STATISTICAL ANALYSIS PLAN

STUDY CODE No.: CUSA-081-HEM-01

NCT03594175

READY 1: A PHASE 3, RANDOMIZED, DOUBLE-BLIND, ACTIVE AND PLACEBO-CONTROLLED STUDY ON THE USE OF CUSA-081 FOR DYSFUNCTIONAL CENTRAL VENOUS ACCESS DEVICES (CVADs)

Version No.: 1.0
Date: 07 Nov 2023

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Contents

List of Abbreviations

ADaM	Analysis Dataset Model
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
BMI	Body Mass Index
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
CRBSI	Catheter Related Bloodstream Infection
CSR	Clinical Study Report
CVAD	Central Venous Access Device
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
HR	Heart Rate
ICH	International Council for Harmonisation
IRT	Interactive Response Technology
ITT	Intention-to-Treat
K-M Estimate	Kaplan-Meier Estimate
PP	Per-Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment Emergent Adverse Event
WHO	World Health Organization

VERSION HISTORY

Version	Date	Change History
1.0	*07 Nov 2023*	*First Version*

1 Introduction

This document presents the Statistical Analysis Plan (SAP) for Chiesi Farmaceutici S.p.A. protocol CUSA-081-HEM-01: READY 1: A Phase 3, Randomized, Double-Blind, Active and Placebo-Controlled Study on the use of CUSA-081 for Dysfunctional Central Venous Access Devices (CVADs).

This analysis plan is based on the final protocol (version 8.0), dated 21Feb2023 and the final electronic case report form (eCRF) dated 05Apr2022.

The SAP provides the description of the final analyses. In case of deviations from the SAP, explanations will be provided in the Clinical Study Report (CSR).

[redacted] is contracted to support statistical analyses and is responsible for the production and quality control of all outputs described in this document.

2 Study Design

This is a phase 3 multinational, multicenter, prospective, randomized, double-blind, parallel-group, active and placebo-controlled study examining the effect of instillations of CUSA-081 versus placebo or alteplase in subjects with dysfunctional non-hemodialysis CVADs. Restoration of CVAD function is defined as follows: the ability to both withdraw at least 3 mL of blood and infuse 5 mL of saline.

Subjects will be screened according to the Study Inclusion and Exclusion criteria and will be candidates for randomization if all eligibility criteria are met.

A minimum of 841 subjects, within approximately 100 sites, will be randomized, in a 9:1:6 ratio of CUSA-081:Placebo:alteplase in order to achieve a minimum of 800 subjects completing the study:

Treatment Arm A (CUSA-081 [reteplase])	473 subjects
Treatment Arm B (Placebo)	53 subjects
Treatment Arm C (alteplase)	315 subjects

A total of 2-3 visits will be performed during the study, as follows (refer to the Study Treatment Schema in Figure 1 for more details):

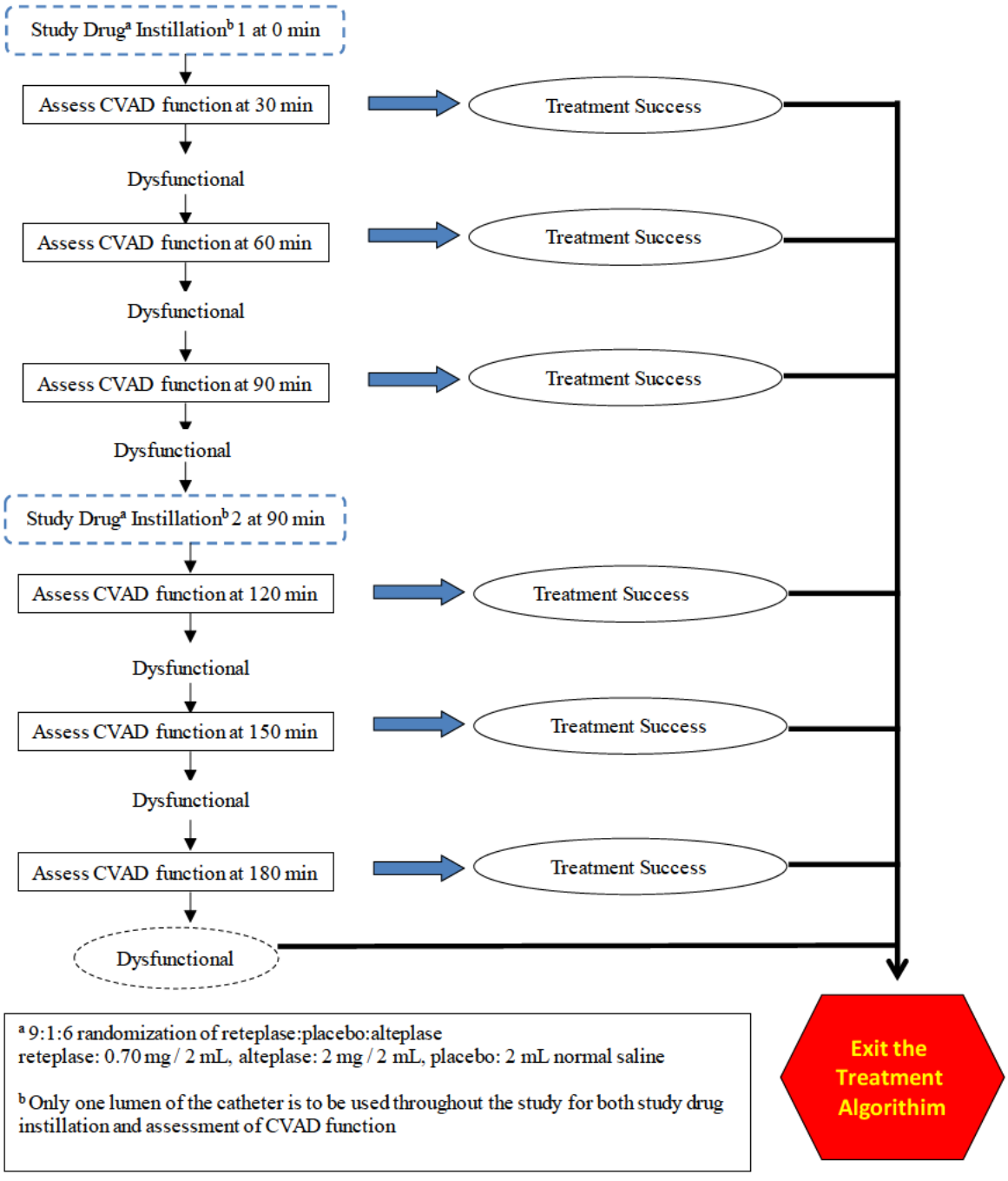
- Screening (Baseline Visit) (Day 0 or Day 1).
- Treatment Visit 1 (V1) (Day 1):
    - Subjects will receive the first instillation of study drug (CUSA-081, placebo or alteplase) into the catheter via the single lumen designated for this study.
    - If patency is not restored after 90 minutes following the first instillation, a second dose of study drug (same drug as at first instillation) will be administered.
- Follow-up Visit 2 (V2) (Day 30 ± 2 days) (can be performed by telephone).

An extra visit could be performed as Screening (Baseline Visit) for logistical reasons. Day 1 must be the following calendar day (for example, Monday and Tuesday; not Friday and Monday). Informed consent will be signed during this visit.

Safety will be monitored throughout the study.

The end of the trial is defined as the last follow-up contact of the last subject to receive study drug in the trial.

Figure 1: Treatment Schema



A futility analysis is planned to occur when approximately 416 subjects have completed the study (see Section 7.5 for additional details).

The futility analysis will assess the conditional power for the test of non-inferiority of CUSA-081 compared to alteplase in the rate of treatment success following a single administration of study drug with a dwell time up to 90 minutes.

If the futility analysis finds that it is unlikely to demonstrate non-inferiority of CUSA-081 compared to alteplase, then the study will be terminated early.

A separate independent and unblinded team will be established to perform the futility analysis and prepare the data for review ("Unblinded Statistical/Programming Team").

An independent and unblinded Data Monitoring Committee (DMC) will be established to review the data and provide a recommendation regarding the continuation of the study. Details of the DMC, including roles, responsibilities, communication processes, and frequency of meetings will be provided in a separate DMC Charter.

The DMC will provide a recommendation regarding the continuation as follows:

- the study should continue without modification;
- the study should be terminated prematurely.

The study team and the other blinded team members will remain blinded throughout the futility analysis.

Treatment Allocation

A balanced block randomization scheme will be prepared via a computerized system. Once the subject meets all inclusion and no exclusion criteria and has provided informed consent, the investigational pharmacist or designee at the study site will enroll the subject and request the study drug assignment using the Interactive Response Technology (IRT) at the time of randomization. Randomization of study drug must only occur on the day of study drug administration.

Assignment to double-blind treatment arms will be determined by the randomization schedule programmed into the IRT. Once a subject is randomized, the study site unblinded Pharmacist will be provided a study drug kit allocation and the appropriate ancillary kit allocation via the IRT. The unblinded Pharmacist will prepare the study drug and affix a blinded label to the syringes for dispensation to the blinded site personnel for administration to the subject.

2.1 Study Schedule

The study schedule (Table 1) summarizes the study assessments by visit and time point.

Due to the short nature of the treatment period and the ability for the follow up visit to be conducted via telephone, no missing data or modifications are anticipated due to COVID-19. Additionally, no modifications to study procedures or study drug administration are anticipated. In the event that a subject withdraws from the study due to COVID-19, this reason will be documented.

Table 1: Study Schedule

Assessment or Procedure	Screening and/or Treatment Visit [1] (Day 1) [2]									Visit 2 – Follow-Up Assessment [3]
	Screen Day 0 Or Day 1	Syringe 1 First Dose (at 0 min)				Syringe 2 Second Dose (at 90 min, if given)				Day 30 (±2 days) after Treatment [4]
		0 Min	30 Min	60 Min	90 Min	90 Min	120 Min	150 Min	180 Min	
Informed consent	X									
Inclusion/exclusion criteria	X									
Demographic data	X									
Medical history	X									
Body weight and height	X									
Blood pressure measurement and heart rate (HR)	X[2]									
Urine pregnancy test [5]	X									
Concomitant medications/procedures	X[1]									X[6]
CVAD history	X									
CVAD function assessment	X[1 2]		X[7 8]	X[7 8]	X[7 8]		X[7 8]	X[7 8]	X[7 8]	X[4 9]
Enrollment into IRT	X									
Study drug administration		X[8]				X[8]				
Adverse events	X[1 10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]

CVAD = central venous access device; d = day; IRT = interactive response technology, min = minutes.

[1] If at any time after the first instillation of study drug, a subject is withdrawn from the study (due to subject's wishes or at the Investigator's discretion), safety monitoring for that subject should still occur for up to 30 days (± 2 days) after the last withdrawal of study drug from the catheter (see adverse event section [AE] collection period in protocol Section 10).

[2] Subjects will be screened for eligibility and treated over the course of one or two study visits. Randomization only occurs on day of treatment and cannot occur on screening visit if not the same as the treatment day. Therefore, the Screening Visit may occur on Day 0 or Day 1 (for example Monday and Tuesday; not Friday and Monday) and the Treatment Visit will occur on Day 1. Screening assessments will occur prior to the first dose of study medication. Blood pressure, heart rate, CVAD assessment and all other eligibility for inclusion criteria must be reassessed if screening and treatment are conducted on separate days.

[3] Subjects who are unable to be reached for follow-up assessment after discontinuing study drug will be categorized as lost to follow up from the study.

[4] The Day 30 (± 2 days) follow-up assessment will occur via phone or may occur in person if the subject has a scheduled clinic visit. The follow-up period is calculated from the date of the randomization/treatment day.

[5] A urine pregnancy test is required for all females of childbearing potential. Women in natural or surgical post-menopause do not need to be tested for pregnancy.

[6] Only concomitant medications and/or procedures ongoing at the time of consent, or stopped within 30 days prior to informed consent, and only new concomitant medications and/or procedures related to spontaneously reported SAEs/AESIs will be collected after randomization.

[7] Note that all catheter assessments are based on the dwell time from the time of study drug instillation (i.e., from "0 min"; NOT from the time of the prior assessment). All efforts should be made to conduct the assessment at the required time point. The window of ± 5 minutes is also from the time of study drug instillation and not time of the prior assessment. Assessments of catheter dysfunction are described in Sections 7.1.1 and 7.2.3 of the protocol. In the event a 2nd dose of study drug is needed, it should be administered within 15 min of withdrawal of the 1st dose from the CVAD.

[8] Once CVAD function has been restored (i.e. the ability to both withdraw at least 3 mL of blood and infuse 5 mL of saline solution), the subject will be deemed a Treatment Success and will exit the treatment algorithm (Figure 1). Therefore, subsequent dosing and catheter function checks will not be performed during V1. At 180 minutes, or in the case of Early Withdrawal, if treatment success is not achieved, any subsequently administered standard of care and related outcome will be documented.

[9] Assessment of recurrent catheter dysfunction as described in Section 7.1.2 of the protocol. Information including, but not limited to, the need for other thrombolytic administration and/or catheter removal or replacement will be collected beyond study drug administration and up through Day 30 (± 2 days). Subjects will be requested to document the date of re-occlusion and any intervention or the date the catheter was removed in order to provide the data when contacted by site personnel.

[10] Collection of AEs and SAEs will begin from the time of Informed Consent signature. All AEs, TEAEs and SAEs on-going at the time the subject's study treatment ends should be evaluated up to 30 days after last administration of Study Drug. After this period, all unresolved TEAEs will be reported as "ongoing" in the CRF.

3 Study Objectives

3.1 Primary Objective

- To demonstrate the superiority of CUSA-081 compared to placebo in the rate of treatment success following a single administration with a dwell time up to 90 minutes. Treatment success is defined as restoration of CVAD functionality measured as the ability to withdraw 3 mL of blood and infuse 5 mL of saline.

3.2 Secondary Objectives

1. To demonstrate the non-inferiority of CUSA-081 compared to alteplase in the rate of treatment success following a single administration with a dwell time up to 90 minutes;
2. To demonstrate the superiority of CUSA-081 compared to placebo in the rate of treatment success following a single administration with a dwell time up to 60 minutes;
3. To demonstrate the superiority of CUSA-081 compared to placebo in the rate of treatment success following up to two administrations with a dwell time up to 180 minutes;
4. To demonstrate the superiority of CUSA-081 compared to alteplase in the rate of treatment success following a single administration with a dwell time up to 90 minutes;
5. To evaluate the safety and tolerability of CUSA-081;
6. To evaluate the rate of recurrent catheter dysfunction defined as first re-occlusion within 30 days following treatment with CUSA-081.

4 Study Variables

4.1 Efficacy Variables

4.1.1 Primary Efficacy Variable

- The primary efficacy variable is the percentage of subjects who have treatment success following a single instillation of study drug (CUSA-081, alteplase, or placebo) with a dwell time up to 90 minutes. Treatment success is defined as the restoration of CVAD functionality measured as the ability to withdraw 3 mL of blood and infuse 5 mL of saline.

4.1.2 Secondary Efficacy Variables

1. Percentage of subjects who have treatment success following a single instillation of study drug with a total dwell time up to 30 and 60 minutes;
2. Percentage of subjects who have treatment success after up to two instillations of study drug with a total dwell time up to 120, 150 and 180 minutes;
3. Rate of recurrent catheter dysfunction (defined as first re-occlusion) within 30 days following treatment with study drug.

4.2 Safety Variables

- Treatment Emergent Adverse Events (TEAE), Adverse Drug Reactions (ADRs), Serious Treatment Emergent Adverse Events (SAE), serious related TEAEs, TEAEs leading to study withdrawal, and TEAEs leading to death;
- Treatment Emergent Adverse Events of Special Interest (AESI) as defined in Section 10.1 of the protocol.

5 Sample Size

For the primary assessment of the superiority of CUSA-081 vs. placebo, a sample size of 450 in the active arm (CUSA-081), and 50 in the control arm (placebo), will provide >99% power to detect a difference of ≥35% using a two-sided test at significance level of 0.05. The expected placebo response rate is approximately 20%.

For the assessment of the non-inferiority of CUSA-081 vs alteplase, a sample size of 450 in the active arm (CUSA-081), and 300 in the control arm (alteplase) will provide 87% power at the 2.5% significance level (that is by using one-sided 97.5% confidence intervals (CI)) with a non-inferiority margin of -10%, assuming an equal response rate of 75% in the control arm (alteplase), and the active (CUSA-081) arm. A sample size of 450 in the active arm (CUSA-081), and 300 in the control arm (alteplase) will also provide 92% power to detect a difference of 10% between the success rates using a two-sided test at significance level of 0.05.

A minimum of 841 subjects will be randomized in order to achieve a minimum of 800 subjects completing the study.

5.1 Statistical Consideration of Non-Inferiority Margin

The selection of the non-inferiority margin was based upon the following reasoning. The non-inferiority margin must be less than the smallest treatment difference between standard therapy and placebo (M1), and at least part of the treatment effect of the standard therapy must be preserved for the test drug (M2).
The NI margin of -10% between reteplase vs. alteplase was selected based on the following statistical consideration:

M1 = the smallest treatment effect of alteplase over placebo

M2 = a fraction 50% of M1 is the most commonly used value

Table 2: Historical Placebo Response

Study / Time point		Number of responders / Sample size	% Response	Lower 95% CI	Upper 95% CI
TROPICS 1 (Gabrail et al, 2010)	120 minutes	11/47	23%	11%	36%
COOL 1 (Cathflo PI, 2017)	120 minutes	12/74	16%	8%	25%

Placebo responses in the treatment of thrombotically occluded CVADs have been reported in hemodialysis setting and in non-hemodialysis setting. We included the available placebo responses data from 2 studies in the non-hemodialysis setting (Table 2) with a definition of treatment success similar to the one used in this study and with a timepoint assessment of ≥ 90 minutes. Based on the data from these two studies, we estimated the placebo response using a weighted analysis based on a random effect model (DerSimonian-Laird). The weighted placebo response is 19% with 95% CI of 12.9% to 26.8%.

Based on the CATHFLO ACTIVASE product label, the restoration of catheter function was assessed at 30 and 120 minutes after the first instillation of alteplase. The response at 90 minutes was estimated based on linear interpolation.

Table **3** shows the observed response rates at 30 minutes and 120 minutes and the estimated 95% CI at 90 minutes.

Table 3: Historical Alteplase Response

Time point (COOL 2)		**# of responders / Sample size**	**% Response**	**Lower 95% CI**	**Upper 95% CI**
30 minutes	observed	516/995	51.9%	48.8%	55.0%
90 minutes	linear interpolation	670/995	67.3%	64.4%	70.3%
120 minutes	observed	747/995	75.1%	72.4%	77.8%

Based on the linear interpolation, the lower bound of the 95% CI of Alteplase response at 90 minutes is 64.4%. The upper bound of the 95% CI for the weighted placebo response is estimated to be 26.8%. Therefore, the alteplase margin over placebo is at least 37.6% at 90 minutes. To preserve 50% of M1 in a NI trial, a NI margin of 18.8% (half of 37.6%) would be reasonable.

A more conservative -10% NI margin between reteplase and alteplase will be used for the 90 minutes endpoint in this trial, which should preserve >70% of M1.

6 Analysis Sets

The definitions of the analysis sets are summarized below. A final agreement on the subjects to be included in or excluded from each analysis set will be reached during the blind review of the data before breaking the blind. Inclusions and exclusions from analysis sets will be fully documented in the Data Review Report.

6.1 Safety Set (SS)

All randomized subjects who receive at least one dose of study drug. Subjects discontinued after dosing will be part of the SS. Analyses based on the SS will be based on the actual treatment received. The SS will be the primary analysis set for all safety analyses.

6.2 Intention-to-Treat Analysis Set (ITT)

All randomized subjects regardless if they received treatment with study drug. The ITT Set will be based on the randomized treatment allocation. The ITT Set will be used for sensitivity analysis for the primary efficacy analyses.

6.3 Full Analysis Set (FAS)

All randomized subjects who receive at least one dose of study drug, and with at least one available evaluation of efficacy after baseline (i.e. at least one CVAD assessment after study

drug administration). Analyses using the FAS will be based on the treatment randomized. The FAS will be the primary analysis set for all efficacy analyses involving assessment of superiority.

6.4 Per-Protocol Analysis Set (PPS)

All subjects from Safety Set without any important protocol deviations. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of key study data or that may significantly affect a subject's rights, safety, or well-being. Important protocol deviations will be assigned in a blinded manner prior to database lock. The PPS will be used for sensitivity analysis for the primary efficacy analyses and the non-inferiority analyses.

6.5 Other Sets Defined for Tables and Listings

For the purposes of tables and listings the following set is defined:

- Enrolled Set: all subjects who provided informed consent for the study.

7 General Considerations for Statistical Analysis

7.1 Statistical Significance

All tests of superiority hypotheses will be two-sided and conducted at the 0.05 significance level, and all confidence intervals will be two-sided at the 95% confidence level.

The assessment of non-inferiority will be based on the 2.5% level of significance (using one-sided 97.5% confidence intervals) with a non-inferiority margin of -10%.

7.2 Multiplicity

7.2.1 Multiplicity Adjustment for Testing of Multiple Hypotheses

A closed testing procedure will be used to control the overall type I error rate at less than 5% across the primary and key secondary variables.

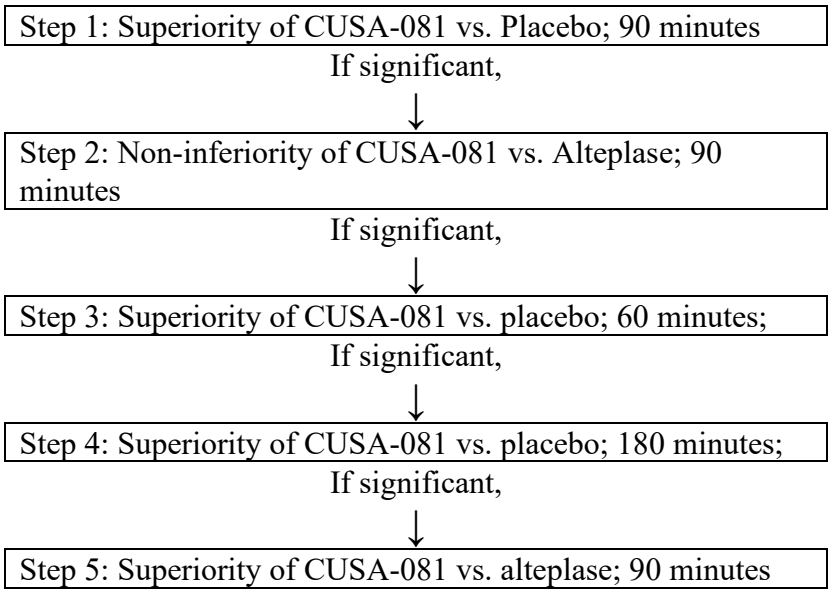
The hypothesis testing will start with the primary efficacy objective, then the secondary efficacy objectives (objectives 1 to 4) will be tested, in the order listed in the study objectives (refer to Section 3.2) and shown in the figure below, until a null hypothesis is not rejected (a p-value >0.05 is observed for superiority assessment, or lower limit of the two-sided 95% CI ≤-10% for the non-inferiority assessment).

At each step of the procedure, no confirmatory claims will be made unless the objectives are met in all the preceding steps. If the two-sided p-values is larger than 0.05 for any of the superiority tests or the lower limit of the two-sided 95% CI is less than or equal to -10% for the non-inferiority test, then the p-values corresponding to the subsequent tests will be considered as exploratory only.

For all other efficacy and safety analyses, no multiplicity adjustment will be made.

Figure: Statistical Testing of Rate of Treatment Success in the READY-1 Trial

Treatment success is defined as restoration of CVAD functionality measured as the ability to withdraw 3 mL of blood and infuse 5 mL of saline.



Notes:

1. *All tests are performed at the 2-sided α=0.05 level of significance.*
2. *For tests at 60 and 90 minutes, the rate of treatment success is assessed as the percentage of subjects achieving treatment success following a single instillation of study drug and a dwell time up to 60 or 90 minutes, respectively.*
3. *For the test at 180 minutes, the rate of treatment success is assessed as the percentage of subjects achieving treatment success following up to two instillations of study drug and a dwell time up to 180 minutes, respectively.*

7.2.2 Multiplicity Adjustment Not Planned for Interim Analysis Futility Analysis

Of note, the interim analysis will not be conducted as a result of the early stopping of the study. The below text in this section is maintained for consistency with the protocol and to maintain a record of the original plan. See Section 12 for additional details.

No multiplicity adjustment will be incorporated for the separate interim futility analysis to assess the conditional power for the non-inferiority test of CUSA-081 compared to alteplase in the rate of treatment success following a single administration of study drug with a dwell time up to 90 minutes (the second step in the closed testing procedure). Of note, there will be no stopping of any arm for efficacy and no claims of efficacy made on the basis of the futility analysis. The recommendation of a threshold to stop the study for futility will be considered as "nonbinding," meaning the futility stopping criteria are guidelines to the DMC that may or may not be followed, depending on the totality of the available interim results.

7.3 Handling of Missing Data

In general, except as described below, missing data will not be imputed.

The number of subjects with missing data will be presented under a "Missing" category. Unless otherwise stated, missing values will not be included in the denominator count when calculating percentages.

When quantitative variables are being summarized, only the non-missing values will be evaluated for calculating summary statistics.

Other critical missing data, if any, will be discussed during the blind review of the data. Decisions will be fully documented in the Data Review Report.

Treatment Success: Missing CVAD Assessment
By design, all subjects exit the treatment algorithm once patency is achieved and no further assessments of catheter clearance are performed. Subjects are considered a treatment success at the time point at which patency was achieved and also at all subsequent time points during the treatment period. Otherwise, if missing data is observed for assessment of treatment success and patency was **not** achieved prior to the time point with missing data, then the subject will be considered as a failure (worst case scenario) at the time point with missing data. The summary statistics for treatment success will display the derived data, including imputation for any missing data observed prior to treatment success.
Medications: Missing/Incomplete Date
In case of missing or incomplete dates/times not directly allowing allocation to any category of medications, a worst-case allocation will be done according to the available parts of the start and the stop dates/times. The medications will be allocated to the first category allowed by the available data, according to the following order: 1. Concomitant medication; 2. Maintained medication; 3. Post-treatment medication; 4. Prior medication.
Procedures: Missing/Incomplete Date
In case of missing or incomplete dates/times not directly allowing allocation to any category of procedure, a worst-case allocation will be done according to the available parts of the start and the stop dates/times. The procedure will be allocated to the first category allowed by the available data, according to the following order: 1. Concomitant procedure; 2. Maintained procedure; 3. Post-treatment procedure; 4. Prior procedure.

Adverse Events (AEs): Missing/Incomplete Date
In case of missing or incomplete date/time not directly allowing allocation to any of the category of AEs, a worst-case allocation will be done according to the available parts of the start and the stop dates/times. The AE will be allocated to the first category allowed by the available data, according to the following order: 1. Treatment emergent; 2. Post-treatment; 3. Pre-treatment.
Adverse Events (AEs): Missing Severity
In case of missing severity, the severity will not be imputed and will be reported as "Missing". For the table of TEAEs by maximum severity, the maximum severity will be considered as the maximum of the non-missing severities for the relevant subject and preferred term.

7.4 Covariates

No covariate adjustment analysis will be performed in any of the efficacy analysis.

7.5 Interim Analyses

Of note, the interim analysis will not be conducted as a result of the early stopping of the study. The below text in this section is maintained for consistency with the protocol and to maintain a record of the original plan. See Section 12 for additional details.

A single interim analysis for futility will be performed to evaluate if the study should be stopped for futility. There will be no stopping rules for efficacy at the time of this interim analysis and no efficacy claims on the basis of the interim analysis. Therefore no statistical adjustment will be done for the final analysis. The futility interim analysis is planned to be performed when approximately 416 patients have completed the study. The timing of the futility interim analysis could be modified based on the progress of the recruitment and planning of other studies.

The futility analysis will assess the conditional power for the test of non-inferiority of CUSA-081 compared to alteplase in the rate of treatment success following a single administration of study drug with a dwell time up to 90 minutes (see Section 14.5 for the calculation details of the condition power).

Conditional Power

The conditional power, CP(d), denotes the conditional power computed as if the observed estimate is the effect size governing the rest of the trial. CP(d) will be derived based on the following formula [3]:

$$CP(d) = \Phi\left(-\frac{1}{\sqrt{1-I}}\left(z_\alpha - \frac{z_I}{\sqrt{I}}\right)\right),$$

where
$\Phi()$ = normal cumulative distribution function
I = information level at time of the interim = $\frac{n_{I1}+n_{I2}}{N_1+N_2}$

n_{I1} = number of subjects in CUSA-081 group at interim

n_{I2} = number of subjects in alteplase group at interim

N_1 = number of subjects in CUSA-081 group planned at the end of the trial (i.e. 473 subjects)

N_2 = number of subjects in alteplase group planned at the end of the trial (i.e. 315 subjects)

z_α = the standard normal critical value for a test with a type I error rate of α (α = one-sided 0.025)

$$z_I = \frac{diff_I - \Delta}{SE_I}$$

$$diff_I = p_{I1} - p_{I2}$$

p_{I1} = proportion of successes in CUSA-081 group at interim

p_{I2} = proportion of successes in alteplase group at interim

Δ = non-inferiority margin = -0.1 (based on the non-inferiority hypotheses presented in section 9.1)

$$SE_I = \sqrt{\frac{p_{I1}(1-p_{I1})}{n_{I1}} + \frac{p_{I2}(1-p_{I2})}{n_{I2}}}$$

Number and Timing of Interim Analyses

A single interim analysis will be conducted when approximately 416 subjects have completed the study.

Statistical Evaluation of Futility

The conditional power for the test of the first secondary objective will be calculated on the basis of the observed data at the time of the interim analysis. The study could be terminated early in case the conditional power at the interim analysis is lower than some pre-defined threshold ("conditional power threshold").

The exact conditional power threshold will be defined in the DMC charter, to be finalized prior to the interim database lock and prior to any unblinding for the interim analysis. Of note, the futility stopping criteria will be considered as "nonbinding" (i.e., they are guidelines that may or may not be followed, depending on the totality of the available interim results). Aside from potentially halting the study for futility, there will be no additional changes to the study design on the basis of the futility analysis. Specifically, there will be no efficacy stopping rules related to the analysis, nor will there be any changes to the planned arms or allocation to the arms, and no formal hypothesis testing of the named study objectives. For this reason, the futility analysis does not cause inflation of type 1 error and no multiplicity adjustment will be conducted on the basis of the futility analysis.

Interim Analysis Results

A separate independent and unblinded team ("Unblinded Statistical/Programming Team") will be established to perform the analysis and prepare the TFLs. An independent and unblinded

DMC will be established to review the data and provide a recommendation regarding the continuation of the study. The Sponsor's and CROs' study teams and the other blinded team members will remain blinded. The outputs produced for the interim analysis will include a designation as "Interim Analysis" next to the analysis population.

7.6 Examinations of Subgroups

The analyses on the percentage of subjects who have treatment success following a single and/or two installations of study drug will be also analyzed for each of the below subgroups:

- Age (<18, ≥18-<65, ≥65-<85, ≥85 years).
- Sex (Female, Male).
- BMI (<18.5 kg/m², ≥18.5–<25 kg/m², ≥25.0–<30 kg/m², ≥30.0 kg/m²).
- Country.
- Region (US vs Non-US).
- Type of CVAD (Non-tunneled or Tunneled Central Venous Catheter (CVC), Implanted Ports, Peripherally Inserted Central Catheters (PICCs)).

  Other category is excluded from the analyses.
- Number of lumens (single lumen, multi-lumen: 2, multi-lumen: 3, multi-lumen: 4).
- Where and by whom was the CVAD identified as dysfunctional (Patient/caregiver identified, Healthcare provider not at study site, Healthcare provider at study site)
- Duration of CVAD dysfunction (0-5 hours, >5–48 hours)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Not Reported).

  In case of multiple races for a same subject, the combination of the races will be displayed as a new category.
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown).

For all subgroup analyses, any category with fewer than 1 subject will be excluded from the analyses.

For treatment comparisons, if one of the 2 treatment groups compared has fewer than 3 subjects, the comparison will not be performed.

7.7 Descriptive Statistics

General descriptive statistics for quantitative variables will include the n (the number of non-missing values), the mean, the standard deviation (SD), the median, the minimum (min) and the maximum values (max).

For categorical variables, the number (n) and percentage (%) of subjects with a specific level of the variable will be presented. The number of missing values will be displayed as a "Missing" category, where appropriate. Unless otherwise specified, the denominator for each percentage will be the number of non-missing observations within the analysis set and treatment group.

7.8 Definitions

7.8.1 Baseline

Baseline is defined as the last non-missing value available before the first study drug administration.

7.8.2 Date of First and Last Randomized Study Medication Intake

The date of first randomized study medication intake is the earliest date of randomized study medication intake considering the eCRF data, corresponding to the date part of the variable RFXSTDTC in the study data tabulation model (SDTM) dataset DM.

The date of last randomized study medication intake is the one recorded in the Treatment Termination form of the eCRF, corresponding to the date part of the variable RFXENDTC in the SDTM dataset DM.

7.8.3 Study Day

If not otherwise specified, all assessment days will be related to the first day of study drug administration (CUSA-081, placebo or alteplase).

The first day of study medication administration is referred to as Day 1. Day -1 is the day that precedes Day 1.

- If the date of the assessment is on or after the first study drug administration date, then

  Study Day = (date of assessment – first study drug administration date) + 1.

- If the date of the assessment is prior to the first study drug administration date, then

  Study Day = (date of assessment – first study drug administration date).

7.8.4 Visit dates

For each visit, the variable SVSTDTC (minimum start date for each of the subject's assessments performed during a specific visit) in the SDTM SV dataset will be considered as the visit date in all the algorithms and the listings.

--TPT variable defined in each relevant SDTM will be used as the timepoint in all the algorithms and the listings.

7.8.5 Duration of Adverse Events or Medications

The duration of an AE or medication will be calculated as follows:

- End date – Start date + 1 (when both dates are completely known);
- Date of study completion/discontinuation – Start date + 1 (when the start date is fully known but the AE or medication still ongoing at the end of the trial): in this case the duration will be presented as ">x" days in the listing rather than "x" days;

- Missing (when the start date is incomplete or unknown, or when the AE or medication ended but with an incomplete or unknown end date, or when the start date is greater than date of study completion/discontinuation).

7.9 Diary Data

Not applicable. Diary data are not collected in this study.

7.10 Data Re-allocation

In general, for by-visit (or timepoint) summaries, data recorded at the nominal visit (or nominal timepoint) will be presented. Data collected at unscheduled time points will be reviewed at the Data Review Meeting prior to database lock. Any re-allocation of unscheduled data will be described and justified in the Data Review Report, which will be finalized prior to database lock. In any case, listings will include scheduled, unscheduled and early discontinuation data.

7.11 Exclusion of Data from the Statistical Analyses

7.11.1 Exclusion of Data from All Statistical Analyses

All data collected in the database will be used in all statistical analyses.

7.11.2 Exclusion of Data from Per-Protocol Analyses

In case of important protocol deviation (e.g., wrong inclusions, incomplete dosing, non-permitted concomitant medications), the subject will be excluded from the PP Set and therefore from all PP analyses.

In case of important protocol deviation impacting specific datapoint, only the specific datapoint will be excluded from the PP analyses.

Protocol deviations will be reviewed during the DRM. Important protocol deviations leading to the exclusion of the subject from the PP analysis, or to the exclusion of isolated data from the PP analysis will be agreed by the study team during the Data Review Meeting and documented in the Data Review Report prior to database lock and unblinding.

7.12 Listings

All data collected in the eCRF will be presented in the individual listings. All listings will be presented for the ITT Set, unless specified otherwise.

7.13 Coding

Medical and surgical history, concomitant diseases, procedures and adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or higher.

Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) version March 2019 or later.

8 Study Population

8.1 Disposition of Subjects and Discontinuations

8.1.1 Disposition of Subjects

The number of subjects screened, the number screen failures and the reasons for screen failure will be presented (overall) based on Enrolled Set.

The number of subjects screened, randomized and completed will be presented by country and by site using ITT Set.

The number of subjects who performed each study visit will be summarized for the ITT Set.

8.1.2 Discontinuation from the Treatment and the Study

The number of subjects who completed the treatment, withdrew from the treatment, the reasons for withdrawal from the treatment, completed the study, withdrew from the study and the reasons for withdrawal from the study will be presented by treatment group using the ITT Set.

The number of subjects who discontinued the treatment and the study will be also presented by country and by site using ITT Set.

An individual subject listing will be provided for the disposition data.

8.1.3 Protocol Deviations and Analysis Sets

Deviations will be classified according to the categories defined in the Data Review Report.

Important protocol deviations affecting the efficacy analyses will be summarized by treatment group using the FAS. The ones excluding from PPS will be also summarized.

The number of subjects included in each of the FAS, Safety and PP Sets will be summarized for each treatment group and overall using the ITT Set.

8.2 Demographic and Baseline Characteristics

No formal comparison between treatment groups on demographic and baseline characteristics will be performed.

8.2.1 Demographic Characteristics

Demographic and baseline characteristics will be summarized by treatment arm and overall using descriptive statistics for the FAS. These will include age, age category, gender, race, ethnicity, height, weight at baseline, body mass index (BMI) at baseline, systolic blood pressure (SBP) at baseline, diastolic blood pressure (DBP) at baseline, heart rate (HR) at baseline and urine pregnancy test results. Separate summaries for demographic and baseline characteristics will also be produced using the Safety, ITT and PP Sets.

Notes:

- BMI will be calculated as: weight at the visit (kg) / height at Visit 1 (m^2).
- Age categories are: <18 years, ≥18-<65 years, ≥65-<85 years and ≥85 years. All categories must be reported even if there are no subjects under a particular category.

An individual subject listing will be provided for demographic and baseline characteristics data.

8.2.2 CVAD History

Time between Screening CVAD assessment and first drug administration (hours), CVAD type, CVAD lumen, number of lumens, indications for CVAD insertion, duration of CVAD dysfunctional (hours) and when and by whom the CVAD was identified as dysfunctional (Patient/caregiver identified, Healthcare provider not at study site, Healthcare provider at study site) recorded at Screening Visit will be presented by treatment group and overall using the FAS. Summaries will be repeated using the Safety, ITT and PP Sets.

Notes:

- Time between Screening CVAD assessment and first drug administration (hours) will be calculated as: Date/Time of first study drug administration – Date/Time of Screening CVAD assessment.

In addition, CVAD history data will be presented in an individual listing.

8.3 Medical History and Concomitant Diseases

Medical/surgical history and concomitant diseases will be summarized by System Organ Class (SOC) and Preferred Term (PT), by treatment group and overall. Summaries will be produced using the Safety Set.

Notes:

- Medical/surgical history is defined as conditions in the medical/surgical history and concomitant diseases eCRF form which are not ongoing at Screening Visit (even if end date is missing);
- Concomitant diseases are defined as conditions in the medical/surgical history and concomitant diseases eCRF form which are ongoing at Screening Visit ("ongoing" tickbox is ticked or end date > Screening Visit date).

In addition, medical, surgical and concomitant diseases data will be listed.

8.4 Medications

Prior medications, medications maintained during the randomized treatment period, and concomitant medications will be summarized by treatment group and overall (except for concomitant medications) for the Safety Set through frequency distributions and percentages by Anatomical Main Group [1st level of the Anatomical Therapeutic Chemical (ATC) classification], Therapeutic Subgroup (2nd level of the ATC classification), Chemical Subgroup (4th level of the ATC classification) and Preferred Name. In addition, maintained

medications and concomitant medications will be summarized using the FAS. Post-treatment medications will only be presented in a listing.

The medications will be classified according to the following rules (See also Section 7.3):

- Prior medication: start date/time < date/time of first randomized study medication intake and stop date ≤ date/time of first randomized study medication intake;
- Medication maintained during the randomized treatment period: start date/time < date/time of first randomized study medication intake and stop date/time > date/time of first randomized study medication intake or ongoing;
- Concomitant medication: date/time of first randomized study medication intake ≤ start date/time < date/time of last randomized study medication intake;
- Post-treatment medication: date/time of last randomized study medication intake ≤ start date/time.

8.5 Procedures

Prior procedures, procedures maintained during the randomized treatment period and concomitant procedures will be summarized by treatment group for the Safety Set through frequency distributions and percentages by SOC and PT. Post-treatment procedures will only be presented in a listing.

The procedures will be classified according to the following rules (See also Section 7.3):

- Prior procedure: start date/time < date/time of first randomized study medication intake and stop date ≤ date/time of first randomized study medication intake;
- Procedure maintained during the randomized treatment period: start date/time < date/time of first randomized study medication intake and stop date/time > date/time of first randomized study medication intake or ongoing;
- Concomitant procedure: date/time of first randomized study medication intake ≤ start date/time < date/time of last randomized study medication intake;
- Post-treatment procedure: date/time of last randomized study medication intake ≤ start date/time.

8.6 Compliance

No treatment compliance will be derived.

9 Efficacy Analyses

All the efficacy comparisons between the treatment arms including the primary will be based on the FAS and the ITT Set will be used for sensitivity analysis for the primary efficacy analysis. The PP Set will be used for sensitivity analysis for the primary efficacy analysis and also as the primary analysis for the non-inferiority analyses.

9.1 Primary Efficacy Variable

The primary efficacy variable is the percentage of subjects who have treatment success following a single instillation of study drug (CUSA-081, alteplase, or placebo) with a dwell time up to 90 minutes. Treatment success will be derived as mentioned in Section 7.3.

Protocol violations and any other intercurrent events will be ignored for analyses performed on the FAS, which target a treatment policy estimand. Subjects with important protocol deviations will be excluded from analyses based on the PPS.

Superiority Hypotheses

The hypothesis corresponding to the primary efficacy analysis is as follows:

The null hypothesis H0: $Rc-Rp=0$
The alternative hypothesis H1: $Rc-Rp>0$

Where Rc=Rate of success of CUSA-081
Rp=Rate of success of placebo

Additional hypotheses are constructed in a similar manner for secondary study objectives to demonstrate superiority.

The number of subjects will be presented by treatment group. The percentage of subjects with treatment success and two-sided 95% Wald CI will be presented by treatment group. Treatment effects will also be presented as the mean difference in proportions (CUSA-081 versus placebo or alteplase) together with the 95% Wald CI and p-value based on a 2-sample Z test for proportions.

Superiority of CUSA-081 over placebo or alteplase will be demonstrated by a statistically significant difference (p-value < 0.05) between treatments with a dwell time up to 90 minutes favoring CUSA-081 using a 2-sample Z test for proportions.

A two-sided 95% confidence interval on the difference in rates of restoration of CVAD function between treatment groups will be constructed from SAS Proc Freq, option Riskdiff for treatment difference (See Section 14.1).

A sensitivity analysis will also be performed as a test of the superiority of alteplase versus placebo in the rate of treatment success following a single administration of study drug with a dwell time up to 90 minutes. This sensitivity analysis will be performed at the same time as the non-inferiority assessment, using the same statistical methodology as for the other analyses of superiority, without adjustment for multiplicity.

Non-Inferiority Hypotheses

The hypotheses for the non-inferiority are as follows:

The null hypothesis H0: $Rc-Ra\leq-10$
The alternative hypothesis H1: $Rc-Ra>-10$

Where Rc=Rate of success of CUSA-081
Ra=Rate of success of alteplase

Assessment of non-inferiority will be based on the 95% confidence interval for the difference in the rate of treatment success between CUSA-081 vs alteplase following a single administration with a dwell time up to 90 minutes.
Non-inferiority will be demonstrated (or null hypothesis will be rejected) when the lower limit of the 95% confidence interval for the difference in rate of success is greater than -10% (See Section 14.1).

The number and percent of subjects with treatment success by treatment group and time point will be summarized. The rate difference and associated 95% Wald confidence intervals between CUSA-081 and placebo or alteplase will be estimated. The between treatment comparisons will be performed using a 2-sample z test for proportions.

For superiority hypotheses, the primary analysis will be the analysis performed on the FAS. Analyses will be repeated based on the ITT and PP Sets as sensitivity analyses. For non-inferiority hypotheses, the analysis based on the PP Set will be considered as the primary analysis.

Sensitivity Analysis

A sensitivity analysis will be performed on the primary efficacy endpoint using a logistic regression model with age (<18, ≥18-<65, ≥65-<85, ≥85 years) and region (US vs Non-US) as factors. The odds-ratio, 95% confidence interval for the odds-ratio and the p-value will be displayed for each treatment group comparison (See Section 14.4).

9.2 Secondary Efficacy Variables

All the below efficacy endpoints will be analyzed based on FAS, ITT and PP Set.

9.2.1 Percentage of Subjects Who Have Treatment Success Following a Single Instillation of Study Drug with a Total Dwell Time Up To 30 and 60 Minutes

The rate of treatment success following a single administration with a dwell time up to 30 and 60 minutes will be analyzed using the same method as the primary efficacy variable.

9.2.2 Percentage of Subjects Who Have Treatment Success After Up to Two Instillations of Study Drug with a Total Dwell Time Up To 120, 150 and 180 Minutes

The rate of treatment success following up to two administrations with a dwell time up to 120, 150 and 180 minutes will be analyzed using the same method as the primary efficacy variable.

9.3 Other Secondary Efficacy Variables

9.3.1 Rate of Recurrent Catheter Dysfunction Within 30 Days Following Treatment with Study Drug

The rate of recurrent catheter dysfunction defined as first re-occlusion within 30 days following treatment (CUSA-081, placebo or alteplase) will be displayed by treatment group.

Time to first re-occlusion will be derived only for subjects with treatment success as follows:

- Time to first re-occlusion (days) = (date of start of first re-occlusion – date of first treatment success assessment date + 1), if subject has a re-occlusion.
- Time to first re-occlusion (days) = (date of CVAD – first treatment success assessment date + 1), if the subject removed the CVAD before end of study (censored).
- Time to first re-occlusion (days) = (date of study completion/discontinuation – first treatment success assessment date + 1), if the subject is censored (i.e. no re-occlusion before end of study and no CVAD removal).

The time to first re-occlusion will be analyzed using the Kaplan-Meier method with median, 25th and 75th percentiles and 95% CI (See Section 14.2). The estimated probability of re-occlusion free at day 30 and its 95% CI will be presented by treatment group. A Kaplan-Meier plot will also be presented.

In addition, time to first re-occlusion will be analyzed using a Cox proportional hazards model including treatment as factor. Treatment effects will be presented as a hazard ratio with the associated 95% Wald CI (See Section 14.3).

These analyses will be based on all subjects with treatment success following up to two administrations of study drug with a total dwell time up to 180 minutes within FAS.

Additional efficacy analyses including demographics and baseline characteristics as covariate/subgroup may be explored, if needed.

10 Safety Analyses

Safety endpoints will be presented using descriptive statistics (Section 7.7). Safety analysis will be based on the Safety Set using actual treatment received.

10.1 Extent of Exposure

The number and percentage of subjects will be summarized by the number of doses received. The number and percentage of subjects assessed at each timepoint for CVAD will be also summarized by number of doses received.

10.2 Adverse Events

An AE will be classified as follow (See also Section 7.3):

- Pre-treatment AE: if it starts before the first study drug intake (AE onset date/time < date/time of first study drug intake);
- Treatment emergent AE (TEAE): if it starts on or after the first dose of study drug intake up to the end of the treatment period (date/time of first study drug intake ≤ AE onset date/time ≤ end date/time of the treatment period);
- Post-treatment AE: if the onset date is after the end of the treatment period (AE onset date/time > end date/time of the treatment period).

The treatment period is defined as the period between first study drug administration and the following end:

- For subjects who completed the treatment period without achieving treatment success, the end of the treatment period will be the date/time of the 180-minutes CVAD assessment;
- For subjects who achieving treatment success, the end of the treatment period will be the date/time of the CVAD assessment where patency is achieved;
- For subjects who discontinued the treatment due to AE or death, the end of the treatment period will be the start date/time of the relevant event and the event will be considered as treatment emergent;
- For subjects who discontinued the treatment due to other reasons, the end of the treatment period will be the date/time the last CVAD assessment performed.

An ADR is an AE related to study medication. A serious ADR is a SAE related to study medication.

A severe AE is an AE with severe intensity. Refer to Section 7.3 for missing severity.

An AE leading to discontinuation is an AE with action taken with study drug equal to “Drug Permanently Withdrawn”.

An AE leading to death is an AE with outcome equal to “Fatal”.

Two AEs with the same PT and classified in the same category (pre-treatment AE, TEAE or post-treatment AE) will be considered as two different events when calculating the “number of events” in the tables.

Pre-treatment AEs, TEAEs and post-treatment AEs will be presented separately. Pre-treatment AEs will be presented in the listings only.

A summary table displaying the number and the percentage of subjects experiencing at least one TEAE, serious TEAEs, ADRs/drug-related TEAE, serious ADRs, severe TEAEs, TEAEs leading to study drug discontinuation, TEAE of special interest (See Section 10.2.1) and TEAEs leading to death, as well as the number of events, will be presented by actual treatment group.

The SOC and PT will also be used for tabulation using the MedDRA dictionary. The number and percentage of subjects with at least one AE and the number of events will be presented by SOC and PT by actual treatment group for treatment emergent AEs, non-serious TEAEs, serious TEAEs, ADRs, serious ADRs, severe AEs, AEs leading to treatment discontinuation and AEs leading to death.

The number of subjects with the most common non-serious TEAEs (reported in >=5% of subjects in any treatment arm) will be also displayed by SOC and PT. The number of events will be also included in this analysis. The number of subjects with TEAEs will be also displayed by SOC and PT and maximum severity.

Tables will be presented by SOC and then by PT, alphabetically sorted within each SOC and PT.

These tables will be repeated for the post-treatment emergent AEs.

10.2.1 Adverse Events of Special Interest (AESI)

AESI include the following:

- Major bleeding (defined as severe blood loss [>5 mL/kg] or blood loss requiring transfusion or causing hypotension requiring use of inotropic agents);
- Embolism;
- Thrombosis;
- Catheter related blood stream infections (CRBSI).

The number and percentage of subjects who experienced treatment emergent AESI and associated exact binomial 95% confidence interval for proportion will be provided in the summary. The number and percentage of subjects who experienced treatment emergent AESI by AESI category will be also summarized.

All AESI will be listed.

10.3 Vital Signs

Vital signs collected at Screening will be presented as baseline characteristics using descriptive statistics. All vital signs results will be listed.

11 Other Analyses

No other analyses planned. All other data collected in the eCRF will be only listed.

12 Changes in the Planned Analyses from Study Protocol

- The protocol Section 12.2 describes the FAS as “the primary analysis set for all efficacy analyses”. The first secondary objective is “to demonstrate the non-inferiority of CUSA-081 compared to alteplase in the rate of treatment success following a single administration with a dwell time up to 90 minutes”. The primary analysis corresponding to this objective, which is included within the hierarchical closed testing procedure, will be based on the Per-Protocol Set, since this approach is considered as more conservative as per Section 5.2.3 of ICH E9. The FAS will be the primary analysis set for all efficacy analyses involving assessment of superiority.
- The protocol Section 12.3.7 describes an interim futility analysis. Since the study has been terminated by the Sponsor prematurely for other reasons, the futility analysis will not be conducted. The analysis to be conducted following the premature closure of the study will be exactly the analysis which is planned for end of study. The database lock and unblinding will be conducted according to the relevant SOPs of the Sponsor and CRO and the analysis conducted will be considered as the final study analysis.
- The definition of the Per-Protocol Set has been modified to use Safety Set instead of ITT Set in order to include in the Per-Protocol Set only treated subjects.

13 Output

13.1 Software

SAS version 9.4 will be used to perform all the statistical analyses.

13.2 Reporting Conventions

13.2.1 Treatment, Visit and Subgroup Descriptors

In the tables, listings and figures, the treatments, visits and timepoints will be identified as described below.

Treatment group (as displayed in outputs)	**Descriptor for treatment**
CUSA-081	One or two doses of "CUSA-081" (reteplase)
Placebo	One or two doses of "Placebo" (normal saline)
Alteplase	One or two doses of "alteplase"

Output	**Descriptor for visits**
Tables	Baseline Visit (Day 0 or Day 1) Visit 1 (Day 1) Follow-up Visit 2 (Day 30) Timepoints will be presented as 30 mins, 60 mins, 90 mins, 120 mins, 150 mins and 180 mins.
Listings	Baseline, Visit 1 and Visit 2 will be presented in the "Visit" column. Timepoints will be presented as 30 mins, 60 mins, 90 mins, 120 mins, 150 mins and 180 mins.
Figures	Baseline, Visit 1 and Visit 2 Timepoints will be presented as 30 mins, 60 mins, 90 mins, 120 mins, 150 mins and 180 mins.

Subgroup	Category descriptor
Age	• <18 years • ≥18-<65 years • ≥65-<85 years • ≥85 years
Sex	• Male • Female
BMI	• <18.5 kg/m² • ≥18.5–<25 kg/m² • ≥25.0–<30 kg/m² • ≥30.0 kg/m²
Country	• All countries to be included in full text.
Region	• US • Non-US
Type of CVAD	• Non-tunneled or Tunneled Central Venous Catheter (CVC) • Implanted Ports • Peripherally Inserted Central Catheters (PICCs)
Number of lumens	• Single lumen • Multi-lumen: 2 • Multi-lumen: 3 • Multi-lumen: 4
Where and by whom was the CVAD identified as dysfunctional	• Patient/caregiver identified • Healthcare provider not at study site • Healthcare provider at study site
Duration of CVAD dysfunction	• 0-5 hours • >5–48 hours
Race	• American Indian or Alaska Native • Asian • Black or African American • Native Hawaiian or Other Pacific Islander • White • Other • Not Reported In case of multiple races for a same subject, the combination of the races will be displayed as a new category.
Ethnicity	• Hispanic or Latino • Not Hispanic or Latino • Not Reported • Unknown

13.2.2 Decimal Places

Quantitative variables will be listed with the same number of decimal places as in the actual data.

The following rules on decimal places will be considered in the listings for the derived variables (in the analyses rounding will not be performed):

Variables	**Decimal Places**
• Duration of AE, medication (days) • Time to first re-occlusion (days)	0 decimal
• BMI (kg/m2) • Time between screening CVAD assessment and first drug administration (hours) • Duration of CVAD dysfunctional (hours)	1 decimal

The following rules on decimal places will be considered for the results of the analyses (if the analyses are performed on derived variables, the level of precision of the actual data is derived from the previous list):

All summary statistics will be rounded (using the SAS® function ROUND) and wherever possible data will be decimal aligned.

Statistic	**Number of decimal places for reporting**
Counts (n)	None
Percentages (%)/Proportion	1 decimal place *Note:* *If the calculated percentage is >0.0% but <0.1% then <0.1% is to be presented in the relevant table and/or listing.* *If the calculated percentage is >99.9% but <100.0% then >99.9% is to be presented in the relevant table and/or listing.*
Mean, Median, SD, 25th percentile, 75th percentile, Confidence intervals, Kaplan-Meier estimate	Actual data + 1 decimal place
Probability of re-occlusion free	3 decimals
Difference between percentages (%)/ Proportions	Actual data + 1 decimal place
Min, Max	Same as actual data
Odds-ratio and its confidence limits	3 decimals
p-values	3 decimal places. *Note:* *If the p-value is less than 0.001, it will be presented as <0.001.* *If the rounded result is a value of 1.000, it will be displayed as >0.999.*

13.2.3 Other Reporting Conventions

Treatments will be presented with the following order in the tables: CUSA-081, Placebo, Alteplase.

In general, dates will be presented on listings in the format ddmmmyyyy (date9.) and time in the format hh:mm (time5.). In case of partial dates or times, missing information will be replaced by dashes.

In the listings, a unit associated with a variable will be presented only once within parentheses either below or next to that variable in the heading portion. If a parameter has multiple units, each unit will be displayed only once, as applicable.

All tables will have their source listing referenced in a footnote. All figures will include the source table in a footnote. Listings should be sorted by subject ID and visit (unless otherwise specified) and have the SDTM and/or ADaM source data referenced in a footnote. The columns of each listing should fit into one page and should not be split into different pages.

When an output is split in multiple pages, page-break should be adequately controlled.

When a table is split in multiple pages, breaking of a block information in different pages is not allowed.

In a listing, in the case that a subject's record has been continued to the next page, an appropriate identification (e.g., the subject ID number and any other relevant information which is split between 2 pages) must be presented at the beginning of that page.

When a listing contains a lot of information, in order to optimize space on the page, some columns can be merged (e.g. "reported term" and "indication" may be presented in the same column.

13.3 Format

The following information should always be presented:

- 'Clinical Study Code No.:<Study Code No.>' followed by Chiesi denomination in the top portion of each page. Chiesi denomination is 'Chiesi Farmaceutici S.p.A'.
- The table/listing/figure number followed by the title, the analysis set used and the output page number in the format of 'Page x of Y' in the top portion of each page of any table/listing/figure.
- The SAS program name followed by the datetime of the output production and the analysis type (e.g. Dry Run; Draft Version; Final Version) in the bottom portion of each page of any table/listing/figure. The source listing/table/dataset will appear bottom left for every table/figure/listing.
- Tables and listings will be produced in rich text format (i.e., they will be tabular in format). Individual outputs must be provided in both portable format document (.pdf) and rich text format (.rtf).
- Combined PDF and RTF documents must also be provided, including a table of contents with hyperlinks. The combined documents should be divided by document type (tables, figures, listings).

- SAS outputs will be provided to the Sponsor in a similar manner (PDF and RTF; combined and with hyperlinked table of contents). The SAS outputs will be a separate deliverable to the Sponsor and are not intended for inclusion within the CSR.
- The combined documents page number in the format of 'Page n of N' will be presented bottom right corner.

The following should be followed for the tables:

- A landscape layout and Letter size will be used.
- A 9-point font size will be used using Courier New font.
- Horizontal lines will appear before and after the column heading of the output.
- Additional footnotes may be included if strictly necessary for clarification. Footnotes will be put under the main body of text at the bottom left of the page and will be displayed on each page of the output and not only on the last one.
- The left and right margins will be a minimum of 2.1 cm from the left and 1.9 cm from the right. The top and bottom margins will be a minimum 2.92 cm. Header and footer will be both 1.27 cm.

The following should be followed for the listings:

- A landscape layout and Letter size will be used.
- An 8-point font size will be used using Courier New font.
- Horizontal lines will appear before and after the column heading of the output.
- Additional footnotes may be included if strictly necessary for clarification. Footnotes will be put under the main body of text at the bottom left of the page and will be displayed on each page of the output and not only on the last one.
- The left and right margins will be a minimum of 2.1 cm from the left and 1.9 cm from the right. The top and bottom margins will be a minimum 2.92 cm. Header and footer will be both 1.27 cm.

The following should be followed for the figures:

- A portrait layout and Letter size will be used.
- A 9-point font size will be used using Courier New font.
- Figures will be produced in RTF and PDF formats (as described above), including relevant titles and footnotes as separate elements on the page (not within the body of the figure).
- Additional footnotes may be included if strictly necessary for clarification. Footnotes will be put under the main body of text at the bottom left of the page and will be displayed on each page of the output and not only on the last one.

- The size of the figures will be: width=16.3 cm, height=12.2 cm. The resolution will be set using the option IMAGE_DPI=400. Figures will have a footer specifying the source table or listing. Figures should clearly identify each treatment arm and require care of colors/symbols.
- The left margin will be a minimum of 2.5 cm, the right margin will be a minimum of 2 cm. The top and bottom margins will be a minimum of 0.8 cm.

13.4 Quality Control

The Quality Control steps will be defined in the Datasets, Tables, Listings, Figures QC Plan.

14 SAS Code

14.1 Comparison of Two Proportions Using 2-Sample Z Test

```
PROC FREQ DATA = <dataset>;
        TABLES trt01pn*Response / RISKDIFF (CL=(WALD) COLUMN=2);
        WHERE <population> = "Y" and ATPT = <timepoint>;
RUN;
```

Notes:

- TRT01PN represents the treatment arm, incorporating the following ordering: 1=CUSA-081, 2=Placebo and 3=Alteplase;
- Response represents the treatment success indicator (1=Yes, 0=No).
- The Chi-square statistic corresponds to the square of the Z-statistics (so the p-value for Table 14.2.1.1.1 corresponds to the Chi-square p-value).

14.2 Kaplan-Meier Estimates

```
PROC LIFETEST data=<dataset> timelist=(0 5 10 15 20 25 30) alpha=0.05;
        TIME time*censor(1);
        STRATA trt01pn;
RUN;
```

Notes:

- Time represents the time to event or time to censoring variable;
- Censor represents the censoring indicator (0=event, 1=censored);
- TRT01PN represents the treatment arm, incorporating the following ordering: 1=CUSA-081, 2=Placebo and 3=Alteplase;

14.3 Cox Proportional Hazards Model

```
PROC PHREG data=<dataset>;
    CLASS trt01pn / param=glm order=internal;
    MODEL time*censor(1) = trt01pn;

    CONTRAST 'CUSA-081 vs Placebo'     trt01pn 1 -1 0 / estimate=exp e;
    CONTRAST 'CUSA-081 vs Alteplase'   trt01pn 1 0 -1 / estimate=exp e;
    CONTRAST 'Alteplase vs Placebo'    trt01pn 0 -1 1 / estimate=exp e;
RUN;
```

Notes:

- Time represents the time to event or time to censoring variable;
- Censor represents the censoring indicator (0=event, 1=censored);
- TRT01PN represents the treatment arm, incorporating the following ordering: 1=CUSA-081, 2=Placebo and 3=Alteplase;

14.4 Logistic Regression Model

```
PROC LOGISTIC data=<dataset>;
    CLASS trt01pn (ref="2") agec region / param=glm;
    MODEL resp = trt01pn agec region;
    LSMEANS trt01pn / e diff oddsratio cl;
RUN;
```

Notes:

- TRT01PN represents the treatment arm, incorporating the following ordering: 1=CUSA-081, 2=Placebo and 3=Alteplase;
- AGEC represents the age in category (<18, ≥18-<65, ≥65-<85, ≥85 years).
- REGION represents the country in category (US vs Non-US).

14.5 Conditional Power

Of note, the interim analysis will not be conducted as a result of the early stopping of the study. The below text in this section is maintained for consistency with the protocol and to maintain a record of the original plan. See Section 12 for additional details.

Create a dataset with a single record and the following variables included as defined below:

- n_i1 = number of subjects in CUSA-081 group at interim
- n_i2 = number of subjects in alteplase group at interim
- n1 = 473 (This is the total number of subjects in CUSA-081 group planned at the end of the trial)
- n2 = 315 (This is the number of subjects in alteplase group planned at the end of the trial)
- e_i1 = number of successes in CUSA-081 group at interim
- e_i2 = number of successes in alteplase group at interim

Next, create a new dataset, based on the prior dataset:

```
DATA <dataset name>;
  SET <name of prior dataset>;
  alpha = 0.025;
  NIMarg = -0.1;

   * Information fraction;
  i=(n_i1+n_i2)/(n1+n2);

   * Interim proportions;
  p_i1=e_i1/n_i1;
  p_i2=e_i2/n_i2;

   * Interim difference between proportions, SE and test statistic (H0: diff <= NI Margin;
   * H1: diff > NI Margin);
  diff_i=p_i1-p_i2;
```

```
  se_i=sqrt( (p_i1*(1-p_i1)/n_i1) + (p_i2*(1-p_i2)/n_i2) );
  z_i=(diff_i-(NIMarg))/se_i;

   * Conditional power CP(d) formula in Gallo, Mao, Shih, Alternative views on;
   * setting clinical trial futility criteria, Journal of Biopharmaceutical Statistics 2014;
  cp=probnorm(-1/sqrt(1-i)*(probit(1-alpha) - z_i/sqrt(i)));
RUN;
```

15 References

1. Cathflo® Activase® (Alteplase) Package Insert. San Francisco, CA. Genentech, 2017.
2. Gabrail N, Sandler E, Charu V, et al. TROPICS 1: a phase III, randomized, double-blind, placebo-controlled study of tenecteplase for restoration of function in dysfunctional central venous catheters. J Vasc Interv Radiol. 2010. 21(12): 1852-8.
3. Gallo P, Mao L, Shih VH (2014). Alternative views on setting clinical trial futility criteria. Journal of Biopharmaceutical Statistics, 24(5):976-993.
4. Chiesi Farmaceutici S.p.A. TLFs_Library_v1.0_signed. 10 Sep 2019.
5. Chiesi Farmaceutici S.p.A. Instructions for Producing Statistical Analysis Plan & Statistical Output. 25 Jan 2016.
6. ICH E9: Statistical Principles for Clinical Trials. Sept 1998.
7. [redacted]-SOP Statistical Analysis Plan v3.0.

16 List of Tables, Listings and Figures

16.1 Tables

The SAS output for the analyses included in the flagged (***) tables below will be provided as separate documents for internal use only and not for inclusion into the CSR.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.1.1	Screen Failures (Enrolled Set)	DST001	Overall column should be displayed.	Source: Listing 16.2.1.1
Table 14.1.1.2	Disposition by Treatment (Intention-to-Treat Set)	DST002	- Overall column should be displayed. - Replace 'Primary Reason for Discontinuation' by 'Primary Reason for Study Discontinuation'. - 'Not Treated', 'Completed the Treatment Period' and 'Discontinued the Treatment Period' sections with the 'Primary Reason of Treatment Period Discontinuation' should be also displayed.	Source: Listing 16.2.1.2 Footnotes: [1] Treatment period corresponds to Visit 1.
Table 14.1.1.3	Disposition by Country (Intention-to-Treat Set)	DST004	- Overall column should be displayed. - Include 'Discontinued from Treatment' and 'Discontinued from Study'.	Source: Listing 16.2.1.2
Table 14.1.1.4	Disposition by Site (Intention-to-Treat Set)	DST004	- Same as Table 14.1.1.4 - Display "Country/Site" and sort by country and by site number.	Same as Table 14.1.1.4
Table 14.1.1.5	Attendance at Study Visits and CVAD Assessment Timepoints (Intention-to-Treat Set)	SVT001	- Overall column should be displayed. - Within Visit, timepoints (based on CVAD page in eCRF) to be added. - Prior to achieving treatment success, a subject is counted in a visit/timepoint if the visit or CVAD assessment at the time point has been performed. Following achievement of treatment success, a subject is counted in a visit/timepoint if they have not discontinued the study.	Source: Listings 16.2.1.4 and 16.2.6.1

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.1.6	Important Protocol Deviations (Full Analysis Set)	DVT001	- Display the summary of "At Least One Deviation Excluding from Per-Protocol Set". - Display the summary of "At Least One Deviation" (i.e. all important protocol deviations regardless if leading or not to exclusion from PP Set).	Source: Listing 16.2.2.2
Table 14.1.1.7	Analysis Sets (Intention-to-Treat Set)	DST005	- Overall column should be displayed. - Populations to be displayed: FAS, Safety, PP Sets. - Display the full names and abbreviations in brackets.	Source: Listing 16.2.3.1 Footnotes: [1] Intention-to-Treat Analysis Set (ITT) includes all randomized subjects regardless if they received treatment with study drug. [2] Full Analysis Set (FAS) includes all randomized subjects who receive at least one dose of study drug, and with at least one available evaluation of efficacy after baseline (i.e. at least one CVAD assessment after study drug administration). [3] Safety Set (SS) includes all randomized subjects who receive at least one dose of study drug. [4] Per-Protocol Analysis Set (PPS) includes all subjects from the ITT Set without any important protocol deviations.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.2.1	Demographic and Baseline Characteristics (Full Analysis Set)	DMT001	- Overall column should be displayed. - Variables to be summarized: Age, Age Category, Gender, Race (categories as per CRF to be displayed), Ethnicity (categories as per CRF to be displayed), Height, Weight, BMI, SBP, DBP, HR and Urine Pregnancy Test (only for females). - All categories should be displayed even if empty.	Source: Listing 16.2.4.1
Table 14.1.2.2	Demographic and Baseline Characteristics (Safety Set)	DMT001	Same as Table 14.1.2.1	Same as Table 14.1.2.1
Table 14.1.2.3	Demographic and Baseline Characteristics (Intention-to-Treat Set)	DMT001	Same as Table 14.1.2.1	Same as Table 14.1.2.1
Table 14.1.2.4	Demographic and Baseline Characteristics (Per-Protocol Set)	DMT001	Same as Table 14.1.2.1	Same as Table 14.1.2.1
Table 14.1.3.1	CVAD History (Full Analysis Set)	BLT001	- Overall column should be displayed. - Variables to be summarized: – Time Between Screening CVAD Assessment and First Drug Administration (Hours) – CVAD Type – CVAD Lumen (Single lumen, Multi-Lumen: 2, Multi-Lumen: 3, Multi-Lumen: 4) – Number of Lumens – Indication for Insertion [1] – Duration CVAD Was Dysfunctional (Hours) – When and By Whom the CVAD Was Identified as Dysfunctional	Source: Listing 16.2.4.2 Footnotes: [1] Several indications may be possible for a subject.
Table 14.1.3.2	CVAD History (Safety Set)	BLT001	Same as Table 14.1.3.1	Same as Table 14.1.3.1
Table 14.1.3.3	CVAD History (Intention-to-Treat Set)	BLT001	Same as Table 14.1.3.1	Same as Table 14.1.3.1
Table 14.1.3.4	CVAD History (Per-Protocol Set)	BLT001	Same as Table 14.1.3.1	Same as Table 14.1.3.1

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.4.1	Medical and Surgical History (Safety Set)	MHT001	- Overall column should be displayed. - Replace <Condition/Procedure> by 'Medical History'.	Source: Listing 16.2.4.3 Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.
Table 14.1.5.1	Concomitant Diseases (Safety Set)	MHT001	- Overall column should be displayed. - Replace <Condition/Procedure> by 'Concomitant Disease'.	Source: Listing 16.2.4.4 Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.
Table 14.1.6.1	Prior Procedures (Safety Set)	MHT001	Overall column should be displayed.	Source: Listing 16.2.4.5 Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.
Table 14.1.7.1	Maintained Procedures (Safety Set)	MHT002	Overall column should be displayed.	Same as Table 14.1.6.1
Table 14.1.8.1	Concomitant Procedures (Safety Set)	MHT002		Same as Table 14.1.6.1
Table 14.1.9.1	Prior Medications (Safety Set)	CMT001	Overall column should be displayed.	Source: Listing 16.2.4.6 Footnotes: [1] ATCs and Preferred Name are coded using WHO-DD XXXX 20XX.
Table 14.1.10.1	Maintained Medications (Full Analysis Set)	CMT001	Same as Table 14.1.9.1	Same as Table 14.1.9.1
Table 14.1.10.2	Maintained Medications (Safety Set)	CMT001	Same as Table 14.1.9.1	Same as Table 14.1.9.1
Table 14.1.11.1	Concomitant Medications (Full Analysis Set)	CMT002		Same as Table 14.1.9.1

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.11.2	Concomitant Medications (Safety Set)	CMT002		Same as Table 14.1.9.1
Table 14.2.1.1.1	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 90 Minutes Following a Single Instillation of Study Drug (Full Analysis Set)	ANT007	- Replace "Adjusted Mean" with "Proportion of Treatment Success (95% CI)" and "Adjusted Mean difference" with "Difference in Proportions (95% CI)". - Do not display Parameter column. - Replace Study Day by Timepoint. - Timepoints to be presented: 30, 60 and 90 mins. - Add column for P-value for all the treatment comparison at all timepoints as last column. - In the column Treatment and after all treatments listed, add the different comparisons: CUSA-081 vs Placebo, CUSA-081 vs Alteplase, Alteplase vs Placebo. - Replace 'n' by 'n Success'.	Source: Listing 16.2.6.1 Footnotes: [1] 'n Success' corresponds to the number of subjects with treatment success. [2] The 95% confidence intervals of proportions and difference of proportions are based on Wald method. [3] The p-value is based on a 2-sample Z test for proportions. [4] Percentages are based on the number of subjects in the treatment group.
Table 14.2.1.1.2 ***	SAS Output: Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 90 Minutes Following a Single Instillation of Study Drug (Full Analysis Set)		Raw SAS output	
Table 14.2.1.2	Summary and Sensitivity Analysis of Proportion of Subjects with Treatment Success Up to 90 Minutes Following a Single Instillation of Study Drug (Intention-to-Treat Set)	ANT007	Same as Table 14.2.1.1.1 The randomized but non-treated subjects will be considered as non-responders.	Same as Table 14.2.1.1.1
Table 14.2.1.3.1	Summary and Sensitivity Analysis of Proportion of Subjects with Treatment Success Up to 90 Minutes Following a Single Instillation of Study Drug (Per-Protocol Set)	ANT007	Same as Table 14.2.1.1.1	Same as Table 14.2.1.1.1

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.1.3.2 ***	SAS Output: Summary and Sensitivity Analysis of Proportion of Subjects with Treatment Success Up to 90 Minutes Following a Single Instillation of Study Drug (Per-Protocol Set)		Raw SAS output	
Table 14.2.1.4.1	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 90 Minutes Following a Single Instillation of Study Drug by Age (Full Analysis Set)	ANT007	Same as Table 14.2.1.1.1 - Add a subgroup title for each age category. - N should display the number of subjects within the subgroup category. - Categories with fewer than 1 randomized patients are excluded from this analysis. - For the treatment comparison rows, if there are <3 subjects in one of the 2 arms compared, then the columns "Difference in Proportions (95% CI)" and "P-Value" will be left empty. - Footnotes [5] and [6] to be displayed only if applicable to the output (it will be displayed on all pages even if not applicable to a specific subgroup).	Source: Listing 16.2.6.1 Footnotes: [1] 'n Success' corresponds to the number of subjects with treatment success. [2] The 95% confidence intervals of proportions and difference of proportions are based on Wald method. [3] The p-value is based on a 2-sample Z test for proportions. [4] Percentages are based on the number of subjects in the treatment group and in the subgroup. [5] Comparisons with less than 3 subjects in one of the treatment group will not be performed. [6] NE = Not estimable.
Table 14.2.1.4.2	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 90 Minutes Following a Single Instillation of Study Drug by Sex (Full Analysis Set)	ANT007	Same as Table 14.2.1.4.1	Same as Table 14.2.1.4.1

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.1.4.3	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 90 Minutes Following a Single Instillation of Study Drug by Race (Full Analysis Set)	ANT007	Same as Table 14.2.1.4.1	Same as Table 14.2.1.4.1
Table 14.2.1.4.4	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 90 Minutes Following a Single Instillation of Study Drug by Ethnicity (Full Analysis Set)	ANT007	Same as Table 14.2.1.4.1	Same as Table 14.2.1.4.1
Table 14.2.1.4.5	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 90 Minutes Following a Single Instillation of Study Drug by Country (Full Analysis Set)	ANT007	Same as Table 14.2.1.4.1	Same as Table 14.2.1.4.1
Table 14.2.1.4.6	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 90 Minutes Following a Single Instillation of Study Drug by Region (Full Analysis Set)	ANT007	Same as Table 14.2.1.4.1	Same as Table 14.2.1.4.1
Table 14.2.1.4.7	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 90 Minutes Following a Single Instillation of Study Drug by Body Mass Index (Full Analysis Set)	ANT007	Same as Table 14.2.1.4.1	Same as Table 14.2.1.4.1
Table 14.2.1.4.8	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 90 Minutes Following a Single Instillation of Study Drug by Type of CVAD (Full Analysis Set)	ANT007	Same as Table 14.2.1.4.1	Same as Table 14.2.1.4.1
Table 14.2.1.4.9	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 90 Minutes Following a Single Instillation of Study Drug by Number of Lumens (Full Analysis Set)	ANT007	Same as Table 14.2.1.4.1	Same as Table 14.2.1.4.1

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.1.4.10	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 90 Minutes Following a Single Instillation of Study Drug by Where and Whom CVAD Identified as Dysfunctional (Full Analysis Set)	ANT007	Same as Table 14.2.1.4.1	Same as Table 14.2.1.4.1
Table 14.2.1.4.11	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 90 Minutes Following a Single Instillation of Study Drug by Duration of CVAD Dysfunction (Full Analysis Set)	ANT007	Same as Table 14.2.1.4.1	Same as Table 14.2.1.4.1
Table 14.2.1.5.1	Summary and Sensitivity Analysis of Proportion of Subjects with Treatment Success Up to 90 Minutes Following a Single Instillation of Study Drug – Logistic Regression Model (Full Analysis Set)	ANT004	- Timepoints to be presented: 30, 60 and 90 mins. - Do not display the row "Overall". - Only the following comparisons will be performed: CUSA-081 vs Placebo and CUSA-081 vs Alteplase. - Add the columns 'n Success' and 'Proportion of Treatment Success (95% CI)' after 'n' column.	Source: Listing 16.2.6.1 Footnotes: [1] n corresponds to the number of subjects included in the analysis. [2] 'n Success' corresponds to the number of subjects with treatment success. [3] P-value, odds ratio and its 95% confidence intervals are based on a logistic regression model with age and region as factors.
Table 14.2.1.5.2	Summary and Sensitivity Analysis of Proportion of Subjects with Treatment Success Up to 90 Minutes Following a Single Instillation of Study – Logistic Regression Model Drug (Intention-to-Treat Set)	ANT004	Same as Table 14.2.1.5.1	Same as Table 14.2.1.5.1

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.1.5.3	Summary and Sensitivity Analysis of Proportion of Subjects with Treatment Success Up to 90 Minutes Following a Single Instillation of Study Drug – Logistic Regression Model (Per-Protocol Set)	ANT004	Same as Table 14.2.1.5.1	Same as Table 14.2.1.5.1

Table 14.2.1.6	Outcome of Futility Analysis (Full Analysis Set)		- This table is generated only for futility analysis.
			- The table has 3 columns 'CUSA-081 (N=xxx)', 'Alteplase (N=xxx)', 'CUSA-081 vs Alteplase'.
			- Display the following rows:
			  - Number of Subjects included in the Futility Analysis
			  - Proportion of Treatment Success at 90 mins at Futility Analysis (%)
			  - Difference in Proportions (95% CI)
			  - Conditional Power: *(no result)*
			  – Information Level at Futility Analysis
			  – Z-statistic
			  – Conditional Power based on a planned total sample size of 788 Subjects included in the CUSA-081 and alteplase arms of the Full Analysis Set
			
			Notes:
			  – The 3 first rows results are based on Table 14.2.1.1.1.
			  – Information Level corresponds to parameter *I* in Section 14.5).
			  – Z-statistics corresponds to parameter z_I in Section 14.5).
			  – Conditional Power corresponds to parameter CP(d) in Section 14.5).
			  – The conditional power is displayed with 1 additional digit compared to the threshold mentioned in the DMC Charter.
				Source: Table 14.2.1.1.1
				
				Footnotes:
				[1] The conditional power is computed assuming that the observed proportions of treatment success in each treatment group are the proportions observed for the full study.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.2.1.1	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 180 Minutes Following Two Instillations of Study Drug (Full Analysis Set)	ANT007	Same as Table 14.2.1.1.1 Timepoints to be presented: 120, 150 and 180 mins.	Same as Table 14.2.1.1.1
Table 14.2.2.1.2 ***	SAS Output: Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 180 Minutes Following Two Instillations of Study Drug (Full Analysis Set)		Raw SAS output	
Table 14.2.2.2	Summary and Sensitivity Analysis of Proportion of Subjects with Treatment Success Up to 180 Minutes Following Two Instillations of Study Drug (Intention-to-Treat Set)	ANT007	Same as Table 14.2.2.1.1	Same as Table 14.2.2.1.1
Table 14.2.2.3	Summary and Sensitivity Analysis of Proportion of Subjects with Treatment Success Up to 180 Minutes Following Two Instillations of Study Drug (Per-Protocol Set)	ANT007	Same as Table 14.2.2.1.1	Same as Table 14.2.2.1.1

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.2.4.1	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 180 Minutes Following Two Instillations of Study Drug by Age (Full Analysis Set)	ANT007	Same as Table 14.2.2.1.1 - Add a subgroup title for each age category. - N should display the number of subjects within the subgroup category. - Categories with fewer than 1 randomized patient are excluded from this analysis. - For the treatment comparison rows, if there are <3 subjects in one of the 2 arms compared, then the columns "Difference in Proportions (95% CI)" and "P-Value" will be left empty. - Footnotes [5] and [6] to be displayed only if applicable to the output.	Source: Listing 16.2.6.1 Footnotes: [1] 'n Success' corresponds to the number of subjects with treatment success. [2] The 95% confidence intervals of proportions and difference of proportions are based on Wald method. [3] The p-value is based on a 2-sample Z test for proportions. [4] Percentages are based on the number of subjects in the treatment group and in the subgroup. [5] Comparisons with less than 3 subjects in one of the treatment group will not be performed. [6] NE = Not estimable.
Table 14.2.2.4.2	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 180 Minutes Following Two Instillations of Study Drug by Sex (Full Analysis Set)	ANT007	Same as Table 14.2.2.4.1	Same as Table 14.2.2.4.1
Table 14.2.2.4.3	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 180 Minutes Following Two Instillations of Study Drug by Race (Full Analysis Set)	ANT007	Same as Table 14.2.2.4.1	Same as Table 14.2.2.4.1

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.2.4.4	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 180 Minutes Following Two Instillations of Study Drug by Ethnicity (Full Analysis Set)	ANT007	Same as Table 14.2.2.4.1	Same as Table 14.2.2.4.1
Table 14.2.2.4.5	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 180 Minutes Following Two Instillations of Study Drug by Country (Full Analysis Set)	ANT007	Same as Table 14.2.2.4.1	Same as Table 14.2.2.4.1
Table 14.2.2.4.6	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 180 Minutes Following Two Instillations of Study Drug by Region (Full Analysis Set)	ANT007	Same as Table 14.2.2.4.1	Same as Table 14.2.2.4.1
Table 14.2.2.4.7	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 180 Minutes Following Two Instillations of Study Drug by Body Mass Index (Full Analysis Set)	ANT007	Same as Table 14.2.2.4.1	Same as Table 14.2.2.4.1
Table 14.2.2.4.8	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 180 Minutes Following Two Instillations of Study Drug by Type of CVAD (Full Analysis Set)	ANT007	Same as Table 14.2.2.4.1	Same as Table 14.2.2.4.1
Table 14.2.2.4.9	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 180 Minutes Following Two Instillations of Study Drug by Number of Lumens (Full Analysis Set)	ANT007	Same as Table 14.2.2.4.1	Same as Table 14.2.2.4.1

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.2.4.10	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 180 Minutes Following Two Instillations of Study Drug by Where and Whom CVAD Identified as Dysfunctional (Full Analysis Set)	ANT007	Same as Table 14.2.2.4.1	Same as Table 14.2.2.4.1
Table 14.2.2.4.11	Summary and Statistical Analysis of Proportion of Subjects with Treatment Success Up to 180 Minutes Following Two Instillations of Study Drug by Duration of CVAD Dysfunction (Full Analysis Set)	ANT007	Same as Table 14.2.2.4.1	Same as Table 14.2.2.4.1
Table 14.2.2.5.1	Summary and Sensitivity Analysis of Proportion of Subjects with Treatment Success Up to 180 Minutes Following Two Instillations of Study Drug - Logistic Regression Model (Full Analysis Set)	ANT004	- Same as Table 14.2.1.5.1. - Timepoints to be presented: 120, 150 and 180 mins.	Same as Table 14.2.1.5.1
Table 14.2.2.5.2	Summary and Sensitivity Analysis of Proportion of Subjects with Treatment Success Up to 180 Minutes Following Two Instillations of Study Drug - Logistic Regression Model (Intention-to-Treat Set)	ANT004	Same as Table 14.2.2.5.1	Same as Table 14.2.2.5.1
Table 14.2.2.5.3	Summary and Sensitivity Analysis of Proportion of Subjects with Treatment Success Up to 180 Minutes Following Two Instillations of Study Drug - Logistic Regression Model (Per-Protocol Set)	ANT004	Same as Table 14.2.2.5.1	Same as Table 14.2.2.5.1

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number

Table 14.2.3.1	Rate of Recurrent Catheter Dysfunction Within 30 Days (Full Analysis Set)	TPT005	Parameters to display:
			- Number (%) of Subjects with Treatment Success [2]
			  - Number (%) of Subjects with Re-Occlusion [3]
			  - Number (%) of Censored Subjects [3]
			- Time to Re-Occlusion (Days):
			  - 25th Percentile (95% CI)
			  - Median (95% CI)
			  - 75th Percentile (95% CI)
			- Probability of Re-Occlusion Free at Day 30 (95% CI)
			- Treatment Comparison vs Placebo [4]
			  - Hazard Ratio (95% CI) *[to be displayed in CUSA-081 and Alteplase columns]*
			- Treatment Comparison vs Alteplase [4]
			  - Hazard Ratio (95% CI) *[to be displayed in CUSA-081 column]*
				Source: Listing 16.2.6.4
				
				Footnotes:
				[1] Time to re-occlusion (Days) = (date of start of first re-occlusion – date of first treatment success + 1). If no re-occlusion the subject is censored to the CVAD removal or study discontinuation/completion date, whichever is the earliest.
				[2] Percentages are based on the number of subjects in the FAS.
				[3] Percentages are based on the number with treatment success.
				[4] Based on Cox proportional hazards model including treatment as a fixed effect.

Table 14.2.3.2 ***	SAS Output: Rate of Recurrent Catheter Dysfunction Within 30 Days (Full Analysis Set)		Raw SAS output	

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.1.1	Study Drug Exposure (Safety Set)	EXT001	The following rows will be displayed: - Exposure - 1 Dose Administered *[n and % to be displayed]* - Timepoint Assessed - 30 Minutes *[n and % to be displayed]* - 60 Minutes *[n and % to be displayed]* - 90 Minutes *[n and % to be displayed]* - 2 Doses Administered *[n and % to be displayed]* - Timepoint Assessed - 120 Minutes *[n and % to be displayed]* - 150 Minutes *[n and % to be displayed]* - 180 Minutes *[n and % to be displayed]*	Source: Listing 16.2.5.1
Table 14.3.1.2.1	Summary of Treatment Emergent Adverse Events (Safety Set)	AET001	Data to display: - Number of Subjects with at Least One TEAE - Number of Subjects with at Least One Serious TEAE - Number of Subjects with at Least One ADR - Number of Subjects with at Least One Serious ADR - Number of Subjects with at Least One Severe TEAE - Number of Subjects with at Least One TEAE Leading to study Drug Discontinuation - Number of Subjects with at Least One TEAE of Special Interest - Number of Subjects with at Least One TEAE Leading to Death	Source: Listing 16.2.7.2 Footnotes: [1] ADR = Adverse drug reaction; TEAE = Treatment emergent adverse event.
Table 14.3.1.2.2	Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)	AET003		Source: Listing 16.2.7.2 Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.1.2.3	Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Set)	AET005	The number of events ("E") columns will not be displayed.	Source: Listing 16.2.7.2 Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x [2] If a subject reports the same AE more than once within that SOC/PT, the AE with the maximum severity will be counted.
Table 14.3.1.2.4	Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)	AET003		Source: Listing 16.2.7.3 Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.
Table 14.3.1.2.5	Non-Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)	AET003		Source: Listing 16.2.7.4 Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.
Table 14.3.1.2.6	Treatment Emergent Adverse Drug Reactions by System Organ Class and Preferred Term (Safety Set)	AET003		Source: Listing 16.2.7.5 Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.1.2.7	Serious Treatment Emergent Adverse Drug Reactions by System Organ Class and Preferred Term (Safety Set)	AET003		Source: Listing 16.2.7.6 Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.
Table 14.3.1.2.8	Severe Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)	AET003		Source: Listing 16.2.7.7 Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.
Table 14.3.1.2.9	Non-Serious Treatment Emergent Adverse Events Reported in >=5% of Subjects in Any Treatment Arm by System Organ Class and Preferred Term (Safety Set)	AET003	If there is no PT within the SOC then the SOC will not be displayed.	Source: Listing 16.2.7.2 Footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.
Table 14.3.1.2.10	Treatment Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term (Safety Set)	AET003		Source: Listing 16.2.7.9 Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.
Table 14.3.1.2.11	Post-Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)	AET003		Source: Listing 16.2.7.11 Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.1.2.12	Post-Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Set)	AET005	The number of events ("E") columns will not be displayed.	Source: Listing 16.2.7.11 Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x [2] If a subject reports the same AE more than once within that SOC/PT, the AE with the maximum severity will be counted.
Table 14.3.1.2.13	Serious Post-Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)	AET003		Same as Table 14.3.1.2.11
Table 14.3.1.2.14	Non-Serious Post-Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)	AET003		Same as Table 14.3.1.2.11
Table 14.3.1.2.15	Post-Treatment Emergent Adverse Drug Reactions by System Organ Class and Preferred Term (Safety Set)	AET003		Same as Table 14.3.1.2.11
Table 14.3.1.2.16	Serious Post-Treatment Emergent Adverse Drug Reactions by System Organ Class and Preferred Term (Safety Set)	AET003		Same as Table 14.3.1.2.11
Table 14.3.1.2.17	Severe Post-Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)	AET003		Same as Table 14.3.1.2.11
Table 14.3.1.2.18	Non-Serious Post-Treatment Emergent Adverse Events Reported in >=5% of Subjects in Any Treatment Arm by System Organ Class and Preferred Term (Safety Set)	AET003	If there is no PT within the SOC then the SOC will not be displayed.	Same as Table 14.3.1.2.11

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number

Table 14.3.2.1	Treatment Emergent Adverse Events of Special Interest by Category (Safety Set)	AET006	Data to display for each category:
			- Number of Subjects with at Least One Event, Percentage of subjects in the relevant treatment period with at least one event, number of events, 95% CI for the percentage
			- AESI categories:
			  - Any AESI
			  – Major Bleeding
			  – Embolism
			  – Thrombosis
			  – Catheter Related Blood Stream Infection (CRBSI)
				Source: Listing 16.2.7.8
				
				Footnotes:
				[1] 95% CIs are the exact binomial confidence intervals for the percentage of subjects experiencing at least one event.

Table 14.3.2.2	Treatment Emergent Adverse Events of Special Interest by Category and Preferred Term (Safety Set)	AET003	Replace SOC with AESI category.	Source: Listing 16.2.7.8 Footnotes: [1] Preferred Term is coded using MedDRA Version xx.x.
Table 14.3.2.3	Treatment Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term (Safety Set)	AET003		Source: Listing 16.2.7.10 Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.

16.2 Listings

Listings will include data at observed time points only, without imputation for missing data.

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.1.7	Randomization Schedule (Intention-to-Treat Set)	DSL001		
Listing 16.2.1.1	Screening Failures (Enrolled Set)	DSL002	- Include only subjects who discontinued before the first dose of study treatment. - Include 'Date of Visit 0'.	
Listing 16.2.1.2	Subjects Disposition (Intention-to-Treat Set)	DSL004	- "Period of last intake of study treatment" and "Last treatment received" columns not to be displayed. - Display the date and the reason of treatment termination before study termination column.	Footnotes: [1] Study Day at Date of Study Discontinuation calculated with reference to the Informed Consent Date. [2] Study Day at Date of Study Discontinuation calculated with reference to the First Study Drug Administration Date. [3] Study Day at Date of Study Discontinuation calculated with reference to the Last Study Drug Administration Date.
Listing 16.2.1.3	Randomization Code Broken (Intention-to-Treat Set)	DSL005		Footnotes: [1] Study Day is the study Day at Visit calculated with reference to the First Study Drug administration at study level.
Listing 16.2.1.4	Study Visits (Intention-to-Treat Set)	SVL001	Remove the word "Retest" in header.	
Listing 16.2.2.1	Violation of Eligibility Criteria (Intention-to-Treat Set)	DVL001	Only deviations from DV in relation to inclusion/exclusion criteria.	

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.2.2	Important Protocol Deviations (Intention-to-Treat Set)	DVL002	- Include all important protocol deviations from DV. - Remove "Randomized sequence" and "Period" columns.	
Listing 16.2.3.1	Analysis Set Disposition (Intention-to-Treat Set)	DSL006	List FAS, Safety and PP Sets	
Listing 16.2.3.2	Subjects Excluded from Analysis Sets (Intention-to-Treat Set)	DSL007	The analysis sets excluded from can be FAS, Safety, and PP Sets	
Listing 16.2.4.1	Demographic Characteristics (Intention-to-Treat Set)	DML001	- Display also Ethnicity, SBP, DBP, HR and Childbearing Potential columns.	
Listing 16.2.4.2	CVAD History (Intention-to-Treat Set)	SCL001	The following columns will be presented: - Subject ID - Randomized Treatment - Date/time of Assessment - Time Between Screening CVAD Assessment and First Drug Administration (Hours) - CVAD Type - CVAD Lumen - Number of Lumens - Indication for Insertion - Date/Time of CVAD Dysfunction - Duration CVAD Was Dysfunctional (Hours) - When and By Whom the CVAD Was Identified as Dysfunctional	
Listing 16.2.4.3	Medical and Surgical History (Intention-to-Treat Set)	MHL001		Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.
Listing 16.2.4.4	Concomitant Diseases (Intention-to-Treat Set)	MHL002		Same as Listing 16.2.4.3

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.4.5	Procedures (Intention-to-Treat Set)	PRL001	- Start and End times to be displayed. - Replace '[CAT]' by '[CAT] [2]'.- Do not display "Indication" column.	Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x. [2] C=Concomitant; M=Maintained; P=Prior; PT=Post-treatment.
Listing 16.2.4.6	Medications (Intention-to-Treat Set)	CML001	- Start and End times to be displayed. - Replace '[CAT]' by '[CAT] [3]'.	Footnotes: [1] ATCs and Preferred Name are coded using WHO-DD XXXX 20xx. [2] [Day] is the study Day at Start Date calculated with reference to the First Dose Date. [3] C=Concomitant; M=Maintained; P=Prior; PT=Post-treatment.
Listing 16.2.5.1	Study Drug Administration (Intention-to-Treat Set)		Variables to be listed: - Subject ID - Randomized Treatment - Actual Treatment - Syringe Number - Date/Time of Administration [Day] - Time of Reconstitution - Kit Number	

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.6.1	Central Venous Access Device by Timepoint (Intention-to-Treat Set)		Variables to be listed: - Subject ID - Randomized Treatment - Actual Treatment - Timepoint - Assessment Completed? - Date/Time of Assessment [Day] - 3 mL of Blood Able to Be Withdrawn? - 5 mL of Saline Infused? - Patency Achieved After the Assessment?	

Listing 16.2.6.2	Central Venous Access Device at End of Treatment (Intention-to-Treat Set)		Variables to be listed:
			- Subject ID
			- Randomized Treatment
			- Actual Treatment
			- Patency Achieved Within 180 Minutes? Assessment
			- If No
			  – What Standard of Care Treatment Was Applied?
			  – Date/Time of Treatment
			  – Outcome	

Listing 16.2.6.3	Central Venous Access Device Follow-up (Intention-to-Treat Set)		Variables to be listed: - Subject ID - Randomized Treatment - Actual Treatment - Achieving Patency During the 180-minute Treatment Period? - Re-Occlusion Since the Treatment Visit? - Date of First Re-Occlusion - Date of Additional Treatment for CVAD Dysfunction - Type of Treatment - Study Treatment CVAD Removed? - Date of CVAD Removal?	

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.6.4	Central Venous Access Device – Time to First Re-Occlusion (Intention-to-Treat Set; Subjects Achieving Patency During the 180-minute Treatment Period)		Variables to be listed: - Subject ID - Randomized Treatment - Actual Treatment - Date/Time of First Study Drug Administration [Day] - Date/Time of Treatment Success [Day] - Date of First Re-Occlusion [Day] - Date of CVAD Removal [Day] - Date of Study Completion/Discontinuation [Day] - Time to First Re-Occlusion (Days)*	Footnotes: [1] * Censored. [2] Time to re-occlusion (Days) = (date of start of first re-occlusion – date of first treatment success + 1). If no re-occlusion the subject is censored to the CVAD removal or study discontinuation/completion date, whichever is the earliest. The time to first re-occlusion is derived only for subjects who have treatment success.
Listing 16.2.7.1	Pre-treatment Adverse Events (Intention-to-Treat Set)	AEL001	Add a new column 'AESI' after the Preferred term one and fulfil the name of the AESI category.	Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version 23.0. [2] "DTH" = results in death, "LTH" = is life-threatening, "HSP" = requires hospitalisation or prolongation of existing hospitalisation, "DI" = results in persistent or significant disability or incapacity, "CA" = is a congenital anomaly or birth defect, "SIG" = is a medically significant adverse event. [3] Onset Day is the study Day at Onset Date calculated with reference to the First Study Drug Administration Date.

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.7.2	Treatment Emergent Adverse Events (Intention-to-Treat Set)	AEL002	Add a new column 'AESI' after the Preferred term one and fulfil the name of the AESI category.	Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version 23.0. [2] "DTH" = results in death, "LTH" = is life-threatening, "HSP" = requires hospitalisation or prolongation of existing hospitalisation, "DI" = results in persistent or significant disability or incapacity, "CA" = is a congenital anomaly or birth defect, "SIG" = is a medically significant adverse event. [3] [D1] is the study Day at Onset Date calculated with reference to the First Study Drug Administration Date. [D2] is the study Day at End Date calculated with reference to the First Study Drug Administration Date.
Listing 16.2.7.3	Serious Treatment Emergent Adverse Events (Intention-to-Treat Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.2
Listing 16.2.7.4	Non-Serious Treatment Emergent Adverse Events (Intention-to-Treat Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.2
Listing 16.2.7.5	Treatment Emergent Adverse Drug Reactions (Intention-to-Treat Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.2
Listing 16.2.7.6	Serious Treatment Emergent Adverse Drug Reactions (Intention-to-Treat Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.2
Listing 16.2.7.7	Severe Treatment Emergent Adverse Events (Intention-to-Treat Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.2
Listing 16.2.7.8	Treatment Emergent Adverse Events of Special Interest (Intention-to-Treat Set)	AEL002	- Same as Listing 16.2.7.2 - List only AESI events.	Same as Listing 16.2.7.2

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.7.9	Treatment Emergent Adverse Events Leading to Study Drug Discontinuation (Intention-to-Treat Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.2
Listing 16.2.7.10	Treatment Emergent Adverse Events Leading to Death (Intention-to-Treat Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.2
Listing 16.2.7.11	Post-Treatment Adverse Events (Intention-to-Treat Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.2
Listing 16.2.8.1	Urine Pregnancy Test (Intention-to-Treat Set)	LBL005	Remove columns “Childbearing potential” and “Test”	

16.3 Figures

Figure Number	Figure Title	Template Code	Notes	Footnotes/Source Listing Number
Figure 14.2.3.1	Time to First Re-Occlusion (Full Analysis Set)		- Y-axis should be "Probability of Re-Occlusion Free" (the curve starts at 1). - X-axis should be "Time (Days)" - Treatment arms to be presented in legend (CUSA-081, placebo, alteplase) - Display below the X-axis, the number of subjects at risk at 0, 5, 10, 15, 20, 25 and 30 days. - The censored subjects should be presented with a "+" on the curve.	Source: Table 14.2.3.1 Footnotes: [1] Only subjects with treatment success are included in the analysis. [2] Time to re-occlusion (Days) = (date of start of first re-occlusion – date of first treatment success + 1). If no re-occlusion the subject is censored to the CVAD removal or study discontinuation/completion date, whichever is the earliest. The time to first re-occlusion is derived only for subjects who have treatment success.