STATISTICAL ANALYSIS PLAN (SAP)

Study Title: A Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Large Simple Trial Evaluating the Use of BE1116 (4-Factor Prothrombin Complex Concentrate [Kcentra® / Beriplex®]) to Improve Survival in Patients with Traumatic Injury and Confirmed or Suspected Acute Major Bleeding

Study Number:	BE1116_3006
Study Product:	BE1116 (Kcentra® / Beriplex®; 4-Factor Prothrombin Complex Concentrate [Human])
Development Phase:	Phase 3
Sponsor:	CSL Behring LLC 1020 First Avenue King of Prussia PA 19406, USA
Version:	Final 2.0
Version Date:	06 December 2024
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Council for Harmonisation) and all applicable national and local regulations.

Table of Contents

List of Tables

List of Figures

1 Revision History

Date	Version	Summary of Changes
07 Dec 2022	1.0	N/A
06 Dec 2024	2.0	General Changes: • Updated rules for handling missing randomization time. • Adapted definition of mITT population. • Modified the analysis of transfusion of blood products to account for non-integer units. • Added derivation rules for missing randomization and treatment start times. • Updated exploratory endpoints due to protocol amendments 1 and 2. Updates due to early study termination and due to reduced sample size constraints: • Removal of interim analysis. • Removal of sensitivity analysis. Some groupings considered for sensitivity analysis are moved to subgroup analysis instead. • Removal of correlation analysis. • Removal of age-group specific adverse event analysis

2 List of Abbreviations

Abbreviation	Term
4F-PCC	4-factor prothrombin complex concentrate
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse events of special interest
AKI	Acute kidney injury
ARDS	Acute respiratory distress syndrome
ATC	Anatomical Therapeutic Chemical
CDISC	Clinical Data Interchange Standards Consortium
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DBL	Database lock
eCRF	Electronic Case Report Form
ED	Emergency department
EFIC	Exception From Informed Consent
EOS	End of Study
FDA	Food and Drug Administration
GCS	Glasgow coma score
ICH	International Council for Harmonisation
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IP	Investigational product
IRT	Interactive Response Technology
ITT	Intent-to-treat Population
IU	International Unit
IV	Intravenous
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	Modified Intent-to-treat Population
PARM	Planned Analysis Review Meeting
PP	Per Protocol

Abbreviation	Term
PT	Preferred Term
RABT	Revised Assessment of Bleeding and Transfusion
RBC	Red blood cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TBI	Traumatic Brain Injury
TEAE	Treatment-emergent AEs
TEE	Thromboembolic event
WHO-DDE	World Health Organization Drug Dictionary Enhanced

3 Purpose

This Statistical Analysis Plan (SAP) provides a detailed and complete description of the planned statistical analyses of the study BE1116_3006 [Evaluation of BE1116 (4-factor prothrombin complex concentrate [4F-PCC]) in patients with traumatic injury and confirmed or suspected acute major bleeding to improve survival] to support the Clinical Study Report (CSR).

This SAP complies with the International Council for Harmonisation (ICH) E9 'Statistical Principles for Clinical Trials' and E9(R1) 'Statistical Principles for Clinical Trials: Addendum on Estimands and Sensitivity Analysis in Clinical Trials', and is based upon the following study documents:

- Clinical Study Protocol (CSP) Amendment 2 dated 06 February 2024
- Electronic Case Report Form (eCRF), Version V5.0, dated 04 April 2024

All decisions regarding the final analysis of the study results, as defined in this SAP, have been made before database lock (DBL) of the study data.

Deviations from the analyses in this SAP will be detailed in the CSR.

4 Study Design

This is a phase 3, prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group, large simple trial to investigate the efficacy and safety of a single intravenous (IV) infusion of BE1116 in subjects who have traumatic injury, with confirmed or suspected acute major bleeding and / or predicted to receive a large volume blood product transfusion.

Randomization will be in a 1:1 ratio (BE1116:placebo) using randomized block design with blocks within each site. The time of randomization is defined as the time at which the selected Investigational Product (IP) study kit is opened by the trauma team (or other applicable site staff) for IP reconstitution and administration.

The IP infusion will be given in addition to the study site's standard resuscitation methods and protocol. All subjects will receive standard of care according to the study site's normal clinical practice at all times during the study. Standard of care should not be interrupted or forgone to enable subject participation in the study.

The study consists of (i) a Screening and Randomization (Enrollment) Period, (ii) a Treatment Period, and (iii) an In-hospital Follow-up Period.

4.1 Objectives, Endpoints and Estimands

The primary objective is to assess the efficacy of a single IV infusion of BE1116 on all-cause mortality within 6 hours after randomization (6-hour mortality) in subjects who have traumatic injury, with confirmed or suspected acute major bleeding and / or predicted to receive a large volume blood product transfusion.

The secondary objectives of the study are as follows:

1. To assess all-cause in-hospital mortality up to 24 hours after randomization (24-hour mortality)
2. To assess all-cause in-hospital mortality up to 30 days after randomization (30-day mortality)
3. To assess the requirement for surgical or interventional radiological procedures to stop bleeding related to the primary injury up to 24 hours after randomization
4. To assess the safety of BE1116

The exploratory objectives of the study are as follows:

1. To assess transfusion of blood products
2. To assess healthcare utilization during primary hospitalization

Table 1 Study Objectives and Endpoints / Summary Measures

Objectives	Endpoints	Summary Measure(s)
Primary	All-cause mortality within 6 hours after randomization	Difference in the proportion of subjects who die in the BE1116 arm compared with the placebo arm during the first 6 hours after randomization as estimated by a Bayesian logistic regression model.
Secondary		
1	All-cause in-hospital* mortality up to 24 hours after randomization	Difference in proportion of subjects who die in-hospital in the BE1116 arm compared with the placebo arm up to the first 24 hours after randomization, as estimated by a Bayesian logistic regression model
2	All-cause in-hospital* mortality up to 30 days after randomization	Difference in proportion of subjects who die in-hospital in the BE1116 arm compared with the placebo arm up to 30 days after randomization, as estimated by a Bayesian logistic regression model
3	Surgical or interventional radiological procedures to stop bleeding related to the primary injury up to 24 hours after randomization	Difference in proportion of subjects who undergo surgical or interventional radiological procedures to stop bleeding related to the primary injury in the BE1116 arm compared with the placebo arm up to 24 hours after randomization, as estimated by a Bayesian logistic regression model
4	Serious adverse events (SAEs) considered related to IP	During the primary hospital stay only, within the 30 days after randomization: • Number and proportion of subjects with SAEs considered related to IP by treatment (BE1116 or placebo)

Objectives	Endpoints	Summary Measure(s)
4	Adverse events of special interest (AESIs): • Thromboembolic events (TEEs), symptomatic or asymptomatic, and arterial or venous (eg, deep vein thrombosis, pulmonary embolism, ischemic stroke [including thromboembolic stroke], myocardial infarction) • Acute respiratory distress syndrome (ARDS) • Multiple organ failure • Acute kidney injury (AKI) requiring renal replacement therapy (dialysis, hemofiltration, or hemodiafiltration) Note: superficial thromboses will not be included as AESI	• TEEs: Number and proportion of in-hospital overall and related TEEs up to 30 days after randomization by treatment (BE1116 or placebo) • Number and proportion of subjects with the following: o ARDS o Multiple organ failure o AKI requiring renal replacement therapy
Exploratory		
1	Transfusion of blood products	Number of units of blood product transfused before arrival at the hospital through the first 24 hours after randomization, overall and by type of product by treatment
2	Ventilator-free days	Number of ventilator-free days during the primary hospital stay up to 30 days after randomization, by treatment
2	Intensive care unit (ICU)-free days	Number of ICU-free days during the primary hospital stay up to 30 days after randomization, by treatment
2	Hospital-free days	Number of hospital-free days up to 30 days after randomization, by treatment

Objectives	Endpoints	Summary Measure(s)
3#	Infusion of tranexamic acid	Amount of tranexamic acid infused in milligram (mg) before arrival at the hospital through the first 24 hours after randomization, overall and by treatment
4#	Death due to hemorrhagic shock/exsanguination	Difference in proportion of deaths that are due to hemorrhagic shock/exsanguination in-hospital in the BE1116 arm compared with the placebo arm up to 30 days after randomization, as estimated by a Bayesian logistic regression model

*In-hospital mortality will only be recorded and assessed for the primary hospitalization.
#Additional endpoints not defined in the CSP but added in the SAP.

Primary and secondary estimands are discussed in Section 10.1.1 and Section 10.2.1.

4.1.1 Primary Endpoint Hypotheses

The primary study hypothesis is that the 6-hour mortality in the BE1116 arm will be reduced compared to the placebo arm, ie, that BE1116 is superior (as evidenced by lower mortality) to placebo.

Null Hypothesis (H_0): The all-cause 6-hour mortality rate in BE1116 is no better than control.

$$p_{\text{kcentra}} - p_{\text{control}} \geq 0$$

Alternative Hypothesis (H_1): The all-cause 6-hour mortality in BE1116 is lower than control.

$$p_{\text{kcentra}} - p_{\text{control}} < 0$$

Superiority will be concluded if the posterior probability for the mortality being lower in the BE1116 group exceeds a predefined threshold based on Bayesian logistic regression (see Section 10.1.2).

Methods to control for multiplicity are described in Section 10.4.

4.1.2 Secondary Endpoints Hypotheses

The hypotheses for the secondary efficacy endpoints are the same as that for the primary hypothesis. These hypotheses will be formally tested in a sequential order if the primary efficacy endpoint reaches success. There will be no formal statistical testing for the occurrence of SAEs and AESI.

4.2 Study Treatments

The active study treatment is BE1116 (4F-PCC) containing human coagulation Factors II, VII, IX, and X, Protein C, and Protein S, powder for reconstitution with sterile water for injection.

A single dose will be administered by IV infusion. The dose is dependent on body weight (estimated or measured):

• Weight < 75 kg (< 165 lbs): 2000 IU

• Weight ≥ 75 kg (≥ 165 lbs): 3000 IU

Patients will receive either BE1116 or placebo.

4.3 Randomization Procedures and Blinding

Subjects will be randomized to BE1116 or Placebo group with a 1:1 ratio. CSL (or designee) will provide blinded IP study kits to the study sites. The IP will be packaged and labeled to ensure blinding is maintained.

Investigational site staff, including the investigators, physicians, nurses, and pharmacists, will be blinded to treatment allocation. Subjects will also be blinded to treatment allocation (double-blind).

CSL personnel (or delegates) will be blinded to treatment allocation, except for those personnel involved in the Interactive Response Technology (IRT) system and clinical trial supply who will be unblinded.

A separate statistician and programming team will provide unblinded data to the Independent Data Monitoring Committee (IDMC) for adequate safety and efficacy reviews as planned. Partially unblinded data (treatment arms are masked as A and B) will be provided for safety only IDMC. If significant difference is observed between two arms which could result in

pause or termination of the study, the actual treatment arms will be released to IDMC. All individuals involved will be placed under strict confidentiality to protect the integrity of the study. If the IDMC makes a recommendation to stop the study, a few designated senior Sponsor stakeholders will access the unblinded data before endorsing the recommendation. These senior stakeholders will not participate in any study conduct or analyses after unblinding.

In addition, individual subjects may be unblinded during the study in emergency situations for reasons of subject safety, if knowing treatment assignment will change medical management.

The randomization date and time will be defined as the date and the time of opening the medication kit and will be recorded.

4.4 Determination of the Sample Size

The originally planned sample size of 8000 subjects (4000 per treatment arm) was determined to achieve 80% power while controlling for a one-sided type I error of 0.025 testing for superiority, accounting for 3 interim analyses.

4.5 Interim Analyses

This section briefly describes the interim analyses as originally planned. In October 2024, it was decided by the sponsor to stop the study early. Therefore, the interim analyses will not take place and only a final analysis with a reduced sample size will be conducted.

The IDMC meetings were scheduled to review unblinded data for both safety and efficacy according to the planned interim analysis schedule shown in Table 2. The safety reviews for 500 and 1000 subjects enrolled took place prior to study stop. Unblinded data for safety were provided to the IDMC.

Table 2 Planned IDMC Reviews

IDMC Meeting Type	Number of Subjects Enrolled
Safety review	500
Safety review	1000
Scheduled Interim Analysis 1 – Safety and futility review*	2000
Safety review*	3000
Scheduled Interim Analysis 2 – Safety, efficacy, and futility review*	4000
Safety review*	5000
Scheduled Interim Analysis 3 – Safety, efficacy, and futility review*	6000

IDMC = Independent Data Monitoring Committee; *=review/analysis will not take place due to early study termination.

Interim Efficacy and Futility Analyses: Interim futility analyses were to be conducted by the IDMC when approximately 25%, 50% and 75% of patients have been enrolled. For the originally planned stopping criteria and their justification refer to SAP Version 1.0 or Section 10.3.4 of the CSP.

4.5.1 Independent Data Monitoring Committee

The composition, activities, analyses, responsibilities, and timing of meetings of the IDMC is described in the IDMC charter.

Safety analyses conducted to support the IDMC are described in Section 12.1.

5 Changes from the Protocol Planned Analyses

5.1 Changes Due to Study Early Termination

In October 2024, it was decided by the sponsor to stop the study early. Therefore, the interim analyses described in the CSP will not be conducted and the success criteria for the final analysis are modified accordingly (see Section 10.4).

Planned sensitivity analysis that would add additional factors into the model has been removed. Instead, the additional subgroups have been added to the subgroup analysis described in Section 10.1.4 compared to the CSP.

5.2 General Changes

Use of tranexamic acid and death due to hemorrhagic shock/exsanguination are additional exploratory endpoints.

Non-trauma related death is changed to SAEs with fatal outcome.

The definition of the Modified Intent-to-treat (mITT) Population has been updated after discussions with the Food and Drug Administration (FDA) (see FDA minutes), and the primary analysis has been updated to be based on the mITT population. This change is also motivated so that subjects not eligible under protocol amendment 2 are not included in the main analysis.

The summary measure for the primary endpoint has been modified to not include the "in hospital" condition, to better match the endpoint.

6 Study Analysis Populations

6.1.1 Intent-to-treat (ITT) Population

The Intent-to-treat (ITT) Population will include all randomized subjects. In this population, analyses will be based on the treatment to which subjects were randomized, regardless of any treatment they received.

Randomization will be considered to have taken place if randomization time or time of infusion start is not missing. If both are missing, subjects will still be included in the ITT Population if their treatment kit is confirmed to have been opened.

6.1.2 Modified Intent-to-treat Population

The mITT Population will include all subjects in the ITT Population who receive a complete or partial dose of BE1116 or placebo. In this population, analyses will be based on the treatment to which subjects were randomized, regardless of which treatment they actually received.

Two requirements that are not part of the CSP have been added for inclusion in the mITT:

- Glasgow Coma Score < 15. Subjects with missing or non-testable score will be included in the mITT.
- Receipt of blood product transfusions prior to randomization (see Section 8.2.9 for the identification of blood products).

Time of randomization and time of transfusion will not be compared to determine the timing relative to randomization. Instead, transfusions will be considered as having been received prior to randomization if they were entered either on the pre-hospital or the arrival to randomization eCRF page.

In the case of missing randomization time subjects will only be included if dosing can be confirmed as per the Study Drug Administration form of the eCRF. Presence of infusion start or end time will be considered confirmation of dosing.

6.1.3 Per-protocol Population

The Per-protocol (PP) Population will include all subjects in the mITT Population with no major protocol deviations that would potentially affect the assessment of the primary endpoint. Protocol deviations will be continuously reviewed and adjudicated as major or minor. The final assessment of whether a specific protocol deviation would potentially affect the analysis will be made in a Planned Analysis Review Meeting (PARM) prior to DBL and unblinding, where protocol deviations and the assignment to analysis populations will be discussed in detail.

6.1.4 Safety Population

The Safety Population will include all subjects in the ITT Population who receive a complete or partial dose of BE1116 or placebo, based on the treatment actually received.

7 General Considerations

Datasets will be created according to Clinical Data Interchange Standards Consortium (CDISC) standards. Study data will be provided in Study Data Tabulation Model (SDTM) format. Analysis data will be provided in Analysis Data Model (ADaM) format.

SAS version 9.4 or higher will be used to perform all data analyses.

Summaries of continuous variables will be in terms of the number of observations, mean, standard deviation, median, first quartile (Q1), third quartile (Q3), minimum and maximum.

Categorical variables will be summarized using frequency counts and percentages.

Analyses that use other descriptive statistics will have the specific descriptive statistics identified with the analysis in the applicable SAP section.

For all Bayesian analysis, posterior credible intervals will be reported, based on the quantiles of Markov Chain Monte Carlo (MCMC) samples. Point estimates will be based on posterior means.

7.1 COVID-19 Impact

No COVID-19 impact on this study is expected given the study population and indication.

8 Data Handling Conventions

8.1 Missing Data

Missing data occurs when any requested data are not provided, leading to blank fields on the collection instrument. These data will be indicated by the use of a “blank” in subject listing displays. Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.

For this study it is expected that time of randomization or treatment may be missing. The impact on study analysis population assignments is discussed in Section 6.

If the full randomization datetime is missing, but treatment start datetime is available, then randomization datetime will be imputed as treatment start datetime – 10 minutes. However, if randomization date is present and is one day before treatment start date, the randomization time will be set to 23:59 instead, if that is earlier.

If actual age is missing, estimated age will be used instead for all summaries and analyses. In listings, it will be indicated whether age was actual or estimated.

8.2 General Derived Variables

8.2.1 Reference Dates, Times, and Study Days

Reference dates are used to assign study periods relative to randomization (Section 8.4).

- The reference date for both safety and efficacy is the randomization date and it will be used to calculate study day for all measures.
- If relative time is needed, the reference time will be the time of randomization.

The randomization date and time will be defined as the date and the time of opening the IP study kit and will be recorded. Rules for imputation of missing randomization time are described in Section 8.1.

The respective study day will be calculated as (date of interest - reference date) + 1 if the date of interest occurs on or after the reference date. If the date of interest occurs before the reference date, then the study day will be calculated as (date of interest – reference date). There will be no study day zero.

8.2.2 Durations

Durations (eg, the duration of an adverse event [AE]) are calculated in days, hours, and minutes as:

- event end date – event start date + 1 day if end time or start time not available.
- event end date / time – event start date / time if both end time and start time available.

Thus, there will be no duration of 0 if end time or start time are not available. If an AE has missing or partially missing start or end date, no duration will be calculated. If duration is provided in a listing, then start and end date will also be included.

For cases, where multiple durations are added up for time on ventilator or time in the ICU see the specific rules provided in Section 10.3.3.

8.2.3 Survival Status

Survival status at 6 hours, 24 hours and 30 days will be determined as follows:

- All-cause 6-hour mortality:
  - If death is not recorded for the subject, the subject will be considered alive.
  - If death is recorded, the subject will be considered alive at 6 hours if time of death – time of randomization is greater than 6 hours. Otherwise, the subject will be considered dead.
- All-cause in-hospital 24-hour mortality:
  - If available, survival status will be taken directly from the 24 Hours Survival Status eCRF page.
  - Otherwise, the subject will be considered alive if no death was recorded, or if death was recorded but took place more than 24 hours post randomization.
  - If death occurred and took place within 24 hours of randomization, the subject will be considered dead.
- All-cause in-hospital 30-day mortality:
  - If available, survival status will be taken directly from the survival status recorded in the Conclusion of Subject Participation eCRF page.
  - Otherwise, the subject will be considered alive if no death was recorded, or if death was recorded but took place more than 30 days post randomization, considering date and time of death.
  - If death occurred and took place within 30 days of randomization, the subject will be considered dead.

These included cases of withdrawal, discharge and declining to continue participation – if no death was recorded, it will be assumed no death occurred.

8.2.4 Time to Death

Time from randomization to death will be calculated in hours by subtracting the datetime of randomization from datetime of death.

This calculated time to death will be used only for Kaplan-Meier analysis, not to determine survival status. The same calculation rule applies for time to any censoring events.

8.2.5 Baseline Definition

Baseline is defined as the most recent, non-missing value before treatment for all assessments unless otherwise stated.

8.2.6 Change from Baseline

Changes from baseline will not be calculated for this study.

8.2.7 Multiple Assessments

Multiple assessments do not apply to this study since there will be no by-visit summaries or analysis. Assessments can be recorded only once in the eCRF.

8.2.8 Actual Treatment

The subject's actual treatment will be assumed to be identical to the assigned treatment unless a protocol deviation indicating otherwise is recorded for the subject. If a subject receives a study treatment that is different from the planned treatment for the entire time of treatment, then actual treatment is the treatment actually received.

In case of other deviations from planned treatment, an evaluation of the case and final treatment assignment will be done before DBL in the PARM.

8.2.9 Blood Products

For the analysis of transfusion of blood products described in Section 10.3.1 and for inclusion in the mITT blood products will be identified via manual clinical expert review of the medications entered into the eCRF, based on both the reported term for the medication and the medical coding.

As blood transfusion can be entered into the eCRF with different units, conversion factors into standard units will be provided by CSL, where necessary. Additionally, blood products will be categorized by CSL into different types, which will be used for summary as described in Section 10.3.1.

The outcome of the final review will be documented as part of the PARM prior to DBL.

8.3 Covariates

The primary analysis is not adjusted for any covariates. See Section 10.1.4 for planned subgroup analyses.

8.4 Study Periods Relative to Treatment

Study Period	Time Window
Screening and Randomization (Enrollment)	Subjects must be screened and randomized within 90 minutes after hospital arrival and before the start of IP infusion
Treatment Period (Start of IP infusion through completion of IP infusion)	IP infusion must be started post-randomization and within 90 minutes after hospital arrival
In-hospital Follow-up Period	Subjects will be followed up until death, discharge from hospital, or Day 30, whichever occurs first. If subject is discharged alive prior to 6 hours, then the subject will be followed up to assess 6-hour survival status, SAEs, and AESIs.

9 Study Population

9.1 Subject Disposition

The following summaries will be provided by treatment group and total population using the ITT Population and mITT Population:

- Subjects in each of the analysis populations described in Section 6.
- Subject study status, including subjects randomized, subjects by treatment status, subjects who completed until death, discharge, or Day 30 (including a further break-down by whichever occurred first), subjects who withdrew by reason. A similar break-down of completed subjects will be provided by up to 6 hours and up to 24 hours.
- Study duration in days for completers, who are alive at discharge.
- Subjects per site.

Reasons for study withdrawal will be presented in the order they are displayed in the eCRF.

Individual subject disposition information including withdrawal details will be listed. Subjects excluded from any analysis population and the reasons for exclusion will also be listed.

9.2 Protocol Deviations

The following summaries will be provided by treatment group using the ITT and mITT Population:

- All major protocol deviations
- All protocol deviations that require exclusion from mITT Population:
    - GCS=15
    - No transfusion of blood products prior to randomization

Inclusion of subjects with a GCS of 15 or without transfusion of blood products prior to randomization is only a protocol deviation for subjects under protocol amendment 2, but subjects will still be excluded from the mITT if they did not fulfil these criteria regardless of protocol version (see Section 6.1.2 for mITT definition).

- All protocol deviations that require exclusion from PP Population. This includes the following but is not limited to:
    - All protocol deviations leading to exclusion from the mITT Population
    - Inclusion/exclusion criteria deviations
    - Treatment more than 90 minutes after arrival at the hospital
    - Incorrect dosage
- No treatment with IP
- Prohibited medications

All protocol deviations will be listed by subject.

9.3 Demographic and Baseline Characteristics

The following summaries will be provided by treatment group using the mITT Population and ITT Population:

- Demographic characteristics (eg, actual age, race, ethnicity, sex [male, female, unknown], estimated or measured weight, height) will be summarized according to the general rule in Section 7. Age will be summarized as both a continuous and categorical variable. The following groupings will be used:
    - <18 years, further subdivided into
        - <15 years;

        - 15-17 years.
    - 18-64 years, further subdivided into
        - 18-25 years;
        - 26-64 years;
    - >64 years.

- Both estimated and measured weight will be summarized and listed. Number and percentage of subjects in each of the weight category (< 75 kg and ≥ 75 kg), as well as the number and percentage of subjects who have different weight categories for estimated and measured weights will also be summarized as part of the demographics table.
- Medical history and concomitant disease (coded using Medical Dictionary for Regulatory Activities [MedDRA], version 27.1 or later) will be presented by System Organ Class (SOC) and Preferred Term (PT). Entries on the Medical History page will be considered to be medical history if the end gate is prior to randomization and concomitant disease if the end date is after randomization, or the condition is ongoing.
- Clinical condition at baseline, including mechanism and type of injury, Injury Severity Score (continuous and by category [1-8, 9-15, 16-24, ≥25]), Abbreviated Injury Scale score by body region, presence of head injury, Charlson Comorbidity Index (continuous and categorical [none (0), moderate (1 to 4), severe(> 4)]), Glasgow coma scale (continuous and by category [≤ 8, 9 to 12, ≥ 13, = 15]) and Revised Assessment of Bleeding and Transfusion (RABT) score (continuous and categorical, ≤ 2 and > 2) will be summarized. Charlson comorbidity index will be derived per the updated weights in Appendix 6 of the CSP. The other scores will be auto calculated in the eCRF, according to the rules in Section 15 of the CSP. Blood transfusions prior to randomization and administration of fibrinogen, cryoprecipitate or tranexamic acid prior to IP administration will also be included, as well as mode of transport and whether systolic blood pressure at admission was below 70 mmHg.
- Vital signs at Baseline:
    - Systolic blood pressure, as continuous variable and by category (≤ 90mmHg, ≤ 70mmHg, > 90mmHg, No Read)
    - Diastolic blood pressure, as continuous variable (and count for No Read)
    - Heart rate as continuous variable

- Respiration rate as continuous variable
- Oxygen saturation as continuous variable (%)
- Temperature (°C) as continuous variable

- The laboratory tests (hematology, coagulation, and blood gas) at Baseline will be summarized. Data will be entered from medical records as available, only the first values obtained after hospital entry will be captured in the eCRF. No changes from baseline will be calculated.

Listings will be provided for all demographic and baseline characteristics.

9.4 Prior/Concomitant Medications

Prior/concomitant medications will be coded using World Health Organization Drug Dictionary Enhanced (WHO-DDE) B3.

Prior medications are those that end before the first IP administration. Per protocol only medications that impact bleeding and coagulation for at least 1 week prior to randomization will be recorded, but if any other medication is recorded it will still be reported.

All other medications are considered as concomitant medications, including those with missing end date.

Concomitant medications will be summarized showing the number and percentage of subjects taking concomitant medications by Anatomical Therapeutic Chemical (ATC) classification level 4 and PT. If the ATC level 4 coding is not available for a PT, the next available lower-level ATC code will be used. Tables will be provided for the mITT Population.

Prohibited concomitant medication will additionally be included into the table as a virtual ATC class “Prohibited Medication” in addition to also being summarized under their actual ATC class. Prohibited medication will be identified by the sponsor medical experts prior to the PARM, based on Table 4 of the CSP.

The following listing(s) will be provided:

- Prior and concomitant medication.
- Prohibited concomitant medication.

9.5 Procedures

Procedures will be coded using MedDRA coded dictionary, version 27.1 or later.

Interventional Radiological Procedures and Surgical Procedures will be summarized separately by System Organ Class and Preferred Term.
The following listing(s) will be provided:

- General Procedures.
- Surgical Procedures.
- Interventional Radiological Procedures.
- Life-saving Interventions (Procedures).

10 Efficacy Analyses

10.1 Analysis of Primary Endpoint

10.1.1 Primary Estimand

The primary estimand to address the trial objective is the difference in proportion of all-cause 6-hour mortality in subjects with traumatic injury, who received a blood transfusion prior to randomization and who have a Glasgow Coma Score less than 15 (mITT Population) between the BE1116 and placebo arms, regardless of IP dosage received or other medications used.

The 4 attributes of the primary estimand (population, primary endpoint, ICEs and summary measure) as defined in the ICH E9 (R1) guidance are described below.

Population

Subjects who have traumatic injury, with confirmed or suspected acute major bleeding and / or predicted to receive a large volume blood product transfusion (mITT Population).

Primary Endpoint

The primary endpoint is all-cause mortality within 6 hours after randomization.

CCI

Summary Measure

The summary measure of the primary estimand is the difference in the proportion of subjects who died in the BE1116 arm compared with the placebo arm during the first 6 hours after randomization as estimated by a Bayesian logistic regression model. The mean of the posterior distribution of the difference in proportions will be used as a point estimate.

Missing data handling is described in Section 8.1 though missing data is expected to be rare due to the nature of the disease and the endpoint.

10.1.2 Primary Efficacy Analysis

A Bayesian logistic regression will be used to compare all-cause 6-hour mortality rate between the BE1116 and placebo arms, in the mITT Population.

Hypotheses:

Null Hypothesis (H_0): The all-cause 6-hour mortality rates in BE1116 is no better than control.

$$p_{kcentra} - p_{control} \geq 0$$

Alternative Hypothesis (H_1): The all-cause 6-hour mortality rate in BE1116 is lower than control.

$$p_{kcentra} - p_{control} < 0$$

Let y_i be the outcome of all-cause 6-hour death (1 = yes, 0 = no), the model is:

$$y_i \sim Bernoulli(p_i)$$

$$logit(p_i) = \beta_0 + \beta_1 treatment_i$$

where p_i is the probability of all-cause 6-hour mortality for subject i and $treatment_i$ is an indicator variable for treatment with BE1116. The coefficient β_0 is the effect of placebo on the primary outcome in the logit scale. The coefficient β_1 is the treatment effect of BE1116 over placebo on the primary outcome in the log-odds ratio scale.

While this model gives direct estimates of ORs, the absolute risk differences (primary outcome of interest) will be derived using posterior draws from the coefficients. We assume independent normal prior distributions for the regression coefficients of the form:

$$\beta_0 \sim Normal(\mu_0, \tau_0^2)$$

$$\beta_1 \sim Normal(\mu_1, \tau_1^2)$$

where, μs and τs are respectively the means and standard deviations of distributions.

The following priors are used:

$$\beta_0 \sim Normal(0, 10^2)$$

$$\beta_1 \sim Normal(0, 1^2)$$

These priors are centered at zero, which for β_1 corresponds to a priori no intervention effect. The prior for β_0 is noninformative, while the prior for β_1 is only very weakly informative and allows for considerable uncertainty; the 95% interval for $\beta_1$on the OR scale ranges from 0.14 to 7.1.

The study will be considered a success and primary objective considered met if the posterior probability

$$\text{Prob}(p_{kcentra} - p_{control} < 0|\text{data}),$$

of lower all-cause 6-hour mortality in the BE1116 arm compared with the placebo arm is greater than the success threshold.

For the final analysis the planned success threshold for the posterior probability will be 97.5%.

The Bayesian logistic regression model will be fitted via Markov Chain Monte Carlo (MCMC) methods in SAS (Version ≥ 9.4) using the PROC MCMC procedure. For each analysis, 4 MCMC chains will be run with a minimum burn-in of 3000 iterations and

sampling from a further 25,000 iterations for each chain. The Gelman-Rubin statistic $\hat{R}$ will be calculated to evaluate whether the 4 chains have mixed sufficiently. The number of iterations per chain will be increased by 10,000 until the Gelman-Rubin statistic is below 1.01 for both β_0 and β_1.

The posterior probability of:

$$p_{kcentra} - p_{control} < 0$$

will be calculated and compared to the efficacy threshold.

For this analysis, 95% credible intervals will be calculated and presented for $p_{kcentra}$, $p_{control}$ and their difference. Point estimates will be presented using the mean value of the posterior distribution.

10.1.3 Supplemental Analysis for the Primary Endpoint

Primary analysis will also be conducted in the ITT and PP populations. The only element of the estimand that changes is the population of interest, which is subjects with traumatic injury (ITT population) and subjects with traumatic injury and no protocol deviation that would potentially affect the assessment of the primary endpoints (Per-protocol population).

The results will be presented in a separate table. Missing data handling is described in Section 8.1

10.1.4 Subgroup Analyses of Primary Endpoint

Subgroup analyses will be used to help determine whether the treatment effect for the primary endpoint is homogeneous across the study population.

Subgroups of interest for this study are as follows:

- Mechanism of trauma injury: penetrating, or blunt .
- Presence of Head Injury: as indicated by Abbreviated Injury Scale(AIS) score > 0 in the “head” region).
- Sex: male, or female.
- Race: White, Black or African American, or Other.
- Age (< 18 years, 18 to 25 years, 26 to 64 years, or > 64 years).

- Weight-based dosing (2000 IU, or 3000 IU).
- IP administration start of infusion (Up to 45 minutes after hospital arrival, or > 45 minute to 90 minutes after hospital arrival.)
- Mode of transport: helicopter, ambulance, or self-presenting.
- RABT: RABT ≤ 2, or RABT > 2.
- Blood pressure at admission: < 70 Systolic, or ≥ 70 Systolic mmHg.
- Glasgow Coma Scale at admission: by categories ≤ 8, 9 to 12, 13-14.
- Injury Severity Score using the following categories:
    - Mild (1-8)
    - Moderate (9-15)
    - Severe (16-24)
    - Profound (≥ 25)
- Whether Fibrinogen was administered before study treatment: yes/no.
- Whether Cryoprecipitate was administered before study treatment: yes/no.
- Whether Tranexamic Acid was administered before study treatment: yes/no.

For the subgroup analysis the primary analysis model will be calculated within each level of the subgroup variable. For mechanism of trauma injury, a subject can have both blunt and penetrating injuries. In this case, the subject is included in both subgroups.

Credible intervals for the mortality within each treatment arm and the posterior probability for a lower mortality in the active treatment arm will be presented for each level of the subgroup variables.

Subgroup analysis of penetrating versus blunt trauma injury will provide evidence of BE1116 efficacy and safety in these populations with different mechanisms of traumatic injury. Blunt trauma, also called nonpenetrating trauma or blunt force trauma, is an injury to the body caused by forceful impact, injury, or physical attack with a dull object or surface. It is in contrast to penetrating trauma, in which an object pierces the body surface, causing an open wound (NIGMC, 2018).

Well documented subpopulation analysis of sex differences has shown that males experience an increased risk of mortality and hospital length of stay, and a higher incidence of complications, when compared with females (Liu T, 2015).

Subjects of unknown sex will be excluded from this subgroup analysis. If the proportion of subjects with unknown is unexpectedly high (> 1%) a sensitivity analysis may be conducted, where the analysis will be repeated first by setting the sex to 'male' for all subjects with unknown gender and then again by setting it to 'female' instead.

Subgroup analysis of subjects aged < 18 years is important to confirm there are no important differences between teenagers and young adults (Liras IN, 2016).

Subjects weighing between 50 and 75 kg will receive 2000 IU and subjects weighing > 75 kg will receive 3000 IU. This dosing regimen was designed to ensure equivalent doses of IP per kg body weight, so that all subjects receive equivalent blood concentrations of the coagulation factors present in the IP. This is the standard dosing used for non-trauma subjects. However, it is possible that the total dose of IP, rather than the blood concentration of IP, will be most important in trauma patients with acute hemorrhage who are at risk of the lethal triad. This analysis will aim to determine whether total dose impacts outcomes. Subjects' planned dosing group will be used regardless of the actual weight or partial dose received.

10.2 Analysis of Secondary Efficacy Endpoints

The secondary endpoints (and corresponding summary measures) of the study are listed in Section 4.1.

All secondary efficacy endpoints will be analyzed using the mITT Population. Missing data handling is described in Section 8.1.

10.2.1 Secondary Estimands

Estimands for secondary endpoints are outlined in the following table.

Secondary endpoint	Population	Endpoint	Intercurrent Events	Summary Measure
1	Subjects with traumatic injury and either acute major bleeding (confirmed or suspected) or predicted to receive a large volume blood product transfusion (mITT Population).	All-cause in-hospital mortality up to 24 hours after randomization	Treatment discontinuation – treatment policy strategy Subject receives other medication between randomization and 24 hours – treatment policy strategy	Difference in proportion of subjects who die in-hospital in the BE1116 arm compared with the placebo arm up to 24 hours after randomization
2	Subjects with traumatic injury and either acute major bleeding (confirmed or suspected) or predicted to receive a large volume blood product transfusion (mITT Population).	All-cause in-hospital mortality up to 30 days after randomization	Treatment discontinuation – treatment policy strategy Subject receives other medication after randomization – treatment policy strategy	Difference in proportion of subjects who die in-hospital in the BE1116 arm compared with the placebo arm up to 30 days after randomization

Secondary endpoint	Population	Endpoint	Intercurrent Events	Summary Measure
3	Subjects with traumatic injury and either acute major bleeding (confirmed or suspected) or predicted to receive a large volume blood product transfusion (mITT Population).	Surgical or interventional radiological procedures to stop bleeding related to the primary injury up to 24 hours after randomization	Treatment discontinuation – treatment policy strategy Subject receives other medication between randomization and 24 hours post randomization – treatment policy strategy	Difference in proportion of subjects who receives surgical or interventional radiological procedures to stop hemorrhage

10.2.2 All-cause In-hospital Mortality Within 24 Hours

All-cause in-hospital mortality during primary hospitalization up to 24 hours after randomization will be analyzed and summarized in the same manner as for the primary endpoint. The same noninformative priors as specified for the primary analysis will be used.

10.2.3 All-cause In-hospital Mortality Within 30 Days

All-cause in-hospital mortality up to 30 days after randomization will be analyzed in the same manner as the primary endpoint.

In addition, Kaplan-Meier (KM) plot will be included to display the time to death (see for Section 8.2.3 for derivation) for each treatment group. Discharged and discontinued subjects will be considered censored at the date of discharge/discontinuation. Log-rank p-values will also be provided as an exploratory measure.

10.2.4 Surgical or Radiological Interventions to Stop Bleeding

The difference in proportion of subjects who undergo surgical or interventional radiological procedures to stop bleeding related to the primary injury up to 24 hours will also be analyzed using the Bayesian Logistic Regression and summarized in a similar manner to the primary endpoint.

Surgical or radiological interventions to stop bleeding will be identified as those procedures, that are entered into the eCRF as surgical procedures or interventional radiological procedures.

10.2.5 Supplemental Analysis for Secondary Endpoints

Secondary efficacy analyses as described above but based on the PP population will be conducted. For secondary endpoints the analysis will not be repeated for the ITT population.

10.2.6 Subgroup Analyses of Secondary Endpoints

The same subgroup analyses as for the primary endpoint will be conducted for secondary efficacy endpoints using the analyses described in Section 10.1.4.

10.3 Analysis of Exploratory Endpoints

10.3.1 Transfusion of Blood Products

Transfusion of blood products is recorded according to the period in which the blood component transfusion started: before arrival at the hospital; from arrival at the hospital to time of randomization; from randomization to 6 hours after randomization; and from 6 to 24 hours after randomization. The assignment of blood products to specific periods will be based on the respective eCRF being used to enter the product.

The number of overall and by type of product in units per hour will be summarized for each treatment arm for each of the two post-randomization periods. Similarly, the summary will be repeated grouping the two periods into one up to 24 hours post-randomization period.

The hourly units will be determined by dividing the total units by the number of hours. For subjects who survived throughout the time span or who were discharged/discontinued, it will be assumed that the length of the time span matches the nominal length, e.g., from randomization to 6 hours after randomization, will be considered as 6 hours. For subjects who died in the time span and have known time of death, time of death – start of the time span will be used instead.

Hourly units will be compared between treatments using the Wilcoxon rank sum test, and the p-value will be displayed as an exploratory measure. Hodges-Lehmann estimates will be used to provide a 95% confidence interval for the median shift between treatments.

All transfusions will be listed.

10.3.2 Death Due to Hemorrhagic Shock/Exsanguination

Proportion of subjects with death due to hemorrhagic shock/exsanguination within 30 days of randomization will be analyzed in the same manner as the primary endpoint. Subjects who died due to other causes will be included in the analysis and not considered events.

All deaths, including primary cause, date and time, time from randomization till death, and cause of death will be listed.

10.3.3 Ventilator-free Days, ICU-free Days and Hospital-free Days

A summary table will be shown summarizing each of the following using the mITT Population:

- Number of days on ventilator during primary hospital stay up to 30 days after randomization.
- Number of days in ICU during primary hospital stay up to 30 days after randomization.
- Primary hospital length of stay (days) up to 30 days after randomization.

Additionally, the following parameters will be both summarized and inferential statistics will be provided for them:

- Number of ventilator-free days .
- Number of ICU-free days.
- Number of hospital-free days.

Hospital length of stay will be calculated directly as date of discharge/death/discontinuation – date of randomization + 1 day, as in this study time in the study is the same as time in the (primary) hospital. Hospital lengths stay larger than 30 days should not occur, but if they do, hospital length of stay will be set to 30 days instead.

Missing start and end dates for ventilation and ICU will be replaced with the start and end date of the in-hospital period respectively. End dates that are after the end date of the in-hospital period will also be replaced with the end date of the in-hospital period for this calculation.

As subjects should be followed up for 30 days, any end date later than study day 30 will be replaced with the date of study day 30. Episodes that start after study day 30 will be disregarded entirely.

If multiple episodes are recorded for ventilation or ICU stay, the duration for each epsiode will be calculated and summed up, except that for cases where the end date of one episode coincides with the start date of the next, in which case the episodes are combined before calculating the duration in order to avoid counting the same day twice.

The number of ICU-free days, ventilator-free days and hospital-free days is calculated as 30 days less the number of days in ICU, on ventilator and in hospital respectively for subjects who do not die and who did not withdraw from the study or decline to continue participation. For subjects who die, it will be set to zero instead.

Subjects who withdrew or declined to continue participation will not be included in the main analysis, but a supplemental worst-case analysis will be conducted. For this worst case analysis the number of free days for subjects who withdrew or declined to continue participation will be calculated as study duration – number of days in ICU/on ventilation/in hospital respectively. The number of free days for all other subjects will be the same as in the main analysis.

The summaries will include statistics such as mean, median, standard deviation, minimum, maximum and the 25% and 75% quantiles. Confidence intervals for the mean based on the t-distribution and non-parametric confidence intervals for the medians based on Hodges-Lehmann estimates will be presented. A Wilcoxon rank-sum test will be conducted between the placebo and the active group, and the p-value will be presented as an exploratory analysis.

These variables will also be listed, including details on start and end dates of the episodes.

10.3.4 Tranexamic Acid

The amount of infused tranexamic acid measured in mg will be summarized descriptively in the same way as the blood products described in Section 10.3.1.

10.4 Multiple Comparisons and Multiplicity

If the threshold of the primary endpoint is met, the efficacy-related secondary endpoints (endpoints for the secondary objectives 1 to 3) will be analyzed sequentially in the order of their respective subsections of Section 10.2. A gated testing approach will be used to

account for multiplicity, where testing will proceed in a stepwise manner conditioned on observing a statistically significant result for each preceding endpoint. Significance will be determined in the same manner as for the primary endpoint, by checking if the posterior probability for a difference in favor of BE1116 exceeds 97.5%.

No adjustment for multiplicity will be performed when p-values are reported for subgroup analysis or exploratory endpoints.

10.5 Missing Data and Imputation

See Section 8.1 on the handling of missing data. Other data will not be imputed.

10.6 Treatment Compliance

Treatment compliance will not be evaluated as only a single dose is given. Issues with the administration of the single dose will instead be included in the exposure summary described in Section 11.1.

11 Safety Analyses

All safety analysis will be based on the Safety Population.

11.1 Extent of Exposure

Exposure to the IP will be descriptively summarized by treatment group, using the following variables:

- Number and percentage of subjects at each dose level (2000 or 3000 IU).
- Infusion duration (min). The infusion duration will be calculated as end time – start time – duration of any interruptions.
- Infusion rate (mL/min), calculated as dose in mL/infusion duration. Dose in mL will be calculating using the conversion factor 1000 IU = 40 mL.
- Number and percentage of subjects with interrupted infusion, including break-down by reason.
- Number and percentage of subjects with stopped infusion due to AE. This will be the number of subjects who have an AE with action taken with study treatment entered as “Drug Withdrawn”.

- Number and percentage of subjects whose dose level would be different if measured weight instead of estimated weight has been used (overdose and underdose).

IP administrations will be listed.

11.2 Adverse Events

Only SAEs and AESIs will be recorded in this study. Treatment-emergent SAEs and AESIs, defined as AEs that started [or worsened] on or after the start of IP infusion, will be summarized. All captured AEs regardless of whether they were treatment-emergent or not will be listed. Where AE start dates and/or times are missing or partially missing, AEs will be assumed to be treatment-emergent, except if the partial start dates and/or times or the AE end date and/or time indicate that the AE started before the first administration of IP (see Table 3).

Table 3 TEAE Assignment in Case of Missing AE Start Date Elements

Missing Elements of AE Start	Rule	
Regardless of any missing information for AE start: AE end date / time < IP start date / time		non-TEAE
Otherwise (ie, if AE end date / time ≥ IP start date / time)		
- All		TEAE
- Day and month	AE start year ≥ IP start year	TEAE
	AE start year < IP start year	non-TEAE
- Day	AE start month / year ≥ IP start month / year	TEAE
	AE start month / year < IP start month / year	non-TEAE
- Time	AE start date ≥ IP start date	TEAE
	AE start date < IP start date	non-TEAE

AE = adverse event; IP = investigational product; TEAE = treatment-emergent adverse event

If AE start dates or end dates are missing or partially missing for an AE, no duration will be calculated. If for a TEAE the relationship to study treatment is missing the worst case will be assumed for summarizing analysis (ie, the relationship to study treatment will be assumed to be “Yes”). No imputation will be done in case of missing study treatment relationship for non-treatment emergent AEs. No other imputations for missing AE information will be done.

AEs will be coded using the MedDRA dictionary, version 27.1 or later. The observation period for the reporting of AESIs and SAEs for an individual subject will start at the time of

randomization and finish with the end of the In-hospital Follow-up Period (ie, up to the time of death / hospital discharge / Day 30, whichever occurs first).

All AESIs are identified based on the respective checkbox in the eCRF.

An overview summary of treatment-emergent SAEs and AESIs, including number and percentages of subjects as well as the number of events, with subcategories of related and not related, will be provided including the following:

- Any SAE or AESI.
- Any SAE.
- Any AESI, with subcategories by type of AESI.
- Any related AESI, with subcategories by type of AESI.
- Related SAEs.
- Any SAE or AESI Resulting in Death.
- Any AESI Resulting in Death.
- Any SAE or AESI Leading to Discontinuation of Study Treatment.
- Any SAE Leading to Discontinuation of Study Treatment.
- Any AESI Leading to Discontinuation of Study Treatment.
- Any SAE or AESI Leading to Dose Interruption.
- Any SAE Leading to Dose Interruption.
- Any AESI Leading to Dose Interruption.
- Any SAE or AESI Leading to Withdrawal from the Study.
- Any SAE Leading to Withdrawal from the Study.
- Any AESI Leading to Withdrawal from the Study.
- SAEs by Maximum Severity.
- AESIs by Maximum Severity.

Where not integrated in the overall overview in the above, additional descriptive tables will be generated by treatment arm, including number and percentages of subjects and the number of events, to have the following summaries:

- Number and percentages of subjects with TEEs by relationship and overall.
- Number and percentage of subjects with AESI, by type of AESI and Relationship (related, unrelated, and overall), including number of events.
- Number and percentage of subjects with AESI leading to death, by type of AESI, and number of events.
- Treatment-emergent Serious Adverse Events by SOC and PT.
- Serious Adverse Events Resulting in Death by SOC and PT.
- Study Treatment-related Serious Adverse Events by SOC and PT.
- Serious Adverse Events Leading to Discontinuation of Study Treatment by SOC and PT.
- Serious Adverse Events Leading to Withdrawal from the Study by SOC and PT.
- Serious Adverse Events by SOC, PT, and Maximum Severity.
- Adverse Events Leading to Death by Primary Cause of Death.

The following listings will be generated:

- SAEs.
- Fatal AEs.
- AEs leading to study Withdrawal.
- AESIs.

11.2.1 Adverse Events of Special Interest

The following AESIs up to 30 days after randomization will be evaluated in additional detail:

1) TEEs, symptomatic or asymptomatic, venous, or arterial (eg, deep vein thrombosis, pulmonary embolism, stroke, and myocardial infarction)
2) Other AESIs; namely
   - ARDS.
   - Multiple organ failure.
   - AKI requiring renal replacement therapy (dialysis, hemofiltration, or hemodiafiltration).

The number of events, the number and percentage of subjects affected in each AEs listed above, will be presented for each treatment group. Relative risk and 95% confidence intervals for the difference between the 2 treatment arms will be included. A forest plot of the relative risk and its 95% confidence intervals for the difference will be displayed along with the percentage of AESIs in each group.

The safety variables will also be compared against the background rates mentioned in the Investigator's Brochure (Section 3). This will be a descriptive analysis, showing the background rates as well as the observed rates, and 95% confidence intervals (based on the normal approximation) in each treatment arm.

12 Interim Analyses

The schedule for interim analyses conducted for the IDMC and the stopping criteria for efficacy are described in Section 4.5.

As it has been decided to stop the study early, before the first interim analysis, Section 12.2 is no longer applicable.

12.1 Safety Analyses and Stopping Rules

The subjects participating in this study are expected to have a high mortality rate and have many significant complications. Given that BE1116 has the potential to reduce mortality, any specific predefined stopping rule for safety reasons for anything other than mortality is inappropriate. The protocol has an efficacy based stopping rule that stops the trial for futility and will stop the trial if there is significantly more mortality in the study arm than in the treatment arm. Hence, this futility stopping rule also serves as a safety stopping rule. In addition, the IDMC will consider other adverse events combined with mortality endpoints as described below.

Commensurate with its mandate to review ongoing safety data, the IDMC will monitor all-cause mortality up to 30 days, adverse events including SAEs and AESI, as well as other safety data with the objective of ensuring the safety of study participants. Upon review of the safety data, the IDMC may recommend stopping the study due to significant safety issues or propose modifications to the study. Partially unblinded data (treatment arms are masked as A and B) will be provided for safety only IDMC. If significant difference is observed between two arms which could result in pause or termination of the study, the actual treatment arms will be released to IDMC.

Beginning at the time of 500 completed subjects, and at every regularly scheduled IDMC review thereafter, the Independent statistician will perform statistical testing for the following safety variables of interest up to 30 days after hospital arrival:

1) All-cause in-hospital mortality up to 30 days
2) SAEs with fatal outcome
3) In-hospital TEEs, symptomatic or asymptomatic, venous, or arterial (eg, deep vein thrombosis, pulmonary embolism, ischemic stroke, and myocardial infarction)
4) Other in-hospital AESIs; namely
   - ARDS
   - Multiple organ failure
   - AKI requiring renal replacement therapy (dialysis, hemofiltration, or hemodiafiltration)

A Fisher's exact test will be used to detect any differences in proportions of the above mentioned safety events between treatment and placebo arms at each predefined IDMC review. Four independent analyses will be performed for each safety variable of interest.

The *p*-value of each independent test will be adjusted for multiplicity using a Bonferroni procedure for each IDMC review. The critical value 0.05 will be divided by 7 which is the total number of tests (number of IDMC meetings). Descriptive statistics (frequency and percentage of each arm or overall) of these events will be presented as the 4 categories above and individually for each treatment arms and overall. Graphical presentation of relative risk and 95% confidence intervals will also be provided. Individual AEs will also be compared against the overall background rates from the PROPPR trial [Holcomb et al, 2015]. For details, please refer to the IDMC charter.

The statistical tests above act as guidelines to inform potential safety concerns in the IP. Significant p-values (after adjustment) observed in the tests above may be used as a trigger for IDMC to request further investigation and/or temporarily pause the enrollment. However, the IDMC should consider the totality of the data, including findings from all best available data at the time of the review, in deciding whether the overall benefit/risk is unfavorable enough to warrant a recommendation to terminate the study for safety concerns.

All descriptive summaries will be repeated for the age groups defined in Section 10.1.4.

12.2 Interim Efficacy Analyses and Stopping Rules

For the originally planned interim analysis refer to SAP 1.0 or Section 10.3.4 of the CSP.

13 Pharmacokinetic Analyses

Not applicable.

14 Pharmacodynamic and Biomarkers Analyses

Not applicable.

15 References

Chang R, K. J. (2019). Earlier time to hemostasis is associated with decreased mortality and rate of complications: Results from the Pragmatic Randomized Optimal Platelet and Plasma Ratio trial. *Trauma Acute Care Surg*, 87(2):342-9.

Galvagno Jr SM, F. E. (2017). Outcomes after concomitant traumatic brain injury and hemorrhagic shock: A secondary analysis from the Pragmatic, Randomized Optimal Platelets and Plasma Ratios trial. *J Trauma Acute Care Surg*, 83(4):668 74.

Gelman A, C. J. (2013). *Bayesian Data Analysis, Third Edition.* London: CRC Press.

Holcomb JB, T. B. (2015). Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA*, 2015;313(5):471-82.

Liras IN, R. E. (2016). When children become adults and adults become most hypercoagulable after trauma: an assessment of admission hypercoagulability by rapid thrombelastography and venous thromboembolic risk. *J Trauma Acute Care Surg*, 80(5);778 82.

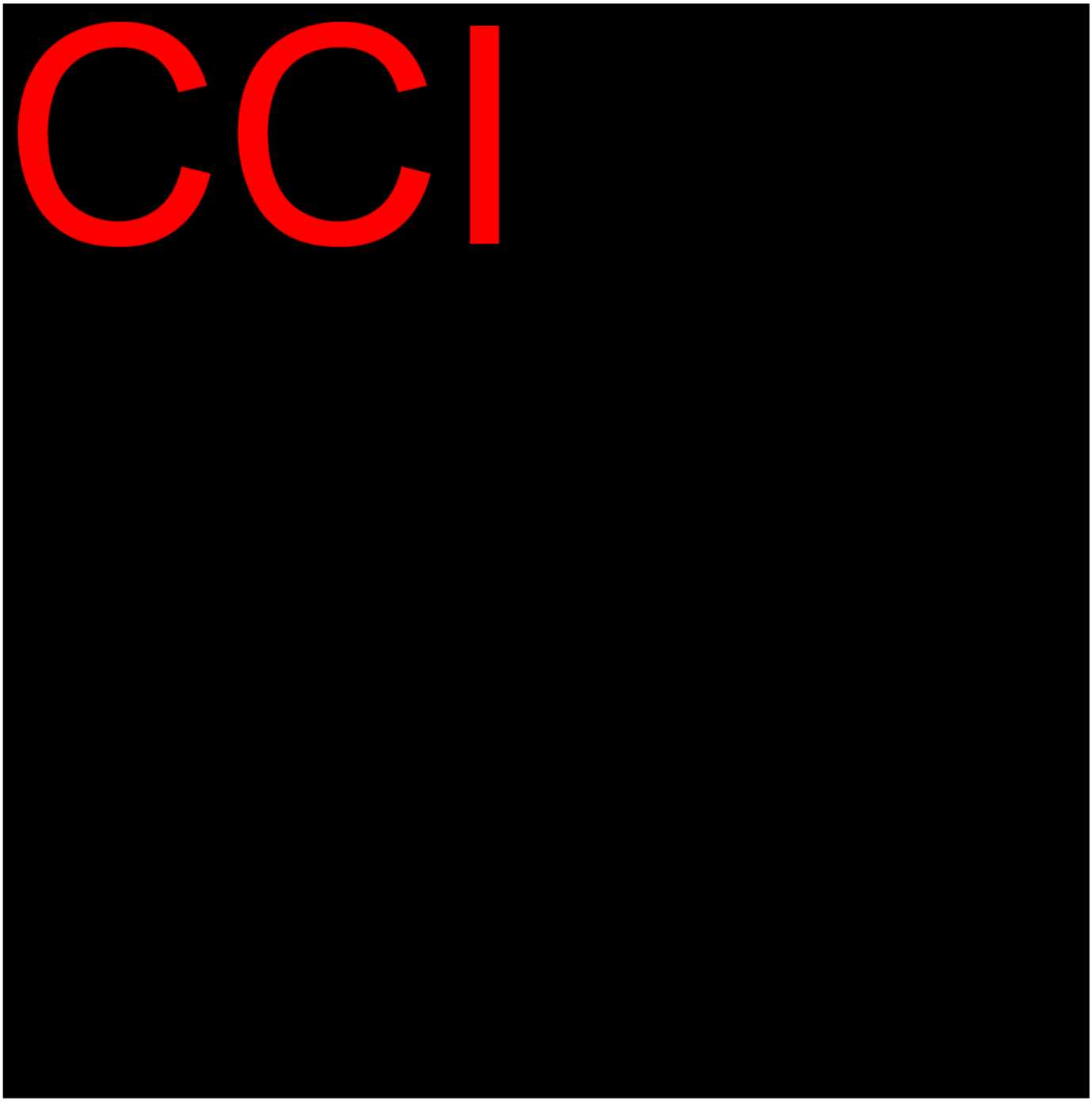
Liu T, X. J. (2015). The influence of sex on outcomes in trauma patients: a meta-analysis. *Am J Surg*, 210(5):911-21.

NIGMC. (2018, January). *Physical trauma.* Retrieved from National Institute of General Medical Sciences: https://www.nigms.nih.gov/education/fact-sheets/Documents/fact-sheet-physical-trauma.pdf

16 Appendices

16.1 SAS Code

The Statistical Analysis System (SAS) code of this document is intended to illustrate how the SAS procedures will be called. In the actual code the variable names will be updated to refer to the correct analysis datasets variables.



CCI

16.2 Simulation Report

The simulation described in the following was done to determine the operating characteristics for the original study design including 3 interim analyses. This simulation report is no longer applicable for the planned analysis, but included in the SAP as it influences the original study design.

16.2.1 Simulation Methodology

The simulation is run by first setting the following parameters:

- Assumed true event rates in the placebo and the control rates for the primary endpoint and the secondary endpoint 'mortality within 24 hours'
- Threshold for success at each analysis (interims 1-3 and final analysis)

The simulation then consists of repeatedly (here, set to 10000 times for each considered treatment difference) running the following steps.

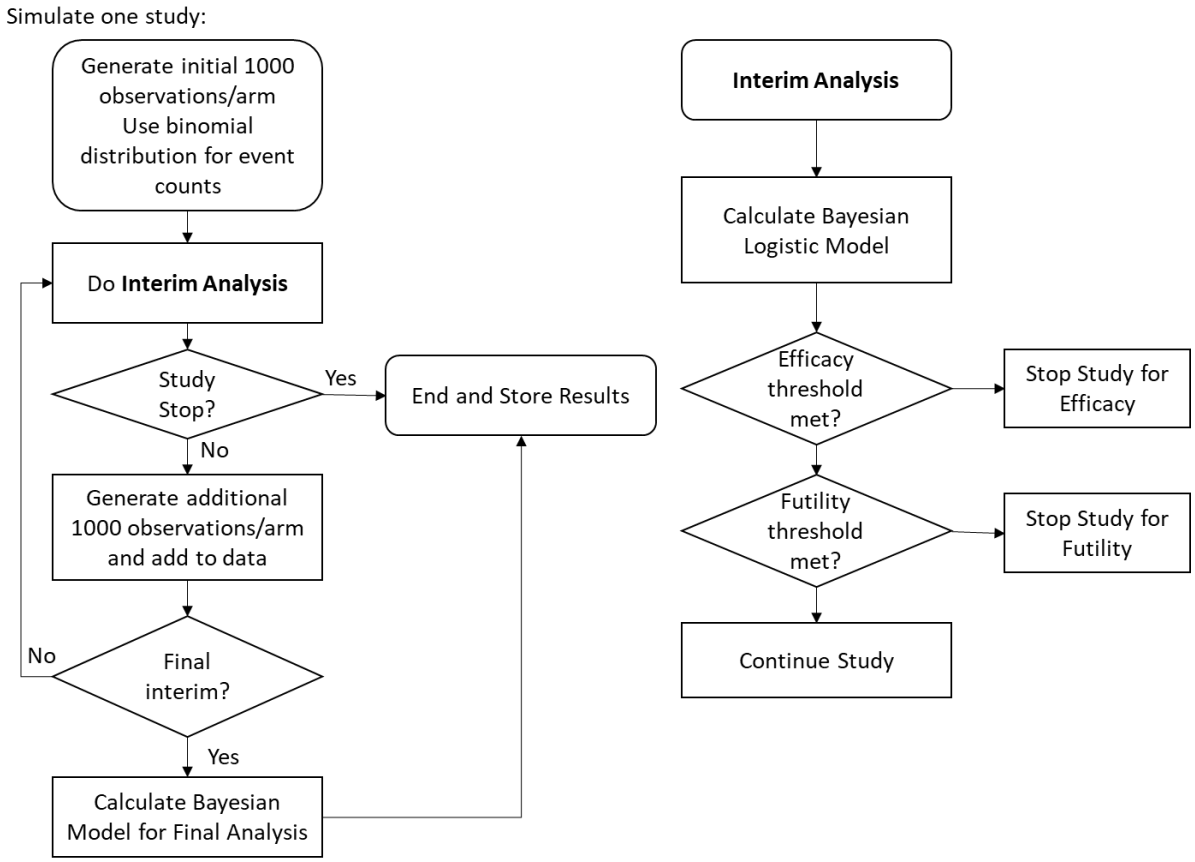


Figure 1 Simulation Flowchart

Each completion of the steps generates one simulated study.

1. Generate data for a 1000 patients per treatment arm using the binomial distribution with the assumed arm specific event rates for the primary endpoint. Data is also generated for the secondary endpoint 'mortality within 24 hours', as that endpoint is assumed to have the largest correlation with the primary endpoint.

2. Conduct the first interim analysis by:

    a. Calculating the model described in Section 10.1.2.

    b. Testing if the posterior probability for $p_{kcentra} < p_{placebo}$ meets the success threshold.

    c. If the success threshold is not met, the futility analysis is conducted by sampling 1000 times from the joint posterior distribution for $p_{kcentra}$ and $p_{placebo}$ and generating a simulated dataset for the final analysis for each sample, by

adding enough patients in each arm to bring the total to 4000 with the event count for the additional patients being generated using the binomial distribution with the sampled event rates.

The futility threshold is evaluated by counting how many of the 1000 simulated final analyses achieve the threshold for the final analysis. Note that the number of simulated datasets created for the interim is smaller than the 5000 specified for the analysis described in Section 10.1.2 in order to speed up the simulation.

3. If the success or futility threshold is met, the simulated study ends. Otherwise, step 1 is repeated to add 1000 additional patients per treatment arm to the dataset.

4. The second interim analysis is conducted in the same manner as the first and whether to continue is determined in the same manner as before (see Steps 2 and 4) using the success threshold for the 2nd interim analysis.

5. The third interim analysis is conducted in the same manner as the first and whether to continue is determined in the same manner as before (see Steps 2 and 4) using the success threshold for the 3nd interim analysis.

6. The final analysis is conducted by repeating Steps 2a and 2b. If the success criteria for the final analysis is not reached, the study is declared as having failed.

7. When the study is stopped for efficacy at either an interim or the final analysis, the posterior probability for the second endpoint is calculated.

In all cases, the outcome of the study (success or failure) and the stage at which the study was stopped is stored.

The frequency of each study outcome at each of the analyses can be calculated to estimate the operating characteristics of the study, e.g., the total Type I error rate can be estimated by looking at the results of the simulation for a 0% difference in mortality and counting how many of the simulated studies met the efficacy threshold. This count is divided by the total number of simulated studies, which was set to 10000 for this report. In total, 194 out of 10000 simulations met the efficacy thresholds, yielding an estimate of 1.94%.

Likewise, the study power given a 20% difference is calculated in the same manner.

The simulation is also illustrated in Figure 1.

Specific Issues

In the initial working version of the simulation program the calculation took a long time (up to multiple weeks for 10000 simulations) due to the nested futility analysis. In the worst case for runtime of a simulated study terminating at the final analysis the model has to be calculated 3004 times using the PROC MCMC procedure. This proved infeasible, especially when wanting to repeat the simulation using different assumptions.

Thus, it was decided to pre-calculate the models for each combination of $events_{placebo}$=1, 2, ..., 1024 and $events_{kcentra}$=1, 2, ..., 1024 and storing the posterior probabilities for $p_{kcentra} < p_{placebo}$ in a SAS dataset, from now on referred to as the library.

In addition, cases with $events_{placebo} \leq events_{kcentra}$ where skipped, because in those cases the posterior probability for $p_{kcentra} > p_{placebo}$ is smaller than or equal to 0.5 due to symmetry of the prior, and no success criteria smaller than 0.5 were planned to be evaluated.

For the simulation instead of calculating the model for each of the 1000 datasets generated at an interim for futility analysis the results are looked up in the library (using a proc sql left join). A check was added to detect any potential cases where a simulated dataset is not covered by the library due to having more than 1024 events in either treatment arm.

Since 1024 events is more than 25% of the final treatment arm size of 4000 it was not considered likely for this event to happen given the sample size and assumed true event rates of 10%.

When running the simulation, the check was not triggered.

Technical Details

Due to the long initial time needed for computation the program has the following additional properties:

- After every 250 simulations the results are saved. In case of interruptions, the program will resume at the last completed multiple of 250.

- The simulation program is written so it can be executed multiple times in parallel for faster execution. A macro variable serves as an identifier about which instance this is. However, this was not used to generate the results described in this SAP.

- Per study design there is no stop for efficacy at the first analysis. This was implemented by setting an impossible (>1) threshold for the posterior probability at the first interim analysis instead of writing custom code for the first analysis. As the interim analysis models are used to generate the datasets for futility analysis, it is still necessary to calculate the model at the first stage.

- Since whether the study is stopped or not is based only on the results for the primary endpoint, the success thresholds for the secondary analysis can be changed in the program summarizing the operating characteristics without rerunning the simulation.

Reproducibility

Reproducibility is achieved as follows: whenever a batch of 250 simulations is started the seed is set to 100000 times the instance identifier (always set to 1 here) + the number of simulations already completed. The state of the random generator is then carried forward by using %sysranend.

As the range of allowable seeds is smaller for the proc surveyselect and proc mcmc procedures used than for data steps, those procedures are seeded with a seed generated in a data step that is in the appropriate range, e.g. using code like this:

```
data _NULL_;
    call streaminit(&sysranend);
    seedsurvey = %RandBetween(1, 2147483647);
    call symput('seedsurvey', seedsurvey);
  run;
```

Reproducibility has been tested by calculating the null effect scenario twice and observing the same results.

16.2.2 Software

The simulation was conducted in SAS 9.4 (TS1M6 MBCS3170) and was executed on the SunOS 5.11 (SUN 64) platform.

16.2.3 Programs

The following programs are executed in the presented order. If the library or simulation program is interrupted, they are restarted to resume the simulation without running any of the preceding programs.

Setup Program

The setup program creates the settings file with the chosen success thresholds and should also create empty simulation outcome files if they do not exist.

Library Program

The library program generates a dataset with posterior probabilities for $p_{kcentra} < p_{placebo}$, assuming 4000 observations per treatment arm and any combination of observed events where no more than 1024 events are observed in either arm. This library is later used in the simulation program to speed up the futility analysis.

As the main simulation program, multiple instances of the program can be run at once to speed up the generation program.

Simulation Program

The simulation programs generate simulated studies for a specific set of assumptions for the respective event rates of KCentra and Placebo. Final outcome for each simulated study is stored.

Operating Characteristics Program

The programs read in the file with simulated study outcome and generates the operating characteristics, that is the observed frequency of stopping for futility or efficacy at each of the interim analyses and the final analysis.

16.2.4 Running and Modifying the Programs

When running the programs, it is important to point to the desired output directory in all cases, by updating the line accordingly:

```
LIBNAME OUT1 "/output/";
```

This applies to all described programs. For more details refer to the program files.

Settings Program

The settings files is run to do the following:

1. Set up empty output files to store the simulation results.
2. Store the success threshold for each applicable interim analysis. This file is later read by the simulation program.

Modifying the settings file is straightforward by changing the numeric value in the final data step.

Library Program

The library file calculated and used for the simulation is attached as a reference. For reproduction of simulation results it is recommended to first use the reference library and afterwards confirm that the reference library can be reproduced as a separate task.

It is assumed that the output file is already present as an empty dataset with 0 rows.

The version attached is set up to generate the part of the library where the number of events in the placebo arm is between 1 and 64 and the number of events in the KCentra arm is between 1 and 1024.

Other parts of the library can be generated by modifying the thread_id macro variable, e.g. if it is set to 2 the next block of 65 to 128 events in the placebo arm will be generated.

To generate the full library programs with thread_ids between 1 and 16 need to be run. Alternately, the program can be modified to generate the entire library with a single SAS program by setting tasks_per_thread to 1024, but this will require more time.

Finally, the maxn macro variable could be modified to change the maximum number of events included in the library, e.g. in order to extend the library to up to 2000 or more events in each arm.

Simulation Program

The simulation program has the following important lines for modifications:

- Line 7 needs to point to the file path with the library file.

- Line 8 needs to point to the intended folder for the outputs files, which also contains the settings file produced by the settings program.
- Lines 327, 343 and 345 all contain the name of the output file for the simulation and need to be changed to write to a different output file.
- Line 342 contains the parameter of the simulation: the last two numeric parameters passed to the %run_simulation macro are the assumed event frequency in the placebo and BE1116 arm respectively.

The simulation program expects that the output file is already present as an empty dataset. The included example simulation program is set up to generate the simulation for a null effect (event frequency of 10% in both treatment arms), as shown in the first row of Table 4.

Operating Characteristics Program

The operating characteristics program contains a simple macro that can be called with the output name used in the simulation program as a parameter, in order to generate the actual operating characteristics.

16.2.5 Results

The characteristics determined via simulation for different differences in mortality are shown in Table 4.

Table 4 Statistical Design Operating Characteristics: Probability of Declaring Success or Futility

Difference in Mortality Rate (%)	Interim 1 [a] (N = 2000)		Interim 2 [a] (N = 4000)		Interim 3 [a] (N = 6000)		Final [a] (N = 8000)	Overall Prob. of Success [b]
	Prob. of Success	Prob. of Futility	Prob. of Success	Prob. of Futility	Prob. of Success	Prob. of Futility	Prob. of Success	
0	NA	42.4	0.16	29.4	0.55	17.0	1.23	1.94
10	NA	17.2	3.3	14.8	9.8	15.1	15.2	28.3
20	NA	4.1	24.1	2.5	35.6	2.4	23.2	82.9
30	NA	0.6	69.3	0.1	26.1	0.13	3.6	99.0
40	NA	0.02	96.3	0.0	3.7	0.0	0.04	99.97

NA = not applicable; Prob. = Probability

[a] Represents individual probabilities of stopping for success or futility at each individual interim look and final look based on a total of 10,000 simulations for each difference in mortality.

[b] Represents total probability of stopping for success.

The simulations were repeated with event rates of 8% and 12% in the placebo group (see Table 5 and Table 6), with the same relative percentage differences between BE1116 and Placebo of 0%, 10%, 20%, 30%, and 40%. A smaller event rate in placebo will yield lower power with the same relative percentage differences and vice versa, a higher event rate will yield higher power.

Table 5 Simulation Report Results – 8% base event rate in placebo

Difference in Mortality rate (%)	Interim 1 [a] (N = 2000)		Interim 2 [a] (N = 4000)		Interim 3 [a] (N = 6000)		Final [a] (N = 8000)	Overall Prob. of Success [b]
	Prob. of Success	Prob. of Futility	Prob. of Success	Prob. of Futility	Prob. of Success	Prob. of Futility	Prob. of Success	
0	NA	42.5	0.2	28.8	0.7	16.7	1.1	2.0
10	NA	19.3	2.7	17.5	7.0	15.8	13.0	22.7
20	NA	6.0	18.0	3.9	30.5	4.4	25.2	73.6
30	NA	1.1	55.0	0.2	33.8	0.2	8.9	97.6
40	NA	0.1	89.5	0.0	10.0	0.0	0.5	99.9

Prob. = Probability

[a] Represents individual probabilities of stopping for success or futility at each individual interim look and final look based on a total of 10000 simulations for each difference in mortality. The differences in this table are relative to the base rate, so a difference of 10% for a base rate of 8% would be a reduction in mortality to 7.2%.

[b] Represents total probability of stopping for success.

Table 6 Simulation Report Results – 12% base event rate in placebo

Difference in Mortality rate (%)	Interim 1 [a] (N = 2000)		Interim 2 [a] (N = 4000)		Interim 3 [a] (N = 6000)		Final [a] (N = 8000)	Overall Prob. of Success [b]
	Prob. of Success	Prob. of Futility	Prob. of Success	Prob. of Futility	Prob. of Success	Prob. of Futility	Prob. of Success	
0	NA	43.0	0.1	28.3	0.5	17.6	1.3	1.9
10	NA	14.9	4.7	12.6	11.4	14.2	18.1	34.2
20	NA	2.6	32.6	1.5	37.6	1.5	19.5	89.8
30	NA	0.3	80.7	0.0	17.4	0.0	1.5	99.6
40	NA	0.01	98.9	0.0	1.1	0.0	0.01	99.99

Prob. = Probability

[a] Represents individual probabilities of stopping for success or futility at each individual interim look and final look based on a total of 10000 simulations for each difference in mortality. The differences in this table are relative to the base rate, so a difference of 10% for a base rate of 8% would be a reduction in mortality to 7.2%.

[b] Represents total probability of stopping for success.

For the secondary endpoints, 2 sets of simulation were conducted. In both sets, the event rate in placebo for the primary endpoint was set to 10% with mortality differences of 0%, 10%, 20%, 30% and 40%, same as in Table 4. In one set of simulation a null effect on the secondary endpoint was assumed with an event rate of 16% in both arms. This set of simulations was used to determine a threshold for the posterior probability maintaining a

Type I error rate of 2.5%. In the second set of simulations the absolute difference for the secondary endpoint was assumed to be the same as for the primary endpoint, e.g., a 40% reduction for the primary endpoint was assumed to lead to a similar decrease for the secondary endpoint, yielding an event rate of 12% in BE1116 vs 16% in placebo.

The results for the first set of simulations are summarized in Table 7 and demonstrate that the type I error rate of 2.5% is maintained. The second set is summarized in Table 8 and displays the power, assuming the same absolute difference for the secondary endpoint as for the primary endpoint. Note that the 0% difference is omitted from Table 8 as this case is covered by Table 7.

Table 7 Simulation Report Results – Null effect for secondary endpoint (Type I error determination)

Difference in Mortality rate (%) in Primary Endpoint	Interim 1 [a] (N = 2000)		Interim 2 [a] (N = 4000)		Interim 3 [a] (N = 6000)		Final [a] (N = 8000)	Overall Prob. of Success [b]
	Prob. of Success	Prob. of Futility	Prob. of Success	Prob. of Futility	Prob. of Success	Prob. of Futility	Prob. of Success	
0	NA	42.4	0.12	29.5	0.23	17.3	0.48	0.83
10	NA	17.2	1.1	17.0	1.0	23.9	0.3	2.4
20	NA	4.1	1.8	24.9	0.3	37.7	0.02	2.1
30	NA	0.6	1.9	67.5	0.02	26.2	0.0	1.9
40	NA	0.02	1.9	94.35	0.0	3.7	0.0	1.9

Prob. = Probability

[a] Probability of success indicates the probability of both stopping at this stage for success due to meeting the threshold for the primary endpoint and then also reaching success for the secondary endpoint based on a threshold of 98.1% for the posterior probability for the secondary endpoint. In case of futility for the primary endpoint the secondary endpoint is not tested.
The probability of failure includes both stopping the study for futility based on the results for the primary endpoint and stopping for success for the primary endpoint but not meeting the threshold for the secondary endpoint.

[b] Indicates overall probability of success for the secondary endpoint defined as meeting the criteria for the primary endpoint at any stage and meeting the criteria for the secondary endpoint at the same stage.

Table 8 Simulation Report Results – Power for the secondary endpoint assuming same absolute difference as for primary endpoint

Relative Difference in Mortality rate (%) in both Primary and Secondary Endpoint	Interim 1 [a] (N = 2000)		Interim 2 [a] (N = 4000)		Interim 3 [a] (N = 6000)		Final [a] (N = 8000)	Overall Prob. of Success [b]
	Prob. of Success	Prob. of Futility	Prob. of Success	Prob. of Futility	Prob. of Success	Prob. of Futility	Prob. of Success	
10	NA	17.2	2.7	19.1	5.8	33.3	6.5	15.0
20	NA	4.1	19.4	7.2	24.5	13.5	13.7	57.6
30	NA	0.6	61.1	8.3	21.2	5.0	2.7	85.0
40	NA	0.02	92.4	3.9	3.3	0.4	0.04	95.7

Prob. = Probability

[a] Probability of success indicates the probability of both stopping at this stage for success due to meeting the threshold for the primary endpoint and then also reaching success for the secondary endpoint based on a threshold of 98.1% for the posterior probability for the secondary endpoint. In case of futility for the primary endpoint the secondary endpoint is not tested.

The probability of failure includes both stopping the study for futility based on the results for the primary endpoint and stopping for success for the primary endpoint but not meeting the threshold for the secondary endpoint.

[b] Indicates overall probability of success for the secondary endpoint defined as meeting the criteria for the primary endpoint at any stage and meeting the criteria for the secondary endpoint at the same stage.

16.2.6 Output Files

Settings File

The settings file has the following variables:

- interim_threshold *i* (i = 1 to 3): Success threshold for the i-th interim analysis.
- final_threshold: the threshold for the final analysis.

Note that for this analysis interim_threshold1 was set to 2 – see technical details in Section 16.2.1

Library File

The output of the library generation has the following variables:

- ev1: number of events in placebo arm. Used in the main simulation to match simulated datasets for futility.
- ev2: number of events in KCentra arm. Used in the main simulation to match simulated datasets for futility.
- seed: random seed used to calculate the model.
- postprob: posterior probability for $p_{kcentra} < p_{placebo}$. Set instead to -1 for ev1 ≤ ev2.
- ess1: effective sample size for $p_{placebo}$.
- ess2: effective sample size for $p_{kcentra}$.

Effective sample size is calculated via the PROC MCMC call based on the lagged autocorrelations of the samples.

Simulation Outcome File

The simulation outcome file contains the final result for each simulated study, with the following variable:

- i: counter variable, resets after each batch of 250 simulations.
- stage: the stage at which the simulated study was ended (1 = first interim analysis, …, 4= final analysis)
- success: set to 1 if study success achieved.
- futility: set to 1 if futility threshold was met or if the final analysis was not successful (if stage = 4)
- ESS: effective sample size for the indicator variable of $p_{placebo} - p_{kcentra} < 0$. This can be 1 if the posterior probability calculated via MCMC is 1 due to overwhelming evidence.

- avgcomp: only defined when the simulated study is ended for futility during an interim analysis. Then set to the proportion of simulated datasets for final analysis that fail to meet the final success threshold.

- postprob_sec: the posterior probability for lower event rates for the secondary endpoint ‘mortality within 24 hours’ in the BE1116 arm of the study. Only populated when the primary endpoint meets the threshold since the secondary endpoint analysis is gated by the primary endpoint analysis.

Effective sample size is calculated via the PROC MCMC call based on the lagged autocorrelations of the samples.

Operating Characteristics File

The operating characteristics file is the output of proc freq analyzing the cross table between success/failure and stage in the simulation outcome file. E.g. the variable Percent for success=1 and stage = 3 gives the proportion of studies that end with success at the third interim analysis. Success=1 and stage=. is the overall power (or type I error rate when considering a null effect).

Where second_sig is blank the results are for the primary endpoint, where second_sig is 0 or 1 the results are for the secondary endpoint ‘mortality within 24 hours’.

16.2.7 Notes on Log Files

The following warnings may be generated:

```
WARNING: The stationary test in the Heidelberger-Welch
diagnostic for the parameter postprob cannot be calculated
because the autocorrelation-adjusted standard error of the
posterior samples is 0. This could be caused by the Markov
chain being a constant vector.
```

```
WARNING: The Geweke diagnostic test for the parameter postprob
cannot be calculated because the variances of the two segments
are both 0. This could be caused by the Markov chain being a
constant vector.
```

```
WARNING: The posterior samples of the parameter postprob
produce a first-order Markov chain in the Raftery-Lewis
diagnostic that is either all 0's or all 1's. As a result,
alpha = beta = 0.0. All the posterior samples are probably
identical. The test cannot be completed.
```

The parameter postprob is the indicator variable for $p_{kcentra} < p_{placebo}$ and can be 0 or 1 for all MCMC samples if the difference in proportion in the simulated data is sufficiently high. This is not a concern as long as the same set of warnings are not generated for the main model parameters such as $p_{kcentra}$, $p_{placebo}$ or the model coefficients.

16.2.8 Files for Report

- Programs
- Example Outputs
- Full library file
- Simulation results and operating characteristics data files for the scenario's described in Section 16.2.5.

Signature Page

BE1116_3006 - Statistical Analysis Plan - V2.0 - 06Dec2024

Signed By	Date (GMT)
PPD	16-Dec-2024 17:03:42
Approved-PPD	
PPD	16-Dec-2024 17:04:48
ApprovedPPD	

--- Do Not Detach This Signature Page ---