Bayesian Adaptive Designs for Healthy Volunteer First in Man Studies

AHPPI 30th October 2014

Richard Peck, Roche Pharmaceutical Research & Development, Roche Innovation Centre, Welwyn

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12344

Methods in Clinical Pharmacology Series

Bayesian adaptive designs in single ascending dose trials in healthy volunteers

David Guédé,[1] Bruno Reigner,[2] Francois Vandenhende,[1] Mike Derks,[2] Ulrich Beyer,[2] Paul Jordan,[2] Eric Worth,[3] Cheikh Diack,[2] Nicolas Frey[2] & Richard Peck[3]

[1]ClinBAY SPRL, ••, Belgium, [2]F. Hoffmann-La Roche Ltd, ••, Switzerland and [3]Roche Products, ••, UK

Correspondence
Dr Bruno Reigner ••, Clinical Pharmacology, Pharma Research and Early Development, B663/247, F. Hoffmann-La Roche Ltd., Basel CH-4070, Switzerland.
Tel.: +416 1688 4507
Fax: +416 1688 0415
E-mail: bruno.reigner@roche.com

Keywords
Bayesian adaptive design, safety, single ascending dose trial

Received
2 October 2013

Accepted
25 January 2014

Introduction

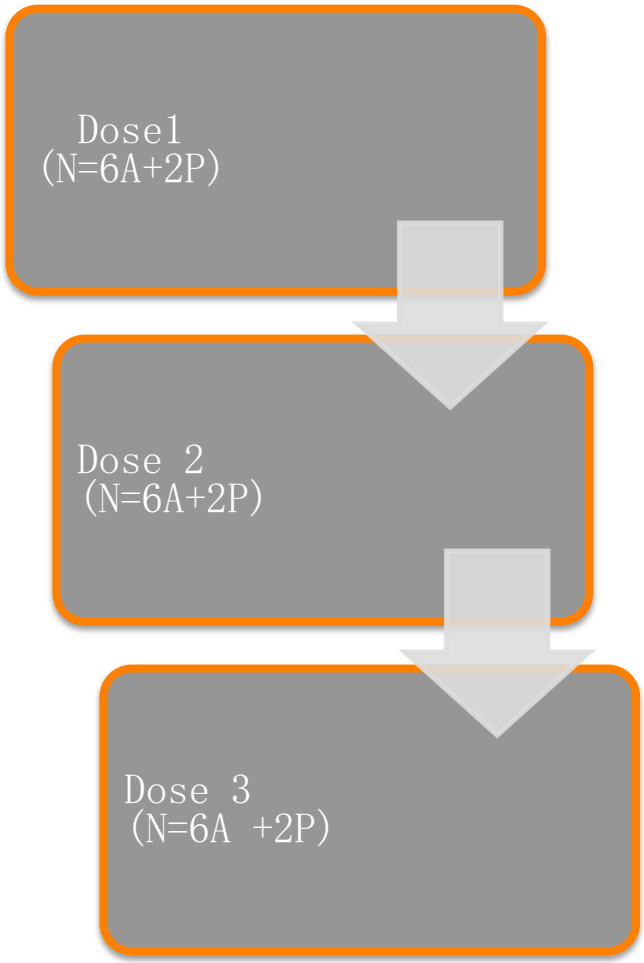
Adaptive Designs

- use accumulating data to modify the design without introducing bias
- are quite common for oncology first in man studies
  - Increase precision of MTD estimate
  - Limit patients dosed above MTD
  - Enable faster dose-escalation
- Adaptations are driven by pre-planned statistical algorithms
- "Traditional" first in man studies are flexible but not adaptive

Bayesian Statistics

- enable the calculation of probabilities based on the observed data and prior beliefs

Classical sequential design



6A + 2P design – Max 8 cohorts

doses: 0, 1, 3, 9, 25, 50, 100, 200, 400

Stopping Rule: 3/6 (50%) with DLEs

- ➔MTD= dose before stopping

Proposed adaptive design

3A + 1P (possibly repeated) per cohort

- Fewer subjects in low dose levels cohorts
- Potential to increase subjects at informative dose levels

Select next dose levels adaptively in order to estimate the Maximum Tolerated Dose (MTD):

- Dose where DLE rate = 30%

Stop when good precision on MTD or highest dose is safe.

Adaptive design features

Design:

- 3A + 1P initially
- Possible doses: 0, 1, 3, 6, 9, 20, 25, 40, 50, 75, 100, 150, 200, 300, 400

Logistic Regression:

- Model p(DLE) as function of dose

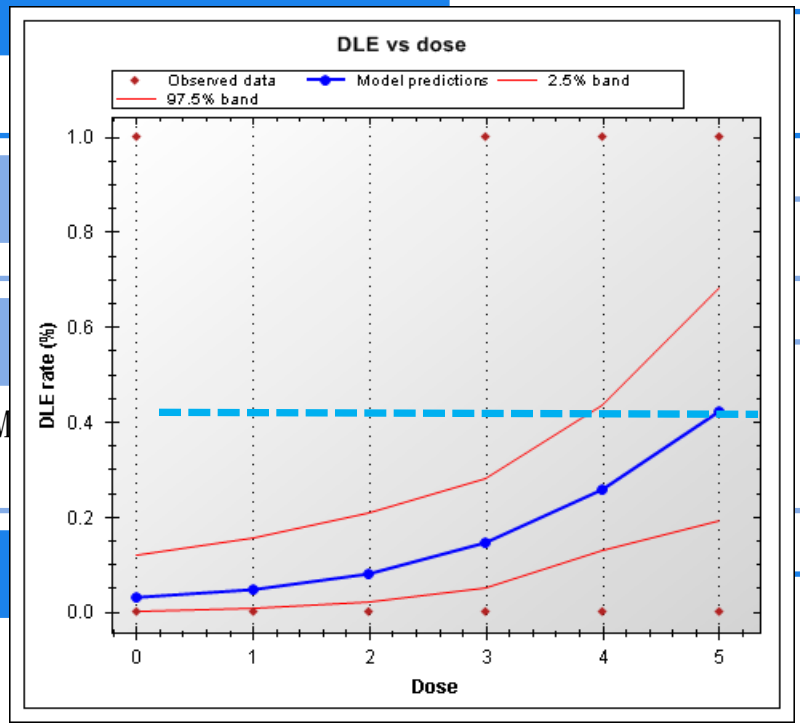
MTD is dose where p(DLE)=30%

Next dose level

- Possible dose closest to predicted M
- Maximum 3-fold increase in doses

Example: predicted MTD=5.8

- Current dose=1 -> Next dose = 3
- Current dose=3 -> Next dose = 6



Adaptive design
Cohort expansion & study stopping rules

Switch from 3A+1P to 6A+2P

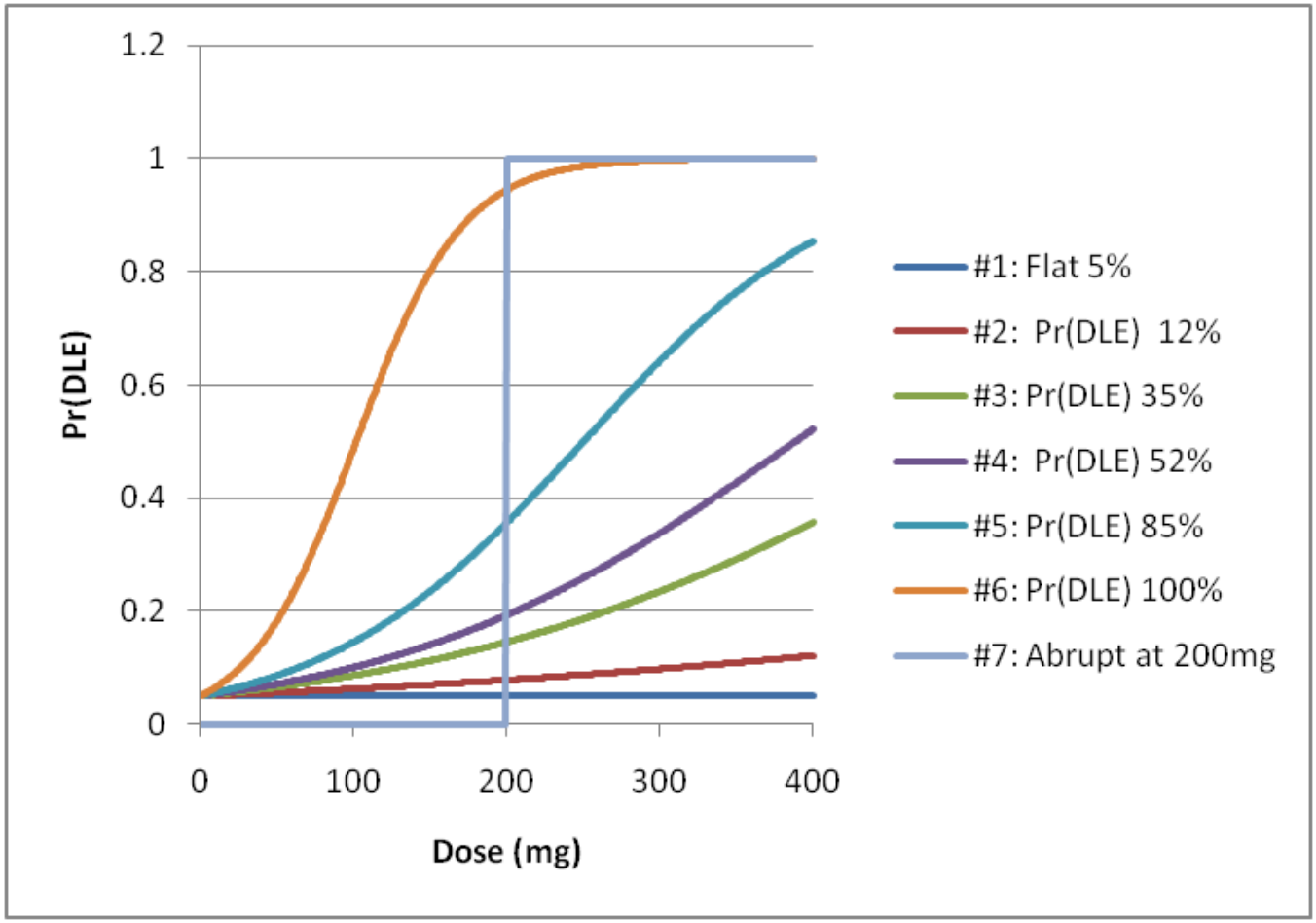
- When the next dose predicted by the model is lower than the last dose given
- In practice, we expand as soon as an MTD is found in the tested dose range.

Stopping Rules

- MTD Found
  - Precision of MTD is strong (CV≤ 30%) or,
  - ~~Any dose level is selected for the third time~~
- MTD not Found
  - MTD is larger than highest possible dose (400mg) with high probability (>80%)
  - Maximum number of cohorts (16)

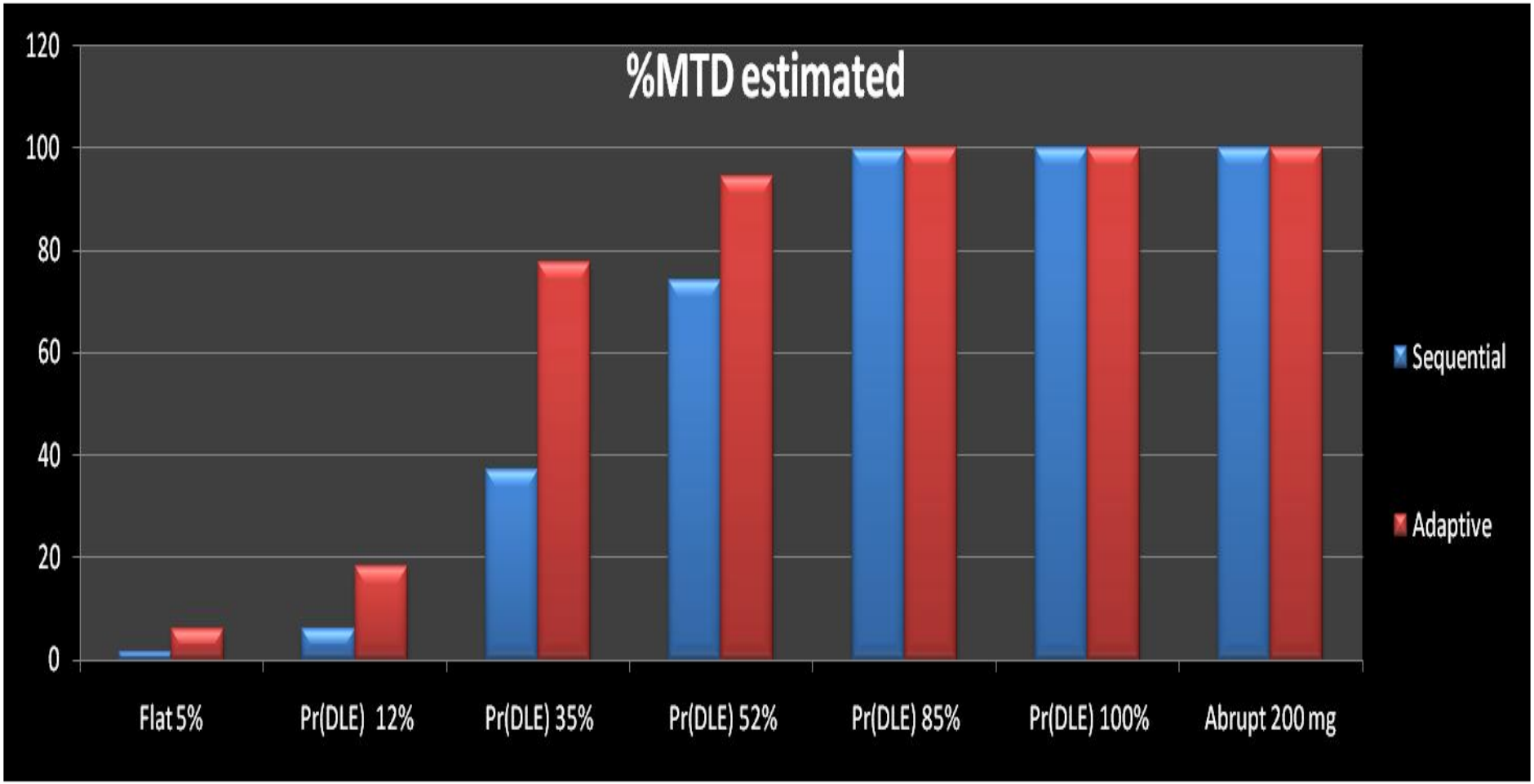
Simulation scenarios

Adaptive and sequential designs simulated for 7 scenarios



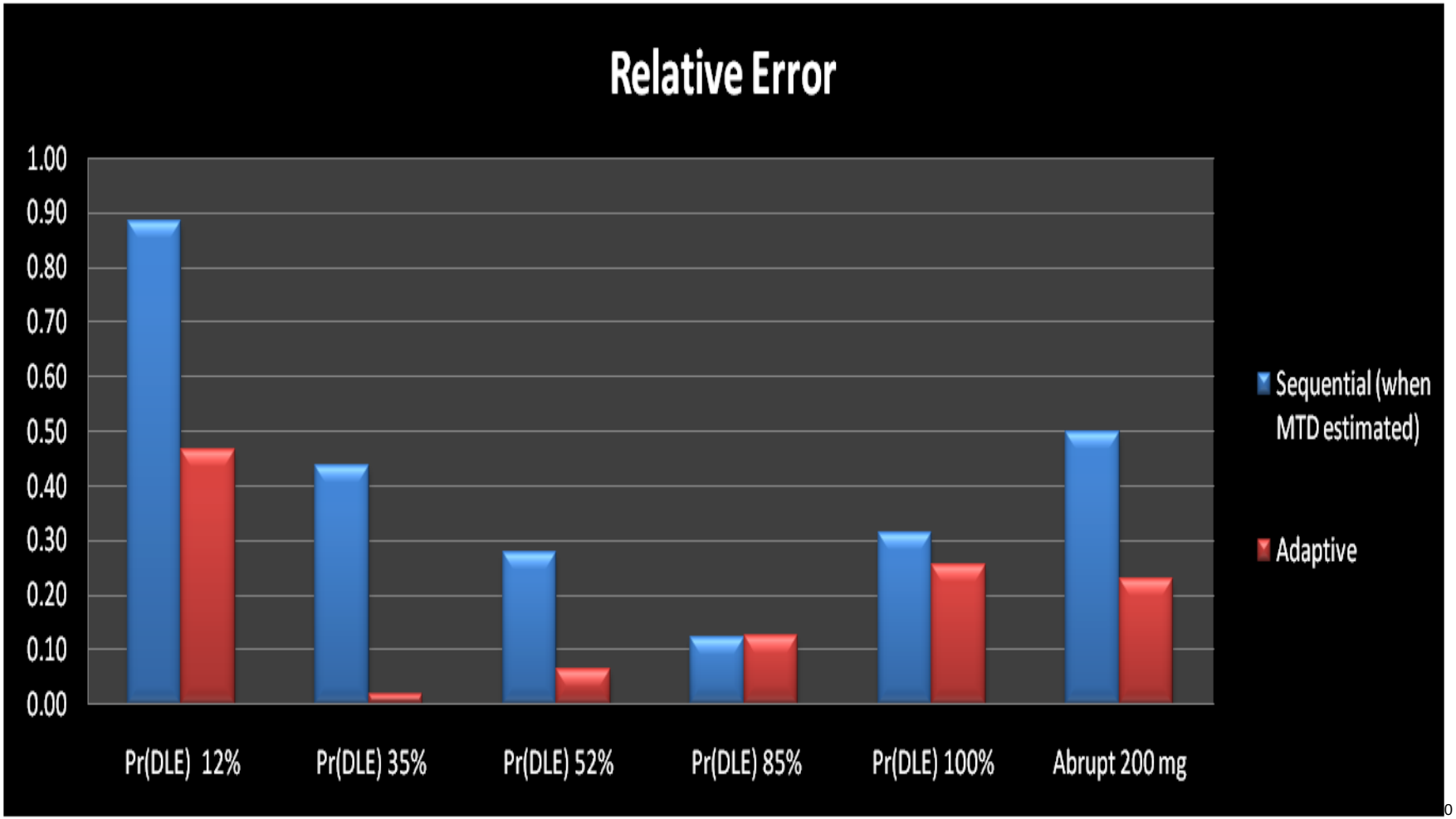
5000 simulations for each scenario and design = 70,000 trials

Adaptive designs identify an MTD more often



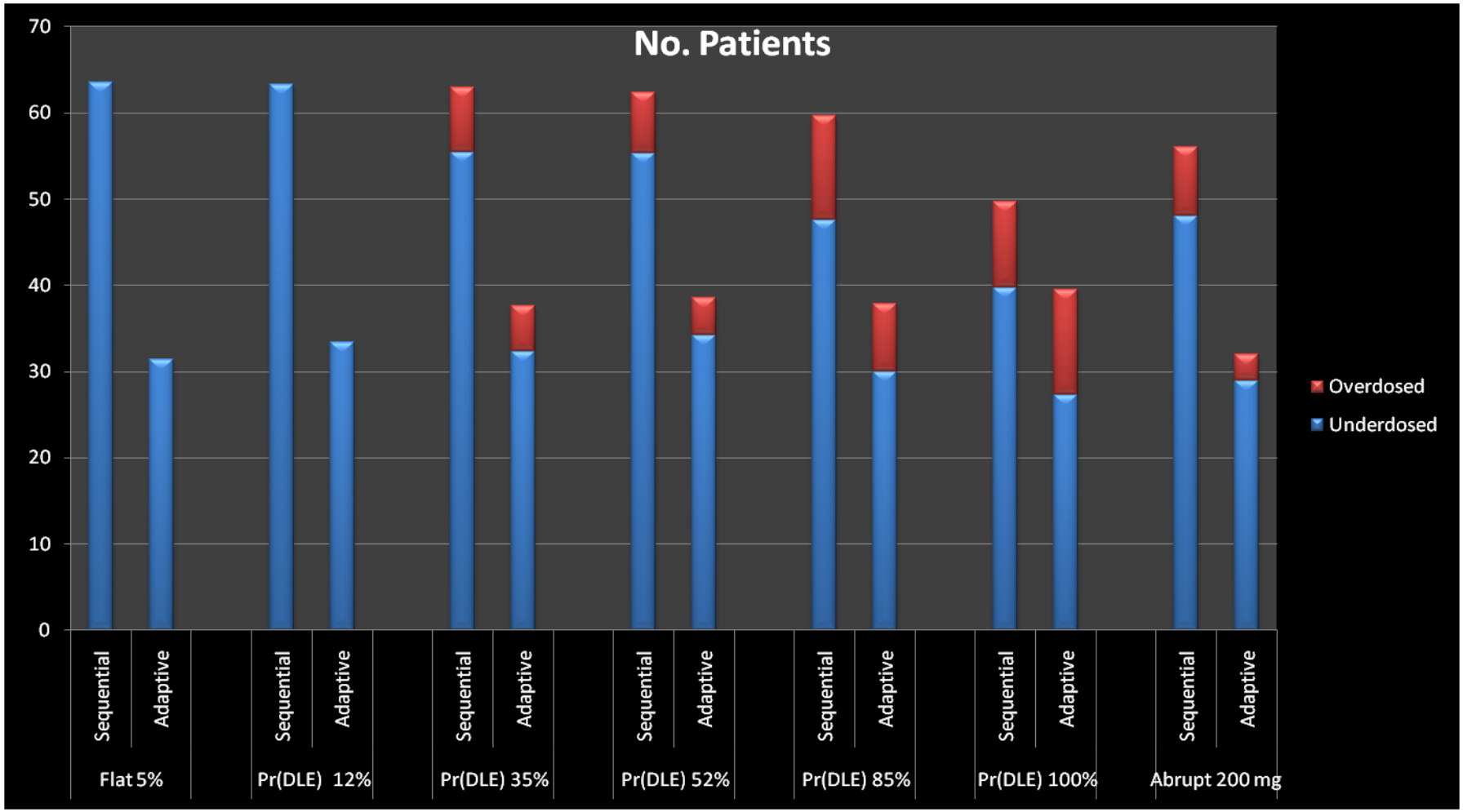
%MTD estimated= % studies where CV(MTD)<30% or same dose chosen for 3rd time - Larger value is better

Adaptive designs give more precise estimate of MTD



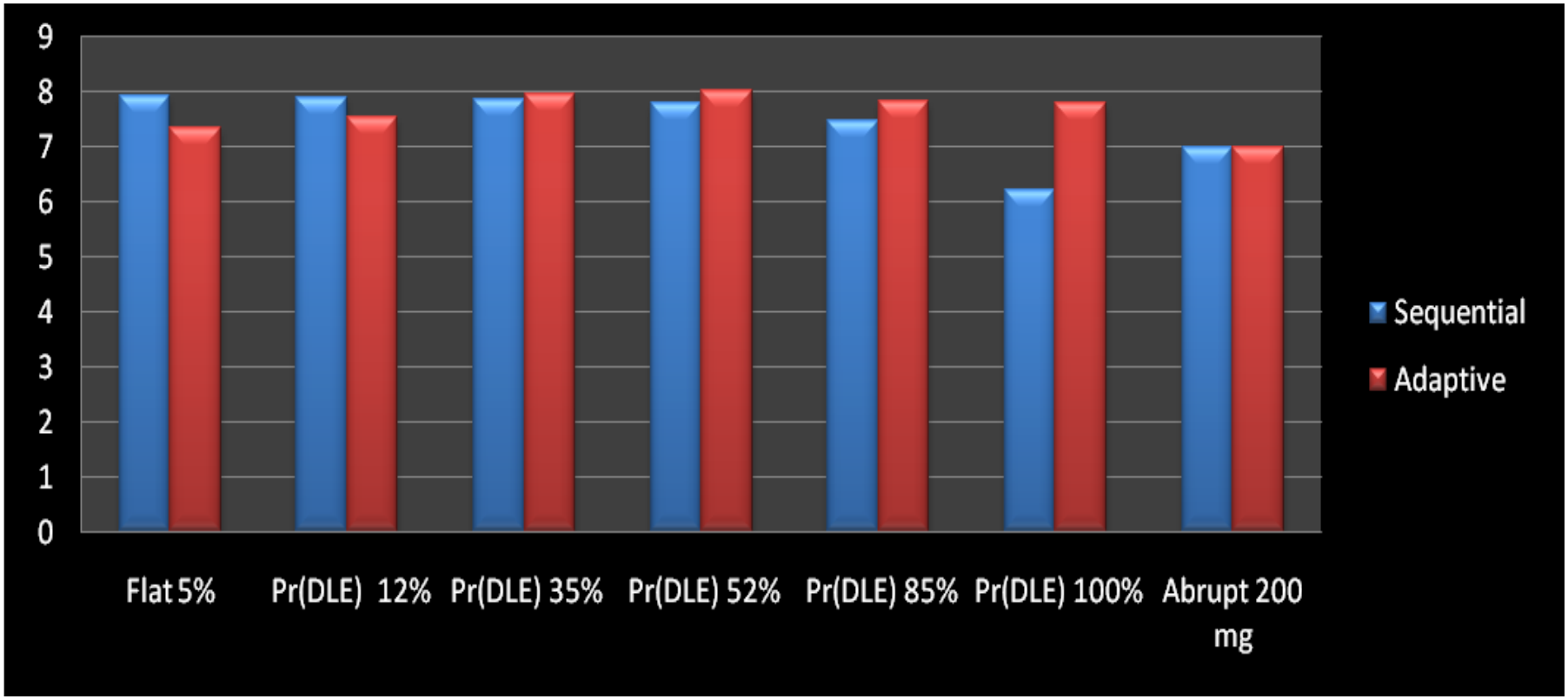
Relative error = % error(estimated MTD – true MTD) - Smaller value is better

Adaptive designs need fewer subjects and expose fewer to poorly tolerated doses



N° Subjects= total sample size.
N° overdosed = Subjects dosed >true MTD - Smaller value is better

Adaptive and sequential designs are similar duration



Duration= Number of dosing periods - Smaller value is better

Conclusion

Large-scale simulation study demonstrated the improved performance of an adaptive dose-escalation design compared to the standard approach in SAD trials

Compared to standard approach

- Better quality of MTD finding
- Decrease in number of subjects
- Comparable duration

Next steps

Implement

- Two adaptive SAD studies completed
- More planned
- Publications expected next year

Simulated crossover/leap frog design

- Challenges dealing with bias from dropouts
- Publication in preparation

Post-doc to develop methods for Bayesian adaptive MAD studies

- First publications submitted/in press

Mueller et al, J Cardiovasc Pharmacol, 2014;63:120-131