



## 2 Introduction

The aim of the *Carotid Artery Stenting during Endovascular treatment of acute ischemic Stroke* (CASES) trial is to assess the efficacy and safety of immediate carotid artery stenting (CAS) in patients undergoing endovascular treatment (EVT) for intracranial large vessel occlusions (LVOs) and concomitant carotid artery atherosclerotic stenosis.

The purpose of this document is to support the statistical analysis plan (SAP) of the CASES study and provide an additional clarification of the original SAP.

## 3 Corrections

On page 4 of the SAP, the secondary endpoint “Any ischemic stroke within 90 days” should be “Any ischemic stroke/TIA within 90 days”

On page 9 of the SAP, it was written: “Note that endpoints 1 to 3, 5, and 7 will not be imputed and an analysis on observed data will be performed. “. This should be “Note that endpoints 1 to 3, and 5 to 7 will not be imputed and an analysis on observed data will be performed.”

## 4 Analysis populations

A blinded-to-outcome review meeting will be conducted prior to final database lock to determine the allocation of patients to each analysis set.

All major protocol deviations leading to exclusion from the Per Protocol Set (PPS), as well as any other exclusions, will be fully documented in the Analysis Sets Specification Document. This document will be finalized, dated, and signed prior to database lock.

The Per Protocol Set (PPS) will include all randomized patients who provided informed consent, or who died before informed consent could be obtained, and who did not have any major protocol deviations. Crossovers will be classified as major protocol deviations irrespective of the reason for crossover. Other major protocol deviations include: absence of an EVT procedure (catheterization only or no arterial access puncture performed, if there was intracranial recanalization at baseline DSA, patients will remain in the PPS) and non-atherosclerotic etiology as determined on baseline CTA following central review by the imaging core laboratory.

In cases of uncertainty based on the core laboratory assessment or data recorded in the eCRF, a third independent assessment will be performed, with the final determination made by the CASES coordinating team.

## 5 Procedure for accounting for missing, unused and spurious data

For all efficacy endpoints and the adjusting factors used in the efficacy analyses, the imputation process is described in the SAP. Several variables required for subgroup analyses will be added to the imputation model: sex, stenosis (intermediate grade stenosis (50-70%), high-grade stenosis (>70%) versus occlusion of the ICA), CTA occlusion location (ICA, M1, M2),

performance of PTA during EVT (yes or no), onset to groin puncture time (tertiles), the ASPECT score ( $>6$  versus  $\leq 6$ ) and prior IVT (yes/no) within 90 days.

Thus, in conclusion, the imputation model will contain the following variables: the assigned treatment group and the endpoints mRS at 90 days, the NIHSS score at 24 hours and at day 5-7, or at discharge, the TICl score after EVT, final infarct volume on brain CT at 24 hours and arterial occlusive lesion (AOL) score on CTA at 24 hours, carotid artery re-occlusion at 24 hours and 90 days, any stroke within 90 days, symptomatic intracranial hemorrhage (Heidelberg criteria) within 90 days, recurrent ipsilateral TIA/ischemic stroke within 90 days, mortality at 90 days and EQ5D-5L at 90 days, age, the pre-stroke mRS score, stroke severity, collateral score, time from symptom onset to randomization), sex, stenosis grade of the symptomatic ICA on CTA, intracranial occlusion location on CTA, ASPECTS score on baseline NCCT, prior IVT, performance of PTA during EVT, and time from onset or last seen well to groin puncture.

The stenosis variable will be included in the imputation model using the categories as recorded in the CRF. The CTA occlusion location variable will be included in the imputation model using the categories as recorded in the CRF, with empty categories excluded. Subgroup categories will subsequently be derived after imputation. For stenosis, categories will be defined as 50–69%, 70–99%, and occlusion. For intracranial occlusion location, categories will be defined as ICA, M1, and M2. Some subgroups are determined by the median or tertiles of a specific variable. The median and tertiles will be derived on the combined 10 imputed data sets. The obtained value will be used in all 10 imputed data sets.

## 5 Safety analysis

The safety analyses will be performed in the Safety Set (SS) by actual treatment received.

The SS extends the FAS by including additional patients from the safety registry who have available mortality and sICH data, but for whom no informed consent had been obtained. No data imputation was performed for these registry patients.

Unadjusted logistic regression analysis for embolization in new vascular territories during EVT, sICH, any ICH, any ECH and mortality within 90 days will be conducted using observed data.

As a sensitivity analysis, the unadjusted regression analyses for sICH and mortality within 90 days will be performed on the imputed safety set (SS), defined as the imputed FAS combined with additional records from the safety registry, for which no imputation is planned. In case the overall event rate is larger than 10%, an adjusted analysis for these will be performed on the imputed SS. The adjustment is made for age, baseline NIHSS score, pre-stroke mRS score, collateral score on baseline CTA and onset to randomization time.