Linking Exploratory Clinical Development Endpoints to Phase 3 Endpoints: A Quantitative Basis for Decision-making

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Overview

- Causes of Phase 3 failures
- Relationship of biomarkers and intermediate endpoints to Phase 3 endpoints
- Totality of evidence: models
- Manage risk and account for uncertainty
- Inform decision-making based on early endpoints
- Probability of success of the next study(ies)

U.S. FOOD & DRUG ADMINISTRATION

22 CASE STUDIES WHERE PHASE 2 AND PHASE 3 TRIALS HAD DIVERGENT RESULTS

January 2017

Success Rates 2003 – 2011

5820 transitions and 4451 drugs

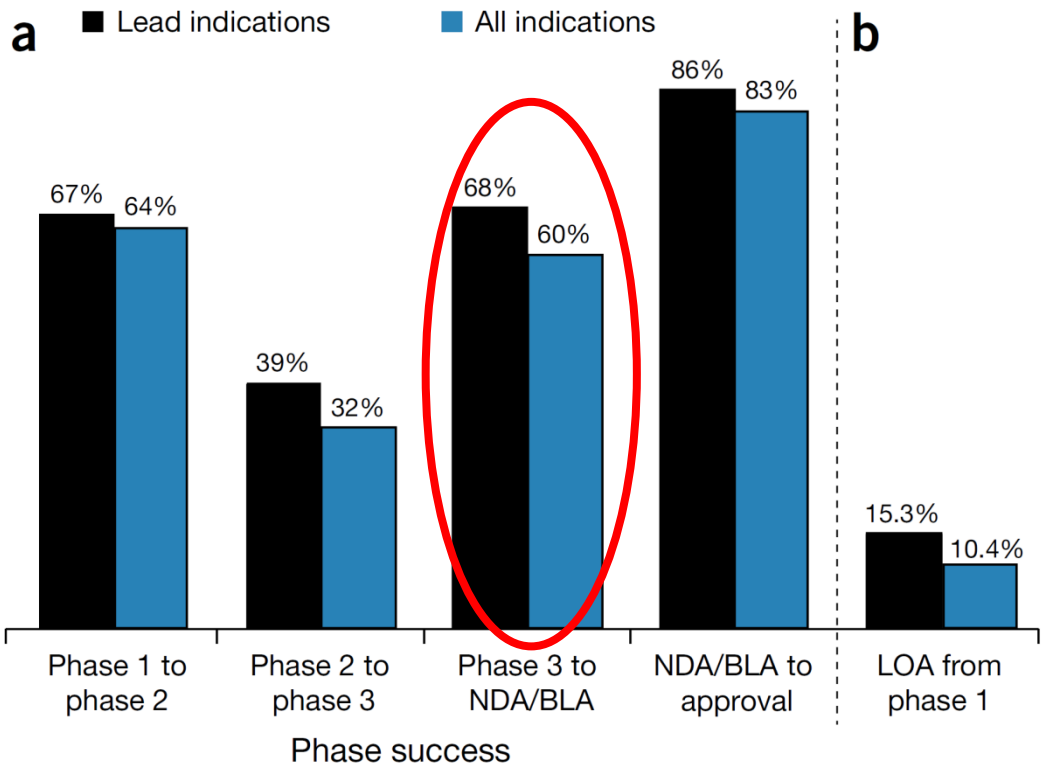
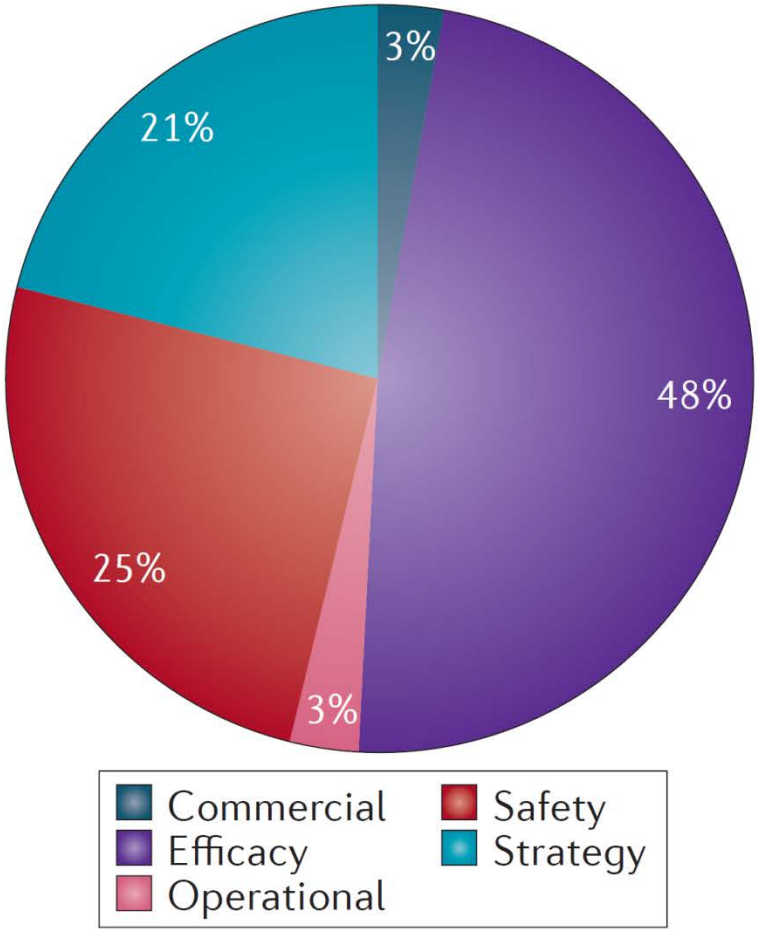


Figure 1 Phase success and LOA rates. (**a**) Phase success rates for lead and all indications. The rates represent the probability that a drug will successfully advance to the next phase. (**b**) LOA from phase 1 for lead and all indications. Rates denote the probability of FDA approval for drugs in phase 1 development.

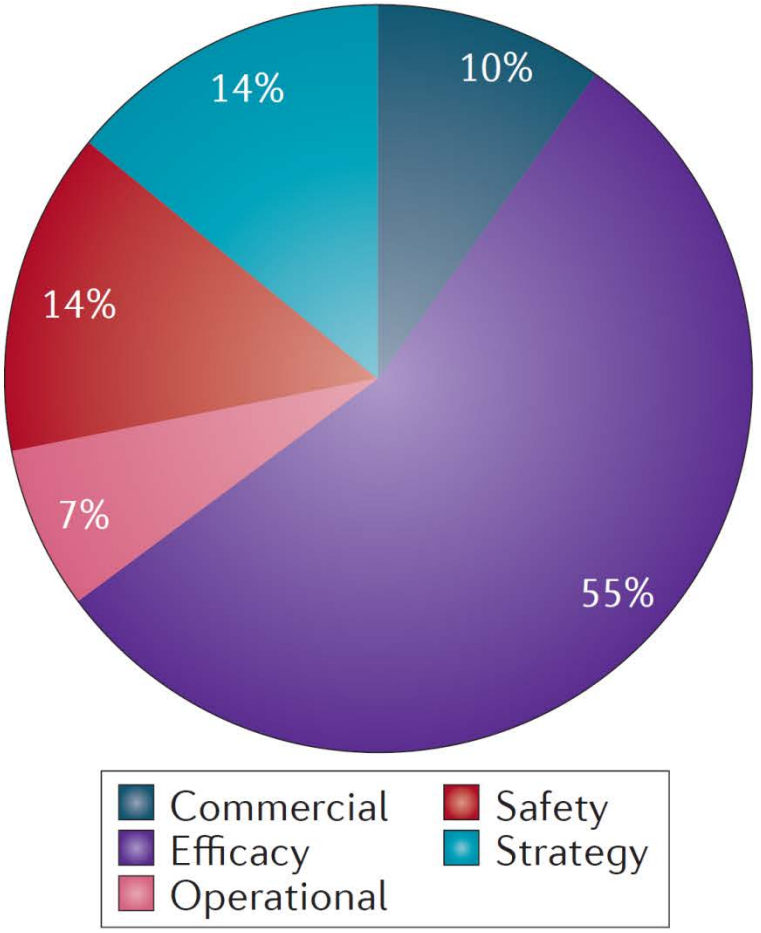
Hay et al, Nature Biotechnology 2014;32:40-51

Causes of Failure: 2013 - 2015

Phase 2



Phase 3

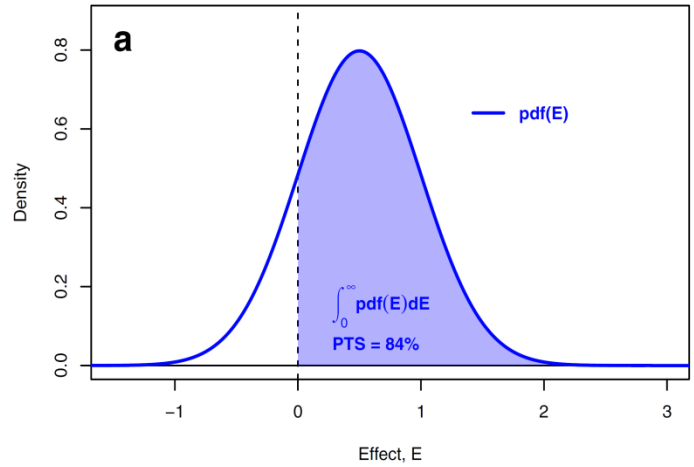


Harrison RK. Nat Rev Drug Discov 2016;15:817-8

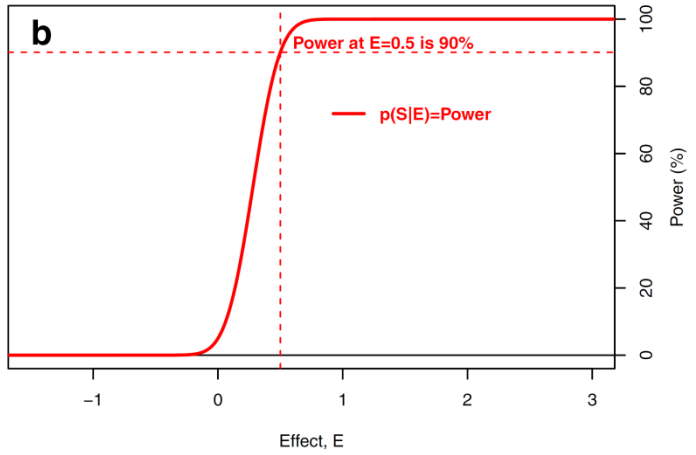
“Ignorance Is Not Bliss: Statistical Power Is Not Probability of Trial Success”

Zierhut et al, Clin Pharm Ther 2016;99:356

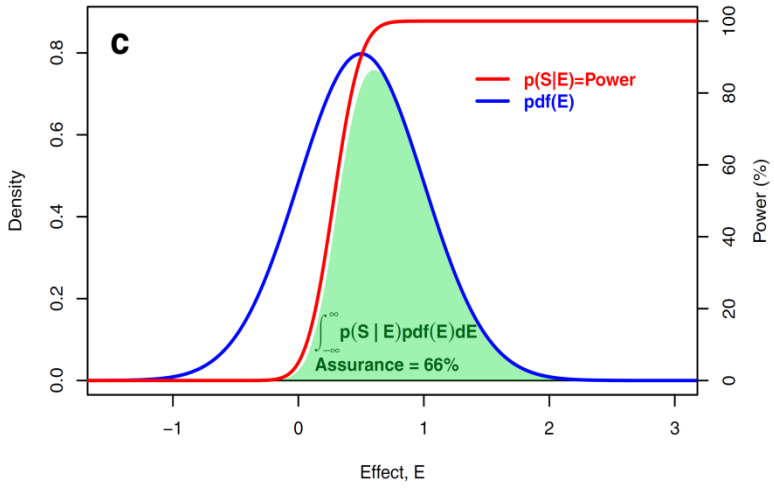
- Should not ignore probability of success and use only statistical power
- Statistical power is typically based on an assumed effect size
  - Conditional probability
  - No uncertainty in effect size
- Probability of (trial) success (PoS)
  - Accounts for expected treatment effect and uncertainty
  - Unconditional probability or “assurance”
- Prior “signal” (e.g. proof of concept) may be relatively weak or uncertain
- PoS could be very low despite a statistical “power” of 90%.
- Could be part of the reason for low success rate in Phases 3



From prior data, trials, model
Probability of "true" effect E > 0
Independent of any future trial



Power as a function of effect size E
For a particular future trial



POS of particular future trial
Accounts for uncertainty in E

Zierhut et al, Clin Pharm Ther 2016;99:356

Understanding Biomarker – Clinical Outcome Relationship

Managing Risk and Uncertainty in Phases 1 – 3

- Setting: Venous thromboembolism (VTE) prophylaxis in patients undergoing an elective total knee replacement
- PD 0348292: an oral direct factor Xa inhibitor
- Dose selection critical for an anticoagulant
  - Underdosing: increased risk of thrombosis
  - Overdosing: increased risk of bleeding
- Objective of Phase 2b dose-ranging trial
  - Find a dose equivalent to the gold standard of enoxaparin 60 mg/day
- Cohen et al, J Thromb Haemost 2013;11:1503-10
- Milligan et al, Clin Pharmacol Ther 2013;93:502-14

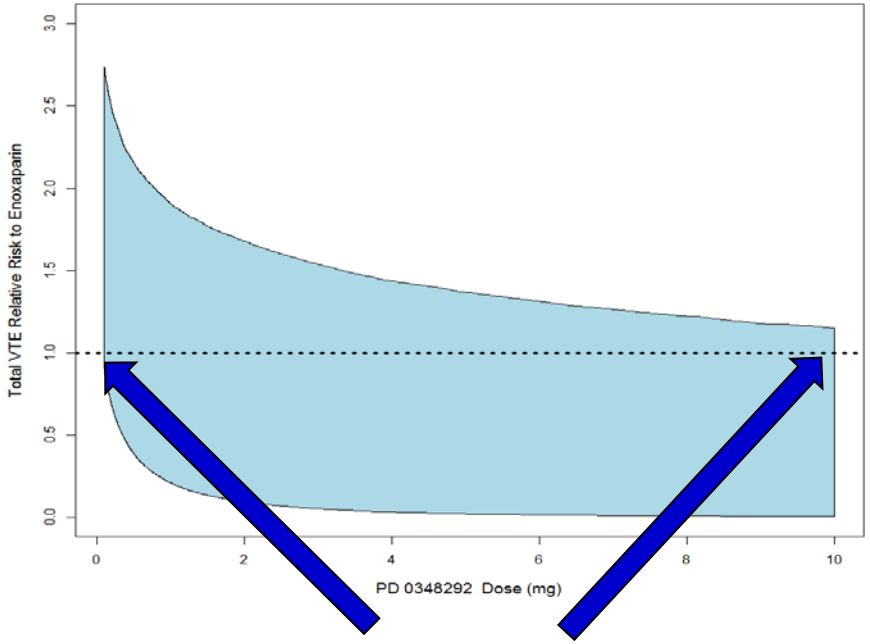
During Phase 1: Used Biomarker Response, Literature Data, and PK-PD Modeling to Estimate Therapeutic Dose

- Biomarker:
  - Inhibition of thrombin generation (10 drugs)
- Literature Data:
  - Clinical outcome (incidence of VTE and major bleeding [MB]) for comparator anticoagulants (5 drugs)
- Model:
  - Linked biomarker response and clinical outcome for comparators with an integrated PK-PD model
- Estimated Dose:
  - Predicted VTE and MB dose-response for PD 0348292 based on its biomarker response and PK

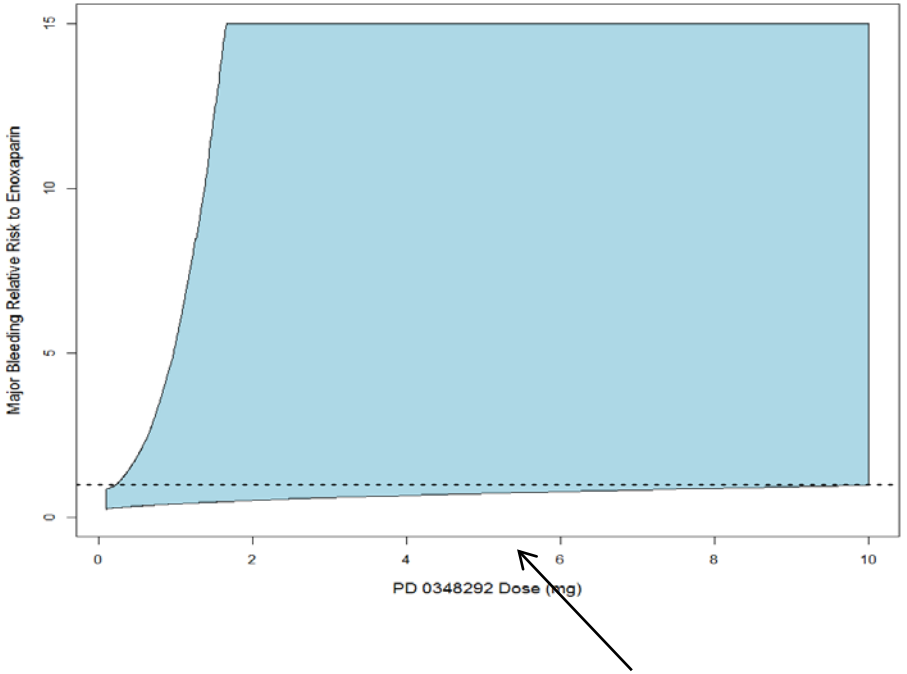
Dose-Response Relationships (Relative to Enoxaparin)

Based on PK-PD Model and Inhibition of Thrombin Generation

Efficacy: VTE



Safety: Major Bleed



- Significant uncertainty in dose equivalent to enoxaparin
- Safety and ethical concerns in designing a dose-ranging trial for VTE prevention

Clinical Trial Simulations Facilitated Evaluation of Many Possible Designs

- Using the VTE and MB dose-response models for PD 0348292, simulated the outcome of each trial design 1000 times
- Assessed trial performance using various metrics;
  - Primarily the power to find a dose equivalent to enoxaparin
  - Limit the number of MB and VTEs
  - Likelihood to prune/add dose in an adaptive trial
- Protect subjects from excessive VTE and MB while evaluating dose-response relationship over a broad range of doses
- Evaluated sensitivity to sample size, doses, adaptive modifications (pruning and adding doses), dose selection criteria, dose response model structure
- Goal was to select one dose for Phase 3

Final Study Design: Adaptive Dose Range

- 6-arm randomized, parallel group study with adaptive dose range based on interim dose decision analyses of VTE and MB
  - Start with 5 doses of PD 0348292 (0.1 to 2.5 mg QD)
  - Prune PD 0348292 doses based on excessive VTE or MB
  - Add higher PD 0348292 doses (4 and 10 mg QD) if prune lower doses and MB rate acceptable
  - Enoxaparin 30 mg BID as control
- Dose decision interim analyses (dose-response logistic regression model) after every 147 evaluable patients
- Total sample size of 1250 patients

Dose-Response Relationships (Relative to Enoxaparin)

Efficacy: VTE

Safety: Major Bleed

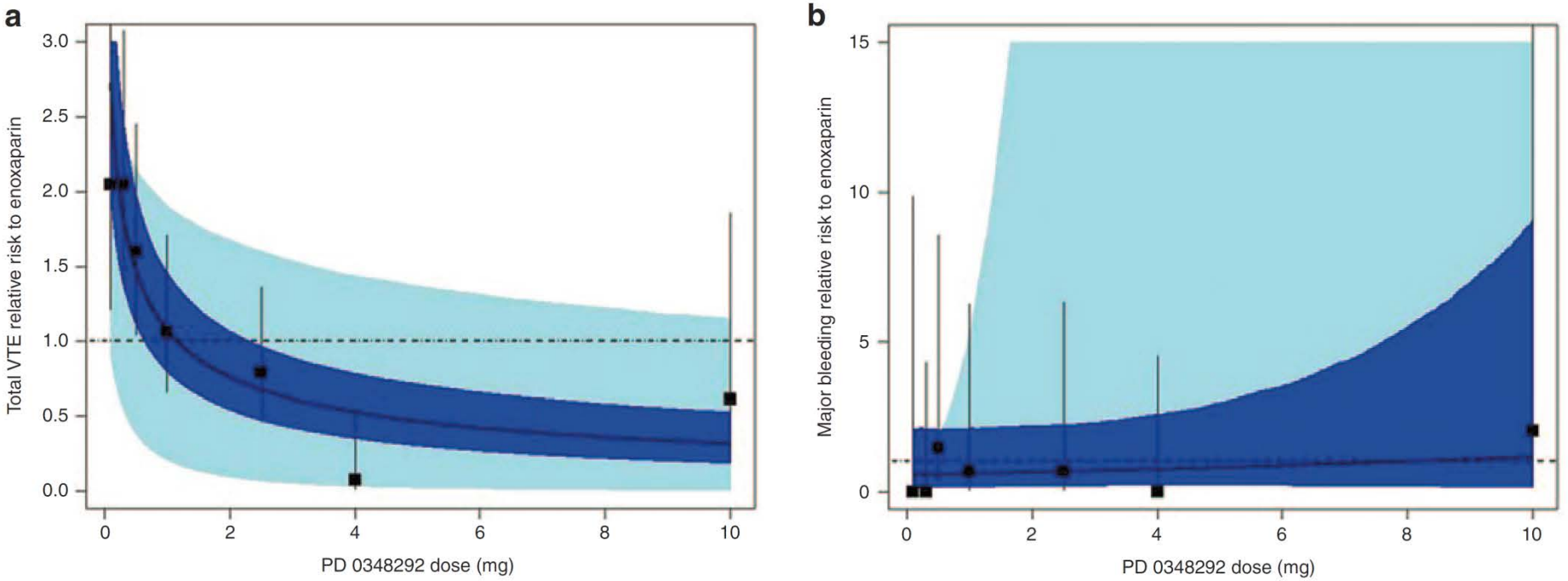


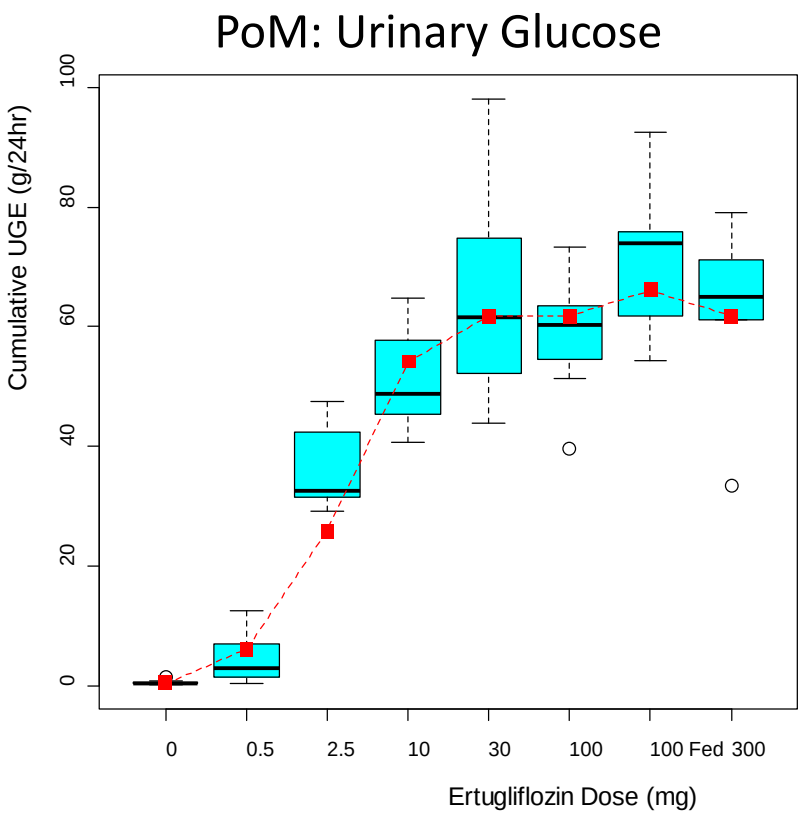
Figure 6 Observed relative risk of PD 0348292 vs. enoxaparin (symbols with 95% confidence intervals (CIs)) for (**a**) VTE and (**b**) MB and logistic regression model fit (solid line with dark blue area covering the 90% CI) in an adaptive phase II study. The light blue area covers the 90% CI before the trial based on the PK–PD model for inhibition of thrombin generation. MB, major bleeding; PK–PD, pharmacokinetics–pharmacodynamics; VTE, venous thromboembolism.

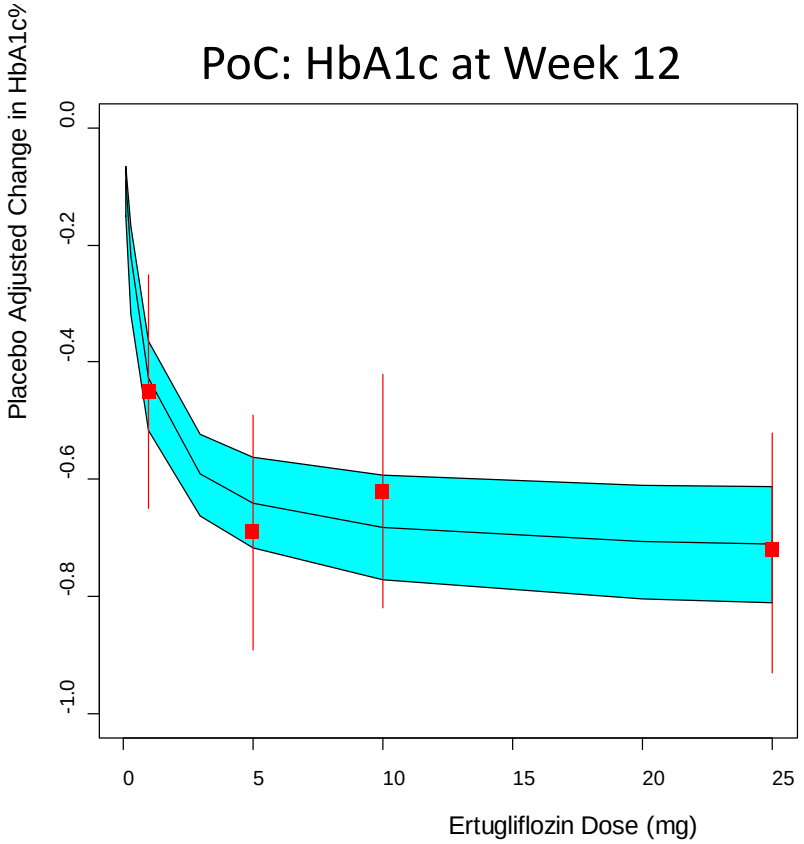
Impact on Drug Development

- Study designed using M&S was approved by senior management and conducted successfully
- Study met key objective
  - Identified the dose equivalent to enoxaparin
  - 1.16mg, 95% CI: 0.56 – 2.41mg
- Safely explored a 100-fold dose range to allow characterization of dose-response relationship for efficacy (vs ~ 4 -12 fold dose range for competitors)
- ~1/3 sample size of traditional parallel group study
  - Savings of 2750 patients
  - Savings >$20M in trial costs
  - Shortened development time by I year
- Manage risk and strategy based on the uncertainty in the relationship between biomarker and clinical outcome

Phase1 Biomarker Linkage to Phase 2 - 3 Endpoint

- Ertugliflozin: sodium/glucose cotransporter 2 inhibitor (SGLT2i)
- Urinary glucose excretion in health subjects after single doses
- HbA1c response in patients with type 2 diabetes at 12 weeks



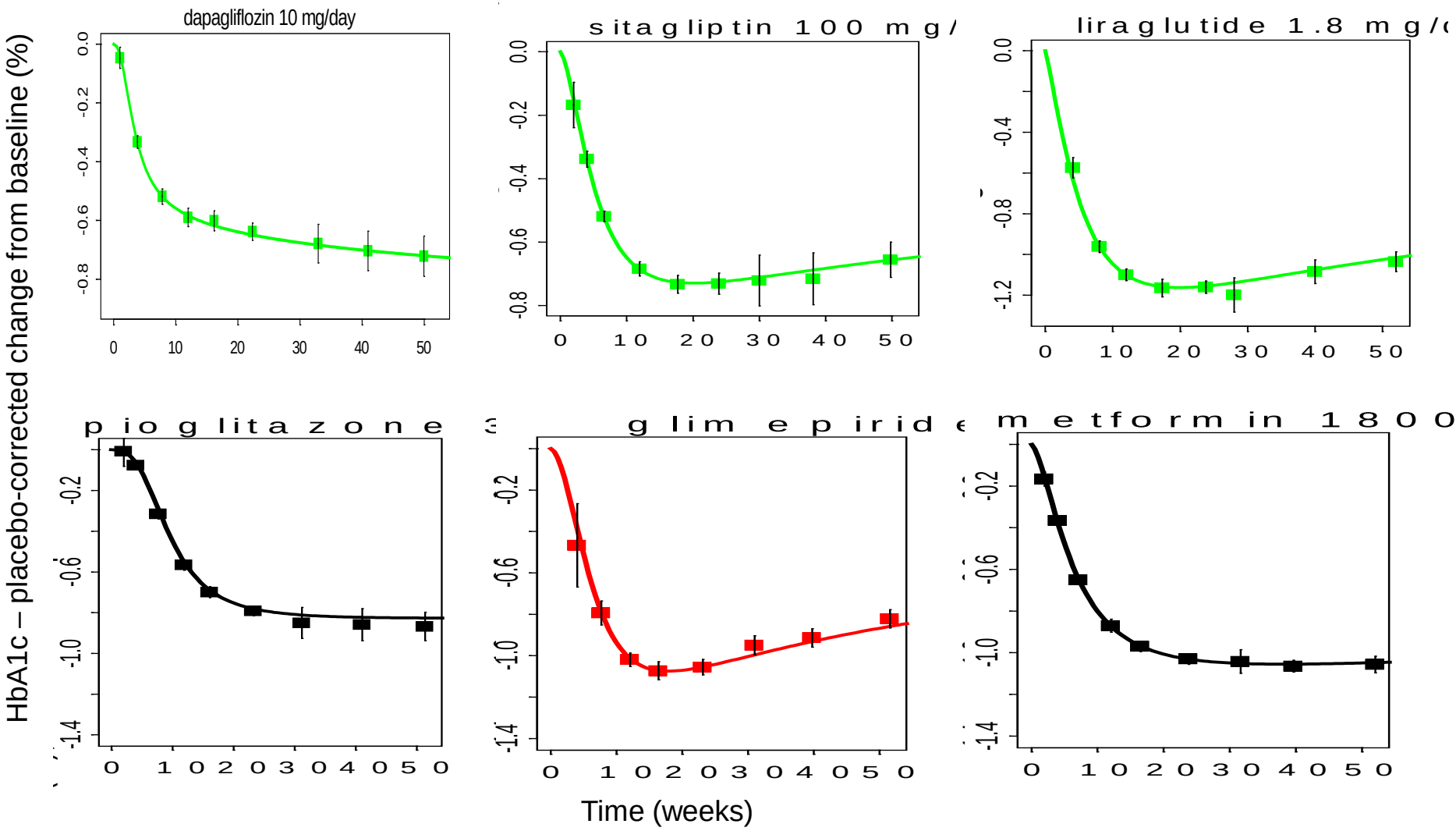


Milligan et al, Clin Pharmacol Ther 2013;93:502-14

Estimated and Observed Time-Course of HbA1c Lowering over 12 Months

Impact of Mechanism of Action

Mandema J, Sweeney K, Terra S, Sahasrabudhe V. ADA 2012

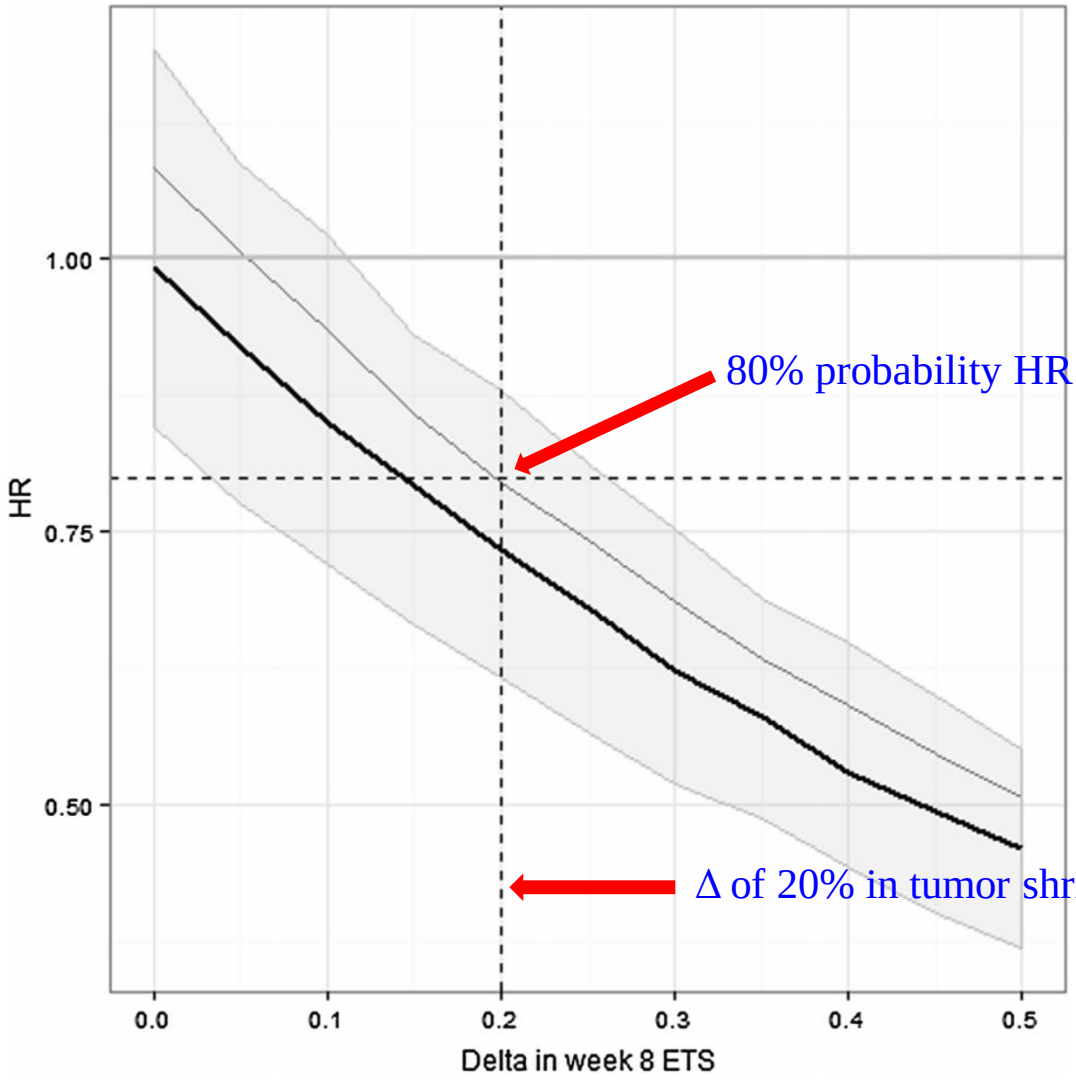


Mean across arms with same daily dose shown; bars are 95% CI; response is for baseline HbA1c of 8% and on metformin background for dapagliflozin, sitagliptin, liraglutide, pioglitazone and glimepiride

Early Tumor Shrinkage (ETS) at 8 weeks and Overall Survival (OS)

Renal Cell Carcinoma

Future Drug versus Sunitinib (n = 300 pts/group)



80% probability HR < 0.8 for OS in Phase 3

Δ of 20% in tumor shrinkage at 8 weeks in Phase 2

Claret et al, Cancer Chemother Pharmacol 2015;76:567-73.

Using Short-term Safety Markers to Predict Clinically Relevant Quantities in Registration Trials

Example

- Tofacitinib
- Objective: Use exposure-response models of continuous, laboratory safety markers (e.g. neutrophils, hemoglobin) to
  - Predict incidence rates based on threshold values of clinical importance
  - Inform Phase 3 dose selection
  - Predict level of risk in registration trials and for clinical management (e.g. monitoring and discontinuation)

Calculating Probability of Success

Gupta, 2012 ASCPT

Utilize E-R models using continuous data to simulate clinical trials

↓

Incorporate:
trial-to-trial uncertainty and patient-level uncertainty

↓

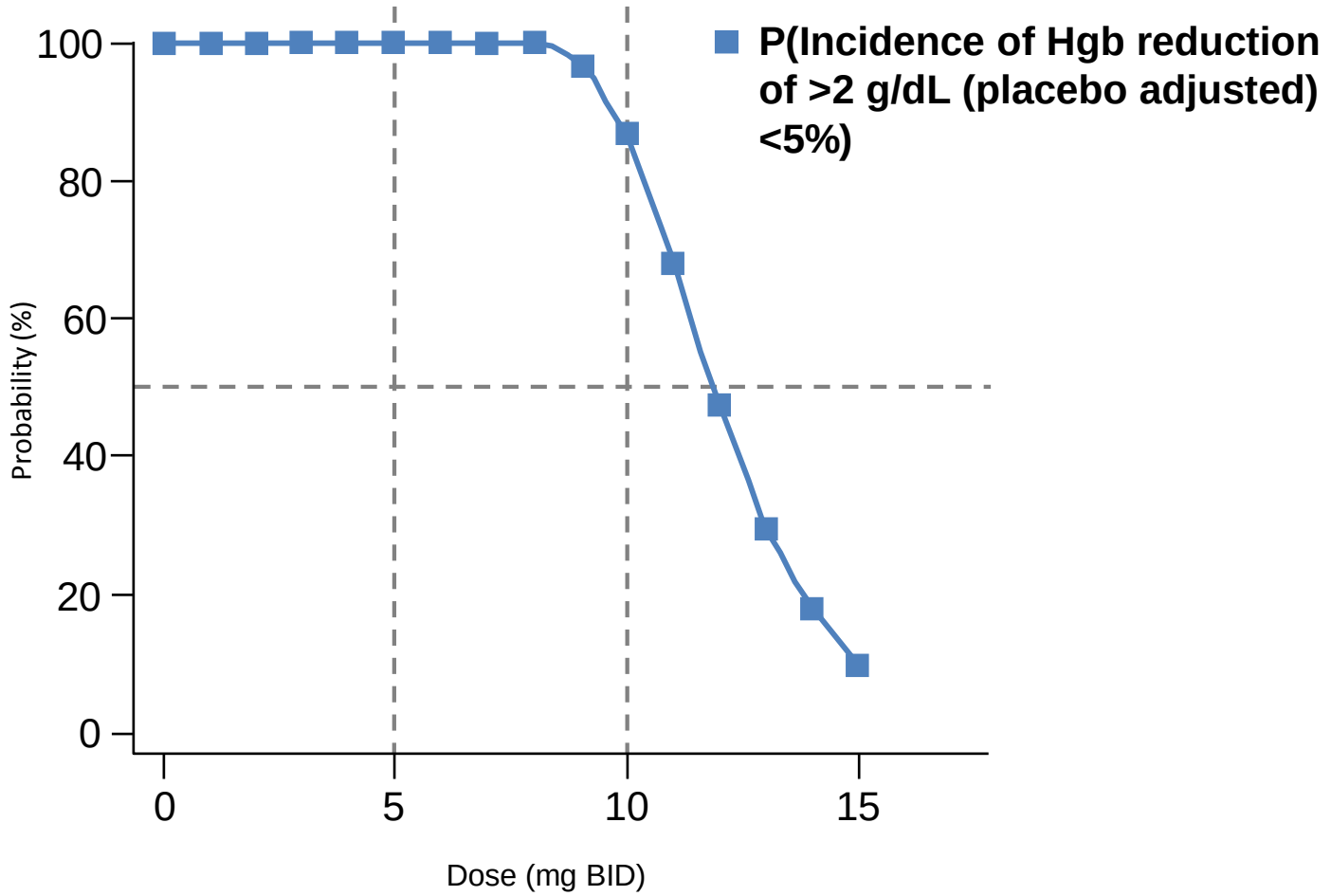
Apply decision rule to the simulated trials
(< 5% incidence of placebo adjusted Hgb drop of >2 g/dL)

↓

Probability that a dose will have < 5% incidence of placebo adjusted Hgb drop >2 g/dL drop
PoS_{dose} = (trials with successful outcome/total number of trials)

Probability of Success for Safety Endpoint: Anemia

Gupta, 2012 ASCPT



Phase 3 trial outcomes over longer durations
consistent with predicted low probability of anemia at ≤10 mg BID doses

Clinical Trial Meta Analysis: Reduction in Cardiovascular Events Even in Patients with Lower LDL Cholesterol

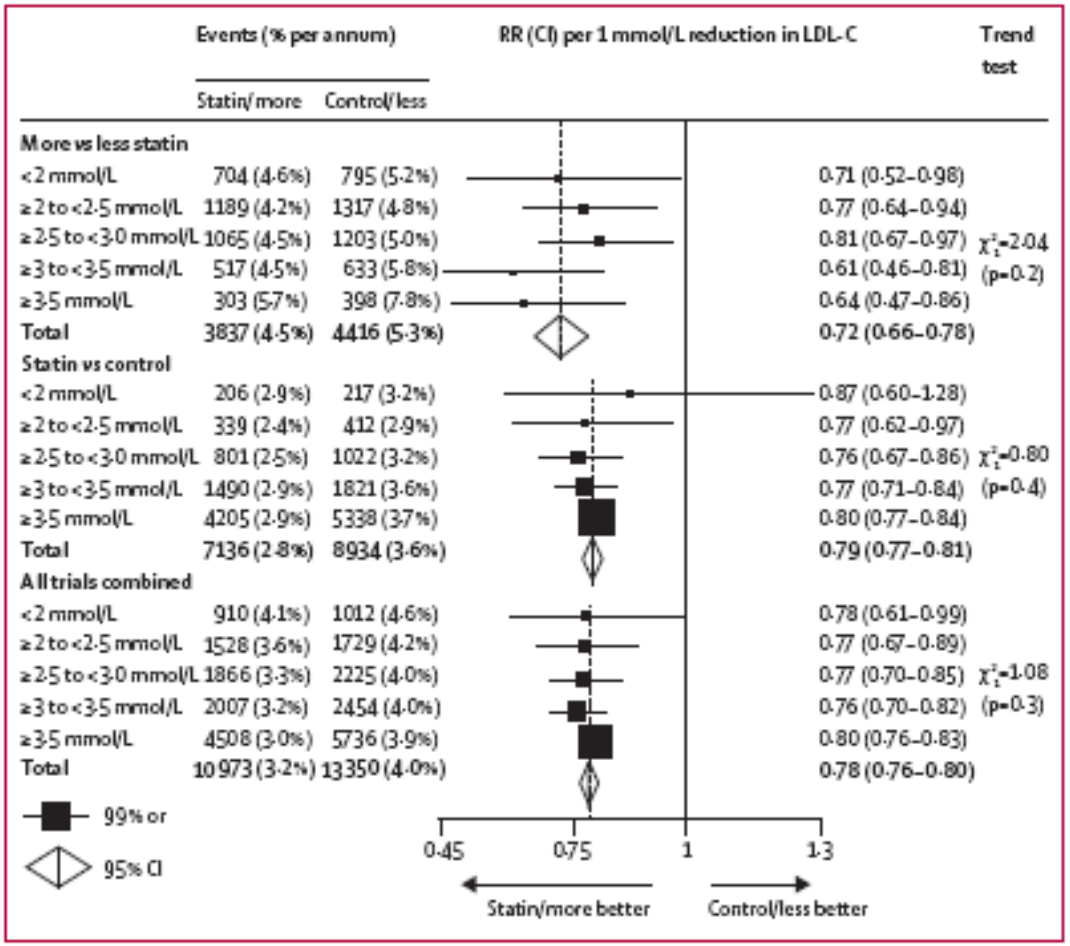


Figure 4: Effects on major vascular events per 1·0 mmol/L reduction in LDL cholesterol, by baseline LDL cholesterol concentration on the less intensive or control regimen

Rate ratios (RRs) are plotted for each comparison of first event rates between treatment groups, and are weighted per 1·0 mmol/L LDL cholesterol (LDL-C) difference at 1 year. Analyses were done with trial-specific and subgroup-specific LDL weights for each baseline LDL cholesterol category. Missing data are not plotted. RRs are shown with horizontal lines denoting 99% CIs or with open diamonds showing 95% CIs.

Cholesterol Treatment Trialists, Lancet 2012;380:581–90

Pfizer PTRS Council
Phase 2 to 3 Transition

- Potential uncertainties for extrapolation from the phase 2 to phase 3
  - Different endpoints
  - Different duration of treatment
  - Different patients (e.g. inclusion and/or exclusion criteria)
  - Different countries
  - Different standards of care
  - Different doses or formulations
- PTRS estimates based on all pertinent information and trial data for new compound and key comparators
- Apply best practices, including pharmacometrics modeling
- Transparency about the key assumptions and uncertainties
  - Efficacy (estimates and confidence intervals)
  - Safety

Conclusions and Key Messages

- Insufficient efficacy is the primary cause of Phase 3 failures
- Need quantitative understanding of the relationship between exploratory clinical endpoints and Phase 3 endpoints
- Totality of previous data: models
  - Quantitative systems pharmacology model: bottom up models
  - Model-based meta-analysis of clinical trials: top down models
- Manage risk and account for uncertainty
- Inform decision-making based on early endpoints
- Emphasis on probability of success of the next study(ies)
- Opportunity to influence important strategic decisions in drug development