

## Ratio: optimizing the efficacy to safety ratio

**Goal:** To select the dose that optimizes the efficacy to safety ratio in a phase II dose-ranging study.

**Background:** This is a constructed diabetes study comparing 5 dose levels to a placebo. Primary efficacy variable is the percent change in HbA1c at endpoint. Safety and tolerability is recorded by an overall indicator variable (1: non tolerated, 0: tolerated).

The objective of the study is to find the dose that optimizes the efficacy to safety ratio.

To that end, the minimum efficacious dose (MED) is determined as the dose where the mean HbA1c ratio from baseline is below 90%. The maximum tolerated dose (MTD) is where the probability of non-tolerability remains below 30%.

A joint utility score for efficacy and safety is defined at each dose level as the product of probabilities:

$$\Pr[\text{HbA1c ratio} \leq 90\%] * \Pr[\text{non-tolerability} < 30\%]$$

The dose level that maximizes this score is selected.

**Bayesian Model:** HbA1c ratio is analysed with a one-way analysis of variance model, using vague priors on the means and precision (tau):

$$\mu_x \sim \text{Normal}(0, 10E-9), \text{ and } \tau \sim \text{Gamma}(0.0001, 0.0001).$$

The incidences of non-tolerability are analysed using an independent proportions model with non-informative priors on the probabilities  $p_x \sim \text{beta}(0.5, 0.5)$  [ $x=0, \dots, 5$ ].

### Adaptive design:

The MED is defined using the CRM criterion as the minimum dose ( $x=1, \dots, 5$ ) where:  $\mu_x \leq 90\%$ .

The MTD is defined using the CRM criterion as the maximum dose ( $x=1, \dots, 5$ ) where:  $p_x < 30\%$ .

**Decision:** For each dose level, we calculate the posterior probability that the dose meets the efficacy criterion  $\mu_x \leq 90\%$  and that the dose meets the safety criterion:  $p_x < 30\%$ . We report these probabilities below and combine them into a joint utility function.

**Data:** Two hundred and fifty patients were randomized in the study, across 5 dose levels and a placebo. Efficacy and safety results are summarized below:

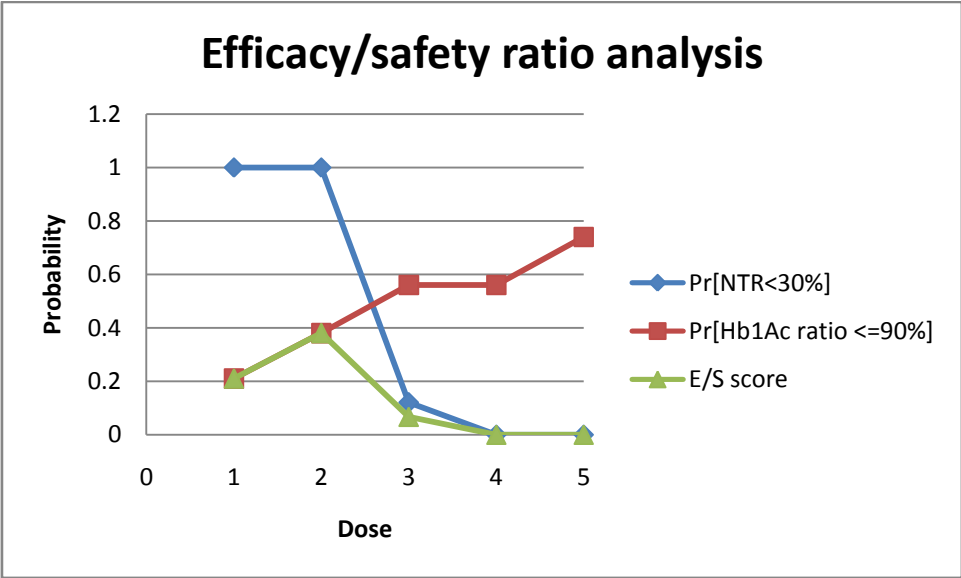
Dose	Efficacy			Safety	
	N	Mean	Std	n	%
0	54	0.975	0.141	1	0.019
1	48	0.917	0.135	2	0.042
2	39	0.908	0.155	2	0.051
3	50	0.896	0.142	19	0.38
4	42	0.896	0.167	22	0.524
5	42	0.885	0.144	23	0.548

**Results:** The MED and MTD estimates are summarized in the table below, together with the probabilities to have reached the safety and efficacy criteria by dose:

Dose	Pr[Dose is MTD]	Pr[Non tolerability rate<30%]	Pr[Dose is MED]	Pr[Hb1Ac ratio <=90%]	Efficacy/Safety Score
1	0	1	0.21	0.21	0.21
2	0.88	1	0.3	0.38	0.38
3	0.12	0.12	0.27	0.56	0.0672
4	0	0	0.12	0.56	0
5	0	0	0.07	0.74	0

Doses 1 and 2 are very safe. The posterior probability of excessive non tolerability is 12% at dose 3. The most likely MTD is dose 2.

Efficacy level increases with dose. The probability of a ratio below 90% is 21% at dose 1 and it increases to 74% at dose 5. The most likely MTD is dose 2. There is a 72% chance that the MED is at or below dose 3.



The value for the combined efficacy/safety ratio criterion is calculated in the last column of the table as the product of probabilities to reach the safety and efficacy conditions. Based on joint efficacy/safety considerations, dose 2 is the optimal dose to recommend.

**Decimaker:** The corresponding Decimaker study project for efficacy may be found [here](#) and for safety [here](#).