# Adaptive designs with adaptive randomization

## Description

The simulation report presents key operating characteristics of an adaptive design for a dose-finding Phase II clinical trial with multiple interim analyses aimed at updating the randomization scheme based on the accumulating efficacy data.

## Table 1. Primary efficacy endpoint

| **Parameter** | **Value** |
| --- | --- |
| Endpoint type | Normal |
| Direction of favorable outcome | A lower value of the endpoint indicates a more favorable outcome |

## Table 2. Trial stages

| **Stage** | **Planned number of enrolled patients** |
| --- | --- |
| Stage 1 | 50 |
| Stage 2 | 50 |
| Stage 3 | 50 |
| Stage 4 | 50 |

## Table 3. Treatment effect assumptions

| **Trial arm** | **Parameter** | **Value** |
| --- | --- | --- |
| Placebo | Mean | -10 |
|  | SD | 14 |
| Dose 1 (100) | Mean | -12 |
|  | SD | 14 |
| Dose 2 (200) | Mean | -14 |
|  | SD | 14 |
| Dose 3 (400) | Mean | -16 |
|  | SD | 14 |
| Dose 4 (800) | Mean | -18 |
|  | SD | 14 |

## Table 4. Decision rule parameters

| **Parameter** | **Value** |
| --- | --- |
| Fixed randomization ratio in the placebo arm (%) | 20 |
| Balance parameter for adaptive randomization | 2 |
| Clinically relevant improvement over placebo | -6 |

## Table 5. Parameters of candidate dose-response models used in the MCPMod method

| **Model** | **Parameters** |
| --- | --- |
| Exponential | Delta = 400 |
| Emax | ED50 = 600 |
| Logistic | ED50 = 400, Delta = 50 |

This table defines non-linear parameters of the candidate dose-response models and therefore no parameters are specified for the linear model.

## Table 6. Trial design parameters

| **Parameter** | **Value** |
| --- | --- |
| Length of the patient enrollment period | 36 |
| Median enrollment time | 24 |
| Patient dropout rate (%) | 5 |
| Length of the treatment period | 4 |

Median enrollment time: Time point by which 50% of the patients will be enrolled into the trial.

## Table 7. Simulation parameters

| **Parameter** | **Value** |
| --- | --- |
| One-sided Type I error rate | 0.025 |
| Number of simulations | 1000 |

## Figure 1. Candidate dose-response models used in the MCPMod method.



Black curve: Linear model, Blue curve: Exponential model, Red curve: Emax model, Green curve: Logistic model.

## Table 8. Simulation results: Sample size by stage

| **Stage** | **Statistic** | **Sample size** |
| --- | --- | --- |
| Stage 1 | Min | 56 |
|  | Median | 70 |
|  | Mean | 69.6 |
|  | Max | 84 |
| Stage 2 | Min | 34 |
|  | Median | 59 |
|  | Mean | 59.1 |
|  | Max | 86 |
| Stage 3 | Min | 28 |
|  | Median | 59 |
|  | Mean | 58.3 |
|  | Max | 81 |
| Stage 4 | Min | 0 |
|  | Median | 13 |
|  | Mean | 13 |
|  | Max | 33 |

## Table 9. Simulation results: Sample size by trial arm

| **Dose** | **Statistic** | **Sample size** |
| --- | --- | --- |
| Placebo | Min | 37 |
|  | Median | 38 |
|  | Mean | 38 |
|  | Max | 40 |
| Dose 1 (100) | Min | 30 |
|  | Median | 35 |
|  | Mean | 35.3 |
|  | Max | 73 |
| Dose 2 (200) | Min | 24 |
|  | Median | 36 |
|  | Mean | 36.3 |
|  | Max | 43 |
| Dose 3 (400) | Min | 28 |
|  | Median | 39 |
|  | Mean | 39 |
|  | Max | 45 |
| Dose 4 (800) | Min | 27 |
|  | Median | 41.5 |
|  | Mean | 41.5 |
|  | Max | 53 |

## Table 10. Simulation results: Comparison of traditional and adaptive designs

| **Design** | **Power (%)** |
| --- | --- |
| Traditional | 77.2 |
| Adaptive | 76.2 |

Probability of a statistically significant dose-response relationship based on the MCPMod method.