APPLICATION OF FRAMINGHAM CVD RISK FUNCTION: A CASE STUDY

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The opinions in this talk are those of the speaker, and do not represent the views and/or policies of the U.S. Food and Drug Administration.

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM300108.pdf

Background

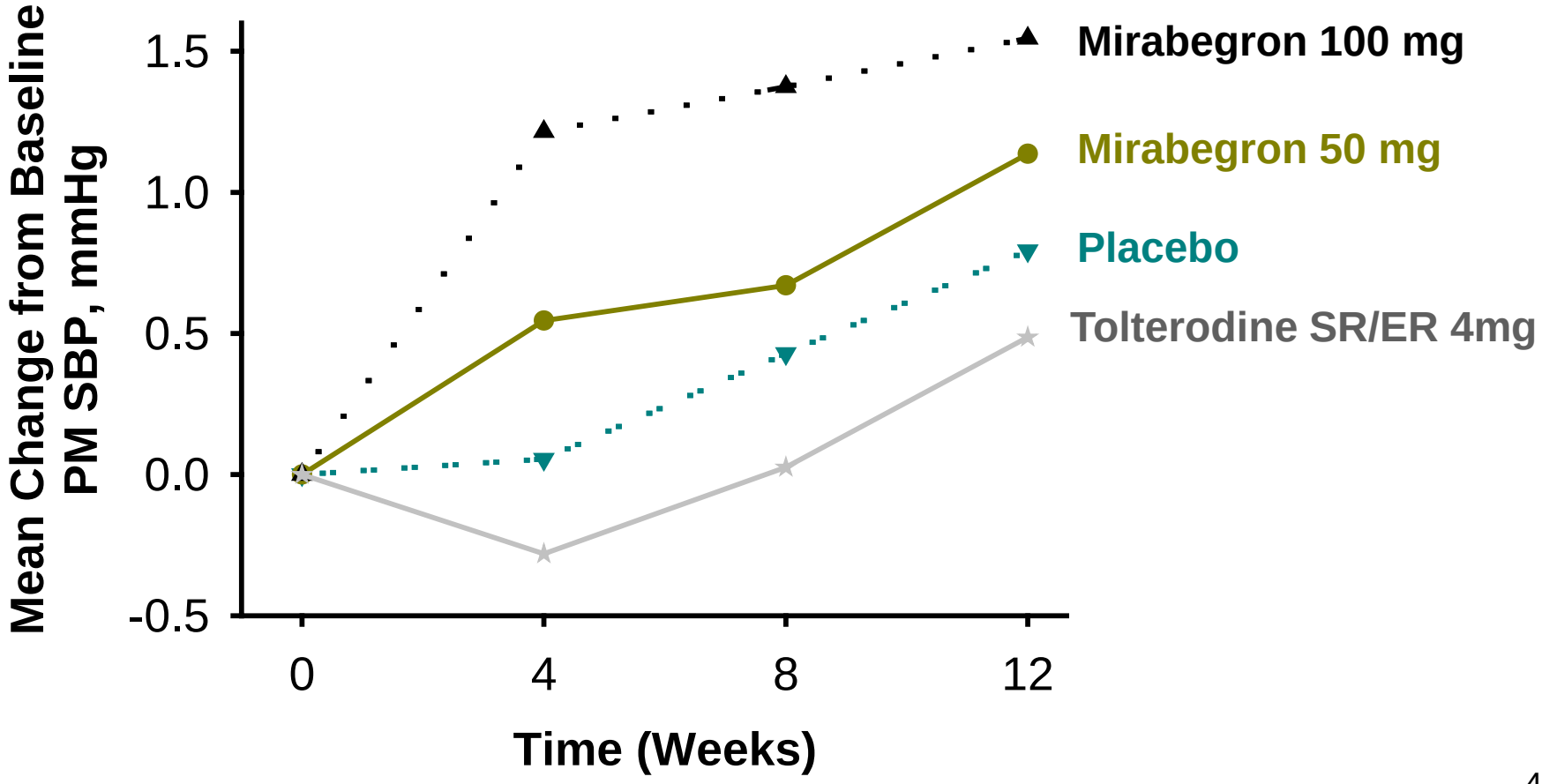
- Assessment of CVD risk based on observed events due to elevation in BP during the registration trials is challenging
  - Trial duration
  - Background event rate
  - Sample size
- Alternative approaches based on epidemiology need to be utilized:
  - Framingham Heart Study
  - Prospective Studies Collaboration
  - Prospective Cardiovascular Munster Heart Study
  - West of Scotland Coronary Prevention Study

Mirabegron Case Study

- Indication : Rx of Overactive Bladder (OAB) with symptoms of urge urinary incontinence, urgency and urinary frequency
- Class: β-3 adrenergic agonist
- Dose: 50 mg QD
- Benefit:
  - Decreases ~0.4 incontinence episodes/24 hr
    - Baseline: 2.5 – 2.8 episodes/24 hr
  - Decreases ~0.4 – 0.6 micturitions/24 hr
    - Baseline: 11.5 – 11.8 episodes/24 hr
- Risk: among others
  - Modest elevation in BP ~0.5 mm Hg in Phase 3
  - Larger elevation in BP ~3.0 mm Hg based on Phase 1

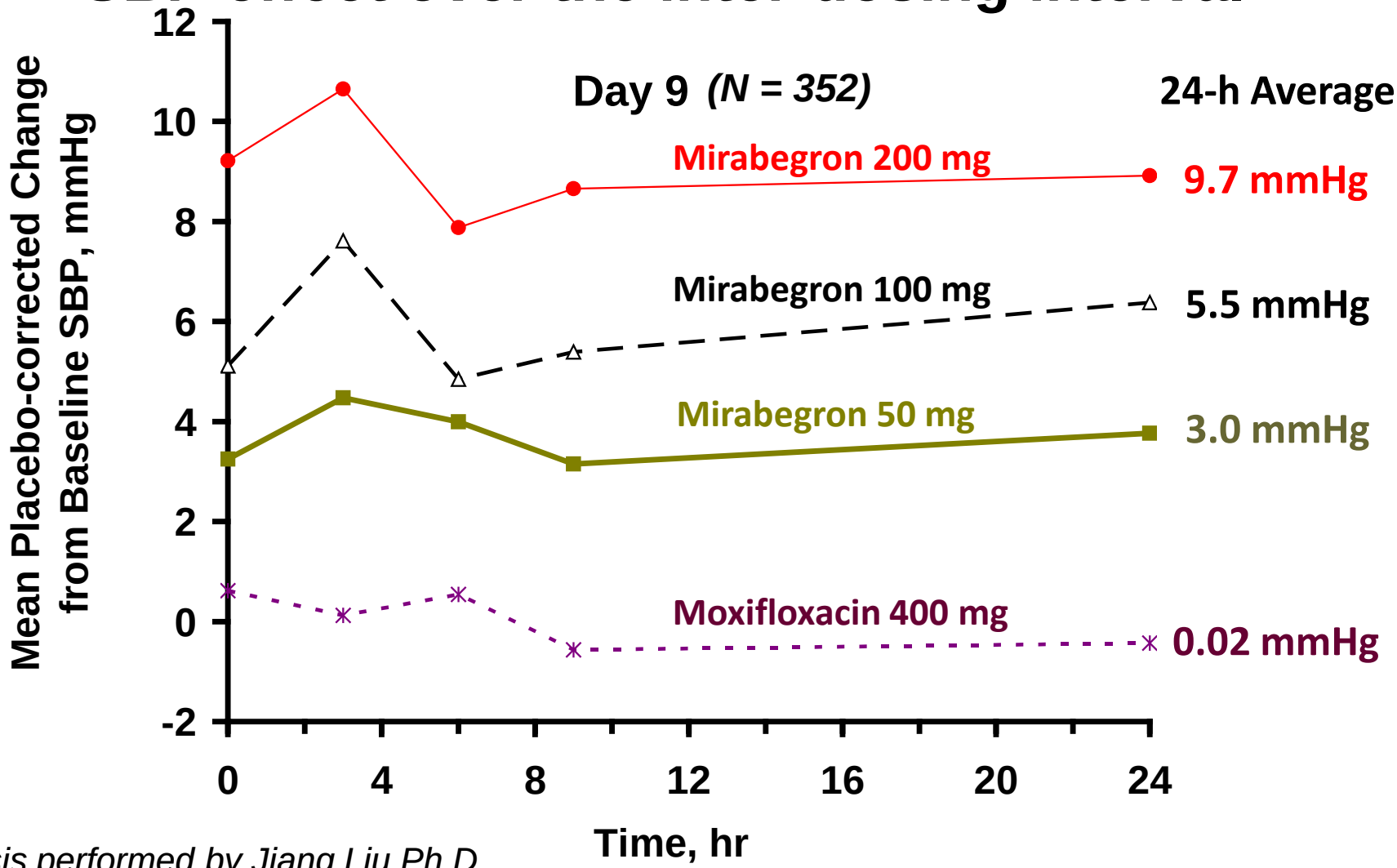
What is the potential for CVD risk of these elevations?

Dose Dependant Increase in SBP Observed in Phase III



Pooled 12-week Phase III Studies

Mirabegron 50 mg exhibits on average 3 mmHg SBP effect over the inter-dosing interval



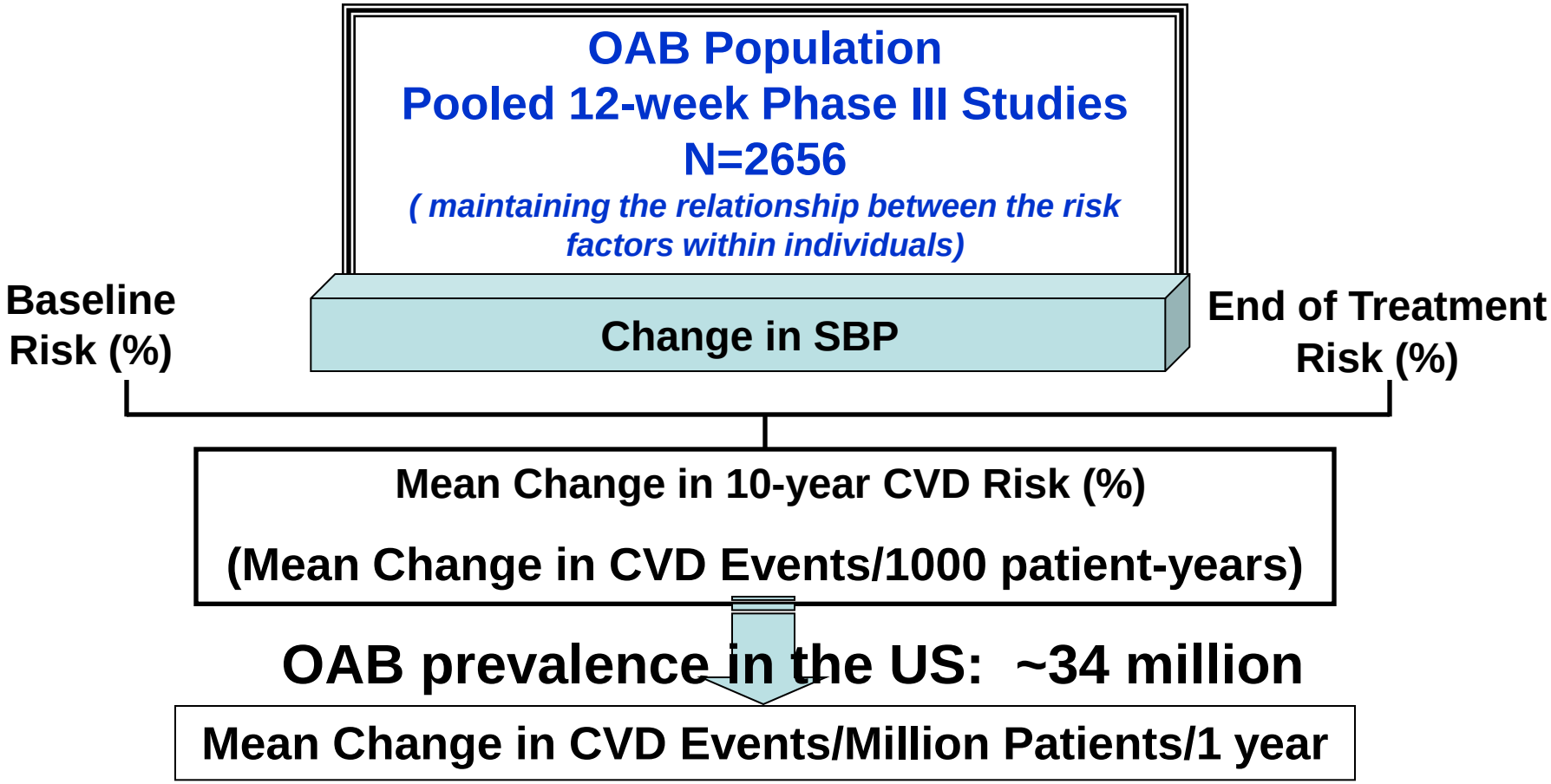
Analysis performed by Jiang Liu Ph.D.

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



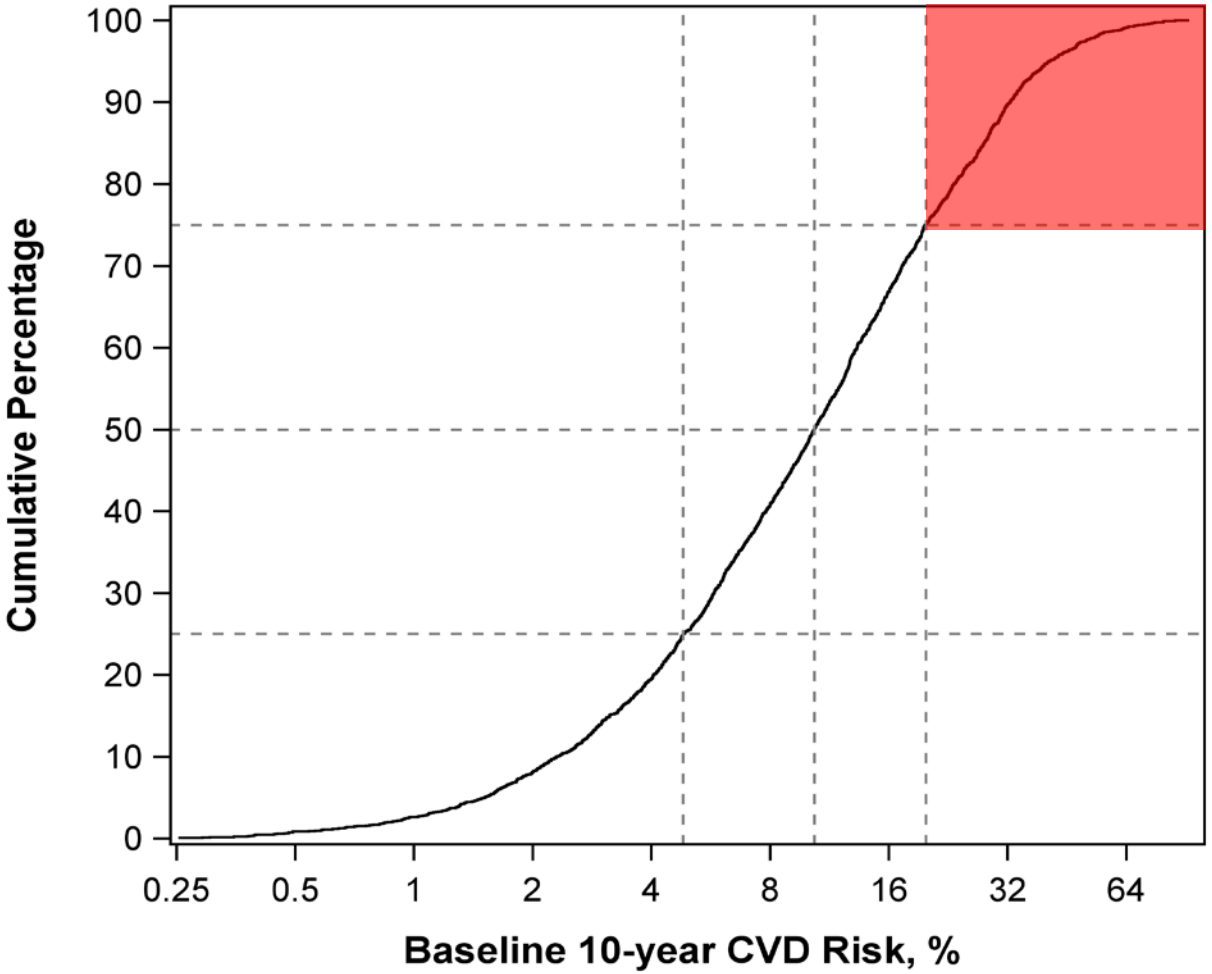
Compare the change in CVD Events between Placebo and Mirabegron 50 mg QD

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)
SBP, mmHg (Mean, [SD])	126 (17)	126 (17)
Gender, M/F	363/966	383/944
Antihypertensive Treatment, %	40	39
Diabetes Status, %	8	9

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

Baseline CVD Risk of OAB Patient Population



High Risk Patients

Age ~ 70 y

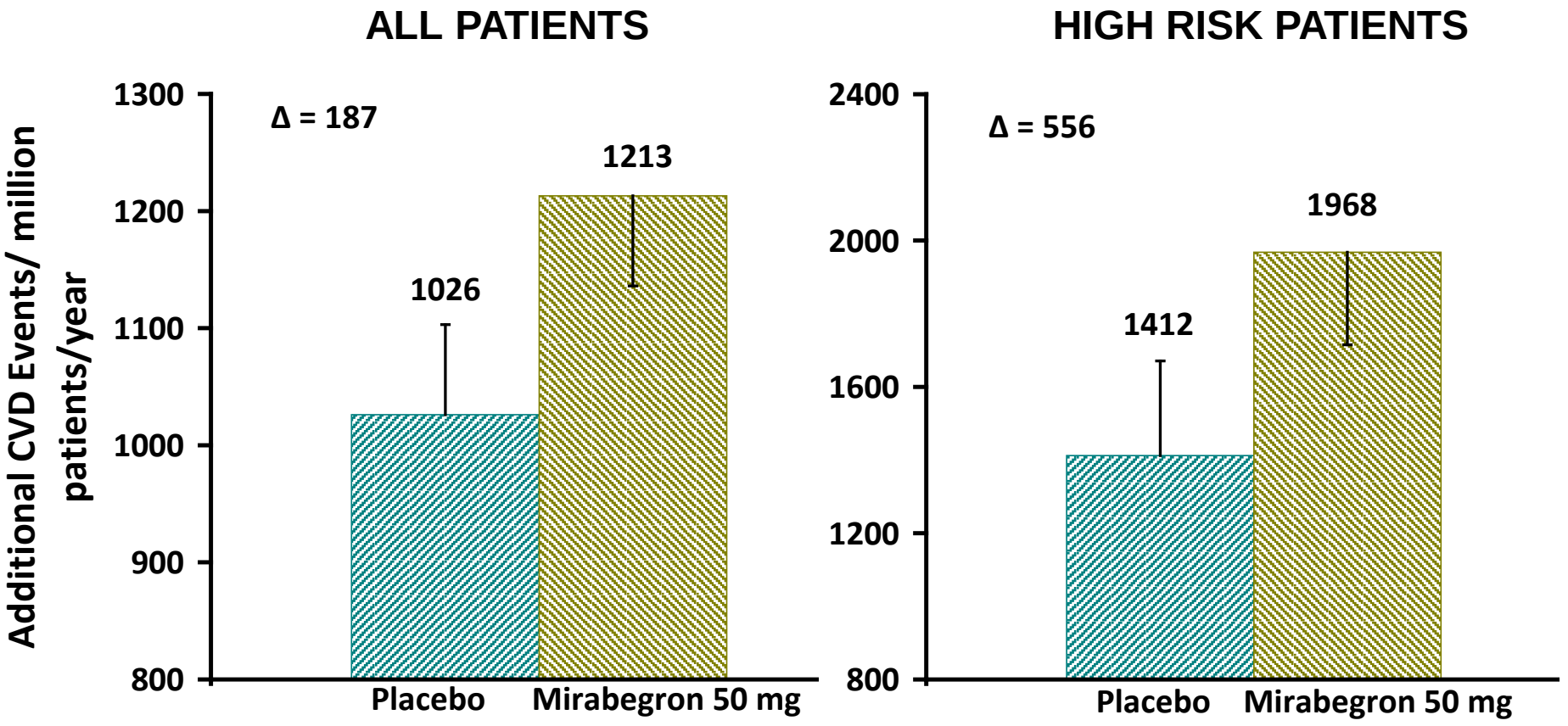
SBP ~ 140 mm Hg

M/F :: 2:1

BP Rx ~ 70%

Diabetes ~20%

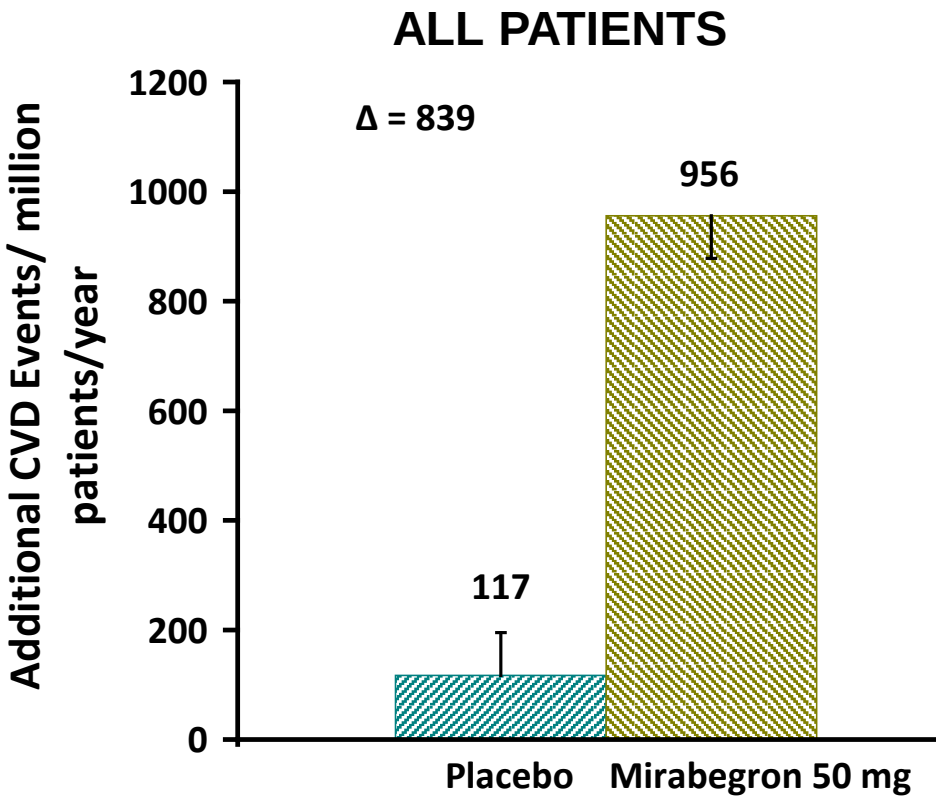
Potential for Increase in CVD Risk with Mirabegron Based on Phase III SBP Effect



Assessment of CVD risk based on Mirabegron 50 mg SBP effect in Phase I

Treatment	Placebo-corrected 24-hour average change in SBP on Day 9, mmHg Mean (SD)
Placebo *(Moxifloxacin)*	0.02 (11.2)
Mirabegron 50 mg QD	3.0 (10.2)

Potential for CVD Risk Based on SBP Effect† Observed in Phase 1



† 24-hour average was used to simulate treatment effect; BP Effect for Moxifloxacin in the study used as Placebo for comparison

Conclusions

- ✓ CVD risk functions can be used to understand the potential impact of small changes in BP
- ✓ Potential impact on subgroups and different scenarios can be projected
- ✓ Provides a framework for Benefit-Risk discussion
  - ✓ Dosing Instruction
  - ✓ Warning & Precautions

Backup

Summary of Available CVD Risk Predictors† at Baseline for High Risk Patients (Quartile 4)

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

Monte Carlo Simulations of 100,000 Trials Show The Projected Change in CVD Risk Estimate Based on TQT Study is Robust

100,000 Trials	10-year CVD Risk (Additional Events/1000 pt-years)		
Population	2.5th Percentile	50th Percentile	97.5th Percentile
All	0.45	0.66	0.87
High Risk	0.53	1.19	1.87