**Study GS-US-454-4646 Japan Sample Size and Probability of Consistency**

Purpose:

To demonstrate the consistency of treatment effect between the Japanese population and rest of world (ROW), Method 2 proposed in ‘Basic Principles on Global Clinical Trials’ to determine Japanese sample size is used in our calculation of the assurance probability.

The estimated enrollment for Japan and ROW (rest of world) for Study GS-US-454-4646 are shown below:

|  |  |  |
| --- | --- | --- |
| **Country/Region** | **No. of Subjects**  **for Primary**  **Histologic Endpoint** | **% of Total** |
| Japan | 102 | 7% |
| ROW | 1398 | 93% |
| **Total** | **1500** | **100%** |

**Primary Histologic Efficacy Endpoint:**

The primary efficacy endpoint for Study GS-US-454-4646 is the proportion of subjects with a ≥ 1‑stage improvement in fibrosis without worsening of NASH at Week 72. The week 72 interim analysis will be conducted after approximately 1500 subjects have completed their Week 72 visit. The assumption of treatment response difference between the CILO/FIR group and the placebo group is 10% with 12% response rate in the placebo group.

Let D1 and D2 be the difference in the rate of fibrosis improvement without NASH worsening in Japan and ROW. Assume the treatment effects are the same across all regions; the probability that D1 and D2 consistently exceed 0 is 90.03% in Study GS-US-454-4646 under the current enrollment plan in each region (where 170\*(1500/2500) = 102 Japan subjects will be included in the Week 72 analysis).

The calculation of the probability of consistency with exact approach is as below:

Denote

as the total number of responders in the active arm for region ,

as the total number of responders in the placebo arm for region ,

as the number of subjects in the active arm for region ,

as the number of subjects in the placebo arm for region .

Then , since according to our sample size allocation of ratio 3:2 between the active arm and the placebo arm.

So, the probability of consistency is

We assume the response rates are the same across all 2 regions. Denote as the response rate for the active arm, and as the response rate for the placebo arm. Then

For each region , by summing over the probability of all cases where , we could derive the probability of . Probability of consistency is calculated by multiplying the probabilities of all regions together.

we assume and

where , the total sample size in Japan

Using the same approach, it is shown that when 48 Japan subjects are enrolled, the probability of consistency for the primary efficacy endpoint will be >80%.