STATISTICAL ANALYSIS PLAN (SAP)

EXAMINATION EXTEND

(NCT04462315)

A Clinical Evaluation of Xience-V stent in Acute Myocardial INfArctTION EXTENDed follow-up

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Statistical Overview of the Study

The Examination study was a prospective, randomized controlled, single blind, parallel two-arm, multi-center clinical evaluation of the XIENCE™ V EECSS (XIENCE V arm) compared to the MULTILINK-VISION bare metal stents (MV BMS arm) in patients presenting with ST-segment elevation myocardial infarction. A total of 1500 patients have be randomized into two arms in a 1:1 ratio (XIENCE V and a Multilink Vision BMS arm). The primary combined endpoint included of all-cause death, any myocardial infarction and any revascularization at 1 year.

The Examination EXTEND study is an investigator-driven 10-year follow-up of the multicenter, prospective, randomized and controlled EXAMINATION trial.

Analysis Populations

All analyses will be performed on the intention-to-treat population. The intent-to-treat population will consist of all randomized patients enrolled in the EXAMINATION trial (N=1498; EES n=751; BMS n=747), regardless of the treatment actually received.

Data management

Outcomes data will be provided by all participating sites and will be imported into SPSS. All variables used in the analysis will be checked for missing values, outliers and inconsistencies and queried.

Analysis of Primary Endpoint

The primary patient-oriented combined endpoint of all-cause death, myocardial infarction and any revascularization at 10 year will be analyzed for the intent-to-treat population. Statistical analysis will be performed with the log-rank test at a two-sided 0.05 significance level. Cox proportional hazard models will be used to estimate hazard ratios (HR) with 95% confidence intervals (CI) for the comparison between EES vs. BMS. Landmark analyses will be performed, setting the landmark points at 1 and 5 years to distinguish the results of EXAMINATION trial from the extended follow-up of the EXAMINATION EXTEND study.

Analysis of secondary endpoints

Secondary endpoints included the device-oriented combined endpoint of cardiac death, target vessel myocardial infarction (MI), or target lesion revascularization (TLR); all-cause and cardiac death; target vessel revascularization (TVR); and, stent thrombosis (according to ARC definitions).[2] Detailed descriptions of the study endpoints and definitions have been reported previously. [1] Statistical analysis will be performed with the log-rank test at a two-sided 0.05 significance level.

Cox proportional hazard models will be used to estimate hazard ratios (HR) with 95% confidence intervals (CI) for the comparison between EES vs. BMS. Landmark analyses will be performed, setting the landmark points at 1 and 5 years to distinguish the results of EXAMINATION trial from the extended follow-up of the EXAMINATION EXTEND study.

Subgroup analysis

Patient-oriented and device-oriented combined endpoints will be analyzed according to prespecified subgroup of patients. The following subgroups have been pre-specified:

- gender,
- age>75,
- diabetes,
- post-PCI TIMI <3,
- multivessel disease,
- ejection fraction <30%,
- Primary PCI (STEMI < 12 h)
- Killip class >I,
- ST-segment resolution >70%,
- use of aspiration thrombectomy catheters,
- left anterior descending as infarct-related artery.

Sample Size Calculation and Assumptions

The sample size of the EXAMINATION EXTEND study was based on the sample size considerations for the original trial, which was powered for a superiority of EES over BMS in terms of patient-oriented composite endpoint at 1-year. [1] After allowing for an expected attrition rate of 7·0%, the overall sample size of 1498 patients (749 per group) resulted in 85% power to detect a 20% reduction in the rate of the primary endpoint at 10 years (i.e., to an approximate event rate of 38·0% in the control group and 30·4% in the EES group) and a 2-sided type I error rate $\alpha = 0.05$. Secondary endpoints are not powered.

Statistical Analyses

Statistical testing of the primary endpoint will be performed with the log-rank test at a two-sided 0.05 significance level for the comparison of XIENCE V arm to VISION arm.

Analyses of other study endpoints will be descriptive in nature, using hazard ratios and their respective two-sided 95% confidence intervals.

Count variables will be presented as percentages, continuous variables as means (and medians and interquartile ranges whenever appropriate).

For time-to-event variables, survival curves will be constructed using Kaplan-Meier estimates, and log rank test results will be displayed for descriptive purposes only. Landmark analyses will be performed, setting the landmark points at 1 and 5 years to distinguish the results of EXAMINATION trial from the extended follow-up of the EXAMINATION EXTEND study.

All statistical analyses will be performed using Stata 15 (StataCorp 2017, Stata Statistical software: release 15. College station, TX, Statacorp LLC) and SPSS software, version 25 (IBM Corporation, Armonk, NY, USA).

REFERENCES

1. Sabate M, Cequier A, Iniguez A, et al. Rationale and design of the EXAMINATION trial: a randomised comparison between everolimus-eluting stents and cobalt-chromium bare-metal stents in ST-elevation myocardial infarction. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology* 2011; **7**(8): 977-84.
2. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007; **115**(17): 2344-51.