Statistical Analysis Plan (SAP)

1. Administrative Information

Title	Treatment of throm*B*ocytopenia with Elt*R*ombopag or *I*ntravenous Immune Globulin (IVIG) Before and *D*ur*ING* Invasive Procedures in Patients with *I*mmune *T*hrombocyto*P*enia- *BRIDGING ITP Study*
Trial Registration Number	NCT01621204
SAP Version Date	April 2, 2019
Protocol Version Date	February 22, 2017
Principal Investigator	Donald M. Arnold, MD
Roles and Responsibilities	Julie Carruthers, MLT, B.Com, Program Manager Na Li, PhD, Statistician
Approval signatures	Person writing the SAP: Na Li, PhD, Statistician Signature: Coordinator: Julie Carruthers, MLT, B.Com, Program Manager Signature: Principal investigator: Donald M. Arnold, MD Signature: Site investigators: Mark Blostein, MD Signature: Cyrus Hsia, MD Signature: Jeannine Kassis, MD Signature: Loree Larratt, MD Signature: Yulia Lin, MD Signature:

	Michelle Sholzberg, MD Signature: Alan Tinmouth, MD Signature: Martin Schipperus, MD Signature: <u>Steering Committee Members:</u> Richard Cook, PhD. Signature: Nancy Heddle, MSc., FCSMLS(D) Signature:

2. Introduction

This document outlines the analysis plans for the Bridging study, an open-label randomized non-inferiority trial in which patients with immune thrombocytopenia (ITP), who require an increase in platelet count before elective surgery, were randomized in a 1:1 fashion to receive either eltrombopag or intravenous immune globulin (IVIG). The primary aim is to compare the proportion of patients achieving the platelet count threshold before surgery (50 $x10^9$/L for minor surgery; 100 $x10^9$/L for major surgery) and maintaining platelet counts within the target range until 7 days after surgical hemostasis is achieved without the use of ITP rescue treatment.

3. Study Method Summary

Study Objective	To compare the effect of eltrombopag and IVIG on the achievement of the platelet count threshold during the period from immediately before surgery to 7 days after surgical hemostasis.
Study Design	Randomized, open label, parallel arm, non-inferiority trial
Treatment Allocations	Experimental arm: Eltrombopag (50 mg starting dose) daily oral pill on Day -21 before surgery and ending 7 days after surgical hemostasis is achieved; Control arm: IVIG infusion (1 or 2 g/kg) given over 1 or 2 days, administered on Day -7 +/- 2 days before surgery.
Patient Population	Thrombocytopenic adult ITP patients who require an elevation in their platelet count because of a planned surgical procedure.
Planned Sample Size	74 total patients (37 per arm) from 8 centres in Canada. Anticipated recruitment period – 3 years.
Eligibility criteria	Inclusion criteria: • Primary or secondary ITP; • Platelet count below 50 $x10^9$/L for minor surgery; or below 100 x 10^9/L for major surgery; • 18 years of age or older; • On stable doses of concomitant ITP medications (no change in dose) or no ITP medication in the past 2 weeks; • At least 3-weeks lead time between randomization and scheduled surgery; • IVIG and eltrombopag are acceptable ITP treatment options. Exclusion criteria: • Pregnancy or breastfeeding; • Treatment with IVIG within the last 2 weeks; • Treatment with a thrombopoietin receptor agonist (eltrombopag or romiplostim) within the last 4 weeks; • AST, ALT above 2X upper limit of normal; • Bilirubin above 1.5X upper limit of normal in the absence of clinically benign liver disorder (e.g. Gilberts syndrome); • Deep vein thrombosis, myocardial infarction, thrombotic stroke or arterial thrombosis in the last 12 months; • History of bone marrow reticulin or fibrosis;

	• Known liver cirrhosis; • Active malignancy (defined as requiring treatment or palliation within the last 6 months); • Any additional laboratory test result, health related illness or other diagnosis which, in the opinion of the treating physician, may put the subject's health or safety at risk.
Study Outcomes	<u>Primary outcome:</u> • Success in achieving the desired platelet threshold during the period immediately before surgery to 7 days after surgical hemostasis. <u>Secondary outcomes:</u> • Time to treatment failure; • Proportion of patients with surgical delays or cancellations; • Proportion of patients with bleeding events; • Proportion of patients with thrombocytosis; • Proportion of patients with blood product transfusions (red blood cells, platelets, plasma); • Proportion of patients with rescue treatment; • Platelet count trend over time; • Patient satisfaction with treatment; • Proportion of patients with hospitalizations; • Proportion of patients with thrombosis; • Proportion of patients with adverse events.
Duration of Study Participation	Eltrombopag (oral pill) will be administered on Day -21 until 7 days after surgical hemostasis is achieved (ie. once surgery-related bleeding has stopped). IVIG (intravenous) will be administered on Day -7 +/- 2days. For most minor procedures, surgical hemostasis is expected to occur on Day 0, immediately after surgery. For major surgeries, hemostasis may take 0 – 7 days to achieve; thus, the duration of treatment post-surgery can be up to 14 days. For most patients, duration of study participation will be 28 days on treatment + 28 days follow up.

4. Statistical Principles

Confidence Intervals (CIs) and P-values	For primary outcomes, two-sided 95% CI for the proportion of treatment success in each arm, and the one-sided 95% CI for the difference in proportions between the two arms will be reported. A p-value less than 0.05 (one-sided alpha level of 0.05) from a one-sided two-sample proportion test will be considered statistically significant for non-inferiority. For secondary outcomes, (two-sided) 95% CIs for proportions or means will be reported for both arms. A p-value less than 0.05 (two-sided alpha level of 0.05) will be considered statistically significant.
Adherence and Protocol Deviations	• Adherence to the intervention is defined as having received at least one dose of the allocated study drug (eltrombopag or IVIG) and maintained the plan for surgery. • Adherence to the intervention will be presented as the proportion of patients who were fully compliant with the dosing of study drug as per protocol, and the proportion of patients who were less than fully compliant with the protocol. • The protocol deviations that will be summarized are interventions that were less than fully compliant with the protocol, eligibility criteria deviations and losses to follow up.
Analysis Populations	The primary analysis is intention to treat (ITT). A per protocol (PP) analysis is also planned for this non-inferiority trial. ITT analysis will be done for all patients who are enrolled and randomly allocated to treatment. PP analysis will be done for patients who are randomized, received study drug and maintained the plan for surgery.

5. Trial population: Screening of Patients, Randomization to Treatment Arm and Study Completion (Figure 1)

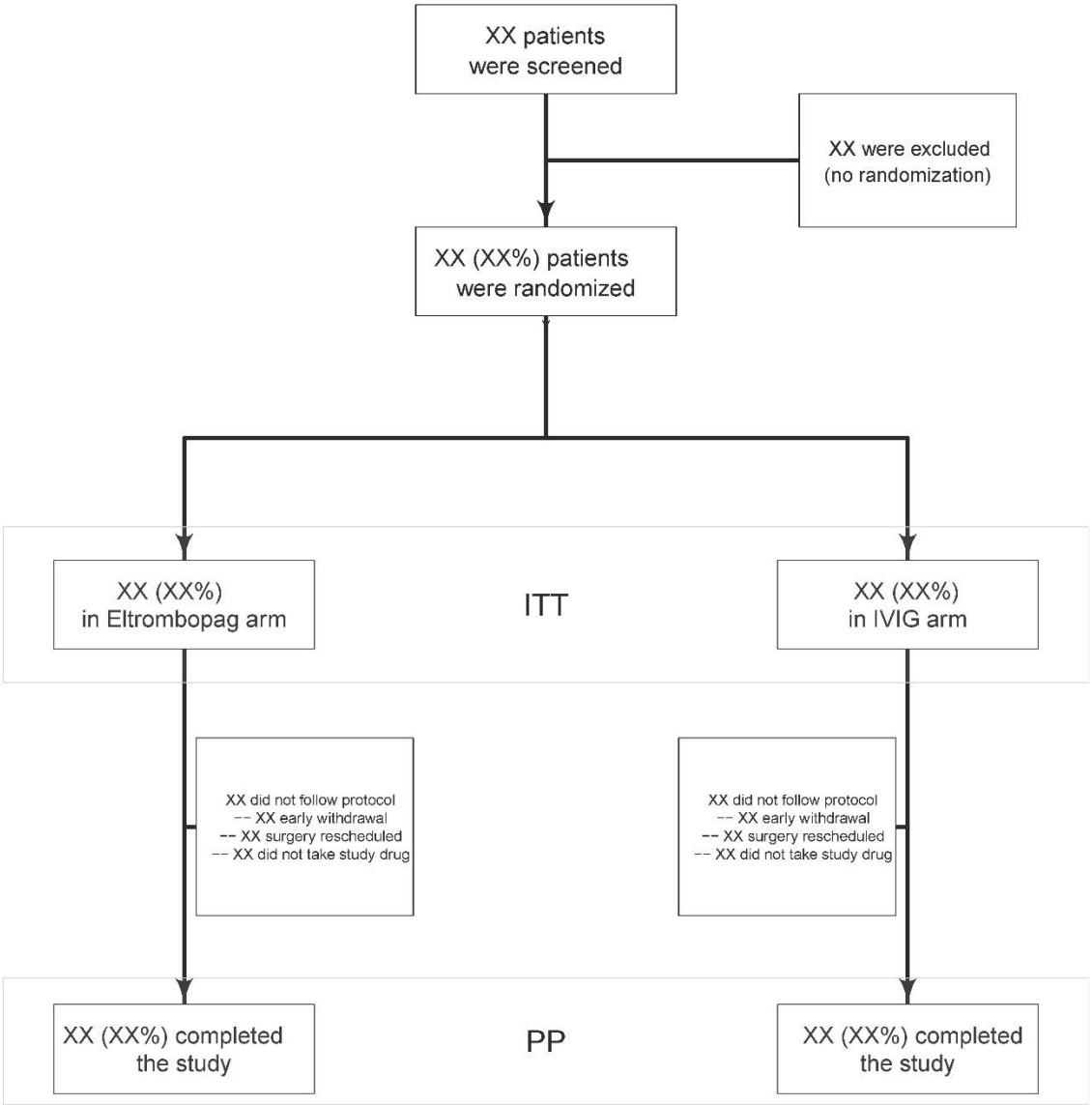

Figure 1. Structure of Anticipated CONSORT Flow Diagram

Table 1. Descriptive Statistics of Baseline Patient Characteristics

Characteristics	Study Arm	
	Eltrombopag	**IVIG**
Gender (Female, n, %)		
Age (mean, SD)		
Baseline platelet count (mean and SD, median and IQR)		
Primary ITP (n, %)		
Chronic ITP (n, %)		
Duration of ITP (years, median, IQR)		
Number of prior ITP treatments (median, IQR)		
Type of surgery		
Major surgery (n, %)		
Minor surgery (n, %)		
Splenectomy (n, %)		

6. Analysis

Outcome Definitions	Primary outcome: • Non-inferiority analysis of the achievement of the desired platelet count threshold immediately before surgery (Day -1) and maintaining platelet count within the target range until 7 days after surgical hemostasis (Day H+7 visit) without the use of ITP rescue treatment. Note "Day -1" refers to the final pre-operative visit, which could have occurred from Day -3 to Day -1. Secondary outcomes: • Superiority analysis for treatment success; • Time to treatment failure: Time to the occurrence of a platelet count level below the designated threshold, or the administration of rescue treatment from the Day –1 visit to the Day H+7 visit; • Surgical delays or cancellations; • Bleeding graded as per the ITP bleeding score (none, grade 1, grade 2)[1]; • Thrombocytosis: Platelet count > 400 x 10^9/L; • Patients requiring any red blood cell, platelet, and/or plasma transfusion; • Rescue treatment: New ITP treatment (typically platelet transfusions, IVIG or high dose corticosteroids) or an increased dose of existing ITP treatment administered to increase platelet counts above threshold from the Day -1 visit to the Day H+7 visit; • Trend of all platelet count measurements during study period; • Patient satisfaction with treatment using a validated patient-reported questionnaire [2]; • Unanticipated admissions to hospital or prolongation of hospitalization; • Symptomatic thrombotic events confirmed with diagnostic imaging; • Adverse events grade 2 or higher, defined using the Common Terminology Criteria for Adverse Events v3.0 [3].
Analysis Methods	Primary analysis: We will report the proportion and two-sided 95% confidence interval (CI) of patients who achieve treatment success in each study arm. A one-sided non-inferiority test of the difference in the success rates will carried out with the non-inferiority margin of 10%. That is the test will be based on whether the difference in the probability of achieving success between eltrombopag and IVIG exceeds -0.1, where the one-sided 95% CI for the difference, the test statistic, and associated p-value will be reported. A p-value less than 0.05 will be considered statistically significant for non-inferiority (e.g. a statistically significant result means that eltrombopag is not inferior to IVIG). We will repeat the analysis for subgroups of patients undergoing splenectomy, major surgery, and with primary ITP. Secondary analysis: • A two-sided test will be performed to detect whether the lower bound of the one-sided 95% CI of the difference in proportions between eltrombopag and IVIG exceeds 0.

	• Treatment success: A stratified logistic regression model[4] will be used to investigate the predictors of treatment success, stratified by site and procedure type, with a single binary covariate indicating assignment to the treatment arm, where other covariates such as age, gender, and baseline platelet count may be included if applicable (due to the sample size limitation). The odds ratio and associated 95% confidence interval will be reported, as well as the p-value will be calculated to test the null hypothesis of no difference in treatment success between the two arms. • Time to treatment failure: We will report the median time with associated 95% CI, and event rates at different specific time points with associated 95% CI. Survival curves estimated by Kaplan-Meier method will be plotted for both treatment arms. The survival curves of two treatment arms will be compared by a log-rank test where the p-value to test the null hypothesis of no difference in the survival times will be reported. The patients will be considered at risk from the Day -1 visit until the date of treatment failure or Day H+7 visit. The relationship between treatment arm and time to treatment failure will be assessed using stratified Cox regression during the risk period[5], stratified by site and procedure type. Proportional hazards assumptions will be tested based on Schoenfeld residuals[6]. The hazard ratio and associated 95% confidence interval will be reported. The survival curves will be reported in a Figure. • Platelet count trend over time: Besides using a Mann–Whitney U test to compare the distributions of platelet count between two treatment arms, a growth mixture model [7] will be used to study platelet count trend over time and to compare trends between treatment arms adjusted for procedure type. Platelet count trends will be reported in a Figure. • The following outcomes in the two arms will be reported by number, proportion and 95% CI, and compared using two-sided two sample proportion test: proportion of patients with surgical delays or cancellations, proportion of patients with bleeding event, proportion of patients with thrombocytosis, proportion of patients with blood product transfusions, proportion of patients with rescue treatment, proportion of patients with hospitalizations, proportion of patients with thrombosis, proportion of patients with adverse event. For severe (Grade 2) bleeding, thrombosis and adverse events, we will use multivariate logistic regression to estimate the odds of the event in the eltrombopag group compared with IVIG, adjusting for site, procedure type, age and gender, if applicable.

	• Treatment satisfaction scores: We will perform Hotelling's T-squared test to exam whether there is a statistically significant difference in mean global score and in the components of the score including mean effectiveness score, mean side effects score and mean convenience score between the two treatment arms. A linear regression model will be used to compare each mean patient satisfaction score between the two treatment arms, adjusted for site, procedure type, age and gender, if applicable. <u>Descriptive Analysis:</u> Patient characteristics will be summarized using descriptive statistics (Table 1), such as mean and standard deviation, median and interquartile range, or number and proportion, as appropriate.
Statistical Software	All data abstraction and analyses will be done using SAS 9.4 [8] and the R language for statistical computing [9].

Table 2. Summary Statistics of Study Outcomes

Outcomes	Randomization		Statistical test to compare two treatment arms
	Eltrombopag	IVIG	
Primary Outcome			
Treatment success (n, %, one-sided 95% CI)			One-sided test of non-inferiority
Secondary Outcome			
Platelet count			
Platelet count per patient on Day -1 pre-operative visit (mean and SD, median and IQR)			Mann–Whitney U test
Mean platelet count per patient (mean and SD, median and IQR)			Mann–Whitney U test
Lowest platelet count per patient (mean and SD, median and IQR)			Mann–Whitney U test
Number of days below platelet count target per patient (median, IQR)			Mann–Whitney U test
Patients with thrombocytosis (n, %, 95% CI)			Two-sided two-sample proportion test
Treatment failure			
Time to treatment failure (median, 95% CI)			Log-rank test
Patients with rescue treatment (n, %, 95% CI)			Two-sided two-sample proportion test
Patients with surgical delays and cancellation (n, %, 95% CI)			Two-sided two-sample proportion test

Table 3. Adverse events

Outcomes	Randomization		Statistical test to compare two treatment arms
	Eltrombopag	IVIG	
Patients with severe (Grade 2) bleeding events (n, %, 95% CI)			Two-sided two-sample proportion test
Number of severe (Grade 2) bleeding events per patient (median, IQR)			Mann–Whitney U test
Number of minor (Grade 1) bleeding events per patient (median, IQR)			Mann–Whitney U test
Patients with serious adverse events (n, %, 95% CI)			Two-sided two-sample proportion test
Patients with adverse events (n, %, 95% CI)			Two-sided two-sample proportion test

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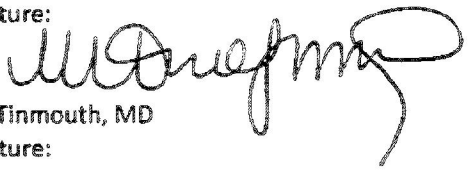
	Michelle Sholzberg, MD Signature:  Alan Tinmouth, MD Signature: Martin Schipperus, MD Signature: <u>Steering Committee Members:</u> Richard Cook, PhD. Signature: Nancy Heddle, MSc., FCSMLS(D) Signature:

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