



FDA Use of Big Data in Modeling and Simulations

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Outline

- Big data definitions
- Big data in the regulatory review process
- Case Studies from Office of Clinical Pharmacology
 - NSCLC Model
 - Physiologically-based Pharmacokinetic Modeling
 - Mirabegron Risk-Benefit Assessment
- Conclusion

Some 'Big Data' Definitions

- "Big data is **high volume, high velocity, and/or high variety information** assets that require new forms of processing to enable enhanced decision making, insight discovery and process optimization." *Gartner, Inc. (2012)*
- "Big data is the term increasingly used to describe the process of applying **serious computing power**—the latest in machine learning and artificial intelligence—to **seriously massive and often highly complex sets of information.**" *Microsoft (2012)*

‘Big Data’ Definitions I Can Relate With

- “Big data is a popular term used to describe the exponential growth, availability and use of information, both structured and unstructured.” “...it applies (per Gartner’s assessment) **whenever an organization’s ability to handle, store and analyze data exceeds its current capacity.**” SAS
- **Our ability to conduct modeling and simulations for regulatory reviews is dependent on our ability to manage ‘Big Data’**



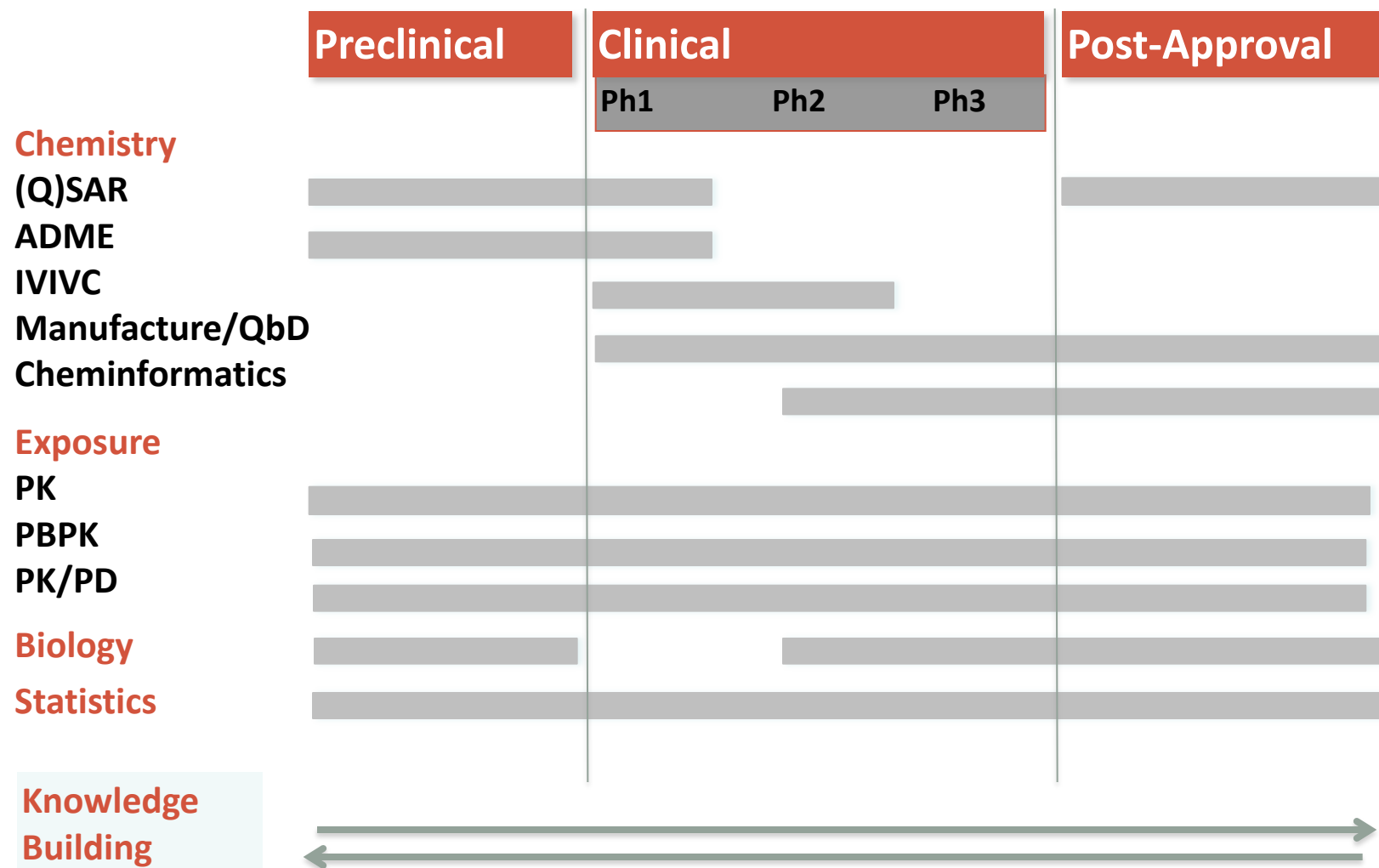
Scientific and Regulatory Reasons for Delay and Denial of FDA Approval of Initial Applications for New Drugs, 2000-2012

Leonard V. Sacks, MBBCh; Hala H. Shamsuddin, MD; Yuliya I. Yasinskaya, MD; Khaled Bouri, PhD, MPH;
Michael L. Lanthier, BA; Rachel E. Sherman, MD, MPH

- “Of the unsuccessful first-time applications, 24 (15.9%) included uncertainties related to dose selection”
- “Failure to determine the most appropriate dose for clinical use was a major reason for nonapproval.”

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.

Modeling and Simulation in the Review Process



Use of Modeling and Simulations in the Review Process

Preclinical

- What is the on-target mechanism of action?
- What safety events should be expected (off-target effects)?
- Can in vitro information substitute for human studies?

Clinical

- What is the effect size?
- What are the drug-disease-trial relationships?
- What population should be studied?
- What studies are necessary to inform use?

Post-Marketing

- Are new safety signals emerging?
- Are findings consistent in under-represented subpopulations?
- Is any additional dose optimization necessary?

- Data needs are driven by the scope of the questions being asked



Case Study 1: NSCLC Tumor Size-Survival Model

(Dr. Yaning Wang)

NSCLC Phase 3 Planning

Information

- Early phase trials:
 - Toxicity is the focus
 - Phase 2 trials measure tumor and survival
 - Small, short
 - Mostly single-arm
 - Tumor (biomarker)-survival relationship is not quantified
 - High uncertainty in survival estimates

Decisions

- Should we invest in this NCE?
 - What is the projected survival advantage over active control?
 - Single or combination?
- Phase 3 design
 - Sample size
 - Dose/regimen

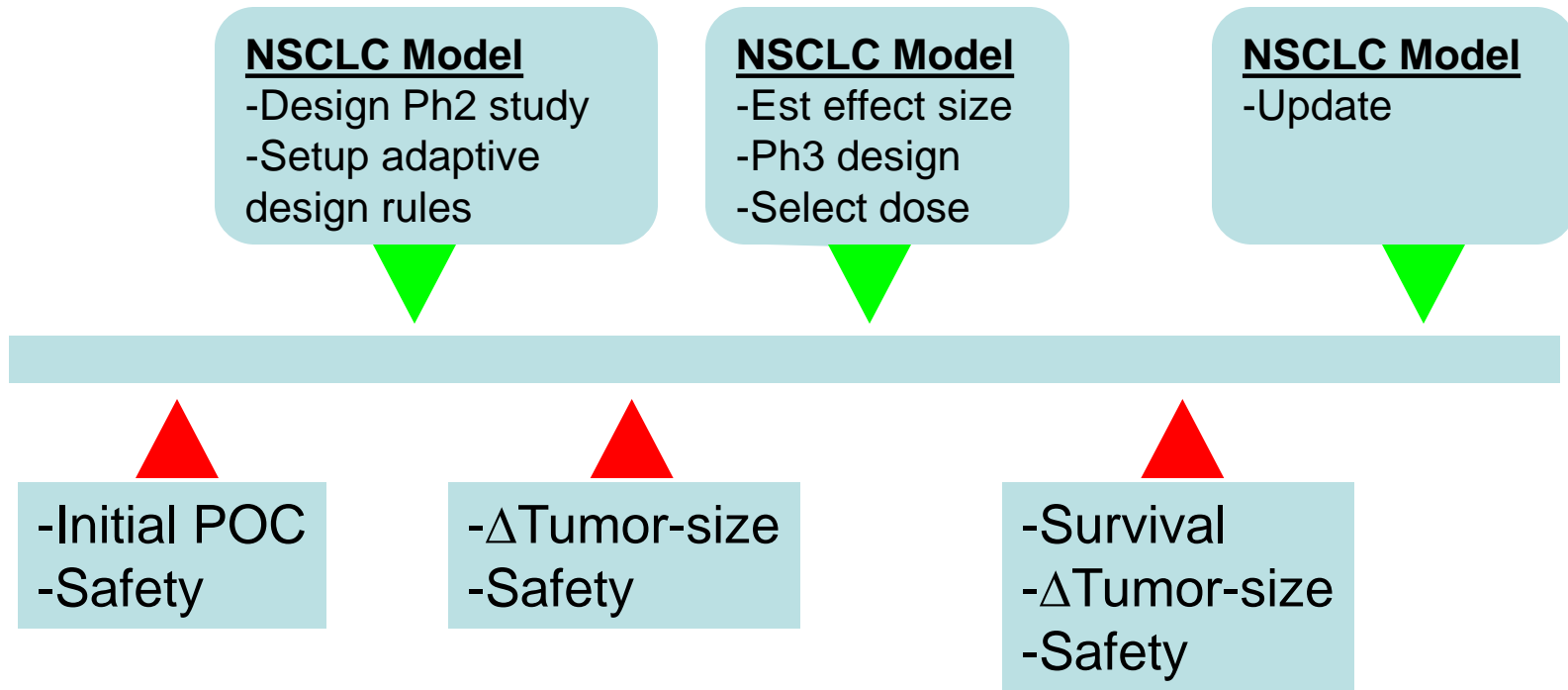
Tumor Size – Survival Model

- Data:
 - 4 Trials, 8 active treatment (e.g. (A1, A2, B1, B2, B3), ~3500 patients, first-line and second line treatment.
- Model:
 - ECOG (0/1), baseline tumor size (centered at 8.5 cm) as covariates
 - Tumor size predictors (early biomarker)
 - Individual predicted tumor size percent reduction at 4, 6 or 8 weeks relative to baseline (TPR_{wkx})

$$\log(T) = \alpha_0 + \alpha_1 \cdot ECOG + \alpha_2 \cdot (Base - 8.5) + \alpha_3 \cdot TPR_{wkx} + \varepsilon$$

- Model development
 - Based on drug A1
 - Parametric survival model (log-normal)
- Model evaluation
 - Model from drug A1 is used to predict survival curves for other drugs (different trials, different mechanism of actions)

NSCLC Model Application





Case Study 2: Application of the FDA PBPK Knowledgebase in Evaluating Drug-Drug Interactions

(Dr. Ping Zhao and Yuzhuo Pan)

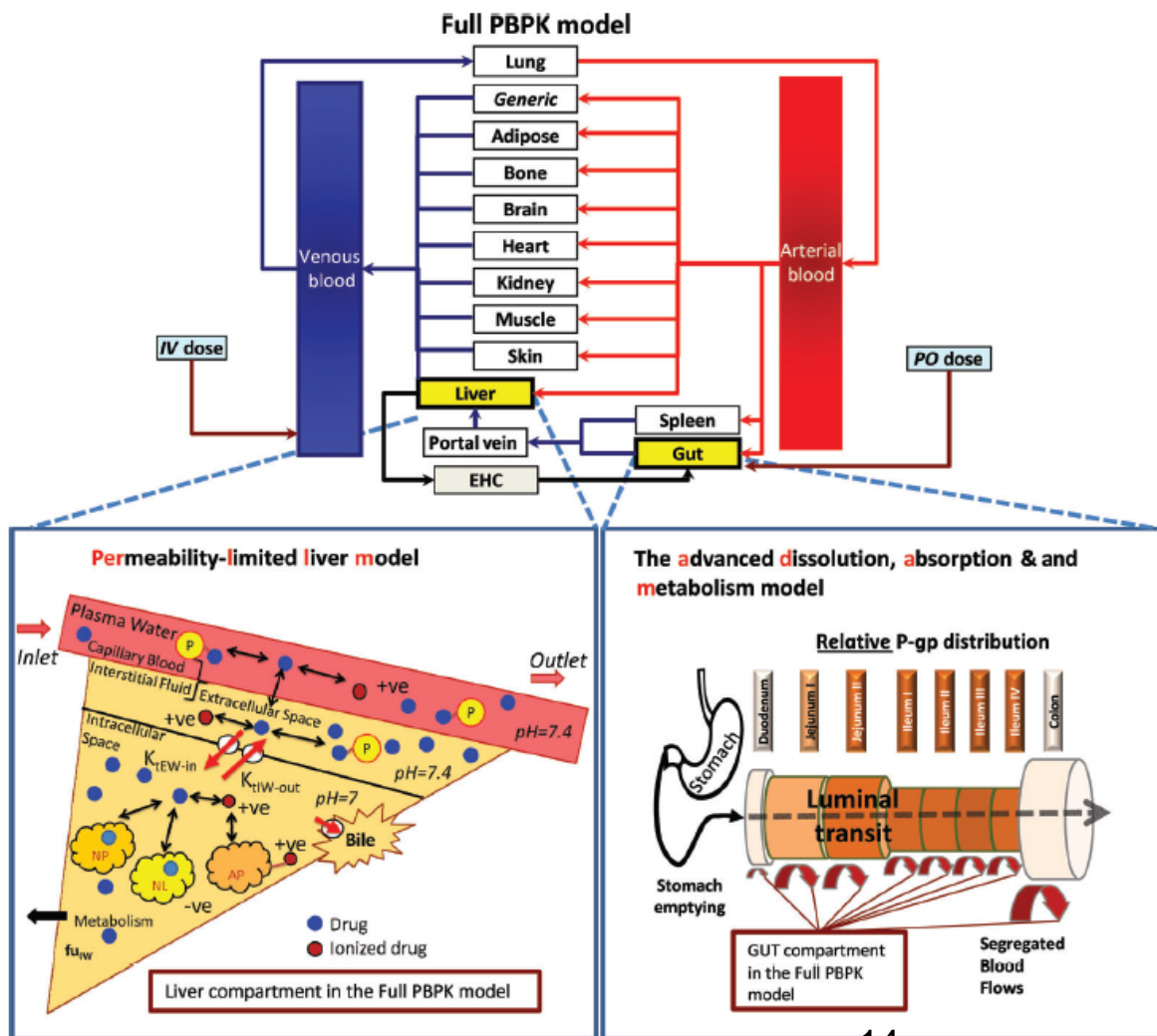


Utility of PBPK in drug development

“As a predictive model, PBPK can be used to support decisions on WHETHER, WHEN and HOW to conduct a clinical pharmacology study”

-- Ping Zhao

Physiologically based pharmacokinetics (PBPK)



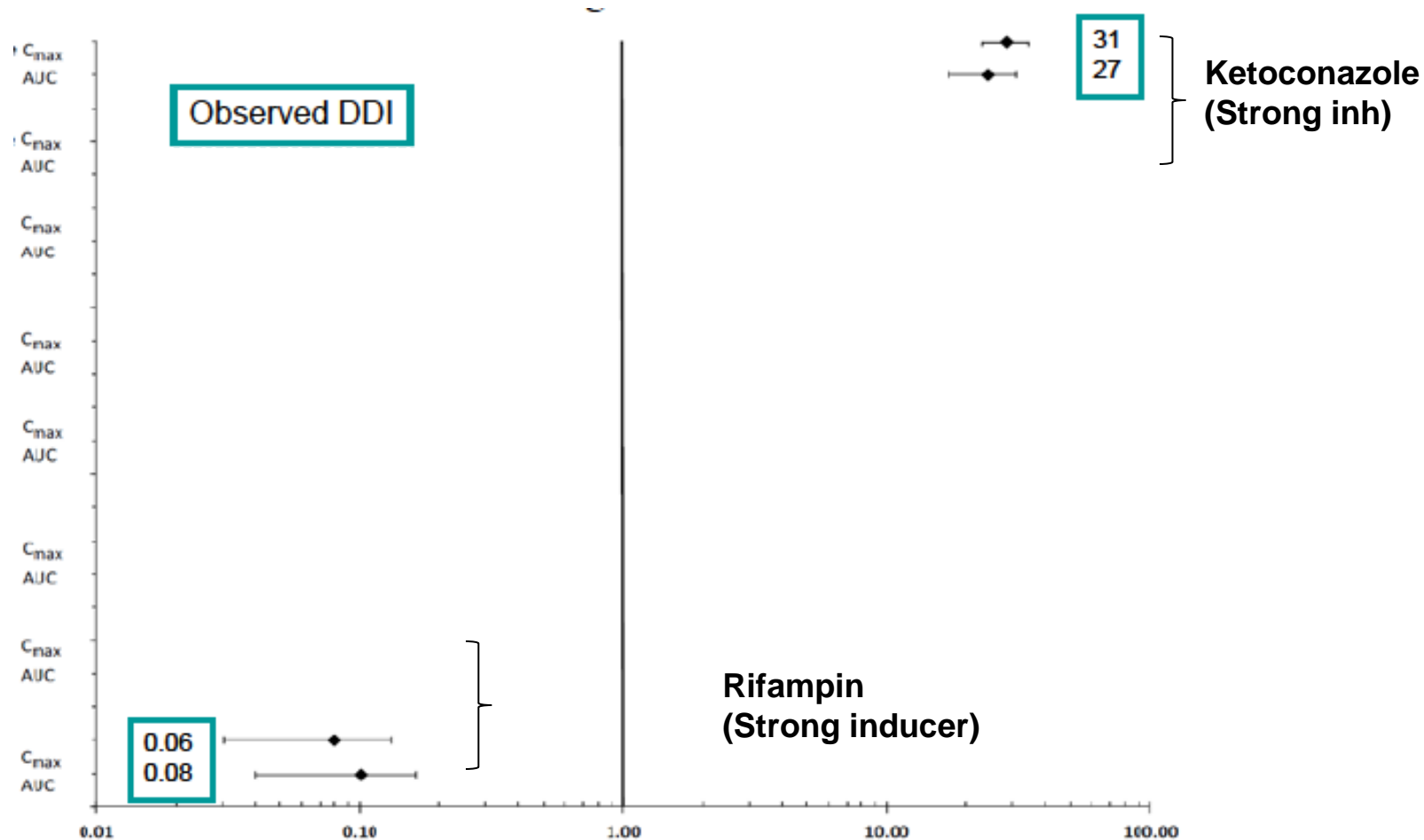
“Physiologically based pharmacokinetic (PBPK) modeling is a mathematical modeling technique for predicting the absorption, distribution, metabolism and excretion (ADME) of synthetic or natural chemical substances in humans and other animal species”.

PBPK prediction of the effect of co-medication: Example of informing drug label

Regulatory questions

Can PBPK model predict ibrutinib exposure change when the drug is co-administered with CYP3A inhibitors or inducers?

Simulated and observed C_{max} and AUC ratios of ibrutinib using PBPK (mean and 95% confidence interval)



PBPK prediction of the effect of co-medication: Example of informing drug label

Regulatory questions

Can PBPK model predict ibrutinib exposure change when the drug is co-administered with CYP3A inhibitors or inducers?

Section 12.3: “Simulations...suggested that moderate CYP3A inhibitors (diltiazem and erythromycin) may increase the AUC of ibrutinib 6 to 9-fold in fasted condition;...a moderate CYP3A inducer (efavirenz) may decrease the AUC of ibrutinib up to 3-fold”

http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205552s000lbl.pdf

- **Analysis of the FDA PBPK knowledgebase is being used to inform and predict in vivo DDI using PBPK models in subsets of cases where clinical DDI data is not available**
 - **Example will be discussed at upcoming PBPK workshop in March**



Case Study 3: PK/PD Risk-Benefit Assessment for Mirabegron *(Jiang Liu and Raj Madabushi)*

Clinical Pharmacology Review Mirabegron, 2012

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202611Orig1s000ClinPharmR.pdf

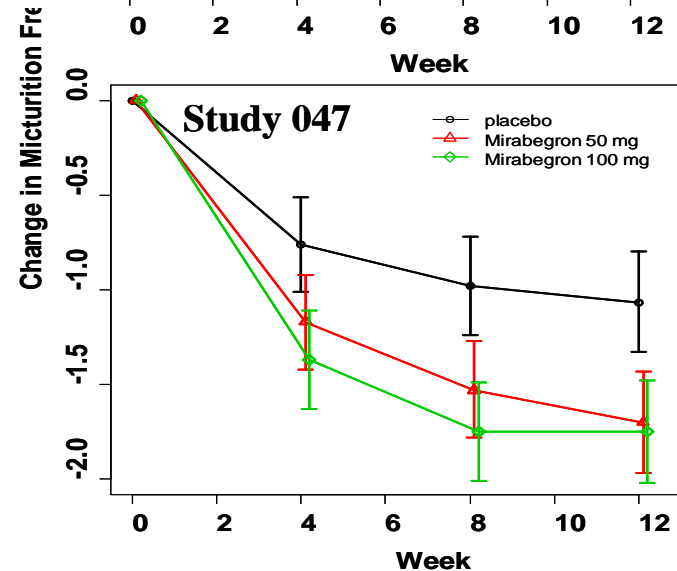
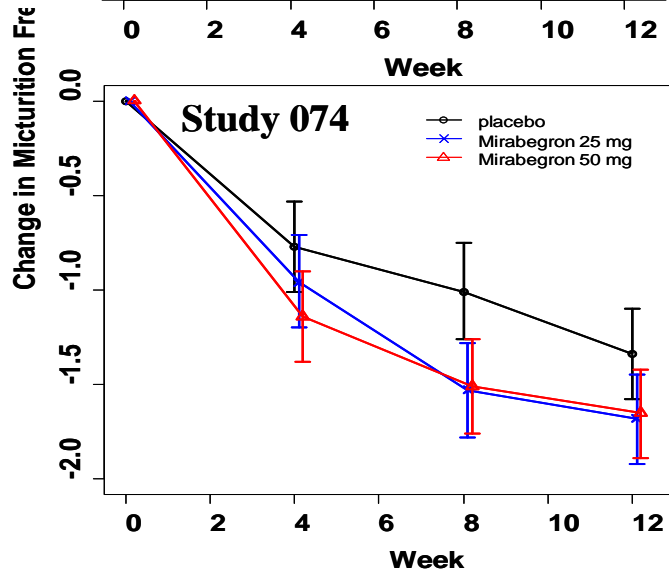
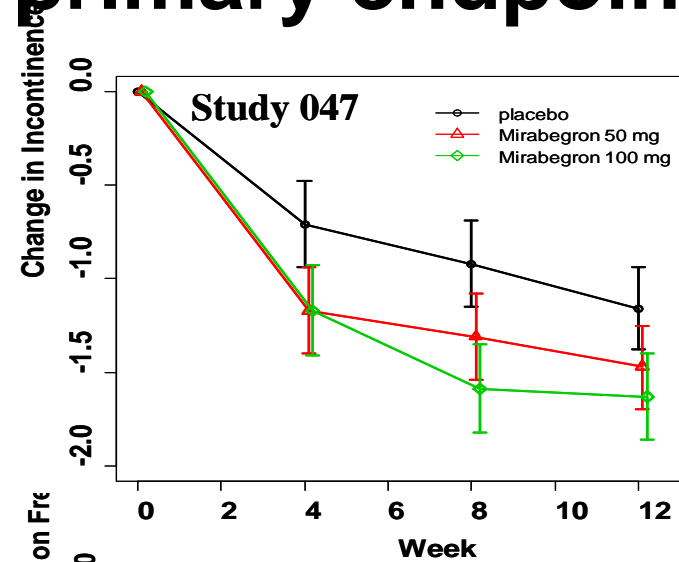
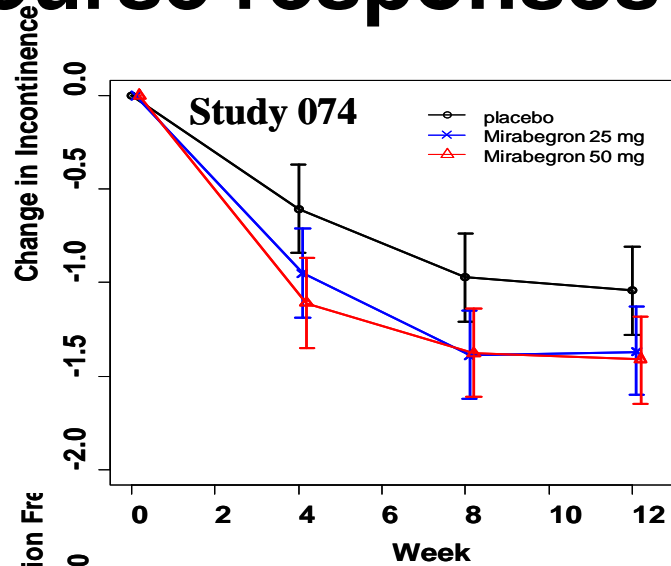
Pivotal trials for mirabegron

Phase 2b

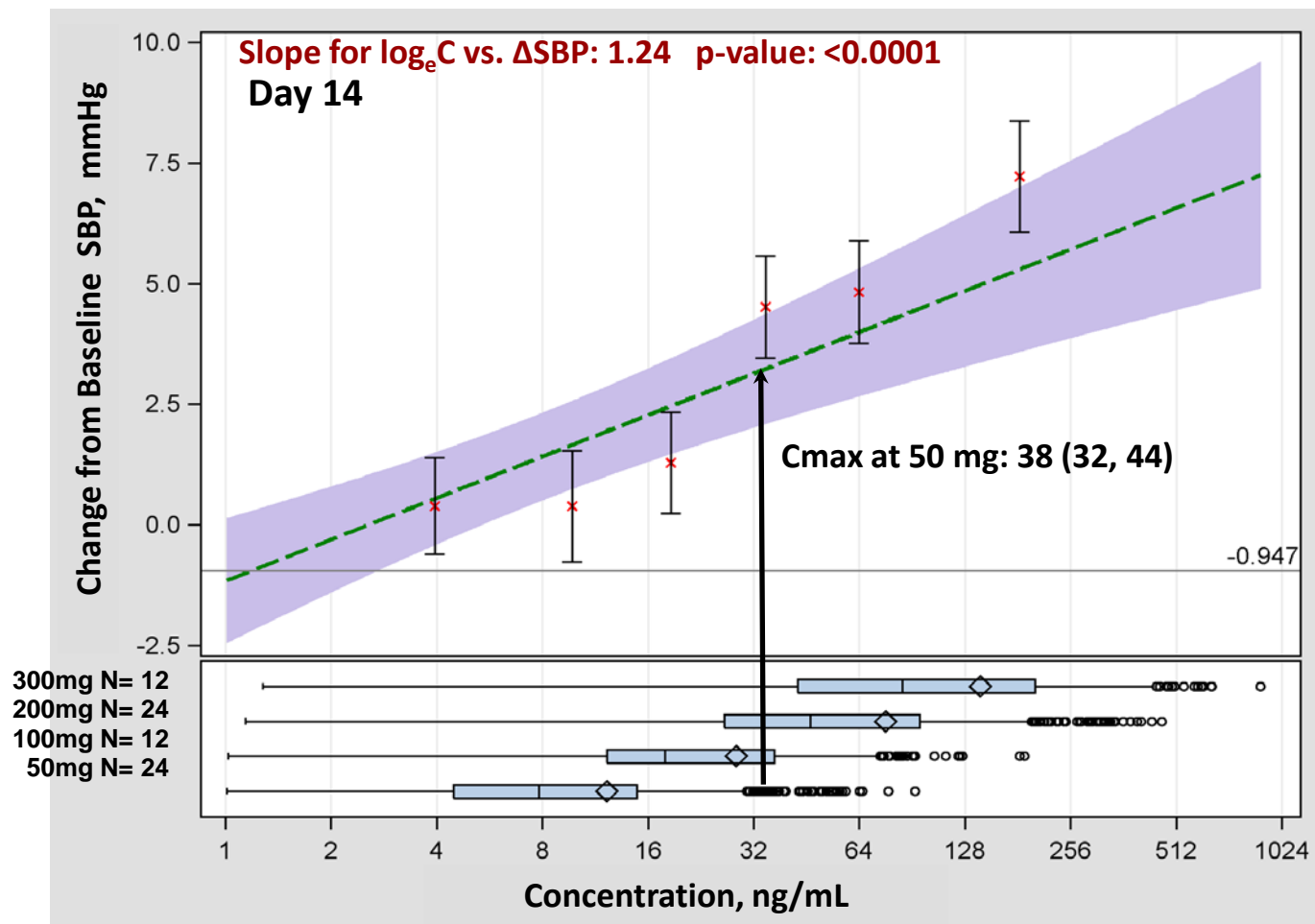
Phase 3 trials

Study	Primary efficacy endpoint	Treatment	No. of subj.
178-CL-044 (Euro)	co-primary efficacy endpoints:	Placebo, mirabegron 25, 50, 100, or 200 mg, or tolterodine 4 mg	928
178-CL-046 (Euro & Aus)	1) change from baseline to final visit (Week 12) in mean number of <u>incontinence episodes per 24 hours</u>	Placebo, mirabegron 50 or 100 mg, or tolterodine 4 mg	1987
178-CL-047 (Can & US)	2) change from baseline to final visit in mean number of <u>micturitions</u> per 24 hours	Placebo, mirabegron 50 or 100 mg	1329
178-CL-074 (Euro & NA)		Placebo, mirabegron 25 or 50 mg	1306

Doses of 25 mg or higher had similar time-course responses for primary endpoints

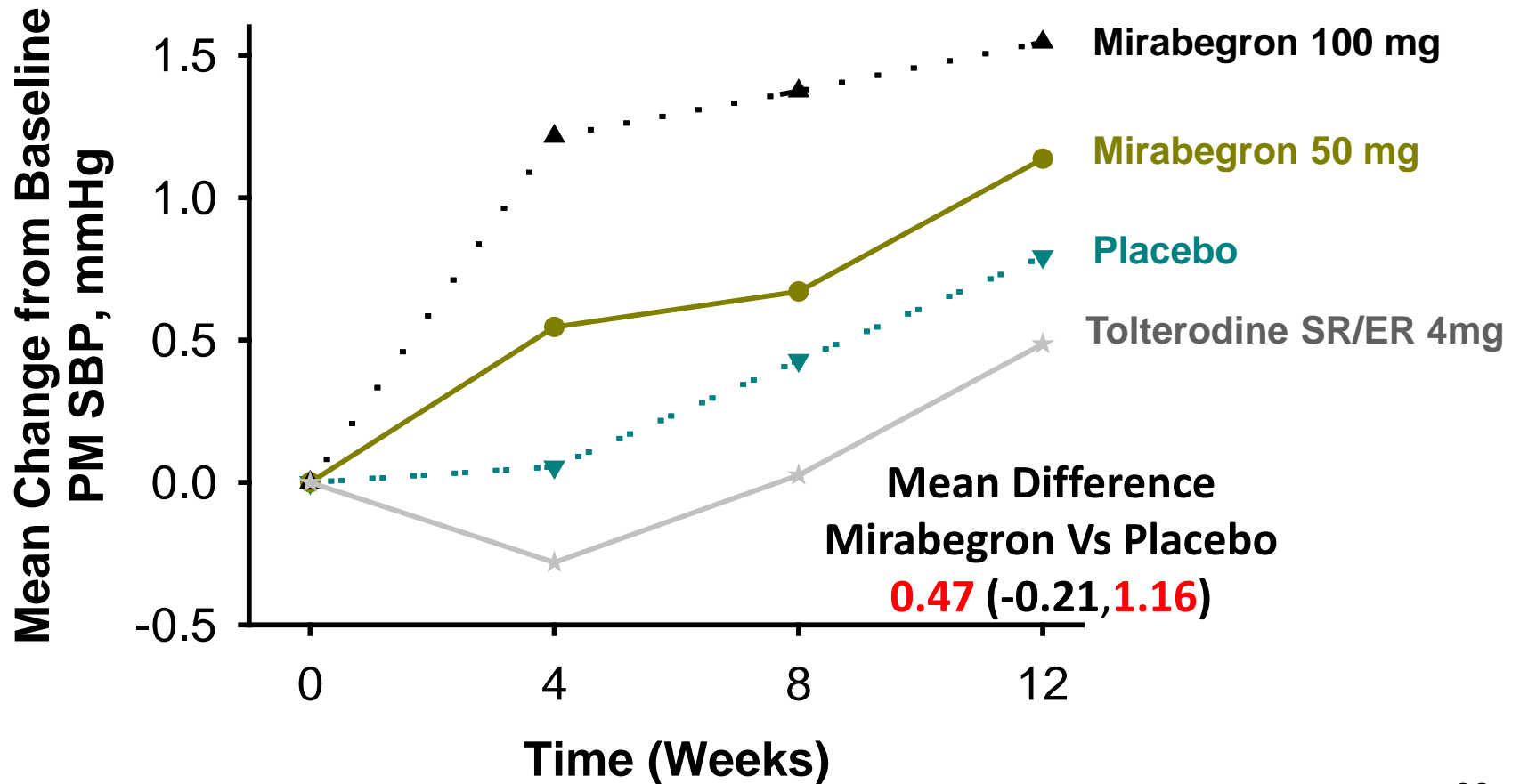


Increase in SBP[†] is exposure dependent



Dose Dependent Increase in SBP Observed in Phase III

Changes greater than 1.2 mmHg are ruled out

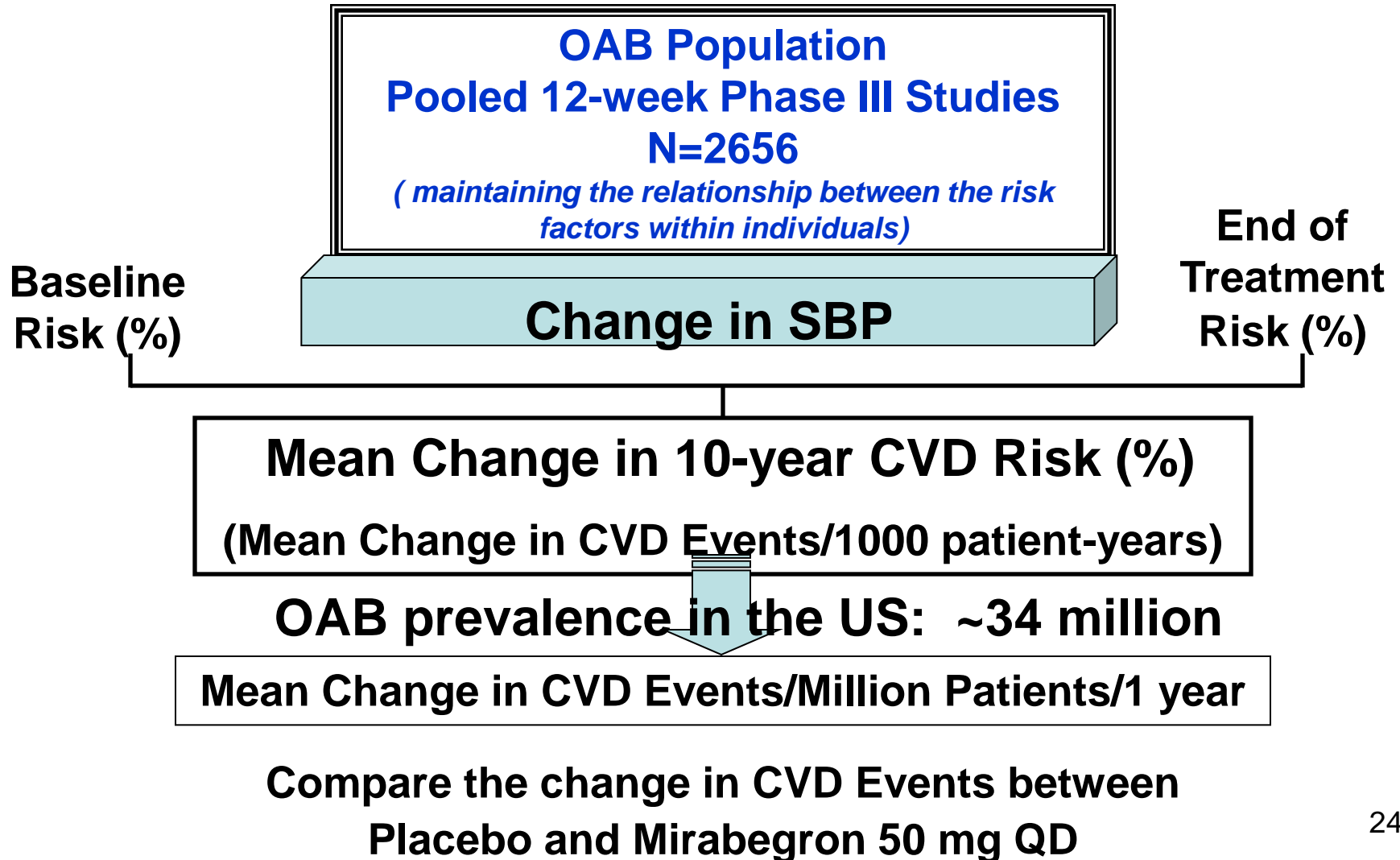


CVD Risk Assessment Approach

- A continuous multivariate risk function* used to predict 10-year risk of developing Cardiovascular Disease (CVD)
- CVD – Coronary Heart Disease, Cerebrovascular Events, Peripheral Arterial Disease, or Heart Failure
- Risk Predictors: Sex, Age, **Systolic Blood Pressure**, Treatment for Hypertension, Diabetes Status, Total and High-Density Lipoprotein Cholesterol, and Smoking Status

**General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study – D’Agostino et al. Circulation 2008;117;743-753*

CVD Risk Assessment Approach



Summary of Available CVD Risk Predictors[†] at Baseline in Pooled 12-week Phase III Studies

Patient Characteristics	Placebo N = 1329	Mirabegron 50 mg N = 1327
Age, yrs (Mean, [SD])	59 (13)	60 (13)
AM SBP, mmHg (Mean, [SD])	126 (17)	126 (17)
Gender, M/F	363/966	383/944
Antihypertensive Treatment, %	40	39
Diabetes Status, %	8	9
10-year CVD Risk (Median)	10%	11%

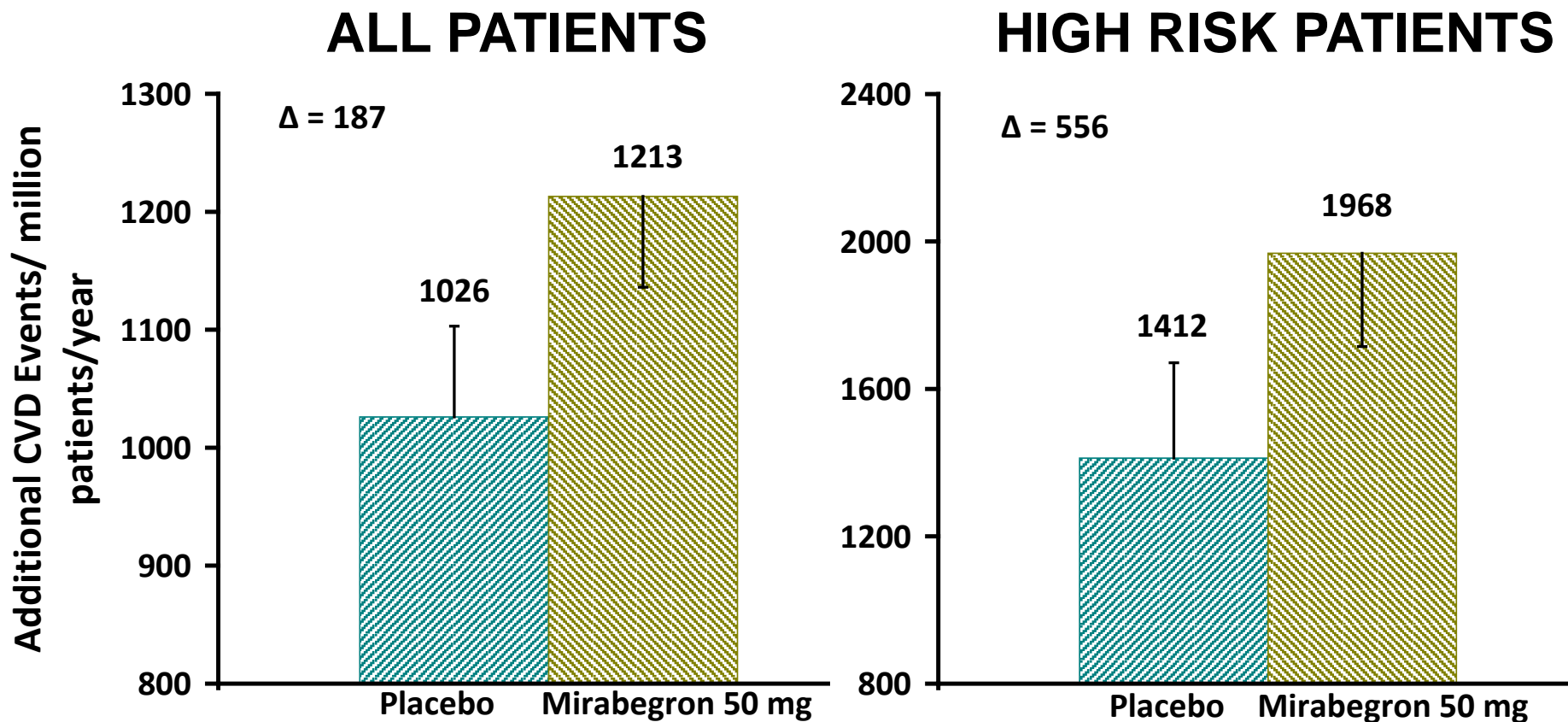
[†]Total and High-Density Lipoprotein Cholesterol, and Smoking Status not collected in Phase III programs. Imputed based on age and sex

Summary of Available CVD Risk Predictors[†] at Baseline for High Risk Patients (Top 25%)

Patient Characteristics	Placebo N = 312	Mirabegron 50 mg N = 328
Age, yrs (Mean, [SD])	70 (8)	70 (8)
AM SBP, mmHg (Mean, [SD])	142 (17)	142 (17)
Gender, M/F	213/99	226/102
Antihypertensive Treatment, %	68	67
Diabetes Status, %	22	23
10-year CVD Risk (Median)	31%	31%

[†]Total and High-Density Lipoprotein Cholesterol, and Smoking Status not collected in Phase III programs. Imputed based on age and sex

Potential for Increase in CVD Risk with Mirabegron Based on Phase III SBP[†] Effect



[†] Maximum mean change in AM SBP post-baseline (at trough)

Summary of Case Study 3

- Benefit-risk assessment performed to evaluate the appropriateness of 50 mg QD dose
 - Based on the phase III data, the 50 mg QD is the lowest dose that has consistently demonstrated significant efficacy in OAB patients.
 - Based on the Phase I and Phase III data, there is evidence mirabegron increases BP.
 - Assessment of these relationships led to approval of 25 mg dose, which was only evaluated in a single Phase III trial.

Conclusions

- 'Big Data' and modeling and simulation go hand-in-hand
- Modeling and simulations have applications throughout drug development
- The more integrated modeling is throughout the drug development program the greater the opportunity for applying the modeling
- What can be done will ultimately be limited by the data/tools available

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Questions

