Statistical Analysis Plan

SPONSOR:	Dova Pharmaceuticals
PROTOCOL TITLE:	An Open-Label Study to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Subjects with Thrombocytopenia Scheduled for a Surgical Procedure
STUDY CODE:	AVA-PST-320
VERSION:	1.0 (22JAN2019)

The undersigned certify that they have read, reviewed and approved this document.

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22 JAN 2019

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1. List of Abbreviations and Definition of Terms

Abbreviation	Term
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Classification
CLD	Chronic Liver Disease
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
ICH	International Conference on Harmonization
ISTH	International Society on Thrombosis and Haemostasis
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
PPS	Per-Protocol Analysis Set
PT	MedDRA Preferred Term
SAE	Serious adverse event
SAF	Safety Analysis Set
SOC	MedDRA System Organ Class
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

2. Introduction

This Statistical Analysis Plan (SAP) describes the statistical methodology and data handling for the clinical trial for Dova Pharmaceuticals with Protocol Number: AVA-PST-320 (An Open-Label Study to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Subjects with Thrombocytopenia Scheduled for a Surgical Procedure).

The ICH guideline E3 "Structure and Content of Clinical Study Reports" was used as a guide to the writing of the plan.

This SAP is based on the following study document(s):

- Clinical Study Protocol V3.0 (Amendment 2), 17 September 2018

2.1 Study Closure and Analysis

The study closed to further enrollment on January 21, 2018 for administrative reasons. Four subjects were enrolled in the study at the time of closure. In this regard, the statistical analysis is limited to the 16.2 data listings described in this Statistical Analysis Plan and presented in the accompanying Mock Outputs document.

3. Study Design and Objectives

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of avatrombopag in increasing platelet counts in subjects with thrombocytopenia scheduled for operations to critical sites or operations with a high risk of bleeding.

3.1.2 Secondary Objectives

The secondary objectives of this study are the following:

- To evaluate the safety of avatrombopag in subjects with thrombocytopenia scheduled for operations to critical sites or operations with a high risk of bleeding,
- To evaluate the effect of avatrombopag on the need for transfusions in subjects with thrombocytopenia scheduled for operations to critical sites or operations with a high risk of bleeding, and
- To evaluate the effect of avatrombopag on bleeding in subjects with thrombocytopenia scheduled for operations to critical sites or operations with a high risk of bleeding.

3.2 Study Design

This is a Phase 3b open-label, multicenter study of the efficacy and safety of oral avatrombopag for the treatment of subjects with thrombocytopenia scheduled for a surgical procedure. Eligible subjects scheduled to undergo operations to critical sites (eg, eye surgery, neurosurgery) or operations with a high risk of bleeding (eg, major abdominal surgery) will be enrolled into the study and receive avatrombopag.

Mean baseline platelet count in subjects without chronic liver disease (CLD) must be between 50 x 10^9/L and <100 x 10^9/L; between 50 × 10^9/L and <75 × 10^9/L in subjects with CLD. Platelet counts must be measured on 2 separate occasions (the Screening Visit and the Baseline Visit), and must be performed at least 1 day apart with neither platelet count ≥100 × 10^9/L in subjects without CLD and ≥75 x 10^9/L in subjects with CLD. One standard of care platelet count measurement may be used if collected within 14 days of Baseline and the mean of these 2 platelet counts (mean baseline platelet count) will be used for entry criteria.

Subjects will receive 60 mg oral avatrombopag once daily for 5 days beginning on Day 1, followed by a wait period prior to the procedure, which will occur on Day 10 (+3 days). The platelet response data will be reviewed after approximately 25% and 50% of subjects have been enrolled in the study. If required, the dose may be adjusted for subsequent subjects based on insufficient increase in platelet counts on Procedure Day. If a higher dose is considered necessary, subjects will receive 80 mg oral avatrombopag once daily for 5 days beginning on Day 1, followed by a wait period prior to the procedure, which will occur on Day 10 (+3 days).

The Follow-up Period will include 2 visits, which will occur at approximately 7 days (+3 days) post-procedure and 30 days (±3 days) after the last dose of study drug.

The total study duration will be approximately 5 to 7 weeks.

3.3 Sample Size Justification

It is estimated from PK/PD modeling that the proportion of subjects treated with avatrombopag expected to achieve a platelet count of ≥100 × 10^9/L on Procedure Day, when measured prior to platelet transfusion (if any), is approximately 85%. Assuming the true response rate is 0.8 and the desired lower boundary of the 2-sided 95% CI is at least 0.65, 60 enrolled subjects will provide greater than 90% power. If the decision is made to increase the dose of study drug at one of the interim reviews of the data based on the pre-defined boundaries, up to an additional 30 subjects may be enrolled in the study for a maximum sample size of 90 subjects.

4. General Analysis Definitions

4.1 Study Period and Visit Window Definitions

Period	Screening	Treatment		Procedure Day	Follow-Up	
Visit	1 *(optional)*	2 (Baseline Visit)	3	4	5	6 (ET Visit)
Day	Day -14 to -1	Day 1 [1]	Day 5	Day 10 [2]	7 Days Post-Procedure	Day 35
Window			(-2 days)	(+3 days)	(+3 days)	(±3 days)
Procedures						
Subject informed consent	X	X [11]				
Inclusion/exclusion criteria		X				
Demographics	X	X [11]				
Medical history [10]		X				
Concomitant medications		X	X	X	X	X
Adverse events	X	X	X	X	X	X
Physical examination [3]		X		X	X	X
Vital signs [4]		X		X	X	X
Hematology		X [5]	X	X	X	X
Platelet count [5]	X	X	X	X	X	X
Coagulation		X [5]	X	X	X	X
Serum chemistry		X		X	X	X
Pregnancy testing [6]		X [7]				X [7]
Assessment of platelet transfusion				X	X	X
Assessment of any rescue procedure for bleeding			X	X	X	X
Procedure-related information (type, risk, etc.)		X				
Contact IRT	X	X	X	X	X	X
Dispense study drug [8]		X				
Study drug dosing [8]		X	X			
Bleeding assessment (ISTH) [9]			X	X	X	X
Collect study drug				X		

Note: Prior to conducting any study-related activities, written informed consent must be signed and dated by the subject. Local laboratories will be used to determine eligibility; however, for study analysis and reporting purposes, only values determined at a central laboratory will be used with the exception of platelet count. Local laboratories may be used if immediate results are clinically needed.

1. All assessments will be performed prior to study drug dosing.
2. The following procedures will be performed pre-operatively on Procedure Day: vital signs, hematology, platelet count, coagulation, serum chemistry, record whether subject requires a platelet transfusion, ISTH non-surgical bleeding assessment (if any bleeding), contact IRT, and collect study drug. The following procedures will be performed post-operatively on Procedure Day: concomitant medications, adverse events, record any rescue procedure for bleeding, and ISTH surgical bleeding assessment (if any bleeding).
3. Physical examinations will consist of the following at a minimum: chest, lungs, heart, abdomen.
4. Vital sign measurements will include height (at the Baseline Visit only), weight, body temperature, blood pressure, and pulse rate and will be measured after resting for 5 minutes.
5. Local and central laboratories. Baseline hematology, platelet count and coagulation laboratories may be collected up to one day prior to the Baseline visit (Visit 2).
6. For female subjects of childbearing potential only. A serum or urine pregnancy test will be performed at the Baseline Visit prior to study drug administration.
7. Either a serum or urine pregnancy test may be used.
8. Subjects will receive 60 mg oral avatrombopag once daily for 5 days beginning on Day 1. For study site visits during the Treatment Period, study drug may be administered at the site or the subject may self-dose. Subjects will self-dose at all other times and be instructed to take study drug with food. The Investigator or designee will provide subjects with sufficient study drug to complete the 5-day regimen.
9. Bleeding will be evaluated, if present, by the Investigator using the non-surgical and surgical ISTH bleeding definitions described in Appendix D. The non-surgical ISTH bleeding definitions (Table 4) will be used when evaluating subjects prior to surgery on Procedure Day, and the surgical ISTH bleeding definitions (Table 5) will be used when evaluating subjects after surgery on Procedure Day. Both the non-surgical and surgical ISTH bleeding definitions will be used to evaluate subjects during the Follow-up Period. For an Early Termination Visit where a subject withdraws from the study prior to surgery on Procedure Day, the non-surgical ISTH bleeding definitions will be used. If a subject withdraws after surgery on Procedure Day, both the non-surgical and surgical ISTH bleeding definitions will be used.
10. Document etiology of thrombocytopenia.
11. If Visit 1 not performed

ET = Early Termination; IRT = Interactive Response Technology; ISTH = International Society on Thrombosis and Haemostasis.

4.2 Definition of Populations

The analysis and reporting of the data from this study will be performed using the following analysis populations:

4.2.1 Full Analysis Set (FAS)

The FAS will include all enrolled subjects who receive at least 1 dose of avatrombopag.

4.2.2 Per-Protocol Analysis Set (PPS)

The PPS will include the subset of subjects from the FAS who are treated according to the protocol without any major deviations that have potential impact on the study endpoints. The list of the major protocol deviations can include, but is not limited to, the following:

- Not meeting selected eligibility criteria
- Taking prohibited medications during the study
- Treatment compliance <80%
- Not undergoing a surgery
- Missing pre-operative platelet count on Procedure Day

A full list of the major protocol deviations will be finalized prior to database lock.

4.2.3 Safety Analysis Set (SAF)

The Safety Analysis Set will include all subjects who receive at least 1 dose of avatrombopag.

4.3 Data Handling Conventions

4.3.1 General Conventions

Data will be analyzed using SAS (Version 9.3 or later). Descriptive analyses will be performed on baseline, safety and efficacy data.

Descriptive statistics will be tabulated as follows:

- Categorical data will be summarized in contingency tables presenting frequencies and percentages, and
- Continuous data will be summarized using number of non-missing values (n), mean, standard deviation, median, minimum, and maximum values.

4.3.2 Definition of Study Day

The first day of study treatment will be Study Day 1. There is no Study Day 0. The day before the first day of study treatment will be Study Day -1. If an event occurs on or after the first day of study treatment, Study Day will be calculated as (Date of Event - Date of first study treatment + 1). If the event occurs prior to the first day of study treatment, Study Day will be calculated as (Date of Event - Date of first study treatment).

4.3.3 Definition of Baseline

In general, a baseline value will be the last non-missing value taken prior to the start of study treatment. Unless otherwise indicated, measurements taken the day of first study treatment are assumed to occur prior to the administration of study treatment.

4.3.4 Visit Windows

No formal visit windowing will be conducted. For by-visit tabular summaries, the scheduled visits will be used in the analyses. Unscheduled visits will be treated as a separate category.

For analyses considering the worst post-baseline grade (laboratory shift tables) or post-baseline liver tests, unscheduled values will be included.

4.3.5 Handling Missing Data

For the primary efficacy analysis, subjects with missing information due to early withdrawal or other reasons are considered as having a platelet count $<100 \times 10^9$/L in the analysis; that is, missing values are considered as non-responders. A similar approach applies to the secondary analyses where the endpoints are the proportion of responders.

For the analysis of change in platelet count from baseline to Procedure Day, a missing value will be kept missing and no imputation will be applied.

4.3.6 Partial Dates

Missing or partially missing dates will not be imputed at data level. However, assumptions for missing or partially missing dates for important variables will be made to allow inclusion of appropriate data records in the analyses. In general, the assumptions about the missing or partially missing dates, when needed, are made conservative to avoid overestimation of treatment effect and underestimation of adverse effects.

If a medication date or time is missing or partially missing, so it cannot be determined whether it was taken prior or concomitantly, it will be considered both as a prior and a concomitant medication.

4.4 Treatment Groups

Data displays for the study will initially have one column for the single-arm 60 mg dose group. If, after the interim analyses, the decision is to begin enrollment at 80 mg, the data displays will be adapted to have columns for both the 60 mg and 80 mg dose groups.

5. Study Subjects

5.1 Disposition of Subjects

Disposition will be summarized for the FAS.

A summary table will include the total number of subjects screened and enrolled and the number and percentage in each analysis set. The summary table will also contain the number and percentage of subjects who discontinued treatment early and subjects who discontinued the entire study duration early, and the reasons for

early discontinuation from the study will be summarized. Details of "Other" reason for discontinuation will be included in a disposition listing.

5.2 Protocol Deviations

The number and percentage of subjects with major protocol deviations that exclude subjects from the PPS will be summarized by category for the FAS. Protocol deviations reported during the study will be provided in a listing.

5.3 Inclusion and Exclusion Criteria Not Met

Details of inclusion/exclusion criteria not met for subjects in the FAS will be provided in a listing.

6. Demographic and other Baseline Characteristics

6.1 Demographics and Baseline Characteristics

Descriptive statistics with respect to subject characteristics at baseline will be displayed for the FAS. The variables to be summarized are:

Demographics

- Age at enrollment
- Age at enrollment (Grouped): <65 years, 65-<75 years, 75+ years
- Sex
- Race
- Ethnicity

Baseline subject characteristics

- CLD (Yes/No)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- Baseline platelet count ($10^9/L$)

6.2 Medical History

Medical history will be coded using the version of the Medical Dictionary for Regulatory Authorities (MedDRA) chosen at the start of the study, and coding may be updated as new versions are released.

Medical history will be tabulated by MedDRA System Organ Class (SOC) and Preferred Term (PT) for the FAS. Subjects with more than one medical history event in a SOC or PT will only be counted once per SOC or PT. The summary table will be sorted by SOC (descending frequency) and by PT within SOC (descending frequency).

Medical history details will also be provided in a data listing.

6.3 Surgical Procedure

Type of surgical procedure will be summarized in FAS for the following categories:

- Cardiothoracic surgery
- General surgery

- Neurosurgery
- Ophthalmic surgery
- Oral and maxillofacial surgery
- Otolaryngology (ENT)
- Plastic surgery
- Orthopedic surgery
- Urology
- Vascular surgery
- Other operative procedure

A listing will be provided which details information collected in the eCRF regarding the surgical procedure for study subjects in the FAS.

7. Prior and Concomitant Treatment

7.1 Medications

Prior and Concomitant medications will be classified according to the most recent version of the World Health Organization Drug Dictionary at the start of the study and may be updated as new versions are released. Medications will be coded per the Anatomical Therapeutic Classification (ATC).

Prior medications are those which start and stop before the first day of study treatment. Concomitant medications are those which start on or after the first day of study treatment. A medication which begins before the start of study treatment and continues into the treatment period will be considered as concomitant.

Separate tabular summaries will be produced for prior medications and for concomitant medications in the FAS. Each summary will display the number and percentage of subjects with at least one medication in ATC Level 2 and preferred term categories and overall. Subjects who have taken a medication more than once will only be summarized once per ATC Level 2 or preferred term. The tabular summaries will be sorted by ATC Level 2 (descending frequency) then by preferred term within ATC Level 1 (descending frequency).

A listing of medications will also be provided. The listing will designate whether a medication is considered prior or concomitant.

7.2 Procedures

Prior procedures are those which occur before the first day of study treatment. Concomitant procedures are those which occur on or after the first day of study treatment.

A listing will be provided for prior and concomitant procedures in the FAS. This listing will specify whether a procedure is prior or concomitant.

8. Efficacy Evaluation

All primary and secondary efficacy endpoints will be analyzed using the FAS. The primary and secondary efficacy endpoints will also be analyzed in the PPS as a supportive analysis. The FAS and PPS analyses of an efficacy endpoint will be displayed in separate columns on the same table for the applicable endpoint.

8.1 Primary Efficacy Analysis

The primary efficacy endpoint is the proportion of subjects achieving a platelet count of $\geq 100 \times 10^9$/L on Procedure Day, when measured prior to a platelet transfusion (if any). Subjects with missing information due to early withdrawal or other reasons are considered as having a platelet count $<100 \times 10^9$/L in the analysis; that is, missing values are considered as non-responders. The primary endpoint will be estimated from a binomial distribution, with exact 95% confidence interval (CI) of the proportion calculated. The study will be claimed successful if the lower boundary of the 2-sided exact 95% CI is above 0.65. Local platelet count values will be used for the primary efficacy analysis.

A data listing of the response status (responder vs. non-responder) of the primary endpoint will be provided.

8.2 Secondary Efficacy Analysis

The following secondary efficacy endpoints will be summarized, and exact 95% confidence intervals will be calculated for the proportions:

- Proportion of subjects without platelet transfusion and any other treatment for bleeding after the Baseline Visit and up to 7 days following Procedure Day
- Proportion of subjects without platelet transfusion after the Baseline Visit and up to 7 days following Procedure Day
- Proportion of subjects without bleeding after the Baseline Visit and up to 7 days following Procedure Day

A summary table of frequencies and percentages will be provided for subjects without platelet transfusion (yes/no), subjects without rescue procedure for bleeding (yes/no), and subjects without platelet transfusion or rescue procedure after the Baseline Visit and up to 7 days following Procedure Day.

A similar summary will be provided for subjects without bleeding (yes/no) after the Baseline Visit and up to 7 days following Procedure Day. For this analysis, bleeding will be defined as major or non-major clinically relevant bleeding according to ISTH Surgical Bleeding Scales, or major bleeding according to ISTH Non-Surgical Bleeding Scales.

A data listing of the response status (yes/no) of the secondary endpoints will be provided.

Platelet count at baseline and each post-baseline visit, as well as change from baseline to each post-baseline visit (including Procedure Day) based on the local laboratory platelet count will be summarized descriptively in a summary table and presented graphically.

8.3 Other Analysis

8.3.1 Sensitivity Analysis

An observed case analysis in subjects with an available platelet count on Procedure Day will also be conducted for the primary efficacy endpoint in the FAS.

8.3.2 Subgroup Analysis

The primary efficacy analysis will be repeated for subgroups based on age group, sex, race categories, and CLD (Yes/No) as displayed in the Demographics table,

and for the baseline platelet count group (categories of the baseline platelet count will be determined later prior to finalization of the SAP). The frequency and proportion of responders in each of the subgroup categories will be presented, along with exact 95% CI. No formal hypothesis testing will be conducted for subgroups.

8.4 Interim Analysis

Two interim data reviews are planned to assess study design assumptions and adjust the study drug dose regimen if necessary.

The first interim data review will be conducted when approximately 25% of subjects (approximately 15 subjects) have been enrolled. For the primary efficacy endpoint, if fewer than 10 responders out of 15 enrolled subjects are observed (the probability of observing <10 responders out of 15 enrolled subjects is 0.0611 if the true response rate is 0.8), the avatrombopag dose increase (to 80 mg) will be considered for the subsequent enrolled subjects. Otherwise, the study will continue as planned until the second interim data review.

In the event that the avatrombopag dose was not adjusted after the first interim data review, the second interim data review will be conducted when approximately 50% of subjects (approximately 30 subjects) have been enrolled. If fewer than 21 responders out of 30 enrolled subjects are observed (the probability of observing <21 responders out of 30 enrolled subjects is 0.0611 if the true response rate is 0.8), the avatrombopag dose increase (to 80 mg) will be considered for the subsequent enrolled subjects. Otherwise, the study will continue as planned until the completion of the study.

9. Safety Evaluation

Safety and tolerability will be assessed by examining exposure/treatment compliance, the incidence of adverse events, clinical laboratory parameters, and vital signs using the SAF. No inferential statistical tests will be conducted on any safety endpoints.

9.1 Exposure and Treatment Compliance

For purposes of calculating individual exposure to study drug, it is assumed that the actual cumulative dose of study drug taken by the subject will be (Number of Tablets Dispensed - Number of Tablets Returned)*Dose, where Dose is the per-tablet dose of avatrombopag.

The planned cumulative dose of study drug for each subject will be based on the dose per tablet which is dispensed at the time of study enrollment. If the dose per tablet is 20 mg and three tablets are taken once daily, it is assumed that the planned cumulative dose of study drug will be (60 mg)*(5 days) = 300 mg. If, after interim analysis, the dose is increased to 80 mg (4 tablets × 20 mg) in subsequently enrolled subjects then the planned cumulative dose will be (80 mg)*(5 days) = 400 mg.

Duration of exposure (in days) will also be summarized descriptively and computed as the last dose day – the first dose day +1.

Treatment compliance (%) will be calculated as (number of tablets taken)/(number of tablets expected) * 100.

A summary table will display the descriptive statistics of treatment compliance and the number and percentage of subjects in each of the following categories of treatment compliance: <80%, 80-100%, >100%.

A data listing will provide details of subject exposure and treatment compliance, including tablets dispensed and tablets returned.

9.2 Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version applicable at the time of the study start, and coding may be updated according to newly released versions of the dictionary.

Severity of AEs is categorized as "Mild", "Moderate", or "Severe" per the definitions in the Study Protocol.

For relationship to avatrombopag, AEs are classified as "Related" or "Not Related".

AEs leading to permanent discontinuation of avatrombopag are AEs where action taken is designated as "Drug Withdrawn" in the eCRF.

Two Adverse Events of Special Interest (AESI) will be summarized and are defined as:

1. Thromboembolic events - All adverse events with MedDRA PT belonging to SMQ 'Embolic and thrombotic events'
2. Bleeding Events - MedDRA PT belonging to 2nd level SMQ 'Haemorrhage terms (excl laboratory terms)'

Tabular summaries of adverse events will only include treatment-emergent adverse events (TEAE). Treatment-emergent Adverse Events (TEAEs) are defined as AEs occurring after the first dose of study treatment.

Listings will include all adverse events (both TEAE and non-TEAE). A flag will be included in the listings to designate whether an adverse event is treatment-emergent.

An overall AE summary table will be prepared and will include the number and percentage of subjects with at least one:

- TEAE
- TEAE related to avatrombopag
- Serious TEAE
- TEAE leading to permanent discontinuation of avatrombopag
- TEAE of special interest
- Death

Separate summary tables by MedDRA SOC and PT will be created for the following categories of TEAEs:

- TEAEs
- TEAEs related to avatrombopag
- Serious TEAEs

TEAE of special interest will be summarized by MedDRA PT for the Thromboembolic events and Bleeding Events.

Each subject will be counted only once within each level of the summary (PT or SOC). Table summaries will be provided by descending frequency by SOC then by descending frequency of PT within SOC.

Summary tables by MedDRA PT in descending frequency will also be provided for the following categories of TEAEs:

- TEAEs
- TEAEs related to avatrombopag
- Serious TEAEs

A tabular summary will also be provided by SOC, PT, and maximum severity. If a subject experiences more than one TEAE within a PT or SOC, only the TEAE with the maximum severity will be included in the summary.

Listings of adverse events will be provided for the following categories:

- All Adverse Events
- AEs related to avatrombopag
- Serious AEs
- AEs leading to permanent discontinuation of avatrombopag
- AEs of special interest

A listing of deaths will be provided which will include any death details available in the eCRF.

9.3 Clinical Laboratory Determination

Clinical safety laboratory assessments will include tests from the serum chemistry, hematology, and coagulation categories. Where applicable, laboratory values will be graded according to the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03.

Local laboratories will be used to determine eligibility; however, for study analysis and reporting purposes, only laboratory values determined at a central laboratory will be used with the exception of platelet count. Local laboratories may be used if immediate results are clinically needed.

Shift tables of Baseline CTCAE grade to worst post-baseline CTCAE grade will be presented separately for gradable Hematology Parameters and Serum Chemistry Parameters. In the case of bi-directional toxicities, parameters will be presented separately (eg Calcium High, Calcium Low). For the purposes of tabulation, laboratory values which are not assigned NCI-CTCAE Grades 1, 2, 3, or 4 due to a toxicity will be assigned Grade 0 (within the normal range).

All laboratory data (including Hematology parameters, Chemistry parameters, Coagulation parameters, and pregnancy tests) will be included in a laboratory listing.

A separate summary table for liver tests (ALT, AST, Alkaline Phosphatase, Gamma-glutamyl Transferase, and Total Bilirubin) will be created. This table will indicate the number and percentage of subjects (presented by lab test) who have a highest post-baseline lab value for the test that is CTCAE Grades 1, 2, 3, or 4.

Observed and changes from baseline values for continuous Hematology and Serum Chemistry laboratory tests will be presented over time in boxplots. Reference lines for the LLN and ULN will be included in the plots.

9.4 Other Safety Measures

9.4.1 Vital Signs

A by-visit summary table will be created displaying the observed values and changes from baseline for vital sign parameters.

A by-subject listing of all vital signs entered in the eCRF will also be provided.

9.4.2 ISTH Bleeding Information

A tabular summary of ISTH Bleeding Information by study visit will be provided and will include the number and percentage of subjects who have experienced bleeding in the following categories: major bleeding, non-major clinically relevant bleeding (Non-Surgical Bleeding assessment only), minor bleeding. Bleeding categories for Surgical and Non-Surgical Information will be presented separately in the table.

Separate listings will detail the Surgical and Non-Surgical ISTH Bleeding Information.

9.4.3 Blood Transfusions

A summary table will be created to display the frequency and percentage of subjects who have blood transfusions (yes/no). The type of blood product (Red Blood Cells, Platelets, Cryoprecipitate) will be summarized (subjects may appear in more than one category) and the reason for transfusion (Thrombocytopenia, Bleeding Event, Adverse Event other than Bleeding Event, Other) will be summarized (subjects may appear in more than one category). The total number of packs/units received per subject will be summarized as a continuous variable.

Details of any blood transfusions occurring on study will be presented by subject in a listing.

9.4.4 Rescue Procedures

A summary table will be created to display the frequency and percentage of subjects with a rescue procedure for bleeding (yes/no). The type of rescue procedures will also be summarized: [Vitamin K (phytonadione), Desmopressin, Recombinant activated factor VII, Aminocaproic acid, Surgical intervention or interventional radiology, Tranexamic acid, Other].

Details of any rescue procedures (other than blood transfusions) for bleeding will be presented by subject in a listing.

10. List of Tables, Listings, and Figures

A separate document will detail the list of the planned tables, listings, and figures for the final statistical analyses, as well as for the interim analyses. The document will also include the mock tables, listings, and figures.

11. References

International Conference on Harmonization (ICH) guideline "Statistical principles for Clinical trials": E9, 1998.