Effect of Endovascular Treatment Alone Versus Intravenous Alteplase Plus Endovascular Treatment on Functional Independence in Patients with Acute Ischemic Stroke: The DEVT Randomized Clinical Trial

Statistical Analysis Plan

This supplement contains the Original/Final Statistical Analysis Plan (SAP). There were no substantive amendments between the Original SAP and the Final SAP which was finalized prior to database lock.

Note: personal identifying information has been redacted from the SAP documents to comply with international privacy legislation.

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SIGNATURE PAGE

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Contents

1. Overview

This is a multicenter, prospective, randomized, open-label, blinded endpoint evaluation study designed to evaluate the efficacy and safety of endovascular treatment alone versus intravenous alteplase plus endovascular treatment for acute ischemic stroke patient with large artery occlusion in the anterior circulation both with eligible for treatment of intravenous alteplase.

Up to 970 patients in total of all five interims will be enrolled over three years from approximately 35 hospitals in China. Each site will be limited to a maximum enrollment of about 194 patients (~20% of total enrollment).

Patients will be randomized 1:1 to receive one of the following:

- Intravenous alteplase plus endovascular treatment (control);
- Endovascular treatment alone(test).

This Statistical Analysis Plan will provide details to further elaborate statistical methods as outlined in the protocol and will describe analysis conventions. The Statistical Analysis Plan will be signed off prior to database lock.

2. Study Success Criteria

The study will be considered a success if the primary efficacy non-inferiority criterion is met.

Primary Effectiveness Non-Inferiority: The proportion of patients in the primary-thrombectomy group who achieve functional independence (defined as a modified Rankin scale score of 0 to 2) at 90-day follow-up is no more than 10% below that proportion of patients in the bridging-therapy group.

Group Sequential Analysis: Interim analyses will be performed when 194 subjects from the intention-to-treat population have provided evaluable primary effectiveness data and then after each subsequent 194 subjects, to a maximum of 970 subjects with evaluable data (i.e. 194, 388, 582, 776, and 970). Table 3 provides the group sequential boundaries including minimum acceptable statistical criteria at each look (including the final analysis).

Additional analyses conducted for secondary endpoints and subgroups will be presented.

3. Sample Size

Up to 194 patients in each interim analysis and 970 in total of five interim analyses are to be randomized in a 1:1 ratio to bridging-therapy group or primary-thrombectomy group.

3.1. Non-inferiority Margin Evaluation

The primary efficacy analysis will be performed by comparing the lower bound of a two-sided, 95% confidence interval, calculated using normal approximation, for the observed difference between endovascular treatment alone and intravenous alteplase plus endovascular treatment on the percentage of subjects that have functional independence with a pre-specified non-inferiority margin Δ (-10%). According to the previous study data[1-4], we hypothesis that the 90-day follow-up functional independence proportion of patients in the bridging-therapy group is 43%. We assumed that the functional independence of primary-thrombectomy group should not be less than that of bridging-therapy group of MR CLEAN trial which indicated that functional independence proportion is about 33%[4]. Therefore, the clinically relevant non-inferiority margin Δ is estimated to be -10%. Should the lower limit of this difference be > -10%, it can be concluded that the endovascular treatment alone is non-inferior to intravenous alteplase plus endovascular treatment with respect to the primary efficacy measure.

3.2. Effectiveness Sample Size Evaluation

The sample size calculations assume that 43% of intravenous alteplase plus endovascular treatment patients

achieve functional independence at 90 days and 43% of endovascular treatment alone patients achieve functional independence at 90 days. The clinically relevant non-inferiority margin Δ was -10.0%. A group-sequential test strategy was designed to have reasonable chances of stopping as early as possible, either because of efficacy or safety reasons. Sample size and power are computed incorporating a five-look group-sequential analysis plan with a two-sided α at 0.05, 918 cases provide 80% power for testing the primary hypothesis of this trial; assuming the attrition rate is 5% for the primary end-point, the total sample size is up to 970. The evaluable sample size is 194 in each interim analysis and 970 in total of all five interim analyses. Therefore, in each interim analysis, 97 cases should be enrolled in each treatment group. PASS 15.0 (NCSS, LLC. Kaysville, Utah, USA) was used to calculate the sample size. See details in Table 1, Table 2, Table 3, Figure 1, and Figure 2.

Table 1. Effectiveness Sample Size Parameters

Parameters	Value
Bridging-Therapy Proportion	0.43
Primary-Thrombectomy Proportion	0.43
Group Allocation (Bridging-Therapy : Primary-Thrombectomy)	1:1
Test Type	Z-Test (Unpooled)
Higher Proportions Are	Better
Simulations	5000
Power	80%
Alpha	0.025
Number of Sides	1
Non-Inferiority Difference	-0.10
Specification of Looks and Boundaries	Simple
Number of Equally Spaced Looks	5
Alpha Spending Function	Pocock Analog
Type of Futility Boundary	None
Estimated Attrition	5%

Table 2. Accumulated Information Details

Look	Accumulated Information	Accumulated Sample Size		
	Percent	Bridging-therapy group	Primary-thrombectomy group	Total
1	20.0	97	97	194
2	40.0	194	194	388
3	60.0	291	291	582
4	80.0	388	388	776
5	100.0	485	485	970

Table 3. Boundaries

Look	Significance Boundary	
	Z-value Scale	P-Value Scale
1	2.35826	0.00918
2	2.45230	0.00710
3	2.35290	0.00931

Look	Significance Boundary	
4	2.41629	0.00784
5	2.36354	0.00905

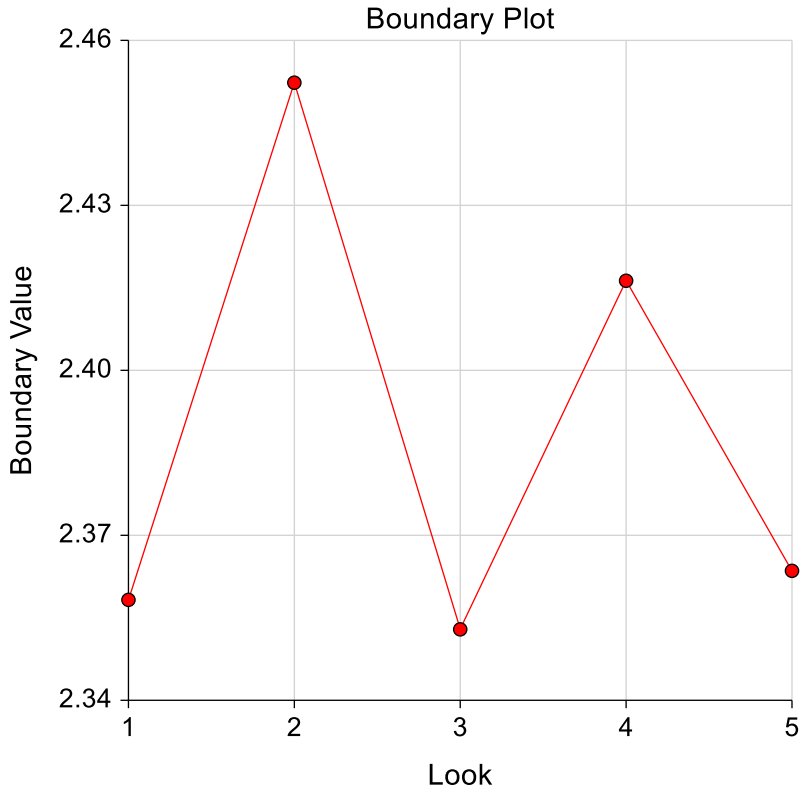

Figure 1. Boundary Plot - Z-Value

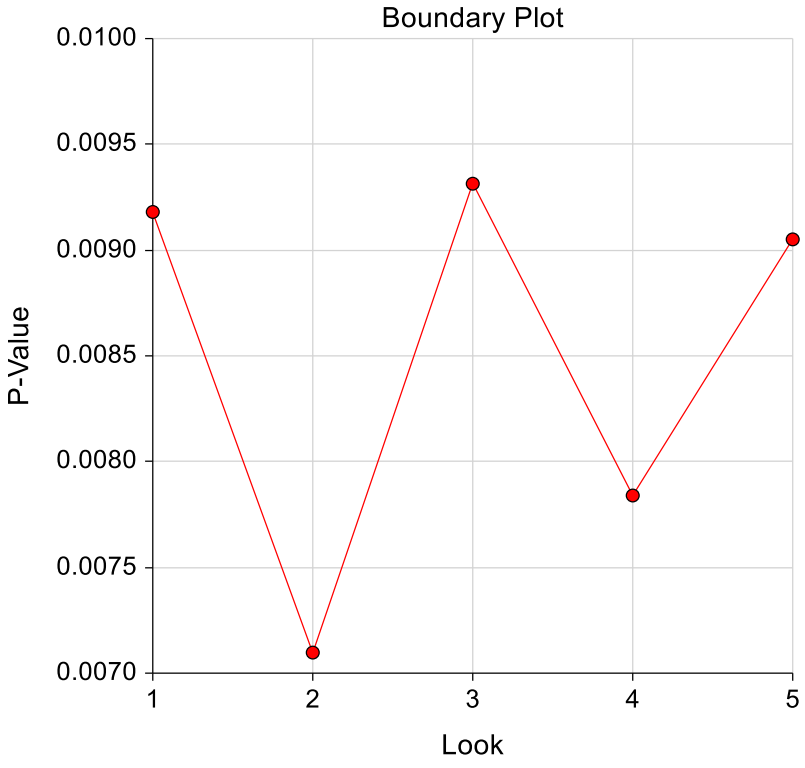

Figure 2. Boundary Plot - P-Value

3.3. Randomization and Allocation Concealment Methods

Subjects who are eligible based on inclusion and exclusion criteria and have had all pre- randomization screening procedures performed will be randomized by center in a 1:1 ratio to one of following two treatment groups:

- Intravenous alteplase plus endovascular treatment (bridging-therapy, control);
- Endovascular treatment alone (primary-thrombectomy, test).

Randomization occurs immediately after baseline (at the endovascular treatment institution) CT/MR brain imaging and CT/MR angiography via a real-time, internet-based randomization method. The randomization was stratified by participating centers.

3.4. Blinding

The investigators, and center study personnel will not be blinded to each patient's randomized treatment group throughout the course of the study. The study subjects, clinical data assessors and collectors, and the Independent Imaging Core Laboratory will be blinded to treatment assignment.

4. Interim Analysis

We desired a maximum of 5 interim analyses when approximately 20, 40, 60, 80, and 100% of the total sample size finish the follow-up, monitoring and data cleaning processes. A group-sequential test strategy was designed to have reasonable chances of stopping as early as possible, either because of efficacy or safety reasons. See details in Table 2, Table 3, Figure 1, and Figure 2.

5. Analysis Populations

All primary, secondary effectiveness, and safety endpoints will be performed for both the intention-to-treat population and per-protocol population. Patients who withdraw informed consent immediately after randomization and are not to receive any treatment should be excluded from all analysis populations.

5.1. Intention-to-treat set

The intention-to-treat population will consist of all patients who signed the informed consent and are randomized in the study. The data from the intention-to-treat population will be analyzed by the treatment group assignment given at the time of randomization, even if the subject does not receive the correct treatment, or does not follow the protocol until completion. All randomized patients will be followed and assessed for 90 days post-procedure, even when no intravenous thrombolysis or endovascular treatment is performed.

5.2. Per-protocol set

For the per-protocol analysis, only patients who actually received the assigned treatment and do not have major protocol violations will be included.

Patients without intracranial large vessel occlusion, not meeting the inclusion criteria, not receiving standard dose alteplase in the alteplase-plus-intervention group, cross over to the alternative treatment will be removed from the per-protocol analysis.

5.3. Safety set

For the safety analysis, patients will be analyzed according to the treatment they received.

Any randomized subjects that did not meet the inclusion criteria, did not accept the relevant treatment, and did

not have any evaluation results should be excluded from per-protocol analysis. The reason(s) for their exclusion from the study will be recorded. Listings will be provided for these patients, and they will be discussed in the clinical report.

6. Statistical Methods

Summary tables (descriptive statistics and/or frequency tables) will be provided for all baseline variables, effectiveness variables, and safety variables, as appropriate. Continuous variables will be summarized with descriptive statistics (n, mean, standard deviation, median, and interquartile). Frequency counts and percentage of patients within each category will be provided for categorical data.

The software used for all statistical analyses will be SAS® (SAS Institute, Inc.) version 9.3 or higher. Figures were drawn using MS Excel software 2019 (Microsoft).

7. Baseline Characteristics

Baseline data will be analyzed to assess the comparability of treatment groups. Baseline data including, but not limited to demographics, clinical characteristics, baseline vessel characteristics, and imaging characteristics will be summarized using descriptive statistics. Differences between the treatment groups and their 95% confidence intervals will be calculated. Statistical testing will be performed as appropriate.

8. Patient Disposition

The number of patients for each of the following categories will be summarized.

- Assessed patients
- Patients completing the study and not completing the study
- Patients included in the intention-to-treat population
- Patients included in the per-protocol population
- Patients included in the safety population

9. Effectiveness Analysis

9.1. Primary Effectiveness Analysis

The primary effectiveness variable is the proportion of patients with a modified Rankin scale score of 0 to 2 (functional independence) at 90 days. The proportion of patients in each group will be calculated based on this criterion. To ensure the reliability, evaluability, and traceability of the modified Rankin scale score, we keep patients' video or voice recording of follow-up at 90 days. The primary functional outcome was centrally assessed by two independent certified neurologists in a blinded manner by the use of the video or voice recording. If video or voice recording is not available, the outcomes determined by the local investigator blindly in person are used as default. Disagreements were resolved by consensus. Electronic Data Capture System did not reveal the group assignment and patients were instructed not to reveal any relevant information that could potentially lead to disclosing their treatment group to the assessors. All recordings will be provided as supplementary material along with the main text.

The primary effectiveness analysis will be the difference between bridging-therapy group (control) and primary-thrombectomy group (test). A binomial comparison will be used to test the one-sided null hypothesis that the difference in proportions is less than or equal to -0.10 (H0: $P_{test} - P_{control} \leq -0.10$) versus the alternative (H1: $P_{test} - P_{control} > -0.10$), where $P_{control}$ and P_{test} are the proportions of functional independence for bridging-therapy (intravenous alteplase plus endovascular treatment) and primary-thrombectomy (endovascular treatment alone), respectively. This is equivalent to evaluating that the lower bound of the two-sided 95% confidence interval for the difference is above -0.10. The effect variable of this endpoint will be analyzed using a

logistic regression model with the following terms in the model: age, baseline NIHSS score, baseline ASPECTS, stroke onset to randomization time, and occlusion site. The primary effectiveness analysis will be performed on the intention-to-treat population. The analysis based on the per-protocol population will be considered as supportive. Statistical analysis will be performed on the SAS 9.3 or higher system.

9.2. Secondary Effectiveness Analysis

The secondary effectiveness variables:

- Proportion of modified Rankin scale score 0 to 1 at 90 days;
- Shift in the distribution of modified Rankin scale scores at 90 days in endovascular treatment alone versus intravenous alteplase plus endovascular treatment (ordinal shift analysis);
- Successful recanalization proportion immediate after endovascular treatment. Successful recanalization is defined as an expanded Thrombolysis In Cerebral Infarction (eTICI) score of 2b (substantial reperfusion), 2c (near-complete perfusion) or 3 (complete reperfusion) in the post-procedure angiography;[5]
- Vessel recanalization rate evaluated by CT or MR angiography within 48 hours;
- The change of the National Institutes of Health Stroke Scale score at 24 hours from baseline;
- The change of the National Institutes of Health Stroke Scale score at 5-7 days or discharge if earlier from baseline;
- European Quality Five-Dimension Five-Level scale score at 90 days.

Continuous variables will be summarized with descriptive statistics (n, mean, standard deviation, median, and interquartile). Frequency counts and percentage of patients within each category will be provided for categorical data. Estimates of the treatment differences and their 95% confidence intervals will be calculated. Subject rates will be compared between treatment groups with Chi-square test or Fisher's exact test. These endpoints will be analyzed using a logistic, ordinal logistic, or linear regression model as appropriate. The adjusted odds ratio, common odds ratio and beta coefficient were estimated by taking the following variables into account: age, baseline NIHSS score, baseline ASPECTS, stroke onset to randomization time, and occlusion site.

9.3. Handling of Multiplicity

There will be no adjustment for multiple comparisons between intravenous alteplase plus endovascular treatment versus endovascular treatment alone on the primary effectiveness variable since the primary comparison is specified in the protocol. All other comparisons will be considered secondary analyses and will be adjusted using the Bonferroni correction.

9.4. Effectiveness Subgroup Analysis

To evaluate the impact of baseline conditions on treatment effect, subgroup analyses will be performed for the primary effectiveness variable, modified Rankin scale score 0 to 2. The subgroups below will be used for these analyses:

(1) Age (< median or ≥ median, years old)
(2) Sex (Female or Male)
(3) Baseline NIHSS score (< median or ≥ median)
(4) Baseline ASPECTS (< median or ≥ median)
(5) Stroke etiology (large artery atherosclerosis, cardioembolism, or others)
(6) Site of occlusion (intracranial internal carotid artery or not)
(7) Onset to randomization time (< median or ≥ median, minutes)

The subgroup analysis will be conducted using a logistic regression with terms of treatment group and

treatment-by-subgroup interaction. The primary statistical inference is the treatment- by-subgroup interaction, which is tested at the significance level of 0.100. These analyses will be performed on the intention-to-treat population. When the treatment-by-subgroup interaction is statistically significant ($P \leq 0.100$) for a specific subgroup, the treatment group differences will be evaluated within each stratum of that subgroup.

10. Safety Analysis

10.1. Primary Safety Analysis

The primary safety endpoint is the proportion of patients with symptomatic intracerebral hemorrhage (SICH) within 48 hours. ICH will be evaluated according to the Heidelberg Bleeding Classification.[6] SICH was diagnosed if the new observed ICH was associated with any of the following conditions: 1) NIHSS score increased more than 4 points than that immediately before worsening; 2) NIHSS score increased more than 2 points in one category; 3) Deterioration led to intubation, hemicraniectomy, external ventricular drain placement or any other major interventions. Additionally, the symptom deteriorations could not be explained by causes other than the observed ICH;

The proportion of patients in each group who experience a safety event based on these criteria will be calculated. The Clinical Events Committee/Data Safety Monitoring Board (CEC/DSMB) data supersede the investigator-reported data in all SICH.

The primary null hypothesis for safety in this study is that there is no difference in SICH rates. This null hypothesis will be tested against the alternative hypothesis that there is a difference between the two groups. The null hypothesis will be rejected at the two-sided significance level of $\alpha = 0.05$. Frequency counts and percentage of patients within each category will be provided for categorical data. Estimates of the treatment differences and their 95% confidence intervals will be calculated. The primary analysis is an analysis of all patients according to treatment received. Subject rates will be compared between treatment groups with Chi-square test or Fisher's exact test.

10.2. Secondary Safety Analysis

The secondary safety variables:

- Mortality at 90 days
- Procedure-related complications such as arterial perforation, arterial dissection, and embolization in previously uninvolved vascular territory

The proportion of patients in each group who meet the safety endpoint based on this criterion will be calculated.

The CEC/DSMB data supersede the investigator-reported data in all analyses. Frequency counts and percentage of patients within each category will be provided. Estimates of the treatment differences and their 95% confidence intervals will be calculated. Subject rates will be compared between treatment groups with Chi-square test or Fisher's exact test.

10.3. Analysis of Adverse Events

The frequencies and incidences of Adverse events occurring in subjects in the intervention-alone and bridging-therapy groups will be summarized within treatment group by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC).

Tabulations of adverse events will be presented with descriptive statistics at baseline hospitalization and follow-up visits. Adverse events will be categorized. Adverse event incidence rates will be summarized by category and severity of the adverse event. Each subject will be counted only once within a category by using the adverse event with the highest severity within each category.

All information pertaining to adverse events noted during the study will be listed by subject, detailing verbatim given by the investigator, category, date of onset, date of resolution, causality and severity. The onset of adverse events will also be shown relative (in number of days) to the day of procedure.
A tabulation of Serious Adverse Events will be provided by subject.
The specific categories analyzed will be those that are reported by at least three (3) percent of the patients.
The CEC/DSMB adjudicated data supersedes the investigator reported data in all analyses of adverse events.

10.4. Handling of Multiplicity

All safety variable comparisons between intravenous alteplase plus endovascular treatment versus endovascular treatment alone will be considered secondary analyses and will be adjusted using the Bonferroni correction.

10.5. Analysis of Deaths

The Kaplan-Meier product-limit method will be the primary method utilized to assess the mortality. With the date of procedure set at day 0, any death occurring on or before calendar day 90 will be counted as a death. If clinical assessment is missing for a patient who has not died, the patient will be censored at the last follow-up date. Patients who are alive at day 90 will be censored at day 90. The log-rank test will be used to compare the groups. This comparison weights earlier and later differences equally. The time to death will be plotted with confidence intervals at monthly intervals.

Additionally, the death data will be presented as 90-day binary deaths. The number of deaths will be presented for each group.

11. Pooling Across Centers

The clinical study will be conducted under a common protocol for each investigational center with the intention of pooling the data for analysis. Every effort will be made to promote consistency in study execution at each investigational center. Analyses will be presented using data pooled across centers.

Because the trial adopts a competitive recruitment approach, the number of participating centers is about 40 and the number of cases in each center may be small, and all centers share a random sequence table, the stratified analysis is not performed by center, and the center effect is not evaluated.

12. Lost to Follow-Up and Missing Data

For sensitivity purposes, the following additional analyses will be conducted:

- Analyze only patients with complete primary endpoint data.
- The missing values of age, baseline NIHSS score, baseline ASPECTS, stroke onset to randomization time, and occlusion site which will be included in multivariable regression analysis are imputed with multiple imputation by fully conditional specification regression for continuous variables or by fully conditional specification logistic regression for binary and ordinal variables.
- For subjects missing data for 90-day follow-up, missing values will be imputed by assuming the missing modified Rankin scale score at 90-day to be unfavorable. If the patient is known to be alive, we will impute a score of 5. Otherwise, we will impute a score of 6.

13. Committees

13.1. Clinical Events Committee/Data Safety Monitoring Board (CEC/DSMB)

A CEC/DSMB will adjudicate serious adverse events for causality and attribution.

13.2. Imaging Core Laboratory

Centralized imaging core laboratories will be used in this trial to provide consistent assessment of all the images. CT/MR and angiographic images will be independently reviewed by two independent central imaging core laboratories respectively. The Imaging Core Laboratory will be blinded to treatment allocation.

14. Changed to Planned Analyses

All changes to the statistical analysis plan will be documented in a revised statistical analysis plan or the clinical study report.

15. References

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4. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372:11-20.

5. Almekhlafi MA, Mishra S, Desai JA, et al. Not all "successful" angiographic reperfusion patients are an equal validation of a modified TICI scoring system. Interv Neuroradiol 2014;20:21-7.

6. von Kummer R, Broderick JP, Campbell BC, et al. The Heidelberg Bleeding Classification: Classification of Bleeding Events After Ischemic Stroke and Reperfusion Therapy. Stroke; a journal of cerebral circulation 2015;46:2981-6.