# STATISTICAL ANALYSIS PLAN

A Prospective, Multicenter, Randomized, Open-label Trial to Compare Efficacy and Safety of Clopidogrel vs Ticagrelor in Stabilized Patients with Acute Myocardial Infarction after Percutaneous Coronary Intervention

Protocol No.: TALOS-AMI

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# STATISTICAL ANALYSIS PLAN

## SIGNATURE PAGE

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**TABLE OF CONTENTS**

**LIST OF ABBREVIATIONS AND DEFINITION OF TERMS**

## 1.0 Introduction

In AMI, adequate platelet inhibition is essential to reduce the risk of recurrent thrombotic events. For this reason, dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor has become the current mainstay of pharmacological treatment in AMI patients managed with PCI. Although, clopidogrel has an indication for use in AMI[1], potent P2Y12 inhibitors, ticagrelor and prasugrel, compared with clopidogrel have shown significantly improved clinical outcomes in terms of reducing recurrent ischemic events in large randomized trials[2,3]. Thus, current guidelines strongly recommended potent P2Y12 inhibitors for 1 year in AMI patients undergoing PCI[1].

However, along with strong anti-platelet efficacy, a higher risk for bleeding was observed for potent P2Y12 inhibitors compared with clopidogrel in these randomized trials. Intriguingly, benefit due to reduction of ischemic events and harm due to bleeding events predominates at different time points during potent P2Y12 inhibitors treatment[4]. Although the ischemic benefit was consistent throughout the first year after the index event, the benefit of ticagrelor and prasugrel over clopidogrel for reducing thrombotic risk was prominent in the early period after acute coronary syndrome (ACS) when the risk of ischemic complications was highest. In the primary PCI cohort of the PLATO (Platelet Inhibition and Patient Outcomes) trial, ticagrelor showed larger risk reduction for stent thrombosis (ST) during the first 30days of treatment compared with clopidogrel but the difference decreased over time[5]. Similarly, in the TRITON-TIMI (Therapeutic Outcomes by Optimising Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) 38 trial, prasugrel led to a 25% reduction in MI during the first month[6]. On the other hands, the opposite was true for bleeding. Landmark analyses of these two randomized trials revealed that the bleeding risk was similar in the early period of treatment, but there was a larger difference during the chronic period of treatment between potent P2Y12 inhibitors and clopidogrel. Actually most bleeding events predominantly occurred during the maintenance period of treatment[7,8]. As a consequence, to optimize net clinical benefit between early ischemic benefit and late bleeding risks in AMI patients, many physicians have focused on the novel therapeutic strategy of stepwise de-escalation using potent P2Y12 inhibitors only in the acute phase of treatment (during the first 30 days) and using the less potent clopidogrel during the chronic phase of treatment (after the first 30 days).

Despite of the evidence for the consistent efficacy and safety of potent P2Y12 inhibitors with

long-term treatment, de-escalation after ACS is quite common in clinical practice[9-12]. Data have shown that the prevalence of de-escalation during hospitalization ranges from 5% to 14%[10,11] and after discharge ranges from 15% to 28%[12]. However, at present, data from large-scale clinical studies on the topic of de-escalating antiplatelet strategy are very limited and the results of small studies are conflicting[9,13]. Recently, some randomized trials of de-escalation enrolling ACS patients have been reported[13,14]. The randomized, open-label, single-center TOPIC trial (Timing of Optimal Platelet Inhibition After Acute Coronary Syndrome) showed that in patients who have been event free for the first month after an ACS on a combination of aspirin plus a potent P2Y12 inhibitor (ticagrelor or prasugrel), de-escalation to aspirin plus clopidogrel strategy was associated with reduction of bleeding complications without increase in ischemic events[13]. Although this study did not show any differences in ischemic events between groups, play of chance cannot be ruled out given the limited sample size of the trial[15]. The open-label, multicenter TROPICAL-ACS trial (Testing Responsiveness to Platelet Inhibition Chronic Antiplatelet Treatment for ACS) randomized patients with ACS undergoing PCI to either standard treatment with prasugrel for 12 months or a de-escalation regimen (1 week of prasugrel followed by 1 week of clopidogrel and platelet function testing [PFT]–guided maintenance therapy with clopidogrel or prasugrel from day 14 after hospital discharge)[14]. The trial showed that a strategy of PFT-guided de-escalation of antiplatelet treatment was noninferior to standard treatment with prasugrel at 1 year in terms of net clinical benefit. The PFT-guided de-escalation strategy did not show any increase in ischemic events, although there was not a statistically significant reduction in bleeding. However, some experts expressed concerns about a lack of power due to the low number of endpoints events[16]. Furthermore, the routine use of PFT in ACS patients undergoing PCI is limited because it is not widely available in real world clinical practice. And, although prasugrel and ticagrelor have similar levels of platelet inhibition, it might be argued that the study findings cannot be applied to ticagrelor because its pleiotropic effects have been advocated to contribute to its overall benefits[17]. In addition, there are no studies for the de-escalation of antiplatelet treatment enrolling only AMI patients treated by PCI with newer generation DES. In PLATO study, only 60% of population were scheduled for PCI and the patients who underwent PCI received older generation DES.

Therefore, we sought to investigate the efficacy and safety of switching from ticagrelor to clopidogrel in AMI patients with no adverse event during the first month after index PCI with second generation DES.

## 2.0 Study Objective

The purpose of this trial is to investigate the efficacy and safety of switching from ticagrelor to clopidogrel in stabilized patients with AMI with no adverse events during the first month after an index PCI.

## 3.0 Study Design

This is a prospective, randomized, open-label, multi-center study. Qualified study patients who conduct screening period for 1 month will be randomized 1:1 to receive either clopidogrel + aspirin as a treatment group or ticagrelor + aspirin as a control one.

## 4.0 Enrollment

A total of 2590 qualified patients will be enrolled into the study.

## 5.0 Study Endpoints

5.1 Primary Endpoint

Composite endpoint of MACCE (CV death, MI, stroke) + BARC bleeding (type 2, 3, or 5) between 1 and 12 months after AMI.

5.2 Main Secondary Endpoints

1.BARC bleeding (type 2, 3, or 5) between 1 and 12 months after AMI.

2. Composite endpoint of MACCE (CV death, MI, stroke) + BARC bleeding (type 3, or 5) between 1 and 12 months after AMI.

3.Composite endpoint of MACCE (CV death, MI, stroke) between 1 and 12 months after AMI.

5.3 Other Secondary Endpoints

1. All-cause death between 1 and 12 months after AMI

2. CV death between 1 and 12 months after AMI

3. Recurrent MI between 1 and 12 months after AMI

4. Stroke between 1 and 12 months after AMI

5. Ischemia driven revascularization including PCI or CABG between 1 and 12 months after AMI

6. Stent thrombosis (definite or probable) between 1 and 12 months after AMI

7. Adverse event at12 months after AMI (dyspnea)

Bleeding according the BARC definition and definite or probable stent thrombosis definition are as follows[18].

Table 1. BARC Definition

| BARC Definition | | |
|---|---|---|
| Type 0 | | No bleeding |
| Type 1 | | Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health care professional |
| Type 2 | | Any overt, actionable sign of haemorrhage (e.g. more bleeding than would be expected for a clinical circumstance; including bleeding found by imaging alone) that does not fit the criteria for Types 3, 4, or 5, but does meet at least one of the following criteria:<br>(1) requiring non-surgical, medical intervention by a health care professional (2) leading to hospitalization or increased level of care<br>(3) prompting evaluation. |
| Type 3 | Type 3a | Overt bleeding plus hemoglobin drop of 3 to <5*g/dL (provided hemoglobin drop is related to bleed)<br>Any transfusion with overt bleeding |
| | Type 3b | Overt bleeding plus hemoglobin drop ≥ 5*g/dL (provided STEMI, NSTEMI drop is related to bleed)<br>Cardiac tamponade<br>Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)<br>Bleeding requiring intravenous vasoactive agents |

| | | |
|---|---|---|
| | Type 3c | Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal)<br>Subcategories; confirmed by autopsy or imaging or LP<br>Intra-ocular bleed compromising vision |
| Type 4 | | Coronary artery bypass graft-related bleeding<br>Perioperative intracranial bleeding within 48 hours<br>Reoperation after closure of sternotomy for the purpose of controlling bleeding<br>Transfusion of ≥5 U whole blood or packed red blood cells within a 48 hour period†<br>Chest tube output ≥2 L within a 24-hour period |
| Type 5 | Type 5a | Probable fatal bleeding: no autopsy or imaging confirmation, but clinically suspicious |
| | Type 5b | Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation |

184 *:Corrected for transfusion (1 U packed red blood cells or 1 U whole blood =1 g/dL hemoglobin)

185 † :Cell saver products are not counted.

186

187 Table 2 Stent Thrombosis Definition

| Stent thrombosis | |
|---|---|
| Definite* | Angiographic confirmation of stent thrombosis†<br>The presence of a thrombus‡ that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:<br>Acute onset of ischemic symptoms at rest<br>New ischemic ECG changes that suggest acute ischemia Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI) |

| | |
|---|---|
| | Non occlusive thrombus<br><br>Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.<br><br>Occlusive thrombus<br><br>TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).<br><br>Pathological confirmation of stent thrombosis<br><br>Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy. |
| Probable | Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:<br><br>Any unexplained death within the first 30 days§<br><br>Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause |

*Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation.

†The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).

‡Intracoronary thrombus.

§For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis.

## 6.0. Subject Inclusion / Exclusion Criteria

6.1 Subject Inclusion Criteria

Subject should meet all of the following criteria.

1. Age ≥ 18 years
2. Patients with AMI (STEMI or NSTEMI) who are administered aspirin and ticagrelor for 30 days after successful PCI with newer-generation drug eluting stents (DES)
3. Female patients with childbearing potential who agree to mandatory pregnancy test and have committed to using adequate contraception
4. Subjects who agree to the study protocol and the schedule of clinical follow-up, and provides informed, written consent, as approved by the appropriate IRB of the respective institution

6.2 Subject Exclusion Criteria

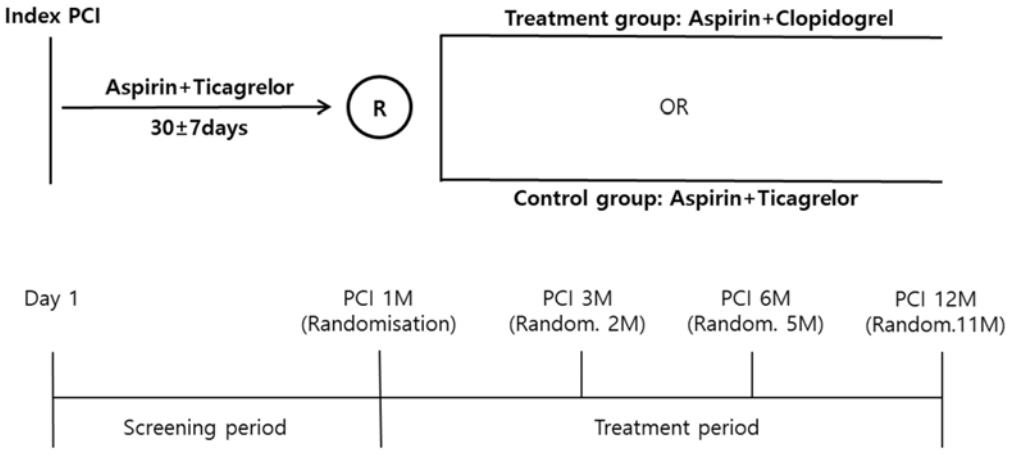
Subject should be excluded if they apply to any of the following criteria.

1. Cardiogenic shock
2. Active internal bleeding, bleeding diathesis, or coagulopathy
3. Gastrointestinal bleeding or genitourinary bleeding, hemoptysis, or vitreous hemorrhage within 2 months
4. Major surgery within 6 weeks
5. History of intracranial bleeding, intracranial neoplasm, intracranial arteriovenous malformation, or intracranial aneurysm
6. Anemia (hemoglobin < 10 g/dL) or platelet count of less than 100,000/$mm^3$ at the time of screening
7. Concomitant treatment with oral anticoagulant agent (vitamin-K antagonists or novel oral anticoagulants such as dabigatran, rivaroxaban, apixaban, or edoxaban)
8. Daily treatment with non-steroidal anti-inflammatory drug (NSAIDs) or cyclooxygenase-2 inhibitors
9. Malignancy or life expectancy of less than one year
10. Moderate or severe hepatic dysfunction (Child Pugh B or C)

11. Symptomatic patients with sinus bradycardia (sick sinus syndrome) or atrioventricular (AV) block (AV block grade II or III, bradycardia-induced syncope; except for patients implanted with permanent pacemaker)
12. Symptomatic patients with chronic obstructive pulmonary disease (Medical research council grade ≥3)
13. Intolerance of or allergy to aspirin, ticagrelor or clopidogrel
14. Subjects who are under renal replacement therapy due to end-stage renal disease or who have history of kidney transplantation
15. Galactose intolerance, lactase insufficiency or glucose-galactose malabsorption
16. Subjects who are actively participating in another clinical trial with 3 months of randomization (except for observational study)
17. Pregnant and/or lactating women
18. Subjects considered unsuitable for this study by the investigator

## 7.0 Study Procedure

7.1 Screening period



To conduct screening AMI patients based on the inclusion/exclusion criteria who (1) have been treated with ticagrelor + aspirin at least 30 ± 7 days after an index PCI, (2) received full explanation of the study details, (3) given written consent.

7.2 Randomization

Randomization will occur centrally. To randomize a patient, the investigative site will enter the subject into the designated electronic system and obtain the treatment assignment (clopidogrel + aspirin or ticagrelor + aspirin) in a 1:1 ratio. At 1 month visit after AMI, eligible subjects were assigned to each treatment group following an access to the interactive web-based response system (IWRS, Medical Excellence Inc., Seoul, Korea) by the investigator or designee. Randomization sequence was created by an independent statistician using SAS 9.3 (SAS Institute Inc. Cary, NC, USA) statistical software and was stratified by study center and type of AMI (STEMI or NSTEMI) and with a 1:1 allocation using hidden random block size.

## 8.0 Statistical Analysis

8.1 Sample Size Calculation

The present study is designed to show non-inferiority of the treatment group with aspirin plus clopidogrel versus the control group with aspirin plus ticagrelor. Sample size is based on the combined occurrence rate of ischemic and bleeding events between 1 and 12 months after AMI. According to the PLATO investigators, the event rate of primary efficacy endpoint including CV death, MI or stroke was 5.28% in the ticagrelor group and 6.60% in the clopidogrel group between 1and 12 months after the index event[2].In the meantime, since there were no reported data on the bleeding event rate associated with ticagrelor from 1 to 12months after AMI, especially BARC bleeding rate at the time of the present study design, we assumed the event rate of BARC 2, 3 and 5 bleeding from the event rates of non-CABG related PLATO major or minor bleeding during a year of ticagrelor therapy (8.7%) and non-CABG related major bleeding of first 30 days (2.47%) and after 30 days (2.17%) in the PLATO trial. For the event rate of BARC 2, 3 and 5 bleeding associated with clopidogrel from 1 to 12 months after AMI, the event rate was assumed from the event rates of non-CABG related PLATO major or minor bleeding during a year of clopidogrel therapy (7.0%) and non-CABG related major bleeding of first 30 days (2.21%) and after 30 days (1.65%) in the clopidogrel group of the PLATO trial[7].

After applying mathematical formula, the estimated BARC 2, 3 and 5 bleeding would be 4.07% in the ticagrelor group and 2.99% in the clopidogrel group. Thus, the expected event

rate of the primary endpoint from 1 to12 months after index PCI was 9.35% (ischemic event of 5.28% + bleeding event of 4.07%) in the ticagrelor group and 9.59% (ischemic event of 6.6% + bleeding event of 2.99%) in the clopidogrel group. We chose the non-inferiority margin in accordance with clinical judgment and other relevant studies with a non-inferiority design at the present study design. The non-inferiority margin of two contemporary trials of antiplatelet treatment after PCI that were available up to that time was equivalent to a 40% increase in the expected event rate[18, 19]. The steering committee decided that the non-inferiority margin in our study should be less than a 40% increase compared to the expected event rate of the control group. After considering clinically acceptable relevance and the feasibility of study recruitment, we finally selected the non-inferiority margin of 3.0%, which was equivalent to a 32% increase in the expected event rate. Sample size calculations (PASS 13, NCSS, LLC, Kaysville, Utah, USA) were performed based on one-sided α of 0.05 and a power of 80 %. To achieve these goals, a total of 2,230 patients were needed. With a loss to follow-up rate of 10%, a total of 2,590 (1,295 patients in each group) patients were required.

8.2 Analysis population

The Intent to Treat (ITT) Population

The ITT population is defined as all randomized patients at 1 month after AMI, regardless of their adherence with the entry criteria, regardless of treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol[19]. Only some specific reasons that might cause an exclusion of a patient from the ITT population:

- No treatment was applied at all
- No data are available after randomization

The Per Protocol (PP) Population

The PP population is the subset of ITT population consisting of all patients who receive and retain the treatment during 12 months after PCI[19]. Some specific reasons that might cause an exclusion of a patient from the PP population:

- Violation of entry criteria including inclusion and exclusion criteria
- Withdrawal of consent

- Concomitant treatment of oral anticoagulant agent (vitamin-K antagonists or novel oral anticoagulants such as dabigatran, rivaroxaban, apixaban, or edoxaban) during the study period
- Poor compliance
  - Conversion from ticagrelor + aspirin to clopidogrel + aspirin during RCT procedure and vice versa
  - Discontinuation of test or control drugs for 7 days or longer

* In the cases of withdrawal of consent, concomitant treatment of oral anticoagulation agent and poor compliance, their data will be used for statistical analyses until such events occur.

8.3 Primary endpoint analysis

- The non-inferiority test between 1 and 12 months after AMI will be based on the Kaplan-Meier estimates. A 95% two-sided confidence interval will be computed for the difference event rate (clopidogrel + aspirin) – event rate (ticagrelor + aspirin). The clopidogrel group will be judged as non-inferior to the ticagrelor if the upper confidence limit is less than the predetermined non-inferiority margin of 3% (absolute risk difference).
- The hypothesis of non-inferiority test will be based on the difference of proportions. Let $r_T$ denote the true event proportion in the test arm (clopidogrel + aspirin) between 1 and 12 months, and $r_C$ denote the true event proportion in the control arm (ticagrelor + aspirin) between 1 and 12 months. The hypotheses are

$$H_0: r_T - r_C \geq \Delta$$

$$H_A: r_T - r_C < \Delta$$

  The $\Delta$ is the non-inferiority margin, and is taken to be 0.03. The test will be performed as a one-sided test at alpha=0.05.

  The null hypothesis shall be rejected at alpha=0.05 if the one-sided p-value is less than 0.05. When this occurs, the upper limit of the two-sided 95% confidence interval will be less than 3%.
- The stratified log-rank test will be performed to test the comparison between time to event distribution Stratification factors will be prior use of STEMI (yes or no).

- Unless otherwise specified, the stratified hazard ratio between two treatment groups along with CI will be obtained by fitting a stratified Cox model with the treatment group variables as unique covariate. Stratification factors will be same as above.
- If the non-inferiority analysis passed the acceptance criterion, a superiority analysis will be performed. Statistical superiority is achieved when the upper limit of the two-sided 95% confidence interval of the risk difference is less than 0%. The type I error for this analysis is protected by the non-inferiority analysis, and no alpha adjustment would be appropriate
- Subgroup analyses will be performed by the primary endpoint categorized by type of AMI (STEMI vs NSTEMI), Subgroup analyses will be performed by the primary endpoint categorized by type of AMI (STEMI vs NTEMI), Gender, Age (≥75 vs <75), Diabetes, LVEF (≥40% vs <40%), eGFR (≥60 vs <60), type of implanted stents (Xience vs Resolute vs Synergy stents), Bleeding risk according to the ARC criteria (high vs low bleeding risk), CYP2C19 loss-of-function carrier status (carrier vs non-carrier).
- The primary analysis population for primary and secondary endpoints will be the Intention-to-Treat (ITT) population. The primary endpoint analysis will also be performed on the Per Protocol (PP) population as subsequent analysis.
- A primary endpoint analysis stratified by the institutions as a sensitivity analysis. Strata will be divided by the accrual number of institution based on quartiles.

## 8.4 Main Secondary Endpoint Analyses

The secondary endpoints will be composed of two families. The first family consists of the composite endpoint of MACCE (CV death, MI, stroke) plus BARC bleeding (type 2, 3, or 5). The second family will consist of MACCE plus BARC bleeding (type 3, or 5), MACCE, and BARC bleeding (type 2, 3, or 5). The endpoints from the second family will be tested hierarchically, thereby maintaining the study-wise alpha level. These secondary endpoints will only be tested if both the primary composite endpoint and BARC bleeding are significant at non-inferiority analysis, and superiority analysis. Composite endpoint of MACCE plus BARC bleeding (type 3, or 5) will be tested first, and only if this is significant, the composite endpoint of MACCE only will be tested afterwards. BARC bleeding (type 2, 3, or 5) will be tested only if both of the above endpoints are tested significant.

## 8.5 Other Secondary Endpoint Analyses

The endpoint in this section will be evaluated according to the secondary endpoints described in section 5.2 under the ITT population. Most of secondary analyses were performed by Cox proportional hazard ratio with 95% confidence interval. The following endpoints will be analyzed in using Chi-square test or Fisher's exact test.

- The occurrence of dyspnea at 12 months

8.6 Analysis of Subgroups

The primary and major secondary endpoints will be analyzed in the pre-specified subgroups to evaluate the consistency of results among subgroups of interest. Outcome will be evaluated in the following subgroups:

1) Type of AMI: STEMI vs NTEMI
2) Gender
3) Age: (≥ vs. < median and ≥ vs. <75 years)
4) Diabetes mellitus
5) LVEF: (≥ vs. < median and ≥ vs. <40%)
6) eGFR: ≥60 vs. <60
7) type of implanted stents: Xience vs. Resolute vs. Synergy stent
8) Bleeding risk according to the ARC criteria: high vs. low bleeding risk
9) CYP2C19 loss-of-function allele carrier status: carrier vs. non-carrier

8.7 General Statistical Methodology

- For continuous variables, summary statistics will include means, standard deviations, medians and interquartile range based on normality of variables. Groups will be compared using t-tests or analysis of variance. Where normality violation is observed, Wilcoxon rank-sum test will be performed to compare groups.
- For categorical variables, summary statistics will include numbers and percentages. Group will be compared using Chi-square test or Fisher's exact test.
- Time-dependent variables will be analyzed using the Kaplan-Meier survival curve and group comparison will be used by log-rank statistics including the number of patients-at-risk.

8.8 Missing data

- Missing variables will not be imputed for planned analyses, except where otherwise specified.
- The primary endpoint will be based on Kaplan-Meier estimates, which automatically account for censored data.
- For sensitivity, purposes, missing data was imputed the most recent data (Last Observation Carried Forward method).

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