The use of model based dose response in choosing doses in a lean clinical development plan

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What is Different About this Program?

First in Human

Proof of Concept/Dose Finding

Conclusions

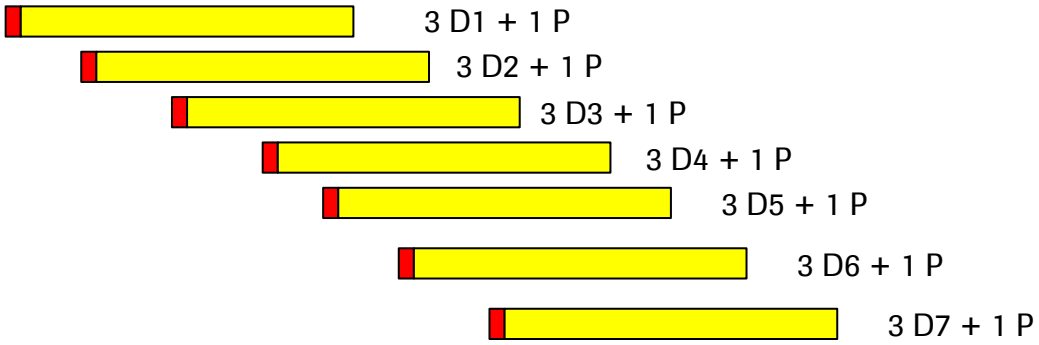
What is different about this project?

- Therapeutic area head wanted a more lean and innovative way of developing molecules through smart designs and decisions, in collaboration with academic institutions.
- Molecule is a large molecule immunotherapy with serious side effects
  - Large numbers cannot be exposed.
- The goal is to move this quickly by using Bayesian methods, adaptive designs and modelling of dose response.
  - From pre-clinical dose finding to choosing a dose in phase 3.
- Question for the team – how can we be innovative?

- **Key – modelling of the dose response all the way through**
- **Assumption – shape of dose response curves (not location) follow through from pre-clinical biomarker to clinical biomarker to clinical response**

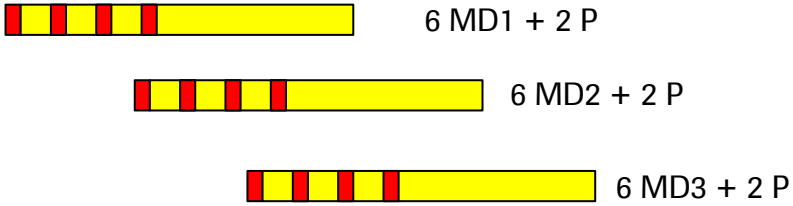
Typical looking First in Human Studies

Single Ascending Dose – 7 doses in cohorts



Total n = 28

Multiple Ascending Dose – 3 doses in cohorts



Total n = 24

Typical looking Proof of Concept Study then Dose Finding in 2b

POC – 1 doses versus placebo

High dose n = 50

Total n = 100

Placebo n = 50

Dose finding

High dose n = 50

Mid dose n = 50

Total n = 200

Low dose n = 50

Placebo n = 50

Proposed First in Human and Proof of Concept/Dose Finding Study Design

FIH	POC/DF
Repeat dose adaptive dose escalation study in a patient population but not the target (N=20) using up to 10 potential doses Objective – characterise the biomarker **dose response** curve	Adaptive repeat dose in target population (N = 110) Objective – characterise the clinical endpoint **dose response** curve

Traditional Paradigm = N = 352

Lean Paradigm N = 130

What is the potential impact?

- Traditional paradigm uses 352 patients taking approx. **7 years to get to Phase III**
  - Assumes 5 patients recruited per month with no dropouts and an analysis takes 3 months.
- Lean paradigm uses 130 patients taking approx. **5 years to get to Phase III**
  - Same assumptions as above but assuming interim analyses will take time but time is saved at the final.

- **Potential two years quicker to market**

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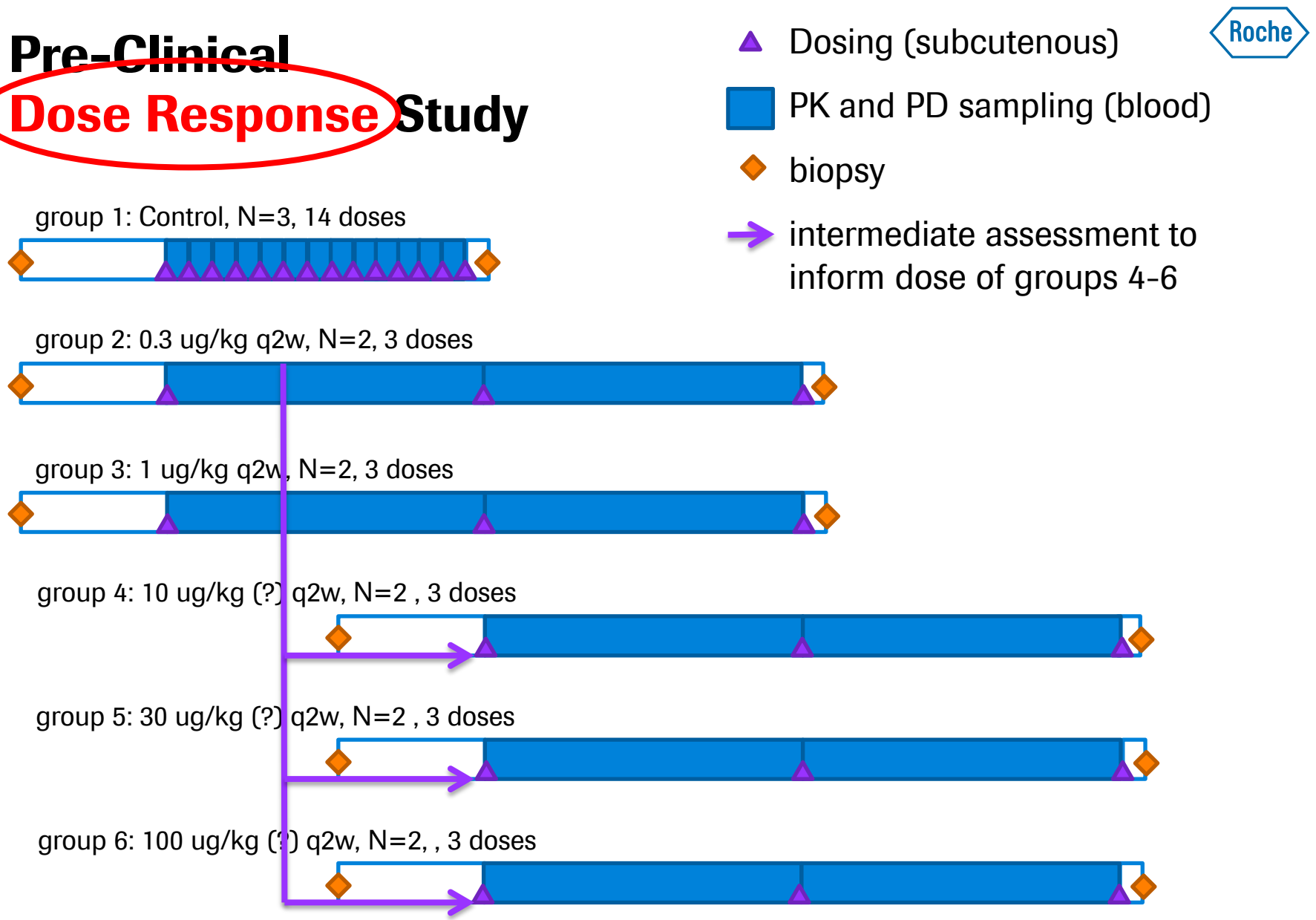
Pre-Clinical
Dose Response Study



Motivating Example FIH Study

Roche

Rationale and study design of the Adaptive study of IL-2 dose on regulatory T cells in type 1 diabetes (DILT1D): a non-randomised, open label, adaptive dose finding trial

Frank Waldron-Lynch,[1] Paula Kareclas,[2] Kathryn Irons,[2] Neil M Walker,[1] Adrian Mander,[3] Linda S Wicker,[1] John A Todd,[1] Simon Bond[2,3]

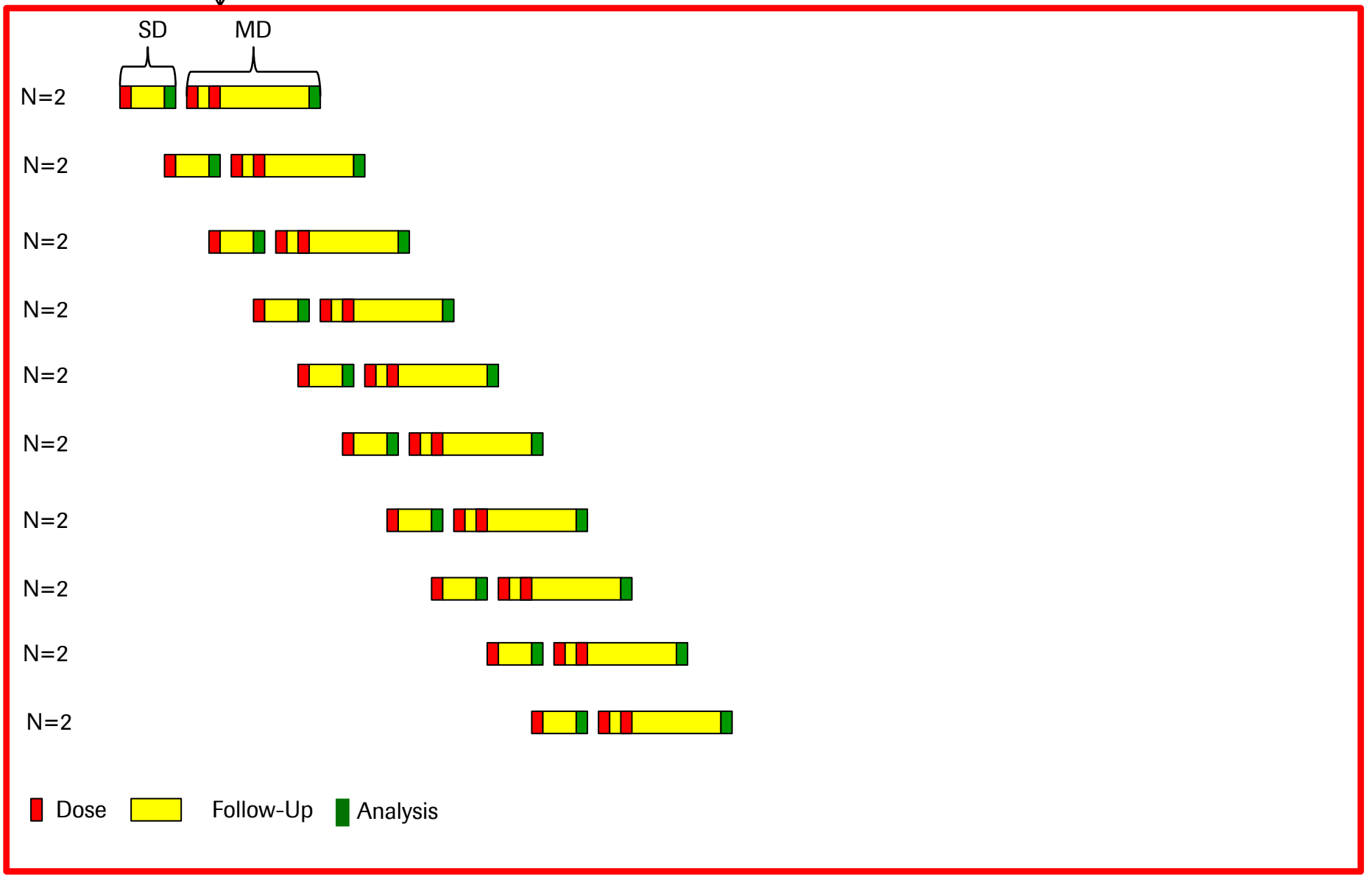
What was the design of this study?

- Primary outcome – dose response of the maximum % increase in regulatory T-cells over baseline.
- Two parts – learning phase, adaptive phase
- Learning phase
  - First 10 patients receive doses 0.04, 0.16, 0.6,1, 1.5 IU/m^2 in ascending order.
  - Two targets are identified – maximal and minimal T-reg increase.
- Adaptive phase
  - Interim analysis after every patient to determine the optimal dose for the next patient.
  - Based on minimizing the variance-covariance matrix of the targets
- Total sample size was 40.

Learnings from this trial

- The adaptive design was more than flexible enough to quantify the dose response curve and identify the dose which achieve the targets.
- However, the team thought it could have been done with less patients.
- Can we do this type of study with a Roche drug????

Prior **dose response shape** from pre-clinical



Adaptive Randomisation (applied at every analysis)

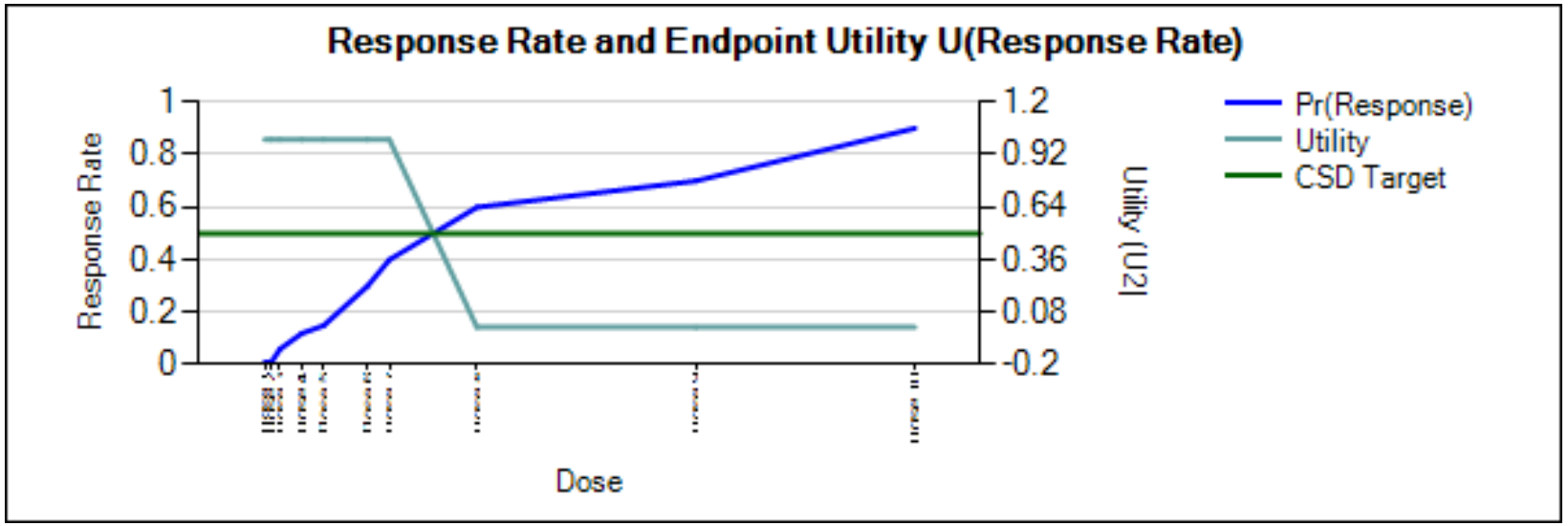
- The process for adaptation uses the methods as outlined by the paper "Dose-Finding Based On Efficacy-Toxicity Trade-Offs" by Peter F. Thall and John D. Cook, Biometrics Sep 2004.
- Dose response models updated after every patient has PD and safety data after both single and multiple dose.
- For this study the utility is a balance PD effect (clinically relevant effect = 0.15) and safety:
  - For PD we assign the utility U_{PD}
  - PD < 0 then $U_{PD} = 0$
  - $0 \leq PD \leq 0.15$ then $U_{PD} = PD * 6.67$
  - PD > 0.15 then $U_{PD} = PD$
  - Then for each safety parameter (1 to X) we assign the following utility (U_{Sx}):
  - Pr(safety exceeding threshold) < 20% then $U_{Sx} = 1$
  - Pr(safety exceeding threshold) ≥ 20% then $U_{Sx} = 0$
- Then the joint utility or gain is: $U_{PD} * U_{S1} * U_{S2} \ldots\ldots * U_{Sx}$ where X is the total number of safety endpoints.
- Pick the next dose which has the highest probability of having the highest utility.

Safety Endpoints – Derived from high dose Proleukin studies (Summary of Product Characteristics 20Jan2015)

Systems	Symptoms AE*	Signs AE*	SAE
CVS	SOB	Increased RR, tachycardia, reduction Bp	Capillary leak
CVS	SOB	Increased RR, decrease O2 sats, crepitations	Pulmonary oedema
Renal	Asymptomatic	Elevated Urea and creatinine Abnormal electrolytes	Renal impairment
Hepatobiliary	Asymptomatic	Elevated LFT's	Liver impairment
Haematological	Fever, bruising, SOB, bleeding	Severely abnormal FBC	Anaemia, leucopoenia, thybocytopenia, DIC, eosinophilia (all severe)
Systematic	Fever	Elevated WCC	Sepsis
Skin	Pain	Skin breakdown	Injection site necrosis

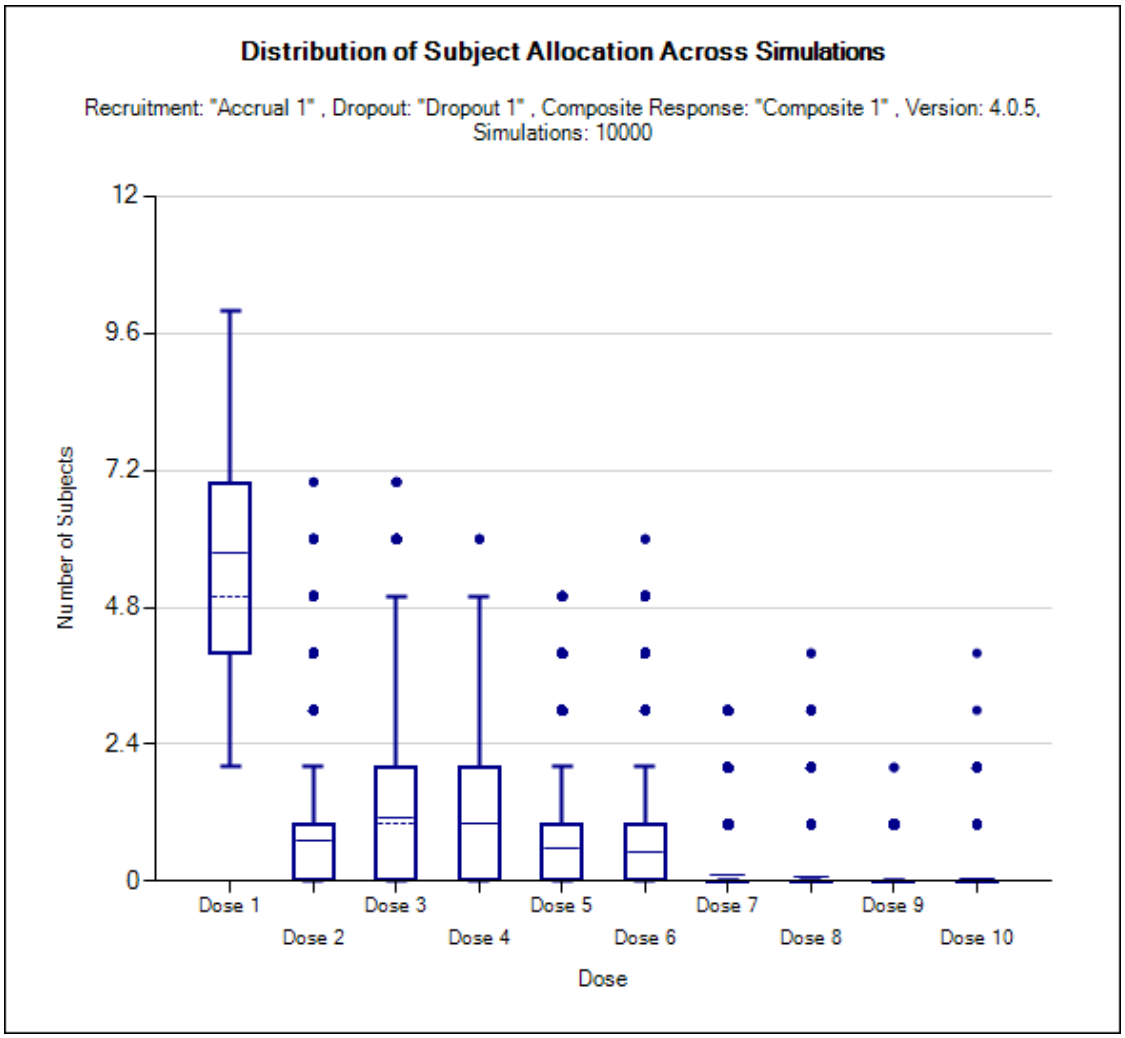
* would restrict dose escalation if evaluated as related to drug by escalation committee

Unsafe Simulated Scenario

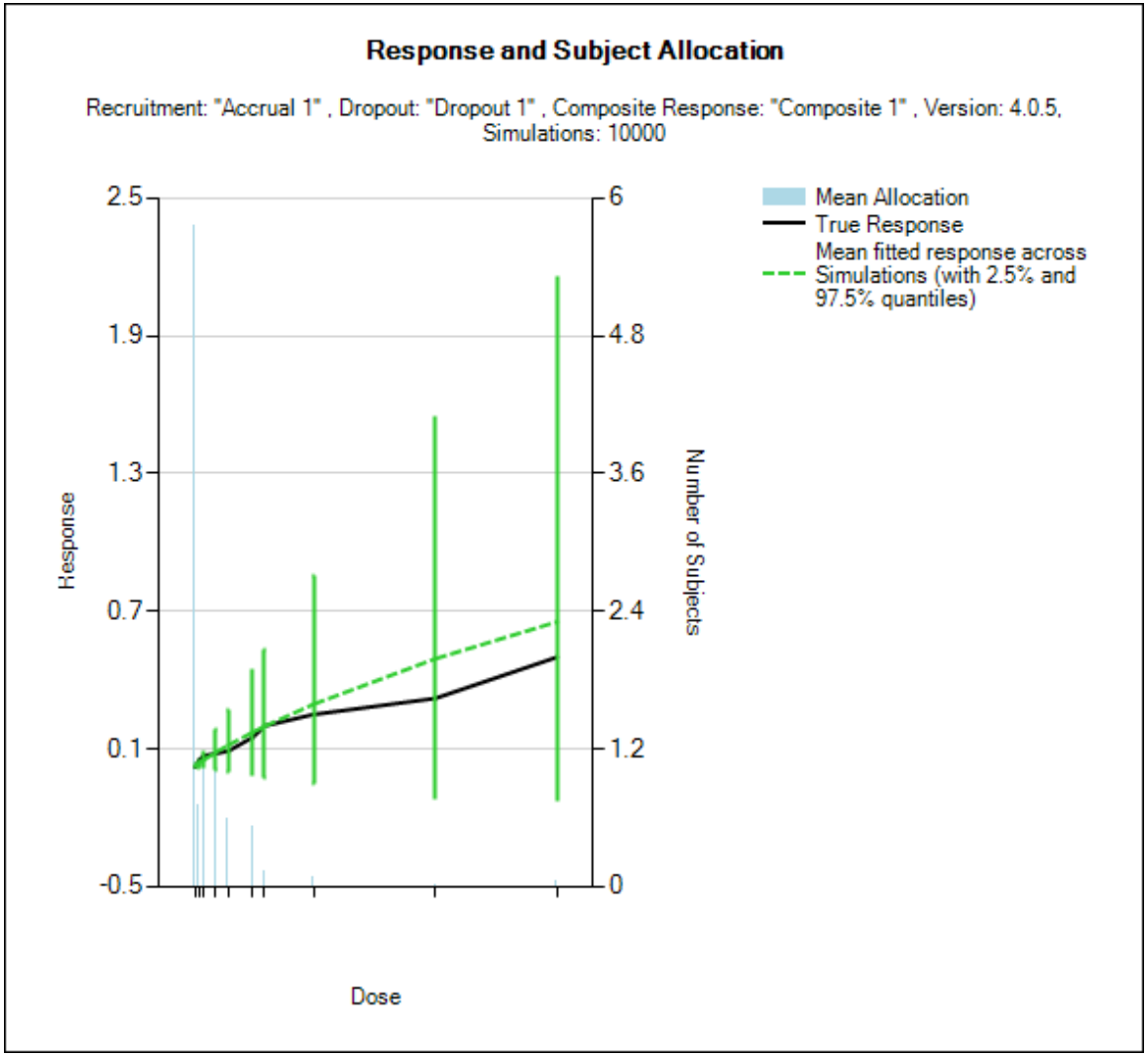


- Above Dose 7 – Pr(safety exceeding threshold) ≥ 20%
- Therefore, the utility is 0 for Doses 8 and above.
- Minimal allocation here.

Results from Simulations of the FIH Design Assuming Unsafe at Dose 7 and Above



Results from Simulations of the FIH SD Design



Roche

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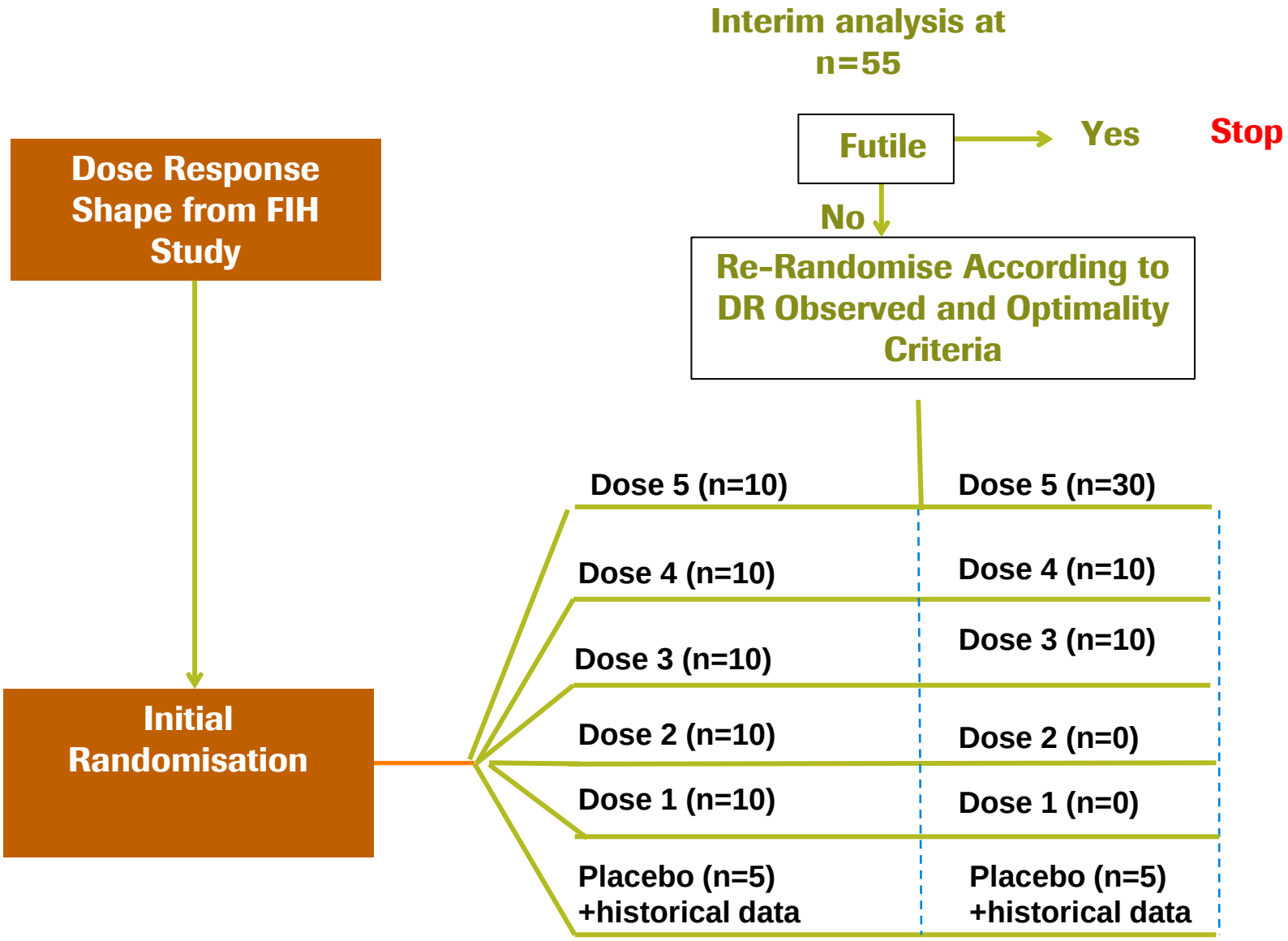
POC/DF in a Patient Population

- Adaptive two stage design with a single dose compared to placebo (plus historical data).
- 5 doses versus placebo – 12 weeks dosing followed by 8 follow-up
- The primary endpoint will be proportion of patients in clinical remission at week 12.
- Clinical significant effect is 30 percentage points above placebo, assuming placebo rate is 10%
- N = 110 with 2:1 randomisation ratio (active:control).
- Historical data will be used to enrich the control arm.
- An interim analysis will be conducted once 55 patients reach week 12.
  - The study will stop for futility if Pr(Difference ≥30%) <0.1 for all doses.
- At the end of the study success will be declared if:
  - Success will be declared if Pr(Difference ≥30%) > 0.7
  - Futility declared if Pr(Difference ≥30%) <0.1 for all doses

POC/DF Design

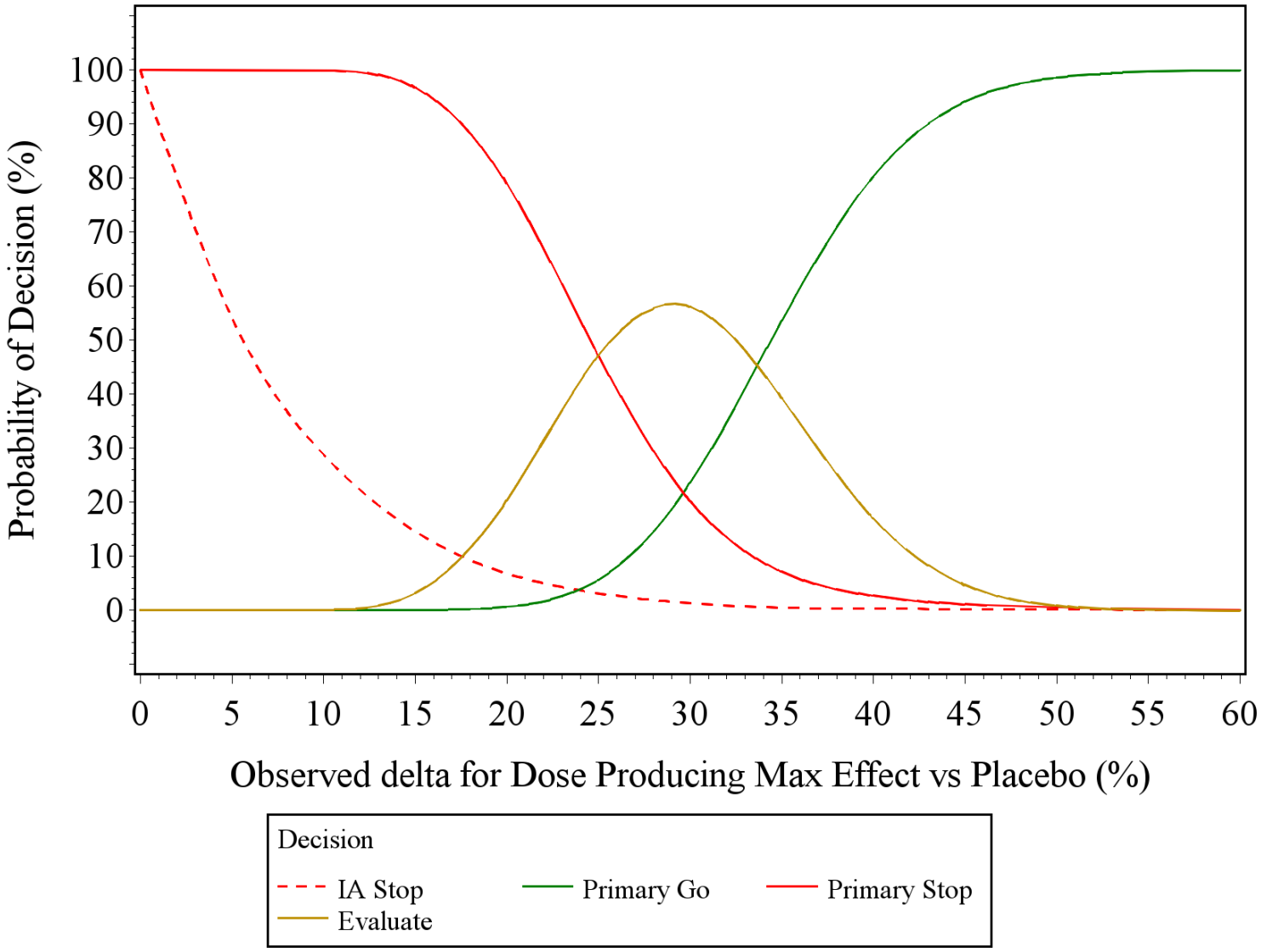


Statistical Assumptions and Decision Criteria

- Historical placebo are exchangeable with trial placebo
- Prior dose response shape for the clinical endpoint assumed to be similar as that for PD in the FIH study
- Randomisation following interim determined by stage 1 dose response with patients being randomised to most informative doses using a combination of C and D-Optimality and fixed rate allocated to placebo.

	INTERIM ANALYSIS N=55	FINAL ANALYSIS N=110
DECISION CRITERIA	No Go – Pr(Δ ≥30%) <0.1 for all doses.	Go - Pr(Δ ≥30%) > 0.7 Otherwise evaluate No Go – Pr(Δ ≥30%) <0.1

Plot of Operating Characteristics



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- It is possible to learn as you go along and develop a lean program.
- Key is not to be tied into SD, MD, POC, DF then Phase III
- Learn versus confirm – when you know enough go confirmatory
- The key is deciding what you need to know
- This program has the potential to be on the market 2 years earlier given the lean paradigm
- At the moment compound is in FIH

Doing now what patients need next