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ETB115/Eltrombopag

Clinical Trial Protocol CETB115JDE01 / NCT04346654

A Phase II, randomized (1:1) open label study to assess the efficacy and safety of eltrombopag in combination with dexamethasone compared to dexamethasone, as first-line treatment in adult patients with newly diagnosed immune thrombocytopenia (XPAG-ITP)

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List of abbreviations

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
[redacted]	[redacted]
BCRP	Breast cancer resistance protein
CR	Complete response
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Event
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EOS	End of study
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full analysis set
GGT	Gamma-glutamyl transferase
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDD	High dose dexamethasone
HIV	Human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IPF	Immature platelet function
IRB	Institutional Review Board
ITP	Immune thrombocytopenia
IVIg	Intravenous immunoglobulin
LDH	lactate dehydrogenase
LFT	Liver function test
MCS	Mental Component Summary
MedDRA	Medical dictionary for regulatory activities
NSAIDs	Nonsteroidal anti-inflammatory drugs
OR	Overall response
ORR	Overall response rate
QD	Once daily
PCS	Physical Component Score
PR	Partial response
PRO	Patient reported outcomes
PT	Prothrombin time
QD	Once daily
QMS	Quality Management System

QTcF	QT interval corrected by Fridericia's formula
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Steering Committee
SD	standard deviation
SF36v2	Short Form 36 version 2
TBIL	Total bilirubin
[redacted]	[redacted]
TEE	Thromboembolic event
TPO	Thrombopoietin
TPO-R	Thrombopoietin receptor
TPO-RA	Thrombopoietin receptor agonist
ULN	Upper limit of normal
WHO	World Health Organization

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 study treatment.
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 subject in a time unit (e.g. 100 mg once a day, 75 mg twice a 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
Premature subject withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized patient
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 any of the study drug(s) 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
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.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
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
Victim drug	The drug that is affected by the drug-drug interaction
Withdrawal of study consent	Withdrawal of consent from the study occurs only when a patient does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 3

Amendment rationale from protocol version 02

The primary purposes of this protocol amendment are as follows:

- Due to slow enrollment the feasibility of this trial has been considered and an amendment is necessary. Recruitment was possible as of June 2020. First patient was recruited on 09th october 2020 and the intended sample size of 106 patient was planned to be recruited within 18 months. So far, only 21 out of the approximately 106 anticipated patients (20%) were enrolled in the study within 24 months. It is very unlikely that the number of patients required to determine the primary endpoint will be achieved within a reasonable time. A repeated problematic pattern in the current pandemic situation is that study centers report fewer eligible patients than anticipated. Study centers with a successful performance in previous studies failed to meet enrollment or failed to enroll any subject at all.
- The inclusion/exclusion criteria were chosen to result in a population that matches the intended general patient population. However, the exclusion criteria 2 (patients with diagnosis of secondary thrombocytopenia) accounts to additional concerns in finding suitable participants in view of the COVID-19 situation and the COVID-19 vaccination. There are two types of ITP: primary and secondary. Secondary ITP is sometimes caused by infectious diseases, vaccines, and other drugs. It is impossible to strictly distinguish between vaccine-induced secondary ITP and incidental primary ITP that occurred soon after COVID-19 vaccination. This complexity poses an additional challenge to timely diagnose suitable patients for this trial.
- In order to report the study results to support therapeutic advances as quickly as is reasonable, we propose the following changes to the protocol:
    - Premature termination of recruitment due to feasibility reasons, resulting in an expected sample size of ca. 24 patients at the time of approval by the EC/HA. A scenario based on 12 patients per group, assuming the above rates of 30 versus 65%, would allow for a power of 24% to analyze the primary endpoint. Consequently, all analyses will be interpreted in a purely descriptive manner.
    - Reduction of the follow-up for responders after Week 52 (secondary endpoint number 3). Assuming that 65% of the patients in the combination arm will be in sustained response off treatment at Week 52 and in respect to slow enrollment, the sample size for this secondary endpoint would be insufficient to detect a meaningful result
    - Based on the proposed changes to reduce the follow-up of the responders it will be able to share the study data 6 months earlier to increase the benefits of future patients and support recent updates in ITP guidelines to prevent an extended and recurrent use of corticosteroids that is associated with substantial toxicity.

Changes to the protocol:

Changes to specific sections of the protocol are shown in track change version.

Changes were made to the following sections:

- Protocol summary section updated to match the body of the protocol.
- Section 2 Table 2-1 Objectives and endpoints: Deleted endpoint 3 to reduce follow-up of patients. With this change no patient will be followed-up after Week 52.
- Section 3.1: Study design: Updated to reflect changed study duration. No follow-up of patients after Week 52.
- Section 4.2.1 Rationale for dose/regimen for eltrombopag adjusted to correct inconsistencies
- Section 5.2: Exclusion criteria: Changed to restrict thromboembolic events to 6 months before enrollment.
- Section 6: Study treatment: Eltrombopag dosing guidelines adjusted to correct inconsistencies
- Section 6 Table 6-1: Changes to reflect the reduction of the follow-up. No follow-up of patients beyond Week 52.
- Section 6.1.4 Treatment duration: Updated to reflect the changed follow-up of patients and to clarify that all patients have to discontinue the study latest at Week 52.
- Section 6 Table 6-2: Changes to reflect the reduction of the follow-up. No follow-up of patients beyond Week 52.
- Section 6.2.3 Rescue Medication: Updated to reflect the changed follow-up of patients and to clarify that all patients have to discontinue the study latest at Week 52.
- Section 8.2 Patient demographics/other baseline characteristics: Changes to required screening assessments to allow use of laboratory exams (hematology except thrombocyte counts, coagulation, chemistry and viral serology) performed as per local practice or under a local protocol within 14 days before randomization (prior to signing the study specific informed consent form and start of screening for the study) for the purposes of study inclusion.
- Section 6 Table 6-4: Eltrombopag dosing adjusted to correct inconsistencies
- Section 8.3.1 Efficacy Assessment 1: Updated to reflect the changed follow-up of patients and to clarify that all patients have to discontinue the study latest at Week 52.
- Section 8 Table 8-1 Assessments Schedule: Footnote added to clarify that if laboratory assessment (hematology except thrombocyte counts, coagulation, chemistry and viral serology) data are already available from exams performed within 14 days before randomization as per local practice or under a local protocol (prior to signing the study specific informed consent form and start of screening for the study, then these may be used for the purposes of study inclusion. No changes to required thrombocyte assessments.
- Section 8.4.2 Table 8-4 Laboratory Assessments: Deletion of chemistry assessment: bicarbonate. Updated coagulation parameters.

- Section 12.5.2 Efficacy endpoints: Updated appropriate endpoints to reflect deleted endpoint 3. With this change no patient will be followed-up after Week 52.
- Section 12.8.1 Primary endpoint: Sample size calculation. As described above, with Amendment 3 recruitment will be prematurely discontinued. A final number of ca. 24 patients is expected to be recruited by the time of approval. The analyses will be interpreted in a purely descriptive manner.
- In addition, minor inconsistencies and typos in the protocol have been corrected

IRB/IEC

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. It is required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 2

Amendment rationale from protocol version 01

The primary purposes of this protocol amendment are as follows:

- Due to slow enrollment an amendment is necessary. Recruitment was possible as of June 2020 and first patient was recruited on 09th October 2020.
- It was decided to relax inclusion criteria to one single assessment of thrombocyte count at the time of screening, and omitting the second threshold check at baseline. This was due to the fact that for some patients the thrombocyte count was below the pre-specified threshold at screening, but above at baseline and after pre-treatment.
- In addition, if pre-treatment is necessary, platelet count data performed directly before pre-treatment (prior to signing the study specific informed consent form and start of screening for the study as per local practice or under a local protocol) will be used for study inclusion (screening value to be used for inclusion/exclusion check and for analysis as a covariate). Treatment-naïve patients will be included based on their platelet counts performed at screening. The rationale was that the baseline thrombocyte threshold check following pre-treatment was deemed of neglible impact regarding the primary outcome of sustained response off treatment at week 52. Thus, it was decided to omit the second check.

  As a consequence, it was decided to also include the screening instead of baseline thrombocyte count as a cofactor into the statistical model for the primary outcome analysis, as this was regarded as the more adequate way of taking into account the initial value at the time of diagnosis and before pre-treatment for all patients. Additional

sensitivity analyses were included to assess the impact of pre-treatment and baseline thrombocyte count.

Changes to the protocol:

Changes to specific sections of the protocol are shown in track change version.

Changes were made to the following sections:

- Protocol summary section updated to match the body of the protocol.
- Section 2 Table 2-1 Objectives and endpoints: Updated appropriate endpoints to include screening instead of baseline thrombocyte.
- Section 3.1: Study design: Changes to allowed dexamethasone treatment in Arm B. In case a patient in the treatment Arm B (dexamethasone monotherapy) needs treatment cycles at an interval of less than 28 days, the dexamethasone can also be given at 14 to 28 days intervals according to current ITP guidelines.
- Section 4.3. Rationale for choice of dexamethasone regimen: Changes to allowed dexamethasone treatment in Arm B (see Section 3.1)
- Section 5.1 Inclusion criteria: Changes to required platelet count assessment data that are required for the purposes of study inclusion. If pre-treatment is necessary, platelet count data performed directly before pre-treatment (prior to signing the study specific informed consent form and start of screening for the study as per local practice or under a local protocol) can be used for study inclusion (screening value). Treatment-naïve patients will be included based on their platelet counts performed at screening.
- Section 5.1 Exclusion criteria: Changes to pre-treatment duration before randomization to optimize recruitment. Patients in need of immediate treatment for thrombocytopenia while diagnosis or eligibility are being determined may receive treatment with any ITP-directed therapy for a maximum of 3 days within 7 days before randomization.
- Section 6.0 Study treatment: Changes to allowed dexamethasone treatment in Arm B (see Section 3.1)
- Section 8 Table 8-1: Footnote added to clarify that if pre-treatment is necessary, platelet count data performed directly before pre-treatment (prior to signing the study specific informed consent form and start of screening for the study as per local practice or under a local protocol) will be used for study inclusion (screening value). Treatment-naïve patients will be included based on their platelet counts performed at screening. In addition a footnote was added to reflect that ocular assessment has to be done within 28 days after study start. If ocular assessment data are already available from exams performed within 28 days prior to screening (prior to signing the study specific informed consent form and start of screening for the study as per local practice or under a local protocol), then these may be used for the purposes of study inclusion.
- Section 8.4.1 Ophthalmic examination: Changes to required ocular assessment data required for the purposes of study inclusion (see previous Section 8 Table 8-1).
- Section 12 Data analysis and statistical methods: Updated to clarify that the baseline is the result of an investigation describing the state of the patient before start of

eltrombopag or dexamethasone study treatment, and after a possible pre-treatment. The screening value describes the result at screening, before pre-treatment. Should a patient not need pre-treatment, screening and baseline values can be identical. In such cases, as only one assessment exists, the baseline value will be taken from screening.

- Section 12.4.1 Definition of primary endpoint: A note of was added to clarify that in case a patient in the treatment Arm B (dexamethasone monotherapy) needs treatment cycles at an interval of less than 28 days (at least 14 days), and meets the definition for sustained response off treatment, such patient will be counted as a responder for statistical analysis.
- Section 12.4.2 Statistical model, hypothesis, and method of analysis: Updated to include the screening instead of baseline thrombocyte count as a cofactor into the statistical model for the primary outcome analysis.
- Section 12.4.4 Sensitivity and Supportive analyses: Additional sensitivity analyses were included to assess the impact of pre-treatment and baseline thrombocyte count on the primary outcome analysis.
- Section 12.5.2 Efficacy endpoints: Updated appropriate endpoints to include screening instead of baseline thrombocyte.
- In addition, minor inconsistencies and typos in the protocol have been corrected

IRB/IEC

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 do not affect the Informed Consent.

Amendment 1

Amendment rationale from protocol version 00

The primary purposes of this protocol amendment are to:

- Address the requirement of the Ethics committee to include a more detailed information on the recruitment procedure in the protocol. Version 00 of this protocol was approved by end of March by the German health authority (Bundesamt für Arzneimittel und Medizinprodukte, BfArM) and by the Ethics Committee Halle-Wittenberg. As feedback, inclusion of recruitment procedures were requested by the Ethics Committee, which is covered in this amendment.
- In addition, other clarifications and administrative changes were included as needed.

Changes from V00 to the protocol:

Changes to specific sections of the protocol are shown in track change version.

Changes were made to the following sections:

- Section 5.0 Population: Information of recruitment procedure of study participants was added.
- Section 8 Table 8-1 Assessment schedule: Footnotes were added to clarify assessments that are required per protocol at the End of Study visit (EOS) for patients with premature study withdrawal before or after week 52 and to clarify when the patients should be seen for a Safety follow-up visit. In addition an administrative change was included to match the appropriate adverse event monitoring.
- Section 8.4.2 Lab assessments: Quick-test was added as measurement to evaluate coagulation.
- Section 12.5.1 Clarification to the secondary endpoint 2. Duration of sustained response off treatment will be assessed until loss of response and not only until Week 52.
- Section: 12.5.2 Safety endpoints: Updated information on safety monitoring to align with information in Section 10.
- In addition, minor inconsistencies and typos in the protocol have been corrected.

IRB/IEC

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 do not affect the Informed Consent.

Protocol summary

Protocol number	CETB115JDE01
Full Title	A Phase II, randomized (1:1) open label study to assess the efficacy and safety of eltrombopag in combination with dexamethasone compared to dexamethasone, as first-line treatment in adult patients with newly diagnosed immune thrombocytopenia (XPAG-ITP)
Brief title	A study to assess efficacy and safety of eltrombopag in combination with a short course of high-dose dexamethasone compared to 1-3 cycles of dexamethasone alone in patients with newly diagnosed ITP
Sponsor and Clinical Phase	Novartis II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to compare the ability of eltrombopag in combination with a short course of high-dose dexamethasone to induce sustained response off treatment in patients with newly-diagnosed ITP versus 1-3 cycles of dexamethasone monotherapy. The unmet clinical need and the potential for eltrombopag when added to steroids to improve the treatment outcome and the potential to induce sustained response off treatment serve as the basis for clinical investigation of eltrombopag in first-line ITP. One ongoing study is assessing the ability of eltrombopag to induce sustained response off treatment in patients with ITP, who are early refractory to or who relapsed after initial treatment with first-line steroids but not in patients with newly diagnosed ITP who have not received any pre-treatment. This trial is designed to assess this.
Primary Objective	To compare the ability of eltrombopag in combination with a short course of dexamethasone to induce a sustained response off treatment at 52 weeks versus a defined course of dexamethasone
Secondary Objectives	1. To compare the ability of eltrombopag in combination with a short course of dexamethasone to induce overall response (OR) after treatment discontinuation at Week 52 versus a defined course of dexamethasone 2. To assess the duration of sustained response off treatment 3. To assess the ability of eltrombopag to induce overall response (OR) by Week 4 4. To assess the ability of eltrombopag to induce complete response (CR) by Week 4 5. To quantify the increase in platelet count from screening to baseline and to 1, 2, 4, 12, 26 and 52 weeks 6. To assess the time to overall and complete response 7. To assess the duration of overall and complete response 8. To evaluate patient-oriented outcomes for health-related quality of life 9. To evaluate the safety and tolerability of eltrombopag + dexamethasone 10. To evaluate the incidence and severity of bleeding events
Study design	This is a Phase II, multicenter, randomized (1:1), open-label study to compare the efficacy and safety of eltrombopag in combination with a short course of high-dose dexamethasone to 1-3 cycles of high-dose dexamethasone monotherapy, as first-line treatment in adult patients with newly diagnosed ITP

Population	The study is designed to include 106 adult patients with newly diagnosed primary ITP with screening platelet count < 30×10^9/L and assessed as required treatment (per physician's discretion). According to Amendment 3 for premature discontinuation of recruitment, the planned sample size will not be reached, expecting in a total of ca. 24 patients by the time of approval of Amendment 3.
Key Inclusion criteria	1. Signed informed consent must be obtained prior to participation in the study. 2. Men and women ≥ 18 years of age 3. Newly diagnosed with primary ITP (time from diagnosis within 3 months) Platelet count < 30×10^9/L at screening and a need for treatment (per physician's discretion) Note: If pre-treatment is necessary, platelet count data performed directly before pre-treatment (prior to signing the study specific informed consent form and start of screening for the study as per local practice or under a local protocol) will be used for study inclusion (screening value to be used for inclusion/exclusion check and for analysis as a covariate). Treatment-naïve patients will be included based on their platelet counts performed at screening
Key Exclusion criteria	1. Previous history of treatment for ITP Note: Patients in need of immediate treatment for thrombocytopenia while diagnosis or eligibility are being determined may receive treatment with any ITP-directed therapy for a maximum of 3 days within 7 days before randomization. These therapies must be discontinued before the patient receives the first dose of study treatment 2. Patients with diagnosis of secondary thrombocytopenia 3. Patients who have life threatening bleeding complications per physician´s discretion 4. Patients with a history of thromboembolic events in the 6 months preceding enrollment or known risk factors for thromboembolism (e.g. Factor V Leiden, ATIII deficiency, antiphospholipid syndrome) are excluded. Patients with other risk factors which may pose an increased thromboembolic event (TEE) risk (prolonged periods of immobilization, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking) would be excluded according to the discretion of the investigator 5. 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 6. Total bilirubin (TBIL) > 1.5 × upper limit of normal (ULN) 7. Aspartate transaminase (AST) > 3.0 × ULN 8. Alanine transaminase (ALT) > 3.0 × ULN 9. Patients who are human immunodeficiency virus (HIV), HCV or hepatitis B surface antigen (HBsAg) positive. 10. Patients with hepatic impairment (Child-Pugh score > 5) 11. Patients with known active or uncontrolled infections not responding to appropriate therapy

	12. History of current diagnosis of cardiac disease or impaired cardiac function denoted by any of the following: • Corrected QTc >450 msec using Fridericia correction (QTcF) on the screening electrocardiogram (ECG) • History of myocardial infarction and unstable angina within 6 months prior to starting study treatment • Clinically significant cardiac arrhythmias or other clinically significant cardiovascular disease (e.g., congestive heart failure, uncontrolled hypertension) within the six months prior to starting study treatment 13. Patients who have active malignancy 14. Patients with evidence of current alcohol/drug abuse 15. Any serious and/or unstable pre-existing medical (including any advanced malignancy other than the disease under study), psychiatric disorder, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance with the study procedures. 16. 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 17. Patients with pre-existing medical conditions that are known precautions with corticosteroid use, in whom the potential risks of participating in the study outweigh the potential benefits as determined by the investigator 18. Female subjects who are nursing or pregnant (positive serum or urine B-human chorionic gonadotrophin (B-hCG) pregnancy test) at screening or pre-dose on Day 1 19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception while taking study treatment and for 7 days after stopping medication. Highly effective contraception methods include: • combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]: • oral • intravaginal • transdermal • progestogen-only hormonal contraception associated with inhibition of ovulation[1]: • oral • injectable • implantable[2] • intrauterine device (IUD)[2] • intrauterine hormone-releasing system (IUS)[2] • bilateral tubal occlusion[2] • vasectomised partner[2,3] • sexual abstinence[4] [1]Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method (see section 4.3). [2] Contraception methods that in the context of this guidance are considered to have low user dependency. [3] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

	[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
Study treatment	Eltrombopag and dexamethasone are both investigational drugs. Patients randomized to Arm A will receive eltrombopag in combination with a short course of high-dose dexamethasone beginning at Day 1. The dose of dexamethasone will be 40 mg QD for 4 consecutive days (dexamethasone therapy is limited to 1 cycle). The starting dose of eltrombopag will be 50 mg QD and treatment will continue at the same dose for 2 weeks to reach a target platelet count of 50 × 10^9/L as necessary to reduce the risk for bleeding. The dose of eltrombopag will be increased by 25 mg increments every 2 weeks to a maximum dose of 75 mg QD for all patients who do not achieve the target platelet count of ≥ 50 × 10^9/L. Treatment with eltrombopag will be continued at the minimal dosage necessary to maintain a platelet count ≥ 50 × 10^9/L to 150 × 10^9/L for 20 weeks. Asian patients will initially receive half of the dose, starting at 25 mg of eltrombopag due to lower clearance of eltrombopag as compared with non-asian patients. The dose of eltrombopag will be decreased by 25 mg if platelet counts are > 150 × 10^9/L to ≤ 400 × 10^9/L by 25 mg and the effect will be assessed after 2 weeks. Patients who reach platelet counts ≥ 30 × 10^9/L and maintain counts ≥ 30 × 10^9/L during the tapering phase will be eligible for treatment discontinuation. Duration of tapering before treatment discontinuation at Week 26 will be 6 weeks. Decrease in dose will be performed by 25 mg reductions every 2 weeks to a minimum dose of 25 mg every other day for all patients. Treatment in Arm B consists of 1-3 cycles of high-dose dexamethasone administered orally at a dose of 40 mg QD for 4 consecutive days at 2-4 weeks intervals. If the platelet counts are > 150 × 10^9/L no further course of dexamethasone will be given. Patients will be treated up to 12 weeks (3 months) during the treatment period with dexamethasone. Patients who reach platelet counts ≥ 30 × 10^9/L and maintain counts ≥ 30 × 10^9/L after 1-3 cycles of high-dose dexamethasone treatment will be eligible for treatment discontinuation. Patients with platelet counts < 30 × 10^9/L after 3 cycles of dexamethasone treatment will be offered a course of eltrombopag treatment within the study and will discontinue the study after completion of treatment with eltrombopag at Week 52.
Efficacy assessments	Platelet count will be assessed at screening visit to assess the eligibility of the subject. If pre-treatment is necessary, platelet count data performed directly before pre-treatment (prior to signing the study specific informed consent form and start of screening for the study as per local practice or under a local protocol) will be used for study inclusion (screening value to be used for inclusion/exclusion check and for analysis as a covariate). Hematology including platelet counts will be performed at Week 1/Day 1 (i.e. baseline), and weekly during the first 4 weeks of treatment. Based on subject's response, hematology will be performed biweekly thereafter until Week 33 Day 1 and every 4 weeks till Week 53 Day 1. Additional assessments of platelet count may be performed more frequently 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 Form (CRF) and in addition on an unique CRF for

	bleeding events. Documentation of the use of any rescue therapy will be documented on the appropriate CRF.
Key safety assessments	• Physical assessments: Physical examination, vital signs, height and weight • Ophthalmic examination • Laboratory evaluations • Electrocardiogram • Pregnancy testing
Other assessments	• Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) • Medical Outcome Trust's Short-Form 36 Health Survey, Version 2 (SF-36 v2)
Data analysis	The primary endpoint is the proportion of patients with sustained response off treatment at 52 weeks. Sustained response off treatment is defined as: • reach platelet count ≥ 30×10^9/L and then maintain platelet counts ≥ 30×10^9/L after treatment discontinuation AND • maintain platelet count ≥ 30×10^9/L in the absence of bleeding events ≥ Grade 2 and without the use of any rescue therapy at all visits until Week 52. The primary analysis will be performed comparing the treatment groups with respect to the primary efficacy outcome, based on the Odds Ratio, in a Logistic Regression model with the factor treatment and cofactors ITP-directed pre-therapy (during 3 out of 7 days before randomization), screening platelet count and age (≤ vs. > 60 years). The odds ratio and its 95% confidence interval (CI) and p-value will be given. As a consequence of Amendment 3, all analyses will be interpreted in a purely descriptive manner.
Key words	Eltrombopag, immune thrombocytopenia, ITP, corticosteroids

1 Introduction

1.1 Background

1.1.1 Current therapies and unmet medical needs

The primary goal of treatment in immune thrombocytopenia (ITP) is to prevent bleeding by increasing the platelet count that confers adequate hemostasis and minimizes the risk of clinically significant bleeding, avoiding as much as possible treatment-related toxicity.

Initial management is dependent upon several factors, including severity of thrombocytopenia, bleeding risk, patient's age and comorbidities, and the side effect profiles associated with therapy. While there is limited evidence to determine a minimum platelet threshold at which a patient with ITP should be treated, there is substantial agreement that treatment is indicated in the presence of bleeding symptoms (Cines and Bussel 2005). Observational data of ITP patient cohorts indicate that risk of clinically significant bleeding increases with increasing severity of thrombocytopenia and as such, a platelet threshold of < 20-30 × 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 et al 2011).

Traditional first-line therapy includes oral corticosteroids, intravenous immunoglobulin (IVIg) and anti-D immunoglobulin. With conventional first-line treatment, initial response rates are 70-80%, however only a small proportion of treated patients will sustain durable platelet responses following the initial treatment course (Provan et al 2010). Corticosteroids will generally induce a response within the first 2 weeks, but < 30% of initial responders will sustain durable responses and will relapse within the first year, most commonly during steroid taper, or shortly after discontinuation (Cooper 2017). Currently available corticosteroids for ITP include prednisone, prednisolone, dexamethasone, with prednisone and dexamethasone being the most widely used.

Options for salvage therapy include retreatment with corticosteroids, a combination of first-line agent(s), or treatment with a second-line agent. Long-term administration of corticosteroids is limited by the development of side effects, including peripheral edema, hypertension, heartburn/peptic ulcers, anxiety, insomnia, agitation, Cushingoid features, diabetes, cataracts, potassium loss, osteoporosis, and other adverse experiences. Furthermore, corticosteroid-treated patients are at increased risk of infections (Portielje et al 2001, Stasi et al 1995, Pizzuto and Ambriz, 1984).

While corticosteroids remain the standard of care, high relapse rates and considerable toxicity associated with long-term corticosteroid use highlight a significant unmet medical need in management of first-line ITP. Novel therapeutic approaches are warranted that achieve durable responses and reduce the need for long-term corticosteroid use.

1.1.2 Overview of disease pathogenesis, epidemiology and current treatment

Primary immune thrombocytopenia is an acquired, immune-mediated disorder of adults and children. It is defined as a platelet count of < 100 × 10^9/L, in the absence of other causes or disorders that may be associated with thrombocytopenia (Rodeghiero et al 2009, Provan et al 2010).

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 et al 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 et al 2013).

The clinical manifestations of ITP are characterized by an increased tendency to bleed, spontaneously or after a hemostatic challenge. The degree of bleeding is largely dependent on the severity of thrombocytopenia, with platelet counts < 20-30 × 10^9/L conferring the greatest risk of clinically significant bleeding (George et al 1996, Guidelines l British Society for Haematology 2003). Mucocutaneous bleeding involving the skin, oral cavity and gastrointestinal tract is the most common clinical manifestation in ITP. 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 most serious and life-threatening bleeding complications are intracranial hemorrhages, reported in 1.5-1.8% of adult patients (Lambert and Gernsheimer 2017, Neunert et al 2015, Kühne et al 2001). The frequency of death from hemorrhage in patients with platelet counts < 30 × 10^9/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 et al 2000).

Based on the disease duration from initial confirmed ITP diagnosis, there are three categories of patients: newly diagnosed (diagnosis ≤ 3 months), persistent ITP (between 3 and 12 months from diagnosis), and chronic ITP (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 et al 2009, Provan et al 2010).

1.1.3 Overview of eltrombopag

Thrombopoietin (TPO) is the principal cytokine involved in the regulation of megakarypoiesis and platelet production. In addition to megakaryocytic cells, hematopoietic stem cells also express the TPO receptor and depend on TPO signaling for their maintenance and expansion (Geddis 2010)

Eltrombopag (ETB115) is an oral, small-molecule, non-peptide thrombopoietin receptor agonist (TPO-RA) that increases hematopoiesis by inducing proliferation and differentiation of early bone marrow progenitor cells leading to increased platelet production (Erickson-Miller et al 2010, Sun et al 2012).

Eltrombopag has demonstrated efficacy in adult and pediatric patients with chronic ITP and has a well-established safety profile. It is approved in over 100 countries for the treatment of thrombocytopenia in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Eltrombopag has also been approved for the treatment of adult patients with hepatitis C virus (HCV)-related thrombocytopenia in over 45 countries.

More recently, eltrombopag has also been approved in both the EU and USA for the treatment of adult patients with SAA who have had insufficient responses to immunosuppressive therapy.

The benefit risk remains favorable in all approved indications,

Rationale for development in first-line ITP:

The efficacy of eltrombopag for achieving hemostatic platelet counts in previously treated adult ITP patients with higher than 6-month disease duration is around 80%. However, not many studies to date analyzing safety and efficacy of TPO-RAs in newly diagnosed ITP are published.

Supporting data on the combination of TPO agonists including eltrombopag in combination with steroids in the setting of first-line ITP include results of a study of 12 newly diagnosed ITP patients treated with a combination of high-dose dexamethasone (Days 1-4) and eltrombopag (Days 1-28), where 6/12 patients exhibited platelet counts $> 100 \times 10^9$/L at 6 months and 8/12 patients maintained platelet counts $> 30 \times 10^9$/L at 12 months (Gomez-Almaguer et al 2014).

A recent study of 196 ITP patients randomized to receive high-dose dexamethasone in combination with subcutaneous recombinant human-TPO or high-dose dexamethasone monotherapy, superior 6-month sustained response rates were exhibited with combination therapy (overall response (OR): 51% vs 36.5%; complete response (CR): 46.0% vs 32.3%) (Wang et al 2017) and supports the idea that a frontline combination therapy with eltrombopag and steroids could restore an immune tolerance in a greater proportion of patients compared to a steroid-monotherapy.

There is also growing literature that suggest that a proportion of patients may exhibit durable platelet responses following discontinuation of eltrombopag.

In a retrospective review of 260 adult primary ITP patients treated with eltrombopag after a median time from diagnosis of 24 months, among the 49 evaluable patients who achieved complete remission with eltrombopag and discontinued further treatment, 26 patients maintained platelet counts $> 100 \times 10^9$/L with a median follow-up of 9 months. These patients had received a median of four previous treatments and were characterized with a median time since diagnosis of 46 months. In an additional retrospective review of 12 patients with chronic ITP with a median time from diagnosis to eltrombopag initiation of 24 months and a median number of 5 prior therapies, sustained responses after discontinuing eltrombopag with platelet counts $> 100 \times 10^9$ were identified in 10/12 patients with a median follow-up of 7 months (Gonzalez-Lopez et al 2015a, Gonzalez-Lopez et al 2015b).

Data from a pilot study evaluating whether a 12-week course of eltrombopag plus pulsed dexamethasone in newly-diagnosed ITP can increase the proportion of patients with prolonged response, showed a prolonged response rate in 19 of 34 evaluable patients (Zhang et al 2018).

The underlying immune mechanism that restores immune tolerance and give rise to a sustained response after discontinuing eltrombopag are unknown. However, there is growing evidence from preclinical studies that TPO-RA dampen immune responses in chronic ITP by increasing the levels of anti-inflammatory cytokines and 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 et al 2010, Liu et al 2016, Qu et al 2017).

1.2 Purpose

The unmet clinical need and the potential for eltrombopag when added to steroids to improve the treatment outcome and the potential to induce sustained response off treatment serve as the basis for clinical investigation of eltrombopag in first-line ITP. One ongoing study is assessing the ability of eltrombopag to induce sustained response off treatment in patients with ITP, who are early refractory to or who relapsed after initial treatment with first-line steroids but not in patients with newly diagnosed ITP who have not received any pre-treatment.

We will therefore conduct a prospective trial of eltrombopag in patients with newly-diagnosed ITP to compare the ability of eltrombopag in combination with a short course of high-dose dexamethasone to induce a sustained response off treatment versus 1-3 cycles of dexamethasone monotherapy.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objectives	Endpoints
Primary Objective	**Endpoint for primary objective**
• To compare the ability of eltrombopag in combination with a short course of dexamethasone to induce a sustained response off treatment at 52 weeks versus a defined course of dexamethasone	• Rates of patients achieving a sustained response off treatment at 52 weeks, comparing the two arms (sustained response off treatment = maintain platelet count ≥ 30 × 10^9/L after treatment discontinuation in the absence of bleeding events ≥ Grade II or use of any rescue medication at all visits until Week 52)
Secondary Objectives	**Endpoints for secondary objectives**
1. To compare the ability of eltrombopag in combination with a short course of dexamethasone to induce overall response (OR) after treatment discontinuation at Week 52 versus a defined course of dexamethasone	• Proportion of patients with platelet count ≥ 30 × 10^9/L and ≥ 2-fold increase of screening platelets after treatment discontinuation in the absence of bleeding events ≥ Grade II and no rescue therapy at all visits until Week 52
2. To assess the duration of sustained response off treatment	• Median duration of sustained response off treatment calculated from the time of treatment discontinuation until platelet count < 30 × 10^9/L or bleeding events ≥ Grade II or use of any rescue therapy

Objectives	Endpoints
3. To assess the ability of eltrombopag to induce overall response (OR) by Week 4	• Proportion of patients with platelet count ≥ 30 × 10^9/L and ≥ 2-fold increase of screening platelet count and absence of bleeding and no rescue therapy at least once by Week 4
4. To assess the ability of eltrombopag to induce complete response (CR) by Week 4	• Proportion of patients with platelet count ≥ 100 × 10^9/L and absence of bleeding and no rescue therapy at least once by Week 4
5. To quantify the increase in platelet count from screening to baseline, and to 1, 2, 4, 12, 26, and 52 weeks	• Absolute values and relative changes in platelet count from screening to baseline, and to 1, 2, 4, 12, 26, and 52 weeks
6. To assess the time to overall and complete response	• Time from starting study treatment to time of achievement of overall and complete response
7. To assess the duration of overall and complete response	• Duration of overall and complete response as defined above
8. To evaluate patient-oriented outcomes for health-related quality of life	• The analysis of Health–Related Quality of Life (HRQoL) parameters by use of Functional Assessment of Chronic Illness Therapy (FACIT) and Short Form 36 version 2 (SF36v2) questionnaires. Change in scores from baseline to 1, 2, 4, 12, 26 and 52 weeks
9. To evaluate the safety and tolerability of eltrombopag + dexamethasone	• Changes from baseline in physical exam findings, clinical monitoring, vital signs, clinical laboratory tests, and evaluation of reported adverse events
10. To evaluate the incidence and severity of bleeding events	• Incidence and severity of bleeding assessed by the World Health Organization (WHO) Bleeding Scale

[redacted]

3 Study design

This is a Phase II, multicenter, randomized (1:1), open-label study to compare the efficacy and safety of eltrombopag in combination with a short course of high-dose dexamethasone to 1-3 cycles of high-dose dexamethasone monotherapy, as first-line treatment in adult patients with newly diagnosed ITP. Randomization to treatment will follow a 1:1 ratio.

- Arm A: Eltrombopag + a short course of high-dose dexamethasone (dexamethasone therapy is limited to 1 cycle)
- Arm B: 1-3 cycles of high-dose dexamethasone

Adult patients with newly diagnosed ITP who have platelet counts < 30 × 10^9/L and require treatment will be screened, and if eligible, will be randomized to either Arm A (eltrombopag QD oral tablet for 26 weeks + 1 cycle of dexamethasone QD for 4 consecutive days) or Arm B (1-3 cycles of dexamethasone QD for 4 consecutive days at 4 weeks intervals; the dexamethasone can also be given at 14 to 28 days if needed according to current ITP guidelines; if the platelet counts are > 150 × 10^9/L no further course of dexamethasone will be given). The study will be conducted in the following periods:

- Screening Period: Patients will be screened based on the inclusion and exclusion criteria specified in Section 5.1 and Section 5.2, respectively.
- Treatment Period:

  Arm A: Patients will be treated for 26 weeks (6 months) during the treatment period. Patients who reach platelet counts ≥ 30×10^9/L and maintain counts ≥ 30×10^9/L during the tapering phase will be eligible for treatment discontinuation. Duration of tapering before treatment discontinuation at Week 26 will be 6 weeks.

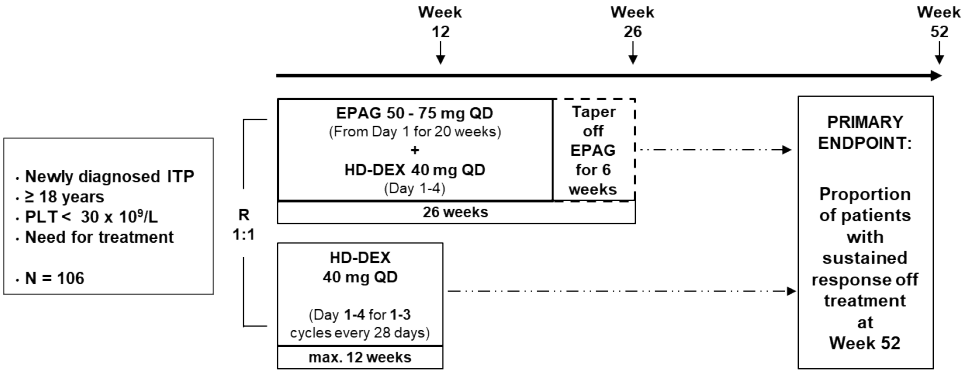
  Arm B. Patients will be treated up to 12 weeks (3 months) during the treatment period. Patients who reach platelet counts ≥ 30×10^9/L and maintain counts ≥ 30×10^9/L after 1-3 cycles of dexamethasone treatment will be eligible for treatment discontinuation. Patients with platelet counts < 30×10^9/L after 3 cycles of dexamethasone treatment will be offered a course of eltrombopag treatment within the study and will discontinue from study at Week 52.
- Observation period: After completion of treatment period, patients will be observed for sustained response off treatment.

  Arm A: Patients who successfully taper off, discontinue eltrombopag and maintain platelet counts ≥ 30×10^9/L in the absence of bleeding or use of any rescue therapy will be observed until Week 52 after study start. Patients who relapse after eltrombopag discontinuation will reinitiate treatment with eltrombopag till Week 52 and will discontinue from study at Week 52. Patients with platelet counts < 30×10^9/L after 26 weeks of treatment with eltrombopag will continue eltrombopag treatment till Week 52 and discontinue from study at Week 52.

  Arm B: Patients who successfully discontinue dexamethasone treatment and maintain platelet counts ≥ 30×10^9/L in the absence of bleeding or use of any rescue therapy will be observed until Week 52 after study start. Patients who relapse (platelet count < 30×10^9/L) after dexamethasone discontinuation and need treatment will be treated with eltrombopag until Week 52 after study start and discontinue from study at Week 52. Patients with platelet count < 30×10^9/L after 3 cycles with dexamethasone will initiate treatment with eltrombopag and discontinue the study at Week 52.

The study will consist of a 14-day screening phase (after signing the study informed consent form (ICF)), 26 week (6 months) treatment phase, 26 weeks (6 months) observational phase, as described in Figure 3-1.

Figure 3-1 Study Design



4 Rationale

4.1 Rationale for study design

This is a Phase II, multicenter, 1:1 randomized, open-label study to compare the efficacy and safety of eltrombopag in combination with a short course of high-dose dexamethasone to 1-3 cycles of high-dose dexamethasone monotherapy, as first-line treatment in adult patients with newly diagnosed ITP.

The randomized, parallel group design was chosen to minimize treatment assignment bias, balancing both known and unknown prognostic factors including pre-treatment in the assignment of treatments. Due to different treatment durations and regimens in Arm A and Arm B an open-label study design was chosen.

4.2 Rationale for dose/regimen and duration of treatment

4.2.1 Rationale for dose/regimen for eltrombopag

The dose selected for first-line treatment of ITP with eltrombopag is based on prior experience in chronic ITP and is consistent with the dosing guidelines that have been approved for use in adult patients with chronic ITP.

The starting dose of eltrombopag for patients with ITP is 50 mg QD and the total duration of treatment will be 26 weeks including tapering. Asian patients, in whom eltrombopag clearance has been shown to be lower than non-Asian patients, will initially receive half of the dose, starting at 25 mg of eltrombopag. After initiating eltrombopag, the dose must be adjusted to achieve and maintain a platelet count $\geq 50 \times 10^9$/L as necessary to reduce the risk for bleeding. The standard eltrombopag dose adjustment would be 25 mg once daily. It is necessary to wait for at least 2 weeks to see the effect of any dose adjustment on the patient's platelet response prior to considering another dose adjustment. A daily dose of 75 mg must not be exceeded for all patients. The dose of eltrombopag will be decreased if platelet counts are $> 150 \times 10^9$/L to $\leq 400 \times 10^9$/L by 25 mg and the effect will be assessed after 2 weeks. Eltrombopag should be interrupted if counts are more than 400×10^9/L and resumed at a lower dose when platelets are less than 100×10^9/L.

4.2.2 Rationale for duration of treatment with 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. No predictive factors for the subjects who will be able to taper off are identified to date.

Promising data from a recent retrospective study indicate that a median duration of eltrombopag treatment of 6 months qualify for a successful sustained remission after treatment discontinuation (Gonzalez-Lopez et al 2015).

The treatment goal of this study is to have a platelet count in a safe hemostatic range (no counts below 30×10^9/L) in order to allow treatment discontinuation in as many patients as possible and not to normalize the platelet counts to a predefined value.

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 dexamethasone regimen

Corticosteroids have been the standard initial treatment for adults with moderate to severe thrombocytopenia since their introduction several decades ago (George et al 1996). Several studies have examined whether more intensive dosing of steroids, with high dose methylprednisolone or dexamethasone, as initial therapy in ITP, could lead to more durable remissions.

In a trial evaluating the efficacy of high dose dexamethasone (HDD) as initial therapy in ITP, 192 adults were randomized to HDD for one to two cycles or prednisone 1 mg/kg/day for 4 weeks. One or two courses of HDD resulted in a higher incidence of overall initial response (82.1% vs 67.4%) and CR (50.5% vs 26.8%) and a shorter time to response compared with prednisone. Sustained response was achieved by 40.0% of patients in the HDD arm and 41.2% in the prednisone arm. Sustained response was defined as a platelet count > 30 x 10^9/L with an absence of bleeding symptoms or no requirement for additional ITP-modifying treatment of 6 consecutive months following achievement of initial response (Wei et al 2016).

The results of this randomized, controlled trial suggest that HDD may have some important advantages over a longer course of prednisone for the initial treatment of ITP. First, this option would likely be preferred by many patients simply on the basis of convenience. For most patients, a shorter duration of treatment will be much less burdensome. If the physician and the patient value these potential advantages, they can now proceed with HDD knowing that it is at least as effective as a prednisone taper for both short- and long-term responses.

The dose of dexamethasone selected for this study is based on prior experience in newly diagnosed patients and on established guidelines. The dexamethasone regimen selected for this study consists of one course of high-dose dexamethasone 40 mg/day for 4 consecutive days in Arm A. In order to provide a less toxic regimen and to avoid possible adverse reactions of the combination therapy the dexamethasone treatment in Arm A is limited to a short exposure of 4 consecutive days from day 1.

In Arm B the treatment consists of maximum 3 courses of high-dose dexamethasone 40 mg/day for 4 consecutive days at 4 weeks intervals (the dexamethasone can also be given at 14 to 28

days intervals if needed according to current ITP guidelines). If the platelet counts are $> 150 \times 10^9$/L no further course of dexamethasone will be given. According to current guidelines the most common treatment regimen with dexamethasone is defined as 40 mg/day for 4 days every 2-4 weeks for 1-4 cycles. According to the most recent trial in relapsed/refractory ITP patients with eltrombopag, the treatment with steroids is restricted to a maximum of 12 weeks and was confirmed by medical experts. Therefore we have chosen the same regimen of maximum 12 weeks of treatment with dexamethasone.

4.4 Purpose and timing of interim analyses/design adaptations

No formal interim analysis is planned for this study.

4.5 Risks and benefits

4.5.1 Risk associated with Eltrombopag use

The risks to patients in this study may come from adverse events (AEs), adverse events of special interest (AESI) 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 Section 8.3 and Section 8.4; and dose modifications as described in Section 6.5.

Eltrombopag is approved in more than 100 countries. The benefit risk profile of eltrombopag for the treatment of chronic ITP, HCV associated thrombocytopenia and severe aplastic anemia continues to be favorable. Important identified risks for the ITP indication include hepatotoxicity, thromboembolic events, post-therapy reoccurrence of thrombocytopenia, and cataract. Important potential risks of eltrombopag for the ITP include thrombotic microangiopathy with acute renal failure, potential for increased bone marrow reticulin formation, hematological malignancies, renal tubular toxicity, phototoxicity, potential for hematological changes, and potential for endosteal hyperostosis. The clinical benefit of the platelet count improvements by eltrombopag was demonstrated by a decrease in bleeding symptoms and a reduction in the proportion of eltrombopag-treated patients who required rescue therapy compared with patients in the placebo group. Refer to the [Eltrombopag Investigator's Brochure].

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 contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

Hepatotoxicity:

Eltrombopag administration can cause hepatobiliary laboratory abnormalities, severe hepatotoxicity, and potentially fatal liver injury. In clinical studies of adult and pediatric patients (aged 1 to 17 years) with chronic ITP who received eltrombopag, increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and indirect bilirubin were observed. Exercise caution when administering eltrombopag to patients with hepatic disease.

Thrombotic/thromboembolic complications:

Platelet counts above the normal range present a theoretical risk for thrombotic/thromboembolic complications. In eltrombopag clinical trials 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.

Cataracts:

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 subjects 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 subjects received up to 57 weeks of eltrombopag at doses up to 100 mg, there was a numerically higher incidence of cataracts in the eltrombopag treatment group compared with the placebo group. Routine monitoring of patients for cataracts is recommended.

Bleeding following discontinuation of eltrombopag

Thrombocytopenia is likely to reoccur in ITP patients upon discontinuation of treatment with eltrombopag. Following discontinuation of eltrombopag, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increases the bleeding risk and in some cases may lead to bleeding. This risk is increased if eltrombopag treatment is discontinued in the presence of anticoagulants or anti-platelet agents.

In HCV clinical studies, a higher incidence of gastrointestinal bleeding, including serious and fatal cases, was reported following discontinuation of peginterferon, ribavirin, and eltrombopag. Following discontinuation of therapy, patients should be monitored for any signs or symptoms of gastrointestinal bleeding.

Bone marrow reticulin formation and risk of bone marrow fibrosis

Eltrombopag may increase the risk for development or progression of reticulin fibres within the bone marrow. The relevance of this finding, as with other thrombopoietin receptor (TPO-R) agonists, has not been established yet.

4.5.2 Benefits associated with Eltrombopag use

Eltrombopag is an oral TPO-RA approved in over 100 countries for the treatment of patients aged 1 year and above with primary ITP lasting 6 months or longer from diagnosis and who are refractory to other treatments. 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 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 subjects to reduce/discontinue concomitant (corticosteroid) medication use (RAISE Study) (Cheng et al 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 $< 30 \times 10^9$/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 $\geq 30 \times 10^9$/L within 6 months of diagnosis). Patients with platelets $< 10 \times 10^9$//L began eltrombopag 75 mg QD while those with a count $\geq 10 \times 10^9$/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 $\leq 30 \times 10^9$/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 $> 100 \times 10^9$/L), partial response (PR) (platelet count $> 50 \times 10^9$/L) or minor response (MR) (platelet $\geq 30 \times 10^9$/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 serious adverse events (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 (Tran 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 chronic ITP 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 et al 2010, Qu et al 2017, Liu et al 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 (see Section 1.1.3).

5 Population

The study is designed to include 106 adult patients with newly diagnosed primary ITP with screening platelet count $< 30 \times 10^9$/L and assessed as required treatment (per physician's discretion).

ITP patients are detected by routine examinations or in the context of preoperative clarifications. If a diagnosis of ITP is confirmed the patients are informed about the trial and the informed consent process is initiated (it is very important that the patient take time to address any question or doubt with the study physician in line with local law). All study specific information is also found in the informed consent form and will be presented to the patient. The informed consent is a voluntary agreement to participate in research. It is not merely a form that is signed but is

a key process for potential study participants, in which the subject has an understanding of the clinical trial and its risk. In case of a consent, the screening activity proceeds, meaning the inclusion and exclusion criteria as well as the concomitant medication and the medical history are evaluated (Section 5.1 and 5.2).

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. Men and women ≥ 18 years of age
3. Newly diagnosed with primary ITP (time from diagnosis within 3 months)
   Platelet count < 30×10^9/L at screening and a need for treatment (per physician's discretion) Note: If pre-treatment is necessary, platelet count data performed directly before pre-treatment (prior to signing the study specific informed consent form and start of screening for the study as per local practice or under a local protocol) can be used for study inclusion (screening value). Treatment-naïve patients will be included based on their platelet counts performed at screening.

5.2 Exclusion criteria

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

1. Previous history of treatment for ITP
   Note: Patients in need of immediate treatment for thrombocytopenia while diagnosis or eligibility are being determined may receive treatment with any ITP-directed therapy for a maximum of 3 days within 7 days before randomization. These therapies must be discontinued before the patient receives the first dose of study treatment
2. Patients with diagnosis of secondary thrombocytopenia
3. Patients who have life threatening bleeding complications per physician´s discretion
4. Patients with a history of thromboembolic events in the 6 months preceding enrollment or known risk factors for thromboembolism (e.g. Factor V Leiden, ATIII deficiency, antiphospholipid syndrome) are excluded. Patients with other risk factors which may pose an increased thromboembolic event (TEE) risk (prolonged periods of immobilization, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking) would be excluded according to the discretion of the investigator.
5. 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
6. Total bilirubin (TBIL) > 1.5 × upper limit of normal (ULN)
7. Aspartate transaminase (AST) > 3.0 × ULN
8. Alanine transaminase (ALT) > 3.0 × ULN

9. Patients who are human immunodeficiency virus (HIV), HCV or hepatitis B surface antigen (HBsAg) positive
10. Patients with hepatic impairment (Child-Pugh score > 5)
11. Patients with known active or uncontrolled infections not responding to appropriate therapy
12. History of current diagnosis of cardiac disease or impaired cardiac function denoted by any of the following:
    - Corrected QTc >450 msec using Fridericia correction (QTcF) on the screening electrocardiogram (ECG)
    - History of myocardial infarction and unstable angina within 6 months prior to starting study treatment
    - Clinically significant cardiac arrhythmias or other clinically significant cardiovascular disease (e.g., congestive heart failure, uncontrolled hypertension) within the six months prior to starting study treatment
13. Patients who have active malignancy
14. Patients with evidence of current alcohol/drug abuse
15. Any serious and/or unstable pre-existing medical (including any advanced malignancy other than the disease under study), psychiatric disorder, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance with the study procedures.
16. 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
17. Patients with pre-existing medical conditions that are known precautions with corticosteroid use, in whom the potential risks of participating in the study outweigh the potential benefits as determined by the investigator
18. Female subjects who are nursing or pregnant (positive serum or urine B-human chorionic gonadotrophin (B-hCG) pregnancy test) at screening or pre-dose on Day 1
19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception while taking study treatment and for 7 days after stopping medication. Highly effective contraception methods include:
    - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]:
        - oral
        - intravaginal
        - transdermal
    - progestogen-only hormonal contraception associated with inhibition of ovulation1:
        - oral
        - injectable
        - implantable[2]
    - intrauterine device (IUD)[2]
    - intrauterine hormone-releasing system (IUS)[2]

- bilateral tubal occlusion[2]
- vasectomised partner[2,3]
- sexual abstinence[4]

[1]Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method (see section 4.3).
[2] Contraception methods that in the context of this guidance are considered to have low user dependency.
[3] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

6 Treatment

6.1 Study treatment

Patients randomized to Arm A will receive eltrombopag in combination with a short course of high-dose dexamethasone beginning at Day 1. The dose of dexamethasone will be 40 mg QD for 4 consecutive days and limited to 1 cycle. The starting dose of eltrombopag will be 50 mg QD and treatment will continue at the same dose for 2 weeks to reach a target platelet count of 50×10^9/L as necessary to reduce the risk for bleeding. The dose of eltrombopag will be increased by 25 mg increments every 2 weeks to a maximum dose of 75 mg QD for all patients who do not achieve the target platelet count of $\geq 50 \times 10^9$/L (Table 6-1). Treatment with eltrombopag will be continued at the minimal dosage necessary to maintain a platelet count $\geq 50 \times 10^9$/L to 150×10^9/L for 20 weeks. Asian patients will initially receive half of the dose, starting at 25 mg of eltrombopag due to lower clearance of eltrombopag as compared with non-asian patients. After initiating eltrombopag, the dose must be adjusted to achieve and maintain a platelet count $\geq 50 \times 10^9$/L as necessary to reduce the risk for bleeding. The standard eltrombopag dose adjustment for Asian patients would be 25 mg once daily as well. It is necessary to wait for at least 2 weeks to see the effect of any dose adjustment on the patient's platelet response prior to considering another dose adjustment. A daily dose of 75 mg must not be exceeded. The dose of eltrombopag will be decreased by 25 mg if platelet counts are $> 150 \times 10^9$/L to $\leq 400 \times 10^9$/L by 25 mg and the effect will be assessed after 2 weeks.

Patients will be eligible for taper off and treatment discontinuation once they reach platelet counts $\geq 30 \times 10^9$/L. The duration of tapering will be 6 weeks starting at W21D1: decrease in dose will be performed by 25 mg reductions every 2 weeks to a minimum dose of 25 mg every other day for all patients.

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

Platelet Level	Dose Guidance
Patients with platelet < 30×10^9/L after 4 weeks of eltrombopag therapy at 75 mg/day	Discontinue eltrombopag, initiate second-line therapy, follow-up till week 52 and discontinue from study at Week 52
Patients who relapse (platelet count < 30×10^9/L) during eltrombopag tapering off stage	Use previous dose level (i.e. one dose level higher) and continue treatment till Week 52 and discontinue from study at Week 52
Patients who relapse (< 30×10^9/L) after eltrombopag discontinuation before Week 52	Re-initiate treatment with eltrombopag with a starting dose of 50 mg/day till Week 52 and discontinue from study at Week 52

Treatment in the control arm consists of 1-3 cycles of high-dose dexamethasone administered orally at a dose of 40 mg QD for 4 consecutive days at 4 weeks intervals (dexamethasone can also be given at 14 to 28 days intervals if needed according to current ITP guidelines). If the platelet counts are > 150×10^9/L no further course of dexamethasone will be given. Patients will be treated up to 12 weeks (3 months) during the treatment period with dexamethasone. Patients who reach platelet counts ≥ 30×10^9/L and maintain counts ≥ 30×10^9/L after 1-3 cycles of high-dose dexamethasone treatment will be eligible for treatment discontinuation. Patients with platelet counts < 30×10^9/L after 3 cycles of dexamethasone treatment will be offered a course of eltrombopag treatment within the study and will discontinue the study after completion of treatment with eltrombopag at Week 52 (Table 6-2).

Table 6-2 Dexamethasone dosing guidance for patients not meeting criteria for sustained remission

Platelet Level	Dose Guidance
Patients with platelet count < 30×10^9/L after 3 cycles with dexamethasone	Initiate treatment with eltrombopag with a starting dose of 50 mg/day and continue treatment with eltrombopag till Week 52 after study start and discontinue from study at Week 52
Patients who relapse (platelet count < 30×10^9/L) after dexamethasone discontinuation before Week 52	Initiate treatment with eltrombopag with a starting dose of 50 mg/day till Week 52 after study start and discontinue from study at Week 52

6.1.1 Investigational and control drugs

Study medication will be supplied in commercially available packaging labeled with "Zur klinischen Prüfung bestimmt". Eltrombopag and dexamethasone are both investigational drugs. Eltrombopag study drug will be provided as film-coated tablets.

Dexamethasone is the Standard of Care treatment and will be supplied as tablets. It will be provided through Novartis locally for treatment of patients enrolled in this study.

All investigational treatment is to be stored in a secure locked area while under the responsibility of the investigator. Receipt and dispensing of investigational and Standard of Care 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, dose, frequency, and method of administration of eltrombopag and dexamethasone is provided in Table 6-3.

Table 6-3 Investigational and control drug

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Eltrombopag	Tablet for oral use	25 mg	Daily
Eltrombopag	Tablet for oral use	50 mg	Daily
Dexamethasone	Tablet for oral use	40 mg	Daily

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

Patients will be randomized at visit Week 1 Day 1 to one of the following 2 treatment arms/groups in a ratio of "1:1"

- Arm A: Eltrombopag + a short course of high-dose of dexamethasone
- Arm B: 1-3 cycles of high-dose dexamethasone

For detailed treatment guidance refer to Section 6.1.

6.1.4 Treatment duration

Arm A: The treatment duration for all patients in Arm A (eltrombopag QD for 26 weeks + high-dose dexamethasone QD for 4 consecutive days starting at day 1 and limited to 1 cycle) will be 26 weeks (6 months) including 6 weeks tapering period. All patients who discontinue study treatment as per study design with platelet counts $\geq 30 \times 10^9$/L in the absence of bleeding or use of any rescue therapy will be followed for response assessments till Week 52 after study start. Patients who relapse after eltrombopag discontinuation before Week 52 will reinitiate treatment with eltrombopag till Week 52 and will discontinue from study at Week 52. Patients with platelet counts $< 30 \times 10^9$/L after 26 weeks of treatment with eltrombopag will continue treatment as summarized in Table 6-1 and discontinue from study at Week 52.

Arm B: The maximum duration of treatment with dexamethasone for all patients in Arm B will be 12 weeks. All patients who discontinue study treatment as per study design with platelet counts $\geq 30 \times 10^9$/L in the absence of bleeding or use of any rescue therapy will be followed for response assessments till Week 52. Patients who relapse (platelet count $< 30 \times 10^9$/L) after dexamethasone discontinuation before Week 52 will be treated with eltrombopag as summarized in Table 6-2 and discontinue the study at Week 52. Patients with platelet count $< 30 \times 10^9$/L after 3 cycles with dexamethasone will initiate treatment with eltrombopag and discontinue the study at Week 52.

6.2 Other treatment

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 after the enrollment of the patient in this study must be listed on the Concomitant Medications or the Procedures and Significant Non-Drug Therapies electronic case report form (eCRF).

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 randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis/sponsor to determine if the subject 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 2 hours before or 4 hours after 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 breast cancer resistance protein (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

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 30 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.

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 nonsteroidal anti-inflammatory drugs [NSAIDs]) should not be taken during the study unless there is a very clear indication and the Investigator documents the rationale. This is due to the fact that they may affect the results of the bleeding scale assessments.

Please refer to locally approved SmPC of dexamethasone for information regarding prohibited concomitant medication.

6.2.3 Rescue medication

Any ITP-directed medication or therapy, other than randomized treatment, given during the treatment phase of the trial with the aim to increase platelet count for the subjects who have clinically significant bleeding will be considered a rescue therapy and must be recorded on the appropriate eCRF page. A subject who receives rescue medication or therapy will not be considered in having achieved sustained response off treatment for the primary endpoint. Any ITP-directed medication or therapy given during the follow-up phase after treatment discontinuation until week 52 will be considered non-responders for the primary endpoint.

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 enrolled for screening and is retained as the primary identifier for the subject 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.

6.3.2 Treatment assignment, randomization

Patients will be randomized to one of the two treatment arms in a ratio of 1:1.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased. A randomization list will be produced by or under the responsibility of the Novartis Nürnberg GCP Officer using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio.

The randomization scheme will be reviewed by a Biostatistics Quality Assurance Group and locked by them after approval.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized to one of the treatment arms according to the randomization scheme.

6.4 Treatment blinding

Treatment will be open label to subjects, investigator staff, persons performing the assessments, and the clinical trial team.

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 for eltrombopag 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 $\geq 50 \times 10^9$/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.

Patients who will have platelet $< 30 \times 10^9$/L after 3 cycles with dexamethasone, treatment with eltrombopag will be initiated at 50 mg/day till Week 52 with eltrombopag dose adjustments summarized in Table 6-4.

All escalations and de-escalations must be recorded on the Dosage Administration Record eCRF.

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 6.1.1).

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 6-4. Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-5.

Table 6-4 Eltrombopag Dose Adjustments in ITP

Platelet count	Dose adjustment or response
< 50 × 10^9/L following 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 75 mg/day
> 150 × 10^9/L to ≤ 400 × 10^9/L	Decrease daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments [a]
> 400 ×10^9/L	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is < 150 × 10^9/L, reinitiate therapy at a lower dose

a. For patients taking 25 mg eltrombopag QD, consideration should be given to dosing at 25 mg once every other day.

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 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 AEs and laboratory results, the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 will be used.

Please refer to the label for dexamethasone for guidance of dose adjustments.

Table 6-5 Criteria for dose adjustment based on liver enzyme and bilirubin levels

	Dose modifications for Eltrombopag
Worst toxicity CTCAE[a] Grade (value) during the treatment	**Investigations (Hepatic)**
Isolated Total Bilirubin Elevation	
> ULN – 1.5 × ULN	Maintain dose level
> 1.5 - 3.0 × ULN*	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 × 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.

	Dose modifications for Eltrombopag
Worst toxicity CTCAE[a] Grade (value) during the treatment	**Investigations (Hepatic)**
> 10.0 × 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 × ULN	Maintain dose level
> 3.0 - 5.0 × ULN	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 Progressively increasing LFTs[b] upon repeat testing Persistence ≥4 weeks
> 5.0 - 10.0 × 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 × 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 × 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	

	Dose modifications for Eltrombopag
Worst toxicity CTCAE[a] Grade (value) during the treatment	**Investigations (Hepatic)**
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 5.0) [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 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.	

6.5.3 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.

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

Patients with transaminase increase combined with 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 international normalized ratio (INR) > 1.5 without evidence of cholestasis (no alkaline phosphatase (ALP) elevation)
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 × baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 × baseline AND > 2.0 × ULN]
- For patients with normal baseline ALT: ALT ≥ 5 × ULN

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as 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)/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.
4. 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.

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 and dexamethasone 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 or dexamethasone 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 and dexamethasone dispensed and returned must be recorded in the Drug Accountability Log.

6.6.2 Emergency breaking of assigned treatment code

Not applicable.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

6.7.1 Handling of eltrombopag and dexamethasone

Eltrombopag and dexamethasone study treatment 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.

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. Subjects 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/sponsor monitor or to the Novartis address provided in the investigator folder at each site.

6.7.2 Instruction for prescribing and taking study treatment

A description of eltrombopag and dexamethasone, dose and frequency is provided in Table 6-3.

- Patients should take eltrombopag at approximately the same time each day either 1 hour before eating or 2 hours after eating.
- For 4 hours before taking eltrombopag and 2 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 subjects may only be included in the study after providing IRB/IEC-approved informed consent.

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 subject source documents.

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 subject informed consent and should be discussed with the subject 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 subject.

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.

8 Visit schedule and assessments

Table 8-1 lists all of the assessments and indicates with an “x”, the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation.

Patients should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time (with an allowed “visit window” of ± 1 day for weekly visits and ± 3 days for all other visits) 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 investigational product should be reconciled, and the AE and concomitant medications recorded on the CRF.

Table 8-1 Assessment Schedule

Screening to Week 15

Period	Screening	Assessment Period (52 weeks)									
Visit[a]	**Screening[b]**	**Week 1 Day 1 (Baseline)**	**Week 2 Day 1**	**Week 3 Day 1**	**Week 4 Day 1**	**Week 5 Day 1**	**Week 7 Day 1**	**Week 9 Day 1**	**Week 11 Day 1**	**Week 13 Day 1**	**Week 15 Day 1**
Screening											
Obtain informed consent	x										
Registration	x										
Randomization		x									
Patient History											
Demography	x										
Inclusion/exclusion criteria	x										
Medical history	x										
Prior/concomitant medications	x	x	x	x	x	x	x	x	x	x	x
Physical Examination											
Physical examination	S	S	S	S	S	S	S	S	S	S	S
Height		x									
Weight	S	x				S		S		S	
Vital signs	x	x		x		x	x	x		x	
Laboratory Assessments											
Hematology[g,h]	x	x	x	x	x	x	x	x	x	x	x
Chemistry[h]	x	x		x		x	x	x		x	
Coagulation[h]	x										

Period	Screening	Assessment Period (52 weeks)									
Visit[a]	**Screening[b]**	**Week 1 Day 1 (Baseline)**	**Week 2 Day 1**	**Week 3 Day 1**	**Week 4 Day 1**	**Week 5 Day 1**	**Week 7 Day 1**	**Week 9 Day 1**	**Week 11 Day 1**	**Week 13 Day 1**	**Week 15 Day 1**
Viral serology[h]	x										
Pregnancy Test serum/urine[c]	S	Pregnancy testing must be performed on monthly basis									
Safety assessment											
Occular assessment[d]	x										
ECG	x										
Adverse Events	x										
IMP dispensing		x		x		x	x	x	x	x	x
Compliance		x	x	x	x	x	x	x	x	x	x
WHO Bleeding Scale	x	x	x	x	x	x	x	x	x	x	x
Bone marrow assessments	Per investigator discretion										
Patient Reported Outcomes											
FACIT-Fatigue		x	x	x		x				x	
SF-36v2		x	x	x		x				x	
[redacted]											

Weeks 16 to follow-up

	Assessment Period (52 weeks)																	EOS	Safety Follow-up[f]
Visit[a]	**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 37 Day 1**	**Week 41 Day 1**	**Week 45 Day 1**	**Week 49 Day 1**	**Week 53 Day 1/EOS**					
Patient History																			
Prior / concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x				x	x
Physical Examination																			
Physical examination	x	x	x	x	x	x	x	x	x	x	x	x	x	x				x	
Vital signs					x					x			x	x				x	
Laboratory Assessments																			
Hematology[g,h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x				x	
Chemistry[h]	x		x		x		x		x	x	x	x	x	x				x	
Coagulation[h]																		x	
Pregnancy Test serum/urine	Pregnancy testing must be performed on monthly basis																		
Safety assessment																			
Ocular assessment[d]																		x	
ECG																		x	
Adverse Events	x																		
IMP dispensing	x	x	x	x	x	x	x	x	x	x	x	x	x						

	Assessment Period (52 weeks)																EOS	Safety Follow-up[f]
Visit[a]	**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 37 Day 1**	**Week 41 Day 1**	**Week 45 Day 1**	**Week 49 Day 1**	**Week 53 Day 1/EOS**					
Compliance	x	x	x	x	x	x	x	x	x	x	x	x	x	x				x	
WHO Bleeding Scale	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	X	x	x	
Bone marrow assessments	Per investigator discretion																		
Patient Reported Outcomes																			
FACIT-Fatigue						x								x				x	
SF-36v2						x								x				x	
[redacted]																			

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] "Visit window" of ± 1 day is allowed for weekly visits and ± 3 days for all other visits

[b] Screening should be done within screening window (Day -14 to Day -1)

[c] On monthly basis. Only blood test results will be collected in the eCRF

[d] Ocular assessment to be done within 28 days after study start; If ocular assessment data are already available from exams performed within 28 days prior to screening (prior to signing the study specific informed consent form and start of screening for the study as per local practice or under a local protocol), then these may be used for the purposes of study inclusion

[f] Safety follow-up should be done 30 days after the patient ends his/her participation in the study (prematurely or as per protocol)

[g] If pre-treatment is necessary, platelet count data performed directly before pre-treatment (prior to signing the study specific informed consent form and start of screening for the study as per local practice or under a local protocol) will be used for study inclusion (screening value). Treatment-naïve patients will be included based on their platelet counts performed at screening.

[h]Laboratory evaluations (hematology except thrombocyte counts, coagulation, chemistry and viral serology) available from exams performed 14 days before randomization as per local practice or under a local protocol (prior to signing the study specific informed consent form and start of screening for the study), then these may be used for the purposes of study inclusion. Please refer to footnote g for assessment of thrombocyte counts.

8.1 Screening

Molecular pre-screening

Not applicable.

Screening

All patients will be screened for study eligibility. All patients must sign informed consent prior to any screening procedures being performed. All screening assessments will be done within 1 to 14 days prior to randomization (see Table 8-1 for list of assessments to be performed).

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. Rescreening 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 14 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.

8.1.1 Information to be collected on screening failures

Patients who sign an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate 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 a SAE during the screening phase (see SAE section (Section 10.1.3) for reporting details).

Patients who are randomized and fail to start treatment, e.g. patients randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Patient demographics/other baseline characteristics

The following patient demographics and baseline characteristics will be collected at screening:

- Demography including age, sex, and race
- Primary ITP status (time from diagnosis within 3 months)
- 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 disease which are recorded on the Medical History eCRF should include the toxicity grade.

- Height and weight
- Prior and concomitant medication

Furthermore the following assessments will be performed:

- Physical examination
- Vital signs
- Laboratory evaluations (hematology, chemistry) with thrombocyte assessment at screening and baseline
- Viral serology
- Serum pregnancy test
- Ocular assessment
- Electrocardiogram (ECG)
- Adverse events
- WHO bleeding scale

Ocular assessment can be performed within 4 weeks after the first dose of study treatment. If ocular assessment data are already available from exams performed within 28 days prior to screening (prior to signing the study specific informed consent form and start of screening for the study as per local practice or under a local protocol), then these may be used for the purposes of study inclusion.

If pre-treatment is necessary, platelet count data performed directly before pre-treatment (prior to signing the study specific informed consent form and start of screening for the study as per local practice or under a local protocol) will be used for study inclusion (screening value). Treatment-naïve patients will be included based on their platelet counts performed at screening

In addition, if laboratory evaluations (hematology except thrombocyte counts, coagulation, chemistry and viral serology) available from exams performed 14 days before randomization as per local practice or under a local protocol (prior to signing the study specific informed consent form and start of screening for the study), then these may be used for the purposes of study inclusion.

Bone marrow biopsy 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 compare the ability of eltrombopag in combination with a short course of high-dose dexamethasone to a defined course of high-dose dexamethasone to induce sustained response off treatment at Week 52.

8.3.1 Efficacy assessment 1

Platelet count will be assessed at screening visit to assess the eligibility of the subject. Hematology including platelet counts will be performed at Week 1/Day 1 (baseline) and weekly

during the first 4 weeks of treatment. Based on subject´s response, hematology will be performed biweekly thereafter until Week 33 Day 1 and every 4 weeks till Week 53 Day 1.

Additional assessments of platelet count may be performed more frequently if needed in accordance with the clinical judgment of the investigator as part of clinical routine.

8.3.2 Efficacy assessment 2

Bleeding events will be assessed at each visit and recorded in the AE CRF and in addition on an unique CRF for bleeding events. 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 et al 2010).

8.4 Safety

All the safety assessments will be performed according to the visit schedule as outlined in Table 8-1. For details on AE collection and reporting, refer to Section 10.1. Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the AE page of the patient's CRF. The list of the physical assessments planned for this study are provided in Table 8-2.

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 signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature.
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.

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 slit lamp examination is required. Ophthalmic exams will be performed at screening (within 2 weeks after study entry) and at additional visits according to Table 8-1. Ocular assessment is not required prior to first dose of study treatment, but must be completed within the first 4 weeks of study entry. If ocular assessment data are already available from exams performed within 28 days prior to screening (prior to signing the study specific

informed consent form and start of screening for the study as per local practice or under a local protocol), then these may be used for the purposes of study inclusion.

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

Clinical laboratory analyses (hematology and chemistry) are performed by the local laboratory.

Novartis must be provided with a copy of the laboratory's certification (if applicable), and a tabulation of the normal ranges and units of each parameter collected in the eCRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the new effective date. Additionally, if at any time a patient has laboratory parameters obtained from a different (outside) laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well. The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

At any time during the study, abnormal laboratory parameters which are clinically relevant (as decided by the investigator) and require an action to be taken with study treatment (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE eCRF page. Laboratory data will be summarized using the CTCAE version 5.0 or above. Additional analyses are left to the discretion of the investigator.

Table 8-3 Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), Mean corpuscular volume (MCV), Platelets, Red blood cells (RBCs), White blood cells (WBCs), Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Other
Chemistry	Albumin, Alkaline phosphatase, Alanine aminotransferase (ALT), Aspartate transaminase (AST), Amylase, , Calcium, Chloride, Creatinine, Creatinine kinase, Direct Bilirubin, Total Bilirubin (TBIL), Lactate dehydrogenase (LDH), Glucose (fasting), GGT, Lipase, Magnesium, Phosphorus, Potassium, Sodium, Total Protein, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Lipase,
Coagulation	Prothrombin time or International normalized ratio [INR] or Quick-test (Quick-value), Activated partial thromboplastin time (aPTT), Fibrinogen,
Pregnancy Test	Serum / Urine pregnancy test

8.4.2.1 Hematology

Hematology tests are to be performed according to the visit schedules outlined in Table 8-1. For details of the Hematology panel, refer to Table 8-3.

Hematology should be assessed on the scheduled day, even if study drug is being withheld.

8.4.2.2 Biochemistry

Eltrombopag administration can cause abnormal liver function and severe hepatotoxicity, which might be life-threatening.

Serum ALT, AST and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. Abnormal serum liver tests should be evaluated with repeat testing within 3 to 5 days. If the abnormalities are confirmed, serum liver tests should be monitored until the abnormalities resolve, stabilize, or return to baseline levels. Eltrombopag should be discontinued if ALT levels increase (> 3 × ULN in patients with normal liver function, or ≥ 3 × baseline or > 5 × ULN, whichever is the lower, in patients with pre-treatment elevations in transaminases) and are:

- progressive, or
- persistent for ≥ 4 weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation

Biochemistry tests are to be performed according to the visit schedules outlined in Table 8-1. For details of the biochemistry panel refer to Table 8-3.

Biochemistry should be assessed on the scheduled day, even if study drug is being withheld.

Eltrombopag is highly colored and so has the potential to interfere with some laboratory tests. Serum discoloration and interference with TBIL and creatinine testing have been reported in patients taking Revolade/Promacta. If the laboratory results and clinical observations are inconsistent, evaluation of contemporaneous aminotransferase values may help in determining the validity of low TBL levels in the presence of clinical jaundice and blood urea should be evaluated in the event of an unexpectedly high serum creatinine. Re-testing using another method may also help in determining the validity of the result (Choy et al 2016).

8.4.3 Viral serology

In addition to medical history, screening assessments for hepatitis B, hepatitis C and human immunodeficiency virus (HIV) will be performed by the local laboratory according to Table 8-1.

8.4.4 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.

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.

8.4.5 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Serum or urine pregnancy tests are to be performed according to the Visit Schedules outlined in Table 8-1. At screening, a serum pregnancy test should be performed regardless of the age of the patients, while, during the study, and at the end of study, urinary pregnancy tests (dipstick) are sufficient. Pregnancy testing (serum or urine) must be performed on a monthly basis while receiving study drug until study drug discontinuation. A positive pregnancy test requires immediate interruption of study treatment until the assessment is confirmed. If positive, the patient must be discontinued from the study.

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:

1. Surgical bilateral oophorectomy without a hysterectomy
2. 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 subject regardless of reported reproductive/menopausal status at screening/baseline.

8.4.6 Appropriateness of safety measurements

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

8.5 Additional assessments

Bone marrow biopsies is recommended for patients > 60 years or in the presence of abnormalities and can be performed at the discretion of the investigator.

8.5.1 Clinical Outcome Assessments (COAs)

Patient reported outcomes (PRO)

Immune thrombocytopenia is associated with symptoms of fatigue, bruising, and bleeding, which can interfere with daily activities. Consequently, subjects with ITP have decreased HRQoL compared with healthy individuals. To assess patient-reported outcomes (PROs), HRQoL changes over time will be assessed using standard validated instruments.

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 and Nowinski 2002, Webster et al 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 et al 2011). FACIT-Fatigue will be administered before any study drug administrations at the beginning of treatment and after 1, 2, 4, 12, 26, and 52 weeks and EOS (for patients with premature study withdrawal before W53D1). A minimal clinically important difference from baseline in FACIT-Fatigue score will be evaluated (Cella and Nowinski 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 et al 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. SF-36v2 will be administered before any study drug administrations at the beginning of treatment and after 1, 2, 4, 12, 26, and 52 weeks and EOS (for patients with premature study withdrawal before W53D1), and change from baseline will be evaluated. [redacted].

The site personnel should check the questionnaire for completeness and ask the patient to complete any missing responses. The original questionnaire will be kept with the patient's file as the source document.

Completed questionnaire(s) and any unsolicited comments written by the patient should be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs.

8.5.2 [redacted]

[redacted]

8.5.3 Other Assessments

The modified WHO (Kaufman et al 2015) Bleeding Scale (Page et al 2007) will be administered at every visit (refer Section 16.2).

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 subject or the investigator.

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

Study treatment must be discontinued under the following circumstances:

- Patient/guardian decision
- Pregnancy
- 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 subject's overall status, prevents the subject 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 subject's premature discontinuation of study treatment and record this information.

Subjects 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 subject/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 subject cannot or is unwilling to attend any visits, the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- new / concomitant treatments
- AEs/SAEs

9.1.2 Withdrawal of informed consent

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

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject'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 subject 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 subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law.

9.1.3 Lost to follow-up

For subjects 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 subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed *or until the end of the study*.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider subject welfare and safety. Should early termination be necessary, ongoing subjects must be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come in for a final visit) and treated as a prematurely withdrawn subject. 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 subject's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion 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.

Patients who are still on study treatment at W53D1 will come off trial after completing the W53D1/visit. After discontinuing drug at the W53D1 visit, patients will be followed-up for safety for an additional 30 days (safety follow-up). Patients who complete the W79D1visit, or who discontinue during the follow-up period between Week 52 and Week 78 due to relapse, will be followed up for an additional 30 days (safety follow-up).

For patients with premature withdrawal for any reason an EOS visit will be performed with all of the assessments listed for the EOS. After the EOS visit, patients will be followed-up for safety for an additional 30 days.

Continuing care to study participants should be provided by the investigator and/or referring physician.

10 Safety monitoring and reporting

10.1 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 subject or clinical investigation subject 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 subject 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 subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded in the appropriate CRF capturing AEs 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 5.0
2. its relationship to the study treatment (eltrombopag and/or dexamethasone)
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 AEs must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose reduced/increased
- Drug interrupted/withdrawn
- Subject hospitalized/subject's hospitalization prolonged

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 subject.

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 after the patient has stopped study participation (defined as last dose of study treatment taken or last visit whichever is later).

Once an AE 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 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 Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute AEs 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 subjects with the underlying disease.

10.1.2 Serious adverse events

A SAE is defined as any AE (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 subject 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 subject'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 subject 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 subject 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 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 SAE irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the patient has stopped study participation (defined as last dose of study treatment taken or last visit whichever is later) must be reported to Novartis Safety within 24 hours of learning of its occurrence. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Patient Safety department. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

SAEs occurring after the subject has provided informed consent until the time the subject 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 should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

To ensure subject 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 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 each specific study treatment (eltrombopag and/or dexamethasone) 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, subject 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

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure subject 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.

The following two categories of abnormalities / AEs 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 6-5 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 subject 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 subject 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.

Thrombotic/thromboembolic complications

The risk of TEEs has been found to be increased in patients with chronic liver disease treated with 75 mg eltrombopag QD for 2 weeks in preparation for invasive procedures. Six of 143 (4%) adult patients with chronic liver disease receiving eltrombopag experienced TEEs (all of the portal venous system) and 2 of 145 (1%) patients in the placebo group experienced TEEs (one in the portal venous system and one myocardial infarction). Five of the 6 patients treated with eltrombopag experienced the thrombotic complication at a platelet count >200,000/μL and within 30 days of the last dose of eltrombopag. Eltrombopag is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease in preparation for invasive procedures.

Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. When treatment is considered appropriate, caution is required when administering eltrombopag to patients with hepatic impairment.

Bleeding following discontinuation of eltrombopag

Thrombocytopenia is likely to reoccur in ITP patients upon discontinuation of treatment with eltrombopag. It is recommended that, if treatment with eltrombopag is discontinued, ITP treatment be restarted according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or anti-platelet therapy, reversal of

anticoagulation, or platelet support. Platelet counts must be monitored weekly for 4 weeks following discontinuation of eltrombopag.

Bone marrow reticulin formation and risk of bone marrow fibrosis

Prior to initiation of eltrombopag, the peripheral blood smear should be examined closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of eltrombopag, FBC with WBC count differential should be performed monthly. If immature or dysplastic cells are observed, peripheral blood smears should be examined for new or worsening morphological abnormalities (e.g. teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), treatment with eltrombopag should be discontinued and a bone marrow biopsy considered, including staining for fibrosis.

10.2.2 Steering Committee

The Steering Committee (SC) will be established comprising investigators participating in the trial and one external expert in the field of autoimmune cytopenias

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.

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 (Table 8-1) 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.

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 Electronic Data Capture (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.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification. After database lock, the investigator will receive a CD-ROM or paper copies of the subject 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.

11.2 Database management and quality control

The study will use electronic source documents and source data, and data entry will be done by the sites directly into eSource DDE.

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 AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

[redacted]

PROs should be collected by the investigator or designated and will be sent to a designated CRO for entry into database.

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 Trial Statistician and Statistical Reporting and the Clinical Trial Leader.

11.3 Site monitoring

Before study initiation, at a site initiation visit, a Novartis/delegated CRO representative will review the protocol and eCRF 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 subject 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.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

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 subjects will be disclosed.

11.4 Data privacy impact assessment

11.4.1 Systematic description of the envisaged processing operations and the purposes of the processing

The categories of personal data as well as the purposes, scope and duration of the data processing procedures conducted by the sponsor in connection with this clinical trial are described in the attached Clinical Trials Privacy Impact Assessment (see Appendix 4: Clinical Trials Privacy Impact Assessment) which is, inter alia regarding the involved personal data as well as the processing purposes, further specified in this clinical trial protocol.

11.4.2 Assessment of the necessity and proportionality of the processing operations in relation to the purposes

As set out in this clinical trial protocol the processing of personal data performed by the sponsor will only cover personal data being necessary for the performance of the clinical trial. Furthermore, the sponsor will only process the patients' personal data in a pseudonym form. On the other hand the performance of the clinical trial may create new scientific knowledge which may positively affect the health status and medical treatment of the patients. Therefore, the nature and scope of the conducted data processing is necessary, suitable and proportionate in relation to the purpose of the clinical trial.

11.4.3 Assessment of the risks to the rights and freedoms of data subjects

The performance of the clinical trial involves comprehensive processing of sensitive personal data (e. g. data concerning health). Whereas, any unintended and / or unauthorized disclosure of patients data may likely result in a high risk to the rights and freedoms of the patients. Patients may in particular be stigmatized by their social environment, may lose or fail in obtaining insurance coverage. However, the abovementioned risk is significantly reduced by the fact that the sponsor solely obtains and processes pseudonym data which cannot directly be attributed to an individual patient. In order to safeguard that the patient's data stays pseudonym technical and organizational measures have been established to prevent the sponsor from receiving additional information which allows to link the scientific data to individual patients.

11.4.4 Measures envisaged to address the risks, including safeguards, security measures and mechanisms to ensure the protection of personal data and to demonstrate compliance with the GDPR taking into account the rights and legitimate interests of data subjects and other persons concerned.

First and foremost, the sponsor exclusively processes pseudonym data which cannot directly be attributed to an individual patient. To safeguard that the personal data processed by the sponsor stays pseudonym technical and organizational measures have been established to avoid that the sponsor obtains additional information which allows the sponsor to attribute pseudonym data to an individual patient. Thus, the described risks for the rights and freedoms of the data subjects are reduced substantially. The sponsor's IT systems being used to process personal data in connection with the clinical trial have thoroughly been assessed from an IT security point of view in order to ensure availability, integrity, confidentiality, and correctness of personal data. The implemented IT security measures in particular reflect the respective sensitivity of the data being processed. To the extent IT systems are operated by external companies on behalf of the sponsor, required data processing agreements have been concluded inter alia stipulating technical and organizational measures to prevent data loss. Furthermore, any personal data is solely disclosed on a need to know basis. The personnel having access to personal data related to the clinical trial undertook to maintain confidentiality or is equally bound by confidentiality and professional secrecy obligations.

12 Data analysis and statistical methods

The statistical analysis will be based on all subject data at the time the trial ends. This analysis will be performed once all patients completed their final visits or terminated the study prematurely.

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, 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.

[redacted]

The **baseline** is the result of an investigation describing the state of the patient before start of eltrombopag or dexamethasone study treatment, and after a possible pre-treatment. The screening value describes the result at screening, before pre-treatment, especially for the thrombocyte count (see exclusion criteria). Should a patient not need pre-treatment, Screening

and baseline values can be identical. In such cases, as only one assessment exists, the baseline value will be taken from screening.

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

12.1 Analysis sets

The Full Analysis Set (FAS) will consist of all patients to whom study treatment has been assigned by randomization. The FAS will serve as the primary analysis set for all efficacy analyses. According to the intent to treat principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization procedure.

Before database lock, relevant protocol deviations and potential impact on analyses will be reviewed and adequately processed / documented.

The Safety Set (SAF) includes all subjects who received at least one dose of study treatment. Subjects in the SAF will be analyzed according to the study treatment actually received. Further details will be specified in the SAP.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group and overall for the FAS.

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term, by treatment group and overall.

12.3 Treatments

The Safety set will be used for the analyses below.

The duration of exposure in weeks to eltrombopag and dexamethasone 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, and shown separately as well as combined for both drugs) will be summarized by means of descriptive statistics using the safety set.

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

Furthermore, subjects using rescue treatments as defined in Section 6.2.3 will be summarized by treatment group.

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

12.4 Analysis of the primary endpoint

The primary objective is to compare the ability of eltrombopag in combination with a short course of high-dose dexamethasone to induce sustained response off treatment at 52 weeks in newly-diagnosed ITP patients versus 1-3 cycles course of high-dose dexamethasone.

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

12.4.1 Definition of primary endpoint

The primary endpoint is the proportion of patients with sustained response off treatment at 52 weeks.

Sustained response off treatment is defined as:

- reach platelet count $\geq 30\times10^9$/L and then maintain platelet counts $\geq 30 \times 10^9$/L after treatment discontinuation AND
- maintain platelet count $\geq 30 \times 10^9$/L in the absence of bleeding events $\geq$ Grade II and without the use of any rescue therapy (see Section 6.2.3) at all visits until week 52.
- Of note: in case a patient in the treatment Arm B (dexamethasone monotherapy) needs treatment cycles at an interval of less than 28 days (at least 14 days), and meets the definition for sustained response off treatment as given above, such patient will be counted as a responder for statistical analysis.

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12.4.2 Statistical model, hypothesis, and method of analysis

The analysis of the primary endpoint will be based on the following estimand:

The population will be the Full Analysis Set;

Variable of interest: The primary endpoint is the response rate in terms of sustained response off treatment at 52 weeks, in absence of bleeding or use of rescue therapy as defined above, i.e. a composite estimand.

Intervention effect: effect of eltrombopag in combination with a short course of high-dose dexamethasone versus 1-3 cycles of high-dose dexamethasone alone at 52 weeks, regardless of adherence to randomized treatment.

Summary measure: odds ratio

The statistical hypothesis to be rejected is that the rates of patients achieving sustained response at 52 weeks are equal in both treatment groups. The corresponding alternative hypothesis is that the rates are not equal under eltrombopag combined with a short course of high-dose dexamethasone, compared to 1-3 cycles of high-dose dexamethasone monotherapy.

Let p_A and p_B denote the proportions of patients achieving sustained response off treatment for the treatment groups:

A = eltrombopag combined with a short course of high-dose dexamethasone

B = 1-3 cycles of high-dose dexamethasone “standard”

The following hypotheses will be tested:

H_0: $(p_B / (1- p_B)) / (p_A / (1- p_A)) = OR_{B/A} = 1$

versus H_A: $(p_B / (1- p_B)) / (p_A / (1- p_A)) = OR_{B/A} \neq 1$

In other words:

H_0: The rate of patients achieving a sustained response off treatment at 52 weeks in the eltrombopag plus a short course of high-dose dexamethasone arm is equal to the respective rate in the 1-3 cycles high-dose dexamethasone monotherapy "standard" arm (corresponding to equal odds).

H_A: The rate of patients achieving a sustained response off treatment at 52 weeks in the eltrombopag plus a short course of high-dose dexamethasone arm is higher than the respective rate in the 1-3 cycles of dexamethasone monotherapy "standard" arm.

The primary analysis will be performed comparing the treatment groups with respect to the primary efficacy outcome, based on the Odds Ratio, in a Logistic Regression model with the factor treatment and cofactors ITP-directed pre-therapy (during 3 days within 7 days before randomization), screening platelet count and age (≤ vs. > 60 years). The odds ratio and its 95% confidence interval (CI) and p-value will be given. The null hypothesis of equal odds will be rejected if the 2-sided p-value from the logistic regression model for the factor "treatment" is <0.05; however, superiority of eltrombopag in combination with a short course of dexamethasone will be claimed only if the direction is correct, i.e. if the odds of response are higher under eltrombopag plus a short course of high-dose dexamethasone compared to 1-3 cycles of dexamethasone monotherapy ($OR_{B / A} < 1$).

12.4.3 Handling of missing values/censoring/discontinuations

If patient´s platelet assessment for evaluating the primary endpoint are missing, they will not be considered for sustained response off treatment. Patients dropping out early will be considered as early discontinuation or not evaluable, will be considered in the analysis set as non-responders. Thus, missing values are not expected for the primary analysis. Details will be specified in the respective SAP.

12.4.4 Sensitivity and Supportive analyses

Sensitivity analyses

Sensitivity analyses and supportive analyses will be conducted in order to provide evidence that the results seen from the primary analysis are robust. Furthermore, Bayes analyses may be considered in addition (Fisch et al 2015).

The impact of the analysis assumptions on the result of sustained response off treatment will be assessed as well by repeating the logistic regression model using different populations and ways to handle missing data.

These may include, but are not limited to:

- Multiple imputation
- Using a treatment policy estimand (no matter if intercurrent events such as bleeding, treatment discontinuation or reinitiation, or rescue treatment occurred)

- Using the baseline thrombocyte count (or threshold exceedance, i.e. early increase of thrombocyte count above the screening threshold, instead of or in addition to the thrombocyte count at screening),
- Adding further detail information on pre-treatment to the model (type of medication, dosage, duration)

Supportive analyses

Data defining the primary outcome of sustained response off treatment will be further reported descriptively to give the full picture. This will include

- PLT counts at treatment discontinuation
- Number of patients with PLT $\geq 50 \times 10^9$/L or PLT $\geq 100 \times 10^9$/L or PLT $\geq 150 \times 10^9$/L at treatment discontinuation;
- Time point of reaching PLT $\geq 150 \times 10^9$/L measured from start of study treatment
- Number of patients who are able to discontinue eltrombopag and dexamethasone with PLT $\geq 30 \times 10^9$/L
- Number of patients with loss of response after treatment discontinuation
- Number of patients with bleeding events after treatment discontinuation
- Number of patients receiving rescue treatment

The primary analysis will be repeated in the following subgroups:

- Age ($\leq$ vs. > 60 years).
- Platelet count: thrombocytopenia at screening and at baseline: platelets $< 10 \times 10^9$/L versus platelets $> 10 \times 10^9$/L
- ITP-directed pre-therapy (yes / no)

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 endpoints

1. To compare the ability of eltrombopag in combination with a short course of high-dose dexamethasone **to induce overall response (OR)** after treatment discontinuation at week 52 versus a defined course of dexamethasone

   Number (%) of patients with platelet count $\geq 30 \times 10^9$/L and a 2-fold increase of screening platelet count after treatment discontinuation in the absence of bleeding events $\geq$ Grade II and no rescue therapy at all visits until Week 52 will be provided, analysis will be equivalent to the primary endpoint analysis.
2. To assess the **duration of sustained response off treatment**, median duration of response off treatment (weeks) counted from last dose of study treatment (eltrombopag or dexamethasone) until loss of response will be calculated using a Kaplan-Meier analysis.
3. .
4. To assess the ability of eltrombopag to induce **overall response (OR) by week 4**

Number (%) of patients with platelet count ≥ 30 × 10^9/L and a 2-fold increase of screening platelet count at least once within the first 4 weeks without bleeding events ≥ Grade II and no rescue therapy will be provided, analysis will be equivalent to the primary endpoint analysis.

5. To assess the ability of eltrombopag to induce a **complete response (CR) by week 4**
   Number (%) of patients with platelet count ≥ 100 × 10^9/L at least once within the first 4 weeks without bleeding events ≥ Grade II and no rescue therapy will be provided, analysis will be equivalent to the primary endpoint analysis.
6. To assess the **platelet count** from screening to baseline and to 1, 2, 4, 12, 26 and 52 weeks; absolute and relative change in platelet count from screening to baseline and to 1, 2, 4, 12, 26 and 52 weeks and EOS will be provided. Box plots for absolute and/or relative change in platelet counts from screening to baseline and to different time points will also be provided.
7. To assess the time to response for overall and complete response using a Kaplan-Meier analysis.
8. To assess the duration of response for overall and complete response using a Kaplan-Meier analysis.
9. 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 through FACIT and SF-36v2 questionnaires from baseline to 1, 2, 4, 12, 26, 52 weeks and EOS (for patients with premature study withdrawal before W53D1) will be provided.
10. To evaluate the safety and tolerability of eltrombopag see Section 12.5.2.
11. To evaluate the incidence and severity of bleeding events

12.5.2 Safety endpoints

Safety summary tables include only data from the period from first treatment until 30 days after the patient has stopped study participation (defined as last visit).

Adverse events

All information obtained on AEs will be displayed by treatment group and subject.

The number (and percentage) of subjects with treatment-emergent AEs (events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term

Separate summaries will be provided for study medication related AEs, death, SAEs, other significant AEs leading to discontinuation and adverse events leading to dose adjustment.

The number (and proportion) of subjects with AEs of special interest (i.e. thromboembolic/thrombotic complications, hepatobiliary laboratory abnormalities, bleeding,

bone marrow reticulin formation and bone marrow fibrosis, and ocular changes) will be summarized by treatment.

A subject with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

All information obtained on AEs will be displayed by patient. Summary tables for 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 AE and relation to study treatment.

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

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

All deaths (until 30 days after the patient has stopped study participation defined as last visit.s) 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 study treatment) and post-treatment period will be flagged (until 30 days after the patient has stopped study participation defined as last visit)

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

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. Shift tables using the low/normal/high/ (low and high) *(or project specific)* classification will be used to compare baseline to the worst on-treatment value.

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. 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 v5.0, results will be categorized as low/normal/high based on laboratory normal ranges.

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

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v5.0 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE v5.0

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.

- Shift tables using CTCAE v5.0 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v5.0,

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

[redacted]

Other safety evaluations

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

The change in bleeding scale (WHO) will be provided using the worst value in the relevant time period. Listings will be provided.

[redacted]

12.5.4 Patient reported outcomes

Descriptive statistics will be provided for the FACIT and the SF-36V2 questionnaire including absolute change from baseline up to the end of study for the FAS.

[redacted]

[redacted]

12.7 Interim analyses

No formal interim analysis will be performed on this trial.

12.8 Sample size calculation

12.8.1 Primary endpoint

This trial is intended to estimate the difference in the rates of patients achieving a sustained response off treatment at Week 52.

(sustained response off treatment = maintain platelet $\geq$ 30 $\times$ 10^9/L after treatment discontinuation in the absence of bleeding events $\geq$ Grade II or use of any rescue medication at all visits until Week 52)

The sample size calculation is based on the following assumptions:

1. Sustained response off treatment is achieved in 30% of the patients in the dexamethasone arm and 65% in the eltrombopag + dexamethasone arm
2. Randomization is allocated in a 1:1 ratio (eltrombopag + dexamethasone: dexamethasone)
4. A two-sided 5% level of significance will be applied.
5. The study will have 90% power under the stated assumptions for the primary endpoint.

Based on these assumptions, a total of 47 patients in each treatment arm would need to be randomized. More conservative scenarios based on lower treatment effects and 50 patients per group, assuming rates of 30 versus 60% would lead to a power of 81%, and 30 versus 55% would still allow for a power of 64%, whereas the radius of the respective confidence interval would be between 0.20 and 0.21 based these scenarios.

To allow for some dropouts / protocol violations, a total of 106 patients is planned to be enrolled.

Due to feasibility reasons, resulting in a substantial delay in recruitment, as described above, with Amendment 3 recruitment will be prematurely discontinued. A final number of ca. 24 patients is expected to be recruited by the time of approval.

The patients enrolled by then will be analyzed and reported as described, to allow for adequate use of the present data.

Based on the assumptions described, the resulting power will be ca. 24%. As a consequence, all analyses will be performed in a purely descriptive manner.

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 Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. 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 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 (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 subjects 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 subject 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 subject 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.

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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.

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 et al 2015	

16.3 Appendix 3: HRQoL Questionnaires

Table 16-3 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

English (Universal)

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Table 16-4 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

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	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, 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 <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

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

6. **During the <u>past 4 weeks</u>, to what extent has your <u>physical health</u> 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 <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

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

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> 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

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

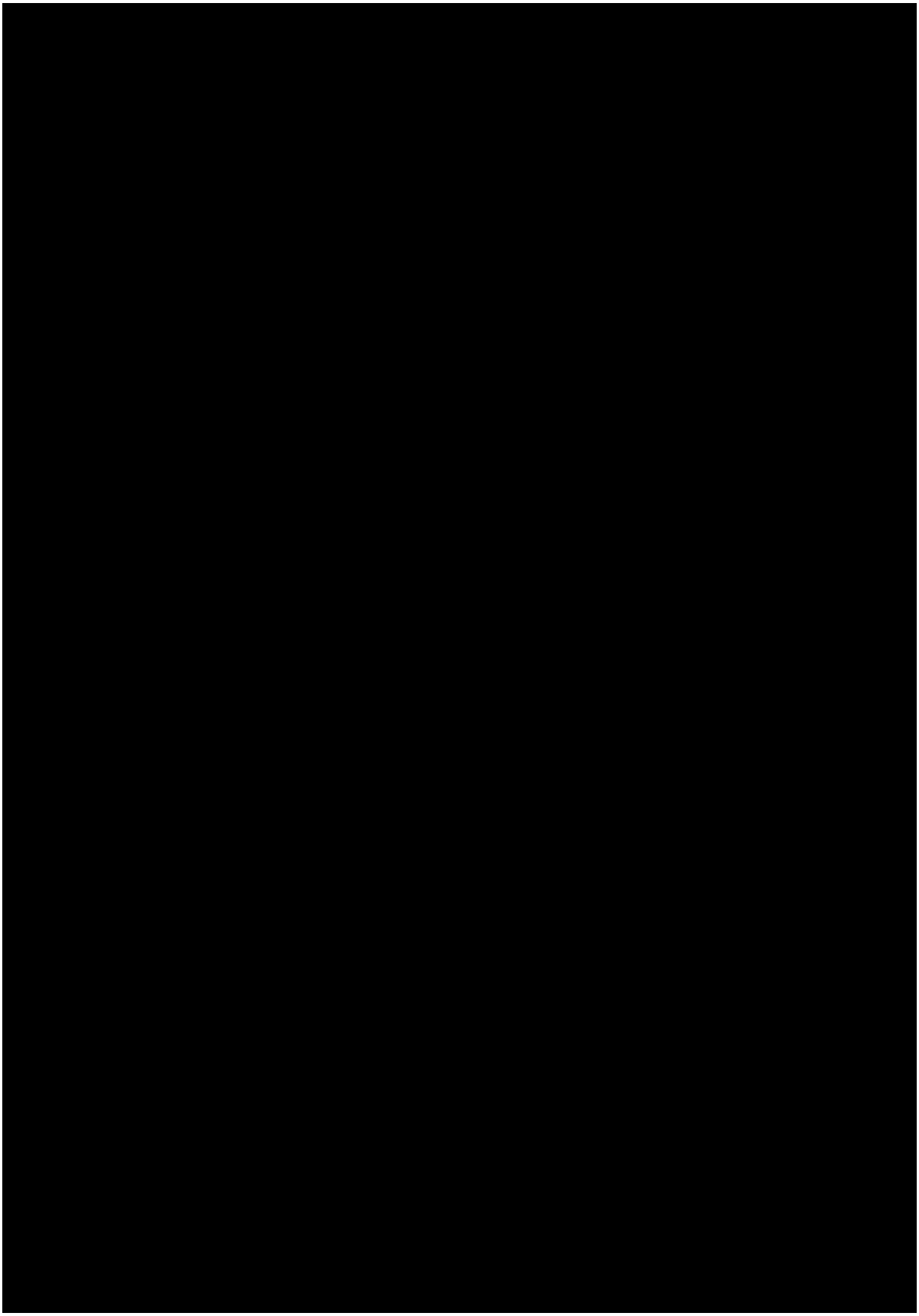
10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visting with friends, relatives, etc.)?

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!



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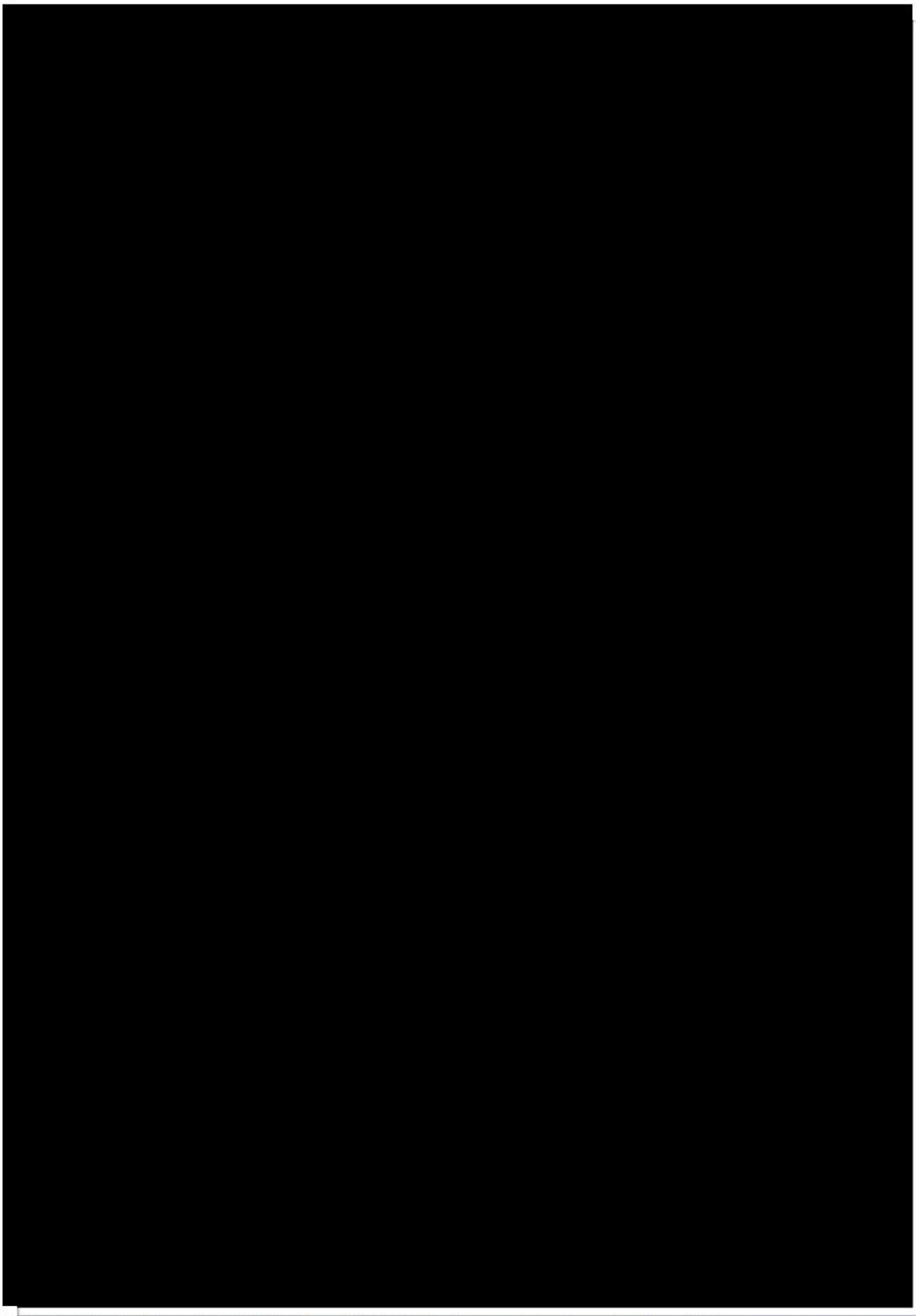

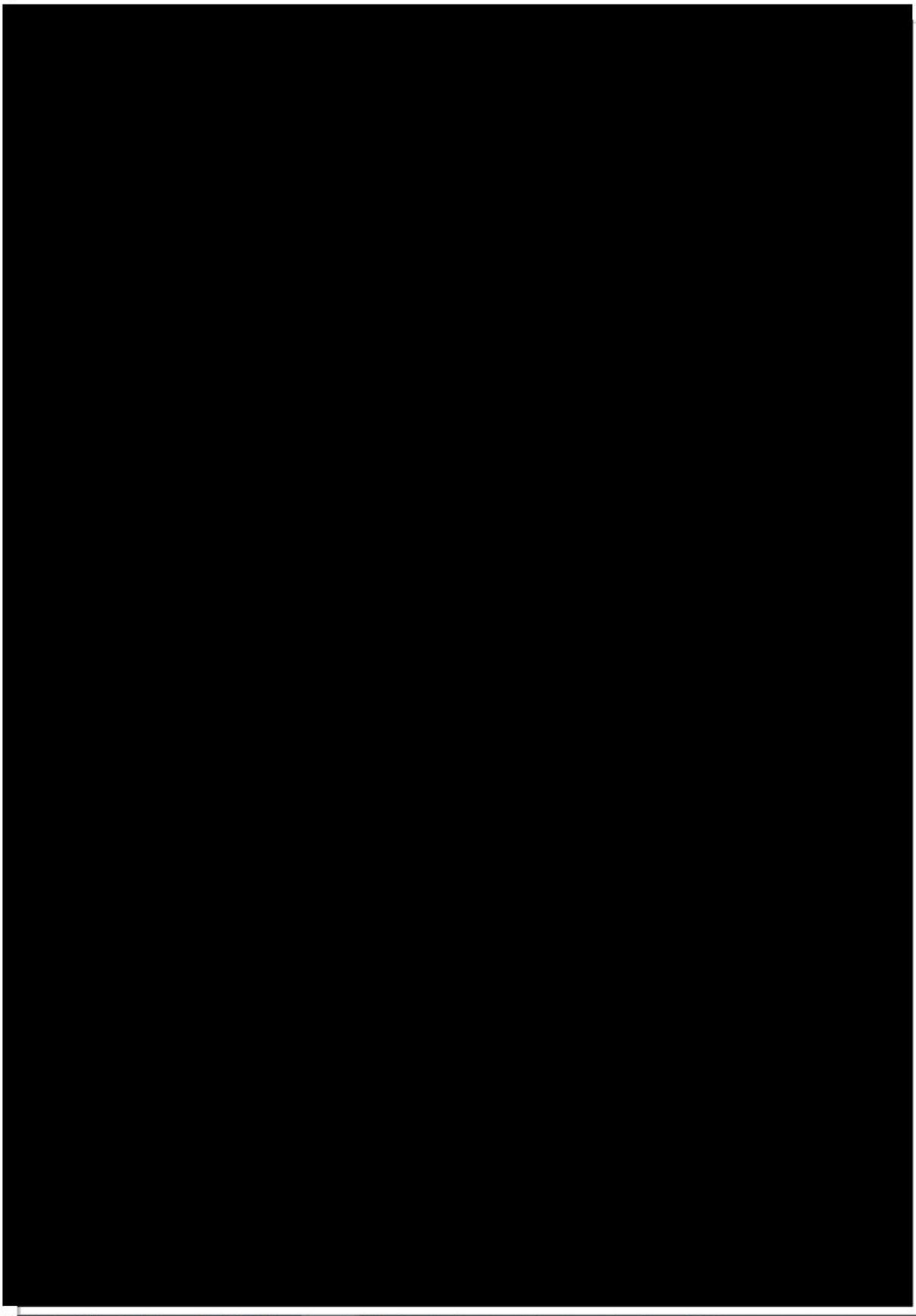

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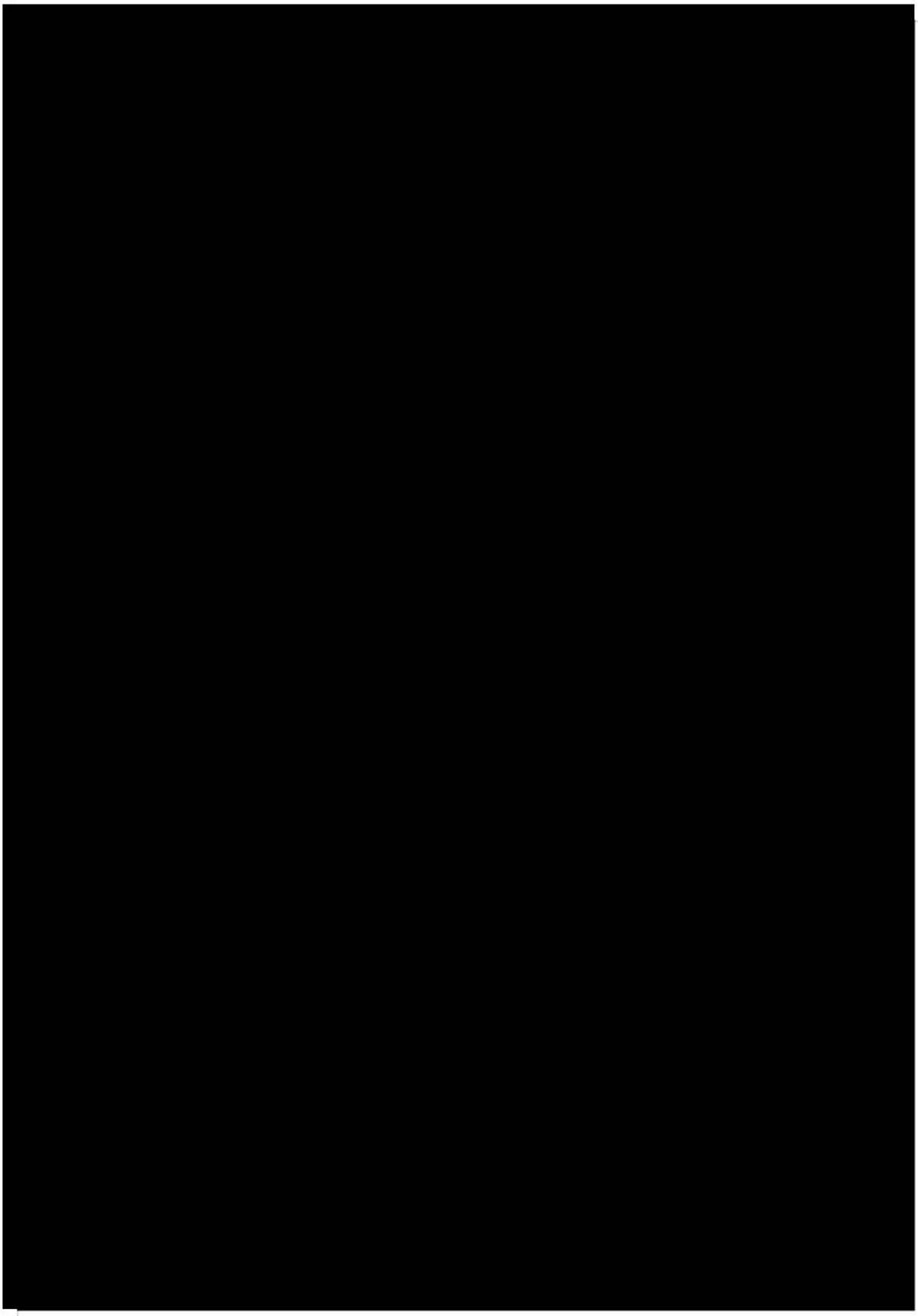

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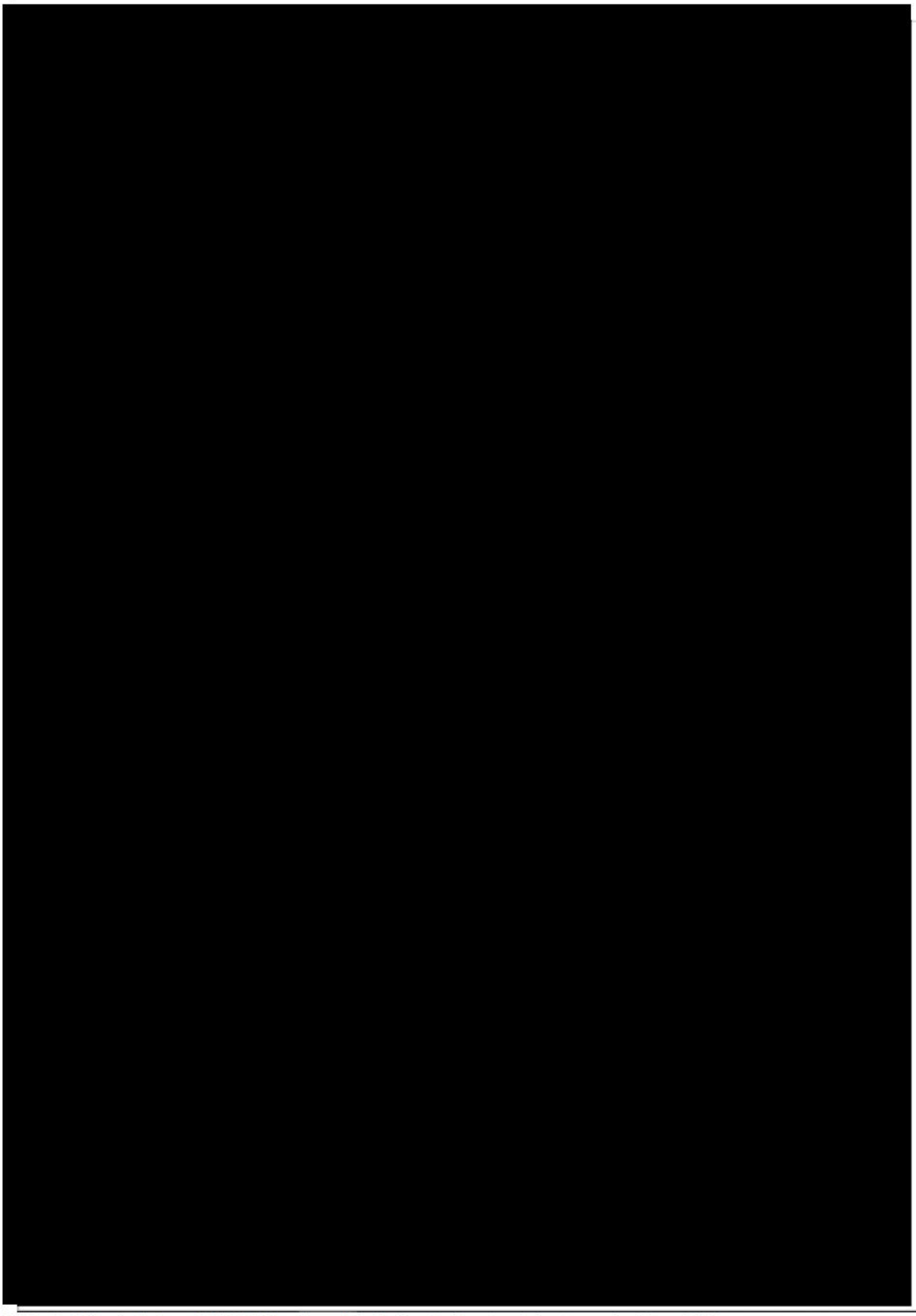

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