Improved study design in phase IIb by the use of optimal design methods, focusing on the precision of dose finding

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Objectives

The objective of dose finding studies is to identify the relationship between dose and efficacy to guide selection of doses to be further studied in phase III. Optimal design based on the D-optimal criteria using a standard E_{max} model may not be adequate since not all parts of the dose exposure response curve are of equal importance and it is difficult to predict how the precision in model parameters translates to precision in dose selection. Thus if optimal design methods are used it is important to have a parameter in the model that has a direct relevance for dose selection and to optimize the study design w.r.t. the precision of that parameter. The objective of this work was to evaluate and compare the performance of designs based on the D and Ds-optimal criteria, by the use of a re-parameterized E_{max} model.

Methods

An alternative parameterization of the sigmoid E_{max} model, described by Groth [1], was used where one of the parameters (C*) is the plasma concentration corresponding to a particular treatment effect (E*). In the optimization, the optimal design tool PopED [2] was used. The D-optimal criteria was used as well as the Ds criteria with C* as the parameter of interest. Assumptions with regards to parameter values were based on a drug intended for the treatment of neuropathic pain where pain is assessed using a numerical rating scale graded 0-10. The study consisted of four arms (54 patients per arm); placebo, 18mg and two doses that were determined by either the D-optimal or the Ds-optimal criteria.

The Ds and D-optimal designs were subsequently evaluated by means of simulation to estimate the probability of correctly estimating the dose corresponding to an efficacy of 1 versus placebo. In the estimation step a linear, E_{max} and a sigmoid E_{max} model were fit to the simulated data. The estimation model for each simulated study was either based on a likelihood ratio test (LRT) at the 5% significance level, or the sigmoid E_{max} model. For each simulated study, the dose corresponding to the target efficacy of 1 was calculated based on the estimated relationship. Estimated doses being in the interval half to double the true dose (12mg) was defined as correct. The same calculation was done for other target effects to illustrate the results.

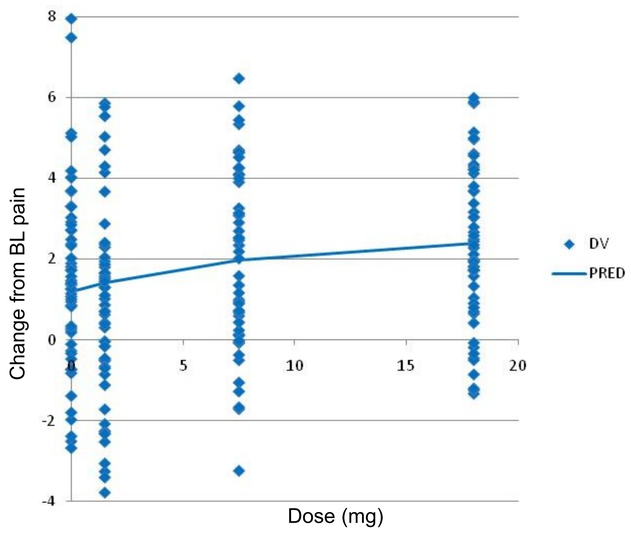
The model

$$Css_i(nM) = \frac{DoseRate}{TVCL * EXP(ETACL)}$$

$$E = E_{placebo} + E^* \cdot \frac{Css_i^{\gamma}}{C^{*\gamma}} \cdot \frac{1+(\alpha \cdot C^*)^{\gamma}}{1+(\alpha \cdot Css_i)^{\gamma}} + \varepsilon$$

E= Pain reduction from BL
$E_{placebo}$=Pain reduction from BL in the placebo group
α=1/EC50
(C*, E*) is a (Conc, effect)-pair on the model-predicted curve.

Fig 1 Simulated dose response (D-optimal design, study 1 of 1000)



Results

The optimal design based on the Ds-optimal criteria was 0, 0.1, 9 and 18mg and the D-optimal design was 0, 1.5, 7.5 and 18 mg.

Table 1 LRT based model selection.

Model	Ds	D
Sigmoid E_{max}	4%	5%
E_{max}	35%	29%
Linear	55%	54%
No effect	6%	12%

True model → Sigmoid E_{max}; Linear model used to estimate dose

Table 2 Probability of correct dose estimation was larger with the Ds optimal design

Model	Ds	D
LRT based	61%	53%
Sigmoid E_{max}	57%	52%

Fig 2 The distribution of the estimated dose with a target efficacy of 1 had a peak closer to the true dose for the Ds-optimal design. The probability that the dose would be very small was however higher compared to the D-optimal design. (Results from sigmoid E_{max} estimation model shown).

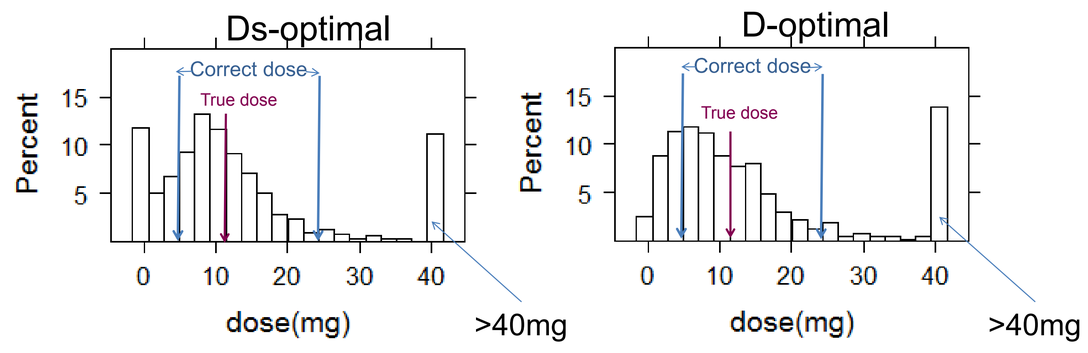


Fig 3 The Ds optimal design resulted in a larger probability of correct dose estimation with a target efficacy in the range 0.7-1.3 based on the sigmoid E_{max} model and the LRT-based model.

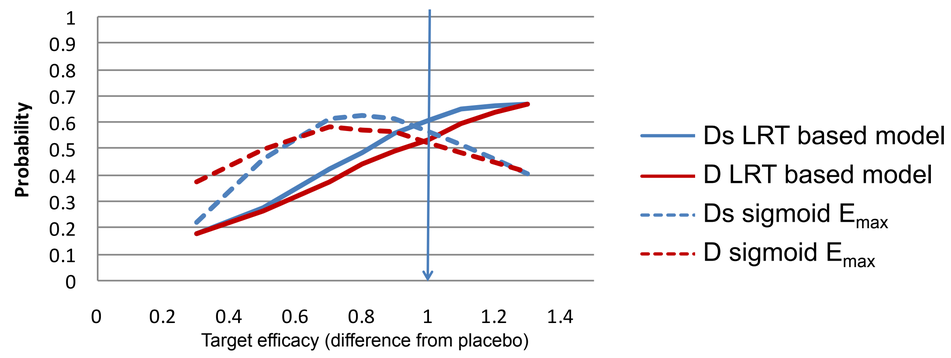
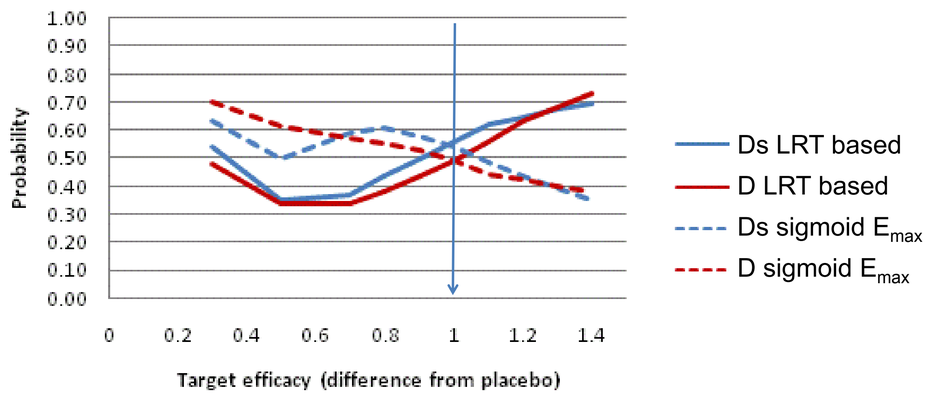


Fig 4 Target efficacy versus probability that the true (simulated) effect is within 0.3 of the target effect.



Discussion and Conclusions

These results show that Ds-optimal design based on the re-parameterized E_{max} model can be better compared to a D-optimal design if a particular target effect is of interest. To apply this method also uncertainty in parameter estimates needs to be considered e.g. by applying the EDs optimal design criteria.

References

[1] Groth PAGE 19 (2010) Abstr 1743 [www.page meeting.org/?abstract=1743]
[2] PopED (http://poped.sf.net)

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