

Efficacy and safety of CUSA-081 in the restoration of central venous access device functionality (READY-1 study)

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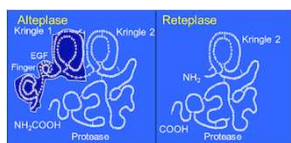
Background

Introduction

- Dysfunction of Central Venous Access Catheters (CVADs) is a serious complication that causes delay in therapy administration, prolonged hospitalization, patient discomfort and increased costs
- Thrombotic occlusion is the most frequent cause of CVAD dysfunction occurring in up to 1/3 of patients within 2 years
- Thrombolytic agents successfully restore the patency of occluded CVADs in up to 80% of cases, and represent a time- and cost-effective treatment, indicated by the guidelines as the preferable alternative to CVAD replacement¹
- Currently, the tissue plasminogen activator (t-PA) alteplase³ is the only thrombolytic agent available on the US market approved by the FDA for restoration of function of CVADs

Reteplase for treatment of dysfunctional CVADs

- Reteplase is a variant of the t-PA as it differs from alteplase lacking the fibrinogen-like finger domain that confers high fibrin binding affinity (Fig. 1)



- Compared to alteplase, Reteplase binds less tightly to fibrin, thus penetrating deeper in the clot and potentially being more rapid in lysing clots²
- Preliminary studies found that reteplase is effective at restoring CVAD patency at the dose of 0.4 units as early as 30 min after within-catheter instillation³⁻⁶
- Chiesi has defined a clinical development program, namely READY, composed of 2 phase-3 studies and 1 pediatric study with the aim to develop reteplase for the restoration of function of dysfunctional CVADs
- The formulation of reteplase under development for this indication is CUSA-081 (0.4 units of reteplase/2ml)

READY-1: Study Design

- READY 1 is a phase III, multicenter, randomized, double-blind, parallel-group, active- and placebo-controlled study examining the use of reteplase versus placebo or alteplase for the treatment of dysfunctional non-hemodialysis CVADs
- It is sponsored by Chiesi Farmaceutici S.p.A. (NCT03594175)
- It plans to randomize 841 adults across 100 sites in 8 countries in Europe, South, and North America (Fig. 2)



Figure 2. Study site countries for READY-1 Study

Key inclusion criteria

- Implanted CVAD (single or multi-lumen, implanted port, or peripherally inserted central catheter) in place for > 24 hours and documented as previously patent.
- Inability to have 3 ml of blood withdrawn.

Key exclusion criteria

- CVAD used for hemodialysis.
- CVAD known to be dysfunctional for > 48 hours.
- Known non-thrombotic occlusion.
- Known or suspected catheter related blood stream infection.
- Known high risk of bleeding or embolic complication.

Randomization

- Subjects will be randomized after screening and eligibility confirmation with an allocation ratio of 9 to CUSA-081, 1 to placebo, 6 to alteplase (Fig. 3)

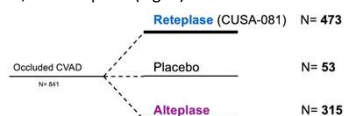


Figure 3. Randomization plan for READY-1

READY-1: Study Methodology

Blinded Study Drug

- Subjects may receive up to 2 intra-catheter instillations of the blinded study drug at Treatment Visit (Fig. 4)

Treatment Arm	Syringe 1 given at visit 0 assessed at minutes 30, 60, 90	Syringe 2 given, if needed, at min 90, assessed at minutes 120, 150, 180
	CUSA-081 0.70 mg (0.4 unit) / 2 mL 2 mL Normal Saline (0.9%)	CUSA-081 0.70 mg (0.4 unit) / 2 mL 2 mL Normal Saline (0.9%)
A		
B	Placebo	Placebo
C	Alteplase 2mg in 2 mL	Alteplase 2mg in 2 mL

Figure 4. Investigational drug dosing and sequence

Study Plan and Evaluation of CVAD patency (Fig. 5)

- Restoration of CVAD patency is defined as the ability to have 3 ml of blood withdrawn and 5 ml of saline infused from the selected and dysfunctional CVAD lumen
- CVAD function will be assessed 30, 60, and 90 min following the first administration of the study drug. If function is not restored at 90 min, a second administration of blinded study drug will follow and CVAD patency will be assessed after 30, 60, and 90 min after the second administration
- At 180 min follow-up, if treatment success is not achieved, the subject may receive the standard of care for CVAD dysfunction

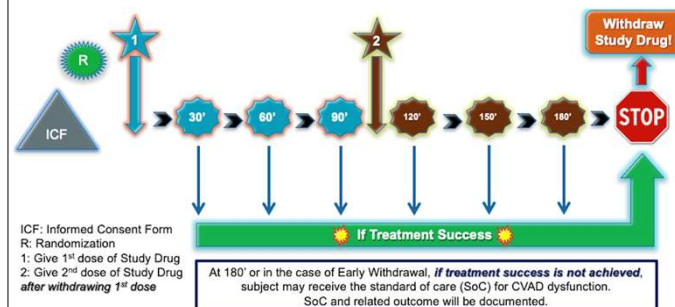


Figure 5. Study Plan and Evaluation of CVAD Patency for READY-1 Study

READY-1: Study Objectives

Primary efficacy endpoint

- 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 min.

Secondary hierarchical endpoints

- To demonstrate non-inferiority of CUSA-081 vs. alteplase (dwell time up to 90 min).
- To demonstrate superiority of CUSA-081 vs. placebo (dwell time up to 60 min).
- To demonstrate superiority of CUSA-081 vs. placebo (dwell time up to 180 min).
- To demonstrate superiority of CUSA-081 vs. alteplase (dwell time up to 90 min).
- To evaluate the safety and tolerability of CUSA-081.
- To evaluate the rate of recurrent catheter dysfunction defined as first re-occlusion within 30 days following administration of CUSA-081.

Sample size calculation

For the primary endpoint, the study has >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, the study has 87% power at the 2.5% significance level (that is by using one-sided 97.5% confidence intervals with a non-inferiority margin of -10%), assuming an equal response rate of 75% in the control arm (alteplase) and in the active (CUSA-081) arm.

References

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