CLINICAL STUDY REPORT

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

EUDRACT No. / IND No.: 2019-002124-32 / 128551

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.: Final 1.0
Date: 12 April 2024

Chiesi Farmaceutici S.p.A.
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1. TITLE PAGE

Study Title:	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)
Product:	CUSA-081 (reteplase)
Pharmaceutical Form:	Sterile, white, lyophilized powder for intra-catheter instillation for restoration of function to CVADs following reconstitution and further dilution with Sterile Water for Injection, United States Pharmacopeia
Indication:	Restoration of function to CVADs
Development Phase of Study:	Phase 3
Study Start Date (First Subject First Visit):	12 February 2020
Study Completion Date (Last Subject Last Visit):	10 July 2023

"This study was conducted in compliance with the International Council for Harmonisation Good Clinical Research Practices (ICH E6), including the archiving of essential documents".

VERSION HISTORY

Version	Date	Change History
1.0	12 April 2024	First version

2. SYNOPSIS

Name of Company: Chiesi Farmaceutici S.p.A.	**Individual Study Table Referring to Part of the Dossier**	*(for National Authority Use only)*
Name of Finished Product: CUSA-081	**Volume:**	
Name of Active Ingredient: Reteplase	**Page:**	

Title of Study: 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)

Investigators: 94 Investigators in Argentina, Belgium, Brazil, the Czech Republic, Poland, Romania, Spain, and the USA

Study Centers: Multinational, 94 initiated centers (61 centers randomized subjects)

Publication (*Reference*): None

Studied Period:	**Phase of Development:**
First Subject First Visit: 12/FEB/2020 Last Subject Last Visit: 10/JUL/2023	Phase 3

Objectives:

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 was defined as restoration of CVAD functionality, measured as the ability to withdraw 3 mL of blood and infuse 5 mL of saline.

Secondary Objectives:

The secondary objectives of the study were as follows:

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.

Methodology *(Study Design):*

This was a phase 3, multinational, multicenter, prospective, randomized, double-blind, parallel-group, active- and placebo-controlled study. The study examined the ability of instillation(s) of CUSA-081 vs. placebo or alteplase to restore CVAD function in adult subjects with dysfunctional non-hemodialysis CVADs. Restoration of CVAD function was defined as the ability to both withdraw at least 3 mL of blood and infuse 5 mL of saline.

The study comprised a total of 2–3 visits: a screening visit, a treatment visit, and a follow-up assessment.

The screening visit took place on the calendar day preceding the treatment visit (Day 0) or on the day of the treatment visit itself (Day 1, Visit [V] 1). At screening, subjects were assessed according to the inclusion and exclusion criteria and were candidates for randomization if all eligibility criteria were met. A minimum of 841 eligible subjects were to be randomized in a 9:1:6 ratio to receive CUSA-081: placebo: alteplase, as shown in the table below.

Following randomization at V1 (Day 1), subjects received the first instillation of study drug (CUSA-081, placebo, or alteplase). If patency was not restored after 90 minutes following the first instillation, a second dose of study drug (the same drug as at first instillation) was administered. Assessment of CVAD function was done at multiple timepoints (at 30, 60, and 90 minutes after each instillation). Of note, catheters with multiple lumens or ports, as well as peripherally inserted central catheters (PICCs), were allowed. If multiple lumens of a multi-lumen CVAD were dysfunctional, the Investigator was to designate only one lumen for instillation of study drug and study assessments. To ensure that the same lumen was used for all study drug instillations and study assessments, the chosen lumen was documented and indicated using a study lumen tag. No other thrombolytics were to be used to treat other dysfunctional lumens of a multi-lumen CVAD during the treatment period (0–180 minutes on Day 1).

Treatment arm	Syringe 1[a]	Syringe 2[b]
A	CUSA-081	CUSA-081
B	Placebo	Placebo
C	Alteplase	Alteplase

[a] Syringe 1, which contained either CUSA-081 (reteplase 0.7 mg/2 mL), placebo (2 mL normal saline), or alteplase (2 mg/2 mL), was given at 0 minutes and assessed at 30, 60, and 90 minutes.
[b] Syringe 2, which contained a second dose of the same study drug as Syringe 1, was given, if needed, at 90 minutes and assessed at 120, 150, and 180 minutes.

A follow-up assessment (V2) was planned on Day 30 (±2 days) after treatment; this assessment could have been conducted in person or by telephone.

Note: The Sponsor issued an initial notification of an enrollment hold to participating study sites on 13 June 2023. On 05 July 2023, an official notification of early termination of study recruitment was issued to all participating sites. By this date, since the start of the READY 1 study in February 2020, just over half of the planned number of subjects had been randomized. As recruitment challenges were ongoing, it became clear that it would not be possible to complete the READY 1 study in a reasonable timeframe. Therefore, the Sponsor made the voluntary decision to terminate the study early.

Number of Subjects *(Planned and Analyzed)*:

It was planned to randomize a minimum of 841 subjects in a 9:1:6 ratio to receive CUSA-081: placebo: alteplase to achieve a minimum of 800 subjects completing the study (i.e., 450, 50, and 300 subjects with CUSA-081, placebo, and alteplase, respectively).

This number of subjects was not finally achieved owing to the early termination of the study (see note in the section above). The number of subjects analyzed is presented in the table below.

	CUSA-081	Placebo	Alteplase	Overall
Randomized, n	261	28	173	462
ITT, n	261	28	173	462
SAF, n	253	27	168	448
FAS, n	253	27	168	448
PP, n	228	23	152	403

FAS = Full analysis set; ITT = Intention-to-treat set; PP = Per-protocol set; SAF = Safety set.
n = Number of subjects in each set.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

Subjects had to meet all the following inclusion criteria to be eligible for enrollment into the study:

1. Inability to have 3 mL of blood withdrawn from the selected study catheter;
2. A single- or multi-lumen CVAD, implanted port, or PICC in place >24 hours and documented as previously being patent and functional;
3. Ability to designate one dysfunctional lumen of a multi-lumen catheter to be used throughout the study for both study drug instillation and assessment of CVAD function;
4. Male and non-pregnant female subjects 18 years or older (see note below);
5. Able to have fluids infused at the volume necessary to instill study drug into the CVAD (i.e., up to 2 mL);
6. Informed consent form signed and dated indicating that the subject had been informed of and agreed with all pertinent aspects of the study and was willing to comply with all study requirements and procedures.

Note: A urine pregnancy test was required for all females of childbearing potential. Females in natural or surgical menopause did not need to be tested for pregnancy. Natural menopause was defined as the permanent cessation of menstrual periods, determined retrospectively after a female had experienced 12 consecutive months of lack of menstruation (amenorrhea) without any other obvious pathological or physiological cause. Surgical menopause was defined as the removal of both ovaries (bilateral oophorectomy) before the natural menopause.

Exclusion Criteria:

The presence of any of the following criteria led to exclusion of the subject from study enrollment:

1. CVAD (any type) used for hemodialysis;
2. CVAD known to be dysfunctional for >48 hours;
3. Reasonable evidence of mechanical or non-thrombotic occlusion in the selected study catheter (e.g., catheter malposition or migration, sutures, kinks, or precipitates causing obstruction), radiographic assessment was not required;
4. Known or suspected catheter-related bloodstream infection;
5. Use of any intravenously administered fibrinolytic agent or anticoagulant (e.g., but not limited to, alteplase, tenecteplase, reteplase, urokinase, or heparin) within 24 hours prior to the treatment period (first instillation of study drug). Use of subcutaneous low molecular weight heparin, unfractionated heparin, or heparinoids for prophylaxis of thromboembolic events was allowed. Furthermore, the use of oral anticoagulants was allowed;
6. Known to be at high risk for bleeding events or embolic complications in the opinion of the Investigator, or had a known condition for which bleeding constituted a significant hazard (e.g., recent stroke, recent intracranial or intraspinal surgery or serious head trauma, intracranial neoplasm, arteriovenous malformation or aneurysm, known bleeding diathesis);
7. Uncontrolled hypertension (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg) at screening;
8. Clinically unstable in the opinion of the site Investigator;
9. Known to be pregnant or breastfeeding at screening;
10. Previously treated in this study (READY 1) or in study READY 2;
11. History of allergic reaction to reteplase, alteplase, or vial ingredients (excipients or diluents);
12. Use of any investigational drug or experimental medical device within 28 days prior to treatment; non-interventional observational studies participation was allowed;
13. Not mentally, socially, or otherwise able to complete the study assessments or not likely to survive beyond 30 days.

Test Product, Dose, and Mode of Administration, Batch Numbers:

Treatment Arm A: One or two instillations of CUSA-081 (reteplase), 0.7 mg/2 mL per instillation, was administered directly into the catheter lumen.

Campaign	Batch number	Expiry date
1	3827953	March 2020
2	3838672	March 2021
3	4090251	July 2021
4[a]	-	-
5	4356516	June 2022
6	4816865	February 2023
7	5087219	December 2023

[a] Only ancillary kits were provided to sites during campaign 4; since these kits did not contain study drug or products made by the Sponsor, no batch number is provided.

Duration of Treatment:

A maximum 180-minute treatment duration. Subjects received the first instillation of blinded study drug (one syringe of CUSA-081, placebo, or alteplase) into the catheter via the single lumen designated for the study. If patency was not restored after 90 minutes following the first instillation, a second dose of the same blinded study drug (the other syringe of CUSA-081, placebo, or alteplase) was administered.

Reference Therapy, Dose and Mode of Administration, Batch Numbers:

Treatment Arm B: One or two instillations of placebo, 2 mL of normal saline per instillation, was administered directly into the catheter lumen.

Campaign	Batch number	Expiry date
1	3827954	March 2020
2	3838675	March 2021
3	4090252	July 2021
4[a]	-	-
5	4356518	June 2022
6	4816867	February 2023
7	5087220	December 2023

[a] Only ancillary kits were provided to sites during campaign 4; since these kits did not contain study drug or products made by the Sponsor, no batch number is provided.

Treatment Arm C: One or two instillations of alteplase, 2 mg/2 mL per instillation, was administered directly into the catheter lumen.

Campaign	Batch number	Expiry date
1	3827955	March 2020
2	3838678	March 2021
3	4284248	July 2021
4[a]	-	-
5	4356519	June 2022
6	4816868	February 2023
7	5087222	December 2023

[a] Only ancillary kits were provided to sites during campaign 4; since these kits did not contain study drug or products made by the Sponsor, no batch number is provided.

Criteria for Evaluation:

Efficacy:

Primary Efficacy Variable:

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

Secondary Efficacy Variables:

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

Safety:

- Treatment-emergent adverse events (TEAEs), treatment-emergent adverse drug reactions (ADRs), serious TEAEs, serious treatment-emergent ADRs, TEAEs leading to study drug discontinuation, and TEAEs leading to death;
- Treatment-emergent adverse events of special interest (AESIs), which for this study included: 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, and catheter-related blood stream infection.

For each adverse event (AE) type, post-treatment events were summarized in addition to treatment-emergent events.

Statistical Methods:

The following analysis sets were used for analysis:

- Intention-to-treat set (ITT) defined as all randomized subjects regardless of whether they received treatment with study drug. The ITT was used for sensitivity analysis of the primary efficacy analyses;
- Safety set (SAF) defined as all randomized subjects who received at least one dose of study drug. The SAF was the primary analysis population for all safety analyses;
- Full analysis set (FAS) defined as all randomized subjects who received 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). The FAS was the primary analysis set for all efficacy analyses involving assessment of superiority;
- Per-protocol set (PP) defined as all subjects from the SAF without any important protocol deviations. The PP was used for sensitivity analysis of the primary efficacy analyses and for the non-inferiority analysis.

Efficacy Analysis:

Hierarchical Closed Testing Procedure

As described above, the primary objective of this study was 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.

The secondary objectives of the study were as follows:

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.

The hypotheses corresponding to the primary objective and the first four secondary objectives were tested following a hierarchical closed testing procedure to control the overall type I error rate to less than 5%.

The hypothesis testing started with the primary efficacy objective, then the relevant secondary efficacy objectives were tested, in the order listed above, until a null hypothesis was not rejected (i.e., a p-value >0.05 was observed for the superiority assessments, or the lower limit of the two-sided 95% confidence interval [CI] was ≤-10% for the non-inferiority assessment).

At each step of the procedure, no confirmatory claims were made unless the null hypotheses were rejected in all the preceding steps. If the null hypothesis was not rejected at any step, then statistical results related to the subsequent tests were considered exploratory and descriptive.

Primary Efficacy Variable:

The primary efficacy variable was the percentage of subjects who had treatment success following a single instillation of study drug (CUSA-081, placebo, or alteplase) with a dwell time up to 90 minutes.

The percentage of subjects with treatment success and two-sided 95% Wald CI was presented for each treatment group. Treatment effects were presented as the mean difference in proportions between treatments together with 95% Wald CI and p-value, based on a 2-sample Z test for proportions.

The primary efficacy variable was used to address several study objectives, as described below.

Superiority Hypotheses

For superiority hypotheses, the primary analysis was the analysis performed on the FAS. Analyses were repeated based on the ITT and PP as sensitivity analyses.

Superiority of CUSA-081 over placebo (**primary objective**, **primary efficacy analysis**) was demonstrated by a statistically significant difference (i.e., p-value <0.05) between treatments with a dwell time up to 90 minutes favoring CUSA-081.

Superiority of CUSA-081 over alteplase (**fourth secondary objective**) was demonstrated by a statistically significant difference (i.e., p-value <0.05) between treatments with a dwell time up to 90 minutes favoring CUSA-081, and by all null hypotheses having been rejected at previous steps in the hierarchical closed testing procedure.

Non-inferiority Hypothesis

For the non-inferiority hypothesis, the primary analysis was the analysis performed on the PP.

Non-inferiority of CUSA-081 to alteplase (**first secondary objective**) was demonstrated (or the null hypothesis was rejected) if the lower limit of the 95% CI for the mean difference in proportions between treatments was >-10%, and if the null hypothesis had been rejected at the previous step in the hierarchical closed testing procedure.

The superiority of alteplase vs. placebo in the rate of treatment success following a single administration of study drug with a dwell time up to 90 minutes was assessed as a test of assay sensitivity. This analysis was 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.

Sensitivity Analysis

Additional sensitivity analysis was performed on the primary efficacy variable using a logistic regression model with age (<18, ≥18–<65, ≥65–<85, ≥85 years) and region (USA, non-USA) as factors. The odds ratio for each treatment comparison and the corresponding 95% CI and p-value were presented.

Subgroup Analyses

The analysis of the primary efficacy variable was also performed on the FAS stratified by relevant factors (i.e., age, sex, body mass index, country, region, type of CVAD, number of lumens, where and by whom the CVAD was identified as dysfunctional, duration of CVAD dysfunction, race, and ethnicity).

Secondary Efficacy Variables:

Secondary efficacy variables related to the percentage of subjects with treatment success were analyzed based on the FAS (primary analysis), ITT, and PP.

- Percentage of subjects who had treatment success following a single instillation of study drug with a total dwell time up to 30 and 60 minutes was analyzed using the same method as used for analysis of superiority vs. placebo on the primary efficacy variable;
  - Superiority of CUSA-081 over placebo (**second secondary objective**) was demonstrated by a statistically significant difference (i.e., p-value <0.05) between treatments with a dwell time up to 60 minutes favoring CUSA-081, and by all null hypotheses having been rejected at previous steps in the hierarchical closed testing procedure;
- Percentage of subjects who had treatment success after up to two instillations of study drug with a total dwell time up to 120, 150, and 180 minutes was analyzed using the same method as used for analysis of superiority vs. placebo on the primary efficacy variable;
  - Superiority of CUSA-081 over placebo (**third secondary objective**) was demonstrated by a statistically significant difference (i.e., p-value <0.05) between treatments with a dwell time up to 180 minutes favoring CUSA-081, and by all null hypotheses having been rejected at previous steps in the hierarchical closed testing procedure;
- Rate of recurrent catheter dysfunction, defined as first re-occlusion within 30 days following treatment with study drug, was summarized by treatment group. The time to first re-occlusion was analyzed using the Kaplan-Meier method; the median, 25th and 75th percentiles, and 95% CI were presented. The estimated probability of being re-occlusion free at Day 30, and its 95% CI, was presented for each treatment group. A Kaplan-Meier plot was also presented. In addition, time to first re-occlusion was analyzed using a Cox proportional hazards model including treatment as a factor. Treatment effects were presented as a hazard ratio with the associated 95% Wald CI.

<u>Safety Analysis:</u>

The number and percentage of subjects who experienced at least one TEAE, serious TEAE, treatment-emergent ADR, serious treatment-emergent ADR, severe TEAE, TEAE leading to study drug discontinuation, treatment-emergent AESI, and TEAE leading to death, as well as the number of events, were summarized by treatment group.

The number and percentage of subjects with at least one AE, and the number of events, were summarized by system organ class (SOC) and preferred term (PT) according to Medical Dictionary for Regulatory Activities (Version 23.0) by treatment group for TEAEs, non-serious TEAEs, serious TEAEs, treatment-emergent ADRs, serious treatment-emergent ADRs, severe TEAEs, TEAEs leading to study drug discontinuation, and TEAEs leading to death.

The number and percentage of subjects with the most common non-serious TEAEs (reported in ≥5% of subjects with any treatment) were also summarized by SOC and PT by treatment group; the number of events was also included. The number and percentage of subjects with TEAEs were also summarized by SOC and PT and by maximum severity.

The number and percentage of subjects with at least one treatment-emergent AESI, the associated exact binomial 95% CI, and the number of events, were summarized by AESI category by treatment group. In addition, the number and percentage of subjects with at least one treatment-emergent AESI and the number of events, were summarized by AESI category and PT, by treatment group.

The above-mentioned analyses were repeated for post-treatment AEs.

Summary – Results:

Study Population:

In this study, 462 subjects were randomized: 261 to CUSA-081, 28 to placebo, and 173 to alteplase. Of those, 14 subjects were not treated and were therefore not included in the SAF/FAS. Approximately 10% of subjects included in the SAF/FAS had important protocol deviations that led to exclusion from the PP. The majority of randomized subjects completed the study with all treatments (90.0%, 82.1%, and 94.8% subjects with CUSA-081, placebo, and alteplase, respectively).

Demographic and baseline characteristics, CVAD history, and medical history of the subjects in the SAF were generally balanced between treatment groups. Overall, the vast majority of subjects were White (94.1%) with a prevalence of females (60.0%). The mean age was 60.7 years, with slightly more than half of the subjects aged <65 years (55.6%). Overall, just under half the subjects had an implanted port (46.0%), 32.6% had a central venous catheter, and 21.4% had a PICC. The most common indication for CVAD insertion was intravenous drug treatment (93.5%); however, several indications for insertion were possible for a single subject. The duration of CVAD dysfunction was short (median of 3 hours) and CVADs were mostly identified as dysfunctional by a healthcare provider.

Efficacy Results:

Hierarchical Closed Testing Procedure

Results of the testing of hypotheses corresponding to the primary objective and the first four secondary objectives were as follows.

Primary Objective

The percentage of subjects who had treatment success following a single instillation of study drug (CUSA-081 or placebo) with a dwell time up to 90 minutes in the FAS was higher with CUSA-081 (62.8%) than with placebo (33.3%). The mean difference in proportions (95% CI) between treatments was statistically significant in favor of CUSA-081 (29.51 [10.76; 48.26], p=0.003). The superiority of CUSA-081 over placebo in terms of the rate of treatment success following a single administration with a dwell time up to 90 minutes was therefore demonstrated.

Analyses of the primary objective in the ITT and PP showed similar results to the analysis in the FAS, as did the logistic regression sensitivity analysis in the FAS. The stratified analyses showed similar trends to those seen in the FAS overall and, for the treatment comparisons performed, the mean differences in proportions were always numerically in favor of CUSA-081 over placebo.

First Secondary Objective

The percentage of subjects who had treatment success following a single instillation of study drug (CUSA-081 or alteplase) with a dwell time up to 90 minutes in the PP was lower with CUSA-081 (66.7%) than with alteplase (77.0%). Non-inferiority of CUSA-081 relative to alteplase was not demonstrated, since the lower limit of the 95% CI for the mean difference in proportions between treatments was ≤-10%; the mean difference in proportions (95% CI) between treatments was -10.31 (-19.38; -1.24), p=0.030.

Since the null hypothesis related to the first secondary objective was not rejected, testing of the subsequent secondary objectives could not ensure preservation of the overall type I error rate. Consequently, based on the pre-specified hierarchical closed testing procedure, no formal testing of statistical significance could be performed for the second, third, and fourth secondary objectives and the analysis results for those objectives are presented with nominal p-values for descriptive purposes.

Of note, as part of this step in the procedure, the superiority of alteplase over placebo in terms of the rate of treatment success following a single administration with a dwell time up to 90 minutes was tested in the FAS and demonstrated: the mean difference in proportions (95% CI) between treatments was statistically significant in favor of alteplase (40.48 [21.49; 59.46], p<0.001); the assay was therefore considered to be appropriately sensitive.

Second Secondary Objective

The percentage of subjects who had treatment success following a single instillation of study drug (CUSA-081 or placebo) with a dwell time up to 60 minutes in the FAS was higher with CUSA-081 (53.8%) than with placebo (29.6%). The mean difference in proportions (95% CI) between treatments was statistically significant in favor of CUSA-081 (24.13 [5.84; 42.41], p=0.017).

Third Secondary Objective

The percentage of subjects who had treatment success following two instillations of study drug (CUSA-081 or placebo) with a dwell time up to 180 minutes in the FAS was higher with CUSA-081 (81.8%) than with placebo (40.7%). The mean difference in proportions (95% CI) between treatments was statistically significant in favor of CUSA-081 (41.08 [21.94; 60.21], p<0.001).

Fourth Secondary Objective

The percentage of subjects who had treatment success following a single instillation of study drug (CUSA-081 or alteplase) with a dwell time up to 90 minutes in the FAS was lower with CUSA-081 (62.8%) than with alteplase (73.8%). The mean difference in proportions (95% CI) between treatments was statistically significant in favor of alteplase (-10.96 [-19.89; -2.04], p=0.019).

Percentage of Subjects Who Had Treatment Success during the Study

In the FAS, the percentage of subjects who had treatment success following instillation of study drug with a dwell time up to 30 minutes was 34.8%, 22.2%, and 44.6% with CUSA-081, placebo, and alteplase, respectively. The percentage of subjects with treatment success increased successively at all subsequent timepoints up to 120 minutes with each study drug; the percentage increased again at 150 minutes and 180 minutes with both CUSA-081 and alteplase but plateaued with placebo. The percentage of subjects with treatment success from 60 minutes to 180 minutes ranged from 53.8% to 81.8% with CUSA-081, from 29.6% to 40.7% with placebo, and from 65.5% to 88.1% with alteplase.

In the FAS, a positive trend for a higher percentage of subjects with treatment success with CUSA-081 than with placebo was observed from the first CVAD assessment at 30 minutes until the end of the treatment period at 180 minutes, with statistically significant differences between treatments favoring CUSA-081 observed at each timepoint from 60 minutes onwards. A positive trend for a higher percentage of subjects with treatment success with alteplase than with CUSA-081 was observed from the first CVAD assessment at 30 minutes until the end of the treatment period at 180 minutes, with statistically significant differences between treatments favoring alteplase observed at each timepoint from 30 minutes up to and including 120 minutes. The percentage of subjects with treatment success was statistically significantly higher with alteplase than with placebo at all timepoints.

Analysis results in the PP were similar to the abovementioned analysis results in the FAS.

Rate of Recurrent Catheter Dysfunction within 30 Days following Treatment with Study Drug

The rate of recurrent catheter dysfunction within 30 days following treatment was low and similar between treatments: re-occlusion occurred in 17 (8.2%), 1 (9.1%), and 18 (12.2%) of those subjects in the FAS who had treatment success with CUSA-081, placebo, and alteplase, respectively.

Accordingly, the probability of being re-occlusion free at Day 30 (95% CI) was similar between treatments: 0.906 (0.852; 0.940) with CUSA-081, 0.909 (0.508; 0.987) with placebo, and 0.857 (0.782; 0.908) with alteplase.

The results of the Cox proportional hazards analysis showed that the time to first re-occlusion was not statistically significantly different for any treatment comparison.

Safety Results:

All subjects in the SAF received at least one dose of randomized study drug. If CVAD function was not restored after 90 minutes following the first instillation, a second dose of study drug (the same drug as at first instillation) was administered. In total, 88 (34.8%), 16 (59.3%), and 42 (25.0%) subjects received a second dose of study drug with CUSA-081, placebo, and alteplase, respectively. The overall number of subjects exposed to study drug decreased at each CVAD assessment, primarily because those subjects with treatment success exited the treatment algorithm.

Analysis of AEs was performed on TEAEs, defined as AEs that started on or after the first instillation of study drug up to the end of the treatment period, and post-treatment AEs, defined as AEs with an onset after the end of the treatment period.

The overall incidence of TEAEs was low: 10 TEAEs were reported in 8 (3.2%) subjects with CUSA-081 and 1 TEAE was reported in 1 (0.6%) subject with alteplase; no TEAEs were reported with placebo. TEAEs by PT reported in >1 subject were device breakage, reported in 3 (1.2%) subjects with CUSA-081 (all 3 TEAEs led to study drug discontinuation), and decreased appetite, reported in 2 (0.8%) subjects with CUSA-081. Most TEAEs were mild or moderate in intensity and the majority were reported as 'not resolved' by the end of each subject's study participation. None of the TEAEs were considered related to the study drug, i.e., none were treatment-emergent ADRs, none led to death, none were serious, and none were treatment-emergent AESIs.

The percentage of subjects reported with post-treatment AEs was higher with placebo (10 [37.0%] subjects had 30 post-treatment AEs) than with CUSA-081 and alteplase (41 [16.2%] subjects had 91 post-treatment AEs and 25 [14.9%] subjects had 39 post-treatment AEs, respectively). Most post-treatment AEs were mild or moderate in intensity, and more than half were reported as 'resolved' or 'resolving' by the end of each subject's study participation. In line with post-treatment AEs overall, the percentage of subjects reported with severe post-treatment AEs was higher with placebo (4 [14.8%] subjects had 5 severe post-treatment AEs) than with CUSA-081 and alteplase (13 [5.1%] subjects had 18 severe post-treatment AEs and 5 [3.0%] subjects had 5 severe post-treatment AEs, respectively). Post-treatment AEs were most commonly reported from the Gastrointestinal Disorders SOC (in 10 [4.0%], 3 [11.1%], and 8 [4.8%] subjects with CUSA-081, placebo, and alteplase, respectively) and the Infections and Infestations SOC (in 12 [4.7%], 4 [14.8%], and 4 [2.4%] subjects with CUSA-081, placebo, and alteplase, respectively). Post-treatment AEs by PT reported in >2 subjects with any treatment were: diarrhoea, pneumonia., neutropenia, and axillary vein thrombosis.

The overall incidence of post-treatment ADRs was very low: 1 post-treatment ADR (PT: hypersensitivity) was reported in 1 (0.4%) subject with CUSA-081 and 1 post-treatment ADR (PT: haematoma) was reported in 1 (0.6%) subject with alteplase. Both post-treatment ADRs were non-serious, were of mild/moderate intensity, and were reported as 'resolved' before the end of each subject's study participation.

During the study period, 9 subjects had post-treatment AEs leading to death: 6 (2.4%) subjects with CUSA-081, 2 (7.4%) subjects with placebo, and 1 (0.6%) subject with alteplase. None of the post-treatment AEs leading to death were considered related to the study drug.

The percentage of subjects reported with serious post-treatment AEs was higher with placebo (4 [14.8%] subjects had 7 serious post-treatment AEs) than with CUSA-081 and alteplase (20 [7.9%] subjects had 29 serious post-treatment AEs and 10 [6.0%] subjects had 12 serious post-treatment AEs, respectively). Serious post-treatment AEs by PT reported in >1 subject with any treatment were: adenocarcinoma of colon, axillary vein thrombosis, deep vein thrombosis, and pneumonia, each in 2 (0.8%) subjects with CUSA-081. Overall, 9 of the 48 serious post-treatment AEs were fatal (see above). Of the remaining events, approximately half were reported as 'not resolved' by the end of the subject's study participation with CUSA-081 and placebo, whereas the majority were reported as 'resolved' or 'resolving' with alteplase. None of the serious post-treatment AEs were considered related to the study drug.

One post-treatment AE was reported as leading to study drug discontinuation in 1 (0.4%) subject with CUSA-081; this event also led to death and was included in the total above.

Post-treatment AESIs were reported in 10 (4.0%) subjects with CUSA-081, 1 (3.7%) subject with placebo, and 2 (1.2%) subjects with alteplase; none of the events were considered related to the study drug. Most

events were mild or moderate in intensity, were serious, and were reported as 'not resolved' by the end of the subject's study participation. With CUSA-081, 1 serious, severe-intensity post-treatment AESI (PT: large intestinal haemorrhage) was fatal.

Conclusion:

This phase 3 randomized, active- and placebo-controlled study showed that, in adult subjects with suspected thrombotic obstruction of non-hemodialysis CVAD, dysfunctional for ≤48 hours, treatment with CUSA-081 was superior to placebo in terms of providing a statistically significantly higher rate of treatment success (restoration of function) following a single administration with a dwell time up to 90 minutes. The advantage of CUSA-081 over placebo was evident throughout the 180-minute treatment period; however, no formal testing of statistical significance could be performed for other timepoints as the non-inferiority of CUSA-081 vs. alteplase in terms rate of treatment success following a single administration with a dwell time up to 90 minutes was not demonstrated in a preceding step in the hierarchical testing procedure. Alteplase, already approved for the management of occluded CVADs, had a consistently higher rate of treatment success compared to CUSA-081. All study drugs were well tolerated, and no particular safety concerns were raised for CUSA-081 compared to active or placebo controls.

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