

## Ceiling: Finding lower doses below the ceiling.

**Goal:** A first trial has shown a saturated response across all tested doses versus placebo. A new study is designed to detect the increasing part of the dose-response relationship.

**Background:** This phase II trial in obesity is (freely) adapted from Ettinger et al. (2003). Twelve-week weight change (WC) was measured in obese adults following the administration of three doses of a drug (0.3, 1 and 2mg) or a placebo. Results showed separation to placebo at each dose, but no dose-response relationship.

The objective is to design a follow-up study testing lower doses than 0.3mg in order to detect the increasing part of the dose-response relationship.

To that end, dose-response data will be modeled using an Emax model and a Bayesian c-optimality criterion will be established to maximize the precision of the ED50 parameter.

The most interesting doses will be selected based on the c-optimality score across the following candidates: 0, 0.0025, 0.005, 0.01, 0.02, 0.0375, 0.075, 0.15, 0.3, 1, 2 mg, where 0.0025mg is the lowest dosage strength possible.

**Bayesian Model:** WC is analysed in relation to the square root of the dose with an Emax model

$$E_0 + E_{\max} * \sqrt{\text{dose}} / (\sqrt{\text{dose}} + ED_{50}),$$

using informative priors on  $E_0$  and  $E_{\max}$  and the residual precision:

$$E_0 \sim \text{Normal}(0,1), E_{\max} \sim \text{Normal}(-4,1), \text{ and } \tau \sim \text{Uniform}(0.001,0.5)$$

that match the historical results.

Flat priors are taken on  $ED_{50}$ .

### Adaptive design:

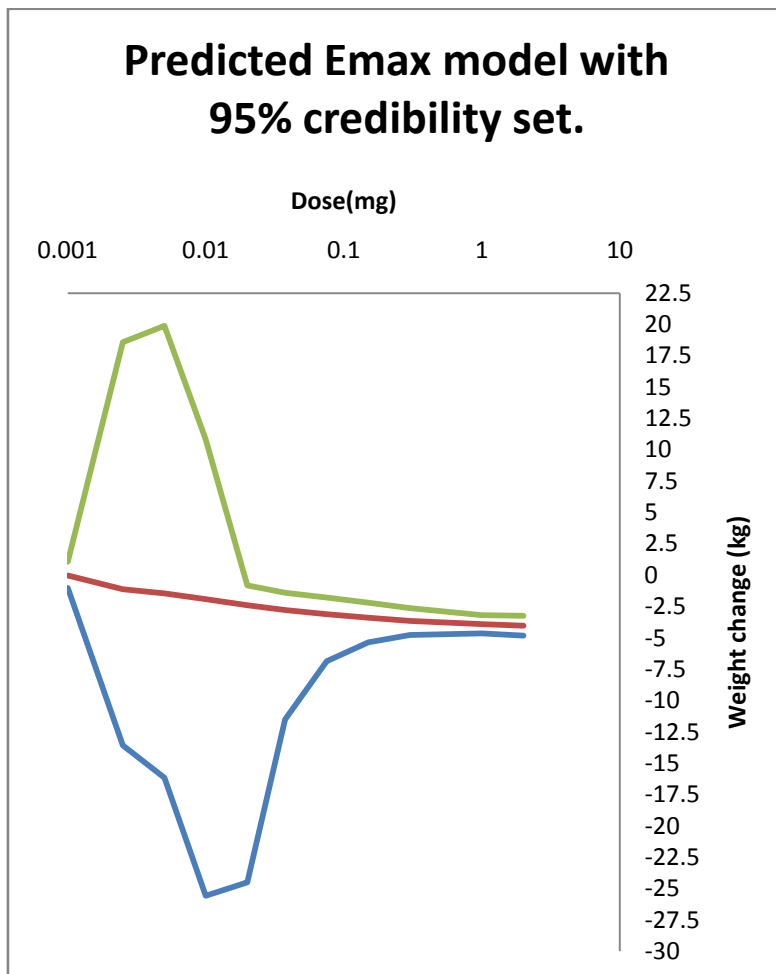
We used a Bayesian c-optimality criterion to minimize the variance of the  $ED_{50}$  parameter.

**Decision:** Not applicable.

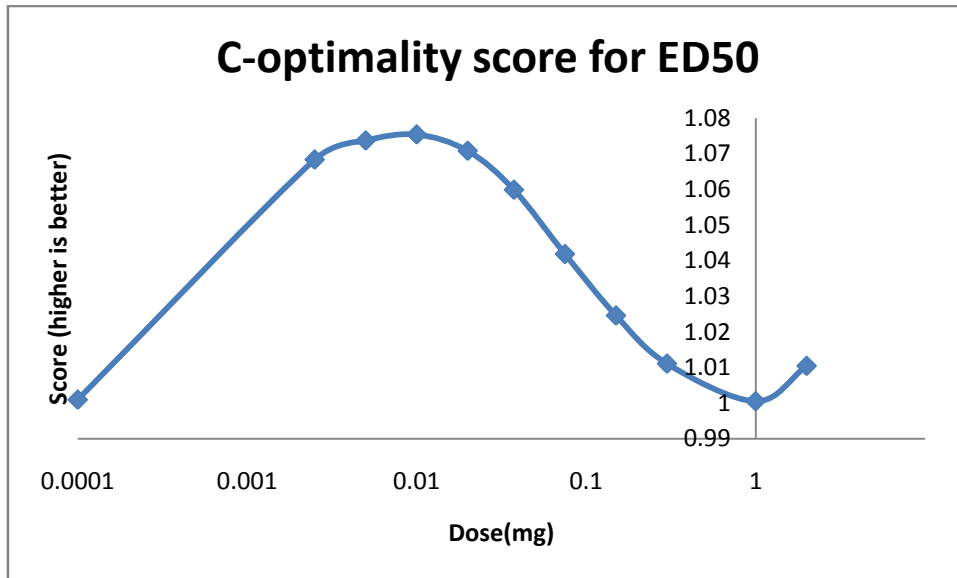
**Data:** One hundred and thirty five patients were randomized in the study, across 3 dose levels and a placebo. Weight changes at 12 weeks are summarized below:

Dose	Mean	Std	n
0	0.416	2.934	32
0.3	-3.627	4.652	32
1	-4.542	4.288	38
2	-3.759	3.148	33

**Results:** As expected, the Emax model fit is good only where data were available, namely under placebo (E0) and between 0.3 to 2mg (near the Emax). The model predictions below 0.3mg are not predictable.



The C-optimality score is the largest at 0.01mg. The subset of 5 doses of highest interest for ED50 estimation includes 0.0025, 0.005, 0.01, 0.02 and 0.0375mg. Doses larger than 0.0375mg or placebo would be less informative.



Dose(mg)	Predicted median WC (kg)	C-efficiency (ED50)
0	-0.022	1.00097
0.0025	-1.127	1.06833
0.005	-1.467	1.07369
0.01	-1.925	1.07537
0.02	-2.39	1.07079
0.0375	-2.778	1.05986
0.075	-3.114	1.04182
0.15	-3.408	1.02458
0.3	-3.646	1.01108
1	-3.916	1.00053
2	-4.041	1.01045

**Decimaker:** The corresponding Decimaker study project may be found [here](#). The figures reported here-in were produced using MS Excel based on Decimaker outputs.

**Reference:**

- MP Ettinger, TW Littlejohn, SL Schwartz, SR Weiss, HH McIlwain, SB Heymsfield, GA Bray, WG Roberts, ER Heyman, N Stambler, SHeshka, C Vicary, and H-P Guler. Recombinant Variant of Ciliary Neurotrophic Factor for Weight Loss in Obese Adults: A Randomized, Dose-Ranging Study. JAMA, Apr 2003; 289: 1826 - 1832.