Appendix D – Trial sequential analysis for a) cumulative 24-hour oral morphine equivalent consumption and b) cumulative difference in area under the curve (AUC) rest pain over 24-hours. The red line represents the cumulative Z-score. The inward sloping red lines represent the trial sequential monitoring boundaries. The outward sloping red lines represent the futility region. The horizontal blue lines represent the threshold for significance.

![Sample Size is a Two-sided graph]

- Sample Size = 198
- Z-curve
- Sample Size = 160
- Number of patients (Linear scaled)
Supplemental material

**Figure 2b:**

Panel showing a two-sided graph with cumulative Z-scores plotted against the number of patients. The graph includes a line labeled "Z-curve" indicating a sample size of 1593.

The X-axis represents the number of patients (linear scaled), while the Y-axis shows the cumulative Z-scores, favoring either the intervention or control groups. The graph illustrates the distribution of effects across different patient numbers.