Cover Page

Protocol Title	A multicenter, open label, prospective, randomized study of the MYNXGRIP Vascular Closure Device in subjects with diagnostic or interventional endovascular procedures (PANDA Study)
NCT Number	NCT03923387
Version Number and Date of SAP	V1.0, 25-Jun-2019

Response to Clinicaltrials.gov Reviewer Comments

Reviewer Comments:

The Document Type or Document Date appear inconsistent with information in an uploaded study document.

Information in the uploaded Statistical Analysis Plan PDF/A document seems to suggest that it was last updated on a date different from June 25, 2019. The document has different dates on the cover page and the header (e.g., "08 Feb 2021", "22 Oct 2024"). Note that the Document Date is defined in the Results Data Element Definitions (https://prsinfo.clinicaltrials.gov/results_definitions.html) as "[t]he date on which the uploaded document was most recently updated and, if needed, approved by a human subjects protection review board." Please review and update, as needed, to address the inconsistency.

Cordis' Response:

Report
Clinical
Clinical Study
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PANDA Study Clinical Study Report 08Feb2021

08 Feb 2021 is the date of the CSR. This SAP is a copy from the CSR as it was included as an appendix to the CSR.

100637155 | Rev: 1
Released: 22 Oct 2024
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22 Oct 2024 is when the CSR was released in Cordis's document control system.

Kun Tuo Medical Research and Development (Beijing) Co., Ltd.

P17-0005
Statistical Analysis Plan

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Statistical Analysis Plan

P17-0005

A Multicenter, Open Label, Prospective, Randomized Study of the MynxGrip Vascular Closure Device in Subjects With Diagnostic or Interventional Endovascular Procedures (PANDA Study)

Author: Chen Ridong
Version No. and Date: 1.0, Jun. 25, 2019

25 Jun 2019 is the correct date for SAP, Version 1.0.

Statistical Analysis Plan

P17-0005

A Multicenter, Open Label, Prospective, Randomized Study of the MynxGrip Vascular Closure Device in Subjects With Diagnostic or Interventional Endovascular Procedures (PANDA Study)

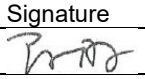
Author: Chen Ridong

Version No. and Date: 1.0, Jun. 25, 2019

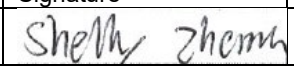
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Statistical Analysis Plan Signature Page

Statistical Analysis Plan version 1.0 (date Jun. 25, 2019), based on protocol [V1.2, Jun. 6, 2018].

	Name	Signature	Date
Author:	Chen Ridong		2019.06.25
Title:	Biostatistician 2		
Company:	Kun Tuo Medical Research and Development (Beijing) Co., Ltd.		

Upon review, the undersigned confirms approval of the current version of the Statistical Analysis Plan and acknowledges that its content complies with the requirements of the study report.

	Name	Signature	Date
Approval by:	Shelly Zhang		2019.06.26
Title:	Sr. Statistician		
Company:	Access Closure, Inc., a Cardinal Health company		

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REVISION HISTORY

Version	Version date	Author	Key changes
1.0	Jun. 25, 2019	Chen Ridong	Not applicable — version 1.0

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Abbreviations

SAP	**STATISTICAL ANALYSIS PLAN**
FAS	**Full analysis set**
PPS	**Per-protocol population set**
SS	**Safety set**
BMI	**Body mass index**
SOC	**System organ class**
PT	**Preferred term**
AE	**ADVERSE EVENT**
MEDDRA	**MEDICAL DICTIONARY FOR REGULATORY ACTIVITIES**
WHODD	**WHO DRUG DICTIONARY**
ECG	**ELECTROCARDIOGRAPH**

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1. INTRODUCTION

This Statistical Analysis Plan (SAP) was developed based on Protocol P17-0005 (Version 1.0, Mar. 16, 2018) and describes the rules and standards to be followed for the presentation and analysis of efficacy and safety data. This document describes the data to be summarized and analyzed, and the specific statistical analyses to be performed.

2. STUDY OBJECTIVES

To assess the safety and effectiveness of the MynxGrip vascular closure device in hemostasis of common femoral artery puncture site in patients who have undergone diagnostic or interventional endovascular procedures,
including:
Effectiveness: To evaluate the superiority of the vascular closure device to the control group in time to hemostasis; to compare the time to ambulation, procedure success rate, and length of stay in hospital between the two groups and to evaluate the device success rate in the test group.
Safety: To evaluate the non-inferiority of the vascular closure device to the control group in major complication rate; to compare the incidence of minor complications, adverse events, and serious adverse events between the two groups.

3. STUDY DESIGN

3.1. General Description

This is a prospective, multicenter, randomized, open-label, parallel-controlled trial. The test group is expected to demonstrate superiority in primary efficacy endpoints and non-inferior primary safety variables compared to the control group. This study aims to evaluate the safety and effectiveness of MynxGrip vascular closure device (test group) in hemostasis of common femoral artery puncture site compared with manual compression hemostasis (control group) in patients who have undergone diagnostic or interventional endovascular procedures utilizing a 5 Fr, 6 Fr, or 7 Fr procedural sheath. Subjects who meet the inclusion criteria of this study will be followed up for 30 days after using the investigational or control device for hemostasis. The time to hemostasis, time to ambulation, procedure success rate, device success rate, length of stay (for patients who have undergone diagnostic procedures), and incidences of major and minor complications, adverse events (AEs), and serious adverse events (SAEs) in the two groups will be recorded and evaluated.

A total of 366 subjects who meet the eligibility criteria will be enrolled in the study, of whom 306 will enter the formal study and be randomized in a 2:1 ratio to the test and control groups. Sixty of the 366 subjects will be designated as roll-in subjects and will receive the investigational device for hemostasis as part of the pilot study designed to familiarize investigators with the use of the device. Up to 10 investigators (surgeons) will participate in the study, with each investigator performing hemostasis using the investigational device on at least 6 roll-in subjects. All subjects, including the roll-in subjects, will complete follow-up per protocol.

This study will be conducted at 6 sites, with an expected enrollment of 51 subjects per site (minimum 26, maximum 77).

Details are shown in the study protocol.

3.2. Schedule of Activities

Visit	Visit 1:	Visit 2:	Visit 3:	Visit 4:	Visit 5:

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assessments	Screening period (-72 h to 0 h)	Interventional diagnosis or treatment and hemostasis (D1)	Ambulatory visit (D1–2)	Discharge visit (day of discharge)	Post-discharge follow-up (D30 ± 7)
Signing of informed consent form	X				
Vital signs	X	X	X	X	X
Physical examination	X				X
Demographics	X				
Eligibility review	X	X			
Past medical history, treatment history, allergy history	X				
Concomitant medications[a]	X	X	X	X	X
Electrocardiography	X				
Laboratory tests[b]	X				X
Reason/details of interventional diagnosis or treatment	X				
Grouping and device dispensing		X			
Post-puncture blood pressure		X			
Hemostasis		X			
Documentation of start time of hemostasis		X			
Completion		X			

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time of hemostasis					
Procedure success rate		X			
Device success rate[c]		X			
Time to ambulation			X		
Length of stay[d]				X	
Complications		X	X	X	X
Adverse events		X	X	X	X

a Concomitant medications: All medications taken by subjects after enrollment will be recorded, except for anesthetics and contrast agents necessary for interventional and diagnostic procedures
b The specific assessments are detailed in the test procedures of each visit. To avoid repeated assessments, laboratory test results obtained within 3 days prior to the procedure are acceptable.
c Only for the test group
d Only for patients undergoing diagnostic procedures

3.3. Changes from Analysis Planned in Protocol

Not applicable.

4. PLANNED ANALYSES

The final planned analyses specified in this SAP will be performed by the Kun Tuo Biostatistics after database lock.

5. ANALYSIS SETS

5.1. Full analysis set (FAS)

All randomized subjects who have received treatment according to the intention-to-treat principle.

5.2. Per-protocol set (PPS)

All subjects in FAS who did not have major protocol deviations affecting the efficacy evaluation.

5.3. Safety analysis set (SS)

All randomized subjects who have received treatment and have post-treatment safety data.

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6. GENERAL CONSIDERATIONS

6.1. Statistical Tests

The default significance level and confidence interval will be 5% and 95%, respectively. All tests will be two-sided unless otherwise specified in the analysis description.

Continuous variables will be statistically described using number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be statistically described using frequency and percentage. Unless otherwise specified, percentages are calculated using the number of subjects in the corresponding analysis set as the denominator. Unless otherwise specified, subjects with missing values will be included in the denominator for percentage calculations, and the number of missing values will be presented separately in a “Missing” row.

6.2. Reference Start Date and Study Day

Study days will be calculated based on the reference start date and used to indicate the start/end days for assessments and events.

The reference start date is defined as the date of the first interventional diagnosis or treatment in the study (e.g., Day 1). Study day is calculated as the difference between the event date and the reference start date, and is used to determine the start or end day of the event.

- *If the event date is not earlier than the reference date:*

  Study day = (event date – reference date) + 1

- *If the event date is earlier than the reference date:*

  Study day = (event date – reference date)

6.3. Baseline

Baseline is defined as the last non-missing measurement (including unscheduled measurements) performed prior to the reference start date.

If the last non-missing measurement is on the reference start date, it is considered pre-baseline. However, AEs and medications occurring on the reference start date will be considered post-baseline.

6.4. Missing Data

If the event date is incomplete or missing, the date will remain as incomplete or missing in the listing. Study day, event duration, and any assessments based on the event date will be derived using the imputation rules specified in Appendix 1 (Incomplete Date Standardization).
Missing efficacy and safety data will not be imputed.

6.5. Visit Windows

No visit windows will be applied in this study.

6.6. Software Version

All analyses will be performed using SAS 9.4.

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7. OUTPUT PRESENTATION

The template provided with this SAP describes the presentation of outputs for this study. The format and content of summary tables, figures, and listings will be provided by Kun Tuo Biostatistics.

8. DISPOSITION AND WITHDRAWAL

All subjects who signed the informed consent form (ICF) will be included in the calculations. The number and proportion of subjects who signed the ICF, were randomized, and completed the study will be summarized by actual treatment group (MynxGrip vs. manual compression hemostasis) and by study site. The number and proportion of early withdrawals and reasons for withdrawal will be summarized. Details of disposition and withdrawals will be presented in listings.
Subjects excluded from the analysis sets and the reasons for exclusion will be presented in a listing.

9. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and other baseline characteristics will be presented for the FAS without statistical testing. Each subject will be tabulated by treatment group. Descriptive analyses will be used to summarize the demographic and baseline characteristics overall and in each treatment group.

The following demographic and other baseline characteristics will reported by treatment group: age (years; defined as the number of years from date of birth to date of informed consent, round down to the nearest integer), sex, ethnicity, height (m), weight (kg), and BMI (kg/m^2).

10. PAST AND CURRENT MEDICAL HISTORY/TREATMENT HISTORY

The information in this section will be summarized for the FAS by treatment group.

Past medical history/treatment history and concomitant medical history/treatment history will be classified based on whether the disease end date occurs before or after the treatment date. All medical/treatment histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), classified by system organ class (SOC) and preferred term (PT) for the FAS, and tabulated.

11. CONCOMITANT MEDICATIONS

Prior and concomitant medications will be classified based on whether the end date of administration occurs before or after the treatment date. All medications in will be coded using the World Health Organization Drug Dictionary (WHODD), summarized by Anatomical Therapeutic Chemical Classification System (ATC) levels 2 and 4 for the FAS, and tabulated.

12. ALLERGY HISTORY

Allergy history will be tabulated.

13. STUDY TREATMENT

Treatment date, treatment start time, introducer sheath model,
serial number, and device models will be tabulated for the SS.

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14. EFFICACY ANALYSES

Statistical analysis of efficacy endpoints will be based on the FAS, and sensitivity analysis will be performed on the PPS.

14.1. Primary Efficacy Analysis

14.1.1. Definition of primary efficacy endpoint

Time to hemostasis: time from introducer sheath removal to immediate hemostasis. “Hemostasis” refers to the absence of significant pulsatile bleeding, dilation, or progressive hematoma at the puncture site.

14.1.2. Analysis of primary efficacy endpoint

A superiority test will be conducted to compare the time to hemostasis between treatment groups. The null and alternative hypotheses are:

$$H_0 : t_{\text{test}} - t_{\text{control}} \geq -5$$
$$H_1 : t_{\text{test}} - t_{\text{control}} < -5$$

Where t_{test} is the mean time to hemostasis in the test group and t_{control} is the mean time to hemostasis in the control group. To assess the superiority of the test group, a one-sided 97.5% confidence interval (CI) will be constructed for $t_{\text{test}} - t_{\text{control}}$.

Depending on the data distribution, either a t-test or Wilcoxon rank sum test will be used to evaluate the difference in differences, with confidence intervals calculated based on the standard error.
The upper bound of the two-sided 95% CI for the difference between the test and control groups corresponds to the upper bound of the one-sided 97.5% CI for $t_{\text{test}} - t_{\text{control}}$.

If the upper bound of the confidence interval is less than -5 min, the null hypothesis will be rejected, and the test group will be concluded to be superior to the control group in time to hemostasis.

14.2. Secondary Efficacy Analysis

14.2.1. Definition of secondary efficacy endpoints

1. Time to ambulation: time from introducer sheath removal to the subject's ability to ambulate at least 6 meters or 20 steps.
2. Procedure success rate: successful hemostasis with the investigational device or control method in the absence of major complications
   (including but not limited to the assigned treatment approach and its auxiliary approach);
3. Device success rate: successful device removal under standard operating procedures (evaluated for the test group only);
4. Length of stay: time from introducer sheath removal to discharge (for subjects undergoing diagnostic procedures).

14.2.2. Analysis of secondary efficacy endpoints

Procedure success rate will be calculated and compared between the treatment groups using the chi-square test or Fisher's exact test based on data distribution.
Time to ambulation and length of stay (patients undergoing diagnostic procedure) will be calculated and compared between groups using the t-test or Wilcoxon rank-sum test based on data distribution.
Device success rate and the percentage of subjects with successful device removal will be summarized for the test group.

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15. SAFETY ANALYSES

Safety analyses will be performed based on the SS.

15.1. Primary Safety Analysis

15.1.1. Primary safety variable

Incidence of major complications. The definition of a major complication is detailed in Section 7.1.7.1 of the protocol.

15.1.2. Analysis of primary safety variable

A non-inferiority test was conducted to compare the incidence of major complications between the treatment groups. The null and alternative hypotheses are:

$$H_0 : P_{\text{test}} - P_{\text{control}} \geq \triangle$$
$$H_1 : P_{\text{test}} - P_{\text{control}} < \triangle$$

Where P_{test} is the incidence of major complication in the test group, P_{control} is the incidence of major complication in the control group, and $\triangle$ is the non-inferiority margin (4%). To assess the non-inferiority of the test group, a one-sided 97.5% CI will be constructed for $P_{\text{test}} - P_{\text{control}}$.
The difference in incidence and its CI will be calculated using the Newcombe [1]method:

```
proc freq data=raw1;
      tables trt*ae1or0 / riskdiff(cl=wilson) nopercent nocol;
run;
```

The upper bound of the two-sided 95% CI for the difference between the test and control groups corresponds to the upper bound of the one-sided 97.5% CI for $P_{\text{test}} - P_{\text{control}}$.

If the upper bound of the one-sided 97.5% CI is less than $\triangle$, the null hypothesis will be rejected, and the test group will be concluded to be non-inferior to the control group in the incidence of major complications.

15.2. Secondary Safety Analysis

15.2.1. Secondary safety variables

Incidences of minor complications, AEs, and SAEs.

Minor complications are defined as:
1) Arteriovenous fistula confirmed by ultrasound or CT scan;
2) Pseudoaneurysms not requiring treatment;
3) Pseudoaneurysms treated with ultrasound-guided injection of thrombin or bioprotein glue;
4) Hematoma at puncture site ≥6 cm;
5) Bleeding at puncture site, with >30 min time to hemostasis;
6) Delayed bleeding at puncture site (e.g., after discharge);
7) Arterial embolism of the ipsilateral lower extremity;
8) Transient loss of arterial pulses in the ipsilateral lower extremity;
9) Deep vein thrombosis in ipsilateral lower extremity;
10) Transient nerve injury related to the puncture site;
11) Vascular tear related to the puncture site;
12) Wound dehiscence at the puncture site;
13) Infection related to the puncture site accompanied by pyrexia and elevated white blood cells, signs of local infection and pus discharge at the puncture site, and positive blood culture, requiring oral

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antibiotic treatment (or intravenous antibiotic treatment for less than 2 days) and/or incision and drainage under local anesthesia;
14) Superficial inflammation at the puncture site, characterized by local symptoms and pus discharge, requiring prophylactic or therapeutic oral antibiotic treatment; absence of pyrexia, elevated white blood cell count, or positive culture results (except for the presence of normal skin flora that are less commonly associated with infection). Analysis of secondary safety variables

15.2.2. Analysis of secondary safety variables

The incidence of minor complications will be compared between the treatment groups using the chi-square test or Fisher's exact test.

Treatment-emergent adverse events (TEAEs) refer to AEs that emerge after treatment or that worsen in severity relative to baseline. If it cannot be determined whether an adverse event is treatment-emergent, it will be conservatively classified as treatment-emergent. Only TEAEs will be statistically analyzed in this study (referred to as AEs in the following sections), and non-TEAEs will only be presented in listings.

AEs will be coded using PT and SOC of MedDRA. AEs, adverse reactions, SAEs, serious adverse reactions, and AEs leading to withdrawal will be summarized by treatment group.

The number of observations and cases of minor complications and major complications will be classified and summarized.

Adverse reaction is defined as any AE that is definitely, probably, or possibly related to the study device.

If a subject reports multiple AEs within the same SOC or PT, the event with the highest severity and strongest causal relationship will be used in the corresponding summary.

15.3. Device Defects

Information on device defects will be presented in a listing.

15.4. Laboratory Evaluations

Hematology, clinical chemistry, and coagulation parameters will be reported in this study. Changes from baseline will be summarized by study period and dose level based on predefined criteria for clinical significance.
Abnormal laboratory values and clinically significant abnormalities (if applicable) will be presented in listings, with the corresponding study period noted.

Details of laboratory evaluations and serum pregnancy tests for women of childbearing potential will be presented in listings.

15.5. ECG Evaluation

Normal ECG findings and abnormalities (with or without clinical significance), along with changes from baseline, will be tabulated by treatment group.

15.6. Physical Examination and Vital Signs

Other safety variables, including physical examination findings and vital signs, will be presented in listings only.

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Definitions:
FAS: all randomized subjects who have received treatment according to the intention-to-treat principle.
PPS: all subjects in FAS who did not have major protocol deviations affecting the efficacy evaluation.
SS: all randomized subjects who have received treatment and have post-treatment safety data.
TEAEs: AEs that emerge after treatment or that worsen in severity relative to baseline.
AE: any untoward medical occurrence during a clinical study, regardless of its relationship to the investigational medical device.
SOC: system organ class.
PT: preferred term.
MedDRA: Medical Dictionary for Regulatory Activities.
WHODD: World Health Organization Drug Dictionary.

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Appendix 1. Incomplete Date Standardization

Classification of prior or concomitant

Start date	End date	Procedure
Known	Known	If end date < study treatment start date, classify as prior If end date ≥ study treatment start date, classify as concomitant
	Incomplete	Impute the end date with the latest plausible date: if the day is missing, impute as the last day of the month; if both the day and month are missing, impute as December 31st of the year. If end date < study treatment start date, classify as prior If end date ≥ study treatment start date, classify as concomitant
	Missing	Classify as concomitant
Incomplete	Known	If end date < study treatment start date, classify as prior If end date ≥ study treatment start date, classify as concomitant
	Incomplete	Impute the end date with the latest plausible date: if the day is missing, impute as the last day of the month; if both the day and month are missing, impute as December 31st of the year. If end date < study treatment start date, classify as prior If end date ≥ study treatment start date, classify as concomitant
	Missing	Classify as concomitant
Missing	Known	If end date < study treatment start date, classify as prior; if end date ≥ study treatment start date, classify as concomitant
	Incomplete	Impute the end date with the latest plausible date: if the day is missing, impute as the last day of the month; if both the day and month are missing, impute as December 31st of the year. If end date < study treatment start date, classify as prior If end date ≥ study treatment start date, classify as concomitant
	Missing	Classify as concomitant

Classification of TEAE

Start date	End date	Procedure
Known	Known	If event start date < study treatment start date, classify as non-TEAE If event start date ≥ study treatment start date, classify as TEAE
	Incomplete	If event start date < study treatment start date, classify as non-TEAE If event start date ≥ study treatment start date, classify as TEAE
	Missing	If event start date < study treatment start date, classify as non-TEAE If event start date ≥ study treatment start date, classify as TEAE
Incomplete, but available data indicates that the event cannot be on or after study treatment start date	Known	Non-TEAE

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Start date	End date	Procedure
	Incomplete	Non-TEAE
	Missing	Non-TEAE
Incomplete, may be on the day of study treatment	Known	If event end date < study treatment start date, classify as non-TEAE
On or later than the start date		If event end date ≥ study treatment start date, classify as TEAE
	Incomplete	Impute the end date with the latest plausible date: if the day is missing, impute as the last day of the month; if both the day and month are missing, impute as December 31st of the year. If event end date < study treatment start date, classify as non-TEAE If event end date ≥ study treatment start date, classify as TEAE
	Missing	Assume TEAE
Missing	Known	If event end date < study treatment start date, classify as non-TEAE If event end date ≥ study treatment start date, classify as TEAE
	Incomplete	Impute the end date with the latest plausible date: if the day is missing, impute as the last day of the month; if both the day and month are missing, impute as December 31st of the year. If event end date < study treatment start date, classify as non-TEAE If event end date ≥ study treatment start date, classify as TEAE
	Missing	Assume TEAE

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16. REFERENCES

[1] NEWCOMBE RG.Interval estimation for the difference between independent proportions: comparison of eleven methods[J].Stat Med, 1998, 17(8):873—890.

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