BTG

BTG-001653-01

# Retrospective and prospective international E**K**oSo**N**ic® registry **O**f the treatment and **C**linical **OUT**comes of patients with **P**ulmonary **E**mbolism

Statistical Analysis Plan (SAP)

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Document Status: 1.0 FINAL

Release Date: 01 March 2019

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Statistical Analysis Plan (SAP) Approval Page

Approved By:

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## SAP Revision History

| Version Number | Date | Brief Description of Changes |
|---|---|---|
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## List of abbreviations

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# 1 Introduction

The purpose of this statistical analysis plan (SAP) is to provide a description of the planned methodology and analysis for Protocol BTG-001653-01 based on protocol version 2.0 dated 09May2018. A mock-up of tables, listings and figures (TLFs) will be provided in a separate document.

## 1.1 Study design

This multicenter, international registry is designed to retrospectively and prospectively collect treatment and outcome data related to pts with submassive (Intermediate-High Risk) or massive (High Risk) PE undergoing the APT treatment. Subjects are treated per Investigator's SoC and in accordance with the IFU. Patients will be categorized according to the APT treatment protocol they received.

Intermediate-High Risk PE will be defined by evidence of RV dysfunction (RV/LV $\geq$ 1.0), hemodynamic stability (normal systemic arterial blood pressure >90 mmHg), and Troponin elevation. High Risk PE will be defined by hemodynamic instability (normal systemic arterial blood pressure <90 mm Hg and/or use of vasopressors).[1]

Retrospective case data will consist of treatment and health outcomes of consecutive patients treated with APT between January 2014 and one year prior to date of site activation.

Prospective subject data will consist of treatment and health outcomes of treated subjects since the site was activated to participate in the registry. For each treated subject enrolled, participation in the registry lasts approximately 12 months. Subjects should be followed per Investigator's SoC. Data will be collected for any echocardiograms and CTAs completed. At minimum, a health status check should be performed at 3 and 12 months. For patients with an abnormal echocardiogram post-APT treatment, an on-site visit with echocardiogram should be performed at 3 months to assess for chronic pulmonary hypertension. An echocardiogram at 12 months is also requested for all patients. Safety data should be reported through 12 months post-index procedure.

[1]

### 1.1.1 Data collection schedule and assessments - Prospective**

Assessments will be performed per Investigator's SoC and collected according to the schedule below. Assessments marked with an asterisk (*) pertain to an outcome measure or eligibility.

| Assessment | Baseline | Procedure/Post Procedure | Follow-up | |
|---|---|---|---|---|
| | Day -1 | Day 0 thru Discharge | 3 Months (±14 Days) Post APT (Phone or Visit) | 12 Months (±1 Month) Post APT (Phone or Visit) |
| Informed Consent | X* | | | |
| Demographics | X* | | | |
| Medical history, risk factors | X* | | | |
| Vital signs[1] | X* | X | | |
| Physical Examination | X | | | |
| CTA | X* | X*[3] (if collected) | | |
| sPESI | X | | | |
| APT Procedure | | X | | |
| Echocardiogram[2] | X* | X[3] (if collected) | X* (if collected) | X* (if collected) |
| Quality of life surveys[4] | | X* | X* | X* |
| Laboratory tests[5] | X[6] | X | | |
| Biomarkers[7] | X* | X | | |
| Adverse/VTE/Bleeding Events | | X* | X* | X* |
| Anticoagulation medications | X | X | X | X |

1. Record heart rate, blood pressure, respiratory rate, oxygen saturation vital signs at admission, at start and end of treatment, and once at same time each day of hospitalization
2. Includes RV/LV ratio, TAPSE, estimated RVSP, and collapse of the inferior vena cava (IVC) with respiration. Echocardiograms collected throughout the follow up period will be slotted by months from index procedure for analysis.
3. Collect 24 – 48 hours after the start of the APT procedure
4. PEmb-QOL and EQ-5D-5L
5. Hemoglobin (Hgb), hematocrit (Hct), platelet count, creatinine, activated partial thromboplastin time (aPTT), partial thromboplastin time (PT), and international normalized ratio (INR)
6. Record if collected within 48 hours prior to the start of APT procedure
7. Troponin, brain natriuretic peptide (BNP)/NT-proBNP, lactate/lactic acid, and D-dimer

** For the retrospective portion of the study, data will be collected as available for 12 months post- index treatment and where possible according to the schedule above.

## 1.2 Study objectives

The objectives of this registry are:

- To understand the APT treatment protocol used as SoC across institutions and document changes in practice following the OPTALYSE PE study results
- To describe the effects of varied APT protocols on long-term patient outcomes

# 2 Statistical methods and analysis

## 2.1 General methodology and definitions

Continuous data will be summarized with means, medians, standard deviations, minima and maxima, unless otherwise specified. Categorical data will be summarized with observed counts and percentages for each category.

All data collected from the eCRF and derived variables will be provided in listings in addition to the summaries described below.

Baseline is defined as the last non-missing assessment prior to the start of APT treatment.

Windowing rules provided below will be used to assign visits to each follow-up assessment for the retrospective and prospective portions of the study. If multiple assessments occur within the same window, the assessment closest to the middle of the "within schedule window" will be used.

Quality of life surveys will be assigned according to the windows: 3 Months (±14 Days) post-APT procedure and 12 Months (±1 Month) post-APT procedure. Echocardiograms will be slotted by month post-APT procedure.

## 2.2 Populations

Safety Population (SP) - The SP will be defined as all patients who receive the APT procedure. Safety and effectiveness summaries will be reported for the SP.

Efficacy Population (EP) - The EP will be defined as all patients who meet eligibility criteria. An additional effectiveness summary will be reported for the EP.

### 2.2.1 Subgroups

Efficacy and safety outcome measures will be summarized separately for the following subgroups:

- APT dose received (ie, >24mg; 20.1-24mg; 12.1-20mg; 4-12mg; <4mg)
- Submassive and massive PE

- Region
- Retrospective and prospective portions of the registry

## 2.3 Disposition, Demographics, Baseline

### 2.3.1 Disposition

Patient disposition will be summarized for all patients and separately by retrospective and prospective portions of the registry, as well as by SP and EP. The following categories will be summarized:

- Number of patients screened
- Number and percentage of patients who were enrolled and treated
- Number and percentage of patients with 3- and 12-month follow-up
- Number and percentage of patients who discontinued
- Reasons for discontinuation
    - Withdrew consent
    - Lost to follow-up
    - Death
    - Study discontinued by sponsor
    - Other
- Number and percentage of patients who completed the study
- Duration on study (months)

Additionally, listings of inclusion/exclusion criteria, disposition, reason for discontinuation and completion will be provided.

### 2.3.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics are collected at screening. Descriptive summaries and/or listings will be summarized for all patients and separately by retrospective and prospective portions of the registry, as well as by SP and EP. The number and percent ages (categorical variables) and descriptive statistics (continuous variables) will be summarized for the following:

**Demographic:**

- Age (years)
- Gender (Male, Female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Not reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported)

**Baseline characteristics**

- Physical examination
- Medical history

- Clinical risk factors including pertinent PE history
- sPESI
- Anatomic location of PE
- Anticoagulation medications

### 2.3.3 Protocol deviations

The number and percentage of patients with informed consent or eligibility protocol deviations will be summarized. Additionally, a listing of deviations will also be presented.

## 2.4 Treatment and other medication and therapies

### 2.4.1 Study treatment

The following APT procedure details will be summarized:

- Location of PE
- Access route
- Fluoroscopy time
- Volume of Contrast
- Ultrasound guidance?
- Time for placement of catheters (h)
- Ultrasound (h)
- Total dose/total dose per catheter
- Technical/procedural deviations
- Frequency of adjunctive therapies following APT

Patients will be categorized according to the thrombolytic dose they received. The following categories will be used:

- >24mg
- 20.1-24mg
- 12.1-20mg
- 4-12mg
- <4mg

For each category, the mean, min, and max time will be summarized. Frequency of each of the APT categories will be summarized with observed counts and percentages for each category overall, by analysis population, by region, and by the retrospective and prospective portions of the registry.

Frequency of use of each of the APT treatment protocols before and after OPTALYSE PE results were made public will also be summarized and compared using fisher's exact test.

### 2.4.2 Anticoagulation medications

The number and percentage of subjects treated with anticoagulation medications will be summarized prior to APT procedure, post procedure until discharge, at 3-month and 12-month follow-up.

## 2.5 Efficacy outcome measures

Efficacy analyses will be performed for both the SP and EP populations. In addition to the analyses described below, efficacy outcome measures will also be summarized by the subgroups described in section 2.2.1. All observed data will be summarized without imputation for missing values.

Efficacy outcomes measured by echocardiogram including RV/LV, TAPSE, IVC Collapse, estimated RVSP and pulmonary arterial pressure will be summarized using descriptive statistics and 95% confidence intervals at each time point and/or study visit including change from baseline for continuous endpoints and shift tables for categorical variables.

## 2.6 Additional outcome measures

Analyses of additional outcome measures will be performed for both the SP and EP populations. In addition to the analyses described below, additional outcome measures will also be summarized by the subgroups described in section 2.2.1. All observed data will be summarized without imputation for missing values.

### 2.6.1 Healthcare Utilization

Time from hospital admission to ICU and time from hospital admission to discharge will be summarized using descriptive statistics.

### 2.6.2 Quality of Life Assessments

For the prospective portion of the study, PEmb-QOL and EQ-5D-5L will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, maximum) and 95% confidence intervals at each time point and/or study visit including change from baseline for continuous endpoints and observed counts, percentages and shift tables for categorical variables.

The PEmb-QOL questionnaire score ranges from 0 to 100. To score: Q1, Q4, Q5, and Q9 are to be reversedly scored with a low score indicating a better quality of life. Two questions (Q2 ‘At what time of day are your lung symptoms most intense?’ and Q3 ‘Compared to one year ago, how would you rate the condition of your lungs in general now?’) are not used for scoring. Item 4a will be considered missing if the answer was ‘I do not work’. For a PEmb-QoL summary score, first transform each answered item score to a scale ranging from 0 to 100 (38 items total). Then average these transformed scores (except items Q2 and Q3) to obtain an overall summary score. No minimum is specified for the number of answered items.

The EQ-5D-5L is a self-administered questionnaire consisting of 5 questions pertaining to specific health dimensions (mobility, self-care, pain, usually activities and anxiety and depression), and health status rating scale (visual analogue scale [VAS]). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. If a patient has died, the last EQ-5D-5L dimension assessment prior to death will be imputed as extreme problems (coded as 5) and flagged in the listing.

The VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labeled 'the best health you can imagine' (Score=100) and 'the worst health you can imagine' (Score = 0). This information can be used as a quantitative measure of health as judged by the individual respondents. If a patient has died, the last EQ-5D-5L VAS assessment prior to death will be imputed as 0 and flagged in the listing.

Each one digit number expressing the level selected for each dimension can be combined into a 5-digit number describing the respondent's health state. For example, the number 11111 represents the respondent not having any problems in all five dimensions. These 5-digit numbers are health states which can be converted to an index value, where 1 represents full health and 0 is equivalent to death. A health state could be considered worse than death and the index values for those states will be less than 0. The index value will be calculated as:

*Index value = 1 – 0.9675 * (Dimension 1 Estimate + Dimension 2 Estimate + Dimension 3 Estimate + Dimension 4 Estimate + Dimension 5 Estimate)*

Each dimension estimate is based on the levels chosen for each dimension and can be found in appendix section 3.1.

### 2.6.3 Adjunctive Therapy

The number and percentage of patients with non or partial response to other interventional procedures prior to APT procedure for index PE (eg, patients receiving other procedures prior to EKOS for their index PE) will be summarized using descriptive statistics.

The number and percentage of patients who receive adjunctive treatment following treatment with EKOS for their index PE will be summarized using descriptive statistics.

### 2.6.4 IVC Filter Placement

The number of occurrence of IVC filter placement will be summarized using descriptive statistics.

## 2.7 Safety analyses

Safety analyses will be performed for the SP during hospitalization and through the 12-month follow-up period. In addition to the analyses described below, safety analyses will also be summarized by the subgroups described in section 2.2.1.

### 2.7.1 Adverse events

#### 2.7.1.1 Coding

Adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 20.1.

#### 2.7.1.2 General

Adverse event summaries will include all treatment emergent adverse events (TEAE). TEAE are defined as AEs starting on or after study day 1 (i.e., on or after the first day of APT treatment). All adverse events will be listed and non-TEAEs will be flagged.

TEAEs will be summarized by presenting the number and percentage of patients having at least one TEAE, having at least one TEAE in each primary system organ class (SOC) and for each preferred term (PT). A patient with multiple occurrences of a TEAE will be counted only once in the category.

Separate summaries will be presented by SOC and PT.

#### 2.7.1.3 Analysis

The following summaries will be provided (within 30 days; within 365 days):

a. Overall summary of AEs
b. All AEs by primary SOC and PT
c. AEs suspected to be related to procedure and/or device by primary SOC and PT
d. Serious adverse events (SAEs) by primary SOC and PT
e. SAEs suspected to be related to procedure and/or device by primary SOC and PT
f. AEs leading to discontinuation by primary SOC and PT
g. Most frequent AEs (5% or 10%) by primary SOC and PT
h. Bleeding Events
i. Major Bleeding Events (within 72 hours; within 30 days; within 365 days)
j. VTE (DVT and PE)
k. diagnosis of pulmonary hypertension
l. composite measure of recurrent symptomatic PE, PE related death or hemodynamic collapse at 30 days
m. Death resulting from AEs by primary SOC and PT

In addition, the following summaries will also be provided by subgroups described in section 2.2.1.

- Overall summary of AEs
- All AEs by primary SOC and PT
- SAEs by primary SOC and PT
- Most frequency AEs (5% or 10%) by primary SOC and PT

### 2.7.2 Deaths

Patient deaths will be summarized as all-cause mortality and by cause of death at 30 days, 90 days and through 12-months. A patient listing of all deaths will also be provided.

### 2.7.3 Vital Signs

Descriptive summaries for vital sign measurements will be presented by visit in mean, median, standard deviation, minimum and maximum. Baseline, time point value and change from baseline will be presented for each visit and patients having both baseline and corresponding time point will be summarized.

### 2.7.4 Laboratory tests and Biomarkers

Descriptive summaries for laboratory tests and biomarkers will be presented by visit in mean, median, standard deviation, minimum and maximum. Baseline, time point value and change from baseline will be presented for each visit and patients having both baseline and corresponding time point will be summarized.

## 2.8 Interim analysis

Periodic statistical summaries will be prepared semi-annually, to include the following at a minimum:

- Disposition summaries as per section 2.3.1
- Study treatment summaries as per section 2.4.1
- Safety summaries as per section 2.7.1 (2.7.1.3 a, d, i-m) and 2.7.2

## 2.9 Sample size

For retrospective cases, up to 1000 cases will be collected to capture details of PE treatment with EKOS from the time the device was cleared for treatment of PE to the time each site was activated. For prospective, up to 500 patients will be treated to collect data on current EKOS use at up to 100 sites.

# 3 Appendix

## 3.1 Imputation rules

### 3.1.1 AE date imputation

The following algorithm should be used to estimate start dates for which only partial information is known:

- Missing day and month
  - If the year is the same as the year of first study treatment, then the day and month of the start date of treatment will be assigned to the missing fields
  - If the year is prior to the year of first study treatment, then December 31 will be assigned to missing fields
  - If the year is after the year of first study treatment, then January 1 will be assigned to the missing fields
- Missing month only
  - Treat day as missing and replace both month and day accordingly to the procedure above
- Missing day only
  - If the month and year are the same as the year and month of first study treatment, then the start date of treatment will b assigned to the missing day
  - If the month and year are before the year and month of first study treatment, then the last day of the month will be assigned to the missing day
  - If the month and year are after the year and month of the first study treatment, then the first day of the month will be assigned to the missing day

If the imputed start date result is after the stop date (and the stop date is complete), the imputed start date will be reset to the stop date.

The following algorithm should be used to estimate stop dates for which only partial information is known:

- Missing year
  - Date left missing
- Missing month
  - Impute “December”
- Missing day
  - Impute last day of that month

## 3.2 EQ-5D-5L Derivations[3]

| Question | Text | Coded Value |
|---|---|---|
| *Mobility* | No problems/No pain/Not anxious | 1 |
| *Self-Care* | Slight problems/Slight pain/Slightly anxious | 2 |
| *Usual Activities* | Moderate problems/Moderate pain/Moderately anxious | 3 |
| *Pain/Discomfort* | Severe problems/Severe pain/Severely anxious | 4 |
| *Anxiety/Depression* | Unable/Extreme Pain/Extremely anxious | 5 |

The following table will be used in calculating the index value from the 5-digit health state.

***Index value*** *= 1 – 0.9675 * (Dimension 1 Estimate + Dimension 2 Estimate + Dimension 3 Estimate + Dimension 4 Estimate + Dimension 5 Estimate)*

The dimension estimates will be taken from the table below. Each estimate corresponds to the level each respondent checked for each dimension. For example, if a patient has a health state of 23245, the following calculation will be used:

1 – 0.9675*(0.051+0.076+0.051+0.276+0.301) = 0.270

| | | |
|---|---|---|
| Constant | | 1.000 |
| Mobility | None | 0 |
| | Slight | 0.051 |
| | Moderate | 0.063 |
| | Severe | 0.212 |
| | Unable | 0.275 |
| Self-care | None | 0 |
| | Slight | 0.057 |
| | Moderate | 0.076 |
| | Severe | 0.181 |
| | Unable | 0.217 |
| Usual Activities | None | 0 |
| | Slight | 0.051 |
| | Moderate | 0.067 |
| | Severe | 0.174 |
| | Unable | 0.190 |
| Pain/discomfort | None | 0 |
| | Slight | 0.060 |
| | Moderate | 0.075 |
| | Severe | 0.276 |
| | Unable | 0.341 |
| Anxiety/depression | None | 0 |
| | Slight | 0.079 |
| | Moderate | 0.104 |
| | Severe | 0.296 |
| | Unable | 0.301 |
| Fixed value | | 0.9675 |

## 4 Reference

[1]Piazza G, Goldhaber SZ. Management of submassive pulmonary embolism. Circulation. 2010;122:1124-1129

[2]Rochat et al. Health and Quality of Life Outcomes. 2014, 12:174

[3]Devlin N et al. Valuing Health-Related Quality of Life: An EQ-5D-5L Value Set for England. EuroQol Research Foundation. 2016.