire for Medication
ULN	Upper Limit of Normal
WHO	World Health Organization

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Baseline	Baseline is defined as the last available assessment on or before the date of start of eltrombopag
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study patient
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 50 mg per day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Investigational drug/treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Patient	An individual with the condition of interest for the study
Screen Failure	A patient who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study treatment	Any single drug or combination of drugs or intervention administered to the patient as part of the required study procedures.
Study treatment discontinuation	When the patient permanently stops taking study drug prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Study treatment interruption	When the patient temporarily stops taking study drug
Subject	A trial participant (can be a healthy volunteer or a patient)
Patient number	A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used to identify the patient throughout the study for all data collected, sample labels, etc.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent	Withdrawal of consent is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already collected biologic material.

[redacted]

Amendment 1 (06-Mar-2019)

Amendment rationale

The primary purposes of this protocol amendment are to:

- Update the pregnancy prevention language to align with the Clinical Trials Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials.
- [redacted]
- Add a follow-up period of 12 months for patients who have sustained remission at month 12 to obtain further data on response and remission duration.
- Add a new secondary objective related to the newly added 12 months follow-up period.
- Update the drug induced liver injury (DILI) guidance to align with current Novartis DILI guidelines.
- Update to align with the current eltrombopag program risk language.

Changes to the protocol:

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Protocol summary section updated to match the body of the protocol.
- End of Study (EOS) has been revised to end of treatment. Patients who are still on study treatment and not in sustained remission at month 12 will come off trial after completing the end of treatment visit. Patients who are still in sustained remission at the end of treatment visit will enter the follow-up period.
- Section 2 Table 2-1 Objectives and endpoints: Added a new secondary objective related to the 12 months follow-up period.
- Section 2 Table 2-1 Objectives and endpoints: Updated appropriate objectives/endpoints to include the 12 months follow-up period.
- Section 3 Figure 3-1: Modified to match the study design.
- Section 3 Figure 3-2: Clarified the figure is for patients with sustained remission by month 12.
- Section 3 Study Design: Updated to define patients of Asian ancestry.
- Section 4.2 Rationale for dose/regimen and duration of treatment: Clarified the starting dose for patients.
- Section 4.5 Purpose and timing of interim analyses/design adaptations: Added the analysis time points.
- Section 4.6 Risks and benefits: Updated to align with the current eltrombopag program risk language.
- Section 4.6 Risks and benefits: Reference updated.
- Section 5.2 Exclusion criteria #7: Updated to include creatinine clearance < 45 mL/min.

[redacted]

- Section 5.2 Exclusion criteria #11: Clarified that local laboratory results for human immune deficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B surface antigen (HBsAg) are allowed to confirm eligibility.
- Section 5.2 Exclusion criteria #23: Clarified that a serum pregnancy test is required for female patients of child bearing potential at screening.
- Section 5.2 Exclusion criteria #24: Updated to state highly effective contraception is required. This criteria was updated to align with the Clinical Trials Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials.
- Section 6.1 Study treatment: Clarified patients who are dose escalated to 75mg QD are eligible for tapering and treatment discontinuation as long as they achieve CR and maintain their platelet counts.
- Section 6.1 Study treatment: Updated to define patients of Asian ancestry.
- Section 6.1.3 Treatment duration: Updated to include the follow-up period and clarified the treatment duration for all patients.
- Section 6.2.1.1 Permitted concomitant therapy requiring caution and/or action: Updated to include language on CYP and UGT inhibitors and inducers.
- Section 6.3.1 Patient Numbering: Updated to include re-screening information.
- Section 6.5.2 Table 6-3 Eltrombopag Dose Adjustments in ITP: Added footnote for rationale for dose adjustment for platelet count $< 100\times10^9$/L following 2 weeks of therapy.
- Section 6.5.2 Table 6-3 Eltrombopag Dose Adjustments in ITP: Added a row to clarify dose adjustment for platelet counts $\geq 100\times10^9$/L to $< 200 \times 10^9$/L.
- Section 6.5.2 Table 6-3 Eltrombopag Dose Adjustments in ITP: Added source for dose adjustment for platelet counts ($\geq 200 \times 10^9$/L to $\leq 400 \times 10^9$/L and $>400 \times10^9$/L).
- Section 6.5.2 Table 6.4 Criteria for eltrombopag dose adjustment based on liver enzyme and bilirubin levels: Title updated and table aligned with current Novartis guidelines for dose reduction/interruption due to Investigations (Hepatic).
- Section 6.5.2 Table 6-4 Criteria for eltrombopag dose adjustment based on liver enzyme and bilirubin levels: Clarified footnote for the guidelines for when total bilirubin > 3.0 – 10.0 x ULN is due to the indirect (non-conjugated) component only.
- Section 6.5.3.2 Follow up on potential DILI cases: Updated to align with current Novartis DILI guidance.
- Section 8 Visit Schedule and Assessments: Added visit window for visits during the follow-up period. [redacted]
- Section 8, Table 8-1 Assessment schedule: Updated to reflect that PE results and weight are recorded at every visit and are recorded within the source documents.
- Section 8, Table 8-1 Assessment schedule: Updated to reflect that pregnancy tests should be performed monthly until the end of treatment visit and results are recorded within the source documents. If no visit is planned the test can be performed at home with urine pregnancy test.

[redacted]

- Section 8, Table 8-1 Assessment schedule: Footnote added to follow-up column to reflect that patients who achieved sustained remission at month 12 will be followed-up for an additional 12 months in order to obtain further data on response and remission duration.
- Section 8, Table 8-1 Assessment schedule: Added table for the 12 months follow-up period for responders.
- Section 8.4 Safety: Updated to include weekly hematology assessments (including platelet counts) for the first four weeks after discontinuing eltrombopag for patients who discontinue treatment early for reasons other than per protocol tapering.
- Section 8.4.4 Pregnancy: Updated to state a serum pregnancy test must be performed within 14 days of the first dose of eltrombopag. Monthly pregnancy tests (serum or urine) are required monthly until the end of treatment visit. A serum pregnancy test is required at the end of treatment visit.
- [redacted]
- Section 8.5.1 Clinical Outcome Assessments: Clarified that PRO assessments are collected during treatment, sustained remission, and the 12 months follow-up period.
- Section 9.2 Study Completion and post-study treatment: Updated to clarify study completion, the end of treatment visit at Week 53, Day 1, and safety follow-up.
- Section 9.3: Added to describe the 12 months follow-up period for patients who have achieved sustained remission at month 12.
- Section 10.2.1 Liver safety monitoring: Clarified that liver safety monitoring tests should be performed at local laboratories used by the site.
- Section 12 Data analysis and statistical methods: Added the following text: The 95% confidence interval (CI) using the Clopper-Pearson method will be provided for selected parameters. Kaplan-Meier method will be used for time to event analyses.
- Section 12.5.1 Efficacy endpoint(s): The first efficacy endpoint was updated to include:
  - Kaplan-Maier analyses for the duration of sustained remission (weeks) counted from last dose of eltrombopag to relapse for patients with sustained remission (R) at month 12 and who enter 12 months follow-up period. The patients who do not relapse/die by month 24 will be censored.
  - Kaplan-Maier analyses for the duration of sustained remission (weeks) counted from last dose of eltrombopag to relapse for all patients. The patients who do not relapse/die by month 24 will be right-censored. The duration will be considered as 0 for patients who do not manage to taper off eltrombopag per protocol i.e. do not reach sustained remission.
- Section 12.5.1 Efficacy endpoint(s): Endpoint added for new secondary objective (related to the 12 months follow-up period):
  - To assess the proportion of patients maintaining a sustained remission after treatment discontinuation until month 24.
  - Number (%) of patients who are in sustained remission at months 15, 18, 21, and 24 will be provided.
- Section 12.5.1 Efficacy endpoint(s): Clarified the fourth endpoint will be to assess the platelet count from baseline and every 3 months until month 24.

[redacted]

- Section 12.5.1 Efficacy endpoint(s): Clarified the fifth endpoint will be to assess the ability of eltrombopag to maintain a platelet count ≥ 30×10^9/L from baseline and every 3 months until month 24.
- Section 12.5.1 Efficacy endpoint(s): Updated to include 12 months as a time point for the analysis of impact of side effects of treatment and treatment satisfaction.
- [redacted]
- Section 15 References: Reference updated.
- Other clarifications, administrative changes and corrections as needed.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Protocol summary

Protocol number	CETB115J2411
Full Title	A phase II, open-label, prospective, single-arm, study to assess ability of eltrombopag to induce sustained remission in subjects with ITP who are refractory or relapsed after first-line steroids (TAPER)
Brief title	A study to assess the ability of eltrombopag to induce sustained remission in subjects with ITP
Sponsor and Clinical Phase	Novartis II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this trial is to assess the ability of eltrombopag to induce sustained treatment-free remission in ITP subjects who relapsed or failed to respond to an initial treatment with steroids. There is limited, mainly retrospective evidence that earlier use of eltrombopag after ITP diagnosis, will allow a larger proportion of patients to achieve sustained remission after tapering off drug. Clinically there is a need for a less toxic regimen that will provide responses and sustained remission with a shorter treatment interval. This trial is designed to assess this.
Primary Objective(s)	To assess ability of eltrombopag to induce sustained remission by month 12 in ITP patients who relapsed or failed to respond to first-line steroid treatment
Secondary Objectives	1. To assess the duration of sustained remission after treatment discontinuation, by month 12, and by month 24. 2. To assess the proportion of patients maintaining a sustained remission after treatment discontinuation until month 24 3. To assess the ability of eltrombopag to induce early response by month 1 4. To assess the ability of eltrombopag to induce a recovery response, in case of loss of response during or after tapering of eltrombopag 5. To assess the platelet count from baseline and every 3 months until month 24 6. To assess the ability of eltrombopag to maintain platelet count ≥ 30×10^9/L within 12 months and every 3 months until month 24 7. To evaluate patient-health-related outcome measures for health-related quality of life by use of Functional Assessment of Chronic Illness (FACIT) & Functional Assessment of Cancer Therapy – Thrombocytopenia 6-item Version (FACT-Th6) and Short Form (SF-36v2) questionnaires from baseline and every 3 months to month 24 and end of treatment 8. To explore the overall impact of side effects on patients' perception of treatment via the GP5 assessment at baseline, month 12, and end of treatment 9. To explore treatment satisfaction with Treatment Satisfaction Questionnaire for Medication (TSQM-9) at baseline, month 12, and end of treatment 10. To evaluate the safety and tolerability of eltrombopag
Study design	This is a phase II, open-label, prospective, single-arm, study to assess ability of eltrombopag to induce sustained remission in patients with ITP who are refractory or relapsed after first line steroids.
Population	The study is designed to include adult patients with ITP who have failed to respond or who relapsed following an initial response to a first-line course of steroid therapy (steroid-relapsed or steroid-refractory). The enrollment target is 101 patients.

[redacted]

Inclusion criteria	1. Signed informed consent must be obtained prior to participation in the study 2. Patients ≥ 18 years old 3. Patients with a confirmed diagnosis of primary ITP, who are not responsive or in relapse after a first line of steroid therapy ± intravenous immunoglobulin (IVIG) (used as a rescue therapy) First line of steroid therapy will be defined as: prednisone/prednisolone 0.5 to 1 mg/kg/day for a minimum of 2 weeks, or minimum of 1 course of high-dose dexamethasone 20-40 mg/day for consecutive 4 days ±IVIG (used as rescue therapy). Maximum exposure to high-dose steroids treatment (steroids tapering time excluded) should be limited to: 4 weeks of high dose prednisone/prednisolone or 3 courses of high-dose dexamethasone. Overall exposure to steroids must not be longer than 3 months, including period of dose tapering. 4. Platelet count < 30×10^9/L and assessed as needing treatment (per physician's discretion)
Exclusion criteria	1. ITP patients previously treated with any ITP second-line therapies, thrombopoietin receptor (TPO-R) agonists for ITP, except steroids / IVIG 2. Patients who relapsed more than one year after the end of first-line full course of steroid therapy 3. Patients with a diagnosis of secondary thrombocytopenia 4. Patients who are unable to participate in assessments/biological studies 5. Patients who have life threatening bleeding complications per investigator discretion 6. Patients who had a deep vein thrombosis or arterial thrombosis in the 6 months preceding enrollment 7. Presence of moderate to severe impaired renal function as indicated by any or all of the following criteria: • Creatinine clearance < 45 mL/min as calculated using Cockcroft-Gault formula • Serum creatinine > 1.5 mg/dL 8. Total bilirubin > 1.5 × upper limit of normal (ULN) 9. Aspartate transaminase (AST) > 3.0 × ULN 10. Alanine transaminase (ALT) > 3.0 × ULN 11. Patients who are human immune deficiency virus (HIV), hepatitis C virus (HCV), hepatitis B surface antigen (HBsAg) positive 12. Patients with hepatic impairment (Child-Pugh score > 5) 13. Patients who are unable to respect the 4-hour interval between eltrombopag and other medications (e.g., antacids), calcium-rich foods (e.g., dairy products and calcium fortified juices), or supplements containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc 14. Patients who are unable to stop medications that are known to cause a drug-drug interaction with eltrombopag 15. Patients who have active malignancy 16. Patients with any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions that could interfere with patient's safety, obtaining informed consent or compliance with the study procedures per investigator discretion 17. Patients with a known immediate or delayed hypersensitivity reaction or idiosyncrasy to eltrombopag or drugs chemically related to eltrombopag or excipients that contraindicate their participation 18. History or current diagnosis of cardiac disease indicating significant risk of safety for patients participating in the study such as uncontrolled or significant cardiac disease or impaired cardiac function including any of the following: • Corrected QTc > 450 msec (male patients), > 460 msec (female patients) using Fredericia correction (QTcF) on the screening ECG • Resting heart rate at screening (physical exam or 12 lead electrocardiogram [ECG]) < 50 or > 90 beats per minute (BPM)

	• Recent myocardial infarction (within last 6 months) • Uncontrolled congestive heart failure • Unstable angina (within last 6 months) 19. Patients with known active or uncontrolled infections not responding to appropriate therapy 20. Patients with evidence of current alcohol/drug abuse 21. Concurrent participation in an investigational study within 30 days prior to enrollment or within 5-half-lives of the investigational product, whichever is longest. Note: parallel enrollment in a disease registry is permitted 22. Known thrombophilic risk factors. Exception: Patients for whom the potential benefits of participating in the study outweigh the potential risks of thromboembolic events, as determined by the investigator 23. Female patients who are nursing or pregnant (positive serum pregnancy test) at screening or pre-dose on Day 1 24. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, and sexually active males unwilling to use highly effective methods of contraception during the study. See Section 5.2 for additional details on highly effective contraception.
Study treatment	Patients will be treated with eltrombopag 50 mg once daily (QD) for 2 weeks to reach a target platelet count of ≥ 100×10^9/L. For those patients who do not achieve the target platelet count within 2 weeks, the dose of eltrombopag will be increased to 75 mg QD. Those patients who have not reached the target platelet count ≥ 100×10^9/L after being treated with eltrombopag 75 mg/day will continue on eltrombopag until month 12. Patients will be eligible for taper off and treatment discontinuation if they have a reached a complete response (CR), defined as platelet counts ≥ 100×10^9/L, and maintained platelet counts around 100×10^9/L for 2 months (no counts below 70×10^9/L). The duration of tapering will be individualized and depend upon starting dose and response of the patient: decreases in dose will be performed by 25 mg reductions every 2 weeks. If platelet counts are stable, the next reduction should be carried out within 2 weeks, with dosing at 25 mg on alternate days for 2 weeks until treatment is totally discontinued. A reduced initial dosage of 25 mg QD is recommended for patients of Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean or Thai).
Efficacy assessments	Platelet count will be performed at screening visit 1 to assess the eligibility of the patient. Hematology including platelet counts will be assessed at week 1/day 1 and weekly during the first 8 weeks of treatment. Based on patient response, hematology will be performed biweekly thereafter until the end of treatment. Additional assessments of platelet count may be performed more frequently than the biweekly schedule if needed in accordance with the clinical judgment of the investigator. Bleeding events will be assessed at each visit and recorded in the adverse event (AE) case report forms (CRF). Documentation of the use of any rescue therapy will be documented on the appropriate CRF.
[redacted]	
Key safety assessments	• Physical assessments: physical exam, vital signs, height and weight • Ophthalmic examination • Laboratory evaluations • Electrocardiogram • Pregnancy testing Patients who discontinue treatment early for reasons other than per protocol tapering require weekly hematology assessments (including platelet counts) for the first four weeks after discontinuing eltrombopag.

[redacted]

[redacted]

Other assessments	• FACIT-Fatigue • Medical Outcome Trust's Short-Form 36 Health Survey, Version 2 (SF-36 v2) • FACT-Th6 • GP5 • TSQM-9
Data analysis	Continuous variables will be summarized by number of patients, mean, standard deviation, minimum, median, and maximum. For selected parameters, 25th and 75th percentiles will also be presented. Categorical variables will be summarized by frequencies and percentages. The 95% confidence interval (CI) using the Clopper-Pearson method will be provided for selected parameters. Kaplan-Meier method will be used for time to event analyses. The primary endpoint is the proportion of patients with sustained remission by month 12, where **sustained remission (R)** is defined as: • reach platelet count ≥ 100×10^9/L (CR) and then maintain platelet counts around 100×10^9/L for 2 months (no platelet count below 70×10^9/L) AND then • taper off the drug until treatment discontinuation while, • maintain platelet count ≥ 30×10^9 /L in the absence of bleeding (no bleeding AE) or use of any rescue therapy until month 12. The number (%) of patients with sustained remission (R) by month 12 will be summarized together with 95% CI using the Clopper-Pearson method. A binomial test for one proportion, H0: P=0.15 vs. H1:P>0.15 will be performed to test if the proportion of patients with sustained remission is greater than 15%.
Key words	Eltrombopag, immune thrombocytopenia, ITP, corticosteroids

[redacted]

1 Introduction

1.1 Background

Primary immune thrombocytopenia (ITP) is an acquired, immune-mediated disorder of adults and children. It is defined as a platelet count of less than 100×10^9/L, in the absence of other causes or disorders that may be associated with thrombocytopenia.

Incidence estimates for adult-onset ITP are reported to range from 1.6 to 3.9 per 100,000 per year. The incidence of ITP follows a multimodal distribution pattern, with peaks in young children, young adults and the elderly, with the highest age-specific incidence in individuals over 60 years (Terrell 2010). The overall prevalence of ITP in adults has been estimated to be 9.5 per 100,000, ranging from 4.1 per 100,000 in younger ages (19 to 24 years) to 16 per 100,000 in older age groups (55 to 64 years). Immune thrombocytopenia is found worldwide and has similar epidemiologic patterns across regions (Arnold 2013).

Most commonly, ITP patients have asymptomatic thrombocytopenia, however patients usually present at hospital and seek medical help once bleeding symptoms occur. Although some patients bleed with platelet counts $< 30\times10^9$/L, many do not. Bleeding symptoms characteristic of ITP ("platelet-type bleeding") include skin bleeding (i.e., bruises, non-palpable purpura, or petechiae), oral hemorrhagic blood blisters (purpura) or oral petechiae, epistaxis, menorrhagia, or gastrointestinal bleeding. The most feared life-threatening complication is intracerebral hemorrhage, reported in 1.5 to 1.8% of adult patients (Lambert 2017, Hoffman 2013).

The degree of bleeding is largely dependent on the severity of thrombocytopenia, with platelet counts < 20 to 30×10^9/L conferring the greatest risk of clinically significant bleeding (George 1996; Guidelines 1 British Society for Haematology 2003). Mild hemorrhages presenting with bruising and petechiae are most common, but severe hemorrhages involving the gastrointestinal and genitourinary tract are well known complications of the disease, and occur in ~ 10% of adult ITP patients. The frequency of death from hemorrhage in patients with platelet counts $< 30\times10^9$/L is estimated to be between 1.6 and 3.9% per patient year, although the frequency is influenced by age, severity and duration of thrombocytopenia (Cohen 2000).

Based on the disease duration from initial confirmed ITP diagnosis, there are 3 categories of patients: newly diagnosed (between time of diagnosis and 3 months), persistent ITP (between 3 and 12 months from diagnosis), and chronic ITP (cITP) (reserved for patients with ITP lasting for more than 12 months). This clinical categorization inversely correlates with patients' chance of achieving spontaneous remission of the disease (i.e., the longer the duration of disease, the lower the chance for spontaneous remission) (Rodeghiero 2009, Hoffman 2013, Provan 2010).

Chronic ITP has been associated with a risk of death that is up to four times higher than that of the general population. ITP patients are more likely to die of bleeding, infection, and hematologic malignancies. Some deaths are attributable to adverse events (AEs) of treatment rather than the disease. Quality of Life (QoL) in patients with ITP is lower than that of the general population, which is at least partially a result of high prevalence of fatigue that appears to be independent of platelet count levels (Portielje 2001, Hoffman 2013, Stasi 2004, Profit 2006, George 2006)

[redacted]

The goal of therapy in ITP is not to normalize the platelet count but to achieve a platelet count that confers adequate hemostasis and minimizes the risk of clinically significant bleeding for the individual patient, avoiding treatment-related toxicity. Therefore, the choice and the management of each treatment must be conducted for each patient on a case-by-case basis. In general, treatment is seldom required when platelets are > 20 to 30×10^9/L. For patients with platelets < 20×10^9/L, treatment is required, but depends on a full assessment of the patient lifestyle, occupation, bleeding history, comorbidities, and other factors (Provan 2010, Rodeghiero 2009).

Observational data from ITP patient cohorts indicate that risk of clinically significant bleeding increases with increasing severity of thrombocytopenia and as such, a platelet threshold of < 20 to 30×10^9/L is typically a trigger for treatment, irrespective of bleeding manifestations. Treatment guidelines established by the American Society of Hematology (ASH) and the International Working Group (IWG) consensus panel of expert clinicians also indicate that it is appropriate to initiate treatment for newly diagnosed ITP patients with platelet counts of < 30×10^9/L (Neunert 2011, Provan 2010).

Current therapies

First-line treatment has remained unchanged for decades and comprises corticosteroids in 60 to 70% of patients, intravenous immunoglobulin (IVIG) in approximately 20%, and anti-D immune globulin (less than 10% in countries where anti-D is available). Corticosteroids are inexpensive and raise platelet counts rapidly within 2 to 14 days in approximately 75% of patients. Corticosteroids will generally induce a response within the first 2 weeks, but less than 25 to 30% of patients will sustain responses and will relapse within the first year, most commonly during steroid taper or shortly after discontinuation (Table 1-1) (Cooper 2017, Wong 2017).

Side effects of steroids are common and predictable, and have a significant impact on patients' QoL. The most common steroid-related AEs include weakness, impaired cognition and insomnia, mood changes, weight gain, headache, impaired glucose metabolism, as well as increased risk of infections due to immunosuppressive effects, and osteoporosis due to the effect on bone marrow density. Currently available corticosteroids for ITP include prednisone, prednisolone, methylprednisolone and dexamethasone, with prednisone and dexamethasone being the most widely used.

Prednisone, rather than dexamethasone, has been used predominantly as first-line treatment, but the rate of sustained response with prednisone and dexamethasone seem overall similar. The typical dosing regimen for prednisone is 0.5 to 2 mg/kg bodyweight daily for four weeks until the maximum dose is achieved, followed by tapering. Approximately two-thirds of patients demonstrate an initial response to prednisone, but only a limited fraction of patients experience long-term remission. However, despite this, prednisone remains the first-line corticosteroid of choice. There are conflicting results, and no clear consensus on whether use of high dose dexamethasone (HD-DEX) vs prednisone is preferable, even though there is increasing evidence, including data from randomized prospective clinical trials demonstrating that HD-DEX provides a more effective and rapid response as the initial treatment regimen for ITP in comparison to conventional prednisone (Mithoowani 2016, Mashhadi 2012, Wei 2016, Nakazaki 2012, Sakamoto 2014).

[redacted]

Table 1-1 First-line treatment options for patients with ITP

Treatment	Typical dose/regimen	Efficacy	Safety
Prednisone	0.5–2 mg/kg/day, for 2–4 weeks until a response is seen, followed by tapering over several weeks	Initial response: 60–80% Sustained response: 20–47%	AEs vary with the dose and duration, but include weight gain, anxiety, insomnia, and diabetes
Dexamethasone	40 mg/day, for 4 days every 2–4 weeks, for 1–4 cycles	Initial response: up to 90% Sustained response: 40–50% Repeated cycles may result in response rates up to 80%	Weakness, insomnia, and impaired cognition
IVIG	0.4 g/kg/d for 5 days or 1 g/kg/d for 1–2 days	Initial response: up to 80% Platelet count usually returns to pretreatment levels within 2–4 weeks, persists for months in few patients	Common: headache, hypertension, and chills Rare: hemolysis and neutropenia
Anti-D	50–75 µg/kg	Similar to IVIG, dependent on dose	Common: hemolysis Rare: intravascular hemolysis, can be fatal

Source: Provan 2010

In general, 60-70% of adults with acute ITP achieve an initial response; even higher response rates are reported in children. Rates of sustained response with corticosteroid treatment (usually defined as a platelet count ≥ 50 or $\geq 100\times10^9$/L at 6-12 months, with different timeline and platelet count thresholds within different publications) are generally low and vary from 20% to 47%. With longer follow-up, the risk of relapse increases in adults who experience an initial response.

Many of the currently available treatments, in particular, high doses of steroids, are associated with significant morbidity. Historical data has shown that mortality from ITP more often results from infectious complications of steroid treatment and splenectomy rather than directly from bleeding. Thus, there is an important need for a tolerable therapy for patients that do not experience early ITP remission with steroid treatment.

Options for salvage therapy include retreatment with corticosteroids, switching from one steroid type to another, a combination of first-line agent(s), or treatment with a second-line agent. According to current guidelines available modalities for second line treatment options for ITP patients have quite different mechanisms of action. They are broadly classified into those that are given only once (or for only one course) and are intended to induce long-term remission (splenectomy, rituximab) and those that need continued or chronic administration (corticosteroids, immunosuppressive agents and Thrombopoietin Receptor Agonists [TPO-RAs]).

[redacted]

There are limited data about duration of steroid recycling, but such regimens vary from a few months up to a few years of repeated steroids use and/or switching from one steroid type to another. The incidence of steroid-derived AEs, in general, depends greatly on both the average dose and cumulative duration of use, indicating that it is essential to both complete whole courses of therapy in as short a period as possible and to reduce the total amount of administered corticosteroids.

While corticosteroids remain the standard of care for ITP, high relapse rates and considerable toxicity associated with long-term corticosteroid use highlight a significant unmet medical need in the management of ITP particularly for those patients who relapse after initial treatment. Novel therapeutic approaches are warranted that achieve a sustained response and reduce the need for long-term corticosteroid use.

1.2 Purpose

The purpose of this trial is to assess the ability of eltrombopag to induce sustained treatment-free remission in ITP patients who failed to respond or have relapsed after an initial treatment with steroids.

This is supported by medical experts´ experience and limited published evidence indicating that a certain proportion of patients are able to achieve a stable response and sustained remission during treatment with TPO-RA earlier in the course of the disease and are able to discontinue treatment (Bussel 2015, Gonzalez-Lopez 2015, Newland 2016). TPO-RA used earlier than 12 months from disease diagnosis might reduce toxicity from steroid exposure and can provide a sustained remission. However, an analysis of data collected prospectively and powered to assess whether TPO-RA can behave in this manner is lacking.

There is insufficient evidence to create a treatment sequence recommendation for patients who relapsed or who failed to respond after first-line steroid treatment within 3-12 months from initial diagnosis. The most appropriate treatment sequence for those ITP patients should eliminate an unacceptable level of uncertainty and currently is not addressed in any of the guidelines.

We will therefore conduct a prospective trial of eltrombopag in patients with ITP, who are refractory to or who relapsed after initial treatment with first-line steroids, to assess the ability of eltrombopag to induce treatment-free sustained remission.

This trial will help by closing a gap that exists in the medical community, which is to generate prospective data within clinical trial setting that will demonstrate that eltrombopag could be the treatment option considered after first-line steroid treatment. The definition of ‘first round of steroids” is not standardized, with different duration of steroids cycles being considered as “first round” (Provan 2011, Neunert 2011, Gutierrez-Espindola 2003).

[redacted]

2 Objectives and endpoints

Table 2-1 Objectives and endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoints for primary objective(s)**
1. To assess ability of eltrombopag to induce sustained remission by month 12 in ITP patients who relapsed or failed to respond to first-line steroid treatment.	1. Proportion of patients with **sustained remission (R)** by month 12 **where sustained remission** is defined as: • reach platelet count ≥ 100×10^9/L (complete response [CR]) and then maintain platelet counts around 100×10^9/L for 2 months (no counts below 70×10^9/L) AND then • taper off the drug until treatment discontinuation (see Section 9.1) while, • maintain platelet count ≥ 30×10^9/L in the absence of bleeding (no bleeding AEs) or use of any rescue therapy (see Section 6.2.3) until month 12.
Secondary Objective(s)	**Endpoints for secondary objective(s)**
1. To assess the duration of sustained remission after treatment discontinuation by month 12 and by month 24	1a. Median duration of sustained remission (weeks) counted from last dose of eltrombopag to month 12 for patients with sustained remission (R) 1b. Estimated median duration of sustained remission (weeks) by month 24 for patients who are in sustained remission (R) at month 12 and enter 12 months follow-up period using Kaplan-Meier method 1c. Estimated median duration of sustained remission (weeks) by month 24 for all patients using Kaplan-Meier method.
2. To assess the proportion of patients maintaining a sustained remission after treatment discontinuation until month 24.	2. Proportion of sustained remission (R) patients at months 15, 18, 21, and 24.
3. To assess the ability of eltrombopag to induce early response by month 1	3. Number (%) of patients with platelet count ≥ 50×10^9/L at least once by month 1 (first month) without bleeding and no rescue therapy
4. To assess the ability of eltrombopag to induce a recovery response, in case of loss of response during or after tapering of eltrombopag until month 24	4. Number (%) of patients with at least one platelet count ≥ 30×10^9/L after eltrombopag is re-introduced, in case of loss of response (< 30×10^9/L and/or bleeding event) without bleeding and no rescue therapy by month 12 and 24
5. To assess the platelet count from baseline and every 3 months until month 24	5. Absolute and relative change in platelet count from baseline to 3, 6, 9,12, 15, 18, 21, and 24 months and end of treatment
6. To assess the ability of eltrombopag to maintain platelet count ≥ 30×10^9/L within 12 months and every 3 months until month 24	6. .Number (%) of patients who maintain a platelet count ≥ 30×10^9/L from the first time of reaching that level to month 3, 6, 9, 12, 15, 18, 21, 24, and end of treatment without bleeding and no rescue therapy

[redacted]

Objective(s)	Endpoint(s)
7. To evaluate patient-Health Related outcome measures for health-related quality of life (fatigue level of the patients through FACIT) & FACT-Th6 and SF-36v2 questionnaires from baseline and every 3 months to month 24 and end of treatment	7. The analysis of HRQoL parameters; fatigue level of the patients through FACIT & FACT-Th6, SF-36v2 questionnaires. Change in scores from baseline to month 3, 6, 9, 12, 15, 18, 21, 24, and end of treatment
8. To explore the overall impact of side effects on treatment via the GP5 at baseline, month 12, and end of treatment	8. Overall change from baseline to month 12 and end of treatment will be assessed
9. To explore treatment satisfaction with TSQM-9 at baseline, month 12, and end of treatment	9. Overall change from baseline to month 12 and end of treatment will be assessed
10. To evaluate the safety and tolerability of eltrombopag	10. Number (%) and severity of patients with AEs, serious AEs (SAEs), AEs leading to discontinuation, AEs leading to dose adjustments, AEs of special interest. Change from baseline in vital signs and clinical laboratory tests
[redacted]	

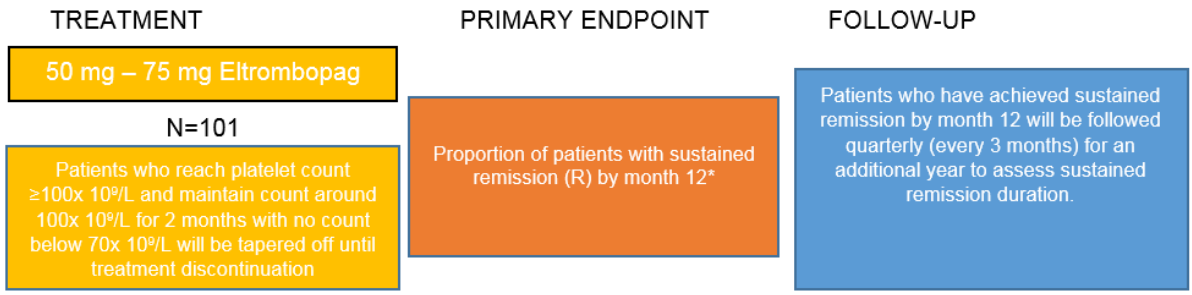
FACIT=Functional Assessment of Chronic Illness Therapy; FACT=Functional Assessment of Cancer Therapy; FACT-Th6=Functional Assessment of Cancer Therapy – Thrombocytopenia 6-item version; GP5-bothered by symptoms component of the FACT-G assessment; HRQoL=Health Related Quality of Life; [redacted] SF-36=Short Form-36; [redacted] TSQM-9=Treatment Satisfaction Questionnaire for Medication; [redacted]

[redacted]

3 Study design

This is a phase II, open-label, prospective, single-arm, study to assess ability of eltrombopag to induce sustained remission in adult patients with ITP who are refractory or relapsed after first line steroids. The study design is provided in Figure 3-1.

Figure 3-1 CETB115J2411 study design



*Sustained remission is defined as patients who:
Reach platelet count ≥100x 10⁹/L (complete response [CR]) and then maintain platelet counts around 100x 10⁹/L for 2 months (with no counts below 70x 10⁹/L) AND then taper off the drug until treatment discontinuation while, maintaining platelet count ≥30x 10⁹/L in the absence of bleeding (no bleeding AEs) or use of any rescue medication until month 12

Population:

- Patients with ITP, ≥18 years of age
- Relapsed or failed to respond after first line steroid treatment
- Platelet count < 30x 10⁹/L and need for treatment

Patients with confirmed diagnosis of ITP, who have failed to respond or who have relapsed following initial response after a first-line of steroid therapy with or without intravenous immunoglobulin (IVIG) (if used as a rescue therapy) will be screened, and if eligible, will receive eltrombopag. First line of steroid therapy will be defined as: prednisone/prednisolone 0.5 to 1mg/kg/day for a minimum of 2 weeks, or minimum of 1 course of high-dose dexamethasone 20 to 40 mg/day for consecutive 4 days ±IVIG (used as rescue therapy). Maximum exposure to high-dose steroids treatment (steroids tapering time excluded) should be limited to: 4 weeks of high dose prednisone/prednisolone or 3 courses of high-dose dexamethasone. Overall exposure to steroids must not be longer than 3 months, including period of dose tapering.

In this study, the starting dose will be 50 mg eltrombopag QD (starting dose for Asian patients will be 25 mg QD, reduced as per Section 6.1).

This eltrombopag starting dose is consistent with the dosing guidelines that have been approved for eltrombopag use in adult patients with chronic ITP.

Taper-off and treatment discontinuation: Patients who reach CR (platelet count $\geq 100\times10^9$/L) and maintain counts around 100×10^9/L for 2 months (no platelet count below 70×10^9/L) will be eligible for taper-off and treatment discontinuation. Duration of tapering will vary depending on the starting dose and the response of the patient: decreases in eltrombopag

[redacted]

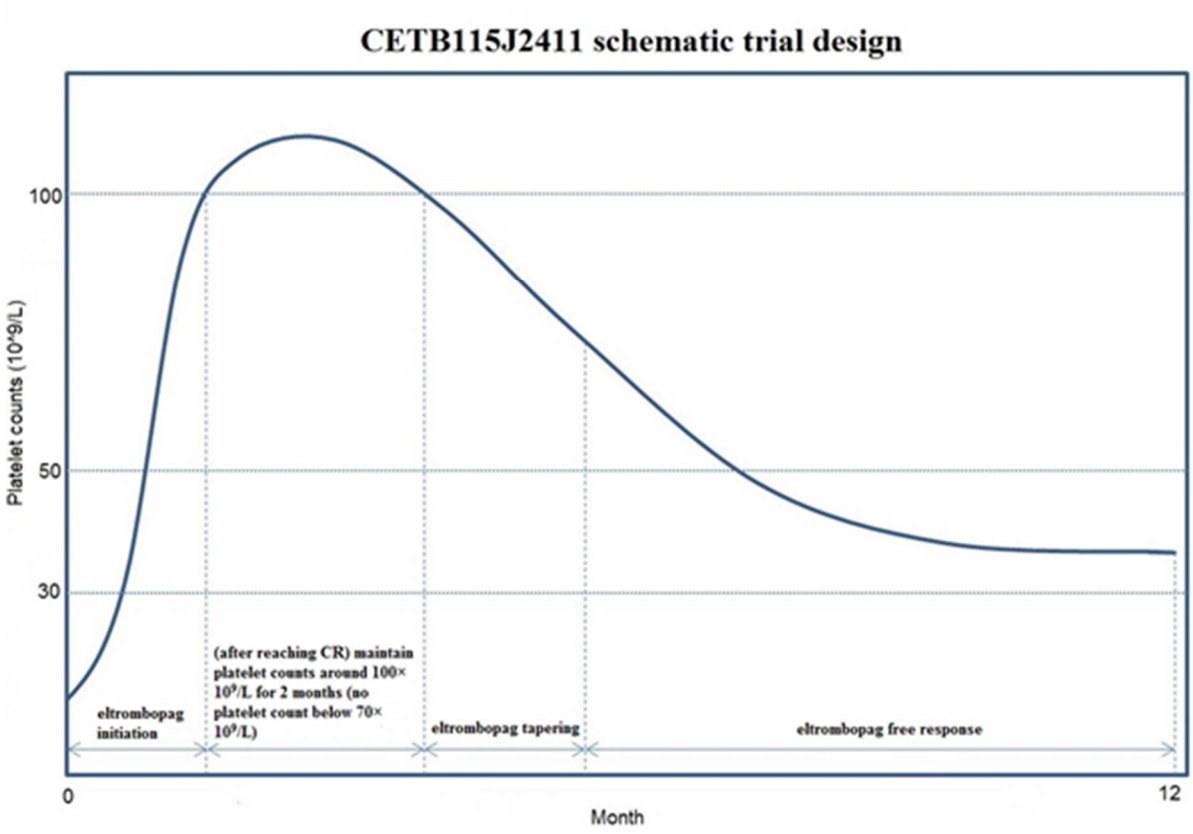
dose will be performed by a 25 mg reduction every 2 weeks up to 25 mg on alternate days for 2 weeks until treatment discontinuation.

Patients who successfully taper off, i.e. discontinue eltrombopag and maintain platelet count ≥ 30×10^9/L in the absence of bleeding or use of any rescue therapy will be followed up through the duration of the trial (to month 12). In case of relapse, patients will be offered a new course of eltrombopag treatment within this timeframe, starting at a dose of 50 mg.

Patients with bleeding, or perceived risk of serious bleeding, will be allowed to receive rescue therapy as per physician decision, irrespective of platelet counts.

A schematic depicting an example of a patient with sustained remission is provided in Figure 3-2. Individual patient study experience will vary dependent on time to response and duration of eltrombopag tapering.

Figure 3-2 Example of a patient with sustained remission by Month 12



4 Rationale

4.1 Rationale for study design

This is a phase II, open-label, prospective, single-arm study to assess ability of eltrombopag to induce sustained remission in patients with ITP who are refractory or relapsed after first line steroids.

In this context, historical control for this trial are patients who are treated with first round of steroids and do not respond or relapse. Based on medical experience and previous data from the literature, it is postulated that approximately 15% of patients in this population would have sustained remission after 12 months on steroid recycling (Dubbeld 1991, Caulier 1995, Arruda 1996, Warner 1997, Demiroglu 1997, Stasi 2000, Gutierrez-Espindola 2007). The definition of 'first round of steroids" is not standardized, with different duration of steroids cycles being considered as "first round" (Provan 2011, Neunert 2011, Gutierrez-Espindola 2003). Published response data is not robust with regards to pattern of steroid treatment, making comparison across studies difficult.

Rationale for single arm-design: Placebo controlled trial in patients who failed to respond or relapsed after first round of steroids treatment would not be considered ethical. According to current treatment guidelines, there is no broadly accepted standard of care in this patient population that could be potentially considered as comparator arm. In addition, there is not sufficient evidence to drive the decision for a comparator arm with one treatment option versus the other. Therefore, single arm design is suitable for phase II trial, to obtain initial insight about ability of eltrombopag to induce treatment-free sustained remission.

There is limited, mainly retrospective evidence that earlier use of eltrombopag after ITP diagnosis, will allow a larger proportion of patients to achieve sustained remission after tapering off drug. Clinically there is a need for a less toxic regimen that will provide responses and sustained remission with a shorter treatment interval. This trial is designed to assess this.

Clinical expertise suggests there will be clinically meaningful improvement if patients are able to be tapered off eltrombopag and have sustained remission by month 12, with an estimated 25% of patients expected to reach this goal.

The results of this study will be discussed in the context of current knowledge and existing historical data.

4.2 Rationale for dose/regimen and duration of treatment

Eltrombopag dosing requirements must be individualized based on the patient's platelet counts.

Rationale for eltrombopag starting dose: In this study, the starting dose will be 50 mg eltrombopag QD (starting dose for Asian patients will be 25 mg QD, reduced as per Section 6.1).

This eltrombopag starting dose is consistent with the dosing guidelines that have been approved for eltrombopag use in adult patients with chronic ITP.

An increase of eltrombopag dose up to 75 mg is typically allowed for patients who do not respond to standard-dosage treatment and to reduce the risk for bleeding. The rationale of this

study is to use the minimal efficacious dosage of eltrombopag in order to achieve a platelet count ≥ 100×10^9/L and maintain it around 100×10^9/L (no counts below 70×10^9/L) for 2 months in order to allow subjects to start the eltrombopag tapering and withdrawal process.

Rationale for CR duration on eltrombopag and taper off initiation: There are no guidelines with clear recommendation about platelet count, nor specified duration of treatment required prior to TPO-RA tapering off. No predictive factors for the patients who will be able to taper off are identified to date.

Medical experts' input indicates that patients who achieve CR with a lower dose of TPO-RA and maintain it are more prone to have sustained remission after drug discontinuation. Scientific explanation is based on eltrombopag immunomodulatory effects and potential to restore immune tolerance to platelet antigens (Červinek 2015).

Rationale for taper off scheme: Tapering off scheme is based on known efficacy profile of eltrombopag, and clinical need to be done by smaller decrements over several weeks.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not applicable

[redacted]

[redacted]

[redacted]

4.5 Purpose and timing of interim analyses/design adaptations

No formal interim analysis is planned for this study. During the course of this study, two analyses will be performed:

- Primary analysis will be done after all patients have enrolled and have either discontinued early from the study or have completed 12 months on study. The primary CSR will be written at this time point.
- Second analysis will be done after all patients in the follow-up period have completed month 24. The final CSR will be written at this time point.

See Section 12 for details on data analyses reported in these CSRs.

4.6 Risks and benefits

The risks to patients in this study may come from adverse events, adverse events of special interest and lack of efficacy. The risk to patients in this study may be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, safety and efficacy assessments as described in Sections 8.3 and Section 8.4; and dose modifications as described in Section 6.5.

There may be unforeseen risks with the study treatment which could be serious. These include but may not be limited to drug to drug interactions and long term safety. Close adherence to eligibility criteria, study procedures safety monitoring, and dose adjustment as described above will help to minimize unforeseen risks. Potential for drug to drug interaction and measures to minimize undesired drug to drug interactions are described in Sections 6.2.1 and Section 6.2.2.

Women of child bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the highly effective contraception requirements outlined in the exclusion criteria. If there is any question that the patient will not reliably comply, they should not be entered or continue in the study.

[redacted]

Risks Associated with Eltrombopag Use

Identified risks as defined by the Risk Management Plan (RMP) for eltrombopag for the ITP indication include hepatotoxicity, thromboembolic events, and post-therapy reoccurrence of thrombocytopenia.

Potential risks as defined by the RMP for eltrombopag for the ITP indication include thrombotic microangiopathy with acute renal failure, increased bone marrow reticulin formation, hematological malignancies, renal tubular toxicity, phototoxicity, and endosteal hyperostosis.

Appropriate eligibility criteria, as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events, i.e., hepatotoxicity, thrombotic complications, and ocular changes are provided below.

Hepatotoxicity

Eltrombopag administration can cause hepatobiliary laboratory abnormalities, severe hepatotoxicity and potentially fatal liver injury. In the controlled clinical studies in chronic ITP with eltrombopag, increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin were observed. Exercise caution when administering eltrombopag to patients with hepatic disease.

Hepatotoxicity will be monitored through serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin levels as described in Section 8.4.2 and additional investigations as clinically indicated. In case hepatobiliary abnormalities are observed, follow the guidelines in Section 10.2.1.

Thrombotic / Thromboembolic complications

In eltrombopag clinical trials in ITP, thromboembolic events were observed at low and normal platelet counts. Caution must be used when administering eltrombopag to patients with known risk factors for thromboembolism including but not limited to inherited (e.g., Factor V Leiden) or acquired risk factors (e.g., ATIII deficiency, antiphospholipid syndrome), patients with prolonged periods of immobilization, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking. Platelet counts must be closely monitored and dose modifications must be made in accordance with parameters provided in the protocol. The risks of thromboembolism and any of the following complications versus the benefit of improved platelet counts must be evaluated by the Investigator for each patient with known risks of thromboembolic events.

Ophthalmic changes

Cataracts were observed in toxicology studies of eltrombopag in rodents. The data from the double-blind and open label ITP and HORT studies, as well as data from the LENS study and the Phase II HCV study did not suggest an increased risk of cataract development in patients treated with eltrombopag. This conclusion was supported by the blinded, independent ocular safety data review from the Clinical Events Committee (CEC). In the pooled data from the Phase III HCV studies (ENABLE studies), where patients received up to 57 weeks of eltrombopag at doses up to 100mg, there was a numerically higher incidence of cataracts in the eltrombopag treatment group compared with the placebo group.

[redacted]

Ophthalmologic monitoring defined per protocol must be performed and investigational treatment (eltrombopag) discontinued in case of suspected cataract development or worsening or in case of retinal hemorrhages.

Benefits Associated with Eltrombopag Use

Eltrombopag is an oral TPO-RA indicated for the treatment of chronic ITP. It has a well-established efficacy and safety profile with evidence of improved QoL responses in addition to improvement in platelet counts.

Eltrombopag has been approved in over 100 countries for the treatment of chronic immune (idiopathic) thrombocytopenia in patients aged 1 year and above who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).

Eltrombopag has been shown to be superior to placebo in raising and maintaining platelet count above 50×10^9/L for 6 months with a significant reduction in bleeding symptoms in previously treated chronic ITP patients. Eltrombopag also enabled more patients to reduce/discontinue concomitant (corticosteroid) medication use (RAISE Study) (Cheng 2011).

Patients with severe "acute" and persistent ITP showed benefit from eltrombopag therapy initiated within 6 months from diagnosis. This was demonstrated in a multicenter, single arm open label study of 39 patients (platelet count $< 30\times10^9$/L despite being dosed with 1 mg/kg prednisone for at least 2 weeks from diagnosis or requiring prednisone $\geq$ 10 mg QD and/or recurrent doses of IVIG to maintain a platelet count of $\geq 30\times10^9$/L within 6 months of diagnosis). Patients with platelets $< 10\times10^9$/L began eltrombopag 75 mg QD while those with a count $\geq 10\times10^9$/L began treatment with 50 mg QD. The eltrombopag dose was increased by 25 mg every 2 weeks to a maximum of 150 mg QD if the platelet count remained $\leq 30\times10^9$/L or there was clinically significant bleeding every 2 weeks. The steroid could be decreased to zero over the subsequent 6 weeks if clinically appropriate. The primary endpoint was overall response rate (ORR) at week 12, defined as the proportion of patients achieving CR (platelet count $> 100\times10^9$/L), partial response (PR) (platelet count $> 50\times10^9$/L) or minor response (MR) (platelet $\geq 30\times10^9$/L with $\geq$ 50% reduction in the dose intensity of concomitant ITP therapy compared with screening). At week 12, the ORR was 64%; at week 26, the ORR was 54%. Two patients had SAEs with two episodes of venous thromboembolism (one deep vein thrombosis at platelet count 97×10^9/L; one pulmonary embolism at platelet count 240×10^9/L). There were no other AEs or deaths (Gonzalez-Lopez et al 2017)).

In addition to the benefits described above, a possible direct immunomodulatory effect of eltrombopag has been postulated from small retrospective reviews. TPO-RA have been shown to dampen immune responses in cITP by increasing the levels of anti-inflammatory cytokines and by reducing the levels of pro-inflammatory cytokines, increasing the suppressive activity of regulatory T-cells and reducing phagocytic activity of monocytes and macrophages, via modulation of Fcγ receptors towards inhibitory phenotype (Bao 2010, Qu 2017, Liu 2016).

There is also evidence that a proportion of patients go into remission and no longer require treatment after a number of months of eltrombopag therapy. This action of eltrombopag on ITP may be the result of a direct immunomodulatory effect that could impact other diseases as well.

[redacted]

In a retrospective review of 260 adult cITP patients treated with eltrombopag, among the 49 evaluable patients who achieved complete remission with eltrombopag (platelet count $\geq 100\times10^9$/L), and then discontinued further treatment, 26 patients maintained platelet counts $\geq 100\times10^9$/L with a median follow up of 9 months (Gonzalez-Lopez 2015). In a small, retrospective review of 12 patients with cITP, following successful discontinuation of eltrombopag (platelet count of 30×10^9/L and 20×10^9/L above initial baseline for at least 6 months without substituting additional anti-ITP therapy), 10 patients maintained platelet counts $> 100\times10^9$/L, with a median follow up of 7 months (Gonzalez-Lopez 2015). These findings are based on retrospective reviews only and need to be evaluated in a prospective manner; however, they suggest that a fixed duration of treatment with eltrombopag in ITP patients may contribute to sustained platelet responses.

The most recent prospective trial in 206 newly diagnosed ITP patients in China, examined the effects of HD-DXM or HD-DXM with recombinant (rh) TPO (Wang 2017). Overall response (OR) was defined as a platelet count $\geq 30\times10^9$/L and at least 2-fold increase of the baseline platelet count and absence of bleeding, while CR was a platelet count $\geq 100\times10^9$/L. The proportion of HD-DXM plus rhTPO patients that reached CR at 2 weeks was 75% compared to 42% of those treated with HD-DXM. After one year, 46% of patients in HD-DXM plus rhTPO group had sustained OR versus 31% in HD-DXM group.

Further investigation is warranted to explore possible treatment strategies for ITP patients who failed to respond or have relapsed after initial steroid therapy. This will address an unmet medical need that a different treatment approach (introducing eltrombopag earlier) can reduce the need for repeated cycles of high dose steroids by reducing time of exposure and provide sustained remission after eltrombopag treatment discontinuation.

5 Population

The study is designed to include adult patients with ITP who have failed to respond or who relapsed following an initial response to a first-line course of steroid therapy (steroid-relapsed or steroid-refractory).

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.1 Inclusion criteria

Patients eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. ≥ 18 years old
3. A confirmed diagnosis of primary ITP, who are not responsive or in relapse after a first line steroid therapy ± IVIG (used as a rescue therapy)

   First line of steroid therapy will be defined as: prednisone/prednisolone 0.5-1mg/kg/day for a minimum of 2 weeks, or minimum of 1 course of high-dose dexamethasone 20-40 mg/day for consecutive 4 days ±IVIG (used as rescue therapy). Maximum exposure to high-dose steroids treatment (steroids tapering time excluded) should be limited to: 4 weeks of high dose prednisone/prednisolone or 3 courses of high-dose dexamethasone.

[redacted]

Overall exposure to steroids must not be longer than 3 months, including period of dose tapering.

4. Platelet count < 30×10^9/L and assessed as needing treatment (per physician's discretion)

5.2 Exclusion criteria

Patients meeting **any** of the following criteria are not eligible for inclusion in this study.

1. ITP patients previously treated with any ITP second-line therapies, TPO-RA for ITP, except steroids / IVIG as described in the inclusion criteria
2. Patients who relapsed more than one year after the end of first-line full course of steroid therapy
3. Patients with a diagnosis of secondary thrombocytopenia.
4. Patients who are unable to participate in assessments/biological studies
5. Patients who have life threatening bleeding complications per investigator discretion
6. Patients who had a deep vein thrombosis or arterial thrombosis in the 6 months preceding enrollment
7. Presence of moderate to severe impaired renal function as indicated by any or all of the following criteria:
   - Creatinine clearance < 45 mL/min as calculated using Cockcroft-Gault formula
   - Serum creatinine > 1.5 mg/dL
8. Total bilirubin > 1.5 × upper limit of normal (ULN)
9. Aspartate transaminase (AST) > 3.0 × ULN
10. Alanine transaminase (ALT) > 3.0 × ULN
11. Patients who are human immune deficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B surface antigen (HBsAg) positive. These assessments can be performed using the local laboratory used by the site. Central laboratory testing is available for HIV, HCV, and HBsAg should local laboratory testing not be available.
12. Patients with hepatic impairment (Child-Pugh score > 5)
13. Patients who are unable to respect the 4-hour interval between eltrombopag and other medications (e.g., antacids), calcium-rich foods (e.g., dairy products and calcium fortified juices), or supplements containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc
14. Patients who are unable to stop medications that are known to cause a drug-drug interaction with eltrombopag
15. Patients who have active malignancy
16. Patients with any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions that could interfere with patient's safety, obtaining informed consent or compliance with the study procedures as per investigator discretion
17. Patients with a known immediate or delayed hypersensitivity reaction or idiosyncrasy to eltrombopag or drugs chemically related to eltrombopag or excipients that contraindicate their participation

[redacted]

18. History or current diagnosis of cardiac disease indicating significant risk of safety for patients participating in the study such as uncontrolled or significant cardiac disease or impaired cardiac function including any of the following:
    - Corrected QTc > 450 msec (male patients), > 460 msec (female patients) using Fredericia correction (QTcF) on the screening ECG
    - Resting heart rate at screening (physical exam or 12 lead electrocardiogram [ECG]) < 50 or > 90 beats per minute (BPM)
    - Recent myocardial infarction (within last 6 months)
    - Uncontrolled congestive heart failure
    - Unstable angina (within last 6 months)
19. Patients with known active or uncontrolled infections not responding to appropriate therapy
20. Patients with evidence of current alcohol/drug abuse
21. Concurrent participation in an investigational study within 30 days prior to enrollment or within 5-half-lives of the investigational product, whichever is longest. Note: parallel enrollment in a disease registry is permitted
22. Known thrombophilic risk factors. Exception: Patients for whom the potential benefits of participating in the study outweigh the potential risks of thromboembolic events, as determined by the investigator
23. Female patients who are nursing or pregnant (positive serum pregnancy test) at screening or pre-dose on Day 1
24. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, (or female partners of male patients) **unless** they are using highly effective methods of contraception while taking study treatment and for 3 months after stopping medication.

    Highly effective methods of contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
    - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example, hormone vaginal ring or transdermal hormone contraception..

    In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

[redacted]

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks in advance. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Sexually active males must be willing to use a condom during intercourse while taking study treatment and for 3 months after stopping study treatment. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm for the time period specified above.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

6 Treatment

6.1 Study treatment

Patients will be treated with eltrombopag 50 mg QD for 2 weeks to reach a target platelet count of $\geq 100\times10^9$/L (CR). For those patients who do not achieve the target platelet count within 2 weeks, the dose of eltrombopag will be increased to 75 mg QD. Treatment with eltrombopag will be continued at the minimal dosage necessary to achieve and maintain a platelet count around 100×10^9/L for 2 months.

Patients will be eligible for taper off and treatment discontinuation once they reach platelet count $\geq 100\times10^9$/L and maintain it around 100×10^9/L (all assessments of platelet count $\geq 70\text{x}10^9$/L) for 2 months. The duration of tapering will be individualized and depend upon starting dose and response of the patient: decreases in dose will be performed by 25 mg reductions every 2 weeks. If platelet counts are stable, the next reduction will be carried out within 2 weeks, with dosing of 25 mg on alternate days for 2 weeks until treatment is totally discontinued. Patients who are dose escalated to 75mg QD are eligible for taper off and treatment discontinuation as long as they achieve CR and maintain a platelet count around 100×10^9/L (all assessments of platelet count $\geq 70\text{x}10^9$/L) for 2 months.

Different treatment options and eltrombopag dosage for patients not meeting criteria for treatment discontinuation are summarized in Table 6-1.

A reduced starting dosage of 25 mg once daily is recommended for patients of Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean or Thai). The dose of eltrombopag in patients with Asian ancestry will be reduced to account for the lower eltrombopag clearance (CL/F) observed in these patients compared to the non-Asian population. Therefore, drug tapering for patients with Asian ancestry will be done in 12.5 mg decrements every second week.

[redacted]

Table 6-1 Eltrombopag dosing guidance for patients not meeting criteria for sustained remission

Platelet Level	Dose guidance
Patients on 75 mg/day eltrombopag and platelet < 100×10^9/L	Continue on eltrombopag 75 mg/day till month 12
Patients who reach CR (platelets ≥ 100×10^9/L) but do not maintain platelets around 100×10^9/L for 2 months (i.e. platelets < 70×10^9/L)	Increase dose to a maximum of 75 mg/day as per Section 6.1 until CR is reached again and maintain platelets around 100×10^9/L (no platelets < 70×10^9/L)
Patients who relapse (< 30×10^9/L) during eltrombopag tapering off stage	Use previous dose level (i.e. one dose level higher)
Patients who relapse (< 30×10^9/L) after eltrombopag discontinuation	Re-initiate treatment with starting dose 50 mg/day (25 mg/day for Asian patients)

6.1.1 Investigational drug

Eltrombopag study drug will be provided by Novartis. Sourcing of study drug by Novartis can be either through clinical supply or local commercial supply. Clinical supply will be provided globally though Global Clinical Supply and labeled as per local regulations. Local commercial supply will be sourced in the country where appropriate and as per local regulations. If eltrombopag is sourced through local commercial supply, drug will be labeled in-country and the locally approved form and packaging of eltrombopag will be used.

Eltrombopag will not be dosed by weight or body surface area.

All investigational treatment is to be stored in a secure locked area while under the responsibility of the investigator. Receipt and dispensing of investigational treatment must be recorded by an authorized person at the investigator's site.

For detailed safety information refer to the [ETB115 Investigators Brochure, current edition] and the approved product labeling. A description of the study treatment, pharmaceutical form and method of administration of eltrombopag is provided in Table 6-2.

Table 6-2 Investigational drug

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Eltrombopag	Tablet for oral use	12.5 mg	Daily
Eltrombopag	Tablet for oral use	25 mg	Daily
Eltrombopag	Tablet for oral use	50 mg	Daily
Eltrombopag	Tablet for oral use	75 mg	Daily

6.1.2 Additional study treatments

No other treatment beyond investigational drug will be considered as study treatments.

6.1.3 Treatment duration

Patients may participate in the study for up to 24 months depending on their response. Patients not in sustained remission at month 12 will only be treated with eltrombopag in the study for 12 months.

[redacted]

Patients in sustained remission at month 12 will enter the follow-up period for an additional 12 months. Patients who relapse during the follow-up period (between months 12 and 24) will be offered retreatment with eltrombopag until the end of month 24. Some of the patients might not need retreatment with eltrombopag during the follow-up period.

Patients who receive treatment options other than eltrombopag within the follow-up period will discontinue the study at that time (see Section 9.3).

Patients may be discontinued from treatment earlier due to unacceptable toxicity at the discretion of the investigator or the patient. These patients will continue to be followed as per study design but will not be considered in having achieved sustained remission for the primary endpoint.

6.2 Other treatment(s)

Not applicable

6.2.1 Concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study treatment. All medications (other than study drug) and significant non-drug therapies (including physical therapy and herbal/natural medications) administered during the study must be listed on the Concomitant Medications or the Procedures and Significant Non-Drug Therapies electronic case report form (eCRF).

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded on the appropriate Case Report Forms (CRF).

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before enrolling a patient or allowing a new medication to be started. If the patient is already enrolled, contact Novartis to determine if the patient should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

HMG-CoA Reductase Inhibitors (statins)

Patients will be permitted to use HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-CoA) inhibitors during the study, but these drugs should be used with caution and a 50% dose reduction of the HMG-CoA reductase inhibitor is recommended, with close monitoring for safety, such as liver chemistry and signs and symptoms of myolysis, and efficacy, such as cholesterol and triglycerides (refer to individual product information for monitoring recommendations).

Polyvalent Cations (Chelation)

Eltrombopag chelates with polyvalent cations such as aluminum, calcium, iron, magnesium, selenium and zinc. Eltrombopag should be taken at least two hours before or four hours after

[redacted]

any products such as antacids, dairy products, or mineral supplements containing polyvalent cations to avoid significant reduction in eltrombopag absorption.

Food Interaction

To avoid significant reduction in eltrombopag absorption, eltrombopag should be taken at least two hours before or four hours after food containing > 50 mg calcium and at least one hour before to two hours after food containing little (< 50 mg) (or preferably no) calcium. The administration of a single 50 mg dose of eltrombopag with a standard high-calorie, high-fat breakfast that included dairy products led to reduced eltrombopag exposure. Foods low in calcium (defined as < 50 mg calcium per serving) including fruit, lean ham, beef and unfortified (no added calcium, magnesium, iron) fruit juice, unfortified soy milk, and unfortified grain did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content.

Substrates of OATP1B1 or BCRP

Concomitant administration of eltrombopag and other OATP1B1 or BCRP substrates should be undertaken with caution.

Examples of drugs which are OATP1B1 or BCRP substrates are given in Appendix 16.1.

CYP and UGT inhibitors and inducers

Eltrombopag is metabolised through multiple pathways including CYP1A2, CYP2C8, UGT1A1, and UGT1A3. Medicinal products that inhibit or induce a single enzyme are unlikely to significantly affect plasma eltrombopag concentrations; whereas medicinal products that inhibit or induce multiple enzymes have the potential to increase (e.g. fluvoxamine) or decrease (e.g. rifampicin) eltrombopag concentrations.

6.2.2 Prohibited medication

Any ITP directed therapy as per investigator assessment, different from what is specified within treatment section of the protocol, should be excluded including, but not limited to, platelet transfusion, new ITP-treating medication, or splenectomy. Detailed explanation related to exception for use of rescue medication is described in Section 6.2.3.

Use of the treatments detailed below are not allowed after screening.

Patients must abstain from using investigational or not use marketed drugs without a well-known safety profile and from using prohibited prescription or nonprescription drugs within 7 days or 5-half-lives (whichever is longer) prior to the first dose of study treatment and until completion of follow-up procedures unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study (see Exclusion Criteria-Section 5.2).

Patients must abstain from taking herbal supplements within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5-half-lives (whichever is longer) prior to the first dose of study treatment until completion of the 30-day follow-up visit, unless the Investigator and Sponsor agree that the medication will not interfere with the study treatment.

Drugs that affect platelet function (including but not limited to, aspirin, clopidogrel and/or non-steroidal anti-inflammatory drugs [NSAIDS]) should not be taken during the study unless there

[redacted]

is a very clear indication and the Investigator documents the rationale. [redacted]

Any other TPO-R agonists are prohibited during this study (e.g., romiplostim).

6.2.3 Rescue therapy

Any ITP-directed medication or therapy, other than eltrombopag, given during the trial with the aim to increase platelet count for the patients who have clinically significant bleeding will be considered a rescue therapy and must be recorded on the appropriate CRF page. A patient who receives rescue medication or therapy will not be considered in having achieved sustained remission for the primary endpoint, unless the patient uses steroids ± IVIG as described below in the first 14 days of start of eltrombopag.

Steroids ± IVIG use as rescue medication:

In case of clinical necessities because of very low platelet count ($< 10\times10^9$/L) and/or significant bleeding, treatment with steroids ± IVIG and platelet transfusion is permitted together with eltrombopag for the first 14 days, calculated from the first dose day of eltrombopag.

6.3 Patient numbering, treatment assignment, randomization

6.3.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is first screened and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Patient No. available.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the patient ID must not be reused for any other patient.

If the patient is re-screened, a new unique number will be assigned to the rescreened patient and the original assigned number will be captured in the rescreening page. If the patient fails to start treatment for any reason, the reason will be entered into the Disposition page. IRT must be notified within 2 days that the patient was not enrolled in the study.

6.3.2 Treatment assignment, randomization

No randomization will be performed in this study. All eligible patients will receive eltrombopag per the treatment schedule.

6.4 Treatment blinding

Not applicable.

[redacted]

6.5 Dose escalation and dose modification

6.5.1 Dose escalation guidelines

Dose escalation will be allowed from 50 mg QD to 75 mg QD as described in Section 6.1.

Patients will be treated with eltrombopag 50 mg QD for 2 weeks to reach a target platelet count of $\geq 100\times10^9$/L (CR). For those patients who do not achieve the target platelet count within 2 weeks, the dose of eltrombopag will be increased to 75 mg QD.

6.5.1.1 Starting dose

In this study, the starting dose will be 50 mg eltrombopag QD (starting dose for Asian patients will be 25 mg QD, reduced as per Section 6.1).

This eltrombopag starting dose is consistent with the dosing guidelines that have been approved for eltrombopag use in adult patients with chronic ITP.

6.5.2 Dose modifications

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or mandated in order to allow patients to continue the study treatment.

These dose modifications are summarized in Table 6-3. Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-4.

Table 6-3 Eltrombopag Dose Adjustments in ITP

Platelet count	Dose adjustment or response
$< 100\times10^9$/L following 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 75 mg/day [a]
$\geq 100\times10^9$/L to $< 200 \times 10^9$/L	Use lowest dose of eltrombopag to maintain platelet counts around 100×10^9/L for 2 months prior to per protocol tapering [a]
$\geq 200 \times 10^9$/L to $\leq 400 \times 10^9$/L	Decrease daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments [b c]
$> 400 \times10^9$/L	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is $< 150 \times10^9$/L, reinitiate therapy at a lower daily dose [b c]

a. This dose adjustment schedule was chosen for this study to have patients use the minimal efficacious dosage of eltrombopag in order to achieve a CR. Patients need to maintain a CR for a minimum of 2 months before tapering off can be attempted.

b. For patients taking eltrombopag once daily, consideration should be given to dosing at 12.5 mg once daily or alternatively a dose of 25 mg once every other day

c. Source: The latest version of the eltrombopag core data sheet (CDS).

These dose changes must be recorded on the appropriate CRF.

Eltrombopag can cause hepatobiliary laboratory abnormalities, severe hepatotoxicity, and potentially fatal liver injury. Serum ALT, AST and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly after establishment of a stable dose. Abnormal serum liver tests should be evaluated with repeat

[redacted]

testing within 3 to 5 days. If the abnormalities are confirmed, serum liver tests should be monitored weekly until the abnormalities resolve, stabilize, or return to baseline levels.

For the grading of adverse events and laboratory results, the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 will be used.

Table 6-4 Criteria for dose adjustment based on liver enzyme and bilirubin levels

	Dose modifications for ETB115
Worst toxicity CTCAE[a] Grade (value) during the treatment	**Investigations (Hepatic)**
Isolated Total Bilirubin Elevation	
> ULN – 1.5 x ULN > 1.5 - 3.0 x ULN*	Maintain dose level Interrupt dosing and weekly monitor liver function tests (LFTs)[b], or more frequently if clinically indicated, until resolved to ≤ 1.5 × ULN: If resolved in ≤ 14 days, then resume at same dose level If resolved in > 14 days, then decrease one dose level[e]
> 3.0 - 10.0 x ULN**	Mandatory: Interrupt dosing and weekly monitor LFTs[b], or more frequently if clinically indicated, until resolved to ≤ 1.5 × ULN: If resolved in ≤ 14 days, then decrease one dose level[e] If resolved in > 14 days, then discontinue patient from study drug treatment. LFTs[b] will continue to be monitored weekly, or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
> 10.0 x ULN	Mandatory: Discontinue patient from study drug treatment The patient should be monitored weekly (including LFTs[b]) , or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
	* Note: If total bilirubin > 1.5 - ≤ 3 x ULN is due to the indirect (non-conjugated) component only, no changes to dose are required. ** Note: If total bilirubin > 3.0 – 10.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then decrease 1 dose level[e] and continue treatment at the discretion of the investigator
Isolated AST or ALT elevation	
> ULN - 3.0 x ULN > 3.0 - 5.0 x ULN	Maintain dose level Maintain dose level. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results. If abnormal lab values are confirmed upon the repeat test, then monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 × ULN Discontinue patient from the study drug treatment if elevation is combined with any of the following: Clinical symptoms of liver injury or evidence for hepatic decompensation

[redacted]

	Dose modifications for ETB115
Worst toxicity CTCAE[a] Grade (value) during the treatment	**Investigations (Hepatic)**
	Progressively increasing LFTs[b] upon repeat testing Persistence ≥4 weeks
> 5.0 - 10.0 x ULN	Mandatory: Interrupt dose. Repeat LFTs[b] as soon as possible; preferably within 48-72 hours from awareness of the abnormal results. Monitor LFTs[b] weekly, or more frequently if clinically indicated until resolved to ≤ 3.0 x ULN then: If resolved in ≤14 days, maintain dose level If resolved >14 days, decrease one dose level[e]
> 10.0 - 20.0 x ULN	Mandatory: Interrupt dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results. Monitor LFTs[b] weekly, or more frequently if clinically indicated until resolved to ≤ baseline. Then decrease one dose level [e]
> 20.0 x ULN	Mandatory: Discontinue patient from study drug treatment Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results. Monitor LFTs[b] weekly, or more frequently if clinically indicated until resolved to ≤ baseline or stabilization over 4 weeks..
Combined [c] elevations of AST or ALT and total bilirubin	
For patients with normal baseline ALT and AST and total bilirubin value [AST or ALT > 3.0 × ULN] combined with [total bilirubin > 2.0 × ULN] without evidence of cholestasis[d] OR For patients with elevated baseline AST or ALT [AST or ALT > 3 × baseline] OR [AST or ALT > 5.0 × ULN], whichever is lower, combined with [total bilirubin > 2× baseline AND > 2.0 × ULN]	Mandatory: Permanently discontinue patients from study drug treatment. Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[b]), or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks
All dose modifications should be based on the worst preceding toxicity. [a] Common Toxicity Criteria for Adverse Events (CTCAE Version 4.03) [b] Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.) [c] "Combined" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative	

[redacted]

	Dose modifications for ETB115
Worst toxicity CTCAE[a] Grade (value) during the treatment	**Investigations (Hepatic)**
action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction [d] "Cholestasis" defined as alkaline phosphatase (ALP) elevation (>2.0 x ULN and R value <2) in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury. [e] "One dose level" defined as eltrombopag dose reduction by 25 mg.	

6.5.2.1 Dose modifications for other reasons

Eltrombopag dosing is to be interrupted in patients unable to ingest the drug due to mucositis or permanent vomiting.

Early discontinuation of treatment

Eltrombopag must be permanently discontinued if any of the following events occur or is identified at any time during the study:

- Cytogenetic abnormalities
  - Monosomy 7 – discontinue eltrombopag
  - Other abnormalities – discontinuation at physician discretion
- Thromboembolism, irrespective of relation to study drug
- Development of myelodysplastic syndrome or acute myeloid leukemia
- Positive pregnancy test, at any time during the study
- Difficulties in continuing eltrombopag due to AE(s)
- Patient is found to be significantly non-compliant with the requirements of the protocol (including treatment noncompliance)
- ALT of AST > 20 x ULN

6.5.3 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately at least 4-week intervals (or more frequently if required by institutional practices, or if clinically indicated), until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, etc. should be consulted as deemed necessary.

Patients who permanently discontinue eltrombopag for an AE or clinically significant laboratory value will be discontinued from the study and then undergo a 30-day safety follow-up.

[redacted]

6.5.3.1 Dose delays, modifications or discontinuation for hematologic side effects

Patients who experience a deep venous thrombosis (other than a line-related upper extremity thrombosis) or a pulmonary embolus, a transient ischemic attack or stroke, or a myocardial infarction at any time while on eltrombopag will discontinue eltrombopag.

6.5.3.2 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal baseline ALT and AST: AST or ALT > 3.0 × ULN combined with TBIL > 2.0 × ULN OR INR > 1.5 without evidence of cholestasis (no ALP elevation)
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]
- For patients with normal baseline ALT: ALT ≥ 5 x Upper Limit of Normal (ULN)

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as Alkaline Phosphatase (ALP) elevation > 2.0 × ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury).

These patients should be immediately discontinued from eltrombopag, and repeat liver function test (LFT) testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results, then with weekly monitoring of LFTs), or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatinine kinase, TBIL, direct and indirect bilirubin, gamma-glutamyl-transferase (GGT), prothrombin time (PT)/ International Normalized Ratio (INR) and ALP.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, nutritional supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.

[redacted]

5. Additional testing for other hepatotropic viral infection (cytomegalovirus [CMV], Epstein Barr virus [EBV] or Herpes simplex virus [HSV]), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

[redacted]

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator must promote compliance by instructing the patient to take eltrombopag exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must also be instructed to contact the investigator if he/she is unable for any reason to take eltrombopag as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts (if applicable) and information provided by the patient. This information should be captured in the source document at each visit. All eltrombopag dispensed and returned must be recorded in the Drug Accountability Log.

[redacted]

6.7 Preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Eltrombopag will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.7.1 Handling of eltrombopag

Eltrombopag study treatment supplies must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

[redacted]

6.7.2 Instruction for prescribing and taking study treatment

A description of eltrombopag, dose and frequency is provided in Table 6-2.

- Patients should take eltrombopag at approximately the same time each day either 1 hour before eating or 2 hours after eating.
- For 2 hours before taking eltrombopag and 4 hours after taking eltrombopag, patients should **avoid eating** dairy products, and calcium- and magnesium-rich foods
- Patients should be instructed not to make up missed doses. Patients who miss a dose of eltrombopag should wait and take the next scheduled dose. Patients should not take more than one dose of eltrombopag in one day.

7 Informed consent procedures

Eligible patients may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

If applicable, in cases where the patient's representative(s) gives consent (if allowed according to local requirements), the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Council of Harmonisation (ICH) Good Clinical Practices (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Novartis will review the investigators/clinical research organization (CRO) proposed informed consent form to ensure it complies with the ICHE6 GCP guidelines and regulatory requirements and is considered appropriate for this study. Any further changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the patient.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

[redacted]

Male patients must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

8 Visit schedule and assessments

Assessment schedule lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

Screening assessments can occur within 28 days prior to the enrollment as per Table 8-1.

There is a ± 1 day visit window permitted on assessments to take into account scheduling over public holidays, from Week 1 Day 1 to Week 9 Day 1. Also a visit window of ± 3 days is allowed from Week 11 Day 1 to end of treatment. [redacted]

A visit window of ±7 days is allowed during the follow-up period for responders.

Every effort should be made to follow the schedule outlined in Table 8-1.

Patients should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed eltrombopag study treatment supplies should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

[redacted]

Table 8-1 Assessment schedule

Screening to Week 9

Period	**Screening**	**Treatment**								
Visit Name	**Screening**	**Week 1 Day 1**	**Week 2 Day 1**	**Week 3 Day 1**	**Week 4 Day 1**	**Week 5 Day 1**	**Week 6 Day 1**	**Week 7 Day 1**	**Week 8 Day 1**	**Week 9 Day 1**
Visit Number	**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**
Obtain informed consent	X									
Patient history	X									
Demography	X									
Inclusion/exclusion criteria	X									
Relevant medical history/current medical history	X									
Physical Exam	S	S	S	S	S	S	S	S	S	S
Height		X								
Weight	S	X	S	S	S	S	S	S	S	S
Vital Signs	X	X		X		X		X		X
Laboratory Assessments										
Hematology	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X		X		X		X		X
Coagulation	X									
Pregnancy Test **	S					S				S
ECG	X									

[redacted]

Period	**Screening**	**Treatment**								
Visit Name	**Screening**	**Week 1 Day 1**	**Week 2 Day 1**	**Week 3 Day 1**	**Week 4 Day 1**	**Week 5 Day 1**	**Week 6 Day 1**	**Week 7 Day 1**	**Week 8 Day 1**	**Week 9 Day 1**
Visit Number	**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**
Adverse Events	X	X	X	X	X	X	X	X	X	X
[redacted]										
Ocular Assessments	X									
Prior/concomitant Medications		X	X	X	X	X	X	X	X	X
[redacted]										
Bone marrow biopsy (optional)	Per investigator discretion									
Patient Reported Outcomes		X								
FACIT-Fatigue		X								
FACT-Th6		X								
SF-36v2		X								
GP5		X								
TSQM-9		X								
Study drug administration		X	X	X	X	X	X	X	X	X

[redacted]

Period	**Screening**	**Treatment**								
Visit Name	**Screening**	**Week 1 Day 1**	**Week 2 Day 1**	**Week 3 Day 1**	**Week 4 Day 1**	**Week 5 Day 1**	**Week 6 Day 1**	**Week 7 Day 1**	**Week 8 Day 1**	**Week 9 Day 1**
Visit Number	**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**
IRT										
IRT registration	X									
IRT enrollment		X								

X = assessment to be recorded in the clinical database or received electronically from a vendor
S = assessment to be recorded in the source documentation only
a= Should be administered before IP administration

**= on monthly basis or as per local standard, if no visit planned the test can be performed at home with urine pregnancy test. Only blood test results will be collected in the eCRF)

[redacted]

Weeks 11 to follow-up

Period	Treatment																					End of Treatment	Safety Follow-up
Visit Name	Week 11 Day 1	Week 13 Day 1	Week 15 Day 1	Week 17 Day 1	Week 19 Day 1	Week 21 Day 1	Week 23 Day 1	Week 25 Day 1	Week 27 Day 1	Week 29 Day 1	Week 31 Day 1	Week 33 Day 1	Week 35 Day 1	Week 37 Day 1	Week 39 Day 1	Week 41 Day 1	Week 43 Day 1	Week 45 Day 1	Week 47 Day 1	Week 49 Day 1	Week 51 Day 1	End of Treatment / Week 53 Day 1*	Safety FUP
Visit Number	200	210	220	230	240	250	260	270	280	290	300	310	320	330	340	350	360	370	380	390	400	1999	SFUP
Physical Exam	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	
Weight		X						X						X								X	
Vital Signs		X						X						X								X	
Laboratory Assessments																							
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry		X		X		X		X		X		X		X		X		X		X		X	
Coagulation																						X	
Pregnancy Test **		S		S		S		S		S		S		S		S		S		S		S	
ECG																						X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																							
Ocular Assessments								X														X	
Prior/concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																							

[redacted]

Period	**Treatment**																					**End of Treatment**	**Safety Follow-up**
Visit Name	**Week 11 Day 1**	**Week 13 Day 1**	**Week 15 Day 1**	**Week 17 Day 1**	**Week 19 Day 1**	**Week 21 Day 1**	**Week 23 Day 1**	**Week 25 Day 1**	**Week 27 Day 1**	**Week 29 Day 1**	**Week 31 Day 1**	**Week 33 Day 1**	**Week 35 Day 1**	**Week 37 Day 1**	**Week 39 Day 1**	**Week 41 Day 1**	**Week 43 Day 1**	**Week 45 Day 1**	**Week 47 Day 1**	**Week 49 Day 1**	**Week 51 Day 1**	**End of Treatment / Week 53 Day 1***	**Safety FUP**
Visit Number	**200**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300**	**310**	**320**	**330**	**340**	**350**	**360**	**370**	**380**	**390**	**400**	**1999**	**SFUP**
[redacted]																							
Bone marrow biopsy (optional)	Per investigator discretion																						
Patient Reported Outcomes																							
FACIT-Fatigue		X						X						X								X	
FACT-Th6		X						X						X								X	
SF-36v2		X						X						X								X	
GP5																						X	
TSQM-9																						X	
Study drug administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

[redacted]

Period	**Treatment**																					**End of Treatment**	**Safety Follow-up**
Visit Name	**Week 11 Day 1**	**Week 13 Day 1**	**Week 15 Day 1**	**Week 17 Day 1**	**Week 19 Day 1**	**Week 21 Day 1**	**Week 23 Day 1**	**Week 25 Day 1**	**Week 27 Day 1**	**Week 29 Day 1**	**Week 31 Day 1**	**Week 33 Day 1**	**Week 35 Day 1**	**Week 37 Day 1**	**Week 39 Day 1**	**Week 41 Day 1**	**Week 43 Day 1**	**Week 45 Day 1**	**Week 47 Day 1**	**Week 49 Day 1**	**Week 51 Day 1**	**End of Treatment / Week 53 Day 1***	**Safety FUP**
Visit Number	**200**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300**	**310**	**320**	**330**	**340**	**350**	**360**	**370**	**380**	**390**	**400**	**1999**	**SFUP**
IRT enrollment																						X	

X = assessment to be recorded in the clinical database or received electronically from a vendor
S = assessment to be recorded in the source documentation only

* Patients who have achieved sustained remission at month 12 will be followed quarterly for an additional 12 months to obtain further data on response and remission duration.

** On monthly basis or as per local standard, if no visit planned the test can be performed at home with urine pregnancy. Only blood test results will be collected in the eCRF)

[redacted]

Follow-up Period for Responders

Period	**Treatment**				**Safety Follow-up**
Visit Name	**FUP Visit #1 M15**	**FUP Visit #2 M18**	**FUP Visit #3 M21**	**End of FUP M24** [b]	**Safety FUP**
Visit Number	**410**	**420**	**430**	**2999**	**SFUP**
Physical Exam	S	S	S	S	
Height	S	S	S	S	
Weight	X	X	X	X	
Vital Signs	X	X	X	X	
Adverse Events	X				X
Prior/concomitant Medications	X				X
Pregnancy Test	S	S	S	S	
Laboratory Assessments					
Hematology	X	X	X	X	
Chemistry	X	X	X	X	
Patient Reported Outcomes					
FACIT-Fatigue	X	X	X	X	
FACT-Th6	X	X	X	X	
SF-36v2	X	X	X	X	
GP5				X	
TSQM-9				X	
Study Drug Administration [a]	X	X	X	X	

X = assessment to be recorded in the clinical database or received electronically from a vendor
S = assessment to be recorded in the source documentation only

a = If the patient relapses during the follow-up period, they may begin re-treatment with eltrombopag. If the patient is treated with treatment options other than eltrombopag they will discontinue the study at that time.

b = Patients who discontinue prior to month 24 and not at a defined study visit should come into complete the end of follow-up / month 24 visit.

[redacted]

8.1 Screening

All patients will be screened for study eligibility. All patients must sign informed consent prior to any screening procedures being performed. Activities for screening will begin up to 28 days prior to initiation of study treatment with eltrombopag.

Information regarding eligibility criteria will be collected on the Inclusion/Exclusion eCRF. Patients who do not meet all entry criteria should not be entered into the study.

A re-screening due to lab abnormalities can be submitted to the sponsor for decision. Re-screening of patients is only allowed **once** per patient if the patient was not enrolled in the treatment phase before. If patient has been enrolled and treated, re-screening of patient is not allowed.

In case rescreening occurs, all evaluations to be re-assessed should meet the eligibility criteria. A new informed consent form must be signed only if there is an interruption in the patient's eligibility evaluation and the investigator chooses to re-screen the patient following screen failure; the 28 day screen period does not apply to the informed consent process. If a new informed consent form is signed, AEs and medical history will be assessed relative to the new informed consent date.

Following registering in the Interactive Response Technology (IRT) for screening, patient eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

8.1.1 Information to be collected on screening failures

Patients who sign an informed consent form and subsequently found not to be eligible will be considered a screen failure. The reason for screen failure should be entered on the applicable CRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced an SAE event during the screening phase (see Section 10.1.3 for reporting details).

Patients who sign an ICF and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition CRF.

8.2 Patient demographics/other baseline characteristics

Country specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF

The following patient demographics and baseline characteristics will be collected on the eCRF:

[redacted]

- Demography including age, sex, predominant race and ethnicity (where permitted)
- Height and weight
- Medical history (e.g., important medical, surgical, and allergic conditions from the patient's medical history which could have an impact on the patient's evaluation)/ current medical conditions (e.g., all relevant current medical conditions which are present at the time of signing informed consent). Ongoing medical conditions, symptoms and diseases which are recorded on the Medical History eCRF should include the toxicity grade when applicable
- Prior and concomitant medications

Bone marrow biopsy is optional and recommended for patients who did not respond to steroids and are considered refractory. It can be performed during treatment at the discretion of the investigator.

All assessments to be completed and documented during screening are detailed in Table 8-1.

8.3 Efficacy

The efficacy objective is to assess the ability of eltrombopag to induce sustained remission by month 12.

8.3.1 Efficacy assessment 1

Platelet count will be performed at screening visit 1 to assess the eligibility of the patient. Hematology including platelet counts will be assessed at week 1 /day 1 and weekly during the first 8 weeks of treatment. Based on patient response, hematology will be performed biweekly thereafter until the end of treatment.

Additional assessments of platelet count may be performed more frequently than the biweekly schedule if needed in accordance with the clinical judgment of the investigator.

8.3.2 Efficacy assessment 2

Bleeding events will be assessed at each visit and recorded in the AE CRF. Documentation of the use of any rescue therapy will be documented on the appropriate CRF.

8.3.3 Appropriateness of efficacy assessments

Efficacy assessments are standard, as done in daily clinical practice and driven by relevant guidelines - ASH 2011 and ICG ITP Guideline (Provan 2010).

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section.

[redacted]

Table 8-2 Physical assessments

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after first administration of investigational drug which meet the definition of an AE must be recorded as an AE.
Vital sign	Vital signs include BP and pulse measurements.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

Patients who discontinue treatment early for reasons other than per protocol tapering require weekly hematology assessments (including platelet counts) for the first four weeks after discontinuing eltrombopag.

8.4.1 Ophthalmic examination

The ophthalmic exam should include the retina, blood vessels, optic disc/nerve. If the presence of a cataracts(s) is suspected, a slip lamp examination is required. Ophthalmic exams will be performed at visits according to Table 8-1.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page of the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the AE page of the patient's eCRF.

8.4.2 Laboratory evaluations

Table 8-3 Laboratory assessments to be performed locally

Test Category	Test Name
Hematology	Hematocrit, HgB, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Other (absolute value preferred, %s are acceptable)
Chemistry	Albumin, ALP, ALT, AST, GGT, lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Direct Bilirubin, TBIL, Total Protein, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting), Creatine kinase
Coagulation	PT, INR, Activated partial thromboplastin time (aPTT), Fibrinogen
Pregnancy Test	Serum / Urine pregnancy test

8.4.3 Electrocardiogram

A standard 12 lead ECG will be performed at the screening visit.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site.

[redacted]

Clinically significant abnormalities present at screening should be reported on the Medical History CRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the AE CRF page.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the investigator.

8.4.4 Pregnancy

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

At screening (or baseline) a serum pregnancy test should be performed within 14 days of the first dose of eltrombopag. Pregnancy testing (serum or urine) must be performed on a monthly basis or as per local standard while receiving study drug until study drug discontinuation. If no visit is planned the test can be performed at home with urine pregnancy test. Additional pregnancy tests may be performed at the investigator's discretion during the study.

A serum pregnancy test is required at the end of treatment visit for all patients including those who discontinue early. Local pregnancy test and associated results will not be collected on eCRF.

Assessments of Fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child bearing potential must also be available as source documentation in the following cases:

- surgical bilateral oophorectomy without a hysterectomy
- reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female patient, regardless of reported reproductive/menopausal status at screening/baseline.

8.4.5 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

8.5 Additional assessments

Bone marrow biopsies can be performed at the discretion of the investigator.

8.5.1 Clinical Outcome Assessments

Patient reported outcomes (PRO)

Immune thrombocytopenia is associated with symptoms of fatigue, bruising, and bleeding, which can interfere with daily activities. Consequently, patients with ITP have decreased

[redacted]

health-related quality of life (HRQoL) compared with healthy individuals. To assess patient-reported outcomes (PROs), HRQoL changes over time and association between HRQoL and platelet response during treatment or while in sustained remission with eltrombopag will be assessed using standard validated instruments in patients with ITP who are refractory to treatment or who relapsed after first-line steroids.

The **Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)** instrument is a 13-item, easy-to-administer, validated tool used to measure an individual's level of fatigue during usual daily activities over the past 7 days (Cella 2002, Webster 2003). FACIT-Fatigue is a subscale of the FACIT measurement system, which is a validated collection of HRQoL questionnaires targeted to the management of chronic illness that are used to measure HRQoL on multiple general and disease-specific domains. FACIT-fatigue is scored using a 4-point Likert scale (4=not at all fatigued to 0=very much fatigued) where the total possible score ranges from 0-5; higher scores represent better HRQoL (Signorovitch 2011). Patients will be administered the FACIT-Fatigue at baseline, every 3 months during treatment or while in sustained remission, at months 15, 18, 21, 24, and end of treatment. A minimal clinically important difference from baseline in FACIT-Fatigue score will be evaluated (Cella 2002). The overall total score will be evaluated; [redacted].

The **Medical Outcome Trust's Short-Form 36 Health Survey, Version 2 (SF-36v2)**, which is a validated instrument used to measure general physical and mental health status (Ware 2000), will be used to assess the impact of ITP on physical function and ability to conduct day-to-day activities. The SF-36v2 is used to measure patients' overall HRQoL via assessment of 8 domains—Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health—over the past 4 weeks or 7 days. The SF-36 is scored using norm-based scoring procedures and scores ranging from 0-100; higher scores represent better HRQoL. Two summary scores, the Physical Component Score (PCS) and the Mental Component Summary (MCS), can also be calculated.

The SF-36v2, specifically the Physical Functioning and the Role Physical domains, demonstrated good reliability and validity for measuring the proposed constructs in the ITP population (Signorovitch 2011). The Physical Functioning domain includes 10 items related to limitations in physical functioning and is scored using a 3-level Likert scale (1=yes, limited a lot; 2=yes, limited a little; and 3=no, not at all limited); higher scores represent less functional limitation. The Role Physical domain is used to measure to what degree physical health interferes with work/other daily activities, includes 4 items (reduction in the amount of time spent on work/other activities, accomplishing less than one would like, limitations in kind of work/other activities, and difficulty performing work/other activities), and is scored using a 5-level Likert scale (1=all of the time; 5=none of the time); lower scores represent less impact on daily activities. Patients will be administered the SF-36v2 at baseline, every 3 months during treatment or while in sustained remission, at months 15, 18, 21, 24, and end of treatment, and change from baseline will be evaluated. [redacted]

The **Functional Assessment of Cancer Therapy - Thrombocytopenia 6-item version (FACT-Th6)** instrument is used to measure worry/concern about bleeding and bruising, and the impact of this worry/concern on physical and social activity (Cella 2006). FACT-Th6 is a [redacted]

6-item subset of the more detailed FACT-Th, which is an 18-item subscale of the validated FACT that specifically measures concerns related to thrombocytopenia in the past 7 days. The FACT-Th6 is scored using a 5-level Likert scale (0=not at all to 4=very much) and is calculated by summing scores for the 6-items; therefore, scores can range from 0–24, with higher scores representing better HRQoL. No minimum clinically important change thresholds have been established for FACT-Th6. Tentatively anchor-based methods (e.g., based on Patient Global Impression of Change [PGIC] and Patient Global Impression-Severity [PGIS]) and distribution-based methods will be used to determine meaningful change in scores. FACT-Th6 demonstrated good reliability and validity for measuring the proposed constructs in the ITP population. Patients will be administered the FACT-Th6 at baseline, every 3 months during treatment or while in sustained remission, at months 15, 18, 21, 24, and at end of treatment.

The **GP5,** which is a single question, is used to assess the overall bothersomeness of treatment side effects. The GP5 is scored using a 5-point rating scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; and 4 = very much), where lower scores reflect less bothersomeness from treatment side effects. The GP5 will be evaluated at baseline and end of treatment.

Treatment Satisfaction Questionnaire for Medication (TSQM-9) will be used to assess treatment satisfaction with medication. The three scales of the TSQM-9 include the effectiveness scale, convenience scale, and global satisfaction scale. TSQM-9 will be evaluated at baseline and end of treatment.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Early discontinuation of study treatment for a patient occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the patient or the investigator.

The investigator must discontinue study treatment for a given patient if, he/she believes that continuation would negatively impact the patient's well-being.

Study treatment must be discontinued under the following circumstances:

- Patient/guardian decision
- Pregnancy of the participating patient
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the patient
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevents the patient from continuing participation in the study

If early discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the patient's premature discontinuation of study treatment and record this information.

Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent section,). **Where possible, they should return for the assessments indicated** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the patient/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule.

After early study treatment discontinuation (i.e., not per protocol tapering), at a minimum, in follow-up visit (30-days after the last dose of eltrombopag) the following data should be collected at clinic visits or via telephone/email contact:

- new / concomitant treatments
- AE / SAEs

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

[redacted]

Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient:

- Does not want to participate in the study anymore
  and
- Does not want any further visits or assessments
  and
- Does not want any further study related contacts

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

9.1.2 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.3 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the patient welfare and safety. Should early termination be necessary, patients must be seen as soon as possible (provide instruction for contacting the patient, when the patient should stop taking drug, when the patient should come for a final visit) and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

[redacted]

9.2 Study completion and post-study treatment

Study completion is defined as when the last patient finishes their end of follow-up / month 24 visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

All patients who are still on study at month 12 will complete the end of treatment visit at Week 53, Day 1. Patients who are still on study treatment and not in sustained remission at month 12 will come off trial after completing the end of treatment visit. After discontinuing drug at the end of treatment visit, patients will be followed-up for safety for an additional 30 days (safety follow-up). The following data should be collected during the safety follow-up: adverse events and concomitant medications. This data can be collected via telephone/email contact or at a clinic visit (as needed).

Patients who still have sustained remission (see Table 2-1) at the end of treatment visit will enter the follow-up period for responders (see Section 9.3). The follow-up period begins after month 12.

Continuing care to study participants should be provided by the investigator and/or referring physician. The treating physician can request access to eltrombopag for patients that are continuing to benefit from treatment. Access will be dependent on the local regulatory authority approval of the product and current reimbursement options.

9.3 Additional 12 months follow-up period for responders

Patients who still have sustained remission at month 12 will be followed quarterly (every 3 months) until month 24 in order to obtain further data on response and remission duration.

Patients will be followed quarterly (every 3 months) for physical exams, adverse events, concomitant medications, hematology and chemistry laboratory assessments, and patient reported outcomes (see Table 8-1 Follow-up period for responders).

In case of relapse during the follow-up period, patients will be offered a new course of eltrombopag treatment within this timeframe, starting at a dose of 50 mg (starting dose for Asian patients will be 25 mg QD, reduced as per Section 6.1).

Only patients receiving retreatment with eltrombopag will be followed until month 24. Patients re-treated with eltrombopag will be followed-up for safety for an additional 30 days (safety follow-up) after month 24. The following data should be collected during the safety follow-up: adverse events and concomitant medications. This data can be collected via telephone/email contact or at a clinic visit (as needed).

Patients who are treated with treatment options other than eltrombopag during the follow-up period will discontinue the study at that time.

Patients who discontinue prior to month 24 and not at a defined study visit (see Table 8-1 Follow-up period for responders) should complete their end of follow-up / Month 24 visit.

[redacted]

10 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An AE is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual patient and identifying AEs.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of AEs must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. Adverse events will be assessed and graded according to the CTCAE version 4.03
2. its relationship to the study treatment
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose reduced/increased
- Drug interrupted/withdrawn

6. its outcome i.e., its recovery status or whether it was fatal

Conditions that were already present at the time of informed consent should be recorded in medical history of the patient.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. Continuing at the end of the study), and assessment must be made at each

[redacted]

visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the IB.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with the underlying disease.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an

[redacted]

emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days following the last dose of eltrombopag must be reported to Novartis Safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

SAEs occurring after the patient has provided informed consent until the time the patient is deemed a Screen Failure must be reported to Novartis.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period following the last dose of eltrombopag should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be

[redacted]

followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to eltrombopag and any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (European Medicines Agency definition) (Table 10-1).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the, respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed. Liver safety monitoring tests should be performed at local laboratories used by the site.

[redacted]

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Significant liver laboratory abnormalities, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate CRFs

Please refer to Table 6-4 for dose modifications/discontinuation for liver laboratory abnormalities.

Every clinically significant liver event should be followed up by the investigator or designated personnel at the trial site, as summarized below. Repeat liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and GGT) to confirm elevation.

- These liver chemistry repeats should be performed locally. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate (CRF). These liver chemistry repeats should be performed using the local laboratory used by the site. Repeated laboratory test results must be reported as appropriate.
- If the initial elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the patient if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF.

10.2.2 Renal safety monitoring

Not applicable

10.2.3 Steering Committee

The Steering Committee (SC) will be established comprising investigators participating in the trial, i.e., not being Novartis representatives from the Clinical Trial Team.

The Steering Committee will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

[redacted]

11 Data Collection and Database management

11.1 Data collection

Data not requiring a separate written record will be defined in the protocol and the assessment schedule and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

Designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

Remote monitoring of the original electronic source records will take place, however on-site monitoring inspections will continue to take place in order to review data entry of source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess site operational capabilities, and to perform other monitoring activities that cannot be performed remotely.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the electronic data capture (EDC) system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments, prior medications and rescue medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by GMA Novartis management.

[redacted]

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/delegated CRO representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

12 Data analysis and statistical methods

All analyses will be performed by Novartis or a designated CRO. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Continuous variables will be summarized by number of patients, mean, standard deviation, minimum, median, and maximum. For selected parameters, 25^{th} and 75^{th} percentiles will also be presented.

Categorical variables will be summarized by frequencies and percentages.

The 95% confidence interval (CI) using the Clopper-Pearson method will be provided for selected parameters. Kaplan-Meier method will be used for time to event analyses.

In addition to the statistical methods outlined below, further details and any additional exploratory analyses that may be performed will be described in the Statistical Analysis Plan (SAP).

[redacted]

The **baseline** is the result of an investigation describing the "true" state of the patient before start of eltrombopag.

The last available assessment on or before the date of start of eltrombopag is taken as "baseline" assessment. In case, assessment is captured pre-dose on first day of eltrombopag (e.g. PROs), this assessment is used for baseline.

12.1 Analysis sets

The **Full Analysis Set (FAS)** includes all patients who received at least one dose of eltrombopag.

The **Safety Set** includes all patients who received at least one dose of eltrombopag.

[redacted]

12.2 Patient demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively based on the FAS.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term.

12.3 Treatments

The Safety set will be used for the analyses below.

The duration of exposure in weeks to eltrombopag, as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics.

The number of patients with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized and all dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment, including rescue medication therapy, will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system.

12.4 Analysis of the primary endpoint(s)

The primary objective is to assess ability of eltrombopag to induce sustained remission by month 12 in ITP patients who relapsed or failed to respond first-line steroid treatment.

For the primary and supportive analyses the FAS will be used.

[redacted]

12.4.1 Definition of primary endpoint

The primary endpoint is the proportion of patients with sustained remission (R) by month 12.

Sustained remission (R) is defined as:

- reach platelet count ≥ 100×10^9/L (CR) and then maintain platelet counts around 100×10^9/L for 2 months (no counts below 70×10^9/L) **AND** then
- taper off the drug until treatment discontinuation (see Section 9.1) while,
- maintain platelet count ≥ 30×10^9 /L in the absence of bleeding (no bleeding AEs) or use of any rescue therapy (see Section 6.2.3) until month 12.

12.4.2 Statistical model, hypothesis, and method of analysis

The number (%) of patients with sustained remission (R) by month 12 will be summarized together with 95% confidence interval (CI) using the Clopper-Pearson method.

A binomial test for one proportion, H0: P=0.15 vs. H1:P>0.15 will be performed to test if the proportion of remission patients is greater than 15%.

12.4.3 Handling of missing values/censoring/discontinuations

If patients' platelet assessments for evaluating the primary endpoint are missing, they will not be considered for sustained remission. No imputation will be used for missing platelet values.

A patient who discontinues early from the study (before month 12 e.g. withdrawal of consent) will not be considered for sustained remission.

12.4.4 Supportive analyses

The number (%) of patients:

- with CR (reaching platelet count ≥ 100×10^9/L)
- who maintained platelet counts around 100×10^9/L for 2 months (no counts < 70×10^9/L)
- who managed to start tapering eltrombopag after maintaining platelet counts around 100×10^9/L (no counts < 70×10^9/L) for 2 months
- who are able to discontinue eltrombopag after tapering

will be provided together with 95% CI using the Clopper-Pearson method.

In addition bar plot(s) for the percentage of patients in each category may be provided.

12.5 Analysis of secondary endpoints

For all efficacy and PRO analyses, the FAS will be used. For all safety analyses the safety set will be used.

12.5.1 Efficacy endpoint(s)

1. To assess the **duration of sustained remission** after treatment discontinuation

   1a) Summary statistics for the duration of sustained remission (weeks) counted from last dose of eltrombopag to month 12 for patients with sustained remission (R) will be provided.

[redacted]

1b) Kaplan-Maier analyses for the duration of sustained remission (weeks) counted from last dose of eltrombopag to relapse for patients with sustained remission (R) at month 12 and who enter 12 months follow-up period. The patients who do not relapse/die by month 24 will be censored.

1c) Kaplan-Maier analyses for the duration of sustained remission (weeks) counted from last dose of eltrombopag to relapse for all patients. The patients who do not relapse/die by month 24 will be right-censored. The duration will be considered as 0 for patients who do not manage to taper off eltrombopag per protocol i.e. do not reach sustained remission.

2. To assess the proportion if patients maintaining a sustained remission after treatment discontinuation until month 24.

   Number (%) of patients who are in sustained remission at months 15, 18, 21, and 24 will be provided.

3. To assess the ability of eltrombopag to induce **early response by month 1**

   Number (%) of patients who reach platelet count $\geq 50\times10^9$/L at least once within the first month (month 1) without bleeding events and no rescue therapy will be provided.

4. To assess the ability of eltrombopag to induce a **recovery response**, in case of loss of response during or after tapering of eltrombopag

   Number (%) of patients with at least one platelet count $\geq 30\times10^9$/L after eltrombopag is re-introduced, in case of loss of response ($< 30\times10^9$/L and/or bleeding event) without bleeding events and no rescue therapy will be provided.

5. To assess the **platelet count** from baseline to 3, 6, 9, 12, 15, 18, 21, 24 months

   Absolute and relative change in platelet count from baseline to 3, 6, 9, 12, 15, 18, 21, 24 months and end of treatment will be provided. Box plots for absolute and/or relative change in platelet counts from baseline to different time points will also be provided.

6. To assess the ability of eltrombopag to **maintain platelet count $\geq 30\times10^9$/L** within 12 months and every 3 months until month 24

   Number (%) of patients who maintain a platelet count $\geq 30\times10^9$/L from the first time of reaching that level to month 3, 6, 9, 12, 15, 18, 21, 24 and end of treatment, without bleeding events and no rescue therapy will be provided.

7. To evaluate patient **HRQoL** outcome measures for Health-Related Quality of Life (fatigue level of the patient through **FACIT**), **FACT-Th6 and SF-36v2** questionnaires.

   Change in each domain score and total score of HRQoL parameters: (fatigue level of patients through FACIT), FACT-Th6 and SF-36v2 questionnaires from baseline to 3, 6, 9, 12, 15, 18, 21, 24 months and end of treatment will be provided. In addition, summary statistics for the two main summary scores, the PCS and the MCS for SF36 v2 as per sustained remission (R) status (sustained remission versus no sustained remission) will also be provided. Listings will be provided.

   Scoring for SF-36v2 will be provided by an external vendor.

8. To explore the overall impact of side effects of treatment via the **GP5** at baseline, 12 months, and end of treatment

[redacted]

Overall change from baseline to end of treatment score will be assessed. A listing will be provided.

9. To explore treatment satisfaction with **TSQM-9**

   Overall change from baseline, 12 months, and end of treatment score will be assessed. A listing will be provided.

10. To evaluate the safety and tolerability of eltrombopag see Section 12.5.2.

12.5.2 Safety endpoint(s)

Safety summary tables include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate.

The on-treatment period lasts from the date of first dose of eltrombopag to 30 days after the date of the last dose of eltrombopag.

Adverse events

All information obtained on adverse events will be displayed by patient. Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs (TEAEs).

The incidence of TEAEs will be summarized by system organ class (SOC) and or preferred term, severity based on the CTCAE grades, type of adverse event and relation to eltrombopag.

Serious adverse events, AEs leading to discontinuation, AEs leading to dose adjustment and adverse events of special interest (AESI) which includes bleeding events during the on-treatment period will be tabulated.

Specific groupings of AESI will be considered and the number of patients with at least one event in each grouping will be reported. Such groups consists of AEs for which there is a specific clinical interest in connection with eltrombopag treatment or AEs which are similar in nature (although not identical). Note that certain AEs may be reported within multiple groupings/AESIs.

AESIs are defined by MedDRA terms. Definition for retrieval and maintenance is done in the electronic case retrieval sheet (eCRS).

The incidence of AESIs will be summarized by SOC and Preferred Term (PT).

The AESIs as specified in the latest version of the case retrieval sheet (CRS) at the time of analysis will be used.

All deaths (on-treatment and post-treatment [starting at day 30+1 after last dose of eltrombopag]) will be summarized.

All AEs, deaths and SAEs will be listed and those collected during the pre-treatment (from day of patient's informed consent to the day before first dose of eltrombopag) and post-treatment period will be flagged.

A patient with multiple AEs within a primary SOC is only counted once towards the total of the primary SOC.

[redacted]

Clinical laboratory evaluations

Grading of laboratory values will be assigned programmatically as per the CTCAE version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests where grades are not defined by CTCAE version 4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for key hematology and biochemistry tests laboratory tests:

- Shift tables comparing baseline to the worst on-treatment value. Each patient will be counted only once for the worst grade observed post-baseline.
- For laboratory tests where grades are not defined shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value will be used.

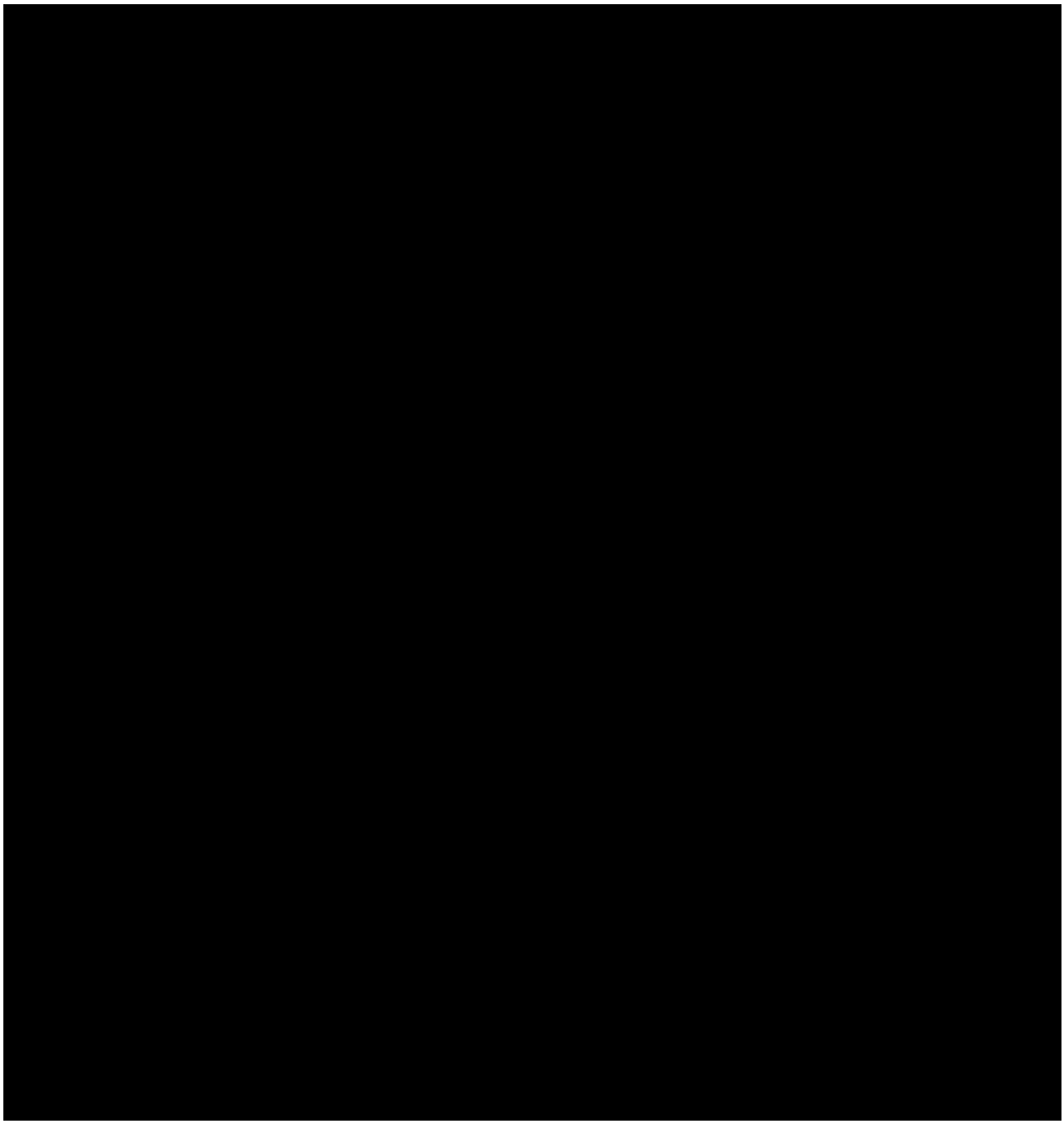
In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the statistical analytical plan (SAP) and tables/listings/figures (TLF) shells. Listings will be provided for all data.

Other safety evaluations

Data on ECG, vital sign, height, weight, ocular findings will be summarized descriptively, listed and flagged as appropriate. Any significant findings will be documented as AEs and reported as such.

[redacted]

[redacted]



12.7 Interim analyses

Not applicable

12.8 Sample size calculation

12.8.1 Primary endpoint

Based on medical experts' advice, it is postulated that approximately 15% of patients who do not respond or relapse after a first round of steroid therapy would have sustained remission by

12 months if on steroid recycling. In this study, at least a 10% higher sustained remission rate is expected by month 12, i.e., a sustained remission rate of at least 25% by 12 months is expected in patients who will receive eltrombopag after failing first-line steroids.

The sample size calculation is based on an exact binomial test for single proportion using a target alpha level of 0.05 and power of 80% to compare the null hypothesis H0: P=0.15 against the alternative hypothesis H1: P>0.15, where P is proportion of patients with sustained remission by Month 12.

A sample size of 101 gives at least 80% power if the true sustained remission rate with eltrombopag is 25% or more with an actual significance level of 0.043. The null hypothesis will be rejected if the number of patients with sustained remission is 22 or more.

Table 12-1 shows the sample size, cut-off, actual alpha, beta and power for different sustained remission rates. PASS 11 (version 11.0.10) is used for the sample size calculation.

Table 12-1 Numeric results for testing H0: P = P0 versus H1: P > P0 using exact binomial test statistic

Proportion given H0 (P0)	Proportion given H1 (P1)	Sample size (N)	Cut-off (Reject H0 if R>=This)	Actual Alpha	Actual Beta	Actual Power
0.150	0.250	101	22	0.043	0.196	0.804
0.150	0.300	48	12	0.048	0.181	0.819
0.150	0.350	28	8	0.049	0.182	0.818
0.150	0.400	22	7	0.037	0.158	0.842
0.200	0.300	116	31	0.049	0.193	0.807
0.200	0.350	56	17	0.043	0.194	0.806
0.200	0.400	35	12	0.034	0.195	0.805

At the end of the study, for decision-making purposes, the cut-off will be determined based on the final sample size and the target alpha and beta.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data

[redacted]

and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion *(*e.g., defined as last patient last visit*)* and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

14.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis/, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for patient safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

[redacted]

15 References (available upon request)

[redacted]

Arnold DM, Zeller MP, Smith JW, et al. (2013) In: Hematology: Basic Principles and Practice ebook. Hoffman R, Benz EJ, Silberstein CE, et al. Eds. 6th Edition. 2013. Sanders Elsevier. Philadelphia, PA.

Arruda VR, Annichino-Bizzacchi JM. (1996) High-dose dexamethasone therapy in chronic idiopathic thrombocytopenic purpura. Ann Hematol. 73:175-177.

Bao, W, Bussel, J, Heck, S, et al. (2010) Improved regulatory T-cell activity in patients with chronic immune thrombocytopenia treated with thrombopoietic agents. Blood; (116)22:4639-4645.

Bussel JB, Mahmud SN, Brigstocke SL, Torenten SM. Tapering eltrombopag in patients with chronic ITP: how successful is this and in whom does it work? Blood 2015;126:Abstract 1054.

Caulier MT et al. (1995) Pulsed high-dose dexamethasone in refractory chronic idiopathic thrombocytopenic purpura: a report on 10 cases. Br J Haematol. 91:477-479.

Cella D, Nowinski CJ. (2002) Measuring quality of life in chronic illness: the functional assessment of chronic illness therapy measurement system. Arch Phys Med Rehabil. 83(12Suppl):S10-S17.

Cella D, Beaumont JL, Webster KA, et al. (2006) Measuring the concerns of cancer patients with low platelet counts: the Functional Assessment of Cancer Therapy - thrombocytopenia (FACT-Th) questionnaire. Support Care Cancer. 14(12):1220-1231.

Červinek L, Mayer J, Doubek M. (2015) Sustained remission of chronic immune thrombocytopenia after discontinuation of treatment with thrombopoietin-receptor agonist in adults. Int J Hematol. 102:7-11.

Cheng G, Saleh N, Marcher C, et al. (2011) Eltrombopag management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. Lancet. 377(9763):393-402.

Cohen, Y, Djulbegovic, B, Shamai-Lubovitz, O, et al. (2000) The bleeding risk and natural history idiopathic thrombocytopenic purpura with persistent low platelet counts. Arch Intern Med. (160)11:1630-1638.

Cooper N. (2017) State of the art - how I manage thrombocytopenia. Br J Haematol. 177(1):39-54.

Demiroğlu H, Dündar S. (1997) High-dose pulsed dexamethasone for immune thrombocytopenia. N Engl J Med. 337:425-427.

Dubbeld P, van der Huel C, Hillen HF. (1991) Effect of high-dose dexamethasone in prednisone-resistant autoimmune thrombocytopenic purpura (ITP). Neth J Med. 1991;39:6-10

[redacted]

George JN. (2006) Management of patients with refractory immune thrombocytopenic purpura. J Thromb Haemost. 4:1664-1672.

George JN, Woolf SH, Raskob GE, et al. (1996) Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. Blood; 88(1):3-40.

Gonzalez-Lopez, T, Pascual C, Álvarez-Román M, et al. (2015) Successful discontinuation of eltrombopag after complete remission in patients with primary immune thrombocytopenia. Am J Hematol; 90(3):E40-43.

González‐López T, Fernández-Fuertes F, Hernández-Rivas J, et al. (2017) Efficacy and safety of eltrombopag in persistent and newly diagnosed ITP in clinical practice. Int J Hematol; 106:508–516

(2003) Guideline for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. Br J Haematol. 120(4):574-596.

Gutierrez-Espindola GR, et al. (2007) High doses of dexamethasone in adult patients with idiopathic thrombocytopenic purpura. Arch Med Res 34:31-34.

Gutierrez-Espindola GR, Morales-Polanco MR, Guerrero-Rivera S, et al. (2003) High doses of dexamethasone in adult patients with idiopathic thrombocytopenic purpura. Arch Med Res 34:31-34.

Hoffman, R, Benz, E, Silberstein, L, et al. eds. (2013) Hematology: Basic Principles and Practice. 6th ed. Philadelphia, PA: Elsevier Saunders; Chapter 133.

Kaufman RM, Djulbegovic B, Gernsheimer T, et al. (2015) Platelet transfusion: a clinical practice guideline from the AABB. Ann Int Med.162(3):162-205.

[redacted]

Lambert M, Gernsheimer M. (2017) Clinical updates in adult immune thrombocytopenia. Blood. 29:2829-2835

Liu, X, Liu S, Feng Q, et al. (2016) Thrombopoietin receptor agonists shift the balance of Fcgamma receptors towards inhibitory receptor IIb on monocytes in ITP. Blood. 6:852-861.

Liu X, Zhong H, Bao W, et al. (2012) Defective regulatory B-cell compartment in patients with immune thrombocytopenia. Blood. 120(16):3318-3325.

Mashhadi MA, Kaykhaei MA, Sepehri Z, et al. (2012) Single course of high dose dexamethasone is more effective than conventional prednisolone therapy in the treatment of primary newly diagnosed immune thrombocytopenia. Daru J Pharmaceut Sci. 20(1):7.

Mithoowani S, Gregory-Miller K, Goy J, et al. (2016) High-dose dexamethasone compared with prednisone for previously untreated primary immune thrombocytopenia: a systematic review and meta-analysis. Lancet Haematol. 3(10):e489-e496.

[redacted]

Nakazaki K, Hosoi M, Hangaishi A, et al. (2012) Comparison between pulsed high-dose dexamethasone and daily corticosteroid therapy for adult primary immune thrombocytopenia: a retrospective study. Intern Med. 51(8):859-863.

Neunert C, Lim W, Crowther M, et al. (2011) The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 117:4190-4207.

Newland A, Godeau B, Priego V, et al. Remission and platelet responses with romiplostin in primary immune thrombocytopenia: final results from a phase 2 study. Br J Haematol. 2016;172:262-273.

[redacted]

Perera M, Garrido T. (2017) advances in the pathophysiology of primary immune thrombocytopenia. Hematol. 22(1):41-53.

Portielje JE, Westendorp RG, Kluin-Nelemans HC, et al. (2001) Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. Blood. 97:2549-2554.

Profit L. (2006) Eltrombopag: the emerging evidence of its therapeutic value in thrombocytopenia. Core Evid. 1:221-231.

Provan D, Stasi R, Newland AC, et al. (2010) International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 115:168-186.

Qu, M, Liu X, Feng Q, et al. (2017) Cytokine Changes in Response to TPO Receptor Agonist Treatment in Primary Immune Thrombocytopenia. Cytokine. 92:110-117.

Rodeghiero F, Stasi R, Gernsheimer T, et al (2009) Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children; report from an international working group. Blood. 113:2386-2393

Sakamoto K, Nakasone H, Tsurmi S, et al. (2014) Prednisone versus high-dose dexamethasone for untreated primary immune thrombocytopenia. A retrospective study of the Japan Hematology Group & Oncology Clinical Study Group. J Thrombosis & Thrombolysis. 37(3):279-286.

Signorovitch J, Brainsky A, Grotziner KM (2011) Validation of the FACIT-fatigue subscale, selected items from FACT-thrombocytopenia, and the SF-36v2 in patients with chronic immune thrombocytopenia. Qual Life Res. 20(10):1737-1744.

Stasi R, Brunetti M, Pagano A, et al. (2000) Pulsed intravenous high-dose dexamethasone in adults with chronic idiopathic thrombocytopenic purpura. Blood Cells Mol Dis. 26:582–586.

Stasi R, Provan D (2004) Management of immune thrombocytopenic purpura in adults. Mayo Clin Proc. 79(4):504-522.

Terrell DR, Beebe LA, Vesely SK, et al (2010) The incidence of immune thrombocytopenic purpura in children and adults: a critical review of published reports. Am J Hematol. 85:174-180.

[redacted]

Wang, M, Qin, P Zhou, H, et al. (2017) Recombinant Human Thrombopoietin (rhTPo) and High-Dose Dexamethasone (HD-DXM) Versus High-Dose Dexamethasone Monotherapy as Frontline Treatment in Newly Diagnosed Adult Immune Thrombocytopenia (ITP): a Prospective, Multicentre, Randomised, Controlled Trial. ASH 59th Annual Meeting, Oral Poster.

Ware JE (2000) SF-36 health survey update. Spine. 25:24:3130-3139.

Warner M, Wasi P, Couban S, et al. (1997) Failure of pulse high-dose dexamethasone in chronic idiopathic immune thrombocytopenia. Am J Hematol. 54:267-270.

Webster K, Cella D, Yost K. (2003) The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes. 1:79.

Wei Y, Ji XB, Wang YW, et al. (2016) High dose dexamethasone versus prednisone for treatment of adult immune thrombocytopenia: a prospective multicenter randomized trial. Blood. 127(3):296-302.

Wong RSM, Saleh MN, Khelif A, et al. (2017) Safety and efficacy of long-term treatment of chronic/persistent ITP with eltrombopag: final results of the EXTEND Study. Blood. Epub. DOI10.1182/blood-2017-04-748707.

[redacted]

16 Appendices

16.1 Appendix 1: Examples of OATP and BCRP substrates

Table 16-1 OATP and BCRP Substrates

OATP Substrates	aliskiren, ambrisentan, anacetrapib, atenolol, atrasentan, atorvastatin, bosentan, bromociptine, caspofungin, cerivastatin, celiprolol, danoprevir, empangliflozin, ezetimibe, fimasartan, fexofenadine, fluvastatin, glyburide, maraviroc, SN-38, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, rifampin, valsartan, olmesartan, telmisartan, montelukast, ticlopidine.
BCRP Substrates	atorvastatin daunorubicin, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, pitavastatin, rosuvastatin, SN-38 (irinotecan), ethinyl estradiol, simvastatin, sulfasalazine, sofosbuvir, topotecan, sulfasalazine

OATP1B1 and OATP1B3 substrates and inhibitors are combined into one list due to the following reasons, (1) over-lapping substrate and inhibitor specificity and (2) lack of clinical evidence implicating the sole involvement of either OATP in the observed PK interaction.

[redacted]

16.2 Appendix 2: Bleeding Scales

Table 16-2 Modified WHO Bleeding Scale

WHO Bleeding Grade	Examples
1	Oropharyngeal bleeding ≤30 minutes in 24 hours Epistaxis ≤30 minutes in previous 24 hours Petechiae of oral mucosa or skin Purpura ≤1 inch in diameter Spontaneous hematoma in soft tissue or muscle Positive stool occult blood loss Microscopic hematuria or hemoglobinuria Abnormal vaginal bleeding (spotting)
2	Epistaxis ≥30 minutes in 24 hours Purpura >1 inch in diameter Joint bleeding Melanotic stool Hematemesis Gross/visible hematuria Abnormal vaginal bleeding (more than spotting) Hemoptysis Visible blood in body cavity fluid Retinal bleeding without visual impairment Bleeding at invasive sites
3	Bleeding requiring red blood cell transfusion over routine transfusion needs Bleeding associated with moderate hemodynamic instability
4	Bleeding associated with severe hemodynamic instability Fatal bleeding CNS bleeding on imaging study with or without dysfunction

CNS=central nervous system; WHO=World Health Organization
Source: Kaufman 2015

[redacted]

Table 16-3 ITP Bleeding Scale

Site	Bleeding Grade		
	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 blood that cleans easily with rinsing	Multiple blood blisters and/or gum bleeding
Skin (history)	None	1-5 bruises and/or scattered petechiae	>5 bruises with size >2 cm and/or diffuse petechiae
Oral (history)	None	1 blood blister or >5 petechiae and/or gum bleeding <5 minutes	Multiple blood blisters and/or gum bleeding > 5 minutes
Epistaxis	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 the time of normal period	Bleeding >spotting not at the time period or very heavy period
Pulmonary	None	N/A	Yes
Intercranial hemorrhage	None	N/A	Yes
Subconjunctival hemorrhage	None	Yes	N/A
GI=gastrointestinal; GYN=gynecologic; PE=physical exam; U=urinary Source: Page 2007			

[redacted]

16.3 Appendix 3: HRQoL Questionnaires

Table 16-4 FACIT-Fatigue Scale Version 4

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

16 November 2007
Page 1 of 1

[redacted]

Table 16-5 SF-36V2

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

sfs.S008_1 SF-36v2 Std.-English/US 1 of 6

[redacted]

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

[redacted]

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

[redacted]

6. **During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much bodily pain have you had during the past 4 weeks?**

None	Very Mild	Mild	Moderate	Severe	Very Severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

[redacted]

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

[redacted]

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

[redacted]

Table 16-6 FACT-Th6 (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
An7	I am able to do my usual activities	0	1	2	3	4
Th3	I worry about problems with bruising or bleeding	0	1	2	3	4
Th4	I worry about the possibility of serious bleeding	0	1	2	3	4
Th10	I avoid or limit physical activity (because of concern with bleeding or bruising)	0	1	2	3	4
Th11	I avoid or limit social activity (because of concern with bleeding or bruising)	0	1	2	3	4
Th12	I am frustrated by not being able to do my usual activities	0	1	2	3	4

[redacted]

Table 16-7 FACT-G (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the **past 7 days**.

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

[redacted]

Table 16-8 Treatment Satisfaction Questionnaire (TSQM)

Instructions:

Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it.*

For each question, please place a single check mark below the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

Extremely Dissatisfied	Very Dissatisfied	Dissatisfied	Somewhat Satisfied	Satisfied	Very Satisfied	Extremely Satisfied
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

Extremely Dissatisfied	Very Dissatisfied	Dissatisfied	Somewhat Satisfied	Satisfied	Very Satisfied	Extremely Satisfied
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

Extremely Dissatisfied	Very Dissatisfied	Dissatisfied	Somewhat Satisfied	Satisfied	Very Satisfied	Extremely Satisfied
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

[redacted]

4. How easy or difficult is it to use the medication in its current form?

Extremely Difficult	Very Difficult	Difficult	Somewhat Easy	Easy	Very Easy	Extremely Easy
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

5. How easy or difficult is it to plan when you will use the medication each time?

Extremely Difficult	Very Difficult	Difficult	Somewhat Easy	Easy	Very Easy	Extremely Easy
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

6. How convenient or inconvenient is it to take the medication as instructed?

Extremely Inconvenient	Very Inconvenient	Inconvenient	Somewhat Convenient	Convenient	Very Convenient	Extremely Convenient
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

[redacted]

7. Overall, how confident are you taking this medication is a good thing for you?

Not at All Confident	A Little Confident	Somewhat Confident	Very Confident	Extremely Confident
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

8. How certain are you that the good things about your mediation outweigh the bad things?

Not at All Certain	A Little Certain	Somewhat Certain	Very Certain	Extremely Certain
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. Taking all things into account, how satisfied or dissatisfied are you with this medication?

Extremely Dissatisfied	Very Dissatisfied	Dissatisfied	Somewhat Satisfied	Satisfied	Very Satisfied	Extremely Satisfied
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

[redacted]