ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
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ClinicalTrials.gov ID: NCT00678587

Study Identification

Unique Protocol ID:	TPL104054
Brief Title:	Eltrombopag To Reduce The Need For Platelet Transfusion In Subjects With Chronic Liver Disease And Thrombocytopenia Undergoing Elective Invasive Procedures (ELEVATE)
Official Title:	Randomised, Double-Blind, Placebo-Controlled, Multi-Centre Study to Evaluate the Safety and Efficacy of Eltrombopag to Reduce the Need for Platelet Transfusion in Thrombocytopenic Subjects With Chronic Liver Disease Undergoing Elective Invasive Procedures
Secondary IDs:	

Study Status

Record Verification:	January 2013
Overall Status:	Terminated
Study Start:	June 2008
Primary Completion:	October 2009 [Actual]
Study Completion:	October 2009 [Actual]

Sponsor/Collaborators

Sponsor:	GlaxoSmithKline
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	
IND/IDE Protocol?:	Yes
IND/IDE Information:	Grantor: CDER IND/IDE Number: 75,863 Serial Number: TBD Has Expanded Access? No
Review Board:	Approval Status: Approved Approval Number: 20071049 Board Name: Western Institutional Review Board (WIRB) Board Affiliation: Phone: 001 800 562 4789 Email:
Data Monitoring?:	Yes
Plan to Share Data?:	
Oversight Authorities:	European Union: European Medicines Agency United States: Food and Drug Administration

Study Description

Brief Summary:	The purpose of this study is to assess the ability of eltrombopag to elevate platelet counts thereby reducing the need for platelet transfusions in chronic liver disease patients with thrombocytopenia undergoing elective invasive procedures. The clinical benefit of eltrombopag will be measured by the proportion of subjects who avoid platelet transfusions, before, during and up to 7 days after undergoing an invasive procedure. In addition, bleeding events will be monitored during this time. The number of transfusions, safety events and medical resource utilisation will be monitored during this time and for up to 30 days after undergoing an invasive procedure to help further evaluate clinical benefit.
Detailed Description:	

Conditions

Conditions:	Non-alcoholic Steatohepatitis Chronic Liver Disease HCV NASH. HIV Infection Thrombocytopenia Hepatitis C Virus HBV

Human Immunodeficiency Virus
Liver Diseases
Hepatitis B Virus

Keywords: elective invasive procedure.
platelet transfusion
chronic liver disease-related thrombocytopenia
platelets
thrombopoietin

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 3

Intervention Model: Parallel Assignment

Number of Arms: 2

Masking: Double Blind (Subject, Investigator, Outcomes Assessor)

Allocation: Randomized

Endpoint Classification: Safety/Efficacy Study

Enrollment: 292 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Placebo Comparator: Placebo placebo, once daily, oral	Drug: Placebo placebo, once daily, oral
Active Comparator: Active 75 mg, once daily, oral	Drug: Eltrombopag 75 mg, once daily, oral Other Names: • Eltrombopag

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Male and female subjects, 18 years of age or more with chronic liver disease.
- Child-Pugh score of 12 or less.
- Model of End Stage Liver Disease (MELD) score of 24 or less.
- Subjects who, in the opinion of the investigator, are appropriate candidates to undergo an elective invasive procedure and who require a platelet transfusion to manage the risk of bleeding associated with the procedure.
- A baseline platelet count <50,000/µL.
- A baseline serum sodium level >130mEq/L.
- Haemoglobin concentration >8g/dL stable for at least one month.
- A female is eligible to enter and participate in the study if she is of:

Non-childbearing potential (i.e., physiologically incapable of becoming pregnant) including any female who:

- Has had a hysterectomy
- Has had a bilateral oophorectomy (ovariectomy)
- Has had a bilateral tubal ligation
- Is post-menopausal (demonstrate total cessation of menses for greater than one year)

Childbearing potential, has a negative urine and/or serum pregnancy test at screening, and within the 24 hour period prior to the first dose of investigational product and uses one of the following acceptable methods of contraception:

- Complete abstinence from intercourse for two weeks before exposure to the study drug, throughout the clinical study, and for 28 days after completion or premature discontinuation from the study to account for the elimination of the study drug (minimum of 5 half-lives).
- Any intrauterine device (IUD) with a documented failure rate of less than 1% per year.
- Double-barrier contraception (condom with spermicidal jelly, or diaphragm with spermicide).
- Male partner who is sterile (diagnosed by a qualified medical professional) prior to the female subject's study entry and is the sole sexual partner for that female.
- Oral contraceptive (either combined or progesterone only).
- Any other contraceptive method with a documented failure rate of <1% per year.
- Subject has no physical limitation to ingest and retain oral medication.
- Subject is able to understand and comply with protocol requirements and instructions and is likely to complete the study as planned.
- Subject is able to provide signed and dated written informed consent.
- In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

Exclusion Criteria:

- Subjects with a known hypersensitivity, intolerance or allergy to any of the ingredients in eltrombopag tablets.
- Evidence of portal vein thrombosis on abdominal imaging (ultrasound with Doppler or appropriate MRI/CT imaging techniques) within 3 months of study start.
- History of arterial or venous thrombosis, including Budd-Chiari Syndrome, AND ≥ two of the following risk factors: hereditary thrombophilic disorders (e.g. Factor V Leiden, ATIII deficiency, etc.), hormone replacement therapy, systemic contraception therapy (containing oestrogen), smoking, diabetes, hypercholesterolemia, medication for hypertension or cancer.
- Any disease condition associated with current active WHO Grade 3 or 4 bleeding.
- Active infection requiring systemic antibiotic therapy. Prophylactic use of antibiotics is permitted.
- Pregnant or nursing women.
- Treatment with an investigational drug within 30 days or five half-lives (whichever is longer) preceding the first dose of study medication.
- History of platelet agglutination abnormality that prevents reliable measurement of platelet counts.
- History of porphyria.
- Previous participation in TPL104054.

Contacts/Locations

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References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Reporting Groups

	Description
Placebo	Matching placebo
Eltrombopag 75 mg	Eltrombopag 75 mg administered orally once daily

Overall Study

	Placebo	Eltrombopag 75 mg
Started	147	145
Completed	127	127
Not Completed	20	18
Adverse Event	3	3
Lack of Efficacy	1	0
Protocol Violation	2	1
Study Closed/Terminated	1	0
Lost to Follow-up	3	5
Investigator Discretion	2	6
Withdrew Consent	8	3

Baseline Characteristics

Reporting Groups

	Description
Placebo	Matching placebo
Eltrombopag 75 mg	Eltrombopag 75 mg administered orally once daily

Baseline Measures

	Placebo	Eltrombopag 75 mg	Total
Number of Participants	147	145	292
Age, Continuous [units: Years] Mean (Standard Deviation)	53.5 (11.78)	51.6 (11.04)	52.5 (11.44)
Gender, Male/Female [units: Participants]			
Female	55	49	104
Male	92	96	188
Race/Ethnicity, Customized [units: participants]			
White	93	85	178
Central/South Asian Heritage	33	41	74
Japanese/East Asian/South East Asian Heritage	19	14	33
African American/African Heritage	2	4	6
Native Hawaiian/Other Pacific Islander and White	0	1	1
Number of participants categorized into the indicated Child-Pugh (CP) Class [1] [units: participants]			
Child-Pugh Class A	59	68	127
Child-Pugh Class B	64	57	121

	Placebo	Eltrombopag 75 mg	Total
Child-Pugh Class C	17	10	27
Model for End-Stage Liver Disease (MELD) Score at Baseline [2] [units: scores on a scale] Median (Full Range)	12 (6 to 25)	12 (6 to 24)	12 (6 to 25)

[1] The CP score (ranging from 5 to 15; 5=mild, 15=severe), calculated based on total bilirubin, serum albumin, international normalized ratio, ascites, and hepatic encephalopathy, is used to assess liver disease severity. A CP score of 5 or 6 is classified as Class A (mild), a score of 7-9 is classified as Class B (moderate), and a score >=10 is classified as Class C (severe). Participants with a CP score <10 were enrolled in the study. The number of participants analyzed is 140 for placebo and 135 for Eltrombopag; not all participants were compliant and had their baseline CP score measured.

[2] MELD uses the following formula to calculate a participant's likelihood of dying within 3 months from liver disease: 3.8 x log (e) (bilirubin milligrams [mg]/deciliter [dL]) + 11.2 x log (e) (international ratio for prothrombin time) + 9.6 log (e) (creatinine mg/dL). Scores range from 6 (least ill) to 40 (most ill): 40 or more, 71.3% mortality; 30-39, 52.6% mortality; 20-29, 19.6% mortality; 10-19, 6.0% mortality; <9, 1.9% mortality. The number of participants analyzed is 140 for placebo and 135 for Eltrombopag; not all participants were compliant and had their baseline MELD score measured.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Number of Participants With Chronic Liver Disease and Thrombocytopenia (Platelets <50 Gi/L) Who do Not Require a Platelet Transfusion Prior to, During, and up to 7 Days Following Elective Invasive Procedures
Measure Description	A platelet transfusion was given if the platelet count was <50 giga (10^9) per liter (Gi/L) before the procedure. A platelet transfusion was not given if the platelet count was >80 Gi/L (based on a primary endpoint of success). For participants with platelet counts between 50 Gi/L and 80 Gi/L, platelet transfusions were administered at the discretion of the investigator and the physician performing the elective invasive procedure.
Time Frame	Prior to, during, and up to seven days following elective invasive procedures (Study Days 16-19); therefore, this covers a time period from Baseline to Day 26
Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) Population: all participants who were randomized to treatment

Reporting Groups

	Description
Placebo	Matching placebo

	Description
Eltrombopag 75 mg	Eltrombopag 75 mg administered orally once daily

Measured Values

	Placebo	Eltrombopag 75 mg
Number of Participants Analyzed	147	145
Number of Participants With Chronic Liver Disease and Thrombocytopenia (Platelets <50 Gi/L) Who do Not Require a Platelet Transfusion Prior to, During, and up to 7 Days Following Elective Invasive Procedures [units: participants]	28	104

Statistical Analysis 1 for Number of Participants With Chronic Liver Disease and Thrombocytopenia (Platelets <50 Gi/L) Who do Not Require a Platelet Transfusion Prior to, During, and up to 7 Days Following Elective Invasive Procedures

Statistical Analysis Overview	Comparison Groups	Placebo, Eltrombopag 75 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Absolute difference in proportions]
	Estimated Value	52.8
	Confidence Interval	(2-Sided) 95% 43.2 to 62.4
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Number of Participants With a World Health Organization (WHO) Bleeding Score >=2 During and up to 7 Days Following Elective Invasive Procedures
Measure Description	The WHO Bleeding Scale was used to assess bleeding during the study. The range of possible scores is 0 to 4. Grade 0 is no bleeding; Grade 1 is petechiae (small [1-2 millimeter] red or purple spot on the body, caused by a minor hemorrhage); Grade 2 is mild blood loss; Grade 3 is gross blood loss (requiring a transfusion; and Grade 4 is debilitating blood loss (retinal or cerebral associated with fatality).
Time Frame	Prior to, during, and up to 7 days following elective invasive procedures (Study Days 16-19); therefore, this covers a time period from Baseline to Day 26
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Placebo	Matching placebo
Eltrombopag 75 mg	Eltrombopag 75 mg administered orally once daily

Measured Values

	Placebo	Eltrombopag 75 mg
Number of Participants Analyzed	147	145
Number of Participants With a World Health Organization (WHO) Bleeding Score >=2 During and up to 7 Days Following Elective Invasive Procedures [units: participants]	34	25

Statistical Analysis 1 for Number of Participants With a World Health Organization (WHO) Bleeding Score >=2 During and up to 7 Days Following Elective Invasive Procedures

Statistical Analysis Overview	Comparison Groups	Placebo, Eltrombopag 75 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	-5.9
	Confidence Interval	(2-Sided) 95% -15.1 to 3.3
	Estimation Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Number of Participants With the Indicated Number of Platelet Transfusions Administered
Measure Description	Platelet transfusion use was documented at every visit throughout the study from screening until the 4-week (30-day) post-procedure follow-up visit or at the time of participant withdrawal from the study.
Time Frame	Prior to, during, and up to 4 weeks (30 days) following elective invasive procedures (Days 16-19); therefore, this covers a time period from Baseline to Day 26
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Placebo	Matching placebo
Eltrombopag 75 mg	Eltrombopag 75 mg administered orally once daily

Measured Values

	Placebo	Eltrombopag 75 mg
Number of Participants Analyzed	147	145
Number of Participants With the Indicated Number of Platelet Transfusions Administered [units: participants]		
0	30	106
1	93	24
2	3	1
3	2	0
4	3	0

	Placebo	Eltrombopag 75 mg
5	0	0
6	1	0
Died/withdrew prior to any platelet transfusions	15	14

Statistical Analysis 1 for Number of Participants With the Indicated Number of Platelet Transfusions Administered

Statistical Analysis Overview	Comparison Groups	Placebo, Eltrombopag 75 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Median Platelet Count at Screening; Days 1, 8, 15, 16-19; Procedure + 7, 14, 21, 30 Day Follow-up; Early Withdrawal; and Maximum Post-baseline
Measure Description	Procedure +7 = Days 23-26; +14 = Days 30-33; +21 = Days 37-40; +30 = Days 46-49. Early withdrawal can occur at any time. Maximum post-baseline refers to any time point listed above for which the maximum value was reached (therefore this time point is variable).
Time Frame	Screening; Days 1, 8, 15, 16-19; Procedure + 7, 14, 21, 30 day follow-up; early withdrawal; and maximum post-baseline
Safety Issue?	No

Analysis Population Description

ITT Population. The number of participants analyzed decreases over time due to missing measurements and to participants dropping out of the study.

Reporting Groups

	Description
Placebo	Matching placebo

	Description
Eltrombopag 75 mg	Eltrombopag 75 mg administered orally once daily

Measured Values

	Placebo	Eltrombopag 75 mg
Number of Participants Analyzed	147	145
Median Platelet Count at Screening; Days 1, 8, 15, 16-19; Procedure + 7, 14, 21, 30 Day Follow-up; Early Withdrawal; and Maximum Post-baseline [units: Gi/L] Median (Full Range)		
Screening, n=147, 145	40.0 (8 to 70)	40.0 (3 to 55)
Day 1, n=145, 141	40.0 (8 to 222)	40.0 (12 to 62)
Day 8, n=139, 134	41.0 (6 to 190)	58.5 (20 to 337)
Day 15, n=132, 131	39.0 (6 to 200)	103.0 (25 to 397)
Days 16-19, n=50, 49	41.5 (18 to 250)	107.0 (30 to 406)
Procedure + 7 day follow-up, n=128, 125	44.0 (17 to 150)	148 (30 to 493)
Procedure + 14 day follow-up, n=116, 125	47.5 (13 to 370)	110 (18 to 805)
Procedure + 21 day follow-up, n=120, 117	44.5 (11 to 200)	62.0 (15 to 967)
Procedure + 30 day follow-up, n=125, 127	40.0 (10 to 200)	50.0 (14 to 999)
Early withdrawal, n=9, 8	40.0 (11 to 195)	41.0 (32 to 140)
Maximum post-baseline, n=144, 140	53.0 (16 to 370)	152 (32 to 999)

5. Secondary Outcome Measure:

Measure Title	Number of Participants With the Indicated Platelet Count at Screening; Days 8 and 15; Procedure + 7, 14, 21, 30 Day Follow-up (FU); and Maximum Post-baseline
Measure Description	Procedure +7 = Days 23-26; +14 = Days 30-33; +21 = Days 37-40; +30 = Days 46-49. Early withdrawal can occur at any time. Maximum post-baseline refers to any time point listed above for which the maximum value was reached (therefore this time point is variable).
Time Frame	Screening; Days 8 and 15; Procedure + 7, 14, 21, 30 day follow-up; and maximum post-baseline
Safety Issue?	No

Analysis Population Description

ITT Population. The number of participants analyzed decreases over time due to missing measurements and to participants dropping out of the study.

Reporting Groups

	Description
Placebo	Matching placebo
Eltrombopag 75 mg	Eltrombopag 75 mg administered orally once daily

Measured Values

	Placebo	Eltrombopag 75 mg
Number of Participants Analyzed	147	145
Number of Participants With the Indicated Platelet Count at Screening; Days 8 and 15; Procedure + 7, 14, 21, 30 Day Follow-up (FU); and Maximum Post-baseline [units: participants]		
Screening, <50 Gi/L, n=147, 145	133	136
Screening, >=50-<=80 Gi/L, n=147, 145	14	8
Screening, >80-<=200 Gi/L, n=147, 145	0	0
Screening, >200-<=400 Gi/L, n=147, 145	0	0
Screening, >400 Gi/L, n=147, 145	0	0
Day 8, <50 Gi/L, n=139, 135	98	48
Day 8, >=50-<=80 Gi/L, n=139, 135	34	50
Day 8, >80-<=200 Gi/L, n=139, 135	7	33
Day 8, >200-<=400 Gi/L, n=139, 135	0	3
Day 8, >400 Gi/L, n=139, 135	0	0
Day 15, <50 Gi/L, n=132, 131	98	14
Day 15, >=50-<=80 Gi/L, n=132, 131	26	31
Day 15, >80-<=200 Gi/L, n=132, 131	8	67
Day 15, >200-<=400 Gi/L, n=132, 131	0	19
Day 15, >400 Gi/L, n=132, 131	0	0

	Placebo	Eltrombopag 75 mg
Procedure + 7 Day FU, <50 Gi/L, n=128, 126	78	11
Procedure + 7 Day FU, >=50-<=80 Gi/L, n=128, 126	38	20
Procedure + 7 Day FU, >80-<=200 Gi/L, n=128, 126	12	60
Procedure + 7 Day FU, >200-<=400 Gi/L, n=128, 126	0	30
Procedure + 7 Day FU, >400 Gi/L, n=128, 126	0	4
Procedure + 14 Day FU, <50 Gi/L, n=117, 125	63	22
Procedure + 14 Day FU, >=50-<=80 Gi/L, n=117, 125	40	21
Procedure + 14 Day FU, >80-<=200 Gi/L, n=117, 125	11	62
Procedure + 14 Day FU, >200-<=400 Gi/L, n=117, 125	2	17
Procedure + 14 Day FU, >400 Gi/L, n=117, 125	0	3
Procedure + 21 Day FU, <50 Gi/L, n=121, 117	80	38
Procedure + 21 Day FU, >=50-<=80 Gi/L, n=121, 117	30	33
Procedure + 21 Day FU, >80-<=200 Gi/L, n=121, 117	10	38
Procedure + 21 Day FU, >200-<=400 Gi/L, n=121, 117	0	7
Procedure + 21 Day FU, >400 Gi/L, n=121, 117	0	1
Maximum Post-Baseline, <50 Gi/L, n=144, 140	60	11
Maximum Post-Baseline, >=50-<=80 Gi/L, n=144, 140	53	23
Maximum Post-Baseline, >80-<=200 Gi/L, n=144, 140	28	62
Maximum Post-Baseline, >200-<=400 Gi/L, n=144, 140	3	37
Maximum Post-Baseline, >400 Gi/L, n=144, 140	0	7

6. Secondary Outcome Measure:

Measure Title	Number of Participants Experiencing an Adverse Event (AEs) and Serious Adverse Event (SAEs) Within the Indicated Category
Measure Description	An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An SAE is any untoward medical occurrence that, at any dose: results in death; is life-threatening; requires hospitalization or prolongation of existing hospitalization; results in disability/incapacity; is a congenital anomaly/birth defect or an ocular event of clinical concern. Medical or scientific judgement is exercised in deciding whether reporting is appropriate in other situations.
Time Frame	Screening to Procedure +30 day follow-up or early withdrawal
Safety Issue?	No

Analysis Population Description

Safety population: all randomized participants who received at least one dose of study medication

Reporting Groups

	Description
Placebo	Matching placebo
Eltrombopag 75 mg	Eltrombopag 75 mg administered orally once daily

Measured Values

	Placebo	Eltrombopag 75 mg
Number of Participants Analyzed	145	142
Number of Participants Experiencing an Adverse Event (AEs) and Serious Adverse Event (SAEs) Within the Indicated Category [units: participants]		
AEs during study	85	79
Drug-related AEs in >1 participant	15	31
Throboembolic AEs	2	6
Bleeding AEs	25	19
Hepatobiliary AEs	16	24
Malignancy AEs	1	1

	Placebo	Eltrombopag 75 mg
Renal AEs	4	2
Death on study	2	3
SAEs in >1 participant during study	17	19
Drug-related SAEs in >1 participant	4	9
Thrombocytopenia	1	1
Progression of pre-existing cataract n=145,143	2	0
Incident cataract develpment n=145,143	2	4
Decrease in visual acuity n=121,124	19	21
Renal function abnormality n=145,143	27	28
Clinically significant change in ECG n=128,130	0	1

7. Secondary Outcome Measure:

Measure Title	Number of Participants With a Serious Adverse Event That Occurred in Greater Than One Participant
Measure Description	
Time Frame	Screening to Procedure +30 day follow-up or early withdrawal
Safety Issue?	No

Analysis Population Description
Safety Population

Reporting Groups

	Description
Placebo	Matching placebo
Eltrombopag 75 mg	Eltrombopag 75 mg administered orally once daily

Measured Values

	Placebo	Eltrombopag 75 mg
Number of Participants Analyzed	145	143

	Placebo	Eltrombopag 75 mg
Number of Participants With a Serious Adverse Event That Occurred in Greater Than One Participant [units: participants]	4	9

8. Secondary Outcome Measure:

Measure Title	Number of Participants With the Indicated Event Relating to Vision
Measure Description	The progression of pre-existing cataracts was measured by the use of slit lamp examination. Decrease in visual acuity is defined as the loss of 3 or more lines of visual acuity in either eye (0.3 log minimal angle of resolution [logMAR], 15 letters on the standard Early Treatment Diabetic Retinopathy Study chart).
Time Frame	Screening or Baseline and at End of Study (Procedure +30 day follow-up or withdrawal visit)
Safety Issue?	No

Analysis Population Description

Safety Population: all randomized participants who received at least one dose of study medication. Data are missing for some participants.

Reporting Groups

	Description
Placebo	Matching placebo
Eltrombopag 75 mg	Eltrombopag 75 mg administered orally once daily

Measured Values

	Placebo	Eltrombopag 75 mg
Number of Participants Analyzed	145	143
Number of Participants With the Indicated Event Relating to Vision [units: participants]		
Progression of pre-existing cataract, n=145, 143	2	0
Cataract development, n=145, 143	2	4
Decrease in visual acuity, n=121, 124	19	21

9. Secondary Outcome Measure:

Measure Title	Number of Participants With Renal Function Abnormality
Measure Description	Renal function abnormality was defined by threshold values for: serum creatinine: change from baseline of >=0.3 and <0.5 milligrams (mg)/deciliter (dL) (>=26.6 and <44.3 micromoles [umol]/L) or change from baseline of >=0.5 mg/dL (>=44.3 umol/L); microscopic urine analysis: cellular casts pathologic (as defined by local standards of microscopic urine analysis); urine protein/creatinine ratio (UP/CR): >0.5 mg/mg; Glomerular Filtration Rate (GFR) as determined by the Cockcroft-Gault formula and urine dipstick test.
Time Frame	Screening to Procedure +30 day follow-up or early withdrawal
Safety Issue?	No

Analysis Population Description
Safety Population

Reporting Groups

	Description
Placebo	Matching placebo
Eltrombopag 75 mg	Eltrombopag 75 mg administered orally once daily

Measured Values

	Placebo	Eltrombopag 75 mg
Number of Participants Analyzed	145	143
Number of Participants With Renal Function Abnormality [units: participants]	27	28

10. Secondary Outcome Measure:

Measure Title	Number of Participants With a Clinically Significant Change in Electrocardiogram (ECG) Results
Measure Description	A 12-lead ECG was obtained in duplicate at screening, baseline, Day 15, and withdrawal from the study. Participants rested supine for 5 minutes before the 12-lead ECG was recorded. A 30 second rhythm strip was obtained, and the ECG was calibrated, labelled, and initialled by the person performing the recording. A written, interpretive assessment detailing clinical significance was produced, dated, and signed off by the physician at the site.
Time Frame	Screening, Baseline, Day 15, and Withdrawal
Safety Issue?	No

Analysis Population Description

Safety Population. Data were missing for some participants.

Reporting Groups

	Description
Placebo	Matching placebo
Eltrombopag 75 mg	Eltrombopag 75 mg administered orally once daily

Measured Values

	Placebo	Eltrombopag 75 mg
Number of Participants Analyzed	128	130
Number of Participants With a Clinically Significant Change in Electrocardiogram (ECG) Results [units: participants]	0	1

11. Secondary Outcome Measure:

Measure Title	Pharmacokinetics (PK) of Eltrombopag, Steady State AUC(0-tau)
Measure Description	AUC(0-tau) is the area under a concentration versus time curve between dose interval following repeat dosing. It is a measure of systemic drug exposure.
Time Frame	Day 14
Safety Issue?	No

Analysis Population Description

PK Subpopulation: all participants who were treated with eltrombopag and provided evaluable PK samples

Reporting Groups

	Description
Eltrombopag 75 mg	Eltrombopag 75 mg administered orally once daily

Measured Values

	Eltrombopag 75 mg
Number of Participants Analyzed	41
Pharmacokinetics (PK) of Eltrombopag, Steady State AUC(0-tau) [units: hour*micrograms (ug)/milliliter (mL)]	250 (211 to 296)

	Eltrombopag 75 mg
Geometric Mean (95% Confidence Interval)	

12. Secondary Outcome Measure:

Measure Title	Pharmacokinetics (PK) of Eltrombopag, Cmax
Measure Description	Cmax is the steady state peak plasma concentration of a drug observed after its administration.
Time Frame	Day 14
Safety Issue?	No

Analysis Population Description
PK Subpopulation

Reporting Groups

	Description
Eltrombopag 75 mg	Eltrombopag 75 mg administered orally once daily

Measured Values

	Eltrombopag 75 mg
Number of Participants Analyzed	41
Pharmacokinetics (PK) of Eltrombopag, Cmax [units: ug/mL] Geometric Mean (95% Confidence Interval)	11.6 (9.8 to 13.6)

13. Secondary Outcome Measure:

Measure Title	Pharmacokinetics (PK) of Eltrombopag, t1/2
Measure Description	t1/2 is the half life of a drug based on its terminal phase. Half life is defined as the time necessary to halve the plasma concentration.
Time Frame	Day 14
Safety Issue?	No

Analysis Population Description
PK Subpopulation

Reporting Groups

	Description
Eltrombopag 75 mg	Eltrombopag 75 mg administered orally once daily

Measured Values

	Eltrombopag 75 mg
Number of Participants Analyzed	41
Pharmacokinetics (PK) of Eltrombopag, t1/2 [units: hours] Geometric Mean (95% Confidence Interval)	70.3 (60.7 to 81.5)

14. Secondary Outcome Measure:

Measure Title	Pharmacokinetics (PK) of Eltrombopag, CL/F
Measure Description	CL/F is the apparent plasma clearance, where CL is an estimate of the total body clearance, and F is the fraction of dose absorbed. Total clearance is the volume of blood cleared of the drug by the various elimination processes (metabolism and excretion) per unit time.
Time Frame	Day 14
Safety Issue?	No

Analysis Population Description
PK Subpopulation

Reporting Groups

	Description
Eltrombopag 75 mg	Eltrombopag 75 mg administered orally once daily

Measured Values

	Eltrombopag 75 mg
Number of Participants Analyzed	41
Pharmacokinetics (PK) of Eltrombopag, CL/F [units: Liters/hour] Geometric Mean (95% Confidence Interval)	0.30 (0.25 to 0.36)

15. Secondary Outcome Measure:

Measure Title	Mean Number of Days Spent in the Hospital
Measure Description	The number of days spent in the hospital was analyzed as an indication of medical resource utilization throughout the study.
Time Frame	Prior to, during, and up to 4 weeks (30 days) following elective invasive procedures (Days 16-19); therefore, this covers a time period from Baseline to Day 26
Safety Issue?	No

Analysis Population Description

ITT Population. Data are missing for some participants.

Reporting Groups

	Description
Placebo	Matching placebo
Eltrombopag 75 mg	Eltrombopag 75 mg administered orally once daily

Measured Values

	Placebo	Eltrombopag 75 mg
Number of Participants Analyzed	144	144
Mean Number of Days Spent in the Hospital [units: days] Mean (Standard Deviation)	1.3 (3.77)	1.7 (6.43)

16. Secondary Outcome Measure:

Measure Title	Mean Number of Unscheduled Office Visits, Unscheduled Laboratory Tests, and Unscheduled Procedures
Measure Description	The number of unscheduled events was analyzed as an indication of medical resource utilization throughout the study.
Time Frame	Prior to, during, and up to 4 weeks (30 days) following elective invasive procedures (Days 16-19); therefore, this covers a time period from Baseline to Day 26
Safety Issue?	No

Analysis Population Description

ITT Population. Data are missing for some participants.

Reporting Groups

	Description
Placebo	Matching placebo
Eltrombopag 75 mg	Eltrombopag 75 mg administered orally once daily

Measured Values

	Placebo	Eltrombopag 75 mg
Number of Participants Analyzed	144	144
Mean Number of Unscheduled Office Visits, Unscheduled Laboratory Tests, and Unscheduled Procedures [units: unscheduled events] Mean (Standard Deviation)		
Unscheduled office visits	0.8 (1.64)	1.0 (2.91)
Unscheduled laboratory tests	1.1 (3.78)	1.8 (5.67)
Unscheduled procedures	0.3 (0.81)	0.4 (1.65)

Reported Adverse Events

Time Frame	Adverse events (AEs) and serious adverse events (SAEs) with an onset on or after the start date of study medication were collected until the end of the study (up to the end of Week 7).
Additional Description	The Safety Population, comprised of all randomized participants who received at least one dose of study medication, was used for the collection of AEs and SAEs.

Reporting Groups

	Description
Placebo	Matching placebo
Eltrombopag 75 mg	Eltrombopag 75 mg administered orally once daily

Serious Adverse Events

	Placebo	Eltrombopag 75 mg
	Affected/At Risk (%)	Affected/At Risk (%)
Total	17/145 (11.72%)	19/143 (13.29%)
Blood and lymphatic system disorders		
Thrombocytopenia [A] †	1/145 (0.69%)	0/143 (0%)
Thrombocytosis [A] †	0/145 (0%)	1/143 (0.7%)
Cardiac disorders		
Acute myocardial infaction [A] †	1/145 (0.69%)	0/143 (0%)
Atrial fibrillation [A] †	0/145 (0%)	1/143 (0.7%)
Eye disorders		
Cataract [A] †	3/145 (2.07%)	1/143 (0.7%)
Macular degeneration [A] †	0/145 (0%)	1/143 (0.7%)
Visual accuity reduced [A] †	0/145 (0%)	1/143 (0.7%)
Gastrointestinal disorders		
Abdominal pain [A] †	0/145 (0%)	1/143 (0.7%)
Appendix disorder [A] †	0/145 (0%)	1/143 (0.7%)
Ascites [A] †	0/145 (0%)	1/143 (0.7%)
Colitis ischaemia [A] †	0/145 (0%)	1/143 (0.7%)
Gastric ulcer haemorrhage [A] †	1/145 (0.69%)	0/143 (0%)
Ileus paralytic [A] †	0/145 (0%)	1/143 (0.7%)
Impaired gastric emptying [A] †	1/145 (0.69%)	0/143 (0%)
Intestinal perforation [A] †	0/145 (0%)	1/143 (0.7%)
Mesenteric vein thrombosis [A] †	1/145 (0.69%)	3/143 (2.1%)
Nausea [A] †	1/145 (0.69%)	0/143 (0%)

	Placebo	Eltrombopag 75 mg
	Affected/At Risk (%)	Affected/At Risk (%)
Oesophageal haemorrhage [A] †	0/145 (0%)	1/143 (0.7%)
Oesophageal varices haemorrhage [A] †	1/145 (0.69%)	0/143 (0%)
Pancreatitis acute [A] †	0/145 (0%)	1/143 (0.7%)
Peritonitis [A] †	0/145 (0%)	1/143 (0.7%)
Rectal haemorrhage [A] †	2/145 (1.38%)	0/143 (0%)
Upper gastrointestinal haemorrhage [A] †	0/145 (0%)	1/143 (0.7%)
General disorders		
Multi-organ failure [A] †	1/145 (0.69%)	0/143 (0%)
Pyrexia [A] †	0/145 (0%)	1/143 (0.7%)
Hepatobiliary disorders		
Chronic hepatic failure [A] †	0/145 (0%)	1/143 (0.7%)
Hepatorenal syndrome [A] †	1/145 (0.69%)	0/143 (0%)
Portal vein thrombosis [A] †	2/145 (1.38%)	4/143 (2.8%)
Infections and infestations		
Appendicitis [A] †	0/145 (0%)	1/143 (0.7%)
Gastroenteristis [A] †	1/145 (0.69%)	1/143 (0.7%)
Peritonitis acute [A] †	1/145 (0.69%)	0/143 (0%)
Pneumonia [A] †	0/145 (0%)	1/143 (0.7%)
Pyelonephritis acute [A] †	0/145 (0%)	1/143 (0.7%)
Sepsis [A] †	0/145 (0%)	2/143 (1.4%)
Tuberculosis [A] †	1/145 (0.69%)	0/143 (0%)
Injury, poisoning and procedural complications		
Wound dehiscence [A] †	1/145 (0.69%)	0/143 (0%)

	Placebo	Eltrombopag 75 mg
	Affected/At Risk (%)	Affected/At Risk (%)
Metabolism and nutrition disorders		
Fluid retention [A] †	0/145 (0%)	1/143 (0.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
B-cell lymphoma [A] †	0/145 (0%)	1/143 (0.7%)
Nervous system disorders		
Encephalopathy [A] †	1/145 (0.69%)	1/143 (0.7%)
Hepatic encephalopathy [A] †	3/145 (2.07%)	2/143 (1.4%)
Renal and urinary disorders		
Renal failure acute [A] †	1/145 (0.69%)	0/143 (0%)
Respiratory, thoracic and mediastinal disorders		
Acute respiratory failure [A] †	0/145 (0%)	1/143 (0.7%)
Hepatic hydrothorax [A] †	0/145 (0%)	1/143 (0.7%)
Pneumonia aspiration [A] †	0/145 (0%)	1/143 (0.7%)
Pneumothorax [A] †	1/145 (0.69%)	0/143 (0%)
Vascular disorders		
Orthostatic hypotension [A] †	1/145 (0.69%)	0/143 (0%)
Shock [A] †	1/145 (0.69%)	0/143 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA, v12.1

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Placebo	Eltrombopag 75 mg
	Affected/At Risk (%)	Affected/At Risk (%)
Total	35/145 (24.14%)	40/143 (27.97%)
Gastrointestinal disorders		
Abdominal pain [A] †	7/145 (4.83%)	7/143 (4.9%)
Diarrhoea [A] †	5/145 (3.45%)	7/143 (4.9%)
Nausea [A] †	7/145 (4.83%)	7/143 (4.9%)
General disorders		
Pyrexia [A] †	10/145 (6.9%)	8/143 (5.59%)
Nervous system disorders		
Headache [A] †	6/145 (4.14%)	11/143 (7.69%)

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA, v12.1

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

GSK agreements may vary with individual investigators, but will not prohibit any investigator from publishing. GSK supports the publication of results from all centers of a multi-center trial but requests that reports based on single-site data not precede the primary publication of the entire clinical trial.

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