

Diabetes: a first-in-human study

Goal: To estimate precisely the maximum tolerated dose (MTD) in first-in-human safety trials.

Background: This example is taken from Tibaldi *et al* (2008).

This was a randomized, double-blind, placebo-controlled, single ascending dose trial of a new diabetes compound in which safety and tolerability were monitored.

Ascending doses of 0.05, 0.3, 1, 3, 5 and 8mg or placebo were administered in successive cohort counting 9 subjects each. Each cohort included pbo (N=2) and 2 dose levels (N=3, each).

Dose-limiting toxicity (DLT) was the primary endpoint. It was assessed as a binary (Y/N) response.

The maximum tolerated dose (MTD) was defined as the maximum dose at which

$$\Pr[\text{DLT}] \leq 30\%.$$

An adaptive dose escalation procedure (see details below) was pursued up until the MTD was precisely estimated.

Adaptive design: They adopted the following constrained continual reassessment method (CRM) for dose escalation targeting the MTD:

- The doses for the initial cohort were 0.05 and 0.3 mg.
- The doses for the next cohorts were admissible doses including the target dose and the dose just below the target.
- The target dose was defined as the dose having the largest posterior probability of being the MTD among a set of admissible doses.
- A dose was considered as admissible if all lower doses were administered up to the current cohort.

Bayesian Model: They analysed the probability of DLT (p) with a logistic regression model:

$$\text{logit}(p) = \alpha + \beta \text{ dose},$$

considering somewhat informative priors :

$$\alpha \sim \text{Normal}(-4, 4), \text{ and}$$

$$\beta \sim \text{Normal}_+(0.3, 0.0227),$$

where $\text{normal}(\mu, \sigma^2)$ is the Normal distribution with mean μ and variance σ^2 and $\text{normal}_+(\mu, \sigma^2)$ is the censored normal distribution restricted to positive values.

Decision: The predicted MTD from the logistic model was estimated as

$$\text{MTD} = [\text{logit}(30\%) - \alpha] / \beta.$$

The posterior mean and standard deviation (sd) of the MTD were reported. The study was terminated as soon as the standard deviation of the MTD was:

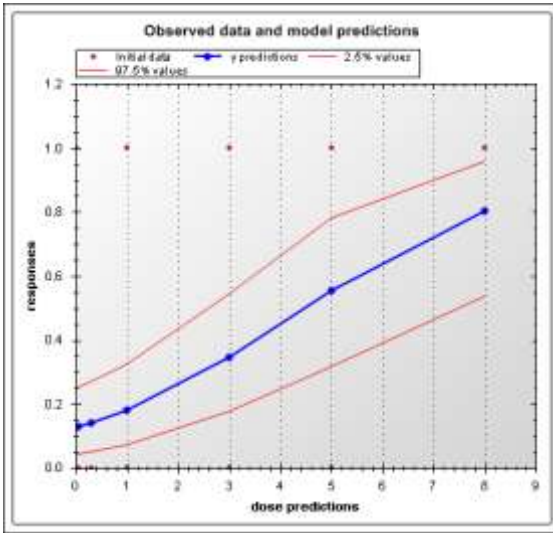
$$\text{sd}(\text{MTD}) < 1.1.$$

Results: The study enrolled a total of 4 cohorts. Results are summarized below.

Cohort		Pbo	0.05mg	0.3mg	1mg	3mg	5mg	8mg
1	N	2	3	3	-	-	-	-
	#DLT	0	0	0	-	-	-	-
	Pr(dose is MTD)	0%	0.1%	0.4%	2.2%	6.5%	13.7%	76.9%
	Mean MTD	22.43mg	sd(MTD)	64.31				
2	N	4	3	3	3	3	-	-
	#DLT	0	0	0	0	1	-	-
	Pr(dose is MTD)	0%	0%	0.3%	3.6%	17.1%	33.3%	45.7%
	Mean MTD	12.62mg	sd(MTD)	37.26				
3	N	6	3	3	3	3	3	3
	#DLT	0	0	0	0	1	2	3
	Pr(dose is MTD)	0%	0.2%	0.5%	30%	58.7%	10.2%	0.1%
	Mean MTD	3.61mg	sd(MTD)	1.17				
4	N	9	3	9*	6	3	3	3
	#DLT	1	0	2	2	1	2	3
	Pr(dose is MTD)	0%	0.4%	3.4%	64.2%	29.1%	2.1%	0.1%
	Mean MTD	2.59mg	sd(MTD)	1.09				

*: Six subjects had received 1mg in cohort 4.

A



B

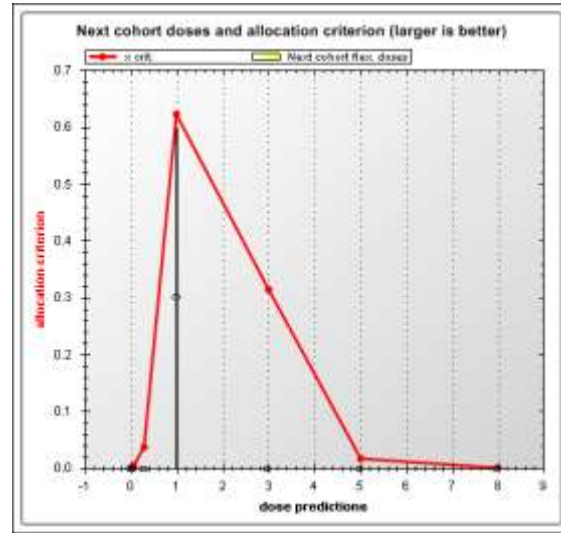


Figure 1. Results after cohort 4. A: Logistic regression of rate of NLT versus dose with 95% credible set. B: Probability that dose is MTD among candidate set.

Decimaker: The corresponding Decimaker study project may be found [here](#). It involves data from all 4 cohorts.

References:

- Tibaldi F, Beck B and Bedding A. Drug Information Journal, 2008.