TRIAL STATISTICAL ANALYSIS PLAN

BI Trial No.:	1321.0023
Title:	Post marketing surveillance program of Praxbind™ use in India.
Investigational Product(s):	Praxbind™
Responsible trial statistician(s):	Phone: Email:
Date of statistical analysis plan:	11-Jul-2018
Version:	Final 1.0

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3 LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
EDC	Electronic Data Capture
ICH	International Conference On Harmonisation
MedDRA	Medical Dictionary For Regulatory Activities
MQRM	Medical Quality Review Meeting
PT	Preferred Term
PV	Protocol Violation
Q1	Lower Quartile
Q3	Upper Quartile
SA	Statistical Analysis
SD	Standard Deviation
SOC	System Organ Class
ToC	Table of contents
TSAP	Trial Statistical Analysis Plan

4 INTRODUCTION

"As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP)version 3.0, dated 13 Sep 2017 and Case Report Form (CRF) Final version 3.0, dated 11 Apr 2018 In particular, the TSAP is based on the planned analysis specification as written in CTP Section 10.6 "Data Analysis". Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size."

SAS® Version 9.2 or higher will be used for all analyses.

The aim of this drug administration surveillance program is to capture a large proportion of the patients treated with Praxbind™ in order to collect data on Praxbind™ prescription patterns in a clinical practice setting in India, with special focus on ADRs and fatal AEs.

5 CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

No changes made in the planned analysis of the study mentioned in the protocol version 3.0, dated 13 Sep 2017.

6 OUTCOMES

6.1 PRIMARY OUTCOMES

- Any suspected ADRs and fatal AEs; with special focus on hypersensitivity and thrombotic event, occurred within 7 days after Praxbind™ administration.

6.2 SECONDARY OUTCOMES

6.2.1 Secondary outcome

- Percentage of patients who either received Praxbind™ for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding at the end of 2 years.

6.2.2 Key secondary outcome

- This section is not applicable as no key secondary out come has been specified in the protocol.

6.4 OTHER VARIABLES

In this study, the following variables will be considered.

- **Site characteristics:**

  To evaluate the diversity of sites the following information will be collected for each participating site:

- Multi-specialty hospitals with emergency management facilities and having access to Praxbind™
- Practice type (academic, non-academic, private, Government)
- Availability of prescription/medical records at the site.

- **Patient Data:**

- Year of Birth
- Gender: Male or Female
- Vital Signs
- Physical Examination
- Laboratory data (Data would be collected of lab results performed as a routine practice. No additional lab tests should be performed specifically for this study purpose)
- Pregnancy status in case of female patient

- **Medical History:**

- Name, dose and last intake of previous anticoagulant medications (Dabigatran);
- Pertaining to haemorrhagic risk factors or impact on safety outcomes (e.g. renal impairment, congenital or acquired coagulation disorders, thrombocytopenia or functional platelet defects, recent biopsy, recent surgery, major trauma, bacterial endocarditis, esophagitis, gastritis, gastroesophageal reflux, hepatic disorders, vascular disorders, neoplasms/cancer, inherited vascular disorder (aneurysms, arteriovenous malformation, microangiopathy) and the HAS-BLED score).
- Concomitant treatment pertaining to haemorrhagic risk factors or impact on safety outcomes (e.g. acetylsalicylic acid, non-steroidal anti-inflammatory drugs, clopidogrel, selective serotonin reuptake inhibitors or serotonin‑norepinephrine reuptake inhibitors, Strong P-Gp inhibitors (e.g. Ketoconazol, Clarithromycin, ticagrelor), chemotherapy, radiation therapy).

- **Praxbind™ utilization:**

- Department (emergency, operating room, ICU, other patient setting);
- Type of surgery /procedure if applicable;
- Information on bleeding event including location (Gastrointestinal tract; Intracranial; Skin, Urogenital tract, Intramuscular, Retroperitoneal, Undefined location, otherdefined location) if applicable, and if bleeding was life-threatening (yes/no);

- Indication: life-threatening or uncontrolled bleeding requiring urgent medical intervention, emergency surgery or other urgent medical procedure necessitating rapid reversal of the anticoagulant effect of dabigatran prior to surgery/procedure, scheduled or planned surgery/procedure, other.
- Dosage and administration (total dose administered and time interval between the administration of the two vials; vials to be taken one after the other, immediate administration of the second vial is mandatory);
- Premature Praxbind™ administration discontinuation (yes/no).
- In case if the patient requires an additional 5 g dose for the following conditions as per the label:

  i. recurrence of clinically relevant bleeding together with prolonged clotting times, or

  ii. if potential re-bleeding would be life-threatening and prolonged clotting times are observed, or

  iii. patients require a second emergency surgery/urgent procedure and have prolonged clotting times.
- Information on restart of anticoagulation therapy (which anticoagulation treatment including dose and when was it restarted).
- All adverse drug reactions (ADRs, serious and non-serious) associated with Praxbind™.
- All AEs with fatal outcome in patients exposed to Praxbind™.

7 GENERAL ANALYSIS DEFINITIONS

7.1 TREATMENT

This is a post marketing surveillance study wherein patients will be eligible for the study if they are prescribed Praxbind as per the approved label. The drug administration surveillance program is designed as a multi-center program enrolling patients administered with Praxbind. Data will be collected for patients who have been treated with Praxbind within 2 years. There are no protocol mandated follow-up visits or procedures associated with the program. No interference with usual medical care is involved, and thus it will not affect the treatment of patients.

7.2 IMPORTANT PROTOCOL VIOLATIONS

This surveillance is mainly focused on prescription patterns of use of Praxbind in a clinical practice setting, with special focus on ADRs and fatal AEs. So in this surveillance per protocol (PP) analysis will not be considered. Hence, the iPV table will be included for completeness and also to demonstrate a level of quality (or adherence to the protocol).
The following table defines, but is not limited to, the different categories of important PVs:

Table 6.2: 1 Important Protocol Violation

Category/ code		Description	Requirements	Detected by	Excluded From;
A		**Entrance Criteria Not Met**			
	A1	**Not met criteria for Treatment with Pradaxa and Praxbind™.**			
	A1.1	Patients not treated with Pradaxa (dabigatran etexilate) capsules or Patients treated with Pradaxa with no requirement of rapid reversal of the anticoagulant effects of dabigatran: • For emergency surgery/urgent procedures (or) • In life-threatening or	Patients did not receive Pradaxa or patients who received Pradaxa but not required Praxbind™ for reversal of anticoagulant effects of Pradaxa.	Programmatically	None

Category/ code		Description	Requirements	Detected by	Excluded From;
		uncontrolled bleeding			
	A2	**Inform consent**			
	A2.1	Written informed consent in accordance with International Conference on Harmonization Good Clinical Practice (GCP) guidelines and local legislation and/or regulations not obtained.	Informed consent not obtained.	Programmatically	None
B		**Exclusion criteria met.**			
	B1	**Participation in Other Clinical Trial**			
	B1.1	Participation in a Praxbind clinical trial.	Patient currently participating or participated previously in other Praxbind clinical trial	Manually	None

KEY:IPV- Important Protocol Violation

Note: Automated PVs are those detected via an automated programming process using SAS. Manual PVs are those identified during the MQRM or review through patients listings and/or Manual PV log.

Important protocol violations will be defined and documented prior to clinical database lock. A strategy for dealing with data affected by protocol deviations will be agreed upon by the coordinator, Sponsor and Biostatistician before clinical database lock.

When the PV cannot be programmed, the individual patient listings with PV category/code will be generated based on data review and should not be included in the TSAP.

7.3 PATIENT SETS ANALYSED

- **Screened Set:**

  Screened set includes all patients who signed the ICF.

- **Entered Set:**

  Entered set includes patients in screened set who met the eligibility criteria.

- **Treated Set:**

  Patients in entered set who have received the study drug Praxbind™.

Analysis for all primary and secondary outcomes will be done on treated analysis set.

The following table defines the patient set is to be used for planned analysis.

Table 6.3: 1 Patient sets analysed

Class of outcomes	Patient set		
	Screened Set	Entered Set	Treated Set
Primary and key secondary outcomes (Safety)	-	-	X
(Other) Secondary and further outcomes	-	-	X
Demographic/baseline outcomes	-	X	-

Note: No other secondary and further endpoints mentioned in CTP.

7.5 POOLING OF CENTRES

This section is not applicable because this is drug administration surveillance and no statistical model is involved in the analysis.

7.6 HANDLING OF MISSING DATA AND OUTLIERS

No missing data analysis is planned for this study. Missing values will be considered as missing, no imputation will be done for the analysis purpose.

Missing or incomplete AE dates are imputed according to BI standards [2] (i.e. "Handling of missing and incomplete AE dates").

7.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Data will be collected for patients who have been treated with Praxbind within 2 years. No formal visits are planned for this surveillance also there is no protocol mandated follow-up visits or procedures associated with the program.

Last non missing values observed prior to receiving the Praxbind™ will be considered as Baseline value.

8 PLANNED ANALYSIS

The general principles listed below will be applied throughout the study:

- All study data will be included in individual patient study data listings. All summary tables will present descriptive statistics for the parameters being analyzed, wherever applicable.
- If the non-formatted data that are received (e.g., from the clinical database) are inconsistently presented, a decision on how to present the final data will be made on a case-by-case basis.
- When rounding is required, numbers 4 or below will be rounded down and number 5 or above will be rounded up.
- Numeric presentations:
  - Descriptive analysis for continuous data will include number of non-missing observations (n), mean, Standard deviation(SD), median, minimum, maximum,Q1, and Q3. Means, medians, Q1 and Q3 will be rounded to 1 decimal place more than the actual data. Minimum and maximum will be displayed with the same decimal precision as the original data.Q1 and Q3 will be presented with 1 decimal.
  - For categorical data, frequency(N) and percentage(%) will be presented. Percentages will be rounded to 1 decimal place. Percentages equal to 100 will be output as '100.0%'.
- All the data analysis will be done using SAS® version 9.2 or higher.
- Baseline assessments are the assessments taken prior to the administration of Praxbind for all patients. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used.
- The change from baseline is defined as the post-baseline value minus the baseline value.
- Missing data will not be imputed but will be analyzed as missing. Missing values will be represented with blank spaces. In cases where a value is missing due to non-evaluable then it will be represented with a hyphen “-”.

- If data summary is planned during the conduct of the trial and no data are generated satisfying the criteria then no data table will be generated with just a comment.

8.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Patient demographic data at baseline visit(age, gender, weight, height, pregnancy status, Systolic blood pressure, Diastolic blood pressure, Pulse rate) will be summarized using descriptive statistics, frequency count and percentage

All the continuous data (age, weight, height, systolic blood pressure, diastolic blood pressure, and pulse rate) will be summarized using descriptive statistics (number of non-missing observations, mean, standard deviation, median, minimum, maximum, Q1 and Q3). Whereas all the categorical data (sex, pregnancy status)will be summarized using frequency counts and percentages.

In addition to the summary tables, listings will be provided by patients for all demographics and baseline characteristics data.

8.2 CONCOMITANT DISEASES AND MEDICATION

Relevant past or present medical history will be listed individually by patient.
Medications used before the first dose will be considered as prior medications and medications started after the first dose in the study or medication used during the study will be recorded as concomitant medications.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD), Version June 2017 or later, and will be summarized using frequency counts and percentages as per ATC level 3 text.

8.3 TREATMENT COMPLIANCE

No analysis planned for compliance of treatment.

8.4 PRIMARY OUTCOME(S)

Any suspected ADRs and fatal AEs; with special focus on hypersensitivity and thrombotic event, occurred within 7 days after Praxbind™ administration will be analysed for primary outcome results.

8.5 SECONDARY OUTCOME (S)

8.5.1 Secondary outcome(s)

Percentage of patients who either received Praxbind™ for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding at the end of 2 years will be analysed for secondary outcome results.

Frequency table for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding will be generated to analyse.

8.5.2 (Other) Secondary outcome(s)

This section is not applicable as no other secondary endpoint has been specified in the protocol.

8.7 EXTENT OF EXPOSURE

This section is not applicable.

8.8 SAFETY ANALYSIS

Patients who have taken at least one dose of Praxbind will be considered for the safety analysis.

In general, safety analyses will be descriptive in nature and will focus on any suspected ADRs (serious and non-serious), serious AEs and AEs leading to death.

Additionally, physical examinations, vital signs, clinical laboratory test will be listed.

8.8.1 Adverse events

Analysis of Adverse Events:

All AEs captured in the eCRF will be listed for each patient and system organ class (SOC) and preferred term (PT) assigned to the AEs. The adverse events will be listed and analysed by taking the Overall count, counts as per SOC and PT, as per the relationship with drug and Seriousness category.

No imputation is planned for missing AE data except for missing onset dates which will be handled according to BI standard[(2)].

No adverse events of special interest (AESI) have been defined for this surveillance.

An AE is considered to be an ADR if either the physician who has reported the AE or the sponsor assesses its causal relationship as 'related'.

The incidence and grading of AEs will be tabulated by system organ class and preferred term. Adverse events will be categorized by serious adverse event (SAE), non serious adverse event, death or withdrawal. These categories will be further summarized by the causal relationship to study drug. An overall summary of the number and percentage of patients in each category will be presented in each category.

The following AE summary tables will be prepared:

- Overall Summary of AEs
- Summary of AEs by SOC and PT
- Summary of AEs by maximum severity (Intensity), SOC, and PT
- Summary of AEs related to treatment by SOC and PT
- Summary of Serious AE by SOC and PT
- Summary of deaths by SOC and PT
- Summary of Serious AEs related to treatment by SOC and PT
- Summary of non-serious AEs related to treatment by SOC and PT
- Summary of AEs causing discontinuation from study drug by SOC and PT

- Summary of AEs causing dose reduction of study drug by SOC and PT

The frequency of AEs/SAEs and ADRs will be tabulated by system organ class and preferred term.

The following list of Adverse Events will be considered under the category of Hypersensitivity and Thrombotic Events

- **Hypersensitivity:**

- Acute respiratory failure
- Anaphylactic reaction
- Anaphylactic shock
- Bronchospasm
- Circulatory collapse
- Erythema
- Generalised oedema
- Localised oedema
- Mouth ulceration
- Pneumonitis
- Pruritus
- Rash
- Respiratory arrest
- Respiratory distress
- Respiratory failure
- Scrotal oedema
- Shock
- Skin oedema
- Urticaria
- Wheezing

- **Thrombotic events**

- Ischemic Stroke
- Myocardial Infarction
- DVT only
- Pulmonary Embolism only
- DVT+ Pulmonary Embolism
- Systemic Embolism only
- Systemic Embolism + DVT

Multiple overlapping or adjacent AE occurrences of same AEs are collapsed into one AE event if all AE attributes are identical (patient number, LLT, outcome, therapy, intensity, action taken, seriousness, reason for seriousness, causal relationship).

Two AEs are considered to be time-overlapping if the start date of the second, later occurrence is earlier or equal to the end date of the first occurrence.

Two AEs are considered to be time-adjacent if the start date of the second, later occurrence is one day later than the end date of first occurrence.

After the collapsing the events to remove duplication and clarify any inconsistencies, the resulting data will form the basis for all reporting of AE data in the listing, table and figures.

Patients reporting more than one AE for a given MedDRA Preferred Term will be counted only once for that term using the most severe incident. Patients reporting more than one type of event within a SOC will be counted only once for that SOC. Any deaths, other SAEs, and other significant adverse events including those leading to premature discontinuation, will be separately identified.

Duration of AEs will be derived and presented in all listings.

AE Duration: (AE End date – AE Start date)+1. If date and time are not missing then the duration will be calculated in day and time.

AEs will be coded using the version 20.0 or higher of the Medical Dictionary for Regulatory Activities (MedDRA).

The grading of adverse events will be done by using Common Terminology Criteria for Adverse Events version 4 (CTCAE v4).

8.8.2 Laboratory data

Listings of laboratory results and laboratory test performance date prescribed for each patient. Values outside of the laboratory's reference range (i.e., those with high or low values) will be flagged in the laboratory listings.

Laboratory tests with continuous results will be summarized descriptively. For categorical data will be summarized using frequency and proportion.

Frequency count with percentage for possibly clinically significance abnormalities will be presented separately.

8.8.3 Vital signs and Physical Examinations

Vital sign and physical examination results (including pulse rate, systolic and diastolic blood pressure, height, weight) will be listed by patient as baseline characteristics. Also, continuous results of vital sign and physical examinations will be summarized descriptively (n, mean, SD, median, Q1, Q3, minimum, and maximum) as baseline characteristics.

8.8.4 ECG

This section is not applicable as no ECG data are collected.

8.8.5 Others

This section is not applicable as no other analysis is needed.

9 REFERENCES

1.	001-MCS-40-415_RD-02: "Trial Statistical Analysis Plan (TSAP) Template (annotated, PDF copy)",version: 1.0
2.	001-MCG-156_RD-01: "Handling of Missing and Incomplete AE Dates", version: 3.0
3.	001-MCS-90-140: "Post-Authorization Safety Studies", version: 3.0
4.	001-MCS-05-504: "Reconciliation of Adverse Events Information in BI studies, version: 7.0
5.	001-MCS-50-408: "Medical and Quality Review in Clinical Trials", version: 5.0

11 HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections Changed	Brief description of change
Final 1.0	11-Jul-2018		None	This is the Final V1.0 of TSAP with necessary information for trial conduct

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NON-ELECTRONIC SIGNATURE STATEMENT

The signatories with no access to the Boehringer Ingelheim Electronic Document Management System (EDMS) sign the Trial Statistical Analysis Plan.

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SIGNATURES:

Meaning of Signature	Signed by	Signature	Date
Approval - Biostatistics	Email:		22/11/2018
Approval - Data Management	Email:		22/11/2018
Approval - SAS Programming	Email:		22/11/2018

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Meaning of Signature	Signed by	Sign	Date
Author- Team Member Biostatistics and SAS programming	Email:		11 JUL 2018
Approval- Biostatistics	Email:		11 Jul 2018
Approval- SAS Programming	Email:		11 Jul 2018