Statistical Analysis Plan

A prospective, multicenter study to evaluate the performance and safety of Comet™ Pressure Guidewire in the measurement of FFR in Chinese patients

COMET CHINA

Study Reference number (S2434)

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APPROVALS (Check/Complete one below):

☐ Approvals are captured electronically

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Revision History

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Document Revision Number	Section	Change	Reason for Change
Version **AA**/ 18DEC2019	None	None	Initial Release
Version **AB**/ 25FEB2020	Section 3.1 Section 5.2.4	• Added text based on the Primary Effectiveness endpoint for paired measurements. Included that t-test based on the difference of the test and control device can also be used for analysis. • Added Lesion characteristics analysis	• Specified both methods for understanding as both methods generate same values. • This analysis added after the first initial release of SAP

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

The study is to evaluate the performance and safety of Comet™ Pressure Guidewire in FFR (Fractional Flow Reserve) measurements in Chinese population in order to support the regulatory submission in China.

1.1 Study design :

The COMET China study is a prospective, open-label, multi-center study designed to validate the agreement of Comet™ Pressure Guidewire and Pressure Wire Certus® in FFR measurements. Patient with stable angina or any form of non-ST elevation acute coronary syndrome, who are scheduled for diagnostic angiography and pressure wire assessment, and signed the informed consent, will be screened for enrollment in this study.

1.2 Study objectives :

The primary objective of this study is to evaluate the performance and safety of Comet™ Pressure Guidewire in FFR (Fractional Flow Reserve) measurements in Chinese population.

1.2.1 Primary efficacy endpoint :

The primary efficacy endpoint is the acceptable agreement between Comet™ Pressure Guidewire and Pressure Wire Certus® in FFR measurements.

1.2.2 Secondary endpoint :

The safety endpoint is the rate of following major adverse events:

- Pressure wire-related death
- Pressure wire-related cardiac tamponade
- Pressure wire fracture
- Pressure wire-related unanticipated adverse event (UADE)

1.3 Number of sites and patients:

The COMET China trial will be conducted in at least 2 sites in Mainland China with planned enrollment of up 100 paired measurements from up to 50 subjects. The study is planned to have approximately 6 months of enrollment. But due to inclusion/exclusion criteria in this study is easier, the subject enrollment happened quick than the anticipated and within a 2-3 months duration all the 100 paired measurements from nearly 39-40 subjects been enrolled for the study.

1.4 Description of the study population:

All subjects will be screened according to the protocol inclusion and exclusion criteria. All eligible subjects will receive Pd/Pa and FFR measurements simultaneously by both Comet™ Pressure Guidewire and Pressure wires Certus®. For the two pressure wires which should be passed the target lesion first, each site

will be provided a randomized digital table with a 1:1 ratio at target vessel level. Subject follow-up will end at hospital discharge post FFR measurement. The study will be considered complete after all subjects have discharged from hospital or withdrawn from the trial (due to death or having been lost to follow-up).

Patient with stable angina or any form of non-ST elevation acute coronary syndrome, who are scheduled for diagnostic angiography and pressure wire assessment, and signed the informed consent, will be screened for enrollment in this study. Prior to enrollment in the trial, a subject should meet all of the clinical and angiographic inclusion criteria and none of the exclusion criteria.

1.5 Description of device(s) including model numbers used in the study :

This is a comparative parallel study which include a multi-device involvement. All eligible subjects will receive Pd/Pa and FFR measurements simultaneously by both Comet™ Pressure Guidewire and pressure wires Certus®. For which wire should be passed the target lesion first, randomization will be performed as described.

1.5.1 Test devices - Comet Pressure Guidewire

The Comet Pressure Guidewire is a single use, hydrophilic-coated, steerable wire with a custom optical cable. A pressure sensor is mounted approximately 3 cm from the distal end of the radiopaque and shapeable straight tip. For product specifications, including wire diameter, length, and radiopaque tip length, please refer to the product labeling/DFU.

The Comet Pressure Guidewire is indicated to direct a catheter through a blood vessel and to measure physiological parameters in the coronary blood vessels.
The characteristics of the Comet Pressure Guidewire are described below :

Characteristic	Description
Labeled diameter	0.014”
Wire length	185 cm
Flexible portion of wire length	31 cm
Tip length	3 cm
Tip shape	Straight

1.5.2 Test devices – FFR link

The FFR Link (see Figure 5.1- 2 transmits aortic (Pa) and distal (Pd) blood pressure under the control of the Polaris software or Hemodynamic System with Licensed FFR Calculation Module. The FFR Link is a hardware module that is installed with either an existing or a new iLab Polaris system. In this use scenario, the FFR Link can be used to obtain the pressure measurement from the Comet Pressure Guidewire and provide an analog Pd out signal.

1.5.3 Test Devices - iLab™ Polaris Multi-Modality Guidance System

The iLab Polaris Multi-Modality Guidance System is an upgrade to the iLab Ultrasound Imaging System to add a Fractional Flow Reserve (FFR) modality to the existing ultrasound imaging modality (IVUS). The iLab Polaris System is designed to provide both ultrasound imaging and fractional flow reserve modalities. Only one modality can be used at a time and are independent of one another.

1.5.4 Control Devices - Pressure Wire Certus

Pressure Wire Certus is a 0.014'' guidewire with an integrated sensor element at the tip to enable measurements of physiological parameters. Pressure wire is available in different lengths. Please refer to the label for information about pressure wire length and thermos compatibility.

1.5.5 Control Devices – RadiAnalyzer system

RadiAnalyzer is a diagnostic computer designed to compute, record and display information from Pressure Wire and other external transducers.

1.6 Medication treatment :

Maximal hyperemia will be induced by intravenous adenosine-5'-triphosphate (ATP) via the median cubital vein.
Subjects will receive routine drug treatment required for diagnostic angiography and PCI according to the standard clinical practice in China.

2 INTRODUCTION

This Statistical Analysis Plan (SAP) has been designed and intend to document the planned analyses to be consistent with the objectives study protocol. This is a guiding document for conducting analysis for COMET China Study Protocol, 92340494 Rev/Ver AB. The specified analyses may be provided in reports to competent authorities and/or for scientific presentations and/or manuscripts

This trial is designed to evaluate the performance and safety of Comet™ Pressure Guidewire in FFR (Fractional Flow Reserve) measurements compare to PressureWire Certus in Chinese population. Subjects will receive routine drug treatment required for diagnostic angiography and PCI according to the standard clinical practice in China. And FFR measurement will be based on the current FFR guidelines in China.

After a subject has signed the IRB/IEC-approved study ICF, the screening process may begin. The screening process will be used to determine the inclusion or exclusion of a subject in the study. This process includes the investigator's assessment of subject's medical records and diagnosis and following pre-procedure data must be collected within 14 days prior to the index procedure (unless otherwise specified), for all subjects.

The study planned to do analysis based on the index procedure results and during pre-hospitalization discharge. The procedure assessment is collected during index procedure for both Test and control devices. Subjects will receive FFR measurements simultaneously by both Comet™ Pressure Guidewire and pressure wires Certus.

3 ENDPOINT ANALYSIS

Based on the design, the primary endpoint focuses on the agreement between the two devices during the index procedure. The endpoint analysis been detailed below:

3.1 Primary Effectiveness Endpoint

Acceptable agreement between CometTM Pressure Guidewire and Pressure Wire Certus® in FFR measurements. For understanding the difference between two wires, a simplified prediction interval to examine the extent of agreement. we consider Bland-Altman plot will be used to assess the agreement between CometTM Pressure Guidewire and Pressure Wire Certus® paired measurements. we need to consider both baseline pd/pa and FFR values (all 100 paired measurements) for the primary end point analysis.

All 100 paired measurements defined as, sum of baseline PD/PA" of each lesion from both Comet and Certus pressure wires [50 (lesions)] with FFR value of each lesion from both Comet and Certus pressure wires [50 (lesions)].

A table generated for both pressured wires including subject and observations (individual paired record) counts with Mean, SD and 95% Confidence limits

include the device difference (bias) . The Level of agreement(LoA) of both lower and upper limits with standard error presented in connecting the individual pressure wired descriptive. These results are in connection to Bland-Altman plot. These LoA's are used as bands are further act as intervals for calculated 95% confidence limits.

The Bland-Altman (mean-difference or limits of agreement) plot and analysis used to compare two measurements of the same variable. a method comparison technique. In this design, each of the two measurement-methods is measured once on each subject at nearly the same point in time. The average of the two measurements is plotted along the horizontal axis and the difference between the two methods is plotted along the vertical axis. his plot adds confidence intervals for the mean difference and the agreement limits. Using SAS, Proc SGPLOT we can plot the agreement lines. The agreement determined based on the dots plotting outside the agreement lines. SAS code for Bland-Altman plot is specified in Agreement analysis section.

Also, in support to the primary endpoint we generate a Scatter plot of Comet™ Pressure Guidewire vs Pressure Wire Certus® FFR values for all lesions.

A sample code for scatter plot is defined below:

```
proc reg data=diffs;
model ffr1=ffr2;
 ods output ParameterEstimates=PE;
run;

ods graphics on;
proc corr data=diffs pearson plots=scatter ;
var FFR1 FFR2 ;
ods output PearsonCorr=pears (Rename= (FFr2=FFR));
run;
ods graphics off;
```

From the regression extract intercept and slope from PROC REG and Pearson correlation value from PROC CORR using SAS software, we plot the scatter plot with the generated values. PROC SGPLOT will be used to generate the scatter plot.

```
proc sgplot data=diffs;
reg x=ffr1 y=ffr2;
inset "Correlation= &r" "Intercept = &Int" "Slope = &Slope" /
         border title="Parameter Estimates" position=topleft;
             xaxis values= (0.4 to 1 by 0.2) label="COMET FFR";
yaxis values= (0.4 to 1 by 0.2) label="CERTUS FFR";
run;
```

Also, a paired t-test will be used to test the mean difference of the 2 methods are equal to determine the agreement between the methods. The primary endpoint is analyzed based on ITT and per-protocol analysis.

Use Yi and Xi to denote assessment values using Comet Pressure guidewire and Pressure wire Certus. The extent of agreement can be examined through the difference di =Yi -Xi .

A 95% prediction interval for the assessment difference for a subject is:

$$d \pm t_{0.975}^{(n-1)} * S * \sqrt{1 + 1/n}$$

- d is the mean of the differences, di
- s is standard deviation of the differences
- $t_{(n-1)}^{0.975}$ is the critical point of a t-distribution.

Since, we need to check the mean paired difference is within +/- 0.005, we need to frame the null hypothesis based on the specified cut-off. Using paired t-test considering Schuurman's TOST equivalence test we will check the lower and upper bound values with the achieved mean difference value between the two pressure guidewires. SAS code detailed in the Paired T-test based on TOST section. Can also generate the 90% Confidence limits using t-test based on the difference of the two pairs.

3.1.1 Hypotheses

There are no specific hypotheses been determined for this study. However, the primary objective specification states that the mean difference should exist between the lower and upper bounds of (-0.005, 0.005). This can be done based on TOST equivalence test, under paired t-test using SAS.

3.1.2 Sample Size

The sample size was estimated based on the following assumptions:

- Pre-defined agreement limits = [-0.08, 0.08]
- Expected paired mean difference = 0.0013
- Expected paired standard deviation (SD) = 0.03
- Two-sided significance level=5% (alpha)
- Power > 80%

A minimum of 100 paired measurements1 from 50 patients are needed for this study. Based on the above assumptions,39 subjects selected and randomized each treatment group will be required.

3.1.3 Statistical Methods

The primary endpoints should be analyzed based on per-protocol sample, as per the protocol. However, the primary endpoint analyzed based on both ITT and PP populations. The definitions of these analysis sets been clearly defined in Analysis set section. There is no certain specification of per-protocol analysis in the protocol, but however as a standard routine practice of Analysis, per-protocol is

All the eligible subjects enrolled will be analyzed with a Bland-Altman plot, to assess the agreement between Comet™ Pressure Guidewire and Pressure Wire Certus® in FFR measurements. A scatter plot to assess the association specifying the correlation between the two FFR measurement values and , a paired t-test will be used to test the mean difference of the 2 methods are equal to determine the agreement between the methods. The primary endpoint is analyzed based on ITT and per-protocol analysis.

All the primary efficacy and safety endpoint categorical variables will be summarized with frequencies and percentages and continuous variables will be tabulated with n, mean, median, standard deviation, minimum, maximum excluding the missing observation records. Missing observations are not included for the summary as per the Boston scientific specifications.

3.2 Primary Safety Endpoint

The primary safety endpoint is based on the below endpoints.

- Pressure wire-related death
- Pressure wire-related cardiac tamponade
- Pressure wire fracture
- Pressure wire-related unanticipated adverse event (UADE)

All the endpoints are summarized with frequencies and percentages and also a p-value generated based on a chi-square test. If any cell has expected counts < 5, then the Fisher's exact test is used instead. For this we will consider only safety analysis set data. Also suggested to include the frequency and rates of serious and non-serious adverse events by SOC and PT with device related.

4 GENERAL STATISTICAL METHODS

4.1 Analysis Sets

The primary endpoints will be analyzed on a per-protocol basis. Only enrolled subjects who are measured paired FFR data with the Comet and Certus pressure wires in the target lesion will be included in the primary endpoint analysis sample. Safety analysis will be based on the ITT basis. Subjects with unpaired data will be

included as appropriate, if any. All primary and additional endpoints will be analyzed both on an intent-to-treat (ITT) basis and on a per-protocol (PP) basis.

For ITT analyses, all patients who sign the IRB/IEC-approved study ICF and are enrolled in the study will be included in the analysis, regardless either of the study device Comet or test device Certus pressure wires was implanted. The historical control for the S2434 study is a blended control comprised of patients from the preclinical study (91050762) was conducted to assess Comet thrombogenicity.

For per-protocol analyses, only patients who signed the IRB/IEC-approved study ICF and had the measured paired FFR data of both Comet and Certus pressure wires in the target lesion will be considered.

4.2 Control of Systematic Error/Bias

Selection of subjects will be made from the investigators' general or professional referral population. All subjects meeting the inclusion/exclusion criteria that have signed the protocol-specific ICF will be eligible for enrollment in the trial. Consecutively eligible subjects should be enrolled into the study to minimize selection bias. In determining subject eligibility for the study, the investigator's assessment of imaging will be used.

4.3 Number of Subjects per Investigative Site

A maximum of 35 patients (70% of total enrolled subjects) will be recruited from one site to avoid treatment center bias and ensure homogeneous study results.

5 ADDITIONAL DATA ANALYSES

5.1 Other Endpoints/Measurements

Clinical event rates will be presented as proportions and continuous data will be summarized by presenting sample sizes, means, standard deviations, minimums, and maximums. Point estimates and 95% confidence intervals will be provided. No statistical testing will be performed for the additional endpoints.

5.2 Other Statistical considerations

5.2.1 Patient disposition/status

Number of subjects enrolled by investigator and site will be summarized with counts and percent based on Intent population, categorized it with respect two pressured wires. A listing also specified with center, location and patients enrolled.

5.2.2 Baseline and Demographic analysis

Baseline characteristics with physical examinations, with medical history, 12-Lead ECG characteristics, Antiplatelet and Anticoagulant Medications and concomitant medications will be summarized at screening or baseline

visit and data collected points. Continuous measurements will be summarized descriptively and categorical measurements with counts and percent. Complete blood count information descriptive are also provided for all the available parameters. P-values been generated for all 12 Lead ECG measurements for ECG performance and abnormal findings of ECG using a chi-square test or if cell has expected counts less than 5, then the Fisher exact test is used instead.

5.2.3 Procedure and device characteristics

Procedure characteristics based on size of guiding wires and two pressured wires tracing summarized. Target lesion characteristics of both pressured wires summarized for desired location, passthrough time, Drift of pressure guidewire and Technical success of the device. Post-FFR measurements are also summarized in this section. P-value generated based on independent t-test for continuous variables and a chi-square test or if cell has expected counts less than 5, then the Fisher exact test is used instead. Other parameters such as Coronary injection of nitroglycerine administration will be summarized by counts and percent.

5.2.4 Lesion characteristics

Lesion characteristics based on Initial Angiographic Assessment will be summarized by counts and percent. Post FFR measurements are also summarized in this section.

5.2.5 Analysis of Adverse and Serious adverse events

Subject-level event rates will be calculated at various time points (e.g. exact days) based on all events reported by the site regardless of whether they are ultimately adjudicated. Frequency of site reported Serious adverse events and non-serious adverse events and also Frequency of site-reported Serious adverse events and Non-serious adverse events are associated with the implant procedure up to End of study are exhibited using counts and percent with total available subjects based on safety population. The events are summarized by MedDRA system organ class and MedDRA system preferred terms with events and rates.

For calculating events and rates, need to consider ‘Events numbers’ are total episodes of each type of event among all subjects. ‘Rate of Subjects with Event’ numbers are percent of subjects who experienced one or more episodes of the event. ‘Events’ numbers for “TOTAL” are the sum of the individual event category totals. ‘Rate of Subjects with Event’ numbers for “TOTAL” is the percent of subjects who experienced an adverse event.

5.2.6 Protocol Deviations

A summary table for Deviations from Investigational Protocol collated during procedure and post procedure for all the planned events as specified in protocol.

5.2.7 Device Deficiencies

A table exhibited based on device deficiencies with count and percent for the available parameters with a supported listing. Also, a listing based on Device deficiency identifier with description and connected to SAE with occurrence instance been listed for Implant population.

5.3 Interim Analyses

No formal interim analyses are planned for the purpose of stopping this study early for declaring effectiveness or for futility.

5.4 Subgroup Analyses

No sub-group analysis is planned.

5.5 Justification of Pooling

No Pooling of analysis groups for this study

5.6 Multivariable Analyses

No multivariable analyses are planned in this study

5.7 Other Analyses

No other analyses are planned in this study

5.8 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to database lock will be documented in a Statistical Analysis Plan approved prior to DBL. Changes from the planned statistical methods DBL will be documented in the clinical study report along with a reason for the deviation.

6 VALIDATION

All clinical data reports generated per this plan will be validated per 90702587, Global WI: Clinical Data Reporting Validation. The validation level R1 chosen for all primary, secondary, safety and other additional endpoints. The validation program includes checking logs and generating compare reports in comparing with main programming datasets.

7 PROGRAMMING CONSIDERATIONS

All statistical programming tasks will be performed by IQVIA™ independently.

7.1 Statistical Software

All statistical analyses will be done using The SAS System Version 9.2 software or above (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved.).

7.2 Format of Output

Results of analysis will be output programmatically to Microsoft Office® Word documents from SAS with no manual intervention. All output for the final statistical report will be in the form of a Word document containing tables, figures, graphs, and listings, as appropriate.

7.3 Methods for Handling Missing Data

No imputation method will be performed for the missing data handling. Missed or late visits will be recorded as Protocol Deviations. When calculating rates of treatment-emergent adverse events, missing and partial dates will be handled as shown in the table below.

Partial Date	Action Taken
Entire adverse event onset date is missing	The procedure date will be used for the onset date.
The month and the day of the month are missing but the year is available	January 1st will be used for the month and day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.
Day is missing, but the month and year are available	The 1st will be used as the day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.

7.4 Rules and Definitions

For baseline categorical variables, missing values will not be counted in rate denominators. Number of patients completing the visit will be considered in denominators. Any other imputations and rules updated further will be included in the report template version before DBL.

7.5 SAS code for primary endpoint analysis

7.5.1 Agreement analysis

The primary endpoint analysis is to check the acceptable agreement between CometTM Pressure Guidewire and Pressure Wire Certus® in FFR measurements.

To check the agreement, need to consider Bland-Altman plot will be used to assess the agreement between CometTM Pressure Guidewire and Pressure Wire Certus® in FFR measurements.

```
/*SAS code for Bland-Altman plot */
data diffs ;
set all ;
/* calculate the difference */
diff = FFR1-FFR2 ;
/* calculate the average */
mean = (FFR1+FFR2)/2 ;
run ;

proc print data = diffs;
run;

proc sql noprint ;
select mean(diff)-1.96*std(diff),  mean(diff)+1.96*std(diff)
into :lower,  :upper
from diffs ;
quit;

proc sgplot data = summdi (where=(ITT="Y"));
      band x=mean upper=&iluclm  lower=&illclm/ name=  "Lower
Agreement Limit"   lineattrs=(color=aliceblue pattern=dot);
      band x=mean upper=&iuuclm  lower=&iulclm/ name = "Upper
Agreement Limit"   lineattrs=(color=aliceblue pattern=dot);
      scatter x = mean y = diff;
      refline 0  / LABEL = ("zero bias line" )
lineattrs=(color=black pattern=dot);
      refline  &imeandiff/ LABEL = ("Mean difference" )
lineattrs=(color=red pattern=dash);
      refline &ittupper &ittlower / LABEL =("95% upper limit with
Agreement limits" "95% lower limit with Agreement Limits")
lineattrs=(color=purple pattern=dash);
      ;
      xaxis values= (0 to 1 by .1) label="Mean of FFR1 & FFR2";
      yaxis values= (-0.25 to 0.25 by 0.05) label="Difference of
FFR1 & FFR2";
      TITLE 'Bland-Altman Plot- Intent to Treat population';
      footnote 'Accurate prediction with 10% homogeneous error';
run;

quit;
```

band option in PROC SGPLOT used to plot the gray bands.

The lower and upper reference lines in bands are based on the upper and lower confidence limits means calculated from mean(diff)-1.96*std(diff), mean(diff)+1.96*std(diff). The center reference line is the mean difference between paired measurements

7.5.2 Paired T-test based on TOST

Agreement between the two methods tested based on the mean paired difference is within +/- 0.005.

```
ODS OUTPUT EquivLimits=eqlmts;
ODS OUTPUT EquivTests=EQTEST;
PROC TTEST data=all ALPHA=0.025 TEST=DIFF tost(-0.005,0.005) ;
PAIRED FFR1*FFR2  ;
TITLE 'Mean difference between two pressure guide wires';
RUN;
```

The above SAS code generate the below output.

Paired t-test mean difference between two pressure guide wires

The TTEST Procedure

Difference: FFR1 - FFr2

N	Mean	Std Dev	Std Err	Minimum	Maximum
50	-0.00060	0.0440	0.00622	-0.1600	0.1200

Mean	97.5% CL Mean		Std Dev	97.5% CL Std Dev	
-0.00060	-0.0150	0.0138	0.0440	0.0359	0.0567

TOST Level 0.025 Equivalence Analysis

Mean	Lower Bound		95% CL Mean			Upper Bound	Assessment
-0.00060	-0.005	>	-0.0131	0.0119	>	0.005	Not equivalent

Test	Null	DF	t Value	P-Value
Upper	-0.005	49	0.71	0.2414
Lower	0.005	49	-0.90	0.1863
Overall				0.2414

From the code, option “tost” will split the two sides separately based on the confidence bounds of -0.005 and +0.005.

8 REFERENCES

- Comet China Protocol, 92340494, Rev/Ver AB, study protocol
- COMET CHINA Version2.1_12NOV2019– Super, Annotated Blank Case Report Form
- Form/Template 90702621 Rev/Ver AE, Statistical analysis plan Template.

- William F. Fearon, MD; Jeffrey W. Chambers, MD, et.al, ACIST-FFR Study (Assessment of Catheter-Based Interrogation and Standard Techniques for Fractional Flow Reserve Measurement)
- Henry Seligman, Matthew J Shun-Shin, Anushkumar Vasireddy, et.al. Fractional flow reserve derived from microcatheters versus standard pressure wires: a stenosis-level meta-analysis
- https://ncss-wpengine.netdna-ssl.com/wp-content/themes/ncss/pdf/Procedures/NCSS/Paired_T-Test_for_Equivalence.pdf