**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 (Clinical Endpoint)** | **% of Total** |
| Japan | 120 (200) | 8% |
| ROW | 1380 (2300) | 92% |
| **Total** | **1500 (2500)** | **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 92.19% in Study GS-US-454-4646 under the current enrollment plan in each region (where 200\*(1500/2500) = 120 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 all three such probabilities 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%.

**Clinical efficacy endpoint:**

The clinical efficacy endpoint for Study GS-US-454-4646 is the event free survival (EFS) at the end of the study. Assuming the clinical event rate in the placebo group at year 5 is 30% (EFS rate 70%), CILO/FIR is expected to improve the EFS rate to 75.2% (hazard ratio [HR] of 0.80). To obtain the required 691 clinical events, a total of 2500 subjects (n = 1500 CILO/FIR, n = 1000 placebo, ratio 3:2) will be enrolled and followed for up to approximately 7 years (including an accrual period of 2 years), with a dropout rate of 20% for both treatment groups.

Using Method 2, let be the treatment effect between CILO/FIR group and the placebo group, the probability of consistency for the clinical efficacy endpoint is

wheredenotes the two regions, Japan and ROW, denote the hazard rate in the placebo arm and the CILO/FIR arm in region *i*.

Under the normal approximation, , where are the number of events in the placebo group and the CILO/FIR group in region *i.*

Knowing for all *i*’s, we can calculate the assurance probability for the clinical efficacy endpoint as 79.32% when number of Japan subjects is 200 for final analysis. To obtain an assurance probability of 80% or higher for clinical efficacy endpoint, 213 Japan subjects are needed.