

Dose Selection in Drug Development and Regulation: Possible Future Direction

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Overview

- ◆ What is the problem and how did we get here
- ◆ Examples of the challenge
- ◆ Potential solution
 - Led by regulators and supported by industry
 - Stimulate discussion at this meeting

Scientific and Regulatory Reasons for Delay and Denial of FDA Approval of Initial Applications for New Drugs, 2000-2012

Sacks et al, JAMA. 2014;311:378-384

RESULTS Of the 302 identified NME applications, 151 (50%) were approved when first submitted and 222 (73.5%) were ultimately approved. Seventy-one applications required 1 or more resubmissions before approval, with a median delay to approval of 435 days following the first unsuccessful submission. Of the unsuccessful first-time applications, 24 (15.9%) included uncertainties related to dose selection, 20 (13.2%) choice of study end points that failed to adequately reflect a clinically meaningful effect, 20 (13.2%) inconsistent results when different end points were tested, 17 (11.3%) inconsistent results when different trials or study sites were compared, and 20 (13.2%) poor efficacy when compared with the standard of care. The frequency of safety deficiencies was similar among never-approved drugs compared with those with delayed approval (43 of 80 never approved [53.8%] vs 37 of 71 eventually approved [52.1%]; difference, 1.7% [95% CI, -14.86% to 18.05%]; $P = .87$). However, efficacy deficiencies were significantly more frequent among the never-approved drugs than among those with delayed approvals (61 of 80 never approved [76.3%] vs 28 of 71 eventually approved [39.4%]; difference, 36.9% [95% CI, 20.25% to 50.86%]; $P < .001$).

CONCLUSIONS AND RELEVANCE Several potentially preventable deficiencies, including failure to select optimal drug doses and suitable study end points, accounted for significant delays in the approval of new drugs. Understanding the reasons for previous failures is helpful to improve the efficiency of clinical development for new drugs.

Tufts CSDD Estimates of Cost/Drug Approved \$2.6B (£1.7B, €2.1B)

FOR IMMEDIATE RELEASE

BOSTON - **Nov. 18, 2014** - Developing a new prescription medicine that gains marketing approval.....is estimated to cost **\$2,558 million**, according to a new study by the Tufts Center for the Study of Drug Development.

- Out of pocket cost of \$1.4B + “Time” cost of \$1.2B
- 145% increase since 2003 after adjusting for inflation
- Main causes of cost increase
 - Higher cost of clinical trials
 - Higher failure rate in clinical development
- Inadequate dose selection strategy a contributing factor

Importance of Appropriate Dose Selection

- ♦ What happens if you take the “wrong” dose into Phase 3?
 - \$ to repeat unsuccessful trials (could be \$100M or more)
 - Delays in regulatory approval
- ♦ Many examples of compounds originally marketed at the wrong dose (generally too high)
 - e.g. captopril, hydrochlorothiazide
 - Pharmacoepidemiol Drug Safety 2002;11: 439–446.

ORIGINAL REPORT

Postmarketing drug dosage changes of 499 FDA-approved new molecular entities, 1980–1999[†]

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SUMMARY

Purpose Risks and benefits of marketed drugs can be improved by changing their labels to optimize dosage regimens for indicated populations. Such postmarketing label changes may reflect the quality of pre-marketing development, regulatory review, and postmarketing surveillance. We documented dosage changes of FDA-approved new molecular entities (NMEs), and investigated trends over time and across therapeutic groups, on the premise that improved drug development methods have yielded fewer postmarketing label changes over time.

Methods We compiled a list of NMEs approved by FDA from 1 January 1980 to 31 December 1999 using FDA's website, Freedom of Information Act request, and PhRMA (Pharmaceutical Research and Manufacturers of America) database. Original labeled dosages and indicated patient populations were tracked in labels in the *Physician's Desk Reference*[®]. Time and covariate-adjusted risks for dosage changes by 5-year epoch and therapeutic groups were estimated by survival analysis.

Results Of 499 NMEs, 354 (71%) were evaluable. Dosage changes in indicated populations occurred in 73 NMEs (21%). A total of 58 (79%) were safety-motivated, net dosage decreases. Percentage of NMEs with changes by therapeutic group ranged from 27.3% for neuropharmacologic drugs to 13.6% for miscellaneous drugs. Median time to change following approval fell from 6.5 years (1980–1984) to 2.0 years (1995–1999). Contrary to our premise, 1995–1999 NMEs were 3.15 times more likely to change in comparison to 1980–1984 NMEs ($p = 0.008$, Cox analysis).

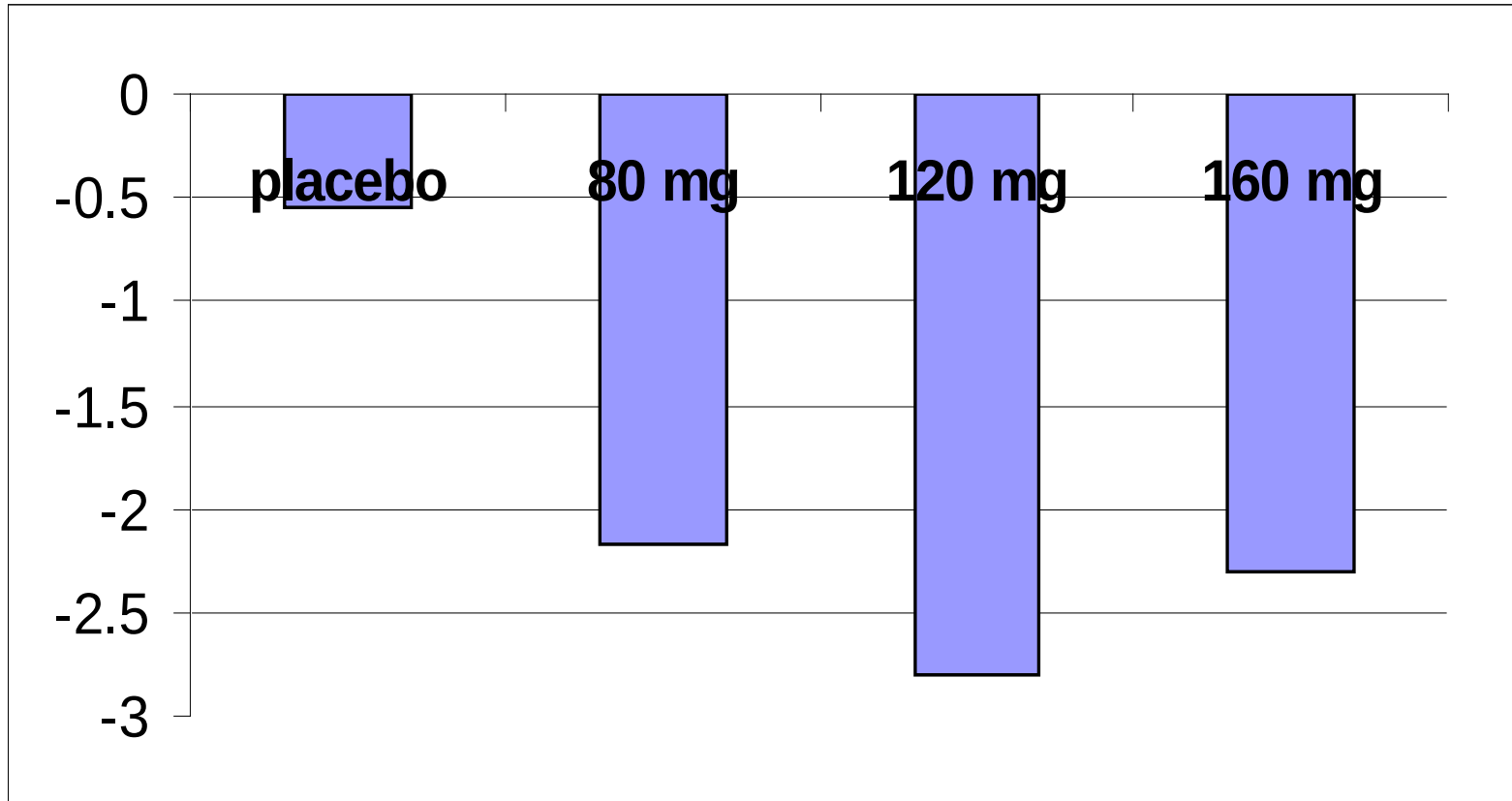
Conclusions Dosages of one in five NMEs changed, four in five changes were safety reductions. Increasing frequency of changes, independent of therapeutic group, may reflect intensified postmarketing surveillance and underscores the need to improve pre-marketing optimization of dosage and indicated population. Copyright © 2002 John Wiley & Sons, Ltd.

Common Problem in Phase 2b

- ◆ We too often focus on maximizing efficacy and thus we evaluate doses near the maximum tolerated dose
- ◆ and.....
- ◆ We limit the number of doses because we try to power for pairwise comparisons
- ◆ We think we know more than we actually do about dose-response

Drug X Study 1

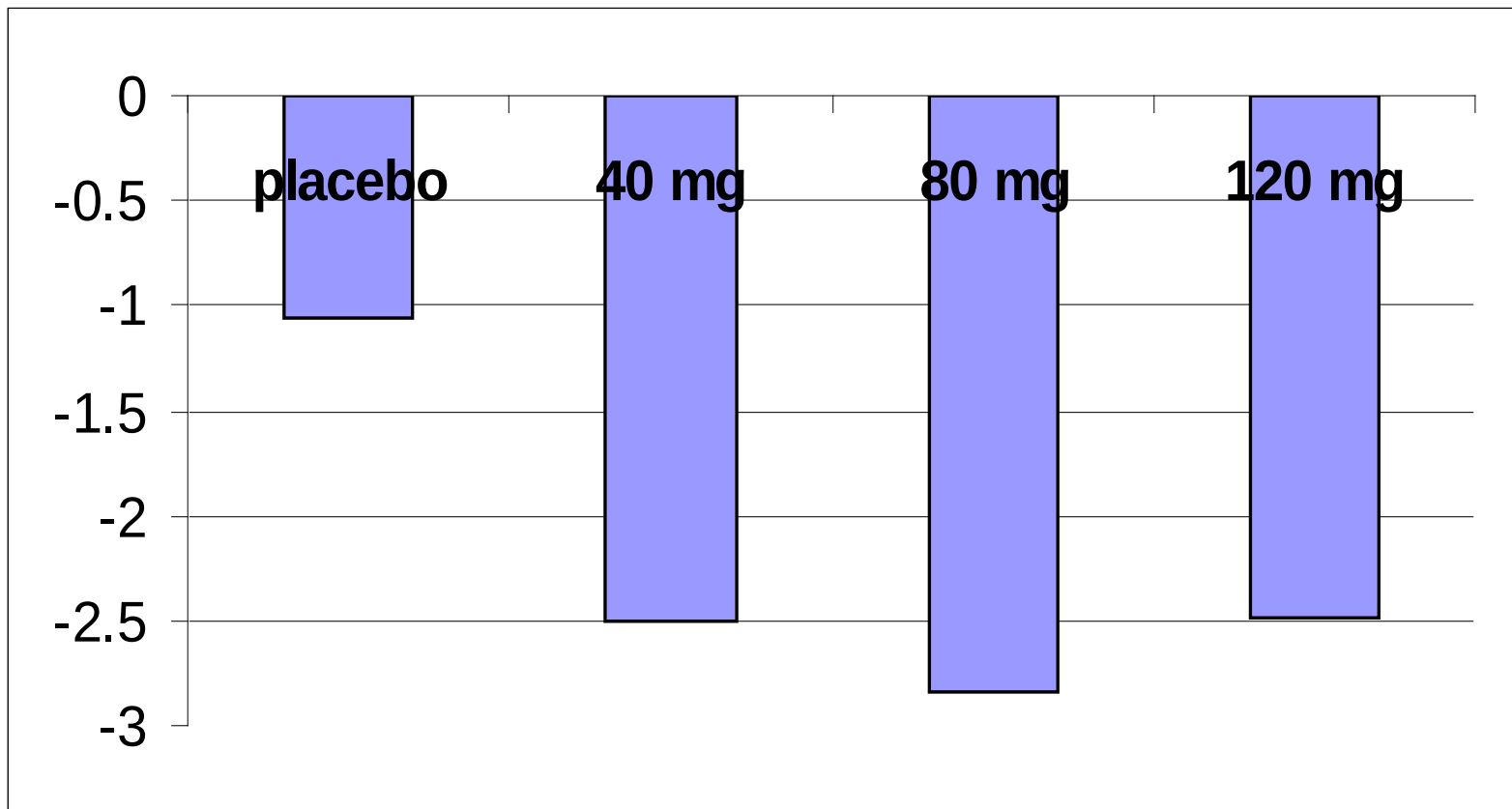
Clinical Efficacy Outcome in Phase II Trial



All doses are statistically different from placebo but no dose-response

Drug X Study 2

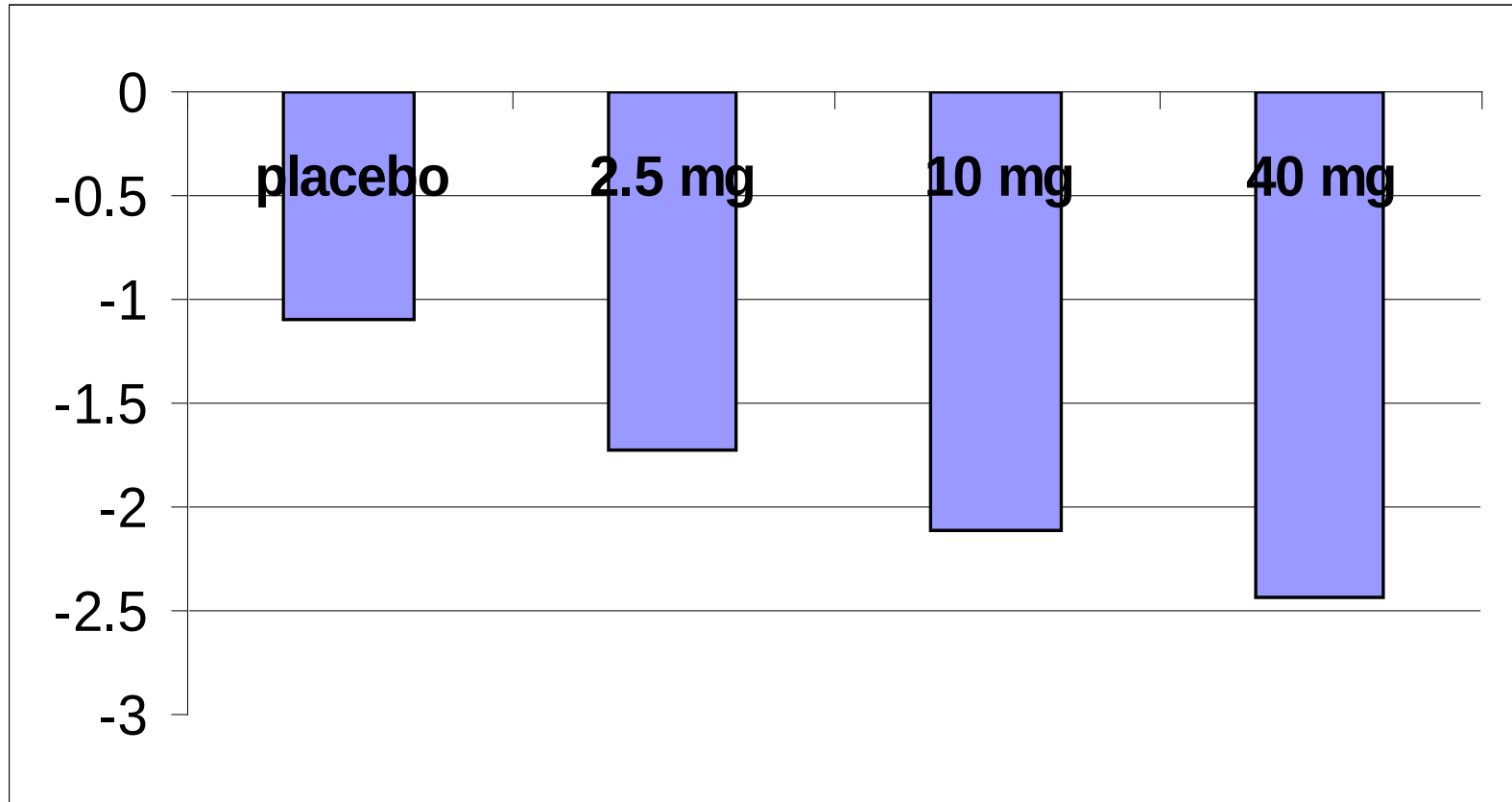
Clinical Efficacy Outcome in Phase II Trial
1 year and 9 months later



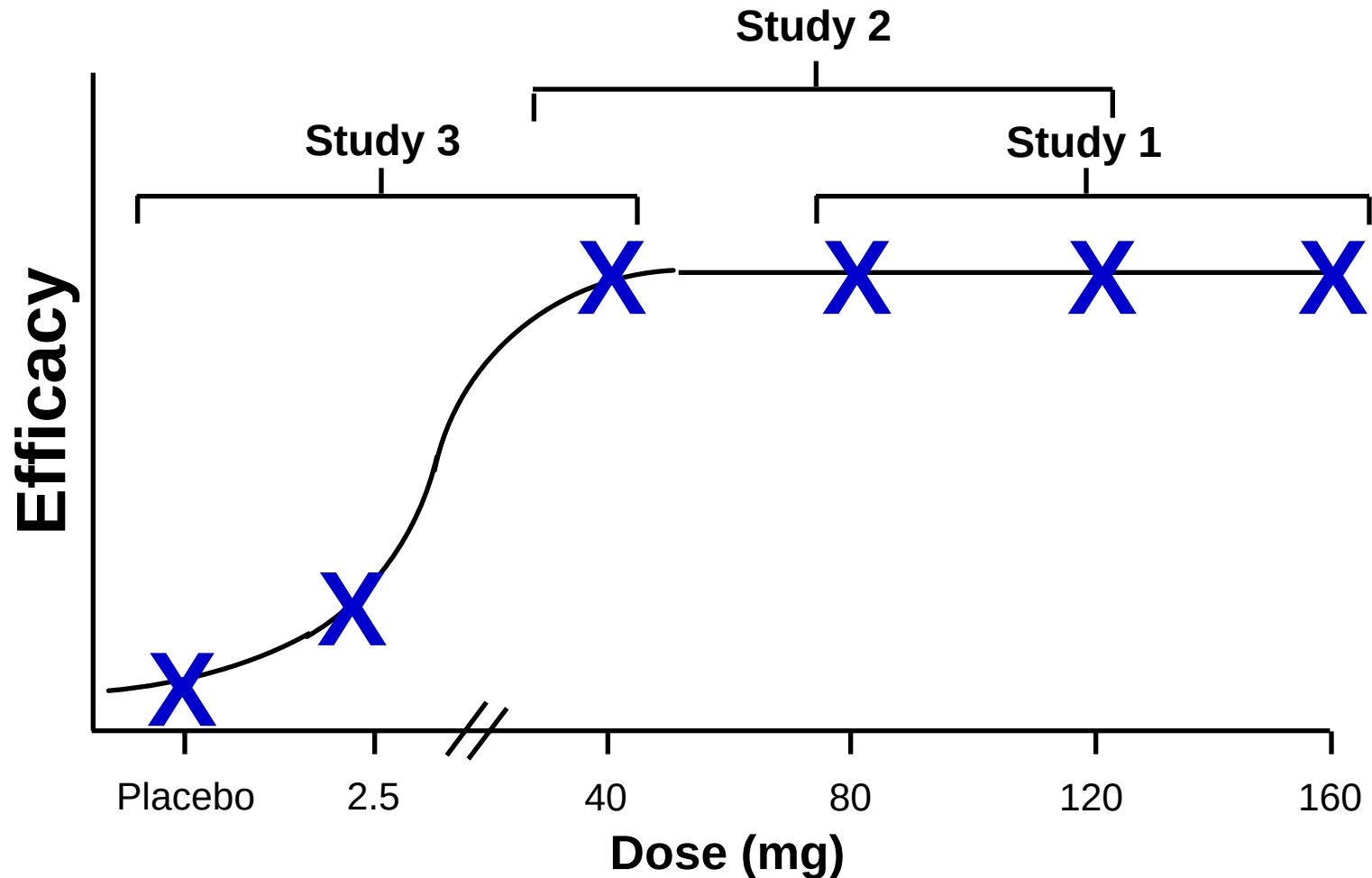
All doses are statistically different from placebo but no dose-response

Drug X Study 3

Clinical Efficacy Outcome in Phase II Trial
3 years later



Example of What Can Go Wrong in Phase 2b & 3



**Phase 2b Solution: >10-fold dose-ranging study
more doses with fewer subjects per dose**

Key Learnings For Dose-Ranging Studies

- ♦ Dose ranges have been too narrow
 - Did not characterize the dose-response relationship
- ♦ Design and power studies to estimate dose-response characteristics (learning instead of confirming analysis)
 - Dose-response regression instead of pairwise comparison
- ♦ Evaluate more doses over a wider range with fewer subjects at each dose
 - >10-fold range
 - e.g. 0.1 - 1.0 MTD

Case Study: Modeling & Simulation for Phase 2b Trial

Adaptive Design: Dose-Response for Safety and Efficacy

- ◆ PD 0348292: an oral direct factor Xa inhibitor
 - Prophylaxis and treatment of venous thromboembolism (VTE)
- ◆ 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 current gold standard of enoxaparin 60 mg/day
- ◆ Setting: VTE prophylaxis in patients undergoing an elective total knee replacement
- ◆ 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
- ◆ **Literature Data:**
 - Clinical outcome (incidence of VTE and major bleeding [MB]) for comparator anticoagulants
- ◆ **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

Dose-Response Relationships for Efficacy (VTE) and Safety(MB)

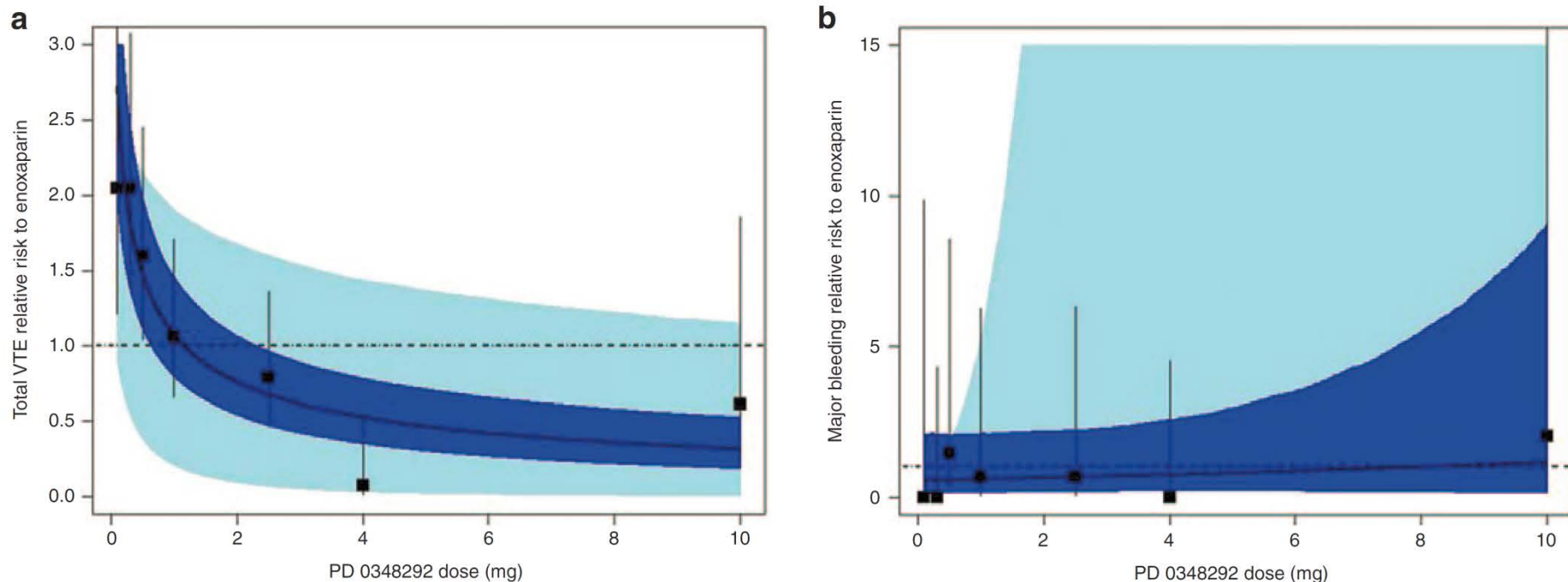


Figure 6 Observed relative risk of PD 0348292 vs. enoxaparin (symbols with 95% confidence intervals (CIs)) for (a) VTE and (b) MB and logistic regression model fit (solid line with dark blue area covering the 90% CI) in an adaptive phase II study. The light blue area covers the 90% CI before the trial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

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
 - But also the number of bleeds 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

Predicted PD 0348292 Dose-Response Relationships for VTE and MB

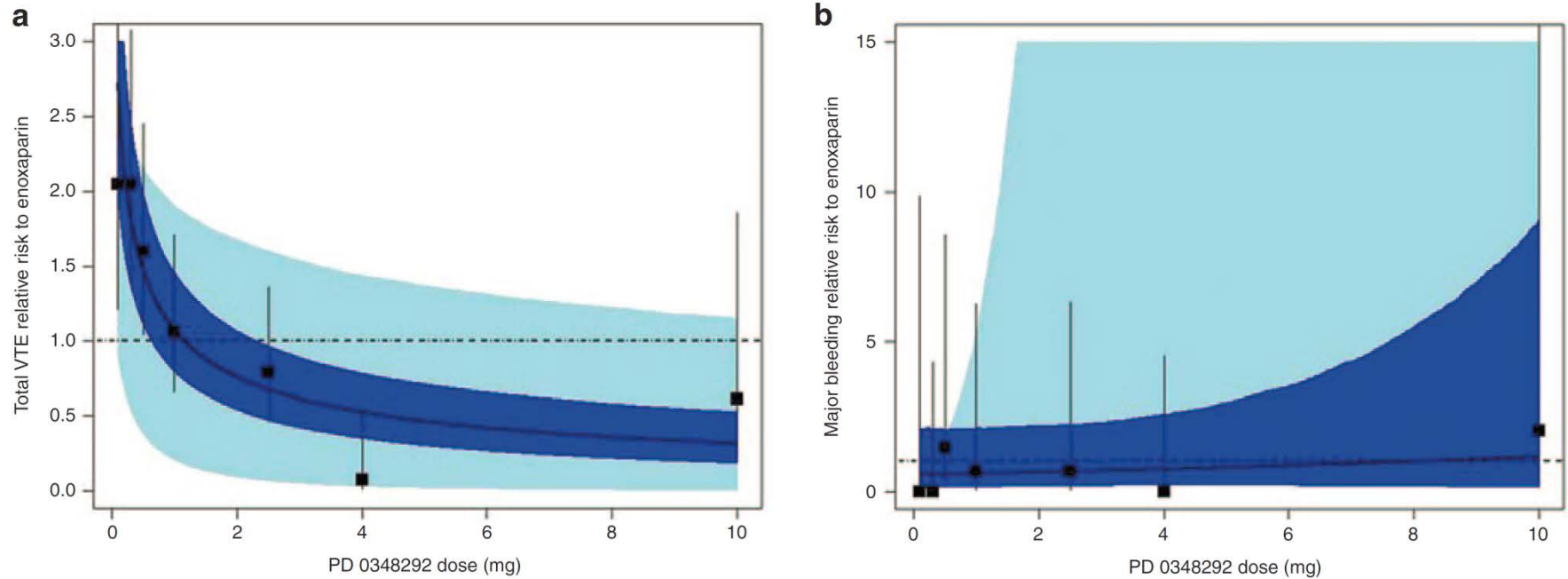


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Impact of M&S, Adaptive Design

- ◆ Study designed using M&S was approved by senior management and conducted successfully
- ◆ Study met key objective
 - Identified the dose equivalent to enoxaparin with good precision
- ◆ Safely explored a 100-fold dose range to allow characterization of dose-response relationship for efficacy (vs ~ 4-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 1 year

A Potential Solution

1 Pivotal Trial + Confirmatory Evidence from Dose-Response Trial

CLINICAL PHARMACOLOGY & THERAPEUTICS

VOLUME 73 NUMBER 6

JUNE 2003

COMMENTARY

Hypothesis: A single clinical trial plus causal evidence of effectiveness is sufficient for drug approval

Carl C. Peck, MD, Donald B. Rubin, PhD, and Lewis B. Sheiner, MD *Washington, DC, Cambridge, Mass, and San Francisco, Calif*

Clin Pharmacol Ther 2003;73:481-90

A Potential Solution

- ◆ Need to break the vicious cycle with pairwise comparisons
 - Leads to more subjects per dose group and therefore fewer dose groups
- ◆ Proposal: Adequate and well controlled Phase 2b dose-response trial serves as confirmatory evidence along with 1 pivotal Phase 3 trial for primary evidence of efficacy.
 - Designed and analyzed with appropriate dose-response regression model
- ◆ Provides better evidence of effectiveness than replication of 2 similar or identical Phase 3 trials at the same dose.
 - Causal confirmation via dose-response versus empiric confirmation
- ◆ A win-win-win for regulators, society and industry
 - Better dose-response evidence to support dose-selection
 - More efficient drug development
 - More informed regulatory decision-making
 - Generalizability

A Potential Solution

- ♦ ICH E4: has not had the desired impact over the past 20 years
 - Insufficient specific guidance on dose-response regression approach
- ♦ Need clear regulatory guidance/statement from EMA, FDA for Phase 2b dose-ranging studies
 - Specifically support regression approach for design and analysis
 - Encourage broad range of doses (e.g. >10-fold)
 - Model-based estimation as a basis for dose selection for Phase 3 even without “statistically significant differences” between groups
 - Guidance on what should be pre-specified for the regression model to address the important concern about false positive error rate
 - Support estimation approach to supplement traditional confirmatory analyses from Phase 3 trial for regulatory decisions (approval, dose recommendations)
- ♦ A concerted regulatory effort/guidance can broadly and rapidly influence whole industry
- ♦ Generate further discussion during this meeting
 - Recommendations for next steps