TITLE PAGE

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Author: [redacted]

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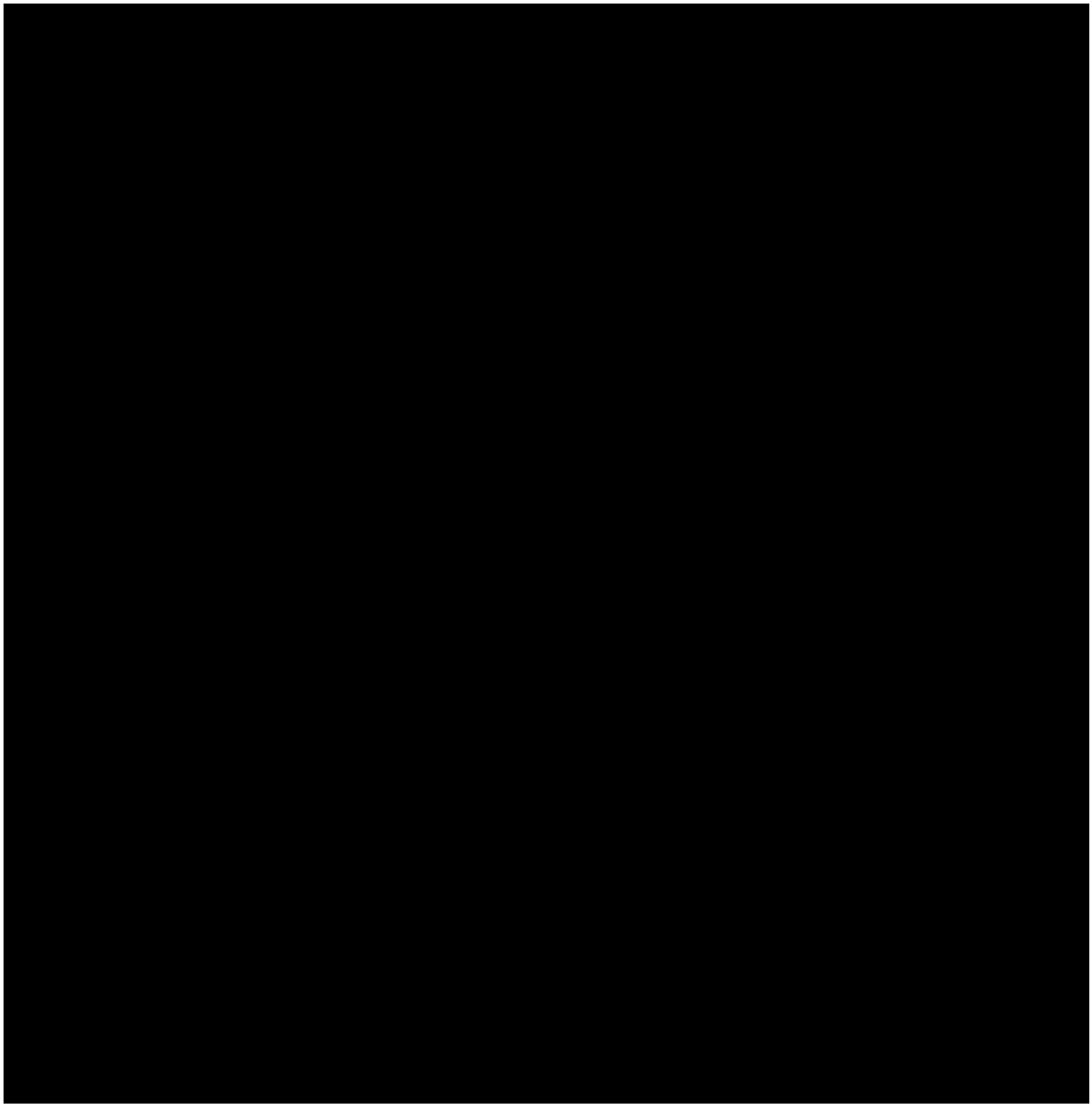
2012N154431_01	2013-JUL-08	Amendment No. 01: Streamlining of laboratory and ocular assessments within the text and T&E Tables and the Data Analysis and Statistics section. Clarification of study objective.

[redacted]

Sponsor Signatory:	Signature:	Date:
[redacted] MD	[redacted]	8-July-2013

SPONSOR INFORMATION PAGE



INVESTIGATOR AGREEMENT PAGE

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	All Treated Subjects
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
β-hCG	Beta-human chorionic gonadotropin
BMI	Body mass index
CBC	Complete blood count
CL/F	Apparent clearance following oral dosing
Cmax	Maximum observed concentration
Cτ	Concentration at the end of the dosing interval
CPK	Creatine phosphokinase
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EW	Early Withdrawal
FDA	Food and Drug Administration
FU	Follow-Up
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
h/hr	Hour(s)
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITP	Immune (idiopathic) thrombocytopenic purpura
IU	International Unit
IV	Intravenous
Kg	Kilogram
L	Liter
Ln	Naperian (natural) logarithm
µg	Microgram
µL	Microliter
M	Month
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams

mL	Milliliter
MSDS	Material Safety Data Sheet
PfOS	Powder for Oral Suspension
PGx	Pharmacogenetics
PK	Pharmacokinetic
QC	Quality control
RBC	Red blood cells
RNA	Ribonucleic Acid
SAE	Serious adverse event(s)
SOC	System Organ Class
SPM	Study Procedures Manual
tmax	Time of occurrence of Cmax
ULN	Upper limit of normal
WBC	White blood cells
WHO	World Health Organization
W (or) WK	Week

PROTOCOL SUMMARY

Rationale

Study TRA117366 is an extension study for pediatric chronic ITP patients who have previously been enrolled in the TRA115450/PETIT2 study and obtain clinical benefit from treatment with eltrombopag.

Objective(s)

- To provide continued treatment to patients who have completed the TRA115450 study and to describe the safety and tolerability of eltrombopag when administered to pediatric subjects with previously treated chronic ITP.

Study Design

This is an open-label Phase III extension study to evaluate the long-term safety of eltrombopag in pediatric patients with chronic ITP who previously participated in study TRA115450. This study will allow dosing of eltrombopag at an individualized dose for each subject based upon platelet count. The starting dose will be based on the subject's dose at the end of the TRA115450 study, unless a dose adjustment is warranted due to platelet count. The maximum dose will be 75 mg daily.

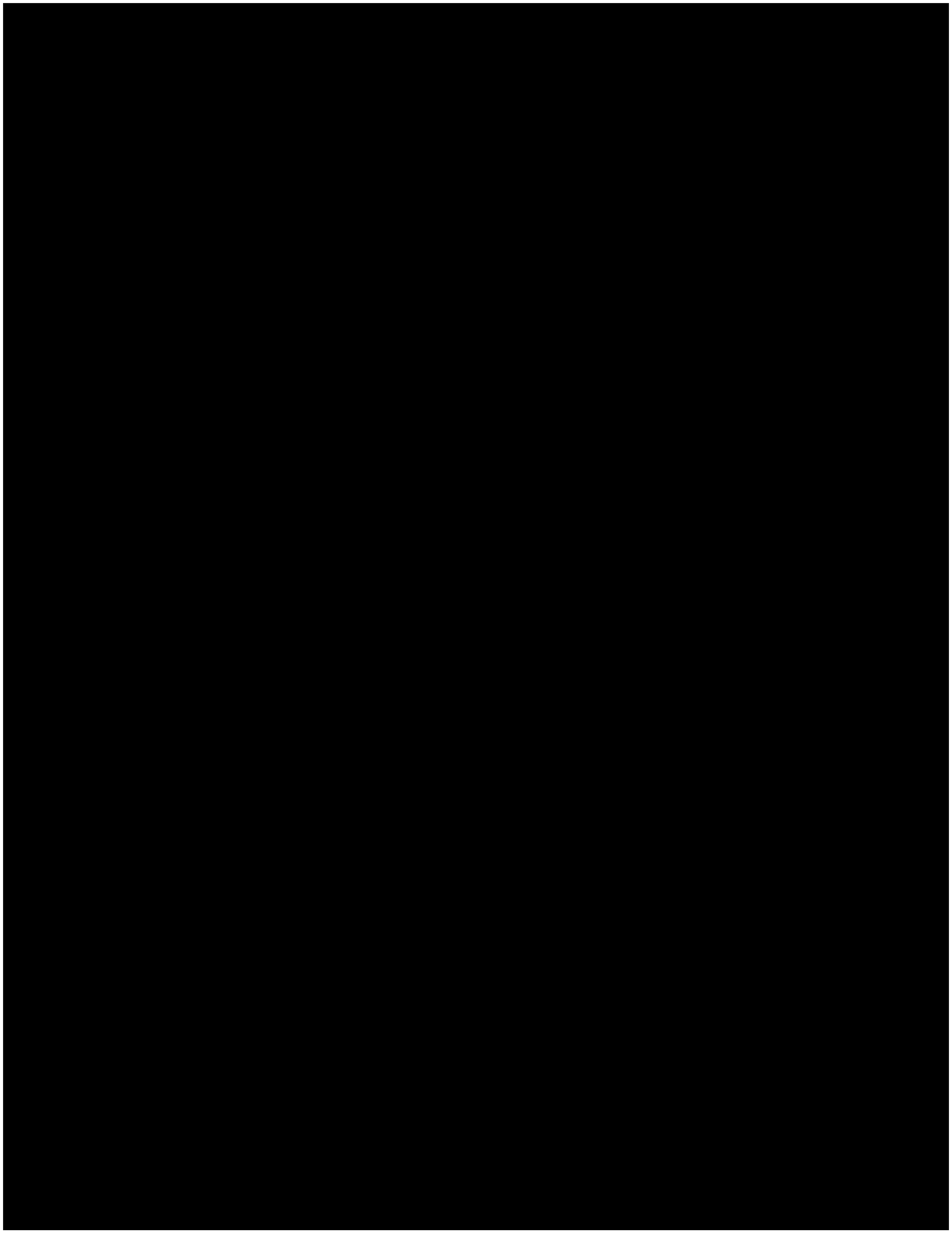
Maximum twelve (n = 12) patients will be enrolled into the study. Subjects may remain on treatment in this study until at least one of the following criteria is met: the subject reaches 18 years of age or eltrombopag receives local regulatory approval for the treatment of pediatric chronic ITP.

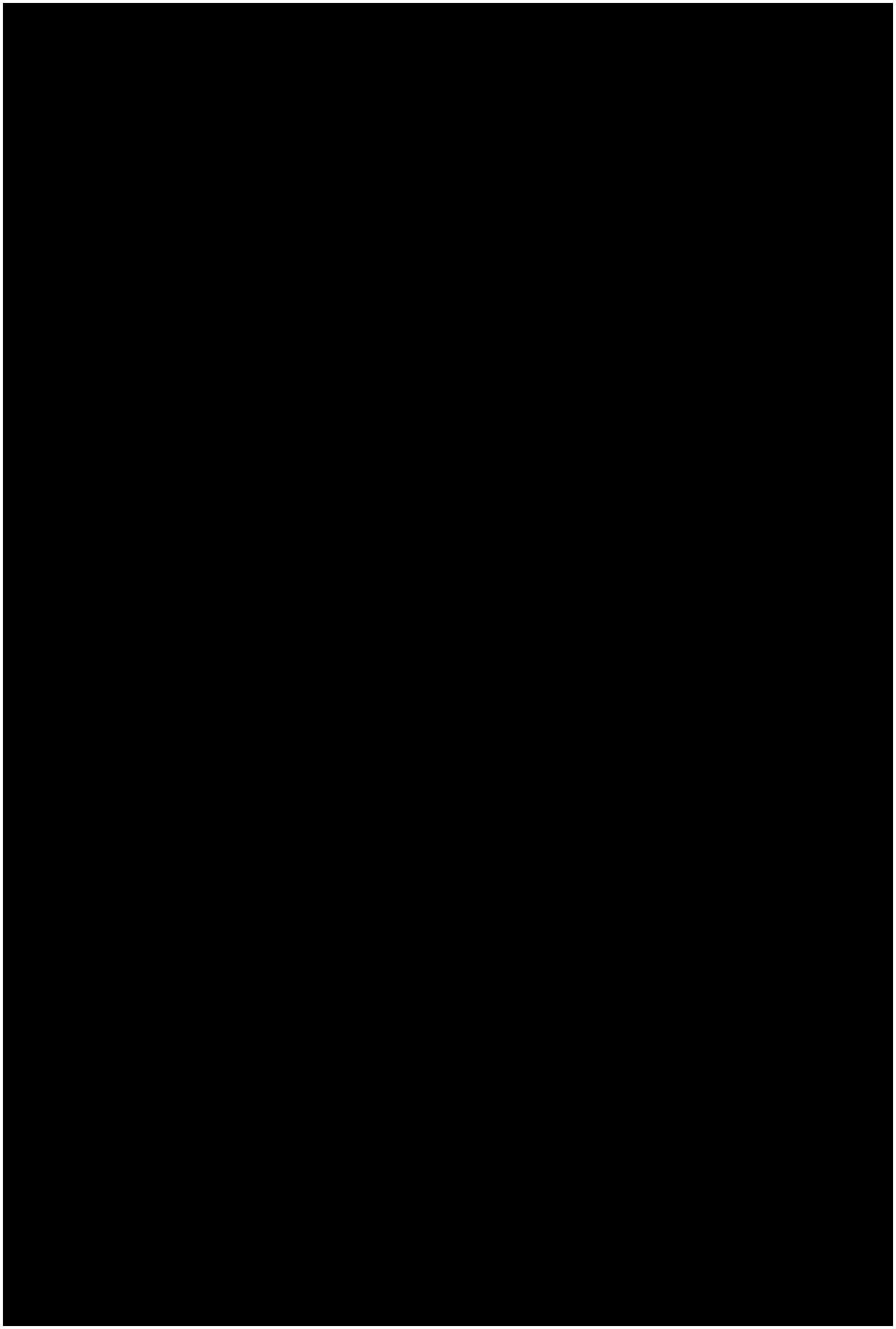
Study Assessments

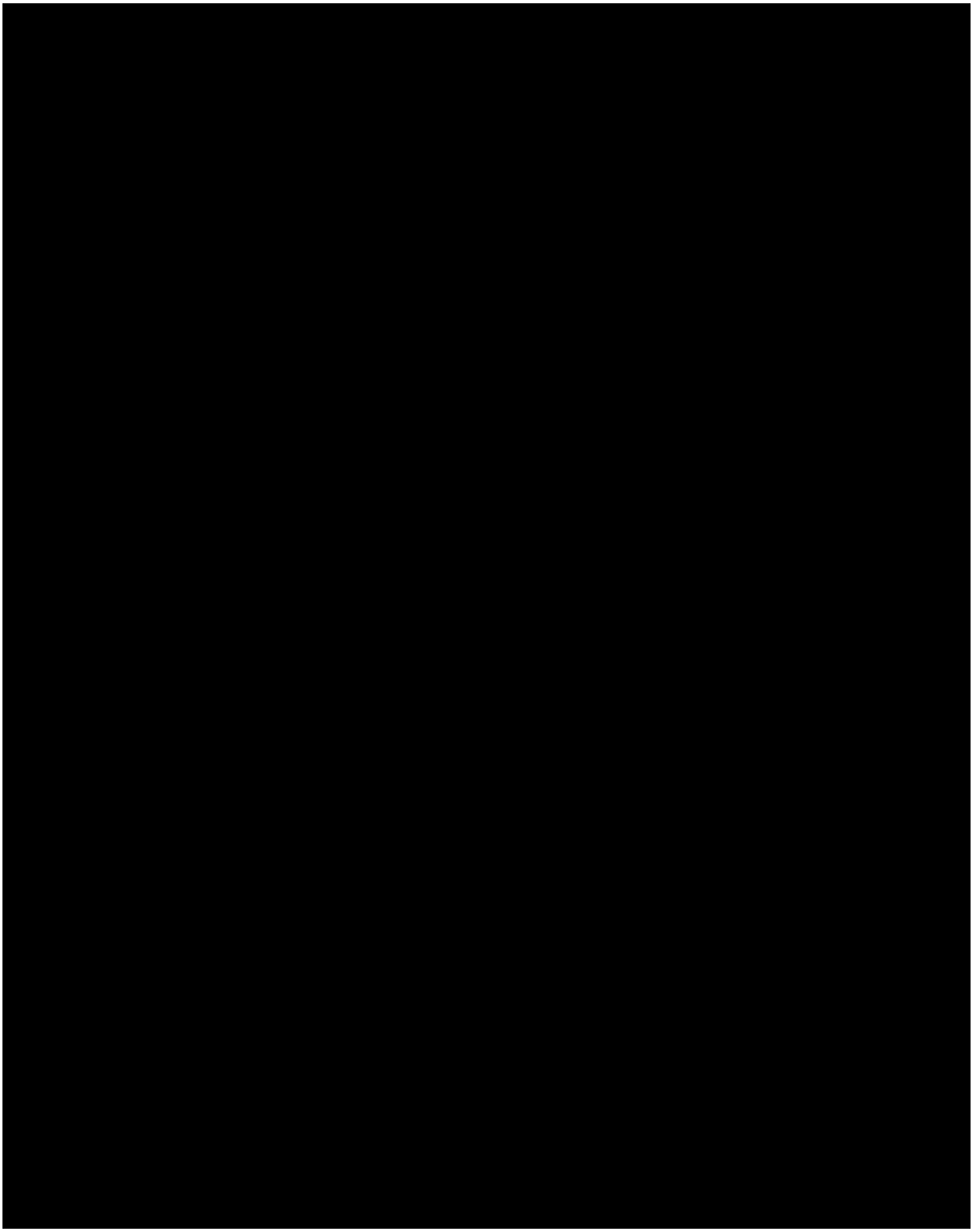
The primary endpoint is the assessment of long-term safety. Safety assessments will include clinical laboratory tests, ocular examinations, and adverse event reporting.

1. INTRODUCTION

1.1. Background







1.2. Study Rationale

Study TRA117366 will be conducted to evaluate the long-term safety of eltrombopag in pediatric chronic ITP population. This study will allow dosing of eltrombopag at an individualized dose for each subject based upon platelet counts.

2. OBJECTIVE(S) AND ENDPOINTS

Objective	Endpoint
To provide continued treatment to patients who have completed the TRA115450 study and to describe the safety and tolerability of eltrombopag when administered to pediatric subjects with previously treated chronic ITP.	Safety parameters include clinical laboratory assessments, and frequency of all adverse events, categorized using Common Terminology Criteria for Adverse Events (CTCAE) toxicity grades.

3. STUDY DESIGN

This is a Phase III study in which a screening period will be followed by a single arm treatment period and a follow-up period:

- A screening period of up to 28 days prior to Day 1 of treatment in this study
- Open-label, single arm, dose-adjustment, long-term treatment period, in which subjects may continue treatment until at least one of the following criteria are met:
    - Subject reaches 18 years of age: Subject will be considered to have completed the study, and will be discontinued from study treatment within 3 months of his/her 18th birthday.
    - Eltrombopag receives local regulatory approval for pediatric chronic ITP.
- Follow-up period. All subjects must complete the 4-week follow-up period, as described below, as part of their participation in this study:
    - Subjects who elect not to continue treatment with eltrombopag (i.e., non-study treatment) after completion of the study treatment period, will have weekly follow-up visits for 4 weeks after the last dose of study treatment.
    - Subjects who continue treatment with eltrombopag (i.e., non-study treatment) after completion of the study treatment periods will have a follow-up visit 4 weeks after the last dose of study treatment.

Maximum twelve (n = 12) subjects will be enrolled in the study.

The term ‘study treatment’ is used throughout the protocol to describe the product under evaluation in this protocol.

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 the Time and Events Table, are essential and required for study conduct

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.

4. SUBJECT SELECTION AND DISCONTINUATION/ COMPLETION CRITERIA

4.1. Subject Selection Criteria

4.1.1. Number of Subjects

Up to twelve (n = 12) subjects will be enrolled.

4.1.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product that may impact subject eligibility is provided in the IB [redacted]

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 must be obtained from the subject's guardian and accompanying informed assent from the subject (for children over 6 years old).
2. Subjects must be between 1 year and <18 years of age at Day 1.
3. Subjects must have enrolled in TRA115450/PETIT2 study.
4. Subjects must have completed Part 1 and Part 2 of TRA115450/PETIT2 study.
5. Female subjects of child-bearing potential (after menarche) must:
    - have a negative pregnancy test within 24 hours of first dose of study treatment,
    - agree and be able to provide a blood or urine specimen for pregnancy testing during the study,
    - agree to use effective contraception, as defined in Section 7.2.3, during the study and for 28 days following the last dose of study treatment, and
    - not be lactating.
6. Male subjects with a female partner of childbearing potential must agree to use effective contraception as described in Section 7.2.3 from 2 weeks prior to administration of the first dose of study treatment until 3 months after the last dose of study treatment.

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. Subjects with any clinically relevant abnormality, other than ITP, identified on the screening examination or any other medical condition or circumstance, which in the opinion of the investigator makes the subject unsuitable for participation in the study or suggests another primary diagnosis (e.g. Thrombocytopenia is secondary to another disease).
2. Any subject considered to be a child in care, defined as one who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. This can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or who has an appointed legal guardian.
3. Subjects who have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to eltrombopag or excipients that contraindicates their participation.
4. Any serious and/or unstable pre-existing medical, psychiatric disorder, or other conditions that could interfere with the subject's safety or compliance to the study procedures.

4.2. Permanent Discontinuation from Study Treatment and Subject Completion Criteria

4.2.1. Permanent Discontinuation from Study Treatment

Study treatment must be permanently discontinued for any of the following reasons:

- The subject is pregnant.
- The subject is significantly non-compliant with the requirements of the protocol.
- The subject has an adverse experience that would, in the investigator's judgment, make continued participation in the study an unacceptable risk.
- The subject has a thrombotic event, unless in the opinion of the investigator interruption of eltrombopag would lead to a risk of bleeding that would outweigh the risk of thrombosis.
- The subject meets stopping criteria for liver chemistry defined in Section 5.8.1.
- At the request of the subject or proxy

In addition study treatment may be permanently discontinued for any of the following reasons:

- Due to deviation(s) from the protocol
- At the investigator's discretion
- The subject is lost to follow-up
- The study is closed or terminated.

Study treatment will be discontinued within 3 months for the following reasons, and subject will be considered to have completed the study per Section 4.2.2:

- The subject reaches 18 years of age.
- The subject is in treatment phase when local regulatory approval is received for eltrombopag for the treatment of pediatric chronic ITP.

The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and CRF.

If the subject (or guardian) withdrawals consent, the Investigator must document the reason for withdrawal of consent in the CRF if specified by the subject or guardian.

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

Once a subject has been permanently discontinued from study treatment, retreatment with study treatment will not be allowed.

All subjects who discontinue from study treatment will have safety assessments at the time of discontinuation and will have follow-up visits at 1, 2, 3, and 4 weeks after the final dose of study treatment, as specified in Time and Events Table, Table 3.

4.2.2. Subject Completion

A subject will be considered to have completed the study if the subject meets at least one of the following conditions:

- Subject reaches 18 years of age while in the treatment phase of the study. Study treatment should be discontinued within 3 months after the 18th birthday.
- Subject is in the treatment phase of the study at the time of local regulatory approval of eltrombopag for pediatric chronic ITP. Study treatment should be discontinued within 3 months after regulatory approval is received.

5. STUDY TREATMENTS

The term 'study treatment' is used throughout the protocol to describe the product under evaluation in this protocol.

5.1. Eltrombopag GSK Investigational Product

[redacted]

Eltrombopag Tablets

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

Tablets will be packaged in white 45cc HDPE bottles with white plastic, induction-seal child-resistant caps. Each bottle will contain 35 tablets.

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.

Refer to Section 5.2 for the required preparation of the sachets, which is to be performed by the subject/parent/guardian prior to dosing.

5.1.1. Eltrombopag Dosage and Administration

For subjects between the ages of 6 to 17 years old, eltrombopag tablets will be administered, however, subjects between the ages of 6 to 11 years old may use PfOS if they have difficulty swallowing tablets and are receiving a dose of eltrombopag of < 40

mg. For subjects between the ages of 1 to 5 years old, either eltrombopag tablets or PfOS will be administered.

Any change between PfOS and tablet formulations 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 Cmax compared to the tablet formulation. When switching from PfOS to tablets, the nearest tablet strength rounding up should be used.

The maximum dose allowed will be 75 mg once daily.

Site personnel will instruct the subjects (and their parents/guardians) 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, which will be given to each subject's parents/guardians starting on Day 1.

For subjects who receive tablets, new study treatment containers (bottles) will be dispensed at each change in dose or dose frequency, and study treatment compliance will be assessed as described in Section 5.7. For subjects who receive PfOS, study treatment compliance will be assessed at each visit as described in Section 5.7, and additional packs of sachets will be dispensed when the site personnel determine the current supply will not be sufficient until the next study visit. All subjects/parents/guardians should be instructed to bring all bottles or sachets with any unused drug to each visit with the investigator.

5.1.2. Study Treatment Starting Dose

After completion of treatment in TRA115450, subjects will continue on the same dose during this study unless adjustments are warranted according to the dosing guidelines. For children between the ages of 1 to 11 years old, a change in formulation (between PfOS and tablets) may also be considered based upon guidelines in Section 5.1.1.

5.1.3. Dose Adjustment

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 Investigators are allowed to use their clinical judgment in determining dose adjustments. In this study, the target platelet count range is between 50 Gi/L and 200 Gi/L. As previously stated, the goal is to have a platelet count in a safe haemostatic range, not necessarily in the normal range.

5.1.3.1. General Dose Adjustment Considerations

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 following considerations should be taken into account when modifying the dose of study treatment. These considerations should be used in conjunction with the specific guidelines for the tablet formulation (Refer to Section 5.1.3.2), and with the specific guidelines for the suspension formulation (Refer to Section 5.1.3.3).

1. Changes in concomitant ITP medications that could affect the platelet count.
2. Other clinical situations which, in the opinion of the investigator, may affect the platelet count, **for example, among others**:
    - Subject received systemic corticosteroids for a different condition
    - A viral infection that may decrease OR increase the platelet count
3. Subject's response to eltrombopag during prior study participation (TRA115450). 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 desired range (<50 or > 200 Gi/L), alternating doses of different strength tablets or changes in frequency may be considered. For example:
    - If a subject taking 50 mg daily has a platelet count >200 Gi/L and hence requires a dose reduction, but 37.5 daily has proven to result in a platelet count below 50 Gi/L, the subject may require 50 mg and 37.5 mg doses on alternate days.
    - If a subject taking 12.5 mg daily has a platelet count <50 Gi/L and hence requires a dose increase, but 25 mg has proven to result in a platelet count > 200 Gi/L, the subject may require 12.5 mg and 25 mg on alternate days.
    - If a subject is on a 12.5 mg daily dose and has a platelet count >200 Gi/L, a dose of 12.5 mg every other day may be required (changing the frequency of dosing).

After a dose adjustment, investigators must wait at least 2 weeks before making any other adjustment, with the exception of reducing eltrombopag if the platelet count rises above 200 Gi/L and interrupting eltrombopag if the platelet count rises above 400 Gi/L.

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. (Refer to Dose Decrease guidelines in Section 5.1.3.2, below.)

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.

5.1.3.2. Dose Adjustment Guidelines for subjects receiving the tablet formulation

Dose adjustment guidelines for the tablet formulation are provided in the below sections and in Table 1.

Dose Increase

Dose increases can be made every 2 weeks until the target platelet count or the maximum allowed dose of 75 mg daily is achieved.

If a subject has a platelet count < 50 Gi/L and requires a dose increase, and the next higher dose (increase of 12.5 mg) has already proven to be associated with platelet counts > 200 Gi/L, then alternating doses may be used (e.g., 25 mg and 37.5 mg on alternating days).

Dose Decrease

If platelets rise above 200 Gi/L, subjects will reduce their dose by 12.5 mg at 2 week intervals until the platelet count is below 200 Gi/L. If platelets rise above 400 Gi/L, subjects will interrupt eltrombopag and platelet counts will be monitored within 1 week and every 3-4 days thereafter; once platelets are below 150 Gi/L, eltrombopag will be re-started at the next available lower dose level.

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 implemented as described in Section 5.1.3.1. Such alternate regimens must be documented in the CRF.

Table 1 Dose Adjustment Guidelines - Tablet formulation

Platelet count	Dose	Dose adjustment
<50 Gi/L[3]	12.5 mg	Increase to 25 mg
	25 mg	Increase to 37.5 mg
	37.5 mg	Increase to 50 mg
	50 mg	Increase to 62.5 mg
	62.5 mg	Increase to 75 mg
	75 mg	Maintain 75 mg dose[1]
50 – 200 Gi/L	Maintain current dose	
200 – 400 Gi/L[2,3]	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[4]	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. 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 (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, as described in Section 5.1.3.1.
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. Once the subject's platelet count is ≤150 Gi/L, study treatment should be started at the next lower dose or frequency.

5.1.3.3. Dose Adjustment Guidelines for subjects receiving the suspension formulation

The starting dose of eltrombopag for subjects receiving the PfOS formulation will be the subject's last dose in TRA115450 unless an adjustment is required based on the platelet count.

The dose of eltrombopag will be increased or decreased according to platelet counts as outlined in Section 5.1.3.1. These modifications will initially be in strength intervals of 30% (rounded up) as shown in Table 2, 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. The starting dose and each adjusted dose will be documented in the CRF.

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 2 Dose Adjustment Guidelines – suspension formulation

Weight (kg)	Initial Dose (mg)	Initial Dose (ml)	Adjust dose by[1] (mg)	Adjust dose by (ml)
8	10	5	3	1.5
9	11	5.5	4	2
10	12	6	4	2
11	13	6.5	4	2
12	14	7	5	2.5
13	16	8	5	2.5
14	17	8.5	6	3
15	20 [2]	10	6	3
16	20 [2]	10	6	3
17	20 [2]	10	6	3
18	20 [2]	10	6	3
19	20 [2]	10	6	3
20	20 [2]	10	6	3
21	25	12.5	8	4
22	26	13	8	4
23	28	14	9	4.5
24	29	14.5	9	4.5
25	30	15	9	4.5
26	32	16	10	5
27	33	16.5	10	5
28	34	17	11	5.5
29	35	17.5	11	5.5
30	36	18	11	5.5
31	38	19	12	6
32	39	19.5	12	6
33	40	20	12	6
34	41	20.5	13	6.5
35	42	21	13	6.5
36	44	22	14	7
37	45	22.5	14	7
38	46	23	14	7
39	47	23.5	15	7.5
40	48	24	15	7.5

1. This table illustrates the doses based upon a subject's weight and the corresponding 30% dose adjustment. Subsequent dose adjustments would be calculated based upon the current dose (and not the starting 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

Weight (kg)	Initial Dose (mg)	Initial Dose (ml)	Adjust dose by[1] (mg)	Adjust dose by (ml)

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.

5.2. Preparation of Study Treatment

Eltrombopag Tablets

Tablets will be provided to the site and no specific preparation of study treatment is required prior to administration.

Eltrombopag Powder for Oral Suspension

The powder for oral suspension PfOS is presented as a reddish brown to yellow powder, which when reconstituted with water forms a reddish-brown suspension. 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.

5.3. 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. Study treatment must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

Eltrombopag tablets and PfOS sachets will be stored at a controlled room temperature of 20-25°C (68-77°F); excursions between 15-30°C (59-86°F) are permissible.

5.4. Treatment Assignment

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

Upon completion of all the required screening assessments, eligible subjects will be registered into the trial by the investigator or authorized site staff. All enrolled subjects will receive eltrombopag (tablets or PfOS).

5.5. Blinding

This is an open-labeled study.

5.6. 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 GSK, 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.

5.7. Treatment Compliance

At each visit, an evaluation of subject compliance with taken medication will be performed.

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

A record of the number of eltrombopag tablets or sachets dispensed to and 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 IP dispensing log.

The investigator will make every effort to bring non-compliant subjects into compliance. If in the opinion of the investigator, there are any significant irregularities in compliance, and the subject cannot be brought back into compliance, then the subject should be withdrawn from the study.

5.8. Monitoring, Interruption and Stopping Criteria for Hepatobiliary Events

5.8.1. Liver chemistry stopping criteria

Liver chemistry stopping criteria and follow up requirements have been designed to assure subject safety and evaluate liver event etiology in alignment with the FDA Guidance for Industry – Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009, www.fda.gov).

Liver chemistry stopping criteria 1-5 are **defined as follows:**

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

   NOTE: If serum bilirubin fractionation is not immediately available, study drug should be discontinued if ALT ≥ 3x ULN **and** bilirubin ≥ 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 ≥ 5x ULN
3. ALT ≥ 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 ≥ 3x ULN persists for ≥ 4 weeks
5. ALT ≥ 3x ULN and cannot be monitored weekly for 4 weeks

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

- **Immediately discontinue** study treatment
- Report the event to GSK **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 ≥ 3x ULN **and** bilirubin ≥ 2x ULN (>35% direct bilirubin) (or ALT ≥3x ULN 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, study treatment should be discontinued if ALT ≥ 3x ULN **and** bilirubin ≥ 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.
- 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
- Do not rechallenge with investigational product.

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 (refer to Section 5.8.1.1), 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 – 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 (refer to Section 5.8.1.1)
- 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.

5.8.1.1. 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
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2x 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 form.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications form.

- Record alcohol use on the liver event alcohol intake form.

The following assessments are required for subjects with ALT ≥3x ULN and bilirubin ≥2x ULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

5.8.1.2. Liver Chemistry Monitoring Criteria

For subjects with ALT ≥3x ULN **but** <5x ULN **and** bilirubin <2x ULN, without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks, the following actions should be taken:

- Notify the GSK Medical Monitor within 24 hours of learning of the abnormality to discuss subject safety
- Can 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 the subject meets any of the liver chemistry stopping criteria 1 – 5, proceed as described above
- If, after 4 weeks of monitoring, ALT <3x ULN and bilirubin <2x ULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

Refer to Appendix 1 for algorithm of liver chemistry monitoring, stopping and follow up criteria.

6. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

6.1. Permitted Medications and Non-Drug Therapies

Any medication taken within 7 days of study medication administration must be recorded in the CRF .

All concomitant medications taken during the study will be recorded in the CRF with indication, dose information, as well as start and stop dates of administration.

If any medication is required at any time within 7 days before study treatment administration until completion of the 4-week follow-up visit, subjects should consult the investigator and details should be recorded in the CRF.

6.1.1. Antacids and Vitamin/Mineral Supplements

Ingestion of polyvalent cation-containing antacids, and vitamin/mineral supplements (aluminum, calcium, iron, magnesium, selenium, strontium among others) with study treatment may result in a decrease in exposure of eltrombopag. Therefore, every effort must be made to educate subjects on how to take study treatment with these medications. Details of these and all concomitant medications should be recorded in the CRF.

Administration of eltrombopag, as the tablet or the PfOS formulation, with polyvalent metal cation-containing antacids or with high-calcium (425mg calcium) meals reduced plasma eltrombopag AUC(0-∞) and Cmax 60 to 80%. Administration of eltrombopag PfOS 2 hours after a high-calcium (425mg calcium) meal reduced plasma eltrombopag AUC(0-∞) and Cmax approximately 50%. Administration of eltrombopag PfOS 2 hours before a high-calcium (425mg calcium) meal attenuated the effect, resulting in plasma eltrombopag AUC(0-∞) and Cmax values 15 to 20% lower compared to fasting. Administration of eltrombopag with low-calcium (<50mg calcium) meals did not significantly alter plasma eltrombopag exposure. Given these data, the recommendations in the following sections (Section 6.1.1.1 and Section 6.1.1.2) for administration of eltrombopag relative to polyvalent metal cation-containing products such as some antacids, vitamin/mineral supplements, and dairy products should be followed.

6.1.1.1. Antacids

Subjects requiring routine (e.g. daily) acid suppression should be encouraged to take H2 antagonists like ZANTAC™, Famox, Pepzan, Pepcidine, Axid or proton pump inhibitors like Losec, Nexium, Zoton, Protium.

Subjects requiring occasional acid suppression may take liquid or chewable antacids (TUMS™, Maalox, Mylanta, Amphogel, Milk of Magnesia) provided study medication is taken at least 2 hours before or 4 hours after consumption of polyvalent cation containing antacids.

6.1.1.2. Calcium and Vitamin/Mineral Supplements

Calcium and/or vitamin/mineral supplements as described above are permitted during the study but study treatment must be taken at least 2 hours before or 4 hours after consumption of these products.

6.1.2. 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 OATP1B1 and 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 Cmax 2.03-fold and AUC(0-∞) 55%. When co-administered with eltrombopag, a 50% dose reduction of the HMG-CoA reductase inhibitor is recommended.

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

6.1.3. Concomitant ITP Therapy

Subjects will be permitted to use stable maintenance ITP therapy (including, but not limited to: corticosteroids, azathioprine, danazol, cyclosporine A, mycophenolate mofetil), as per local ITP treatment protocols.

Use of rescue ITP medication is allowed at any time the investigator deems it is indicated. Rescue medication is defined as the addition of new therapies intended to raise the platelet count, including medications, platelet transfusions, splenectomy or the increase of the dose of any concomitant ITP medications taken at baseline.

Concomitant ITP medications may be reduced at the discretion of the investigator according to the platelet count and provided the dose of eltrombopag has been stable for 3 consecutive weeks.

Investigators may use accepted local protocols or guidelines for reduction of concomitant ITP medications; however, 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 CRF.

6.2. 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 (see Section 4.1 Subject Selection Criteria).

Drugs that affect platelet function (including but not limited to, aspirin, clopidogrel and/or NSAIDS) should not be taken during the study unless there is a very clear indication and the Investigator documents the rationale. This is due to the fact that they may affect the results of the bleeding scale assessments.

Any other TPO-R agonists are prohibited during the study.

Subjects must abstain from taking herbal supplements within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study treatment until completion of the 4-week follow-up visit, unless the Investigator and medical monitor agree that the medication will not interfere with the study treatment.

6.3. 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 patient's medical condition whether or not GSK is providing specific post-study treatment.

6.4. Treatment of Eltrombopag Overdose

Treatment of any suspected or confirmed overdose with eltrombopag should be symptomatic, and supportive care is recommended in cases where overdose is suspected, as per the IB for eltrombopag [redacted]
No specific antidote is known. A hematologist will be consulted and appropriate treatments will be determined.

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

7. STUDY ASSESSMENTS AND PROCEDURES

A signed, written informed consent form must be obtained from the subject's guardian prior to any screening or study-specific procedures or assessments. Subjects over 6 years old will be asked to sign an assent form.

Subjects must be screened to ensure they meet the eligibility criteria specified in Section 4.1, Subject Selection Criteria. All screening and baseline evaluations must be completed prior to initiating treatment with study treatment.

Refer to the Time and Events Table for the timing of all assessments (Table 3). Details on safety assessments are presented in Section 7.2, respectively. Further details of study procedures and assessments can be found in the study procedures manual (SPM).

Weekly visits will take place within ±3 days of the nominal visit date, in reference to Day 1. Monthly visits will take place within ±7 days of the nominal visit date, in reference to Day 1. Every effort should be made to keep to the nominal schedule.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained prior to signing of informed consent may be used for screening or baseline purposes provided the procedure meets the protocol-defined requirements and has been performed in the timeframe required for the study.

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.

Table 3 Time and Events Table

TRA117366	**Screening[1]**	**Open-Label Treatment Period**					**Follow-up Period**				
Study Day		**Day 1**	**Weekly**	**Every 4 weeks**	**Every 6 weeks**	**End of Treatment[2]**	**1W FU[3]**	**2W FU[3]**	**3W FU[3]**	**4W FU**	
Informed consent	X										
Medical history and evaluation of eligibility	X										
Physical exam[4]	X										
Concurrent medication review		X	X	X	X	X	X	X	X	X	
Pregnancy test (urine)[5]		X[5]	At least every 8 weeks							X	
CBC [6]		X	X	X	X	X	X	X	X	X	
Peripheral blood smear[7]		X	X	X	X	X					
Clinical chemistry[8]		X	X	X	X	X	X	X[9]	X[9]	X[9]	
AE questioning		X	X	X	X	X	X	X	X	X	
Cataract assessment[10]			Every 12 months								

Table 3 Time and Events Table (Continued)

W: week; FU: follow-up; M: month

Note: If the subject continues on a stable dose of eltrombopag for 3 consecutive weeks, also if at the day 1 patient received stable dose in TRA115450 for at least 3 consecutive weeks (without changes in concomitant ITP therapy), assessments may be scheduled every 4 weeks (±7 days of nominal visit day) rather than weekly. If the subject continues on a stable dose of eltrombopag for 3 consecutive monthly visits (without changes in concomitant ITP therapy), including any consecutive monthly visits in TRA115450 prior to coming into this study, assessments frequency may be further reduced and may be scheduled every 6 weeks (±7 days of nominal visit day). If the dose of eltrombopag is not stable, weekly visits (±3 days of nominal visit day) will be required.

1. Screening visit may occur on the same day as the Day 1 visit.
2. All subjects will attend the End of Treatment visit on the day of or within 3 days after the last dose of study treatment.
3. Subjects who continue on treatment with eltrombopag (i.e., non-study treatment) will not be required to attend the Week 1, 2 and 3 Follow-up visits.
4. Physical Exam to be performed at screening.
5. For female subjects of child-bearing potential, a negative pregnancy test (urine or blood sample) MUST be obtained within 24 hours prior to the first dose. Tests to confirm that female subjects of childbearing potential are not pregnant will be conducted at least once every 8 weeks while receiving study treatment and after 4 weeks following completion or discontinuation of study treatment.
6. CBC parameters: platelet count, hemoglobin, and WBC, .
7. Peripheral blood smear to be performed on Day 1 and at least once every 6 weeks, regardless of the visit schedule (weekly, 4-weekly or 6-weekly).
8. Clinical Chemistry: Alkaline phosphatase, AST, ALT, total bilirubin, and direct bilirubin.
9. If clinical chemistry at follow-up week 1 is normal, no clinical chemistry will be measured at follow-up weeks 2, 3 and 4.
10. An age-appropriate standard of care exam will be performed to assess the presence of cataracts every 12 months while in the study treatment period.

7.1. Screening and Baseline Assessments

A signed, written informed consent form must be obtained from the subject's guardian prior to any screening or study-specific procedures or assessments. Subjects over 6 years old will be asked to sign an assent form.

Subjects must be screened to ensure they meet the eligibility criteria specified in Section 4.1, Subject Selection Criteria. Screening assessments will be performed within 4 weeks (28 days) prior to the first dose of study treatment. All screening and baseline evaluations must be completed prior to initiating study treatment. The following baseline results must be reviewed prior to initiating study treatment, including:

- Urine or serum pregnancy test, for females of childbearing potential, within 24 hours of first dose of study treatment.

The required screening assessments are outlined in Table 3, Time and Events Table.

If a subject is not eligible for the study per the Inclusion and Exclusion Criteria at the initial attempt, and in the investigator's opinion the subject may become eligible at a later date during the enrolment period, the investigator is allowed to re-screen the subject.

7.2. Safety

7.2.1. Safety Endpoints

Safety and tolerability endpoints include clinical laboratory assessments and frequency of all adverse events, categorized using Common Terminology Criteria for Adverse Events (CTCAE) toxicity grades. Refer to the SPM for current version.

7.2.1.1. General Considerations

Once the dose of eltrombopag and other ITP medications has been stable for 3 consecutive weeks, which may include the prior 3 weeks in the TRA115450 study, monthly visits will be acceptable unless in the investigator's opinion there is a specific medical reason for more frequent evaluations. If the dose is not stable, weekly visits will be required.

Planned time points and more detailed information for all safety assessments are listed in the Time and Events Tables (Section 7 Table 3).

7.2.1.2. Physical Exam and Vital Signs

Physical Exam

A physical examination will be done at Day 1 per the investigator's usual practice and any abnormal findings will be recorded on the appropriate form in the CRF, e.g, Medical History or AE/SAE form.

7.2.1.3. Clinical Laboratory Assessments

Hematology and clinical chemistry parameters to be tested are listed in Section 7.2.4; Table 4 lists the parameters to be tested locally. The amount of blood drawn for all routine clinical laboratory assessments for this study is anticipated to be approximately 15-20 mL per study visit. Every effort will be done to reduce this to a minimum according to each local lab's requirements.

7.2.1.4. Cataract Assessment

Ophthalmic safety, with focus on cataracts, will be assessed in all subjects following procedures used in standard practice at the times listed in the Time and Events Table.

Ocular examinations will be performed by an ophthalmologist or an optometrist under the guidance of an ophthalmologist. Assessments should be performed, whenever possible, by the same examiner.

Any abnormal findings will be recorded in the appropriate CRF form, e.g., Medical History or AE/SAE form.

7.2.1.4.1. Ocular Changes of Clinical Concern

Ophthalmic events of clinical concern as defined by the examiner, include, but are not limited to:

- Decreased vision due to cataractous changes;
- Progressive lens changes: Worsening cataractous changes observed on slit lamp examination; and
- Need for cataract surgery.

7.2.2. 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 7.2.2.1 and Section 7.2.2.2.

7.2.2.1. Definition of an AE

An AE is 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 either study treatment or a concomitant medication (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).
- "Lack of efficacy" or "failure of expected pharmacological action" *per se* is not to be reported as an AE or SAE. However, any signs and symptoms and/or clinical sequelae resulting from "lack of efficacy" will be reported as an AE or SAE, if they fulfill the definition of 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.

7.2.2.2. Definition of a SAE

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

a. Results in death

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-subject setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils 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 SAE.

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 ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) or 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 ≥ 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

- All Grade 4 laboratory abnormalities assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (see The Study Procedures Manual for: Common Terminology Criteria for Adverse Events), except Grade 4 thrombocytopenia.
- An ocular event of clinical concern as defined in Section 7.2.1.4.1 Ocular Changes of Clinical Concern.

7.2.2.3. 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.

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.

Bleeding events should be reported as an AE or SAE as appropriate according to the Investigator's judgment.

7.2.2.4. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

Thrombocytopenia that results in the administration of rescue medication is to be considered treatment failure rather than an AE or SAE.

7.2.2.5. 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 the first dose of study treatment is administered until the 4-week follow-up visit.

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) or study treatment must be recorded from the time a subject consents to participate in the study up to and including the 4-week follow-up period. All SAEs will be reported to GSK within 24 hours, as indicated in Section 7.2.2.6.

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 the 4-week follow-up visit the investigator may report any adverse event that they believe possibly related to study treatment.

7.2.2.6. Prompt Reporting of SAEs and Other Events to GSK

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

	Initial Reports		**Follow-up Information on a Previous Report**	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form
Liver chemistry abnormalities:				
ALT≥3xULN and bilirubin≥1.5xULN (>35% direct) (or ALT≥3xULN and INR>1.5, if INR measured) [3]	24 hours[1]	SAE data collection tool. Liver Event Case Report Form (CRF) and liver imaging and/or biopsy CRFs if applicable[2]	24 hours	Updated SAE data collection tool. Updated Liver Event CRF[2]
ALT≥5xULN; ALT≥3xULN with hepatitis or rash **or** ALT ≥3xULN and <5xULN that persists ≥4 weeks	24 hours[1]	Liver Event CRF[2]	24 hours	Updated Liver Event CRF[2]
ALT≥3xULN and <5xULN and biliribin <1.5xULN	24 hours[1]	Liver Event CRF does not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[2]		

1. GSK to be notified at onset of liver chemistry elevations to discuss subject safety.
2. Liver event documents should be completed as soon as possible
3. INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.

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

7.2.2.7. Regulatory reporting requirements for SAEs

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

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK 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 GSK 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 GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.2.3. Pregnancy, Testing, Prevention and Reporting

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

7.2.3.1. Pregnancy Testing and Prevention

A screening pregnancy test is mandatory for all female subjects of childbearing potential, as defined below, but in no event longer than 24 hours prior to the first administration of study treatment. Unless a serum pregnancy test is required by the medical institution, a urine pregnancy test is sufficient. If the screening pregnancy test cannot be performed within 24 hours prior to the first administration of study treatment, a urine pregnancy test must be performed and results must be negative on Day 1 prior to dosing with eltrombopag. The results of this test must be negative. Thereafter, the pregnancy test will be repeated at least once every 8 weeks while receiving study treatment or more frequently if clinically indicated or required per local regulation (refer to Table 3 Time and Events Table).

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 a pre-menarche female or any female (after menarche) who has had a hysterectomy, bilateral oophorectomy (ovariectomy) or bilateral tubal ligation, or is post-menopausal.

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 urine or serum β-hCG pregnancy test performed within 24 hours prior to the first dose of study treatment. Female subjects with positive pregnancy test result must be excluded from the study. Subjects with 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.

Male subjects with a female partner of childbearing potential must agree to use one of GSK acceptable effective contraception during the study until 28 days following the last dose of study

GSK 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 least 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 for 28 days following the last dose of study treatment.

7.2.3.2. Pregnancy Reporting

Any pregnancy that occurs during study participation (including treatment and follow-up periods) 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.

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 GSK.

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 GSK as described above.

7.2.4. Laboratory Assessments

All protocol required laboratory assessments listed in Table 4 will be performed by a local laboratory, in accordance with Table 3, Time and Events Table, and recorded in the CRF, unless otherwise specified.

If any additional local laboratory assessments are undertaken during the course of the trial and they result in a change in patient management (for example SAE or AE or dose modification) the assessment data must be recorded in the patients CRF.

Table 4 Local Laboratory Assessments

Peripheral Blood Smear	Chemistry
	AST
Hematology	ALT
Platelet Count	Total bilirubin
Hemoglobin	Direct bilirubin
WBC count (absolute count)	Alkaline phosphatase
Urine Pregnancy[1]	

1. Refer to Section 7.2.3.1. For further details on pregnancy testing. Results are not captured in CRF, but any pregnancy would be reported as specified in Section 7.2.3.

7.2.5. Meals and Dietary Restrictions

Eltrombopag may be taken with food containing little (<50 mg) or preferably no calcium. (See Section 6.1, Permitted Medications and Non-Drug Therapies).

Allow at least a 4 hour interval between eltrombopag and other medications or products containing polyvalent cations (e.g. calcium, magnesium, aluminium, zinc, selenium or iron) such as antacids, dairy products (milk, yogurt, cheese, ice cream, etc), and mineral supplements to avoid significant (70-75%) reduction in eltrombopag absorption due to chelation.

8. DATA MANAGEMENT

For this study subject data will be collected using GSK defined case report forms (CRFs) and data entered in a validated 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 MedDRA and an internal validated medication dictionary, GSKDrug. In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

Original CRFs will be retained by GSK, while the investigator will retain a copy.

9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

9.1. Hypotheses

Subjects are being assessed to investigate the safety of eltrombopag.

Since this is an open-label study there are no formal statistical hypothesis tests planned.

9.2. Study Design Considerations

9.2.1. Sample Size Assumptions

As this is an extension study for pediatric chronic ITP patients who have previously been enrolled in the TRA115450/PETIT2 study the sample size will be based on the number of patients previously enrolled in the PETIT2 study and to be included in this study (n = 12).

9.2.2. Sample Size Sensitivity

Since participation in this study is dependent on enrolment in previous studies (e.g., TRA115450) it was not considered necessary to carry out any sample size sensitivity.

9.2.3. Sample Size Re-estimation

No sample size re-estimation is planned for this study.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

All subjects who receive at least one dose of study medication will be evaluable for safety and will comprise the All Treated Subjects (ATS) population.

9.3.2. Analysis Data Sets

No data sets are planned for this study.

9.3.3. Treatment Comparisons

9.3.3.1. Primary Comparisons of Interest

As this is a single arm study, there are no treatment comparisons. The endpoints will be summarized utilizing the ATS population.

9.3.3.2. Other Comparisons of Interest

As this is a single arm study, there are no other comparisons of interest..

9.3.4. Interim Analysis

No interim statistical analyses are planned for this study.

9.3.5. Key Elements of Analysis Plan

Data will be displayed according to the GSK reporting standards, where applicable.

All data up to the time of study completion/withdrawal from study will be included in the displays, 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.

Demographic and baseline data will be displayed.

9.3.5.1. Safety Analyses

Safety displays will present safety and tolerability endpoints that include , clinical laboratory assessments and frequency of all adverse events, categorized using Common Terminology Criteria for Adverse Events (CTCAE) toxicity grades.

"All Treated Subjects" (ATS) population will be used for the presentation of safety data.

9.3.5.1.1. *Extent of Exposure*

Exposure data will be presented according to the duration of the subject's therapy.

9.3.5.1.2. *Adverse Events*

Adverse events (AEs) will be coded using the standard GlaxoSmithKline Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class. AEs will be graded by the investigator according to the -CTCAE.

System organ class and preferred term of adverse eventswill be presented. Drug-related AEs, serious AEs and AEs leading to discontinuation of study medication will also be displayed.

If the AE is listed in the NCI CTCAE table, the maximum grade will be utilized where applicable.

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

9.3.5.1.3. *Clinical Laboratory Evaluations*

Hematology and clinical chemistry data will be displayed at each scheduled assessment according to NCI CTCAE grade . Unscheduled data will be included in "overall" and "any post-screening" displays which will capture a worst case across all scheduled and unscheduled visits post first dose of study medication.

10. STUDY CONDUCT CONSIDERATIONS

10.1. 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

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK 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.

GSK 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.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments, unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

10.3. Quality Control (Study Monitoring)

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 CRF 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 and discuss findings and any issues.

GSK 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.

10.4. Quality Assurance

To ensure compliance with ICH GCP and all applicable regulatory requirements, GSK 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.

10.5. Study and Site Closure

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.

GSK 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 GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK 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**, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. GSK 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.

10.6. 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 GSK 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.

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.

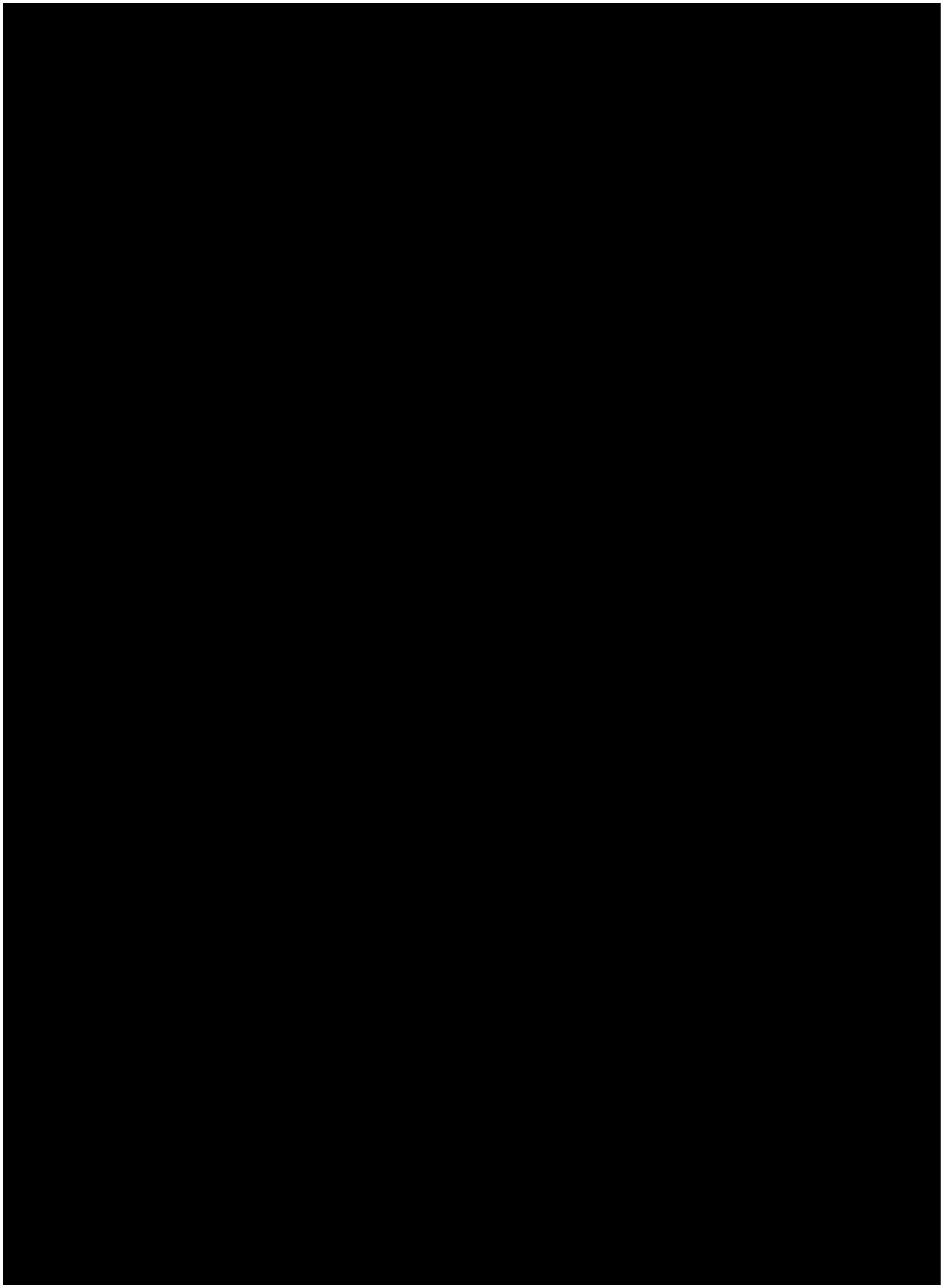
10.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

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 GSK site or other mutually-agreeable location.

GSK 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.

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.

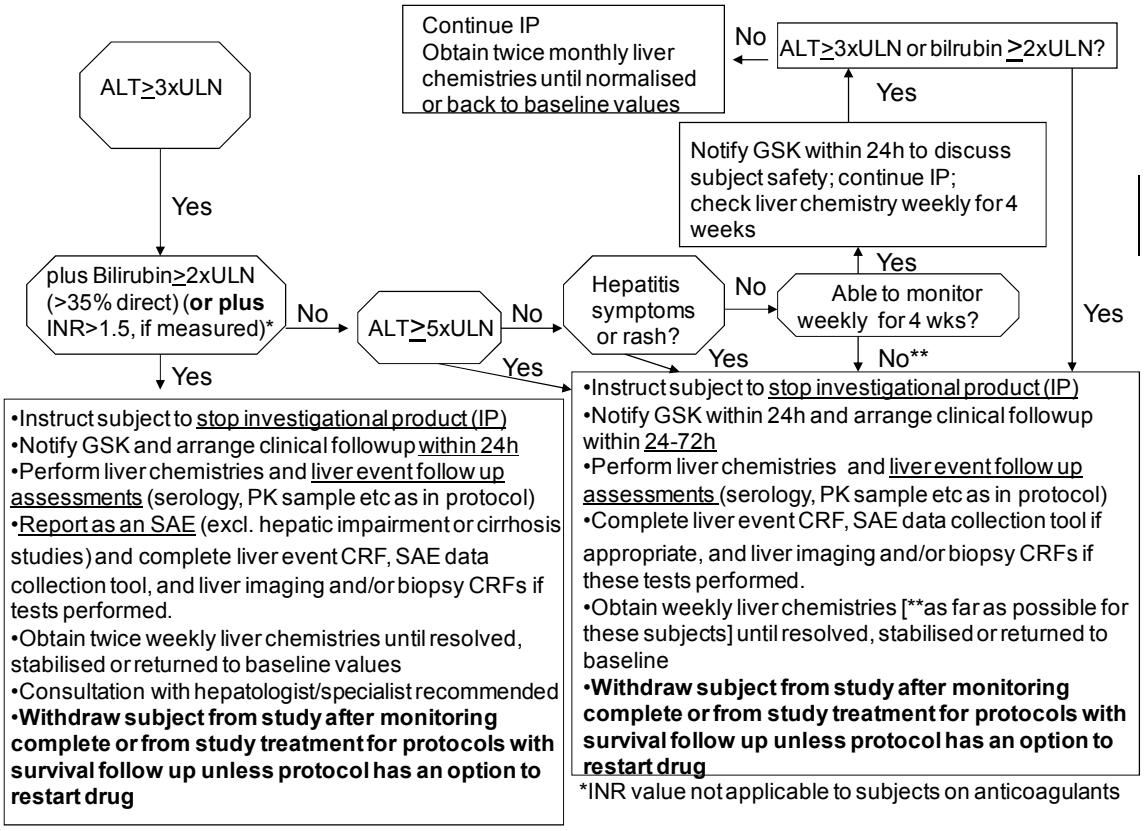
11. REFERENCES



12. APPENDICES

12.1. Appendix 1: Liver Chemistry Monitoring, Interruption Stopping and Follow-up Criteria

Phase II Liver Safety Algorithm



*INR value not applicable to subjects on anticoagulants

12.2. Appendix 2: Protocol Changes

AMENDMENT 01 CHANGES

Changes to Protocol Amendment 01, dated 08-JUL-2013, are outlined below, sequentially by Protocol Section number.

Sponsor Medical Monitor Contact Information

Secondary Medical Monitor has been updated.

List of Abbreviations

PROTOCOL SUMMARY Rationale and Study Assessments

Description and reason for change: Changes were made to clarify the rationale of the study and simplify study assessments.

Original Text:

Rationale

Study TRA117366 is an extension study for pediatric chronic ITP patients who have previously been enrolled in the TRA115450/PETIT2 study.

Amended Text:

Rationale

Study TRA117366 is an extension study for pediatric chronic ITP patients who have previously been enrolled in the TRA115450/PETIT2 study and obtain clinical benefit from treatment with eltrombopag.

Section 2 Objective(s) and Endpoints

Description and reason for change: The objective has been clarified to and endpoints streamlined.

Original Text:

Objective	Endpoint
To describe the safety and tolerability of eltrombopag when administered to pediatric subjects with previously treated chronic ITP.	Safety parameters include clinical laboratory assessments, ophthalmic examinations, and frequency of all adverse events, categorized using Common Terminology Criteria for Adverse Events (CTCAE) toxicity grades.

Revised Text:

Objective	Endpoint
To provide continued treatment to patients who have completed the TRA115450 study and to describe the safety and tolerability of eltrombopag when administered to pediatric subjects with previously treated chronic ITP.	Safety parameters include clinical laboratory assessments and frequency of all adverse events, categorized using Common Terminology Criteria for Adverse Events (CTCAE) toxicity grades.

Section 5 Study Treatments

Description and reason for change: Clarification of the term 'study treatment'.

Original Text:

The term 'stud treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design.

Amended Text:

The term 'study treatment' is used throughout the protocol to describe the product under evaluation in this protocol.

Section 5.1.1. Eltrombopag Dosage and Administration

Description and reason for change: Clarification of dosing by age rather than cohort. Additional guidance has been included for those subjects who switch formulation during the study.

Original Text:

For eltrombopag dosage and administration purposes each eligible subject will be allocated to one of 3 age defined cohorts following the same cohort definition as described in TRA115450. Cohort 1 will describe subjects between 12 and 17 years old, Cohort 2 will describe subjects between 6 and 11 years old, and Cohort 3 will describe subjects between 1 and 5 years old.

For Cohorts 1 and 2, eltrombopag tablets will be administered, however, subjects in Cohort 2 may use PfOS if they have difficulty swallowing tablets and are receiving a dose of eltrombopag of < 40 mg. For Cohort 3, either eltrombopag tablets or PfOS will be administered.

Amended Text:

For subjects between the ages of 6 to 17 years old, eltrombopag tablets will be administered, however, subjects between the ages of 6 to 11 years old may use PfOS if

they have difficulty swallowing tablets and are receiving a dose of eltrombopag of < 40 mg. For subjects between the ages of 1 to 5 years old, either eltrombopag tablets or PfOS will be administered.

Any change between PfOS and tablet formulations 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 Cmax compared to the tablet formulation. When switching from PfOS to tablets, the nearest tablet strength rounding up should be used.

Section 6.1. Permitted Medications and Non-Drug Therapies

Description and reason for change: Clarification around the time period to record prior medications.

Original Text:

All prior ITP treatments that the subject received prior to Day 1 will be recorded in the CRF. A reasonable effort will be made to document any other medications the subject received within 30 days prior to Day 1. Any medication taken within 7 days of study

medication administration must be recorded in the CRF as a prior medication.

Revised Text:

Any medication taken within 7 days of study medication administration must be recorded in the CRF .

Section 6.1.1. and 6.1.2.

Section 7 Study Assessments and Procedures, Table 3

Description and reason for change: Correction of study number within table as well as clarification of assessments.

Original Text:

Table 3 Time and Events Table

TRA115450	Screening[1]	Open-Label Treatment Period					Follow-up Period				
Study Day		**Day 1**	**Weekly**	**Every 4 weeks**	**Every 6 weeks**	**End of Treatment[2]**	**1W FU[3]**	**2W FU[3]**	**3W FU[3]**	**4W FU**	**24W FU**
Informed consent	X										
Medical history and evaluation of eligibility	X										
Physical exam[4]		X									
Vital signs[4]		X	X	X	X	X	X	X	X	X	
Concurrent medication review		X	X	X	X	X	X	X	X	X	
Pregnancy test (urine)[5]		X[5]	At least every 8 weeks							X	
CBC (incl. platelet count)[6]		X	X	X	X	X	X	X	X	X	
Peripheral blood smear[7]		X	X	X	X	X					
Clinical chemistry[8]		X	X	X	X	X	X	X[9]	X[9]	X[9]	
Coagulation assays (INR/aPTT)		X									
AE questioning		X	X	X	X	X	X	X	X	X	
Ophthalmic assessments[10]			Every 6 months			X[10]					X
Additional renal assessment[11]			If indicated[11]								

Table 3 Time and Events Table (Continued)

W: week; FU: follow-up; M: month

Note: If the subject continues on a stable dose of eltrombopag for 3 consecutive weeks, also if at the day 1 patient received stable dose in TRA115450 for at least 3 consecutive weeks (without changes in concomitant ITP therapy), assessments may be scheduled every 4 weeks (±7 days of nominal visit day) rather than weekly. If the subject continues on a stable dose of eltrombopag for 3 consecutive monthly visits (without changes in concomitant ITP therapy), including any consecutive monthly visits in TRA115450 prior to coming into this study, assessments frequency may be further reduced and may be scheduled every 6 weeks (±7 days of nominal visit day). If the dose of eltrombopag is not stable, weekly visits (±3 days of nominal visit day) will be required.

1. Screening visit may occur on the same day as the Day 1 visit.
2. All subjects will attend the End of Treatment visit on the day of or within 3 days after the last dose of study treatment.
3. Subjects who continue on treatment with eltrombopag (i.e., non-study treatment) will not be required to attend the Week 1, 2 and 3 Follow-up visits.
4. Physical Exam, including meadusrement and recording of the height and weight, to be performed at on Day 1. Vital signs to be performed at each visit and to include: heart rate and blood pressure.
5. For female subjects of child-bearing potential, a negative pregnancy test (urine or blood sample) MUST be obtained within 24 hours prior to the first dose. Tests to confirm that female subjects of childbearing potential are not pregnant will be conducted at least once every 8 weeks while receiving study treatment and after 4 weeks following completion or discontinuation of study treatment.
6. CBC parameters: to include platelet count, hemoglobin, hematocrit, RBC, WBC, WBC differential (absolute numbers). Reticulocytes will be measured if haemoglobin <10g/dl.
7. Peripheral blood smear to be performed on Day 1 and at least once every 6 weeks, regardless of the visit schedule (weekly or monthly).
8. Clinical Chemistry: Creatinine, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin and albumin at each visit.
9. If clinical chemistry at follow-up week 1 is normal, no clinical chemistry will be measured at follow-up weeks 2, 3 and 4.
10. The last full ophthalmologic assessment conducted in the TRA115450 study will be used as the baseline ophthalmic assessment for this study. An age-appropriate full ophthalmologic assessment is required once standard of care exam will be performed to assess the presence of cataracts every 6 months while in the study treatment period, at the End of Treatment visit if not conducted within the prior 12 weeks, and at the 24 week follow-up visit.
11. The 'Additional renal assessments' will be done any time there is a creatinine increase considered clinically significant by the ininvestigator. Additional Renal assessments: urine dipstick, microscopic urinalysis, creatinine clearance, urine protein/creatinine ratio. If the urine protein/creatinine ration is > ULN, then a Urine Protein Electrophoresis should be performed,

Revised Text:

Refer to revised Time and Events table in Section 7, Table 3.

Section 7.2.1 Safety Endpoints

Description and reason for change: Clarification of endpoints.

Original Text:

Safety and tolerability endpoints include blood pressure, heart rate, ocular examinations, clinical laboratory assessments and frequency of all adverse events, categorized using Common Terminology Criteria for Adverse Events (CTCAE) v4.03 toxicity grades.

Revised Text:

Safety and tolerability endpoints include clinical laboratory assessments and frequency of all adverse events, categorized using Common Terminology Criteria for Adverse Events (CTCAE) toxicity grades. Refer to the SPM for current version.

Section 7.2.1.1 General Considerations

Description and reason for change: Clarification to be consistent with revised assessments and match Time and Events Table.

Original Text:

Subjects will initially be evaluated on Day 1 with clinical assessments, vital signs, hematology, albumin, serum creatinine, platelet count and liver enzymes. Once the dose of eltrombopag and other ITP medications has been stable for 3 consecutive weeks, which may include the prior 3 weeks in the TRA115450 study, monthly visits will be acceptable unless in the investigator's opinion there is a specific medical reason for more frequent evaluations. If the dose is not stable, weekly visits will be required.

Revised Text:

Once the dose of eltrombopag and other ITP medications has been stable for 3 consecutive weeks, which may include the prior 3 weeks in the TRA115450 study, monthly visits will be acceptable unless in the investigator's opinion there is a specific medical reason for more frequent evaluations. If the dose is not stable, weekly visits will be required.

Section 7.2.1.2. Physical Exam

Description and reason for change: Clarification and the removal of vital signs.

Original Text:

Physical Exam

A physical examination will be done at Day 1 per the investigator's usual practice and any abnormal findings will be recorded on the appropriate form in the CRF, e.g, Medical History or AE/SAE form.

Revised Text:

Physical Exam

A physical examination will be done at the Day 1 per the investigator's usual practice, including measurement and recording of height and weight.

Vital Signs

Vital sign measurements, done at each visit, will include systolic and diastolic blood pressure and heart rate. Vital sign measurements should be performed before any blood draws are performed.

Section 7.2.1.4 Renal Monitoring

Description and reason for change: Renal assessments have been removed.

Deleted Text:

Serum creatinine will be measured at each study visit and will serve as the main tool to check for global renal function.

'Additional renal assessments' will be performed at any time there is a creatinine increase deemed clinically significant by the investigator. No creatinine threshold value is pre-specified, as the study will cover the whole pediatric age-range and creatinine values differ among the different age groups. When a subject requires the 'additional renal assessments', a visit should be scheduled within a week and the assessments repeated. The monitoring should be done weekly until abnormal renal values return to the normal range or baseline values.

'Additional renal assessments' will be assessed as follows:

- The urine protein/creatinine ratio (UP/CR) will be determined. If the UP/CR is above the upper limit of normal, then a urine protein electrophoresis (UPEP) will be performed.
- A microscopic urine analysis will be performed.
- A urine dipstick will be performed to look for pH, glucose, protein, blood and ketones. Urine dipstick will be performed locally using the dipsticks supplied by the central lab.

The glomerular filtration rate (GFR) will be estimated (creatinine clearance).

Section 7.5.1.5 Ophthalmic Assessments

Description and reason for change: Title has been changed to reflect more streamlined assessment and focus on cataract assessment. Subsections 7.2.1.5.1. Baseline Ocular History and Risk Factors, 7.2.1.5.2 Ophthalmic Examinations and 7.2.1.5.4 Additional Ocular Follow-up have been removed.

Original Text:

Ophthalmic safety will be assessed in all subjects using the procedures listed below at the times listed in the Time and Events Table.

Ocular examinations will be performed by an ophthalmologist or an optometrist under the guidance of an ophthalmologist. Baseline and subsequent ocular assessments should be performed, whenever possible, by the same examiner.

Revised Text:

Ophthalmic safety, with focus on cataracts, will be assessed in all subjects following procedures used in standard practice at the times listed in the Time and Events Table.

Ocular examinations will be performed by an ophthalmologist or an optometrist under the guidance of an ophthalmologist. Assessments should be performed, whenever possible, by the same examiner.

Any abnormal findings will be recorded in the appropriate CRF form, e.g., Medical History or AE/SAE form.

Section 7.2.4 Laboratory Assessments

Description and reason for change: Laboratory assessments were streamlined. Table 4 has been amended to reflect this change.

Original Text:

All protocol required laboratory assessments listed in Table 4 will be performed by a local laboratory, in accordance with Table 3, Time and Events Table.

If any additional local laboratory assessments are undertaken during the course of the trial and they result in a change in patient management (for example SAE or AE or dose modification) the assessment data must be recorded in the patients CRF.

Table 4 Local Laboratory Assessments

Coagulation Assays	**Chemistry**
International normalized ration (INR)	Serum creatinine
Activated partial thromboplastin time (aPTT)	AST
	ALT
Peripheral Blood Smear	Total bilirubin
	Direct bilirubin
Hematology	Alkaline phosphatase
Platelet Count	Albumin
Red blood cell (RBC) count	
Reticulocytes if haemoglobin < 10g/dL	**Urine Pregnancy**[1]
Hemoglobin	
Hematocrit	**Urinalysis**, if indicated
WBC count (absolute count) with automated	Urine Dipstick:
differntial to include:	pH
Total neutrophils (absolute count)	Glucose
Lymphocytes (absolute count)	Protein
Monocytes (absolute count)	Blood
Eosinophils (absolute count)	Ketones
Basophils (absolute count)	Microscopic analysis
	Urine protein/creatinine ratio (UP/CR)
	Urine protein electrophoresis (UPEP), if indicated
	Glomerular filtration rate (GFR) (estimated using creatinine clrearance)

2. Refer to Section 7.2.3.1. For further details on pregnancy testing.

Revised Text:

All protocol required laboratory assessments listed in Table 4 will be performed by a local laboratory, in accordance with Table 3, Time and Events Table, and recorded in the CRF, unless otherwise specified.

If any additional local laboratory assessments are undertaken during the course of the trial and they result in a change in patient management (for example SAE or AE or dose modification) the assessment data must be recorded in the patients CRF.

Table 4 Local Laboratory Assessments

	Chemistry
	AST
	ALT
Peripheral Blood Smear	Total bilirubin
	Direct bilirubin
Hematology	Alkaline phosphatase
Platelet Count	
	Urine Pregnancy[1]
Hemoglobin	
WBC count (absolute count)	

3. Refer to Section 7.2.3.1. For further details on pregnancy testing. Results are not captured in CRF, but any pregnancy would be reported as specified in Section 7.2.3.

Section 7.2.5. Meals and Dietary Restrictions

Description and reason for change: Clarification around administration of eltrombopag.

Original Text:

Eltrombopag may be taken 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. (See Section 6.1, Permitted Medications and Non-Drug Therapies).

Revised Text:

Eltrombopag may be taken with food containing little (<50 mg) or preferably no calcium. (See Section 6.1, Permitted Medications and Non-Drug Therapies).

Section 8 Data Management

Description and reason for change: Clarification to data process and removal of repeated text.

Original Text:

For this study CRF Subject data will be collected using GSK defined case report forms and combined with data provided from other sources in a validated data.

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 MedDRA and an internal validated medication dictionary, GSKDrug. In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

Original CRFs will be retained by GSK, while the investigator will retain a copy.

Revised Text:

For this study subject data will be collected using GSK defined case report forms (CRFs) and data entered in a validated 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 MedDRA and an internal validated medication dictionary, GSKDrug. In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

Original CRFs will be retained by GSK, while the investigator will retain a copy.

Section 9.3.5. Key Elements of Analysis Plan

Description and reason for change: The Reporting and Analysis Plan has been removed. This section and each sub-section within have been changes for the modification of analysis and data collection. Changes for each section are highlighted below.

Original Text:

Data will be listed and summarized according to the GSK reporting standards, where applicable. Complete details will be documented in the RAP. And 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.

Demographic and baseline characteristics will be summarized.

Revised Text:

Data will be displayed according to the GSK reporting standards, where applicable.

All data up to the time of study completion/withdrawal from study will be included in the displays, 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.

Demographic and baseline data will be displayed.

Section 9.3.5.1. Safety Analysis

Original Text:

Safety analyses will be performed based on primary safety and tolerability endpoints that include blood pressure, heart rate, ocular examinations, clinical laboratory assessments and frequency of all adverse events, categorized using Common Terminology Criteria for Adverse Events (CTCAE) v4.03 toxicity grades.

The safety will be evaluated using descriptive statistics.

The SAFETY population defined as “All Treated Subjects” (ATS) population will be used for the analysis of safety data. Complete details of the safety analyses will be provided in the RAP.

Revised Text:

Safety displays will present safety and tolerability endpoints that include , clinical laboratory assessments and frequency of all adverse events, categorized using Common Terminology Criteria for Adverse Events (CTCAE) toxicity grades.

“All Treated Subjects” (ATS) population will be used for the presentation of safety data.

Section 9.3.5.1.1. Extent of Exposure

Original Text:

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

Revised Test:

Exposure data will be presented according to the duration of the subject's therapy.

9.3.5.1.2. Adverse Events

Original Text:

Adverse events (AEs) will be coded using the standard GlaxoSmithKline Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class. AEs will be graded by the investigator according to the –CTCAE (version 4.03).

Events will be summarized by frequency and proportion of total subjects, by system organ class and preferred term. Separate summaries will be fiven 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 4.03) table, the maximum grade will be summarized.

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

Revised Text:

Adverse events (AEs) will be coded using the standard GlaxoSmithKline Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class. AEs will be graded by the investigator according to the -CTCAE.

System organ class and preferred term of adverse events will be presented. Drug-related AEs, serious AEs and AEs leading to discontinuation of study medication will also be displayed.

If the AE is listed in the NCI CTCAE table, the maximum grade will be utilized where applicable.

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

Section 9.3.5.1.3. Clinical Laboratory Evaluations

Original Text:

Hematology and clinical chemistry data will be summarized at each scheduled assessment according to NCI CTCAE grade (version 4.03). The proportion of values lying outside the reference range will be presented for laboratory tests that are not graded because there are no associated NCI CTCAE criteria. Summaries will include date 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.

Revised Text:

Hematology and clinical chemistry data will be displayed at each scheduled assessment according to NCI CTCAE grade . Unscheduled data will be included in "overall" and "any post-screening" displays which will capture a worst case across all scheduled and unscheduled visits post first dose of study medication.

Section 9.3.5.1.4. Other Safety Measures

Original Text:

The results of scheduled assessments of body weight, vital signs, will be summarized. Summaries will include data from scheduled assessments only. All data will be reported according to the nominal visit date for which it was recorded (i.e. no visit windows will be applied). All data will be listed. Further details will be provided in the RAP.