Statistical Analysis Plan

Clinical Investigation Plan V4.0

Clinical Evaluation of the BlueDop Vascular Expert for Assessing Peripheral Arterial Disease

BVE-01

Statistical Analysis Plan (SAP)

Version 2.0

14-Nov-2023

Statistical Analysis Plan

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1.0 SYNOPSIS OF STUDY DESIGN

1.1 Purpose of Statistical Analysis Plan

This Statistical Analysis Plan (SAP) is intended to provide a detailed and comprehensive description of the planned methodology and analysis to be used for Clinical Investigation Plan (CIP) BVE-01-

1.2 Clinical Investigation Objectives

The primary objective of this study is to evaluate the clinical equivalence (accuracy assessment) of the BlueDop Vascular Expert (BVE) in comparison with arterial duplex ultrasound in the diagnosis of significant peripheral arterial disease (PAD) in a group of patients referred for evaluation of PAD of the lower limbs when performed by a vascular specialist.

1.3 Clinical Investigation Design

The clinical investigation of the BVE for assessing PAD is a prospective, multi-center, open-label, non-randomized, single-arm study. The study has been designed to evaluate the clinical equivalence of BVE to arterial duplex in a group of patients referred for evaluation of PAD of the extremities when performed by a vascular specialist.

The study population is expected to be maximal 188 subjects (men and women over 18 years that were referred for arterial duplex ultrasound of the lower limb(s) with suspected or previous history of arterial disease and meet the study eligibility criteria).

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[redacted]	[redacted]

[redacted]

1.4 Endpoints

1.4.1 Primary performance endpoint

The primary performance endpoint is the evaluation of clinical equivalence of BVE compared to arterial duplex in the determination of presence or absence of significant PAD. [redacted]

Equivalence will be evaluated through a binary result (either presence or absence of significant PAD) in BVE compared to a binary summary of the arterial duplex.

1.4.2 Primary safety endpoint

To characterize and confirm the safety of BVE, safety will be evaluated by assessing the AEs and SAEs. [redacted]

1.4.3 Secondary endpoint

The secondary performance endpoint is to evaluate the clinical equivalence of BVE compared to the ABPI in a group of patients referred for evaluation of PAD of the lower limbs when performed by a vascular specialist.

Equivalence will be evaluated through a binary result (either presence or absence of significant PAD) in BVE compared to a binary summary of ABPI.

[redacted]

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

2.1.1 Enrollment population (EnP)

Enrollment population (EnP) includes those subjects with at least one lower limb referred for evaluation of PAD. [redacted]

2.1.2 Eligible population (EIP)

Eligible population (EIP) comprises the subset of enrolled patients who have at least one valid determination of PAD with both devices (BVE and arterial duplex).

[redacted]

2.3 Endpoint Analysis

2.3.1 Primary endpoint

The primary endpoint of this study is the evaluation of the clinical equivalence of BVE compared to arterial duplex in the determination of presence or absence of significant PAD. [redacted]

$$Overall\ accuracy = \frac{TN + TP}{TN + TP + FN + FP} = \frac{Number\ of\ correct\ assessments}{Number\ of\ total\ assessments}$$

Where TN = True Negative, TP = True Positive, FN = False Negative and FP = False Positive.

[redacted]

The primary endpoint is reached when it is shown that BVE is equivalent to the existing measurements (arterial duplex) in the determination of presence or absence of significant PAD (binomial outcome).

[redacted]

In order to determine the equivalence between BVE and arterial duplex measurements, a margin of equivalence (D) is defined. [redacted] the event rates for the standard measurement group and the BVE measurement group can be defined as PS and PT, respectively. Therefore, equivalence will be confirmed if the difference between PS and PT is lower than the margin of equivalence D.

Ha: PS –PT < D

2.3.2 Secondary endpoint(s)

The evaluation of clinical equivalence of BVE compared to ABPI in the determination of presence or absence of significant PAD will be carried out by means of the estimation of overall accuracy [redacted]

$$Overall\ accuracy\ calculation = \frac{TN + TP}{TN + TP + FN + FP} = \frac{Number\ of\ correct\ assessments}{Number\ of\ total\ assessments}$$

Where TN = True Negative, TP = True Positive, FN = False Negative and FP = False Positive.

[redacted]

The secondary endpoint is met when it is shown that BVE is equivalent to the existing measurements (ABPI) in the determination of presence or absence of significant PAD (binomial outcome). [redacted]

[redacted] equivalence will be confirmed if the difference between PS_2 and PT_2 is lower than the margin of equivalence D_2.

Ha_2: $PS_2 – PT_2 < D_2$

2.4 Sample Size Calculations

[redacted]

[redacted]

[redacted] a maximum of 188 subjects will be enrolled in the clinical investigation [redacted]

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2.8 Study/ Trial Success

It will be considered a trial success when:

- All subjects are successfully recruited
- All required limbs are measured
- All values are adequately collected and considered valid
- At least the primary endpoint is met.

2.9 Subgroups of Analysis

The clinical equivalence of BVE testing performed by staff specifically trained on BVE (no vascular technologists/specialists) will be compared to BVE testing performed by vascular technologists/ specialists. [redacted]

In addition, the clinical equivalence of BVE testing performed on subjects with a medical history of diabetes, smoking activity or hypertension, will be compared to BVE testing performed on healthy subjects.

[redacted]

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2.11 [redacted]

[redacted]

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

[redacted]

3.2 Adverse Events

All the AEs, SAEs, adverse device effects (ADEs), serious adverse device effects (SADEs), unanticipated adverse device effects (UADEs), and unanticipated serious adverse device effects (USADEs) will be summarized for all subjects enrolled in this clinical investigation in terms of the number of events, number of subjects with events, the percentage of subjects with events and event rate (number of events per patient per month). [redacted]

3.3 Subject Early Termination

There is no formal statistical rule for early termination of the clinical trial for insufficient effectiveness of the tested device defined. [redacted]

[redacted]

3.5 Number of Subject Imbalance

All efforts will be made to maintain a balanced enrollment among the maximal 6 sites. [redacted]

[redacted]

[redacted]

5.0 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
ABPI	Ankle Brachial Pressure Index
AE	Adverse Event
BVE	BlueDop Vascular Expert
CI	Confidence Interval
CIP	Clinical Investigation Plan
CRF	Case Report Form
DBP	Diastolic Blood Pressure
FN	False Negative
FP	False Positive
ICF	Informed Consent Form
In/Ex	Inclusion/Exclusion
ITT	Intent-To-Treat population
PAD	Peripheral Arterial Disease
PP	per-protocol
SADE	Serious Adverse Device Effects
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	Standard Of Care
TN	True Negative
TP	True Positive
USADE	Unanticipated Serious Adverse Device Effects

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