MEDAL: Design and Simulation Report

Generated by FACTS Core Engine for Time-to-Event Endpoint

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# Introduction

## Background

This document describes the features of the simulated design for the MEDAL trial, including the statistical models, decision rules, and simulation scenarios as input into the (Fixed and Adaptive Clinical Trial Simulator) software. The operating characteristics for the simulations are also summarized.

## Primary Endpoint

The primary endpoint time to recovery, defined as sufficient resolution of symptoms sustained for 5 days. This is a time-to-event where an event is considered to be a positive outcome for a subject. All subjects will be monitored for events until 8 weeks after the last subject enrolled, or until 1320 subjects have had an event , whichever occurs first.

## Treatment Arms

The trial will enroll up to a maximum of 1320 subjects, randomized among 6 treatment arms, including a control arm and 6 treatment arms. We label these arms generically by their arm index as: 0 (Control), 1, 2, 3, 4, 5, 6. We also denote by the effective dose strength of each of the arms.

The arms in the trial are given as follows:

Table-1: Treatment Arms

|  |  |
| --- | --- |
| Arm name | Arm strength |
| control |  |
| arm\_1 |  |
| arm\_2 |  |
| arm\_3 |  |
| arm\_4 |  |
| arm\_5 |  |
| arm\_6 |  |

# Statistical Modeling

This section describes the statistical modeling used in the design. The modeling is Bayesian in nature.

## Primary Endpoint Model

Let be the event time (in weeks) for the primary endpoint for the subject, where an event represents a positive outcome for the subject. We model the event times for the control arm as  
exponential:

where is the baseline hazard rate (events per week). The hazard rate is assumed to be constant over time and is modeled with prior:

The primary endpoint event times for the doses are also modeled as exponential, with hazard rates:

where is the log hazard ratio for dose relative to control. By convention, hazard ratios greater than one indicate treatment benefit.

The doses are modeled independently as:

Thus, for each dose is estimated separately using only data from that dose.

## Quantities of Interest

We define a number of quantities that will be tracked and may be used to make decisions during the trial.

## Posterior Probabilities

For each dose, we calculate the following quantities from the posterior:

* the probability that the primary endpoint hazard ratio on dose is less than arm\_1 by at least :
* the probability that the primary endpoint hazard ratio on dose is less than arm\_2 by at least :
* the probability that the primary endpoint hazard ratio on dose is less than arm\_3 by at least :
* the probability that the primary endpoint hazard ratio on dose is less than arm\_4 by at least :
* the probability that the primary endpoint hazard ratio on dose is less than arm\_5 by at least :
* the probability that the primary endpoint hazard ratio on dose is less than arm\_6 by at least :

## Predictive Probability of Future Trial Success

* For each active dose, we calculate the predictive probability of success in a future trial. We assume a hypothetical trial with a fixed design that would equally randomize subjects between control and one active dose. The final analysis would be a test of superiority after 250 total events (across both arms). The predictive probability of future trial success is the chance of achieving statistical significance (one-sided ) versus control if the active dose was entered into the hypothetical trial. This is different from the power for such a trial, in that the power calculations typically assume a fixed treatment effect, whereas the predictive probability of success averages over the posterior distribution of the treatment effect. Thus, knowledge of the treatment effect and the uncertainty in that knowledge are formally incorporated. We denote this probability as:

## Target Doses

We consider the following target doses:

* The maximum effective dose () is the dose with the greatest treatment effect (HR difference from 1). For each dose, we calculate the probability of being the :
* The minimally effective dose () is the smallest dose that achieves at least a hazard ratio of1.4(difference of relative to ). We calculate the probability that each dose is the :
* The 90% effective dose () is the smallest dose that achieves at least 90% of the treatment effect (HR difference from 1) achieved by . We calculate the probability that each dose is the :

## Decision Quantities

The above quantities are computed for each treatment arm (thus making them vector quantities). To facilitate decisions in the trial, we attach a particular treatment arm to the quantity that will be used for the decision (thus reducing the vector quantity to a scalar quantity). Throughout the trial, decisions may be based on the following quantities:

* $Maximum \(Pr(Max)\) across all doses$

# Study Design

## Timing of Interim Analyses

Interims will occur based on the number of subjects who haveenrolled into the trial.

The schedule for the 2 interims is specified in Table-2.

Table-2: Interim Analysis Schedule

|  |  |
| --- | --- |
| Interim | Subjects Enrolled |
| 1 | 440 |
| 2 | 880 |

## Arm Dropping

Randomization will occur in blocks of size 121 , with subjects allocated in a ratio of 1:20:20:20:20:20:20 among the arms.  
Arm dropping criteria will be evaluated at interims 1, 2 . A dose will be a candidate for dropping if it meets any of the following criteria:

* Pr(*{d}-*{1}<-0.4) > 0.75
* Pr(*{d}-*{2}<-0.4) > 0.75
* Pr(*{d}-*{3}<-0.4) > 0.75
* Pr(*{d}-*{4}<-0.4) > 0.75
* Pr(*{d}-*{5}<-0.4) > 0.75
* Pr(*{d}-*{6}<-0.4) > 0.75

During the study, a maximum of 5 doses may be dropped, and no additional subjects will be allocated to those doses. The control arm may not be dropped at any time.  
More than one dose may be dropped at an interim, as long as the maximum number to drop has not yet been reached.  
If more doses are eligible for dropping than allowed by the maximum, priority is given to the lower doses, such that if the lowest remaining dose is eligible, it will be dropped. If not, then the highest remaining dose will be droppped if it is eligible. If not, then no doses will be dropped.

After arms are dropped, if any, the study proceeds by decreasing the block size. The blocks are simply reduced in size and allocated in the ratio remaining after the dropped arm is removed. The study size is unchanged. After an arm is dropped, follow up of subjects on that arm will continue.

## Criteria for Stopping Accrual

### Stopping for Expected Futility

No early stopping criteria for futility have been defined for this trial.

### Stopping for Expected Success

If a success stopping rule is met at an interim analysis, then subject follow up will be discontinued, and the final evaluation criteria will be applied to the currently available data.

## Final Evaluation Criteria

No final success criteria have been defined for this trial.

No final futility criteria have been defined for this trial.

# Simulation Scenarios

We evaluate the proposed design through trial simulation. We hypothesize several possible underlying truths for the mean response, as well as for trial execution variables such as accrual and dropout. For each of these scenarios, we generate data according to those truths and run through the design as specified above. We repeat this process to create multiple ``virtual trials" and we track the behavior of each trial. In this section, we describe the the parameters used to generate the virtual subject-level data.

## Virtual Subject Response Profiles

### Control Hazard Rates Profiles

We consider 3 profiles for simulating the control arm hazard rate across segments, given as follows.

*good*

Table-3 : Control hazard rate profile for good

|  |
| --- |
| 0 - weeks |
| 0.3 |

*mod*

Table-4 : Control hazard rate profile for mod

|  |
| --- |
| 0 - weeks |
| 0.3 |

*CHaz 1*

Table-5 : Control hazard rate profile for CHaz 1

|  |
| --- |
| 0 - weeks |
| 0.3 |

### Hazard Ratio Profiles

We consider 4 profiles for which subject outcomes for the final endpoint are simulated to have hazard ratios as shown in Table-6.

Table-6: Virtual subject response hazard ratios

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| VSR HR |  |  |  |  |  |  |  |
| 1 | 1 | 1 | 1 | 1.4 | 1 | 1 | 1 |
| 2 | 1 | 1 | 1.4 | 1 | 1.4 | 1 | 1 |
| mod&good | 1 | 1 | 1.2 | 1 | 1.4 | 1 | 1 |
| null | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

## Accrual Profiles

We simulate the random arrival of subjects into the trial from a Poisson process with the mean weekly rates specified in Table-7. Within each accrual profile, there may be differential recruitment rates over time and across regions. Thus for each region, we specify:

* the mean number of subjects per week at peak accrual,
* the start date (in weeks from the start of the trial),
* whether the region will have a ramp up phase, and if so, when the ramp up will be complete, and
* whether the region will have a ramp down phase, and if so, when the ramp down will begin and when it will be complete.  
  Ramp up and ramp down define simple linear increases and decreases in the mean recruitment rate from Thus some simulated trials recruit more quickly than this and some more slowly.

Table-7: Accrual Profiles

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Profile Name | Region Index | Peak Rate | Start Week | Ramp Up | Ramp up Complete | Ramp Down | Start Ramp Down | Ramp Down Complete |
| Acc 1 | 1 | 20 | 0 | NA | NA | NA | NA | NA |

## Dropout Profiles

We consider the following dropout profile:

*Dropout 1*

We simulate subjects dropping out of the trial with the dropout rates (per week, per segment) shown in Table-8

Table-8 : Dropout Profiles for Dropout 1

|  |  |
| --- | --- |
| Arm | 0 - weeks |
| control | 0.01 |
| arm\_1 | 0.01 |
| arm\_2 | 0.01 |
| arm\_3 | 0.01 |
| arm\_4 | 0.01 |
| arm\_5 | 0.01 |
| arm\_6 | 0.01 |

# Operating Characteristics

For the scenarios described above, we simulate multiple virtual trials and track the behavior of each trial, including the final outcome of the trial, the estimated mean response, etc. The results in this section are summarized across all simulated trials for each scenario.

## Overall

This section gives a high-level description of the operating characteristics. Table-9 shows the following information per scenario:

* N sim: the number of simulated trials
* E[N]: the expected sample size
* Pr(success): the proportion of trials that met the final success criteria
* E[duration]: the expected duration of the trial in weeks.

Table-9: Overall Operating Characteristics

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Accrual | Dropout | Hazard Ratio | Control Hazard Rates | N sim | E[N] | Pr(Success) | E[duration] |
| Acc 1 | Dropout 1 | 1 | good | 1000 | 1116.4 | 0.141 | 62.6 |
| Acc 1 | Dropout 1 | 1 | mod | 1000 | 1284.0 | 0.005 | 72.1 |
| Acc 1 | Dropout 1 | 2 | good | 1000 | 1123.4 | 0.010 | 64.0 |
| Acc 1 | Dropout 1 | 2 | mod | 1000 | 1271.2 | 0.002 | 71.5 |
| Acc 1 | Dropout 1 | mod&good | CHaz 1 | 1000 | 1165.5 | 0.045 | 65.9 |
| Acc 1 | Dropout 1 | null | CHaz 1 | 1000 | 1310.8 | 0.000 | 73.5 |

## Trial Outcomes

This section summarizes the outcomes of the simulated trials. For each scenario in Table-10, the columns represent the proportion of simulated trials meeting each of the following definitions:

* Early Success (ES): stopped accrual for expected success and successful at the final analysis
* Late Success (LS): enrolled to the maximum sample size and successful at the final analysis
* Late Futility (LF): enrolled to the maximum sample size and met the futility criteria at the final analysis
* Success to Futility Flip Flop (SFFF): stopped accrual for expected success, but met the futility criteria at final analysis
* Inconclusive (Inconc.): met neither the success nor the futility criteria at the final analysis

Table-10: Trial Outcomes

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Accrual | Dropout | Hazard.Ratio | Control.Hazard.Rates | ES | LS | LF | SFFF | Inconc. |
| Acc 1 | Dropout 1 | 1 | good | 0.141 | 0 | 0 | 0 | 0.859 |
| Acc 1 | Dropout 1 | 1 | mod | 0.005 | 0 | 0 | 0 | 0.995 |
| Acc 1 | Dropout 1 | 2 | good | 0.010 | 0 | 0 | 0 | 0.990 |
| Acc 1 | Dropout 1 | 2 | mod | 0.002 | 0 | 0 | 0 | 0.998 |
| Acc 1 | Dropout 1 | mod&good | CHaz 1 | 0.045 | 0 | 0 | 0 | 0.955 |
| Acc 1 | Dropout 1 | null | CHaz 1 | 0.000 | 0 | 0 | 0 | 1.000 |

# Computational Details

This report reflects the design parameters contained within the MEDAL\_TTE.facts file. The simulations were run using FACTS (Berry Consultants, LLC, Austin, TX) version 6.4.1. Table-11 shows the computational details for each scenario, including the starting date and time, the length of the MCMC chain, the random number seed, and the trial at which the simulation started. The R software package was used to summarize the simulation output and to create tables for this report.

Table-11: Computational Details

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Accrual | Dropout | Hazard Ratio | Control Hazard Rates | Date Time | MCMC Burn-in | MCMC Length | Random Seed | Starting Trial |
| Acc 1 | Dropout 1 | 1 | good | 03/21/2022 09:34:36 | 1000 | 2500 | 417017577 | 1 |
| Acc 1 | Dropout 1 | 1 | mod | 03/21/2022 09:34:37 | 1000 | 2500 | 417017577 | 1 |
| Acc 1 | Dropout 1 | 2 | good | 03/21/2022 09:34:36 | 1000 | 2500 | 417017577 | 1 |
| Acc 1 | Dropout 1 | 2 | mod | 03/21/2022 09:34:37 | 1000 | 2500 | 417017577 | 1 |
| Acc 1 | Dropout 1 | mod&good | CHaz 1 | 03/21/2022 09:34:36 | 1000 | 2500 | 417017577 | 1 |
| Acc 1 | Dropout 1 | null | CHaz 1 | 03/21/2022 09:34:35 | 1000 | 2500 | 417017577 | 1 |