GZME Sample Size Simulation Report

**Background**

This report aims to document the simulation assumptions, method and results of sample size calculation for China in J2S-MC-GZME, *A Phase 3, Multicenter, Randomized, Double-Blind Study to Investigate the Efficacy and Safety of Brenipatide Compared with Placebo for the Treatment of Adult Participants with Moderate-to-Severe Alcohol Use Disorder (RENEW-ALC-1)* for brenipatide (LY3537031).

**The co-primary endpoints** for period I are **reduction in HDDs** or **WHO 2-level reduction in RDLs**. Specifically, from the 4-week baseline period to the final 4 weeks of Period I:

* Mean relative reduction in HDDs
* Percentage of participants who achieve a WHO 2-level reduction in RDLs, assessed by TLFB

HDDs is heavy drinking day(s) and RDL(s) is risk drinking level(s).

**The primary endpoint** for period II is **the percentage of participants who maintain a WHO 2-level reduction in RDLs** for pooled brenipatide doses.

GZME is a 4-arm study to enroll 1100 participants, with allocation ratio of LY 1.5 mg: LY 0.75 mg: LY 0.3 mg: placebo to be 2:2:3:4.

A diagram of a diagram

AI-generated content may be incorrect.

**Simulation Objective**

The simulation is to evaluate the country allocation of China in GZMH and calculate the show trend probability using simulation under 3 samples sizes of China: 82, 90 and 100.

**Simulation Assumption**

Eligible participants will be randomly assigned in a 2:2:3:4 ratio to the intervention groups.

1. **Sample size assumptions for Period I**

A sample size of 1100 participants provides more than 90% power for comparison of at least 1 dose level of brenipatide (0.3 mg, 0.75 mg, and/or 1.5 mg) with placebo for the dual primary endpoints, relative reduction in HDDs or WHO 2-level reduction in RDLs, from the 4-week baseline period to the final 4 weeks of Period I.

***WHO 2-level reduction in RDLs***

A 2-sided chi-squared test is used to evaluate the percentage of participants who achieve a WHO 2-level reduction in RDLs, assessed by TLFB, based on the following assumptions:

* 60% of participants will achieve a WHO 2-level reduction in RDLs for each brenipatide dose level
* 40% of participants will achieve a WHO 2-level reduction in RDLs for the placebo group, and
* a treatment discontinuation rate of 30% for each brenipatide dose level and placebo groups.

***Mean relative reduction in HDDs***

A 2-sided Satterthwaite t-test is used to evaluate the mean relative reduction in HDDs, based on the following assumptions:

* a 20% difference in the mean relative reduction in HDDs for each brenipatide dose level compared with the placebo group
* a standard deviation of 25 for each brenipatide dose level and placebo groups, and
* a treatment discontinuation rate of 30% for each brenipatide dose level and placebo groups.

1. **Sample size assumptions for Period II**

A sample size of 1100 participants also provides more than 80% power, by pooling participants into a single brenipatide group and into a single placebo group for analysis.

A 2-sided chi-squared test is used to evaluate the percentage of brenipatide responders from Period I, who maintain a WHO 2-level reduction in RDLs for the entire duration of Period II, based on the following assumptions:

* 66% of brenipatide responders from Period I will maintain a WHO 2-level reduction in RDLs for the pooled brenipatide group
* 46% of brenipatide responders from Period I will maintain a WHO 2-level reduction in RDLs for the pooled placebo group, and
* a treatment discontinuation rate of 20% for both pooled brenipatide and placebo groups.

**Simulation Method and Analysis Models**

For period I,

* WHO 2-level reduction in RDLs: the binary endpoint is generated using binomial distribution with parameters specified in the “Simulation Assumption” Section.
* Mean relative reduction in HDDs: the continuous endpoint is generated using normal distribution with brenipatide mean relative reduction assumed to be 40% and placebo mean relative reduction assumed to be 20%.

For period II, the binary endpoint is generated using binomial distribution with parameters specified in the “Simulation Assumption” Section. The number of participants entered the period II will be calculated as

where 700/1100 is the proportion of brenipatide in period I, 2/3 and 1/3 are the re-randomization ratio in period II, 0.66 is the assumed proportion of participants who achieved WHO 2-level reduction in RDLs in period II and 20% is the assumed dropout rate.

In each simulation, the p value of comparisons between each brenipatide group and the placebo group are calculated using the corresponding tests for the whole trial and China subgroup. The simulation is repeated 50000 times to evaluate the show trend probability of China. The simulation seed for *j*th iteration is 1000\*j. For the co-primary endpoints, the alpha will be split to be 0.025 each. The alpha will also be equally split by 3 for 3 brenipatide arms.

For show trend probability, both showing 50% effect size and showing same direction are evaluated.

**Computation Tools**

R version 4.3.2

**Simulation Code and Results**

The simulation code is available at

The simulation results:

Period I:

|  |  |  |  |
| --- | --- | --- | --- |
| China Sample Size | Global Sample Size | Show Trend Probability - (50% effect size) | Show Trend Probability - (same direction) |
| 80 | 1100 | 0.9994 | 0.9999 |
| 90 | 1100 | 0.9994 | 0.9999 |
| 100 | 1100 | 0.9997 | 0.9999 |
| 110 | 1100 | 0.9997 | 1 |

Period II:

|  |  |  |  |
| --- | --- | --- | --- |
| China Sample Size | Global Sample Size | Show Trend Probability - (50% effect size) | Show Trend Probability - (same direction) |
| 80 | 1100 | 0.729 | 0.773 |
| 90 | 1100 | 0.735 | 0.821 |
| 100 | 1100 | 0.737 | 0.832 |
| 110 | 1100 | 0.733 | 0.841 |