

Clinical Development

SB-497115

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**Study 200170: A Rollover Study to Provide Continued Treatment with Eltrombopag**

Authors

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## **Amendment 01**

### **Amendment rationale**

Subsequent to the acquisition of GlaxoSmithKline (GSK) compound **SB-497115**, the purpose of this protocol Amendment **01** is to:

- Delete or replace references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship;
- Make administrative changes to align with Novartis processes and procedures;

As of **05-APR-16**:

**21** patients have received study treatment in **11** countries;

**07** patients have completed or discontinued study treatment.

The changes described in this amended protocol require Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) approval prior to implementation.

A copy of this amended protocol will be sent to the IRB/IEC and Health Authorities (HAs).

The changes herein affect the Informed Consent and all sites are required to update and submit for approval, a revised Informed Consent that takes into account the change of study sponsorship described in the protocol amendment.

Upon approval of this amendment, patients who have already been enrolled in the study will sign a new informed consent form indicating Novartis is the new study sponsor and continue the appropriate visit schedule.

**SPONSOR SIGNATORY:**

[REDACTED]  
[REDACTED], MD

[REDACTED]  
**Date**

[REDACTED]  
Novartis Pharma AG

## SPONSOR INFORMATION PAGE

Clinical Study Identifier: 200170

### Sponsor Contact Information:

Novartis Pharmaceuticals Corporation

In some countries, the clinical trial sponsor may be the local Novartis and its authorized agents. Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

### Sponsor Medical Lead Contact Information:

[REDACTED] MD.  
[REDACTED]

Novartis Pharma AG, Basel

WSJ-340.7.25.41

Phone: [REDACTED]  
Mobile : [REDACTED]  
Email [REDACTED]

### Clinical Trial Head Contact Information:

[REDACTED]  
[REDACTED]  
Novartis Pharmaceutical Corporation  
[REDACTED]  
One Health Plaza, Bldg. 337  
East Hanover, NJ 07936  
Phone: [REDACTED]  
Fax: [REDACTED]  
Email: [REDACTED]

If you have any questions regarding the protocol, please contact your local Novartis office.

**Regulatory Agency Identifying Number(s): IND 63,293; EudraCT number 2013-001371-20**

## INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: \_\_\_\_\_

\_\_\_\_\_  
Investigator Signature

\_\_\_\_\_  
Date

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## LIST OF ABBREVIATIONS

β-hCG	Beta-human chorionic gonadotropin
AE	Adverse Event
AI	Adriamycin (doxorubicin) and ifosfamide
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
ATS	All Treated Subjects
AUC(0-∞)	Area under the plasma concentration-time curve from zero (pre-dose) extrapolated to infinite time
BCRP	Breast cancer resistance protein
°C	Degrees Celsius
CIT	Chemotherapy-induced thrombocytopenia
CLD	Chronic liver disease
Cmax	Maximum plasma concentration
CPK	Creatine phosphokinase
CRO	Clinical Research Organization
CTCAE	Common terminology criteria for adverse events
CV	Cardiovascular
eCRF	Electronic case report form
EU	European Union
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
Gi/L	Giga units per liter
GSK	GlaxoSmithKline
HCV	Hepatitis C virus
HDPE	High density polyethylene
HMG-CoA	3-hydroxy-3-methyl-glutaryl-CoA reductase
HORT	Hematology/oncology related thrombocytopenia
HPLC	High performance liquid chromatography
HRT	Hormone replacement therapy
IB	Investigators brochure
ICH	International conference on harmonisation
IDSL	Integrated data standards library
IEC	Independent ethics committee
INR	International normalised ratio
IRB	Institutional review board
ITP	Idiopathic thrombocytopenic purpura
IVRS	Interactive voice response system
LDH	Lactate dehydrogenase
LSLV	Last subject's last visit
MDS	Myelodysplastic syndrome
MedDRA	Medical dictionary for regulatory authorities

MSDS	Material safety data sheet
NCI	National institutes of health
OATP1B1	Organic anion transporting polypeptide
OS	Overall Survival
PBO	Placebo
PCR	Polymerase chain reaction
PfOS	Powder for oral suspension
PK	Pharmacokinetic
RAP	Reporting and analysis plan
RMP	Risk management plan
RNA	Ribonucleic acid
SAE	Serious adverse event
SOC	Standard of care
SOP	Standard operating procedure
SPM	Study procedures manual
SVR	Sustained virological response
TPO	Thrombopoietin
TPO-R	Thrombopoietin receptor
TRALI	Transfusion-related acute lung injury
ULN	Upper limit of normal
US	United States

## PROTOCOL SUMMARY

### Rationale

Eltrombopag is an orally bioavailable, small molecule, thrombopoietin receptor TPO-R agonist that stimulates platelet production by a mechanism similar, but not identical to endogenous thrombopoietin (TPO). Eltrombopag has been approved in more than 90 countries including the United States (US) and the European Union (EU) for the treatment of chronic idiopathic thrombocytopenic purpura (ITP) and in November 2012 was approved in the US for the treatment of thrombocytopenia in patients with chronic hepatitis C. This Phase IV, multicenter, non-randomized, open-label rollover study will provide continued access to eltrombopag to subjects who are currently participating in a Novartis sponsored investigational study with eltrombopag (i.e. parent study such as TRC114968/ASPIRE or TRA105325/EXTEND), and are receiving clinical benefit without unacceptable toxicity.

### Objective

The objective of this study is to provide continuing treatment with eltrombopag for subjects who are currently participating in a Novartis sponsored investigational study of eltrombopag (parent study) and to collect long term safety data.

### Study Design

This Phase IV, multicenter, non-randomized, open-label, uncontrolled, rollover study is designed to provide continued access to eltrombopag to subjects who are currently participating in a Novartis sponsored investigational study of eltrombopag (**parent study**), and are receiving clinical benefit without unacceptable toxicity. Subjects will be enrolled into the appropriate cohort based upon the disease under study in their parent study (e.g. myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), idiopathic thrombocytopenic purpura (ITP) etc). Enrollment into this study will be dependent upon the investigator's agreement to participate in this study. It is estimated that approximately 100 subjects will be enrolled. Instructions for the dose and dose adjustments throughout the duration of the study are described in Section 5.3 and Section 5.4 respectively. Subjects may continue treatment in this rollover study until they are no longer receiving clinical benefit, develop an unacceptable toxicity, withdraw consent, enroll into another interventional study, or until another mechanism is available for the subject to receive eltrombopag such as compassionate use, named patient program, commercially available for the appropriate indication, etc. Subjects participating in Investigator Sponsored Studies will not be eligible to participate in this study.

### Study Assessments

Safety will be evaluated through physical exams, clinical laboratory tests, and monitoring of adverse events as described in the Time and Events table. Additional safety assessments may be done as per standard of care (SOC) and/or when medically indicated.

Assessment of clinical benefit will be performed throughout the study using local SOC as determined by the investigator. Only subjects considered by the investigator to be receiving clinical benefit and without unacceptable toxicity may continue on study treatment.

## **1. INTRODUCTION**

### **1.1. Background**

Eltrombopag is an orally bioavailable, small molecule, thrombopoietin receptor (TPO-R) agonist. Eltrombopag functions in a similar manner to endogenous thrombopoietin (TPO), inducing proliferation and differentiation of megakaryocytes from bone marrow progenitors cells. Administration of eltrombopag in healthy adult subjects and in thrombocytopenic humans has resulted in a dose-dependent increase in platelet counts. Therefore, eltrombopag may be beneficial in medical disorders associated with thrombocytopenia.

The clinical consequences of thrombocytopenia include petechiae, bruising, and mucosal bleeding. Severe thrombocytopenia may be associated with morbidity and mortality due to bleeding, the most severe of which is intracerebral hemorrhage. Thrombocytopenia is a frequent finding in several medical disorders, including chronic idiopathic thrombocytopenic purpura (ITP), chronic liver disease (CLD), cancer and/or its treatments.

As of May 30 2013, Eltrombopag has been approved in more than 90 countries including the United States (US) and the European Union (EU) for the treatment of chronic ITP. The use of eltrombopag for the treatment of hepatitis C virus (HCV)-related thrombocytopenia has been recently approved in the United States (November 2012).

Eltrombopag is being developed for the treatment of a variety of additional medical disorders associated with thrombocytopenia, including myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) [GlaxoSmithKline Document Number UM2005/00217/08].

The safety profile of eltrombopag has been evaluated in 24 completed, concluded or ongoing Novartis-sponsored clinical studies: eleven studies of subjects with ITP, including 2 in pediatric subjects, 7 studies of subjects with CLD related thrombocytopenia (including 5 studies in HCV related thrombocytopenia), 5 studies for MDS/AML and 1 observational study for evaluation of ocular safety.

Please refer to the current version of the Investigator's Brochure (IB) for further information regarding pre-clinical and clinical studies [GlaxoSmithKline Document Number UM2005/00217/08].

#### **1.1.1. Chronic Idiopathic Thrombocytopenic Purpura Clinical Studies**

The eltrombopag adult ITP clinical program consists of a total of 9 studies. Eltrombopag has a well-defined safety profile with consistent findings across all ITP studies irrespective of treatment duration. Eltrombopag was well-tolerated across the ITP program. In placebo-controlled studies conducted globally, similar overall incidences of adverse events (AE), serious adverse events (SAE), and AEs leading to discontinuation from study medication were seen in the placebo (PBO) arms versus eltrombopag arms.

The ITP clinical studies have consistently demonstrated that eltrombopag raises platelet counts rapidly (within 1-2 weeks) and maintains platelet count elevations during therapy, regardless of splenectomy status, use of baseline concomitant ITP medication or baseline platelet counts. Bleeding symptoms were significantly reduced compared to placebo and during long-term treatment with eltrombopag; subjects were also able to reduce the use of concomitant ITP medications (predominantly corticosteroids) and required less rescue medication compared to placebo-treated subjects.

Eltrombopag is also being evaluated in pediatric patients with chronic ITP in 2 ongoing, double-blind placebo-controlled studies. Refer to Investigator's Brochure for Eltrombopag for available data from the pediatric studies [GlaxoSmithKline Document Number UM2005/00217/08].

### **1.1.2. Hepatitis C-Associated Thrombocytopenia Clinical Studies**

The pooled data from two Phase III studies (TPL103922/ENABLE 1 and TPL108390/ENABLE 2) in subjects with HCV-related thrombocytopenia demonstrates that eltrombopag treatment increased platelet counts in thrombocytopenic subjects with HCV infection to a level sufficient to allow initiation and maintenance of antiviral therapy for subjects who would otherwise be ineligible or poor candidates for peginterferon-based antiviral therapy. Therapy with peginterferon and ribavirin plus eltrombopag enabled 21% of patients to achieve sustained virological response (SVR); 13% of subjects in the control arm (which also included eltrombopag during the open label phase of the study) achieved an SVR. The results were statistically significant [GlaxoSmithKline Document Number UM2005/00217/08].

The AE profile of the eltrombopag treatment arm was consistent with a cirrhotic HCV patient population undergoing interferon-based antiviral therapy. Thromboembolic events and events suggestive of hepatic decompensation occurred more frequently in the eltrombopag arm. Hepatic decompensation is a known complication of interferon based antiviral therapy in patients with advanced fibrosis and cirrhosis.

Please refer to the current version of the Investigator's Brochure (IB) for further information regarding pre-clinical and clinical studies [GlaxoSmithKline Document Number UM2005/00217/08].

### **1.1.3. Hematology/Oncology Related Thrombocytopenia (HORT) Clinical Studies**

The HORT clinical program is investigating eltrombopag to treat thrombocytopenia associated with cancer and/or its treatments and includes chemotherapy-induced thrombocytopenia (CIT) and thrombocytopenia associated with hematologic malignancies. Thrombocytopenia is a significant problem for patients with malignancies and can be life-threatening. The etiology of thrombocytopenia depends on the specific type and location of the malignancy, and may encompass an autoimmune component, the presence of splenomegaly and/or prior and current treatments [GlaxoSmithKline Document Number UM2005/00217/08].

In the completed Phase II study, SB-497115/003, treatment with eltrombopag at 3 different dose levels after carboplatin/paclitaxel did not increase the severity of clinically meaningful side effects compared to treatment with placebo in subjects with cancer. The reported toxicities were consistent with the reported side effect profile of eltrombopag in other studies or the known toxicities of the carboplatin/paclitaxel combination. Eltrombopag 50 mg, 75 mg, and 100 mg, when given for 10 days after chemotherapy, failed to meet the study-defined primary endpoint of change in platelet count in Cycle 2 (measured by the difference in the platelet count from Day 1 in Cycle 2 to platelet nadir in Cycle 2), compared with placebo. However, mean platelet counts in the eltrombopag groups began to rise starting between Day 8 and Day 11, and continued to rise through Day 18 (post-nadir period). This same platelet count rise was not observed in the subjects receiving placebo. These results suggest that the tested schedule of administration (and possibly dose) in this study were likely not optimal for this subject population and chemotherapy regimen [GlaxoSmithKline Document Number UM2005/00217/08].

A completed Phase I (TRC105499) study in subjects receiving adriamycin (doxorubicin) and ifosfamide (AI) treatment for locally advanced soft tissue sarcoma, reported toxicities were consistent with the reported side effect profile of eltrombopag in other studies or the known toxicities of the AI combination [GlaxoSmithKline Document Number UM2005/00217/08].

In a completed Phase I/II study (PMA112509) in subjects with advanced MDS/AML reported AEs were consistent with those expected for the disease under study and with those expected during treatment with eltrombopag. No significant differences in post-baseline bone marrow blast percentages were observed for eltrombopag compared to placebo-treated subjects [GlaxoSmithKline Document Number UM2005/00217/08]. Platelet transfusion independence for  $\geq 8$  weeks was reported for 38% of eltrombopag and 21% of placebo subjects. Grade 3 or greater hemorrhages were reported in 16% of eltrombopag subjects compared to 26% of placebo subjects. More eltrombopag subjects started antileukemic/palliative treatment during the study (41%) compared to placebo subjects (32%). Median overall survival OS was 27 weeks for eltrombopag versus 15.7 weeks for PBO (hazard ratio=0.71,  $P=0.1931$ ).

TRC114968/ASPIRE study is a three-part (Part 1: open-label, Part 2: randomized, double-blind, Part 3: open-label extension), multi-center study to evaluate the effect of eltrombopag in subjects with MDS or AML who have thrombocytopenia due to bone marrow insufficiency from their underlying disease or prior chemotherapy. The starting dose was 100 mg (50 mg for East Asians), with a maximum dose of 300 mg (150 mg for East Asians). Subject who enrolled in Part 1 received open-label eltrombopag while those who enrolled in Part 2 received either eltrombopag or matching placebo. After completing Part 1 or 2, subjects could receive open-label eltrombopag in Part 3 (open-label extension). The planned number of subjects for this study is 150.

## **1.2. Study Rationale**

This study will provide continued access of eltrombopag to subjects who are currently participating in a Novartis sponsored investigational study with eltrombopag (parent



study such as TRC114968/ASPIRE or TRA105325/EXTEND), and are receiving clinical benefit without unacceptable toxicity.

### **1.3. Benefit:Risk Assessment**

In chronic ITP, HCV associated thrombocytopenia, and hematology/oncology related thrombocytopenia studies so far, eltrombopag has been able to increase platelet counts with an acceptable safety profile. In the setting of procedures for liver disease (HCV studies), an imbalance in thromboembolic events was observed. Therefore, with the exception of procedures for liver disease, the benefit:risk of eltrombopag in the other studied disease areas so far remain positive. Summaries of findings from both clinical and non-clinical studies conducted with SB-497115 can be found in the GlaxoSmithKline IB and product label. The following sections outline the risk assessment and mitigation strategy for this protocol.

#### **1.3.1. Chronic Idiopathic Thrombocytopenic Purpura**

The safety profile of eltrombopag has been well documented in the approved indication of chronic idiopathic thrombocytopenic purpura (ITP) to increase platelet counts and reduce or prevent bleeding. Eltrombopag has a well-defined safety profile with consistent findings across all ITP studies irrespective of treatment duration. Eltrombopag was well-tolerated across the ITP program. In placebo-controlled studies conducted globally, similar overall incidences of AEs, SAEs, and AEs leading to discontinuation from study medication were seen in the placebo (PBO) arms versus eltrombopag arms.

The ITP clinical studies have consistently demonstrated that eltrombopag raises platelet counts rapidly (within 1-2 weeks) and maintains platelet count elevations during therapy, regardless of splenectomy status, use of baseline concomitant ITP medication or baseline platelet counts.

#### **1.3.2. Hepatitis C virus-related thrombocytopenia**

The use of eltrombopag for the treatment of hepatitis C virus (HCV) related thrombocytopenia has been recently approved in the United States (November 2012), and is still under regulatory review in the European Union.

The pooled data from two Phase III studies (TPL103922/ENABLE 1 and TPL108390/ENABLE 2) in subjects with HCV-related thrombocytopenia demonstrates that eltrombopag treatment increased platelet counts in thrombocytopenic subjects with HCV infection to a level sufficient to allow initiation and maintenance of antiviral therapy for subjects who would otherwise be ineligible or poor candidates for peginterferon-based antiviral therapy.

The AE profile of the eltrombopag-containing treatment arm was consistent with a cirrhotic HCV patient population undergoing interferon-based antiviral therapy. Thromboembolic events and events suggestive of hepatic decompensation occurred more frequently in the eltrombopag arm. Hepatic decompensation is a known complication of interferon based antiviral therapy in subjects with advanced fibrosis and cirrhosis.

### **1.3.3. Hematology/Oncology Related Thrombocytopenia (HORT) Clinical Studies**

In the HORT clinical program, eltrombopag continues to be developed as a treatment of thrombocytopenia associated with cancer and/or its treatments, including chemotherapy-induced thrombocytopenia (CIT) and thrombocytopenia associated with hematologic malignancies. The studies are ongoing and eltrombopag has been well tolerated in the HORT indication to date.

### **1.3.4. Post Marketing**

Eltrombopag was first approved for marketing in the US on 20 November 2008 for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura and is currently available in 90 countries.

The data reported in the post marketing setting are consistent with the known safety profile of eltrombopag. Overall, there was no change in the nature, seriousness or frequency of reported events, based on the post marketing data. The benefit risk profile of eltrombopag for the treatment of chronic ITP continues to be favorable in the post marketing setting.

### **1.3.5. Risk Management**

Risk management strategies for eltrombopag are in place for patient safety.

Novartis has a robust risk management plan (RMP) for eltrombopag where the presentation and management of risks are conveyed. Safety data continue to be collected and analyzed for eltrombopag since the initial approval of PROMACTA™ (eltrombopag) in the United States in 2008 and the subsequent approval of REVOLADE™ (eltrombopag) in the EU in 2010.

A comprehensive Risk Management Plan (RMP) is in place for eltrombopag. Identified risks described in the RMP include hepatobiliary laboratory abnormalities, thromboembolic events, post therapy reoccurrence of thrombocytopenia, and hepatic decompensation in patients with hepatitis C. Potential risks in the RMP include increased bone marrow reticulin formation, cataract, renal tubular toxicity, and photosensitivity.

#### **1.3.5.1. Pharmacovigilance Activities**

Pharmacovigilance measures are in place and include adverse event collection from spontaneous, study, and literature sources, review of individual and aggregate reports, and ongoing signal management including signal detection and evaluation. Additional pharmacovigilance activities include targeted follow-up questionnaires for specific risks. In addition, the safety data from any ongoing and completed study will be reviewed. Any new safety findings discovered from any of these sources will be communicated in a timely fashion.

### **1.3.5.2. Risk Minimization**

Risk minimization activities are based on the communication of benefit risk information to physicians and patients, with the prescribing information as the main tool.

Additionally, there are targeted educational materials for physicians with an emphasis on the benefits and risks associated with the use of eltrombopag. The educational materials are updated as necessary to communicate the benefits and risks.

### **1.3.6. Conclusion**

Eltrombopag has been generally well tolerated in chronic ITP and HCV associated thrombocytopenia, in clinical studies for other indications under development, and in the post marketing setting.

The benefit risk profile of eltrombopag for the treatment of patients with chronic ITP and HCV associated thrombocytopenia to increase platelet counts and reduce or prevent bleeding or help achieve sustained viral response continues to be favorable. Additionally the benefit risk profile of eltrombopag for treatment in other indications under development, and in the post marketing setting continues to be favorable.

## **2. OBJECTIVE**

The objective of this study is to provide continuing treatment with eltrombopag for subjects who are currently participating in a Novartis sponsored investigational study of eltrombopag (parent study) and to collect long term safety data.

## **3. STUDY DESIGN**

This Phase IV, multicenter, non-randomized, open-label, uncontrolled, rollover study is designed to provide continued access to eltrombopag to eligible subjects. Enrollment into this study will be dependent upon the mutual agreement between Novartis and a site to participate in this study.

Subjects must provide written informed consent prior to any study-related assessment or procedure being performed or treatment with eltrombopag for this study. After informed consent is obtained, subjects must meet the eligibility criteria for this study in order to participate.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in each Cohort section and the Time and Events Table [Appendix 1] are essential and required for study conduct.

The study will consist of a Transition Visit, Study Treatment Visits, and a Follow-Up Visit.

Safety will be evaluated through physical exams, clinical laboratory tests, and monitoring of adverse events as described in the Time and Events Table [Appendix 1] Additional safety assessments may be done as per standard of care (SOC) and or when medically indicated.

Assessment of clinical benefit will be performed throughout the study using local SOC as determined by the investigator to determine continued study participation and treatment with eltrombopag. Only subjects considered by the investigator to be receiving clinical benefit without unacceptable toxicity may continue on study treatment.

Subjects will receive a starting dose of eltrombopag at the same dose and administration that they were receiving at the time of their last study treatment visit in the parent study. Instructions for dose adjustments can be found in Section 5.4. Subjects may continue treatment in this rollover study until they are no longer receiving clinical benefit, develop an unacceptable toxicity, withdraw consent, enroll into another interventional study, or until another mechanism is available for the subject to receive eltrombopag such as compassionate use, named patient program, commercially available for the appropriate indication, etc. The duration of the study will be dependent on the length of time the subjects do not meet the protocol stopping criteria, but the study will end in 2023.

Refer to the Time and Events Table [Appendix 1] for timing of all assessments.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

### 3.1. Discussion of Design

The purpose of this study is to allow for continued treatment with eltrombopag in subjects who have participated in a Novartis sponsored investigational study with eltrombopag and met the protocol requirements for transitioning to the rollover study. Subjects participating in Investigator Sponsored Studies will not be eligible to participate in this study. Subjects will be closely monitored for stopping criteria. Subjects will follow the appropriate cohort (Section 3.2) based upon the indication and population of the parent study. The schedule of assessments and procedures to be performed during this study is provided in the Time and Events Table (Appendix 1). Subjects will continue to receive SOC therapies unless otherwise stated in the protocol.

The end of study is defined as the last subject, last visit.

The eltrombopag dose allowed in this study will be individualized based upon the dose/regimen received in the parent study at the time of transition to the rollover study. Optimal dosing of eltrombopag is based on platelet count in individual subjects.

Treatment with eltrombopag may enable subjects to initiate and maintain the dose and schedule of disease-modifying therapy. Disease modifying treatments (e.g. chemotherapy, azacitidine, decitabine and lenalidomide) will be allowed. Supportive SOC will be allowed as indicated by local practice throughout the study.

All subjects will receive eltrombopag at the dose that they were receiving at the time of the Transition Visit, except in the case where the subject required a dose modification in the parent study. If the dose was modified at the last study visit in the parent study, the subject will enter the rollover study and continue treatment on the modified dose, and the visit schedule at entry into the rollover study may be weekly to enable proper monitoring following the adjusted dose (Figure 1). However, if during the rollover study the investigator considers it appropriate to modify the dose of eltrombopag, the dose may be modified as needed based on guidelines in Section 5.4. **Dosage must never exceed the maximum dose allowed by the parent study.**

Each subject's visit schedule may begin at any point of the visit schedule in Figure 1 depending on the stability of their dose. Any time a change in dose is required, the subjects must return for weekly visits and progress through the visit schedule as detailed below.

### 3.2. Cohorts

#### 3.2.1. Cohort A (MDS/AML Adult Subjects)

Cohort A will consist of adult subjects who have completed study treatment with eltrombopag during their participation in a parent study for MDS/AML (i.e. TRC114968/ASPIRE).

#### 3.2.2. Cohort B (ITP Adult Subjects)

Cohort B will consist of adult subjects who have completed study treatment with eltrombopag during their participation in a parent study for ITP (i.e. TRA105325/EXTEND).

#### 3.2.3. Cohort C (ITP Pediatric Subjects)

Cohort C will consist of pediatric subjects who have completed study treatment with eltrombopag during their participation in a parent study for ITP. Once a subject turns 18 years of age, they may remain in the study and follow the Cohort B guidelines.

#### 3.2.4. Visit Schedule for Cohort A, Cohort B, and Cohort C

**Figure 1 Visit Schedule**



1. For Cohort B and Cohort C, more frequent visits may be required (Section 5.4.2.3.)

Subjects in **Cohort A, Cohort B and Cohort C** will complete the Transition Visit assessments (Section 8.1.) and then return for their next scheduled visit in 2 weeks, or

sooner if the visit schedule in the parent study had been more frequent than every two weeks (e.g. weekly schedule). Subjects who have been on a stable dose of eltrombopag for the previous 2 every two week visits may decrease the frequency of visits to once monthly visits. Subjects who are stable on a monthly dose for the previous 3 monthly visits may decrease the frequency of visits to once every 2 months. If any change in the study treatment dose is required, the schedule of visits must begin again with weekly visits for at least 4 weeks, followed by biweekly, then monthly and then bimonthly visits (See schematic in Figure 1).

Once treatment with eltrombopag is permanently discontinued, the subject will attend the follow up visit as per Appendix 1. If there are any uncertainties about the dose(s) of study treatment(s) to be administered or the visit schedule, the Novartis Medical Lead should be consulted.

## **4. SUBJECT SELECTION AND DISCONTINUATION/ COMPLETION CRITERIA**

### **4.1. Subject Selection Criteria**

#### **4.1.1. Number of Subjects**

Approximately 100 subjects will be transitioned to this study from other eltrombopag studies.

#### **4.1.2. Inclusion Criteria**

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on eltrombopag or other approved agent(s) that may impact subject eligibility is provided in the Investigators Brochure (IB) for eltrombopag [GlaxoSmithKline Document Number UM2005/00217/08].

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. Written informed consent has been obtained from the subject (or subject's legally acceptable representative) prior to performance of any study-specific procedure.
2. The subject is participating in a Novartis sponsored investigational study of eltrombopag (parent study) within the past 28 days and is receiving clinical benefit without unacceptable toxicity as determined by the investigator.
3. Subjects with a QTc <450msec or <480msec for subjects with bundle branch block

The QTc is the QT interval corrected for heart rate according to either Bazett's formula (QTcB), Fridericia's formula (QTcF) or another method, machine or manual overread.

For subject eligibility and withdrawal QTcF will be used.

For purposes of data analysis, QTcF will be used.

The QTc should be based on single or averaged QTc values of triplicate electrocardiograms (ECGs) obtained over a brief recording period.

4. Women must be either of non-child bearing potential (see Section 8.4.8.1, for definition) or women with child-bearing potential and men with reproductive potential must be willing to practice acceptable methods of birth control during the study (See Section 8.4.8.1 for acceptable methods of birth control).
5. Women of childbearing potential must have a negative serum pregnancy test within 14 days of the first dose of study treatment and agree to use effective contraception, as defined in Section 8.4.8.1 during the study and for 4 weeks following the last dose of study treatment.
6. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception as described in Section 6.1 from time of first dose until 16 weeks after the last dose of study treatment.
7. In France, a subject will be eligible for inclusion in this study only if either affiliated to, or a beneficiary of, a social security category.

#### **4.1.3. Exclusion Criteria**

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Permanent discontinuation of eltrombopag in the parent study based upon the study treatment discontinuation or study withdrawal criteria from the parent study. Subjects who permanently discontinued treatment because they completed all study related treatments remain eligible.
2. The subject is pregnant or a lactating female.
3. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions at the time of transition to this study that could interfere with subject's safety, obtaining informed consent or compliance with the study procedures, in the opinion of the investigator or Novartis Medical Lead.
4. **French subjects:** the French subject has participated in any study using an investigational drug during the previous 30 days, with the exception of eltrombopag, in the parent study.



## 4.2. Permanent Discontinuation from Study Treatment and Subject Completion Criteria

### 4.2.1. Permanent Discontinuation from Study Treatment

Subjects will receive study treatment until **no longer receiving clinical benefit as determined by the investigator**, death, or unacceptable adverse event, including meeting stopping criteria for liver chemistry defined in Section 5.10.1. In addition, study treatment must be permanently discontinued for any of the following reasons:

- Subject has taken or plans to take any other investigational product(s) during the study
- Subject becomes pregnant
- Significant deviation from the protocol
- Investigator's discretion
- Request of the subject or proxy (withdrawal of consent by the subject)
- Subject has an adverse experience that would, in the investigator's or Sponsor's judgment, make continued participation in the study an unacceptable risk
- Subject meets any of the liver chemistry threshold criteria (Section 5.10.2.)
- Another mechanism is available for the patient to receive eltrombopag such as eltrombopag receives regulatory approval and is commercially available and a reimbursement decision has been made in the patient's country, compassionate use, or a named patient program
- Subject is lost to follow-up
- Study is closed or terminated
- Subject has a QTc  $\geq 500$  msec (if baseline  $< 450$  msec), or QTc  $> 530$  msec (if baseline QTc 450-480 msec) or uncorrected QT  $> 600$  msec

The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and electronic case report form (eCRF).

If the subject voluntarily discontinues from treatment due to toxicity, 'adverse event' will be recorded as the primary reason for permanent discontinuation on the CRF.

Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be retreated.

Investigators will make an attempt to contact those patients who do not return for scheduled visits (e.g. by phone contact or certified letters).

All subjects who discontinue from study treatment will have safety assessments at the time of discontinuation and during post study treatment follow-up as specified in Time and Events Table [Appendix 1] and Section 8.3.

#### **4.2.2. Subject Completion**

A subject will be considered to have completed the study when the subject has completed all study related procedures or dies or withdraws consent. Subjects will continue to be enrolled in this study and receive study treatment until the subject qualifies for Permanent Discontinuation for Study Treatment (See Section 4.2.1).

The cause of death must be documented in the eCRF. A subject will be considered to have withdrawn from the study if the subject has not died and is lost to follow-up, has withdrawn consent, or if the study is closed/terminated.

### **5. STUDY TREATMENTS**

The term ‘study treatment’ is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments. However, for the purpose of this study investigational product will only refer to eltrombopag.

#### **5.1. Eltrombopag (SB-497115) Novartis Investigational Product**

Eltrombopag will be provided to sites by Novartis.

Based upon the supply of eltrombopag used in the parent study, subjects may be dosed with eltrombopag tablets or powder for oral suspension (PfOS). Subjects who had received eltrombopag powder for oral suspension in the parent study may switch to tablets in the rollover study if relevant criteria are met based upon the parent study (e.g., are age-appropriate to receive tablets). If there is a switch from oral suspension to tablets, the doses should take into account the differences in bioavailability between formulations. In a relative bioavailability study conducted under fasted conditions in healthy adult subjects, the eltrombopag PfOS formulation delivered 22% higher plasma eltrombopag AUC(0-∞) and 30% higher C<sub>max</sub> compared to the tablet formulation.

##### **Eltrombopag Tablets**

Eltrombopag tablets will be white, round film coated tablets containing eltrombopag olamine equivalent to 12.5 mg, 25 mg, 50 mg, 75 mg and 100 mg of eltrombopag. The 12.5 mg tablet will be smaller than the 25 mg, 50 mg, 75 mg and 100 mg tablets.

Tablets will be packaged in white high density polyethylene (HDPE) bottles with white plastic, induction-seal child-resistant caps. Each bottle will contain 35 tablets. The contents of the label will be in accordance with all applicable regulatory requirements.

##### **Eltrombopag Powder for Oral Suspension**

Eltrombopag powder for oral suspension (Eltrombopag PfOS) is a reddish-brown to yellow powder contained inside an elongated sachet. Each sachet will contain eltrombopag olamine equivalent to 20 mg of eltrombopag per gram of powder.

PfOS sachets will be packaged in a carton. Each carton pack will hold 35 sachets along with a plastic reconstitution container and a syringe-adapt cap. The pack will also contain an extra syringe-adapt cap as a spare. The clinical site will provide a 10cc syringe with each carton.

The sachet should not be opened until ready to use. Add 9.5 mL of water drawn using a 10cc syringe into the provided plastic container. Cut open the sachet and add the entire content of the sachet into the container with water. The container is capped and shaken for 10-20 seconds. The resulting suspension contains 2 mg/mL of eltrombopag dose. The prescribed volume (dose) is drawn through the syringe port on the cap with a syringe. Upon dosing, the rest of the remaining suspension in the container is discarded. The container and the syringe are rinsed with water and dried.

If the prescribed dose is > 24 mg, which will require that part or all of a second sachet be used, then the suspension can be prepared by adding the contents of the two sachets to 19.0 mL of water, and then following the steps outlined above. The water has to be drawn by using the 10cc syringe twice, and similarly dosing has to occur by using the same 10cc syringe twice.

A fresh dose is prepared everyday just prior to the dosing and no storage of the reconstituted suspension is allowed. Eltrombopag will be provided to sites by Novartis. The contents of the label will be in accordance with all applicable regulatory requirements.

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from Novartis upon request.

## **5.2. Eltrombopag Dosage and Administration**

Site personnel will instruct the subjects (and their parents/guardians if applicable) on how to take their medication. Every effort should be made to encourage subject compliance with the dosage regimen as per protocol.

Study treatment will be dispensed in either bottles containing 35 tablets each, or packs containing 35 unit-dose sachets each. Additional tablets or packs of sachets will be dispensed when the site personnel determine the current supply will not be sufficient until the next study visit.

Study treatment compliance will be assessed as described in Section 5.9. For subjects who receive PfOS, study treatment compliance will be assessed at each visit as described in Section 5.9. All subjects/parents/guardians should be instructed to bring all bottles or sachets with any unused drug to each visit with the investigator.

### 5.2.1. Dietary Restrictions

Eltrombopag should be taken at least four hours before or after any products such as antacids, dairy products, or mineral supplements containing polyvalent cations (e.g. aluminium, calcium (see below), iron, magnesium, selenium and zinc).

Eltrombopag may be taken either on an empty stomach (1 hour before or 2 hours after a meal) or with food containing little (< 50 mg) or preferably no calcium or dairy products

Administration of eltrombopag with a polyvalent cation-containing antacid decreased plasma eltrombopag exposure by 70%, and a similar reduction was observed when eltrombopag was administered with a high-calcium meal [GlaxoSmithKline Document Number UM2005/00217/08]. Therefore, every effort must be made to educate subjects on how to take study medication with medications or foods containing these polyvalent cations. Details of these and all concomitant medications should be recorded in the eCRF.

### 5.3. Eltrombopag Starting Dose

All subjects will receive eltrombopag at the dose that they were receiving at the time of the Transition Visit, except in the case where the subject required a dose modification in the parent study or unless adjustments are warranted according to the dosing guidelines.

### 5.4. Dose Adjustments

Each subject's dose of study treatment will be adjusted as needed following the provided dosing guidelines and based upon their individual platelet response.

The investigator may also make dose adjustments based on safety assessments (e.g. for adverse event or other safety assessments, provided the discontinuation criteria are not met (see Section 5.4.1)). **Dosage must never exceed the maximum dose allowed by the parent study.**

Instructions for dose adjustments throughout the duration of the study are described in Table 1, Table 2, Table 3, and Table 4.

#### 5.4.1. Cohort A (MDS/AML Adult Subjects)

The range of doses of eltrombopag that will be used in this cohort are 50 mg to 300 mg once daily for subjects of non- East Asian heritage. The dose ranges for subjects of East Asian heritage (i.e. Japanese, Chinese, Taiwanese, Thai and Korean) will be 25 mg to 150 mg.

The dose of eltrombopag can be increased every 2 weeks by 100 mg (50 mg for subjects of East Asian heritage) until maximum 300 mg per day (150 mg for subjects of East Asian heritage). Dose adjustments will be dependent on each subject's platelet counts; adjusted to maintain platelet counts  $\geq 100$  Gi/L, and dose reduced for platelet counts  $>400$  Gi/L.

If dose increases or decreases are required based upon the dose adjustment guidelines in Table 1, subjects must return the previous bottle(s) and may be dispensed new bottles containing 35 tablets each. Site personnel will instruct subjects on any modified dosing instructions (i.e. take 2 or 3 tablets per day based on required dose) based upon dose adjustment guidelines below.

The maximum dose will be 300 mg once daily (150 mg daily for subjects of East Asian heritage) and must never exceed the maximum dose allowed by the parent study.

Subsequent dose adjustments will be based upon platelet counts and safety. If dose increases or decreases are required based upon platelet counts, site personnel will instruct subjects on modified dosing instructions based upon the guidelines in Table 1.

#### **5.4.1.1. Dose Escalation**

Intra-individual dose adjustments will be made in a stepwise fashion, by sequentially increasing from 50 mg to the 100 mg to the 200 mg and 300 mg eltrombopag dose levels as needed depending upon platelet counts (dose levels will be reduced by 50% for subjects of East Asian heritage i.e., 25 mg, 50 mg, 100 mg and 150 mg, respectively).

Subsequent dose adjustments will be based upon platelet counts and safety (Table 1). If dose increases or decreases are required based upon platelet counts, site personnel will instruct subjects on modified dosing instructions based upon the guidelines in Section 5.4.1.

#### **5.4.1.2. Dose Reduction**

Subjects whose platelet count exceeds 400 Gi/L at any point during the treatment period must decrease the dosage of study medication. Temporary dose reduction of study medication may also be made by the investigator (i.e. to allow for recovery of AEs) as per Table 1 and Section 5.4.1.3.

If a subject's platelet count increases significantly and if the investigator thinks a dose reduction is medically appropriate, the dose can be decreased even if the platelet count is below 200 Gi/L or a dose modification was done less than 2 weeks before.

#### **5.4.1.3. Dose Interruption**

Temporary interruptions of study medication may be made by the investigator (e.g. to allow for recovery of AEs).

Refer to Section 4.2.1 for criteria for permanent discontinuation of study medication.

**Table 1 Dose Adjustment Guidelines for Adult MDS/AML Patients <sup>a</sup>**

<b>Platelet counts &lt;100 Gi/L</b>	<b>Increase daily dose to the next dose level.<sup>b</sup></b> Wait for 2 weeks to see the effect of the dose increase on platelet counts before another dose increase is considered.
<b>Platelet counts 100-400 Gi/L</b>	<b>Maintain dose.</b>
<b>Platelet counts &gt;400 Gi/L</b>	<b>Decrease daily dose.<sup>b</sup></b> If platelet counts remain >400 Gi/L, wait for 2 weeks to see the effect of the dose decrease on platelet counts before another dose decrease is considered.

**Subjects who have disease progression and also experience clinical benefit will be allowed to continue treatment with study medication, provided that in the investigator judgement the benefit-risk ratio of continuing treatment with study medication is favorable. Given that blasts can be leukemic or benign, blasts counts alone must not be the sole indicator of disease progression: rather, the totality of the available data must be considered when determining whether subjects are receiving clinical benefit or not.**

- a. After any dose adjustment, monitor platelet counts at least weekly for 4 weeks. The investigator may also make dose adjustments based on safety assessments (e.g. for adverse event or other safety assessments, provided the discontinuation criteria are not met [see Section 4.2]). Use the dose levels outlined in Section 5.4.1.1. and in Section 5.4.1.2. for dose adjustments. Investigators may use their clinical judgment in modifying the schedule of eltrombopag if used as monotherapy or in combination with chemotherapy or disease modifying therapies to treat underlying MDS or AML.
- b. See Section 5.4.1. for dose escalation or reduction for further details.

#### **5.4.2. Cohort B and Cohort C (ITP Adults and Pediatric Subjects)**

Dose adjustments will be made as needed following the provided dosing guidelines for tablet formulation (Table 2 or Table 3) or suspension formulation (Table 4) and based upon each subject's individual platelet response. The target platelet count range for ITP patients is between 50 Gi/L and 200 Gi/L.

Investigators are expected to use their clinical judgment and knowledge about each subject's individual disease characteristics (including platelet count fluctuation and response to prior doses) for any dose adjustment.

The investigator should take into account any changes in concomitant ITP medications that could affect the platelet count when modifying the dose of eltrombopag.

If a subject has a platelet count that would require changing the dose to a dose that was previously proven to achieve platelet counts outside of the target range (<50 Gi/L or >200 Gi/L), alternating doses of different strength tablets or changes in frequency may be considered.

If a subject's platelet count increases significantly and if the investigator thinks a dose reduction is medically appropriate, the dose can be decreased even if the platelet count is below 200 Gi/L or a dose modification was done less than 2 weeks before.

If after an interruption the subject's platelet count decreases drastically and if the investigator thinks re-initiation is medically appropriate, the dose can be reinitiated at the next lower dose level even if the platelet count has not yet decreased to below 150 Gi/L.

If a subject's platelet count decreases drastically and the investigator thinks a dose increase is medically appropriate, the dose can be increased even if the platelet count is more than 50 Gi/L.

If dose increases or decreases are required based upon platelet counts, site personnel will instruct subjects on modified dosing instructions based upon the guidelines in Table 2 or Table 3. If dose adjustments are required based upon the dose adjustment guidelines, subjects must return the previous bottle(s) and may be dispensed new bottles containing 35 tablets each, or new cartons containing 35 sachets each.

The maximum dose for ITP subjects will be 75 mg once daily and must never exceed the maximum dose allowed by the parent study.

##### **5.4.2.1. Dose Escalation**

The dose of eltrombopag will be increased in a stepwise fashion, by sequentially increasing to the next dose level, until the target platelet count or the maximum allowed dose is achieved (Table 2, Table 3 or Table 4). After increasing the dose of eltrombopag, investigators must wait at least 2 weeks before increasing the dose again.

If a subject has a platelet count  $<50$  Gi/L and requires a dose increase, and the next higher dose has already proven to be associated with platelet counts  $>200$  Gi/L, then intermediate or alternating doses may be used.

#### **5.4.2.2. Dose Reduction**

If the platelet count exceeds 200 Gi/L, the dose of eltrombopag will be decreased as outlined in Table 2, Table 3 or Table 4.

If a subject requires a dose lower than the available tablet strengths or between 2 available tablet strengths, alternate dosing regimens that modify the frequency of administration may be used.

#### **5.4.2.3. Dose Interruption**

If the platelet count exceeds 400 Gi/L, the dose of eltrombopag will be interrupted until the platelet count  $< 150$  Gi/L. At that point, eltrombopag will be reinitiated at the next lower dose or frequency.

If the platelet count is still above 150 Gi/L within one week after study treatment interruption, the platelet count needs to be monitored 3-4 days later, and twice a week until the platelet count is  $\leq 150$  Gi/L. Once the subject's platelet count is  $\leq 150$  Gi/L, study treatment should be started at the next lower dose or frequency.



#### 5.4.2.4. Dose Adjustment Guidelines for Tablet Formulation

**Table 2 Dose Adjustment Guidelines for Adult ITP Patients**

Platelet count	Dose	Dose adjustment
<50 Gi/L <sup>2</sup>	12.5 mg	Increase to 25 mg
	25 mg	Increase to 50 mg
	50 mg	Increase to 75 mg
	75 mg	Maintain 75 mg dose <sup>1</sup>
50 – 200 Gi/L	Maintain current dose	
200 – 400 Gi/L <sup>2,3</sup>	12.5 mg	Decrease to 12.5 mg every other day
	25 mg	Decrease to 12.5 mg
	50 mg	Decrease to 25 mg
	75 mg	Decrease to 50 mg
>400 Gi/L Interrupt study treatment until platelets < 150 Gi/L <sup>2,4</sup>	12.5 mg	After interruption reinitiate at a reduced frequency, 12.5 mg every other day
	25 mg	After interruption, reinitiate at 12.5 mg
	50 mg	After interruption, reinitiate at 25 mg
	75 mg	After interruption, reinitiate at 50 mg

1. If a subject has reached the maximum allowed dose and has platelet counts < 50 Gi/L, the investigator (or designee) may choose to have the subject continue in the trial if clinical benefit is documented in terms of improved platelet counts OR reduced bleeding symptoms.
2. If a subject requires a dose adjustment, and the next available dose has already proven to be associated with platelet counts outside of the target range (i.e., <50 Gi/L or >200 Gi/L), then alternating doses may be used.
3. The Investigator may consider keeping the current dose if a drop in platelet counts would be expected by reducing the dose.
4. If the platelet count is still above 150 Gi/L within one week after study treatment interruption, the platelet count needs to be monitored 3-4 days later, and twice a week thereafter until the platelet count is ≤150 Gi/L. Once the subject's platelet count is ≤150 Gi/L, study treatment should be started at the next lower dose or frequency.

**Table 3 Dose Adjustment Guidelines for Pediatric ITP Patients receiving tablets**

Platelet count	Dose	Dose adjustment
<50 Gi/L <sup>3</sup>	12.5 mg	Increase to 25 mg
	25 mg	Increase to 50 mg <sup>1</sup>
	37.5 mg	Increase to 50 mg
	50 mg	Increase to 75 mg <sup>1</sup>
	62.5 mg	Increase to 75 mg
	75 mg	Maintain 75 mg dose <sup>2</sup>
50 – 200 Gi/L	Maintain current dose	
200 – 400 Gi/L <sup>3,4</sup>	12.5 mg	Decrease to 12.5 mg every other day
	25 mg	Decrease to 12.5 mg
	37.5 mg	Decrease to 25 mg
	50 mg	Decrease to 37.5 mg
	62.5 mg	Decrease to 50 mg
	75 mg	Decrease to 62.5 mg
>400 Gi/L Interrupt study treatment until platelets < 150 Gi/L <sup>5</sup>	12.5 mg	After interruption reinitiate at a reduced frequency, 12.5 mg every other day
	25 mg	After interruption, reinitiate at 12.5 mg
	37.5 mg	After interruption, reinitiate at 25 mg
	50 mg	After interruption, reinitiate at 37.5 mg
	62.5 mg	After interruption, reinitiate at 50 mg
	75 mg	After interruption, reinitiate at 62.5 mg

1. For a subject who has returned to the 25 mg or 50 mg dose because 50 mg or 75 mg, respectively, led to a response of >200 Gi/L, the dose should be increased to 37.5 mg or 62.5 mg, respectively.
2. If a subject has reached the maximum allowed dose and has platelet counts < 50 Gi/L, the investigator (or designee) may choose to have the subject continue in the trial if clinical benefit is documented in terms of improved platelet counts OR reduced bleeding symptoms.
3. If a subject requires a dose adjustment, and the next available dose (adjusting by 12.5 mg) has already proven to be associated with platelet counts outside of the target range (i.e., <50 Gi/L or >200 Gi/L), then alternating doses may be used.
4. The Investigator may consider keeping the current dose if a drop in platelet counts would be expected by reducing the dose.
5. If the platelet count is still above 150 Gi/L within one week after study treatment interruption, the platelet count needs to be monitored 3-4 days later, and twice a week thereafter until the platelet count is ≤150 Gi/L. Once the subject's platelet count is ≤150 Gi/L, study treatment should be started at the next lower dose or frequency.

#### 5.4.2.5. Dose Adjustment Guidelines for Suspension Formulation

The dose of eltrombopag will be increased or decreased according to platelet counts as outlined in Section 5.4.2. These modifications will initially be in strength intervals of 30% (rounded up) as shown in Table 4, but intermediate dosing levels may be used if the platelet response warrants it. Subsequent dose adjustments should be made based upon the current dose of eltrombopag.

For a calculated dose of 18 to 24 mg, subjects should receive one sachet, which is equivalent to a 20 mg dose. A subsequent dose adjustment would be based upon the actual dose of 20 mg, i.e., a 30% increase in dose would be an increase of 6 mg for a total

of 26 mg. For calculated doses of 38 to 44 mg, subjects should receive a 40 mg dose (two sachets); subsequent dose adjustment would be based on the actual dose received, i.e. 40 mg.

**Table 4 Dose Adjustment Guidelines – suspension formulation**

Initial Dose (mg)	Initial Dose (ml)	Adjust dose by <sup>1</sup> (mg)	Adjust dose by (ml)
10	5	3	1.5
11	5.5	4	2
12	6	4	2
13	6.5	4	2
14	7	5	2.5
16	8	5	2.5
17	8.5	6	3
20 <sup>2</sup>	10	6	3
25	12.5	8	4
26	13	8	4
28	14	9	4.5
29	14.5	9	4.5
30	15	9	4.5

1. This table illustrates the initial dose and the corresponding 30% dose adjustment. Subsequent dose adjustments would be calculated based upon the current dose.
2. For a calculated dose of 18 to 24 mg, subjects should receive one sachet, which is equivalent to a 20 mg dose. A subsequent dose adjustment would be based upon the actual dose of 20 mg, i.e., a 30% increase in dose would be an increase of 6 mg for a total of 26 mg.

## **5.5. Handling and Storage of Study Treatment**

Eltrombopag tablets and PfOS sachets must be stored in a secure area under the appropriate physical conditions for the product according to the requirements listed on the label. Access to and administration of the study treatment will be limited to the investigator and authorized site staff. Eltrombopag must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

The recommended storage condition is stated on the product label and, where required, the label also includes the expiry date.

For US sites, any unused study medication will be returned by the monitor to Novartis for destruction. For non-US sites, any unused study medication will be destroyed locally according to local standard operating procedures (SOP).

## **5.6. Treatment Assignment**

Subjects will be identified by a unique subject number that will remain consistent for the duration of the study.

Subject/treatment numbers originally assigned to subjects during their participation in the parent study will be recorded in the eCRF, but will not be used to identify subjects in the rollover study.

Upon completion of all the required screening assessments, eligible subjects will be registered into an interactive voice response system (IVRS) by the investigator or authorized site staff.

## **5.7. Blinding**

This is an open-labeled study.

## **5.8. Product Accountability**

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to Novartis, when applicable. Product accountability records must be maintained throughout the course of the study. Refer to the SPM for further detailed instructions on product accountability.

## **5.9. Treatment Compliance**

At each visit, an evaluation of subject compliance with taken medication will be performed to confirm whether the patient has taken their medication exactly as prescribed. The investigator should discuss any tablet discrepancies with the patient, document any reasons for the non compliance and make every effort to bring the patient back into compliance. If dose modifications are required, subjects will be instructed to take the appropriate number of tablets from each bottle daily.

All subjects should be instructed to bring all bottles at each visit, with any unused drug, to the investigator.

Compliance with eltrombopag will be assessed through querying the subject during the site visits and documented in the source documents and eCRF.

A record of the number of eltrombopag tablets dispensed and the number of tablets returned, assessing the amount of tablets that should have been taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the eCRF.

## **5.10. Monitoring, Interruption and Stopping Criteria for Hepatobiliary Events**

### **5.10.1. Liver Chemistry Stopping Criteria**

**Novartis liver chemistry stopping and follow up criteria** have been designed to assure subject safety and evaluate liver event etiology in alignment with the FDA premarketing clinical liver safety guidance.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

**Phase II liver chemistry stopping criteria 1-5 are defined below and are presented as a Figure in Appendix 2:**

1. ALT  $\geq 3x$ ULN and bilirubin  $\geq 2x$ ULN (>35% direct bilirubin) (or ALT  $\geq 3x$ ULN and INR >1.5, if INR measured).

NOTE: if serum bilirubin fractionation is not immediately available, study treatment should be discontinued if ALT  $\geq 3x$ ULN and bilirubin  $\geq 2x$ ULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. ALT  $\geq 5x$ ULN.
3. ALT  $\geq 3x$ ULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
4. ALT  $\geq 3x$ ULN persists for  $\geq 4$  weeks
5. ALT  $\geq 3x$ ULN and cannot be monitored weekly for weeks

**When any of the liver chemistry stopping criteria 1-5 is met, do the following:**

- **Immediately discontinue** subject from study treatment
- Promptly report the event to Novartis **within 24 hours** of learning its occurrence

- Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE.
  - All events of ALT  $\geq$  3xULN **and** bilirubin  $\geq$ 2xULN (>35% direct bilirubin) (or ALT  $\geq$ 3xULN **and** INR >1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants), termed ‘Hy’s Law’, **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.
  - NOTE: if serum bilirubin fractionation is not immediately available, stop study treatment for that subject if ALT  $\geq$ 3xULN **and** bilirubin  $\geq$ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed.
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.
  - Withdraw the subject from the study treatment after completion of the liver chemistry monitoring as described below (unless further safety follow up is required For studies where survival is an endpoint, follow-up for overall survival is required following discontinuation from study treatment).

In addition, for subjects meeting liver stopping criterion 1:

- Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries, liver event follow up assessments (Section 5.10.1.1), and close monitoring.
- A specialist or hepatology consultation is recommended.
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

**For subjects meeting any of the criteria 2, 3, 4 and 5:**

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hrs** for repeat liver chemistries and liver event follow up assessments (Section 5.10.1.1).
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values;
  - Subjects meeting criterion 5 should be monitored as frequently as possible.

#### **5.10.1.1. Liver Event Follow Up Assessments**

For subjects meeting any of the liver chemistry stopping criteria 1-5, make every attempt to carry out the **liver event follow up assessments** described below:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody;

- Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
- Hepatitis C RNA;
- Cytomegalovirus IgM antibody;
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Hepatitis E IgM antibody
- Blood sample for pharmacokinetic (PK) analysis, obtained within 24 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin  $\geq 2 \times \text{ULN}$
- Obtain complete blood count with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake case report form

**The following are required for subjects with ALT  $\geq 3 \times \text{ULN}$  and bilirubin  $\geq 2 \times \text{ULN}$  (>35% direct) but are optional for other abnormal liver chemistries:**

- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).
- Serum acetaminophen adduct high performance liquid chromatography(HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]).
- Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. **NOTE:** if hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed [Le Gal, 2005]).
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

### **5.10.2. Liver Chemistry Monitoring Criteria**

For subjects with ALT  $\geq 3$ xULN **but**  $< 5$ xULN **and** bilirubin  $< 2$ xULN, without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks, the following actions should be taken

- Notify the Novartis Medical Lead within 24 hours of learning of the abnormality to discuss subject safety.
- Continue study treatment
- Must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline values
- If at any time these subjects meet the liver chemistry stopping criteria 1 - 5, proceed as described above
- If, after 4 weeks of monitoring, ALT  $< 3$ xULN and bilirubin  $< 2$ xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

Refer to Appendix 2 Liver Chemistry Monitoring, Interruption, Stopping and Follow-up Criteria for algorithm of liver chemistry monitoring, stopping and follow up criteria

## **6. LIFESTYLE RESTRICTIONS**

### **6.1. Male Subjects**

Male subjects with a female partner of child bearing potential must agree to use adequate contraception during the study and for a total of 16 weeks following the last dose of study drug (based upon the lifecycle of sperm). Novartis acceptable contraceptive methods for males, when used consistently and in accordance with both the product label and the instructions of the physician, are as follows:

- Vasectomized male who is sterile prior to participation in the study
- Complete abstinence from sexual intercourse for 14 days prior to first dose of study drug, through the dosing period, and for at least 16 weeks after the last dose of study drug.
- Double-barrier contraception: condom and occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/cream/suppository).

## **7. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES**

Subjects will be instructed to inform the investigator prior to starting any new medications from the time of the Transition Visit until the end of the study (Final Study Visit). Any concomitant medication(s) taken during the study will be recorded in the eCRF.



If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by Novartis and stored in the study file. Any such changes will be communicated to the investigative sites in the form of a letter.

## **7.1. Permitted Medications and Non-Drug Therapies**

All concomitant medications taken during the study will be recorded in the eCRF with information regarding reason for use, route of administration and dates of administration.

The following will be recorded on the concomitant medications eCRF page:

- A complete list of prescription and over-the-counter medications (including herbal remedies) that have been taken within 7 days prior to the first dose of study treatment(s) should be listed as a prior or ongoing medication.
- All concomitant medications taken during the study.

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate.

### **7.1.1. Antacids, Cations and Vitamin/Mineral Supplements**

#### **Antacids**

Subjects requiring routine (e.g. daily) acid suppression should be encouraged to take H<sub>2</sub> antagonists like ranitidine, famotidine or nizatidine, or proton pump inhibitors like omeprazole, esomeprazole or lansoprazole.

Subjects requiring occasional acid suppression may take liquid or chewable antacids (calcium carbonate, aluminum hydroxide or magnesium hydroxide), provided investigational product is taken at least 4 hours before or 4 hours after consumption of cation-containing antacids.

#### **Mineral Supplements and Dairy Products**

Mineral supplements (such as calcium, magnesium, aluminium, zinc, selenium or iron) are permitted during the study but study medication must be taken at least 4 hours before or 4 hours after consumption of these supplements. Similarly, eltrombopag must be taken at least 4 hours before or 4 hours after consumption of dairy products (such as milk, yogurt, and cheese).

### **7.1.2. HMG-CoA Reductase Inhibitors (statins)**

Subjects receiving HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-coenzyme A) inhibitors during the study should be closely monitored 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).

Preclinical data showed that eltrombopag is an inhibitor of the transporters Organic Anion Transporting Polypeptide (OATP1B1) and Breast Cancer Resistance Protein (BCRP). Therefore, a clinical drug interaction study to evaluate the impact of

eltrombopag on the PK of rosuvastatin, an OATP1B1 and BCRP substrate, was conducted in healthy subjects. Co-administration of eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of rosuvastatin administered on Day 5 increased plasma rosuvastatin C<sub>max</sub> 2.03-fold and AUC(0-∞) 55%. When co-administered with eltrombopag, a 50% dose reduction of the HMG-CoA reductase inhibitor is recommended [GlaxoSmithKline Document Number UM2005/00217/08].

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

### **7.1.3. Platelet Transfusions**

In this study, platelet transfusions are permitted based on SOC and at the investigator's discretion. Investigators will be required to document blood and blood supportive care products in the eCRF.

Any platelet-transfusion related complication (e.g. mild fever, shivering, skin rash, bronchospasm, Transfusion-Related Acute Lung Injury [TRALI], etc.) and any treatment administered to treat or prevent these (e.g. antagonists, pethidine, paracetamol, corticosteroids, oxygen, etc.) will be documented in the eCRF.

### **7.1.4. Concomitant Therapy for Cohort A (MDS/AML Adult Subjects)**

Supportive SOC or disease modifying agents will be allowed as indicated by local practice throughout the study.

Investigators must carefully document all concurrent medications received for treatment of MDS/AML and any changes in dosage strength or frequency in the eCRF.

### **7.1.5. Concomitant Therapy for Cohort B and Cohort C (ITP Adult and Pediatric Subjects)**

Concomitant ITP therapy use is permitted based on clinical judgment of investigator. Subjects will be permitted to use stable maintenance ITP therapy as per local ITP treatment protocols.

The dose of eltrombopag should not be reduced while tapering concomitant ITP medications unless clinically indicated. Investigators must carefully document all concurrent medications received for treatment of ITP and any changes in dosage strength or frequency in the eCRF.

## **7.2. Prohibited Medications and Non-Drug Therapies**

Subjects must abstain from using investigational and prohibited prescription or non-prescription drugs within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study treatment and until completion of follow-up procedures unless in the opinion of the investigator and sponsor the medication will not interfere with the study (Section 4.1. Subject Selection Criteria).

The following medications are prohibited or permitted only with restricted use (as outlined below) during the study:

- Any other TPO-R agonists, without exception.
- Deferasirox shares some aspects of the safety profile of eltrombopag (e.g., hepatic abnormalities, renal tubular toxicity in mice and rats, cataract development in young rodents, and inhibition/metabolism of the enzymes CYP2C8, CYP1A2, UGT1A1 and UGT1A3). Therefore, use of this medication is permitted, if a subject is already taking deferasirox at the time of study entry. **No new treatment with deferasirox should be initiated while on study medication.** Continuation of deferasirox is permitted only if any potential deferasirox-related safety events have clearly been documented, and the continuation of deferasirox is deemed clinically important by the investigator. These measures should allow for a better identification of potential eltrombopag-related events without confounding by deferasirox. According to published treatment guidelines, iron chelation therapy with deferasirox should not be considered in patients with advanced MDS and AML [Bennett, 2008].

### **7.3. Treatment after Discontinuation of Study Treatment or withdrawal from/Completion of Study**

The investigator is responsible for ensuring that consideration has been given for the post-study care of the subject's medical condition whether or not Novartis is providing specific post-study treatment.

Post-study treatment will not be provided as part of the protocol. Upon discontinuation from study treatment, subjects may receive additional (non-protocol) therapy at the discretion of the treating physician. New therapy should be documented in the eCRF. Every effort should be made to complete the required post-treatment follow-up evaluations prior to initiating further anti-cancer therapy or dosing of an investigational agent (see Appendix 1) for Final Study Visit assessments and procedures.

### **7.4. Treatment of Study Treatment Overdose**

For the purposes of this study, an overdose of eltrombopag is defined as any dose greater than the highest daily dose allowed in the parent study.

In cases of suspected or confirmed overdose with eltrombopag, consider oral administration of a metal cation-containing preparation, such as calcium, aluminum, or magnesium preparations to chelate eltrombopag and thus limit absorption. Closely monitor platelet counts. Hemodialysis is not expected to enhance the elimination of eltrombopag because eltrombopag is not significantly renally excreted and is highly bound to plasma proteins.

No specific antidote is known. A hematologist will be consulted and appropriate treatments will be determined

## **8. STUDY ASSESSMENTS AND PROCEDURES**

A signed, written informed consent form must be obtained from the subject (or subject's legally acceptable representative) prior to any study-specific procedures or assessments.

Refer to the Time and Events Table (Appendix 1) for the timing of all study specific assessments and procedures. Further details of study procedures and assessments can be found in the study procedures manual (SPM).

Investigators may be requested to perform additional safety tests during the course of the study based on newly available data to ensure appropriate safety monitoring.

Appropriate local regulatory and ethical approvals should be obtained before any additional testing is performed.

Cardiovascular medical history/risk factors will be assessed at baseline.

### **8.1. Transition Visit**

For this study, the Transition Visit must occur within 28 days of the last day of study treatment of the parent study and may be on the same day as the last study treatment visit of the parent study. The results of any specified study assessments performed on the day of the Transition Visit will serve as the baseline value for the said assessment.

At the Transition Visit, the following assessments will be performed once a signed, written consent form for the study 200170 has been obtained from the subject or the subject's legally acceptable representative (prior to any study specific procedures or assessments). Pediatric subjects over 6 years old will be asked to sign an assent form as appropriate per local regulations.

- Demographic data, including date of birth, sex, ethnicity and race.
- Subject-related data from parent study, including parent study protocol number, parent study subject treatment number, previous subject number assigned in the parent study, start date and dose of eltrombopag treatment, dose of eltrombopag at the time of transition to this study; and best response based on last disease assessment in parent study for MDS/AML subjects.
- Complete physical examination.
- 12 lead ECG.
- Clinical laboratory tests: hematology and clinical chemistry as listed in Table 5.
- Documentation of ongoing AEs and SAEs at the time of transition to the rollover study.
- Review of concomitant medications.
- Review and record any blood and blood supportive care products.
- Documentation of bone marrow examination if performed, including cytomorphology and cytogenetic assessment when performed per SOC and/or disease progression.

## **8.2. Continuous Dosing Treatment Period**

The following assessments must be performed at each Treatment Visit as per the Time and Events Table (Appendix 1).

- Complete physical examination.
- Clinical laboratory tests: hematology and clinical chemistry as listed in Table 5.
- Documentation of AEs and SAEs.
- Review of concomitant medications.
- Documentation of bone marrow examination if performed, including cytomorphology and cytogenetic assessment when performed per SOC and/or disease progression.
- Document disease response in MDS/AML subjects only if assessed as per SOC.
- Document disease progression in MDS/AML subjects only if assessed as per SOC.
- Review and record any blood and blood supportive care products.

## **8.3. Final Study Visit**

If the subject is withdrawn from study treatment or has completed the study, the following assessments will be performed within 30 days (+ 7 days) from the last dose of study treatment and prior to initiating any other investigational product:

- Complete physical examination.
- Clinical laboratory tests: hematology and clinical chemistry as listed in Table 5.
- Documentation of bone marrow examination if performed as part of standard care, including cytomorphology and cytogenetic assessment.
- Documentation of AEs and SAEs.
- Document disease response for MDS/AML subjects only.
- Document disease progression for MDS/AML subjects only.
- Review and record any blood and blood supportive care products.

## **8.4. Safety**

Measurements used to evaluate safety will include physical exams, clinical laboratory tests (hematology and clinical chemistry), and monitoring of AEs/SAEs. Planned study visits for all safety assessments are listed in the Time and Events Table (Appendix 1).

Additional, unplanned safety assessments may be performed during the course of the study as clinically indicated at the judgment of the investigator. Additional safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

NOTE: The term ‘baseline’ will refer to the value obtained on the date of the first dose of study treatment following transition to the rollover study and does not refer to the ‘baseline’ value recorded for the same assessment in the parent study.

#### 8.4.1. Physical Examination

A complete physical examination will be performed at the visit schedule as outlined in Figure 1 and the Time and Events Table (Appendix 1).

#### 8.4.2. Bone Marrow Examinations

Disease status may be evaluated in part by means of periodic bone marrow examinations throughout the study, as per SOC and should be considered for subjects who have disease progression.

Information from bone marrow examinations that are performed during the study should be entered in the eCRF. Bone marrow cytomorphology and cytogenetic assessment should also be entered in the eCRF if collected.

#### 8.4.3. Laboratory Assessments

Clinical laboratory tests (Table 5) will be performed as outlined in the Time and Events Table (Appendix 1). At the discretion of the investigator, additional laboratory samples may be taken as clinically necessary.

Local laboratories will be used for hematology and chemistry assessments. Local laboratory reference ranges for all safety parameters should be provided to Novartis by the site **prior** to receiving study medication shipment.

**Table 5 Laboratory Assessments**

Hematology	Standard Chemistry
Hemoglobin	Blood urea nitrogen or urea
Hematocrit	Creatinine
Red blood cell count	AST
Platelets	ALT
White blood cell count with differential	Total bilirubin
Total neutrophils	Direct bilirubin
Lymphocytes	Albumin
Monocytes	<b>Pregnancy<sup>2</sup></b>
Eosinophils	Serum $\beta$ -hCG (human chorionic gonadotrophin)
Basophils	
Blast % from peripheral blood smear <sup>1</sup>	

1. Subjects from Cohort A only

2. Before the first dose of study treatment (-14 days) and at the investigator discretion

#### 8.4.4. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE as outlined in Section 8.4.4.1.

Adverse event and serious adverse events will be reported in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 toxicity grades. The general guidelines for this toxicity grading system are as follows:

- Grade 1 - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 - Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental activities of daily living.
- Grade 3 - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4 - Life threatening consequences; urgent intervention indicated.
- Grade 5 - Death related to AE

#### **8.4.4.1. Definition of an AE**

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits, abuse, or misuse. Examples of events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or grade of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of study treatment (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).

The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

#### **8.4.4.2. Definition of a SAE**

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

NOTE: Death due to disease under study is to be recorded on the Death eCRF form and does not need to be reported as an SAE.

b. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, 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 drug dependency or drug abuse.

g. Protocol-Specific SAEs

- All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT  $\geq$  3xULN **and** bilirubin  $\geq$  2xULN (>35% direct) (or ALT  $\geq$  3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).
- NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin  $\geq$  2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

**8.4.4.3. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs**

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) including those that worsen from baseline, and events felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an AE or SAE, in accordance with the definitions provided.

In addition, an associated AE or SAE is to be recorded for any laboratory test result or other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay.

Any new primary cancer must be reported as an SAE.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

**8.4.4.4. Cardiovascular Events**

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack

- Peripheral arterial thrombosis
- Deep Venous Thrombosis
- Revascularization

This information should be recorded within one week of when the AE/SAE(s) are first reported.

#### **8.4.4.5. Death Events**

In addition, all deaths, whether or not they are considered SAEs, will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (CV) (including sudden cardiac death) and noncardiovascular death.

This information should be recorded within one week of when the death is first reported.

#### **8.4.4.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs**

##### **8.4.4.6.1. Cohort A (MDS/AML Adult Subjects)**

An event which is part of the natural course of the disease under study (i.e., infections, cachexia, anorexia, disease progression or hospitalization due to disease progression) should not be reported as an AE or SAE. If the clinical course is worse than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study medication(s) or protocol design/procedures to the course of the underlying disease, then this must be reported as an SAE. Furthermore, death due to disease under study is to be recorded on the Death CRF form and the specific cause of death must be recorded (e.g. sepsis, gastrointestinal hemorrhage, etc), rather than 'disease under study' or 'progressive disease'.

##### **8.4.4.6.2. Cohort B and Cohort C (ITP Adult and Pediatric Subjects)**

During the assessment period, thrombocytopenia that results in the administration of rescue medication is to be considered treatment failure rather than AEs or SAEs. Also during this assessment period, hospital admissions that are attributable to such treatment failures or related therapy also do not qualify as AEs or SAEs. Hemorrhagic complications of thrombocytopenia not otherwise meeting regulatory serious criteria (see Section 8.4.4.2. Definition of a SAE) will be reported as AEs.

#### **8.4.5. Time Period and Frequency of Detecting AEs and SAEs**

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the time of ICF signature until 30 days following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice.

SAEs will be collected over the same time period as stated above for AEs. In addition, any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), will be reported promptly to Novartis within 24 hours, as indicated in Section 8.4.7.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. At any time after 30 days the investigator may report any adverse event that they believe possibly related to study treatment.

#### **8.4.6. Method of Detecting AEs and SAEs**

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

“How are you feeling?” or for pediatric studies, “How does your child seem to feel?”

“Have you had any (other) medical problems since your last visit/contact?” or for pediatric studies, “Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?”

“Have you taken any new medicines, other than those provided in this study, since your last visit/contact?” or for pediatric studies, “Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?”

#### **8.4.7. Prompt Reporting of SAEs and Other Events to Novartis**

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to Novartis as described in the following table once the investigator determines the event meets the protocol definition for that event.

Type of Event	Initial Reports		Follow-up Information on a Previous Report	
	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours	SAE data collection tool “CV events” and/or “death” data collection tool(s) if applicable	24 hours	Updated SAE data collection tool “CV events” and/or “death” data collection tool(s) if applicable
Pregnancy	24 hours	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form
<b>Liver chemistry abnormalities:</b>				
ALT $\geq$ 3xULN and bilirubin $\geq$ 2xULN (>35% direct) (or ALT $\geq$ 3xULN and INR>1.5, if INR measured) <sup>c</sup>	24 hours <sup>a</sup>	SAE data collection tool. Liver Event Case Report Form (CRF) and liver imaging and/or biopsy CRFs if applicable <sup>b</sup>	24 hours	Updated SAE data collection tool. Updated Liver Event CRF <sup>b</sup>
ALT $\geq$ 5xULN; ALT $\geq$ 3xULN with hepatitis or rash or 3xULN $\geq$ 4 weeks	24 hours <sup>a</sup>	Liver Event CRF <sup>b</sup>	24 hours	Updated Liver Event CRF <sup>b</sup>
ALT $\geq$ 3xULN and <5xULN and bilirubin <2xULN	24 hours <sup>a</sup>	Liver Event CRF does not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks <sup>b</sup>		
a) Novartis to be notified at onset of liver chemistry elevations to discuss subject safety. b) Liver Event Documents (i.e., “Liver Event CRF” and “Liver Imaging CRF” and/or “Liver Biopsy CRF”, as applicable) should be completed as soon as possible c) INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.				

Methods for recording, evaluating, and following up on AEs and SAES and procedures for completing and transmitting SAE reports to Novartis are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

Prompt notification of SAEs by the investigator to Novartis is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

Novartis has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Novartis will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Novartis policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from Novartis will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

#### **8.4.8. Pregnancy, Testing, Prevention and Reporting**

Clear documentation of post-menopausal status (as defined in Section 8.4.8.1.) must be included in each subject's source documents as applicable. Female subjects with this documentation of post-menopausal status are considered to be of non-childbearing potential and do not need to have pregnancy tests performed during this trial. Female subjects without documentation of post-menopausal status are considered to be of childbearing potential and will be required to undergo pregnancy testing at the Transition Visit and prior to first study treatment.

In the event that a pregnancy does occur, the subject will be immediately withdrawn from the study. The subject will receive counselling from the investigator or his/her designee, regarding the nature of the study treatment and the potential risk on fetal development.

##### **8.4.8.1. Pregnancy Testing and Prevention**

The need for a screening pregnancy test depends on whether a female subject is of childbearing potential or non-childbearing potential.

**A female of non-childbearing potential** (i.e., physiologically incapable of becoming pregnant) is defined as any female who is pre menarchal, or who has had a hysterectomy, bilateral oophorectomy (ovariectomy) or bilateral tubal ligation, or is post-menopausal.

A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile, e.g., age appropriate, >45 years in the absence of hormone replacement therapy (HRT). In questionable cases, the subject must have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40pg/mL (<140 pmol/L). Postmenopausal status must be documented in the subject's source documentation.

**A female of child-bearing potential** is defined as any female who does not meet the criteria of non-childbearing potential as described in the previous paragraph.

If a female subject is of childbearing potential, she must have a serum  $\beta$ -HCG pregnancy test performed within 14 days prior to the first dose of study treatment. Subjects with a positive pregnancy test result must be excluded from the study. Subjects with a negative

pregnancy test result must agree to use an effective contraception method as described below during the study until 28 days following the last dose of study treatment.

Novartis acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follow:

- An intrauterine device with a documented failure rate of less than 1% per year.
- Vasectomized partner who is sterile prior to the female subject's entry and is the sole sexual partner for that female.
- Complete abstinence from sexual intercourse for 14 days prior to first dose of study treatment, through the dosing period, and for at 28 days after the last dose of study treatment.
- Double-barrier contraception: condom and occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/cream/suppository).
- Implants of levonorgestrel where not contraindicated for this patient population or per local practice.
- Injectable progesterone where not contraindicated for this patient population or per local practice.
- Oral contraceptives (either combined or progesterone only) where not contraindicated for this patient population or per local practice.

Female subjects who are lactating must discontinue nursing prior to the first dose of study treatment and must refrain from nursing throughout the treatment period and 28 days following the last dose of study treatment.

#### **8.4.8.2. Pregnancy Reporting**

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to Novartis.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to Novartis as described above.

## **9. DATA MANAGEMENT**

For this study, subject data will be entered into the electronic case report forms (eCRFs), transmitted electronically to Novartis or designee and be combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable Novartis standards and data cleaning procedures to ensure the integrity of the data, e.g., resolving errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Authorities (MedDRA) and a custom drug dictionary. Electronic case report forms (including queries and audit trails) will be retained by Novartis, and copies will be sent to the investigator to maintain as the investigator copy.

In all cases, subject initials will not be collected or transmitted to Novartis according to Novartis policy.

## **10. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS**

### **10.1. Hypotheses**

No statistical hypotheses are being tested. Only descriptive methods will be used to summarize of the data obtained from this study.

### **10.2. Study Design Considerations**

#### **10.2.1. Sample Size Considerations**

The sample size will be based on the number of subjects completing their parent study of eltrombopag who are eligible for inclusion in this rollover study.

#### **10.2.2. Sample Size Re-estimation**

Sample size re-estimation is not planned for this study.

### **10.3. Data Analysis Considerations**

#### **10.3.1. Analysis Populations**

The All Treated Subjects (ATS) Population will consist of all subjects that receive at least one dose of eltrombopag on this study. All data will be evaluated based on this population.

#### **10.3.2. Analysis Data Sets**

Construction of data sets relating to the reporting and analysis of study data will be performed in accordance with applicable Novartis standards and procedures.

### **10.3.3. Interim Analysis**

Data will be summarized whenever a sufficient number of subjects in each cohort has accrued to warrant the evaluation of safety data. This will be determined by the study team and may occur multiple times. No decisions will be made at the time of interim analyses to alter the study in any way. All available data at the time of an interim analysis will be included.

### **10.3.4. Key Elements of Analysis Plan**

Data will be listed and summarized according to the Novartis reporting standards, where applicable. Complete details will be documented in the Reporting and Analysis Plan (RAP). Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative, data from all participating centers will be pooled prior to analysis.

All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment.

As the duration of treatment for a given subject will depend on efficacy and tolerability, the duration of follow-up will vary between subjects. Consequently there will be no imputation for missing data.

As this is an open label, single arm study, no statistical comparisons will be made. Data will be summarized where appropriate.

Demographic and baseline characteristics will be summarized.

#### **10.3.4.1. Safety Analyses**

Safety assessments are described in Section 3 and Section 8.4.

The ATS population will be used for the analysis of safety data. Complete details of the safety analyses will be provided in the RAP.

The number of subjects administered study medication will be summarized according to the duration of therapy.

##### **10.3.4.1.1. Adverse Events**

Adverse events (AEs) will be coded using the standard MedDRA and grouped by system organ class. AEs will be graded by the investigator according to the National Institutes of Health (NCI)-CTCAE (version 4.0).

Events will be summarized by frequency and proportion of total subjects, by system organ class and preferred term. Separate summaries will be given for all AEs, drug-related AEs, serious AEs and AEs leading to discontinuation of study medication.



If the AE is listed in the NCI CTCAE (version 4.0) table, the maximum grade will be summarized.

Characteristics (e.g. number of occurrences, action taken, grade, etc) of the following AEs of special interest may be summarized separately: hepatotoxicity and thromboembolism.

The incidence of deaths and the primary cause of death will be summarized.

#### **10.3.4.1.2. Clinical Laboratory Evaluations**

Hematology and clinical chemistry data will be summarized at each scheduled assessment according to NCI CTCAE grade (version 4.0). The proportion of values lying outside the reference range will also be presented for laboratory tests that are not graded because there are no associated NCI CTCAE criteria. Summaries will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (i.e. no visit windows will be applied). Unscheduled data will be included in “overall” and “any post-screening” summaries which will capture a worst case across all scheduled and unscheduled visits post first dose of study medication. Further details will be provided in the RAP.

## **11. STUDY CONDUCT CONSIDERATIONS**

### **11.1. Posting of Information on Publicly Available Clinical Trial Registers**

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins

### **11.2. Regulatory and Ethical Considerations, Including the Informed Consent Process**

Prior to initiation of a study site, Novartis will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

Novartis will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

### **11.3. Quality Control (Study Monitoring)**

In accordance with applicable regulations, GCP, and Novartis procedures, Novartis personnel (or designated Clinical Research Organization [CRO]) will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Novartis requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

The investigator and the head of the medical institution (where applicable) agrees to allow Novartis (or designated CRO) personnel direct access to all relevant documents and to allocate their time and the time to their staff to monitor to discuss findings and any issues.

Novartis (or designated CRO) personnel will monitor the study to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

### **11.4. Quality Assurance**

To ensure compliance with ICH GCP and all applicable regulatory requirements, Novartis may conduct quality assurance assessment and/or audit of the site. Regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

### **11.5. Study and Site Closure**

Upon completion or termination of the study, Novartis personnel (or designated CRO) will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, ICH GCP, and Novartis Standard Operating Procedures.

Novartis reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe

noncompliance. If Novartis determines that such action is required, Novartis will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, Novartis will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, Novartis will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. Novartis will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

### **11.6. Records Retention**

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a Novartis audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless the Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

The investigator must notify Novartis of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

### **11.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication**

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided

reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a Novartis site or other mutually-agreeable location.

Novartis will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

Novartis aims to post a results summary will be posted to the Novartis Clinical Trials Results website ([www.novartisclinicaltrials.com](http://www.novartisclinicaltrials.com)) no later than twelve (12) months after the last subject's last visit (LSLV). In addition, upon study completion and finalization of study report, Novartis aims to submit results of the study for publication.

When publication is not feasible, please refer to the Novartis Clinical Trial Results website ([www.novartisclinicaltrials.com](http://www.novartisclinicaltrials.com)) for a summary of the trial results.

## 12. REFERENCES

Bennett JM. Consensus Statement on Iron Overload in Myelodysplastic Syndromes. *American Journal of Hematology*. 2008; 83:858-861.

GlaxoSmithKline Document Number UM2005/00217/08. Clinical Investigator's Brochure for SB496115-GR. Version 10. Effective date April 23, 2013.

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Protein Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. *Drug Metab Dispos* 2009; 37(8): 1779-1784.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. *Clin Microbiol*. 2005;43(5):2363–2369.

### 13. APPENDICES

#### 13.1. Appendix 1 Time and Events Table

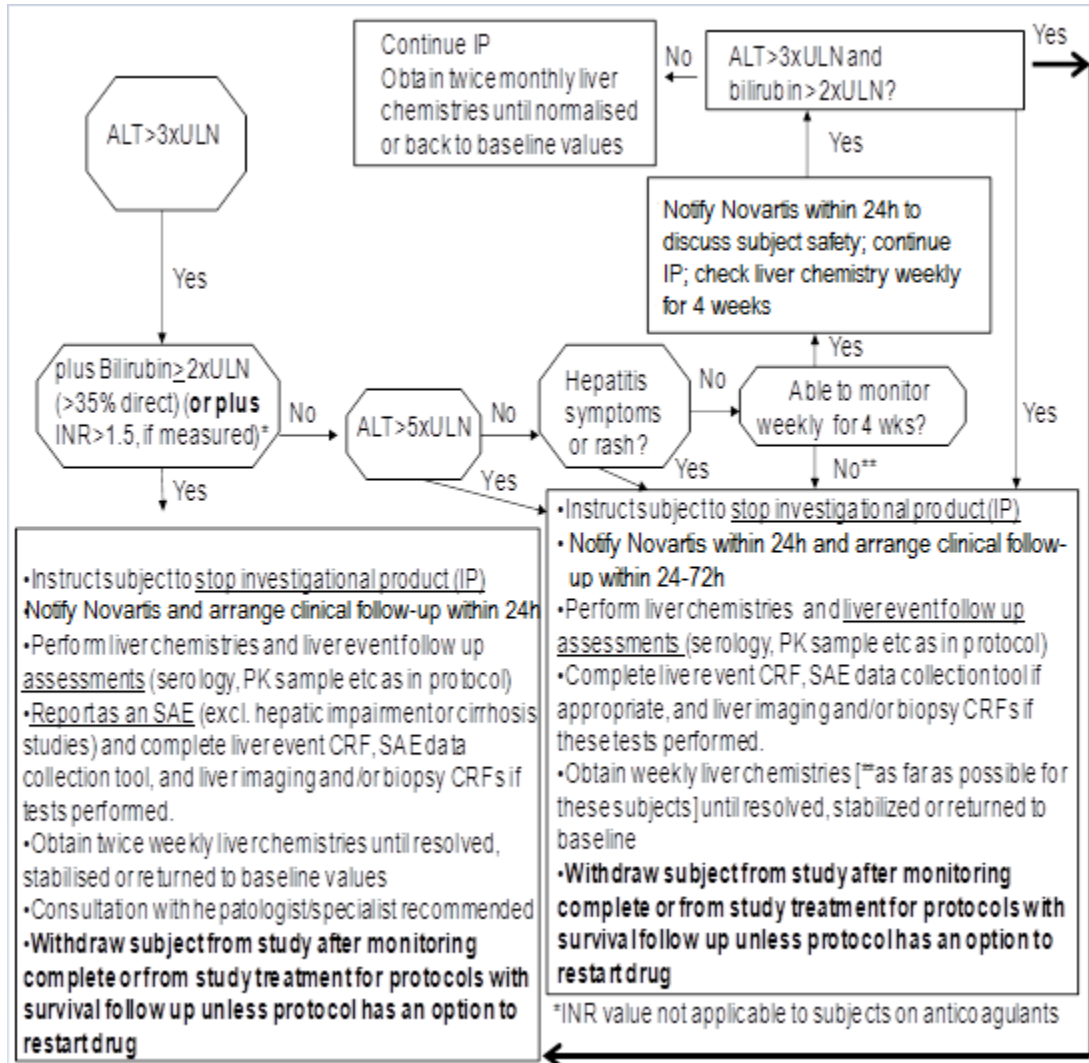
Procedures	Transition Visit <sup>1</sup>	Treatment	End of Therapy	Follow-up
		Weekly/Bi-weekly/Monthly/Bi-Monthly	End of Treatment or Early Withdrawal	30 Days after last study treatment
		Visit Window Per Figure 1 of the Protocol	(+7 days)	(+7 days)
Informed Consent <sup>2</sup>	X			
Inclusion/Exclusion criteria	X			
Demographic and Parent Study Data	X			
Physical Examination <sup>3</sup>	X	X	X	X
12-lead ECG	X			
Concomitant Medication	X	X	X	
Adverse Events	X	X	X	X
Serious Adverse Events	X	X	X	X
Hematology	X	X	X	X
Clinical Chemistry <sup>4</sup>	X	X	X	X
Pregnancy test (serum) <sup>5</sup>	X	o	o	o
Bone Marrow Examination <sup>6</sup>	o	o	o	o
Blood and Blood Supportive Care Products	X	X	X	X
Disease Response/Progression <sup>7</sup>	o	o	o	o
Dispense Study Treatment	X	X		
Assess Study Treatment Compliance		X	X	

o is used to indicate a study procedure is not required at the visit; however, it should be documented in the individual eCRF if it has been performed.

1. All subjects transitioning from parent study will begin this rollover study based on the last day of the study treatment completed during the parent study. All Transition Visit assessments/procedures must be completed prior to the first dose of study treatment in this study. The Transition Visit must occur within 28 days of the end of the last day of the study treatment and may be on the same day as the last study treatment visit of the parent study. Assessments/procedures may be used to fulfill the requirements of both the parent study and this study.
2. Informed consent must be obtained prior to performing any assessments or procedures for this study and before treatment with eltrombopag in this study.
3. PI must document that subject is acceptable to continue study treatment in the subject's source documents.
4. Refer to Table 5 for complete list of clinical laboratory assessments to be performed.
5. To be performed prior to first study treatment and at the investigators discretion. Pregnancy test only performed in women of child-bearing potential (Section 8.4.8.1). Subjects with documentation in source records of post-menopausal status do not need to have any pregnancy tests performed.
6. To be done as per local SOC and at disease progression in Cohort A. Data to be entered into eCRF when procedures are performed.
7. Collected in Cohort A subjects only when assessed as per SOC.

### 13.2. Appendix 2 Liver Chemistry Monitoring, Interruption, Stopping and Follow-up Criteria

Figure 2 Liver Safety Algorithm





### 13.3. Appendix 3 Protocol Changes

Note: deleted language is printed as ~~strike through~~ and added language is printed in **bold**.

#### Protocol Changes for Amendment 1 (05 April 2016) from Protocol (dated 07 May 2013)

This amendment is applicable to all investigational study sites in all countries.

#### Summary of Amendment Changes with Rationale

Section(s)	Change	Rationale
Header/Footer	Changed as per Novartis Requirements	Change in study sponsorship from GSK to Novartis
Title Page	Title Page replaced as per Novartis Requirements	Change in study sponsorship from GSK to Novartis
Sponsor Information Page	GSK contact information has been replaced with Novartis contact details	Change in study sponsorship from GSK to Novartis
Sponsor signatory	Change of sponsor signatory	Change in study sponsorship from GSK to Novartis
Multiple	The terms 'medical monitor' has been replaced by Medical Lead	Change in study sponsorship from GSK to Novartis
Multiple	References to GSK concomitant medications deleted	Change in study sponsorship from GSK to Novartis
Multiple	References to GSK or its staff replaced with that of Novartis and its authorized agents	To align with the change of sponsorship from GSK to Novartis
Multiple	Make administrative changes	To align with the change of sponsorship from GSK to Novartis
Appendix	References in images to GSK and Medical Monitor changed to Novartis and Medical	To align with the change of sponsorship from GSK to Novartis

Section(s)	Change	Rationale
	Lead	

### List of Specific Changes

#### Section 8.4.5 Time Period and Frequency of Detecting AEs and SAEs

PREVIOUS TEXT:

AEs will be collected from the time of the transition visit until 30 days following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice.

SAEs will be collected over the same time period as stated above for AEs. In addition, any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment or GSK concomitant medication must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 8.4.5.

REVISED TEXT:

AEs will be collected from the time of the ~~transition visit~~ **ICF signature** until 30 days following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice.

SAEs will be collected over the same time period as stated above for AEs. In addition, any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), ~~study treatment or GSK concomitant medication must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.~~ All SAEs will be reported **promptly** to ~~GSK- Novartis~~ **Novartis** within 24 hours, as indicated in Section 8.4.5.

#### Section 8.4.7 Prompt Reporting of SAEs and Other Events to ~~GSK- Novartis~~

PREVIOUS TEXT

Type of Event	Initial Reports		Follow-up Information on a Previous Report	
	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours	SAE data collection tool “CV events” and/or “death” data collection tool(s) if applicable	24 hours	Updated SAE data collection tool “CV events” and/or “death” data collection tool(s) if applicable
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form

REVISED TEXT

Type of Event	Initial Reports		Follow-up Information on a Previous Report	
	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours	SAE data collection tool “CV events” and/or “death” data collection tool(s) if applicable	24 hours	Updated SAE data collection tool “CV events” and/or “death” data collection tool(s) if applicable
Pregnancy	<del>2 Weeks</del> 24 hours	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form

### Section 8.4.8.2 Pregnancy Reporting

PREVIOUS TEXT:

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

REVISED TEXT:

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to ~~GSK~~

within ~~2 weeks~~**24 hours** of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

## Section 9 Data Management

### PREVIOUS TEXT:

For this study, subject data will be entered into GSK defined electronic case report forms (eCRFs), transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using Medical Dictionary for Regulatory Authorities (MedDRA) and an internal validated medication dictionary, GSKDrug. Electronic case report forms

(including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy.

In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

### REVISED TEXT:

For this study, subject data will be entered into ~~GSK defined~~ **the** electronic case report forms (eCRFs), transmitted electronically to ~~GSK~~ or designee and **be** combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable ~~GSK~~ **Novartis** standards and data cleaning procedures to ensure the integrity of the data, e.g., ~~removing~~ **resolving** errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using **the** Medical Dictionary for Regulatory Authorities (MedDRA) and ~~an internal validated medication~~ **a custom drug** dictionary, ~~GSKDrug~~. Electronic case report forms (including queries and audit trails) will be retained by ~~GSK~~ **Novartis**, and copies will be sent to the investigator to maintain as the investigator copy.

In all cases, subject initials will not be collected or transmitted to ~~GSK~~ **Novartis** according to ~~GSK~~ **Novartis** policy.

## Section 11.3 Quality Control (Study Monitoring)

### PREVIOUS TEXT:

In accordance with applicable regulations, GCP, and GSK procedures, the site will be contacted prior to the start of the study to review with the site staff the protocol, study

requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents and to allocate their time and the time to their staff to monitor to discuss findings and any issues.

GSK will monitor the study to ensure that the:

- ...

REVISED TEXT:

In accordance with applicable regulations, GCP, and ~~GSK-Novartis~~ procedures, **Novartis personnel (or designated Clinical Research Organization [CRO]) will contact the site** ~~will be contacted~~ prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and ~~GSK-Novartis~~ requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

The investigator and the head of the medical institution (where applicable) agrees to allow ~~the monitor~~ **Novartis (or designated CRO) personnel** direct access to all relevant documents and to allocate their time and the time to their staff to monitor to discuss findings and any issues.

~~GSK-Novartis (or designated CRO) personnel~~ will monitor the study to ensure that the:

- ...

## **Section 11.5 Study and Site Closure**

PREVIOUS TEXT:

Upon completion or termination of the study, the monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, ICH GCP, and GSK Standard Operating Procedures.

REVISED TEXT:

Upon completion or termination of the study, ~~the monitor~~ **Novartis personnel (or designated CRO)** will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, ICH GCP, and ~~GSK-Novartis~~ Standard Operating Procedures.

## **Section 11.6 Records Retention**

PREVIOUS TEXT:

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

REVISED TEXT:

~~GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.~~

**Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless the Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.**

The investigator must notify ~~GSK~~**Novartis** of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

### **Section 11.7 Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication**

PREVIOUS TEXT:

The results summary will be posted to the Clinical Study Register no later than eight months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

REVISED TEXT:

**Novartis aims to post a**~~The~~ results summary will be posted to the **Novartis Clinical Study Register Trials Results website (www.novartisclinicaltrials.com)** no later than twelve (12) ~~eight~~ months after the **last subject's last visit (LSLV)**~~final primary~~

~~completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, upon study completion and finalization of study report, Novartis aims to submit results of the study~~ a manuscript will be submitted to a peer reviewed journal for publication ~~no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.~~

~~When manuscript publication in a peer reviewed journal is not feasible, further study information will be posted~~ **please refer to the GSK Novartis Clinical Study Register Trial Results website for a summary of the trial** ~~to supplement the results summary.~~