Effect of Tirzepatide on Functional Outcomes in Patients With Acute Ischemic Stroke Undergoing Endovascular Thrombectomy: A Multicenter, Randomized, Controlled, Blinded Outcome Assessment Trial (TOPAZ)

V2.5, 03 September 2026
Ethics/IRB Approval: 16 September 2026

Revision History

Version	Date	Description of Changes
V2.4	03 July 2026	Previous version of the Statistical Analysis Plan.
V2.5	03 September 2026	The planned sample size was revised to 726 participants (363 per group), based on a more conservative assumed absolute between-group difference of 10 percentage points in the proportion of patients achieving mRS 0-1 at 90 days. The primary outcome and other key elements of the statistical analysis plan remained unchanged. This amendment was finalized before enrollment of the first participant.

1. Sample Size Calculation

Based on previous studies, approximately 28% of patients with anterior-circulation LVO ischemic stroke achieve a favorable functional outcome (mRS 0-1) at 90 days following successful recanalization. Assuming that early intervention with tirzepatide increases the proportion of patients achieving a favorable outcome by 10%, resulting in a 90-day favorable outcome rate of 38% in the tirzepatide group (a conservative estimate based on the GALLOP-2 study), a total of 344 patients per group would be required to provide 80% statistical power to detect this difference at a two-sided α level of 0.05. Allowing for a 5% loss to follow-up, the estimated total sample size is 726 patients (363 per group).

2. Statistical Analysis Plan

Full Analysis Set (FAS)

The Full Analysis Set will be defined according to the ITT principle and will include all randomized participants who receive at least one study-related treatment:

- Intervention group: tirzepatide plus guideline-recommended standard care.
- Control group: guideline-recommended standard care alone.

The FAS will serve as the primary efficacy analysis population. Missing data will be handled using multiple imputation methods to ensure robustness of the analyses.

Per-Protocol Set (PPS)

The PPS will include participants who complete treatment and follow-up in accordance with the protocol without major protocol deviations.

Major protocol deviations include, but are not limited to:

- Violation of major eligibility criteria;
- Receipt of prohibited concomitant treatments affecting efficacy evaluation;
- Significant deviation from the prescribed tirzepatide dosing regimen;
- Follow-up assessments conducted outside predefined windows (>14 days);
- Missing key efficacy endpoints.

The PPS will be used for supportive sensitivity analyses. Any discrepancies between PPS and FAS results will be investigated and reported.

Safety Analysis Set (SAS)

The Safety Analysis Set will include all participants who receive at least one study treatment and undergo at least one post-treatment safety assessment.

All safety analyses will be conducted using the SAS population regardless of study completion status.

4. Statistical Analysis Methods

(1) Baseline Characteristics

Continuous Variables

Normality will be assessed using the Shapiro-Wilk test.

- Normally distributed variables will be summarized as mean ± standard deviation (SD) and compared using independent-sample t-tests.
- Non-normally distributed variables will be summarized as median (interquartile range [IQR]) and compared using the Wilcoxon rank-sum test.

Categorical Variables

Categorical variables will be summarized as frequencies and percentages.

- Between-group comparisons will be performed using the Chi-square test.
- Fisher's exact test will be used when expected cell counts are <5.
- Ordinal variables (e.g., baseline mRS score) will be analyzed using the Wilcoxon rank-sum test.

(2) Efficacy Analyses

Primary Efficacy Endpoint

Endpoint

Proportion of participants achieving an excellent functional outcome, defined as **mRS 0-1 at Day 90 (±7 days)** after randomization.

Statistical Analysis

The primary analysis will be performed using the FAS population.

A generalized linear model (GLM) with a binomial distribution and log link will be used to estimate:

- Relative Risk (RR)
- 95% Confidence Interval (CI)

A sensitivity analysis using the PPS population will be conducted to assess robustness.

Secondary Efficacy Endpoints

Binary Outcomes

Examples include:

- Proportion achieving mRS 0-2 at Day 90

These outcomes will be analyzed using generalized linear models to estimate RR and 95% CI. Between-group comparisons will be performed using Chi-square tests or Fisher's exact tests as appropriate.

Continuous Outcomes

Examples include:

- Change in NIHSS score from baseline
- EQ-5D-5L utility score

For repeated NIHSS measurements:

- Repeated-measures analysis of variance (ANOVA) will be used for normally distributed data.
- Friedman tests will be used for non-normally distributed data.

EQ-5D-5L utility scores will be compared using:

- Independent-sample t-tests for normally distributed data; or
- Wilcoxon rank-sum tests for non-normal data.

Ordinal Outcomes

The overall distribution of 90-day mRS scores will be analyzed using a proportional odds ordinal logistic regression model.

Results will be reported as:

- Common Odds Ratio (cOR)
- 95% Confidence Interval

to evaluate the overall shift in functional outcomes between treatment groups.

(3) Safety Analyses

Safety analyses will be conducted using the Safety Analysis Set (SAS).

Adverse events, including bleeding events, thrombocytopenia, allergic reactions, gastrointestinal adverse events, and other safety outcomes, will be summarized descriptively according to:

- Incidence
- Severity (graded according to CTCAE Version 5.0)

- Outcome
- Differences in major safety endpoints, including all-cause mortality at Day 90, symptomatic intracranial hemorrhage (sICH), will be analyzed using generalized linear models to estimate RR and 95% CI.

Other adverse-event rates will be compared using Chi-square tests or Fisher's exact tests as appropriate.