The Use of Modeling and Simulation in Regulatory Decisions and Reviews

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Disclaimer: My remarks today do not necessarily reflect the official views of the FDA

Clinical Pharmacology: The Past

The 70's	The 80's	The 90's	The 00's
Formulation Biopharmaceutics	Drug Interactions	Dosing Regimen	Exposure-Response

The Future

Disease model	Drug model	Trial model
Biology	**Pharmacology**	**Patient population**
Biomarker(s)/ outcome relationship	Effectiveness	**Drop-out**
Natural progression	Safety	**Adherence**
Placebo effect	**Preclinical/Healthy/ Patient**	
	Product features	

From Gobburu J and Lesko L, Annu. Rev. Pharmacol. Toxicol. 2009. 49:291–301

Model Based Drug Development

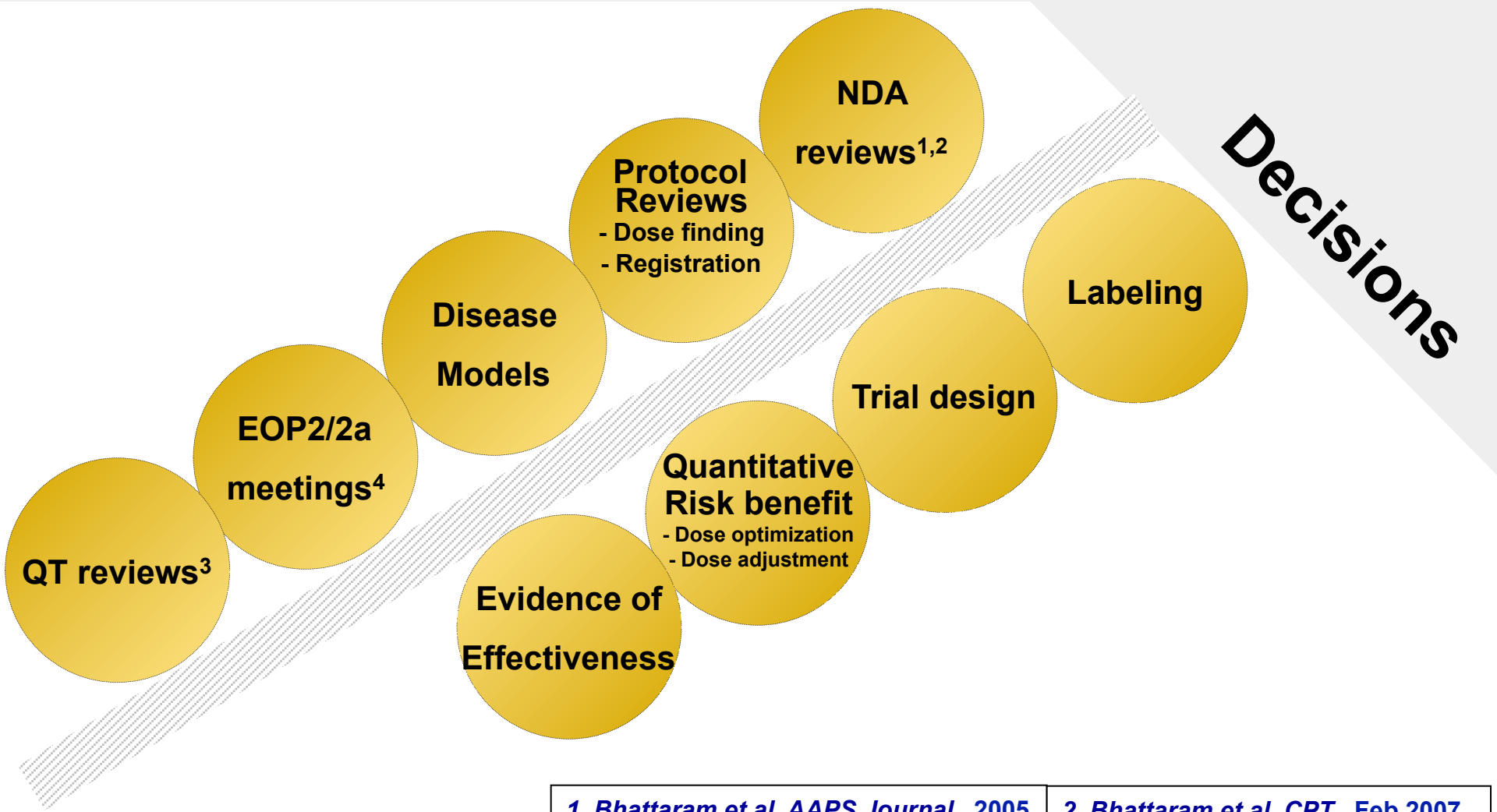
"The concept of model-based drug development, in which pharmaco-statistical models of drug efficacy and safety are developed from preclinical and available clinical data, offers an important approach to improving drug development knowledge management and development decision making."

Lewis B. Sheiner, "Learning vs Confirming in Clinical Drug Development", Clin. Pharmacol. Ther., 1997, 61:275-291.

Office of Clinical Pharmacology Review Deliverables

- Does the dose/exposure response support efficacy of the product?
- Is the appropriate dose or dosing regimen identified based on dose/exposure response for both safety and efficacy?
- Is the proposed dose individualization scheme reasonable?
- Are the metabolic pathways and potential for drug-drug interactions adequately characterized?
- Were the relevant special population studies conducted?
- Are there any "show stoppers" (i.e. issues that could preclude approval) regarding the above key components or other aspects of the application?

Pharmacometrics Scope: Tasks



1. Bhattaram et al. AAPS Journal. 2005	*2. Bhattaram et al. CPT.* Feb 2007
3. Garnett et al. JCP. Jan 2008	*4. Wang et al. JCP.* Jan 2008

Case Study 1: Bridging Interferon Responsiveness from HCV Trials

(Jiang Liu and Jeffry Florian)

Clinical Pharmacology Review of Boceprevir and Telaprevir, 2011

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM254087.pdf

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM254076.pdf

Two new HCV therapies were submitted to the FDA in late 2010. Both submissions were characterized by drastically different drug development programs.

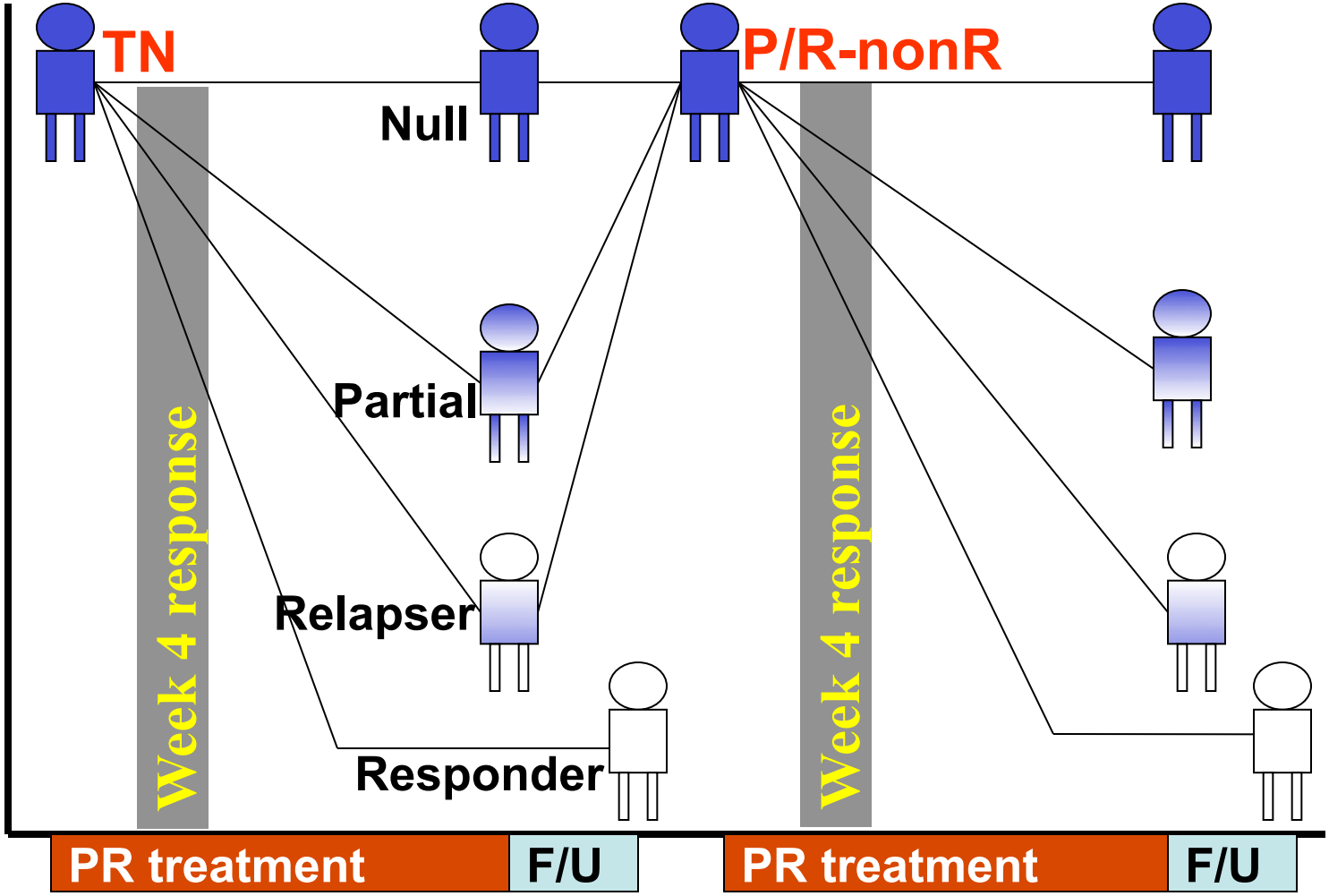
REGISTRATIONAL TRIAL DESIGNS	BOCEPREVIR	TELAPREVIR
Lead-in Phase	YES	NO
Response Guided Therapy	All trials	Only treatment-naïve patients
P/R-nonresponder trial	Excludes null responders	Include relapsers, partial responders, and null responders

Two programs, same story

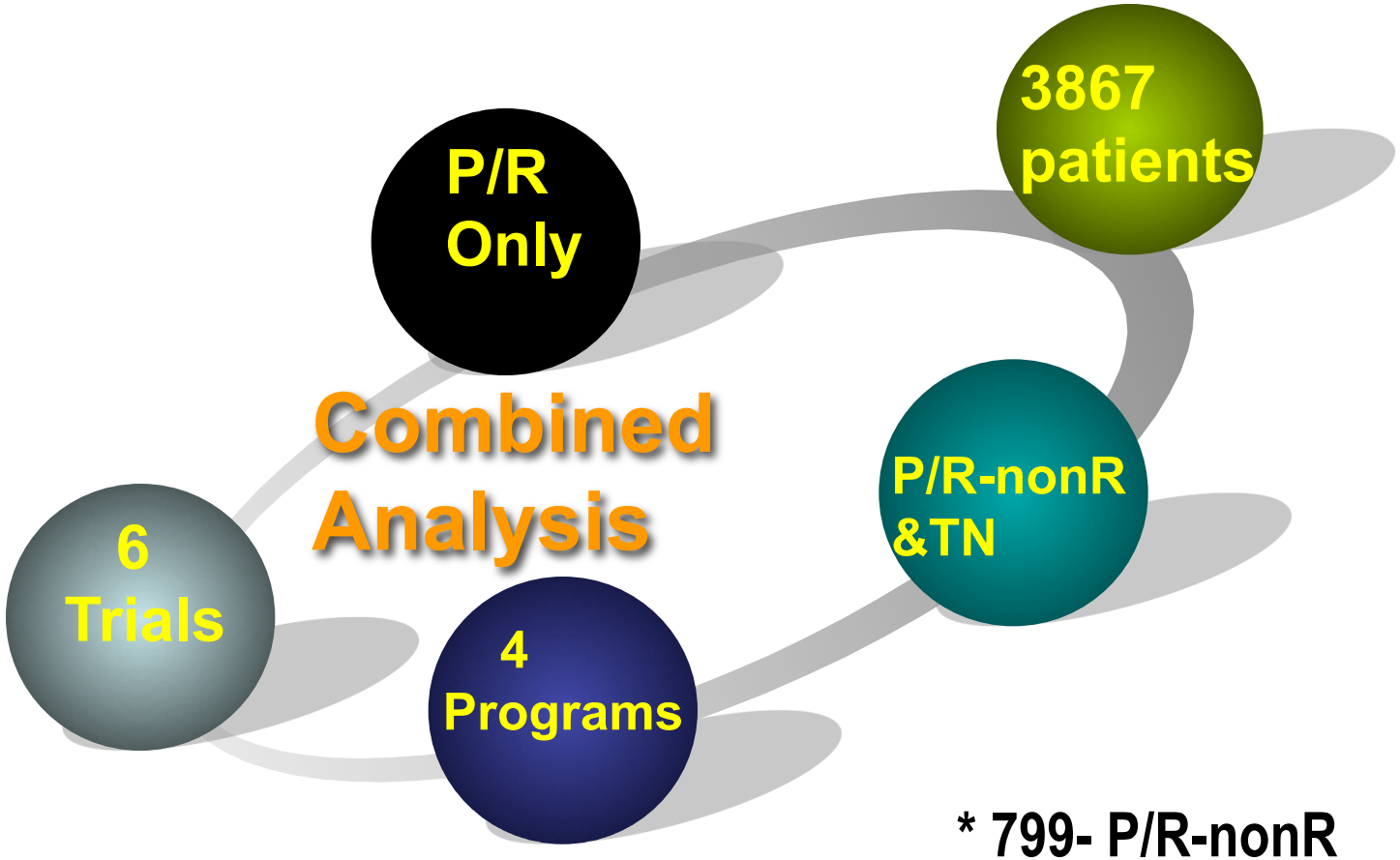
"Bridging" Observations Through Interferon Responsiveness

- Similar response with first or second round of P/R treatment
  - Data for P/R-nonresponders are "bridged" with data from treatment-naive subjects
- Previous P/R-nonresponders are represented within treatment-naive subjects
- P/R treatment for HCV is unlike HIV treatment which frequently leads to resistance and does not yield similar virologic response on subsequent courses of treatment

P/R-nonresponders (P/R-nonR) are represented within treatment-naive (TN) subjects. Decline in HCV RNA at week 4 'bridges' interferon response between treatment populations.

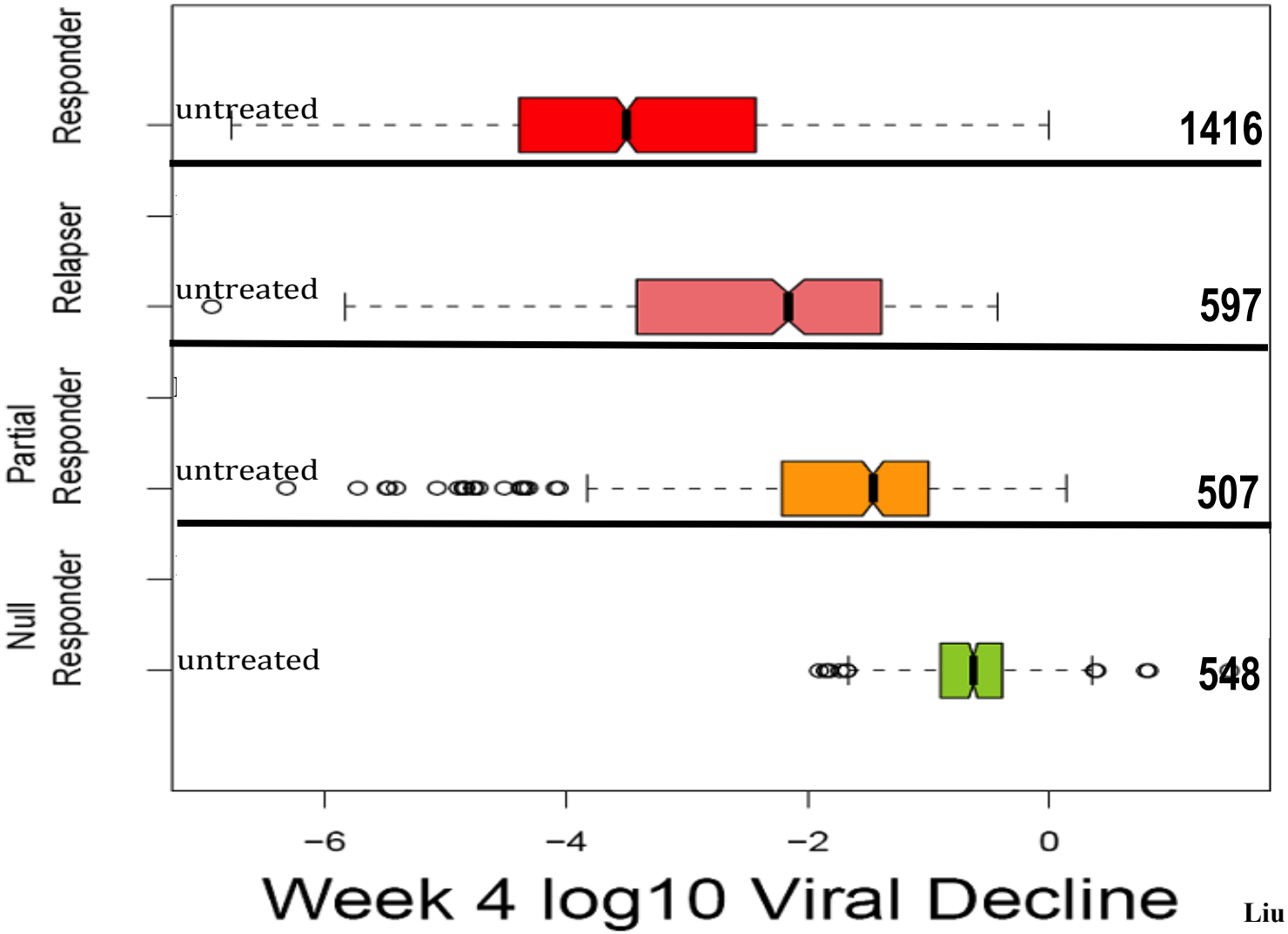


Antiviral Information Management System (AIMS) Database to Leverage Prior Data



* 799- P/R-nonR
* 3068-TN

Similar Virologic Response at Week 4 with First or Second PR treatment (pooled analysis)



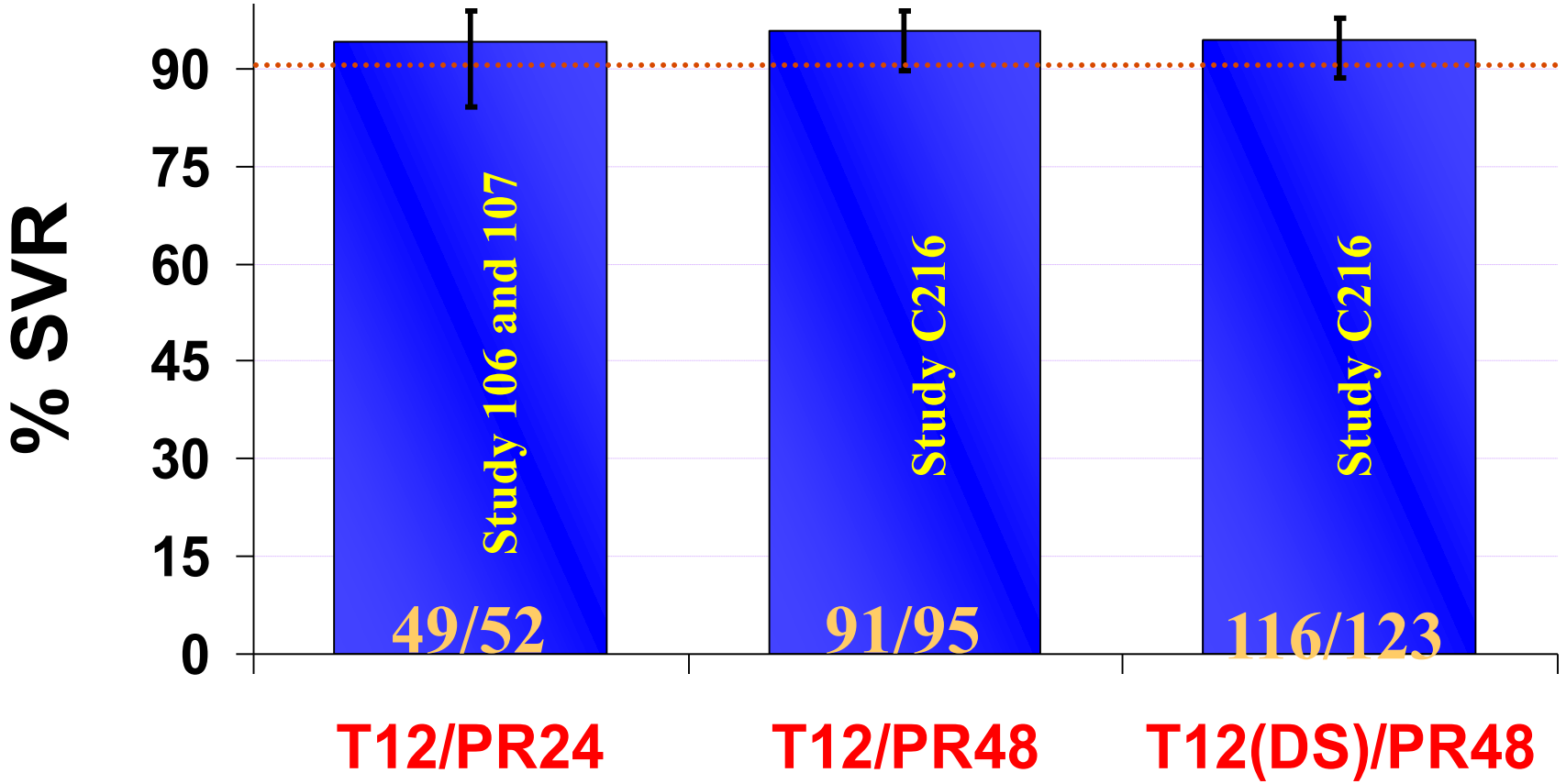
Liu *et al. CID 2012*

Telaprevir: Is RGT for Relapse Subjects Acceptable?

Population	eRVR	Evidence to support RGT
Treatment-Naïve	T12/PR24	Study 111
P/R-nonresponders: Prior Relapse	T12/PR24 ?	❑ Cross-trial comparison of data from Phase 2 and 3 trials ❑ Bridging data from treatment naïve population ❑Viral Dynamics (Applicant's analysis)

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM254087.pdf

Response Rates in Relapse Subjects with eRVR Across Phase 2 and 3 Trials



Relapse subjects with eRVR achieved >90% SVR irrespective of 24 or 48 weeks of PR treatment

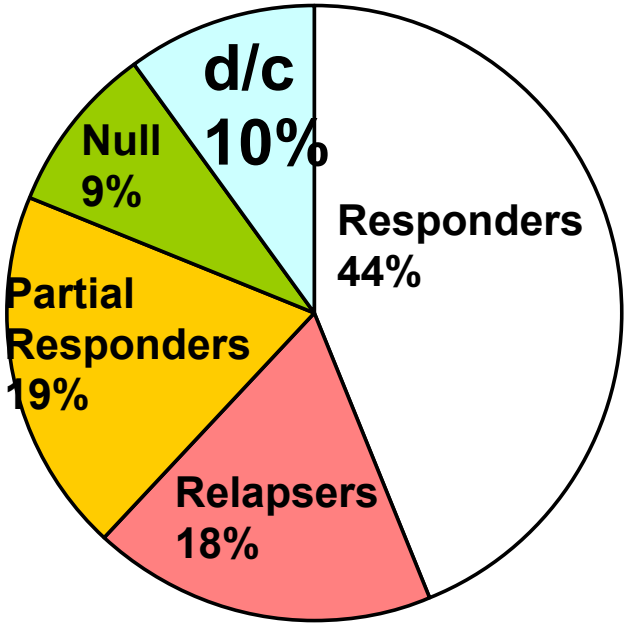
Treatment-Naïve *future* Relapse and P/R-nonresponder (Prior) Relapse Subjects demonstrate similar Virologic Response at Week 4 with First or Second PR treatment

Population	Study	Week 4 Decline in log10 Viral Load	
		Mean	Median
future Relapse (EOS)	108	-2.8	-2.9
Prior Relapse (Baseline)	C216	-2.7	-2.4

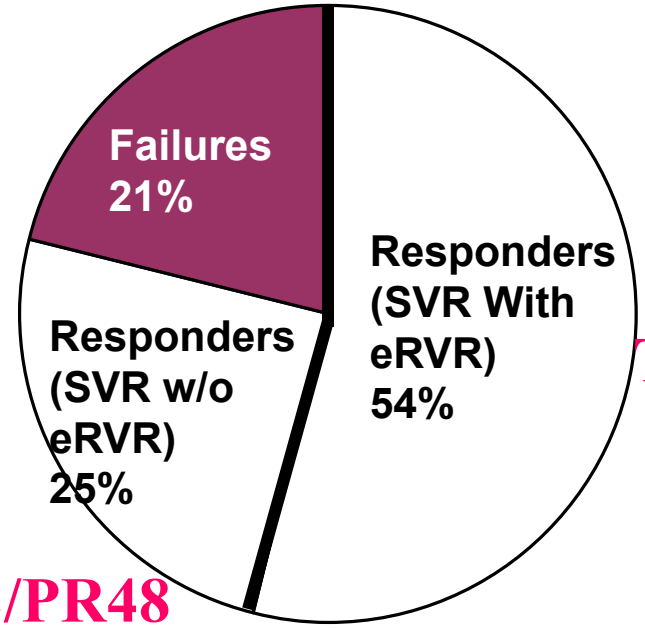
The range of week 4 response (not just mean) is also similar for all comparisons (*future* relapse vs prior relapse; *future* partial vs prior partial; *future* null vs prior null)

RGT is Recommended for *future* Relapse Subjects Among Treatment-Naïve Population

Study 108



PR Response Rate



T12/PR24

T12/PR48

Telaprevir Response Rate

Prior P/R-nonresponders are Represented within Treatment-naive Subjects

Population	% Response SOC	% Response TVR (within group)	%SVR (overall)
Responders	44[a]		
Relapsers	18[a]		
Partial	19[a]		
Null	9[a]		

a- P/R (control) arm from study in untreated subjects (108)

Summary of Case Study 1

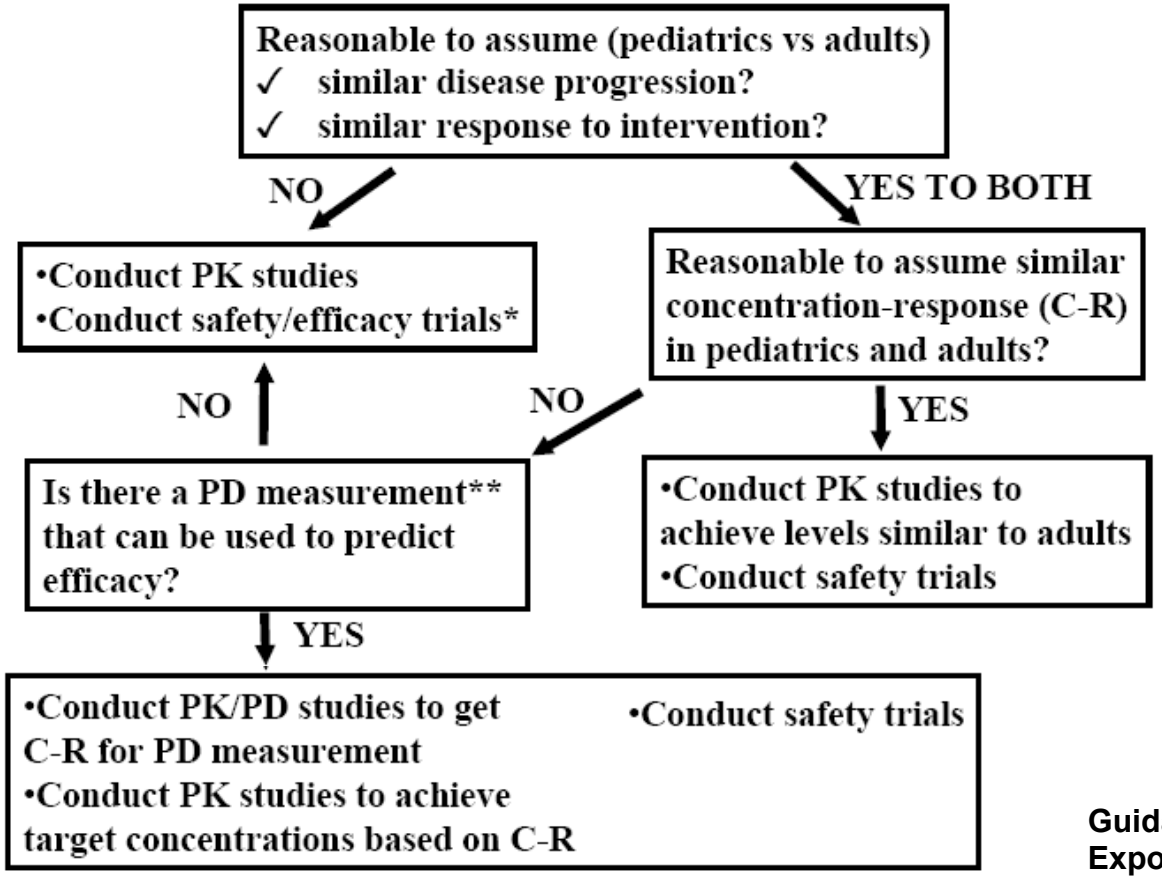
- Similar response with first or second round of PR treatment
  - Data for P/R-nonresponders subjects are "bridged" with data from treatment-naïve subjects
- eRVR on current therapy appears to be more important predictor of SVR than previous response to PR
- Prior relapse subjects with eRVR achieve >90% SVR (Cross-trial comparison) irrespective of 24 or 48 weeks of PR treatment

Case Study 2: PK-Bridging Approach to Approve IV Nexium® and Select Appropriate Doses In Pediatrics

Clinical Pharmacology Review of Nexium IV, 2011

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

Pharmacometrics can Streamline Pediatric Drug Development

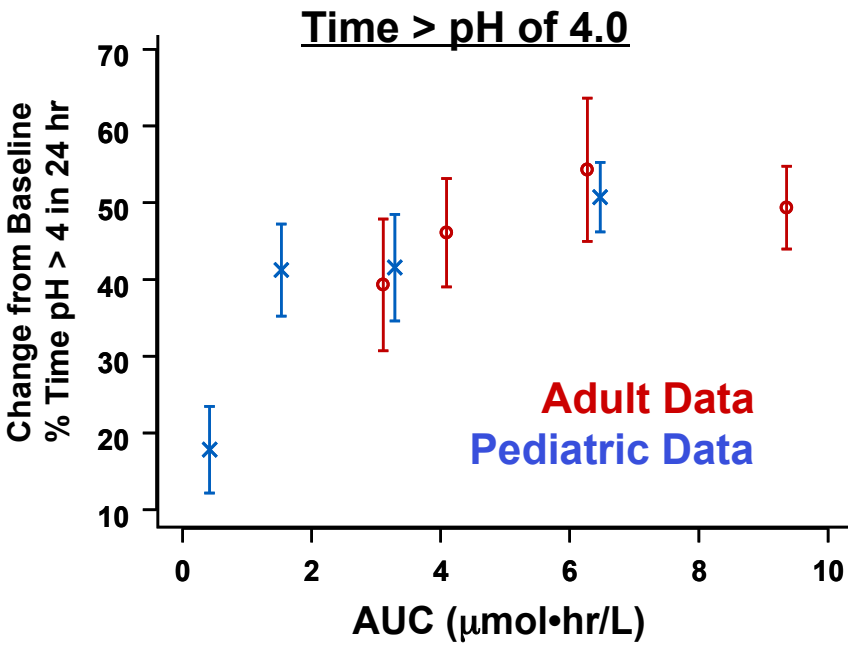


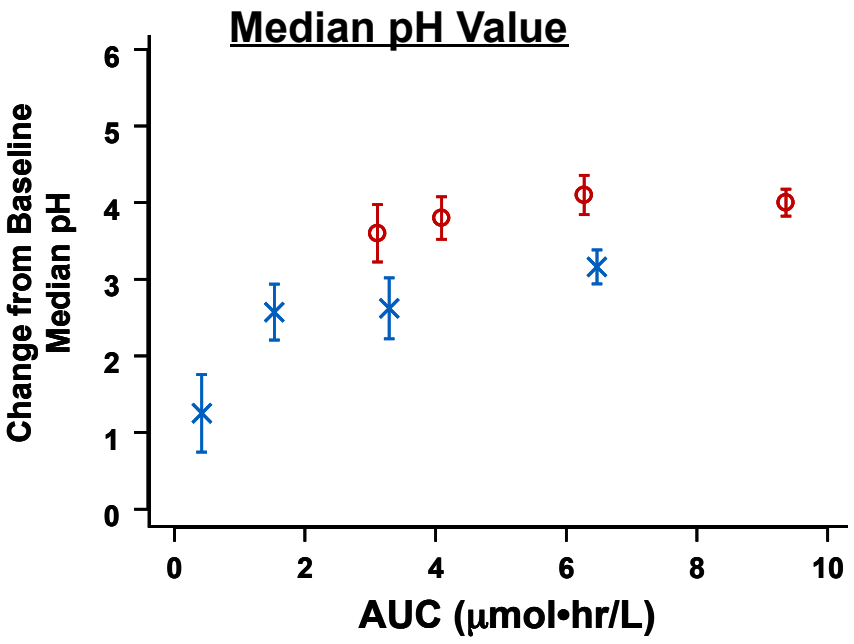
Guidance for Industry: Exposure-Response Relationships

IV Nexium (esomeprazole)

- Regulatory History:
  - Oral Nexium is approved in pediatrics & adults
  - IV Nexium is approved in Adults
- Application for Pediatric Nexium IV
  - Pop PK & Safety Data: 50 pediatrics (0 – 17 yr)
  - Pediatric PK were compared to Adult PK
- Dose Selection:
  - Dosing regimen adjusted so AUC and C_{max} values match adult data

Exposure-Response is Similar Between Adults and Children





Pediatric Dosing Recommendations

Proposed Dosing

Age Group	Treatment of erosive reflux esophagitis	Treatment of Symptomatic GERD
1 – 11 yr	Weight < 20kg: 10 mg QD Weight ≥ 20 kg: 10 mg or 20 mg QD	10 mg QD
12-17 yr	40 mg QD	20 mg QD

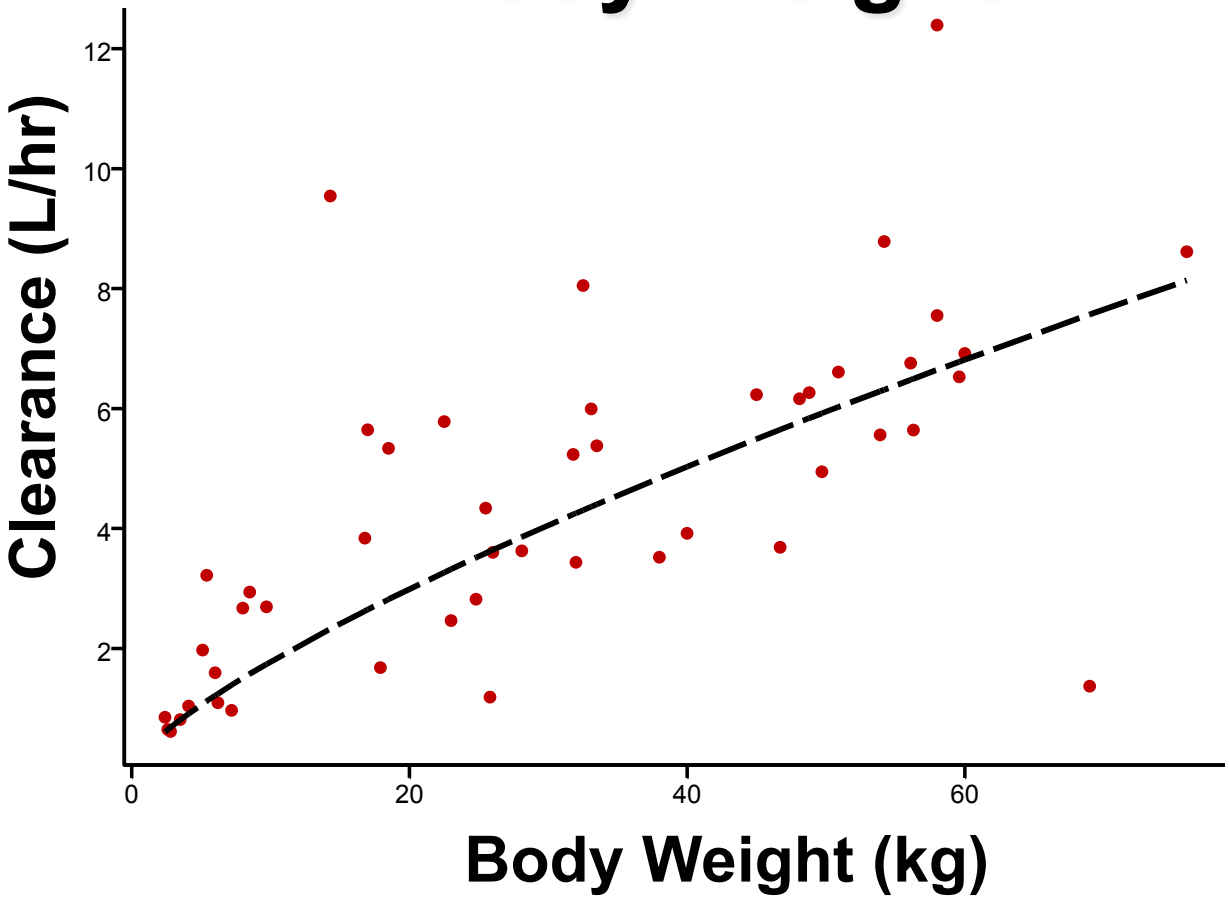
3-min injection,
10-30 min Infusion

FDA Approved Dosing

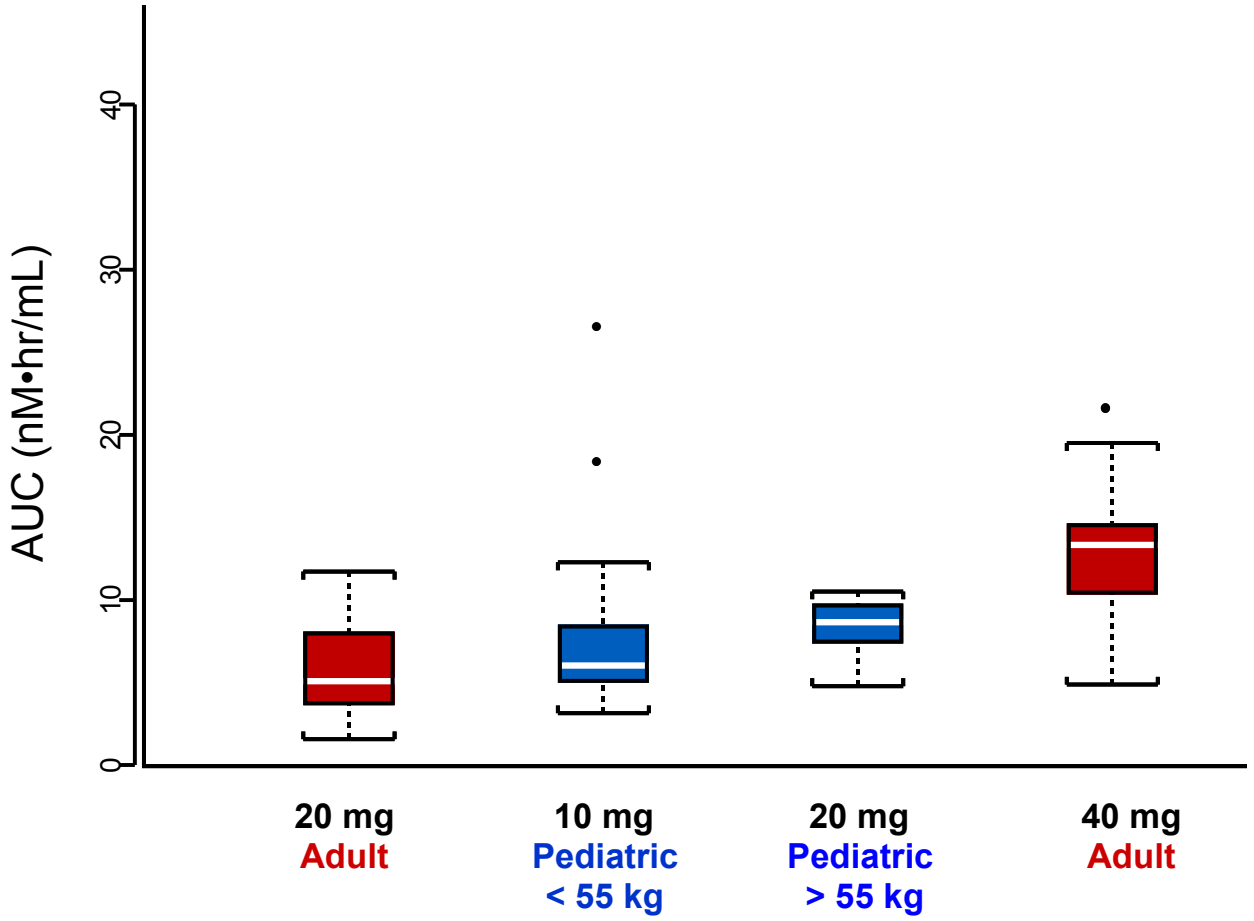
Weight Range	GERD: • Symptomatic GERD • Erosive Esophagitis
< 55 kg	10 mg
> 55 kg	20 mg

10-30 min infusion

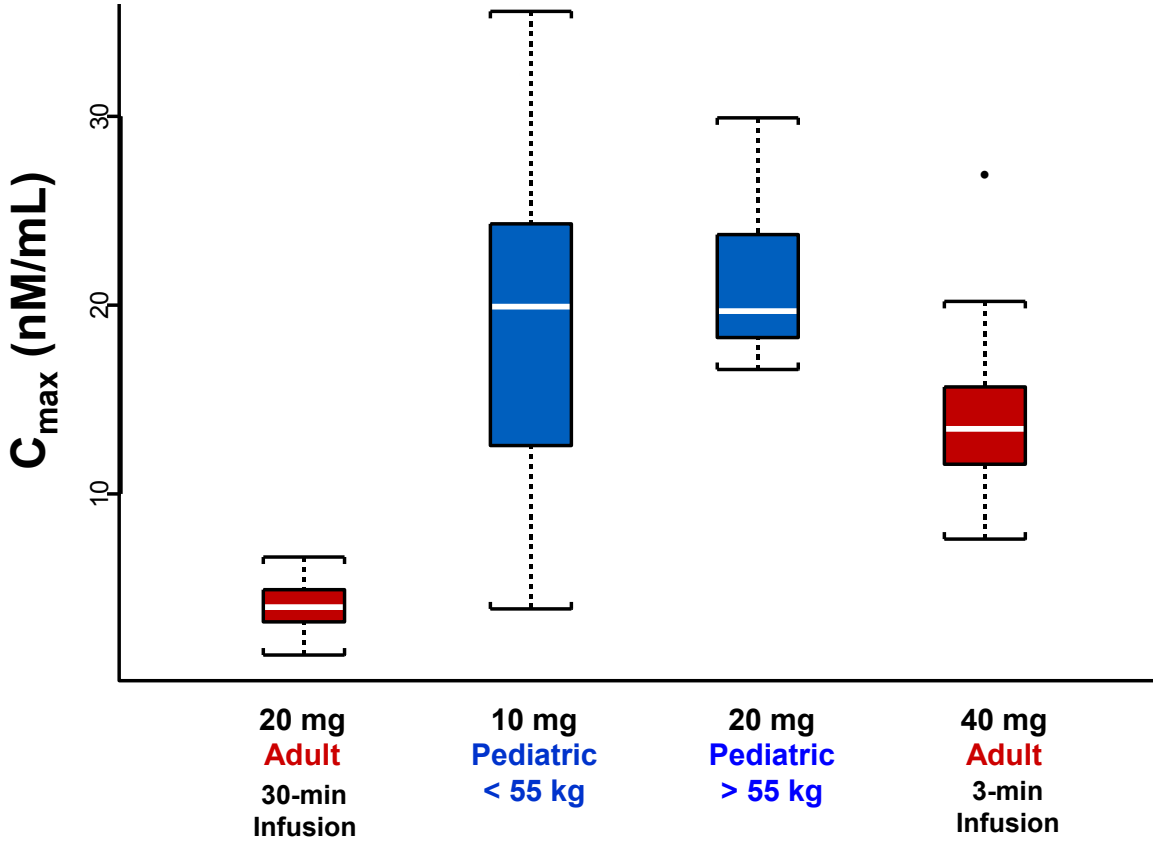
Esomeprazole CL Increases with Body Weight



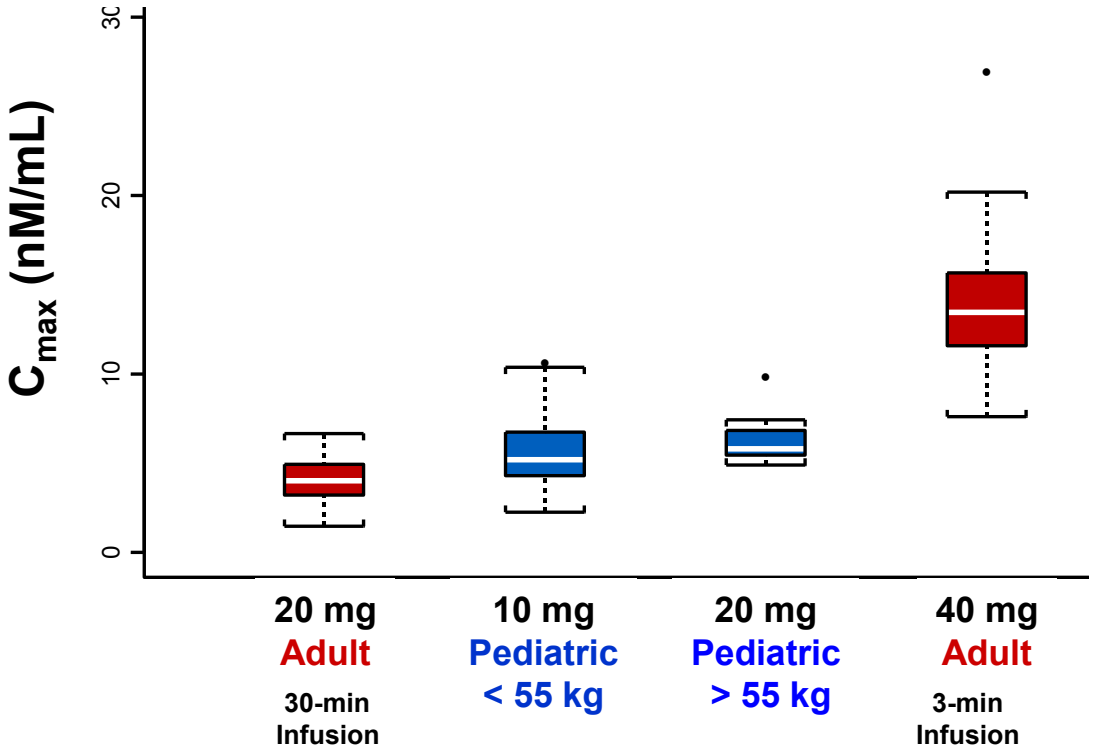
AUCs Values in Pediatrics ~ Adults



C_{max} Values in Pediatrics > Adults for 3 min Injection



30-min Infusion C_{max} Values in Pediatrics ~ Adults



- 10-min infusion: C_{max} < 40 mg in adults (13.5 nM/mL)
- Exposures higher than 20 mg dose for only 2 minutes

Summary of Case Study 2

Value to Drug Development

- Approval of drug without additional safety and efficacy trials
- Approval of dosing regimen not studied directly in clinical trials

Value to Public Health

- Method provides more consistent exposures in pediatrics

Case Study 3: PK/PD Risk-Benefit Assessment for Mirebegron

(Jiang Liu and Raj Madabushi)

Clinical Pharmacology Review Mirabegron, 2012

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

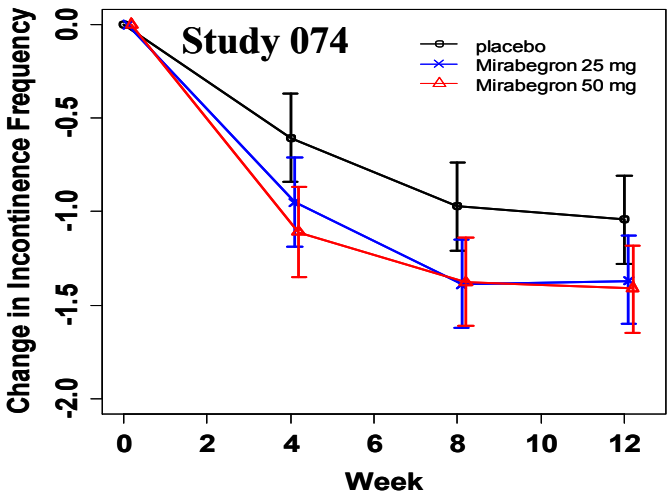
Pivotal trials for mirabegron

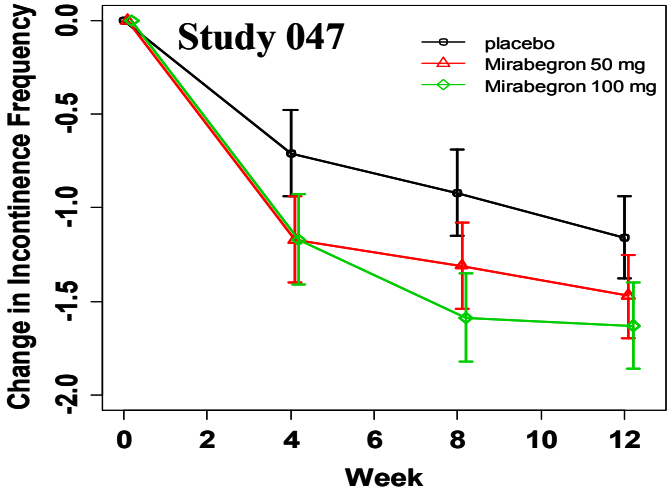
Phase 2b

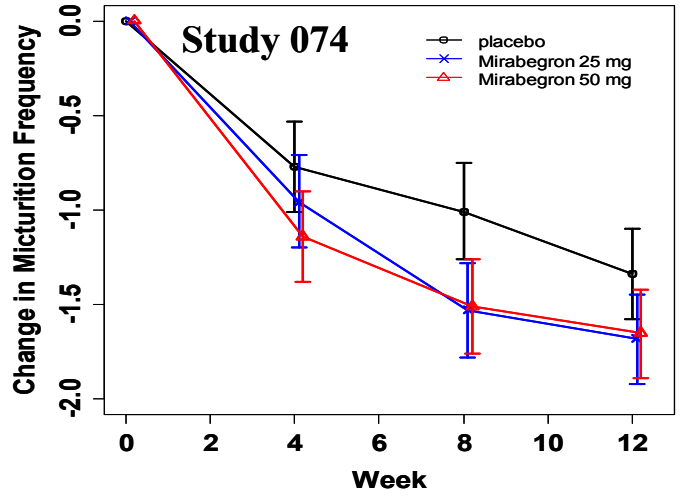
Phase 3 trials

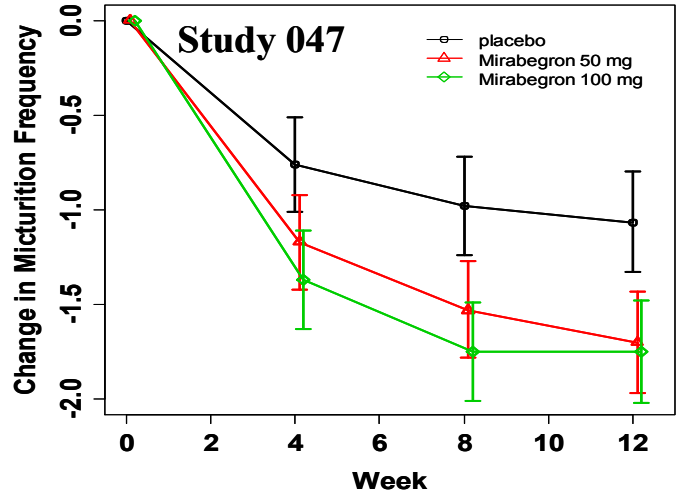
Study	Primary efficacy endpoint	Treatment	No. of subj.
178-CL-044 (Euro)	co-primary efficacy endpoints: 1) change from baseline to final visit (Week 12) in mean number of incontinence episodes per 24 hours 2) change from baseline to final visit in mean number of micturitions per 24 hours	Placebo, mirabegron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

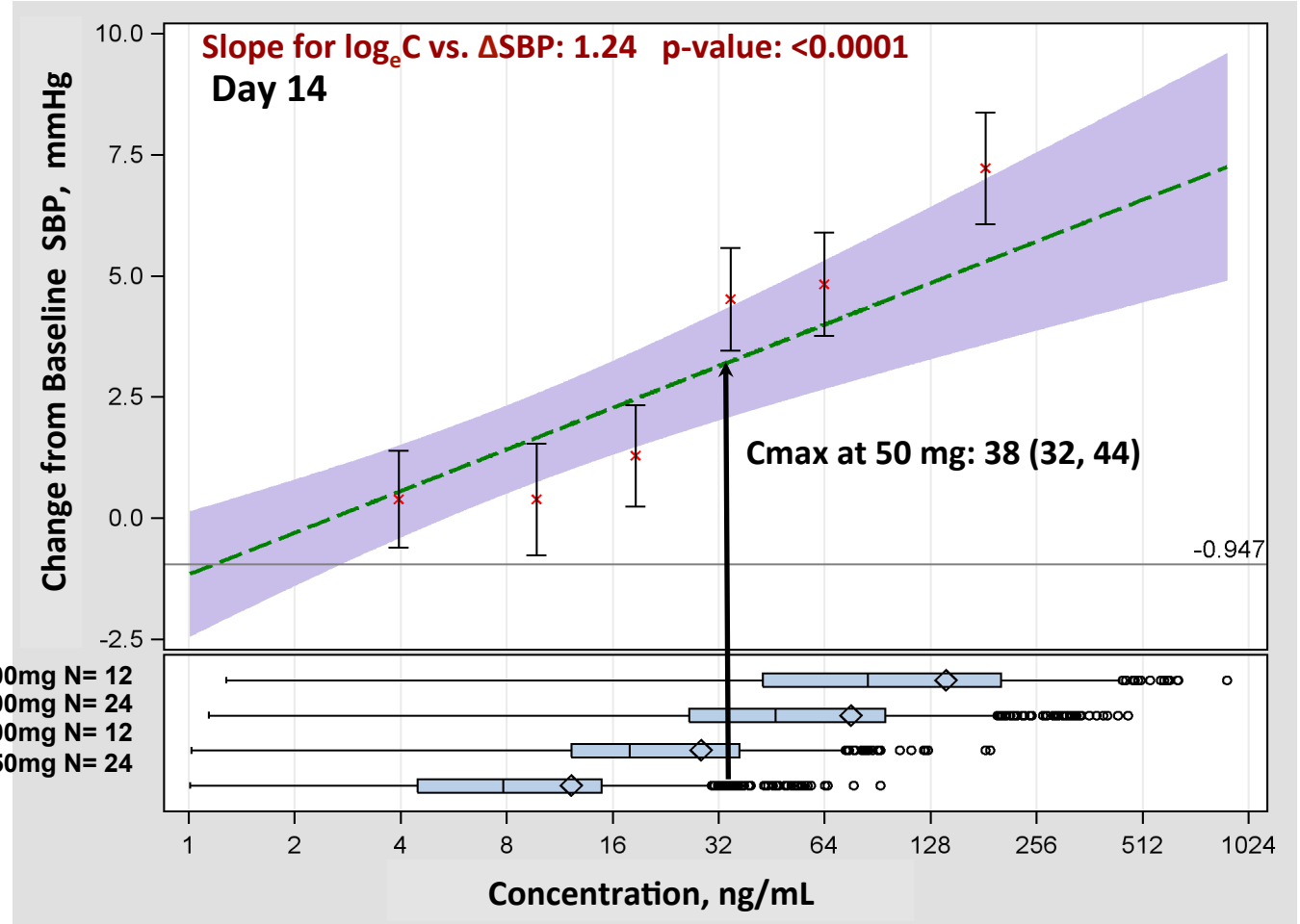








Increase in SBP† is exposure dependent

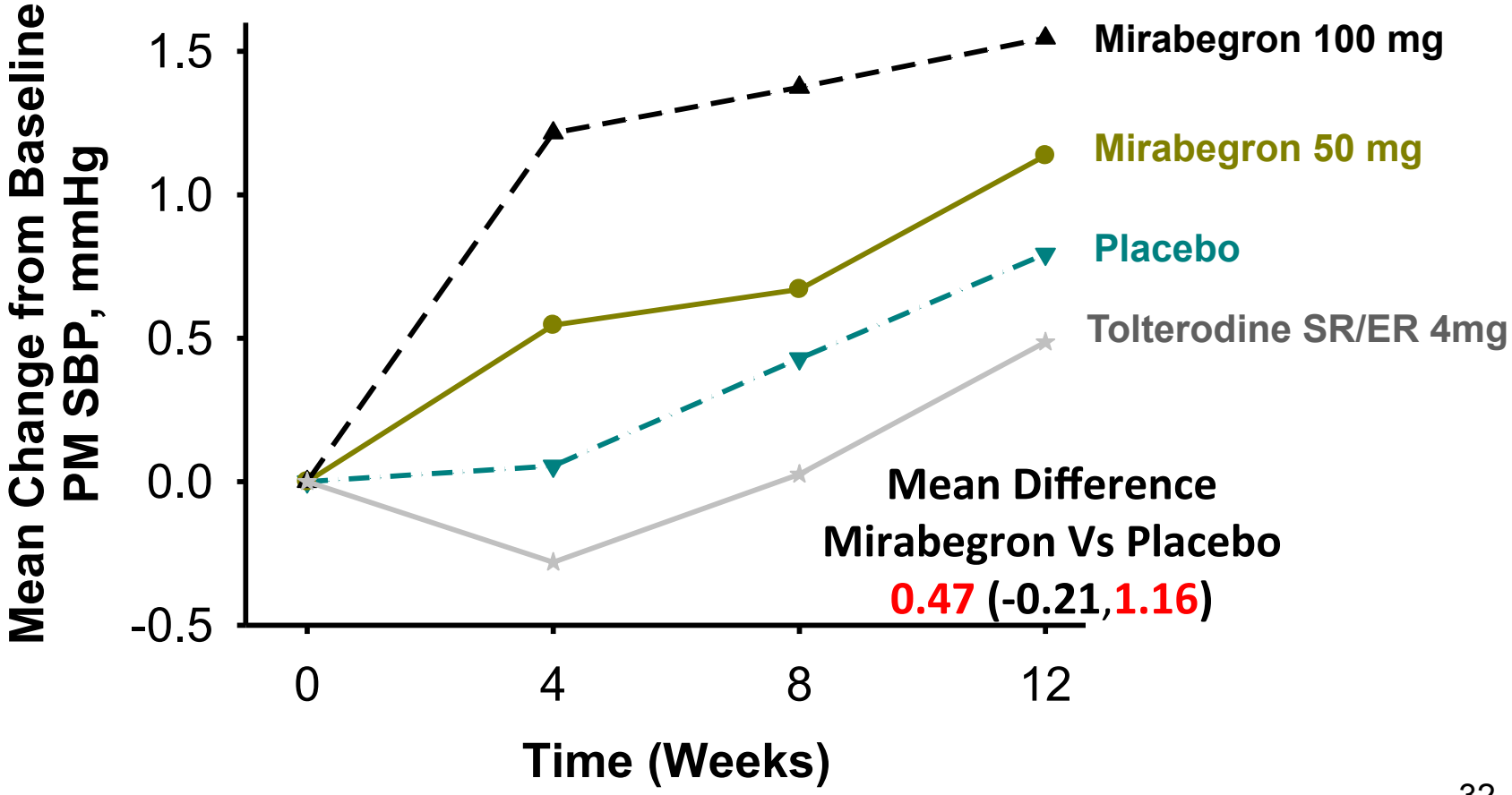


†Study 178-CL-031
Time-matched Concentration and SBP

Analysis performed by Jiang Liu Ph.D.

Dose Dependent Increase in SBP Observed in Phase III

Changes greater than 1.2 mmHg are ruled out



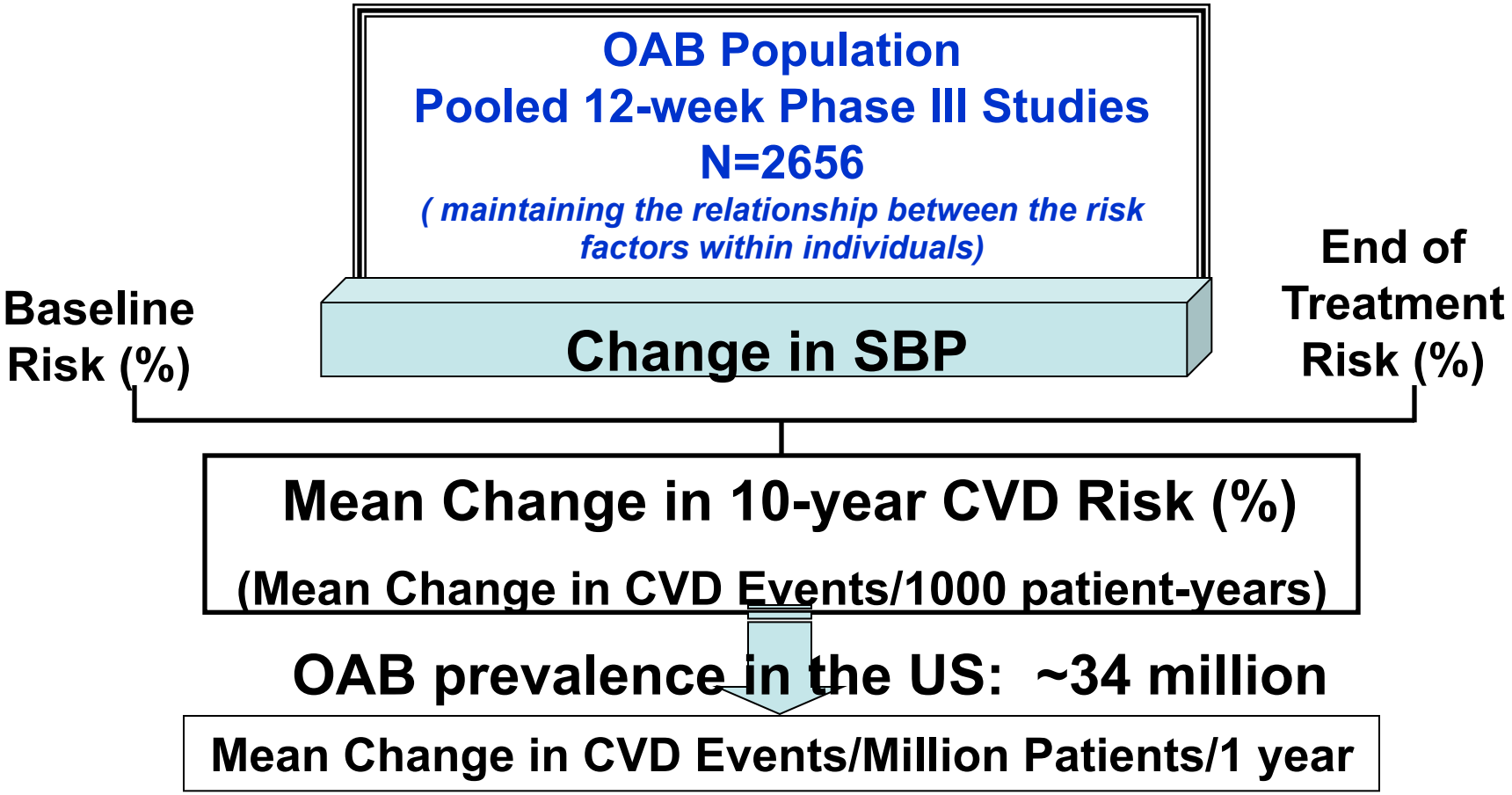
Pooled 12-week Phase III Studies

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)
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%

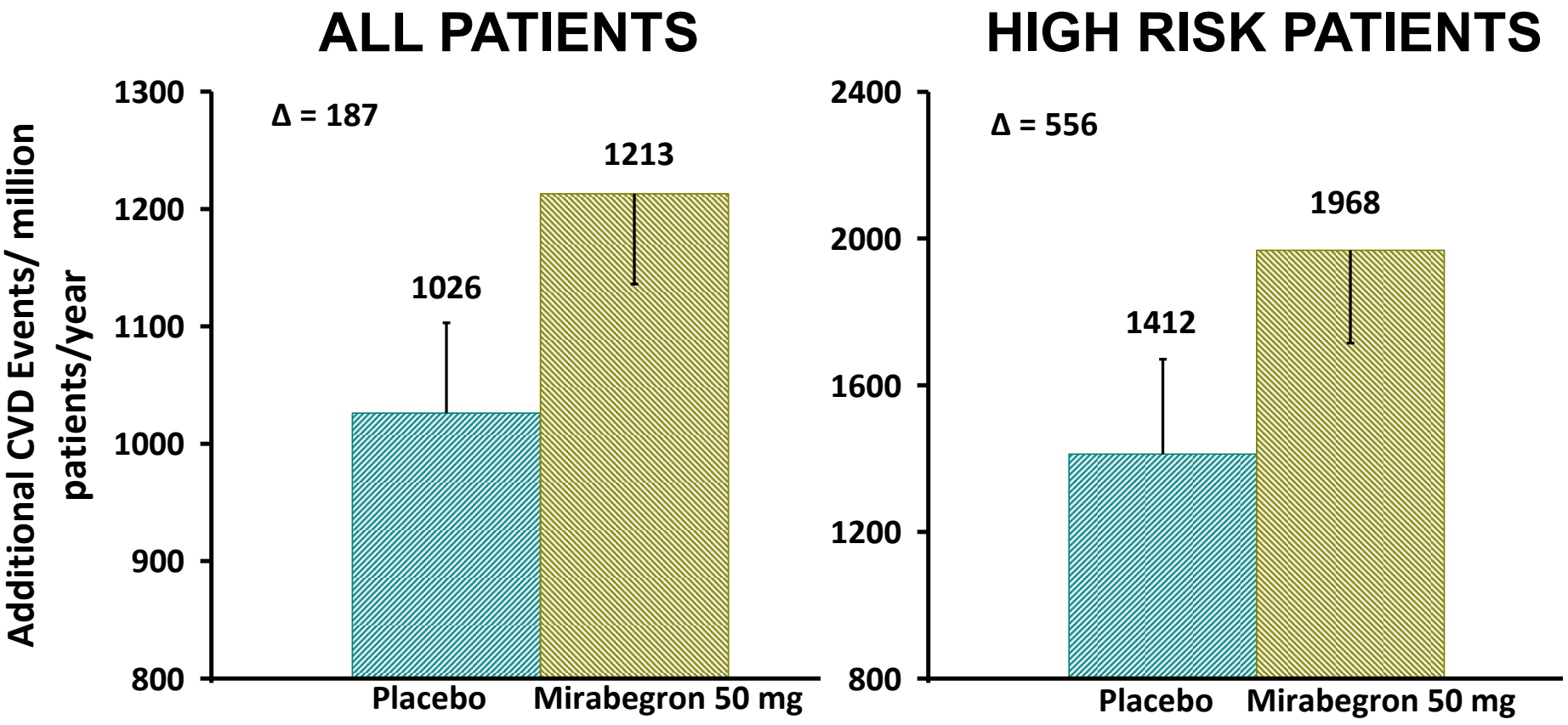
†Total and High-Density Lipoprotein Cholesterol, and Smoking Status not collected in Phase III programs. Imputed based on age and sex

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.

Take Home Messages

- **Exploratory (e.g. Pharmacometrics) analyses are often used to make regulatory decisions**
  - Drug Approval and Labeling are two key decisions
    - Decisions are not entirely driven by the pre-specified analysis
  - Trial Design
  - Quantitative Risk Benefit
- **Decisions occur at all phases of development**
  - Early communication helps ensure the best possible outcome

Division of Pharmacometrics (2013)