1. Appendix A

Relationship between the Overall Treatment Effects and the Regional Treatment Effects. Let $K$ be the total number of participating regions and $m_i$ be the total number of patients in the $i^{th}$ region $(i = 1, 2, \ldots, K)$. The difference in the treatment effects between the test product and the placebo in all participating regions ($\Delta$) can be expressed as follows.

$$\Delta = \mu_T - \mu_P$$

$$= \frac{1}{\sum_{j=1}^{K} m_i} \left[ \sum_{j=1}^{m_i} (X_{ij} - Y_{ij}) + \sum_{i=2}^{K} \sum_{j=1}^{m_i} (X_y - Y_y) \right]$$

$$= \frac{m_1}{\sum_{i=1}^{K} m_i} \sum_{j=1}^{m_1} (X_{ij} - Y_{ij}) + \sum_{i=2}^{K} \frac{m_i}{m_1} \sum_{j=1}^{m_i} \frac{\sum_{j=1}^{m_i} (X_y - Y_y)}{\sum_{i=2}^{K} m_j}$$

$$= \lambda_1 \Delta \lambda_1 + (1 - \lambda_1) \Delta \lambda_1$$

Where,

$$\lambda_1 = \frac{m_1}{\sum_{i=1}^{K} m_i} \Delta \lambda_1 = \frac{\sum_{j=1}^{m_1} (X_{ij} - Y_{ij})}{m_1}$$

$$\lambda_1 = \frac{\sum_{i=2}^{K} \sum_{j=1}^{m_i} (X_y - Y_y)}{\sum_{i=2}^{K} m_j}$$