Pharmacometric Approaches for Extrapolation from Adult to Pediatric T2DM

Tarek Leil, PhD

Satyendra Suryawanshi, MPharm, PhD

Ronald Portman, MD

BMS Pediatric Center of Excellence

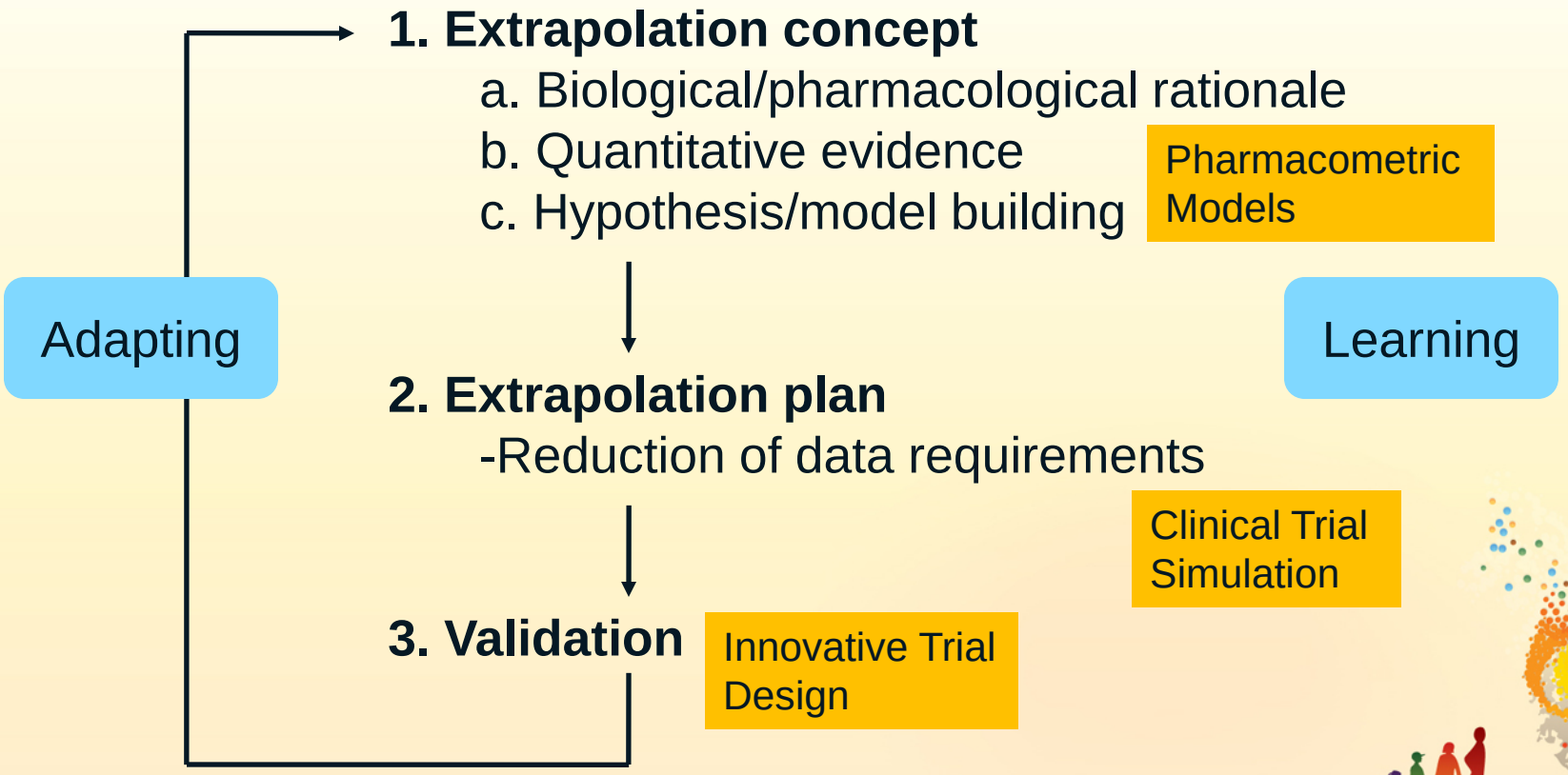
Innovative Medical Science for Children

Advancing the Development of Medicines for Children

Conceptual Framework

Sequential steps of extrapolation

Basic prerequisite: - similarity of disease / progression
- similarity of response to treatment



Definition of Diabetes (adult and pediatric) per American Diabetes Association: Similarity of Disease

1. HbA1c ≥ 6.5% (test performed in a certified laboratory); or
2. Fasting (defined as no caloric intake for at least 8 hours) plasma glucose ≥ 126 mg/dl (7.0 mmol/L); or
3. 2-hour plasma glucose ≥200 mg/dl (11.1 mmol/L) during an oral glucose tolerance test performed as described by the World Health Organization by using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water; or
4. A random plasma glucose ≥200 mg/dl (11.1 mmol/L) with symptoms of hyperglycemia.

Pediatrics 2013;131:364-382

Type 2 Diabetes in Pediatrics and Adults: Thoughts from a Clinical Pharmacology Perspective

JAYABHARATHI VAIDYANATHAN, SALLY CHOE, CHANDRAHAS G. SAHAJWALLA
Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, Food and Drug Administration
2012; J Pharm Sci 101:1659–1671, 2012

	Mechanism	PK	PD	Comments
Metformin	Biguanide; ↓ hepatic glucose production; ↑ insulin sensitivity	Adult and pediatric similar	Adult and pediatric similar reduction in HgbA1c & FPG	Decrease in body wgt; ↓Pinsulin, ↓ insulin resistance, TODAY 51% pts well-controlled; AE difficult to achieve full dose
Rosiglitizone	PPARγ	Adult and pediatric similar	Adult and pediatric similar	Did not reach non-inferiority with metformin, side effect of wgt gain in pediatrics
Glimepiride	Insulin secretagogue	Adult and pediatric similar	Less effective but only 50% of adult dose used	Did not demonstrate non-inferiority with metformin
Glyburide/metformin	combination	Adult and pediatric glucovance similar	Less effective in kids than adults but lower starting HbA1c in kids and effect greatest in adult >9%	Naïve patients in adult and kids had better response

Similarity of drug PK/PD in adult and pediatric T2DM

Potential Approach to Extrapolation of T2DM: DPP-4 Inhibitor Example

Integrate

- **Integrate** prior clinical data on DPP-4 inhibitors using a pharmacometric model
- Understand assumptions of model
- Similar mechanism of action

Extrapolate

- Make adjustments to model to account for potential differences in pediatric subjects
- **Extrapolate** PK/PD and clinical outcomes in pediatric trial
- Optimize design of first pediatric trial

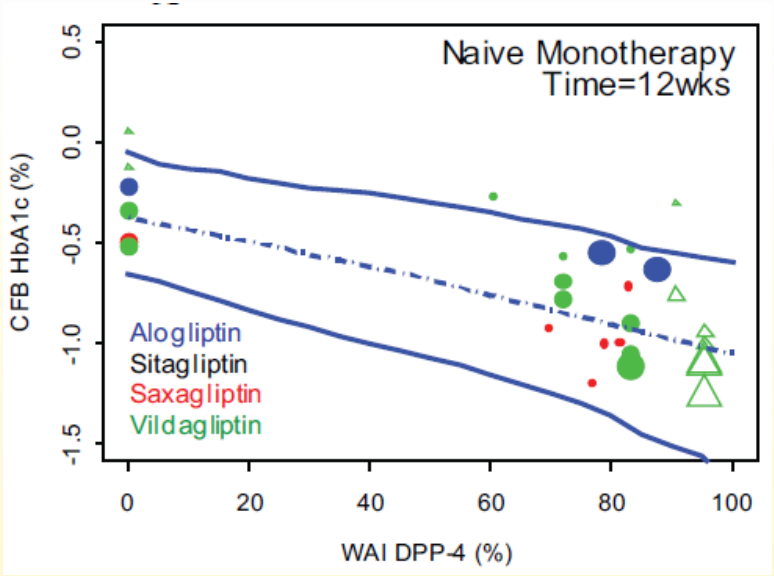
Validate

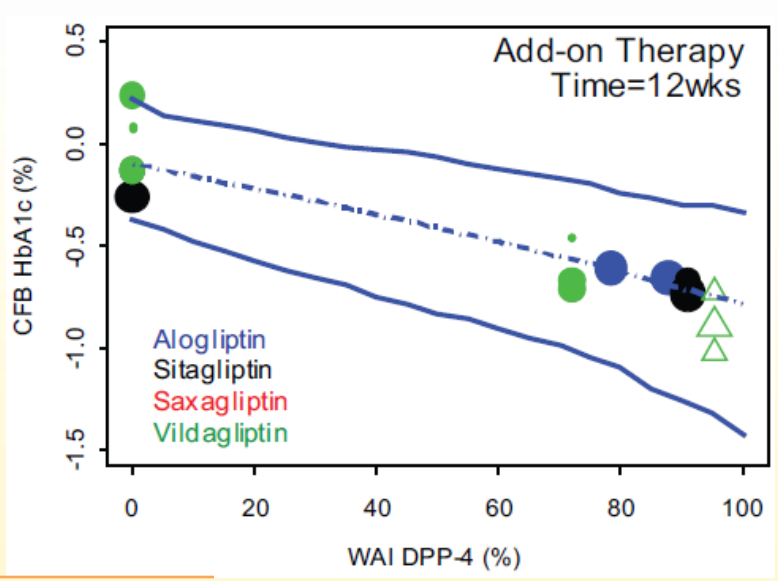
- Conduct clinical trial to **validate** predictions from quantitative model
- Adjust understanding of pediatric PK/PD or clinical outcome if necessary

Maximize Utilization of Prior Knowledge

Integration of Clinical Data on DPP-4 Inhibitors

Pharmacometric Model Incorporating PK, DPP-4 inhibition and HbA1c*





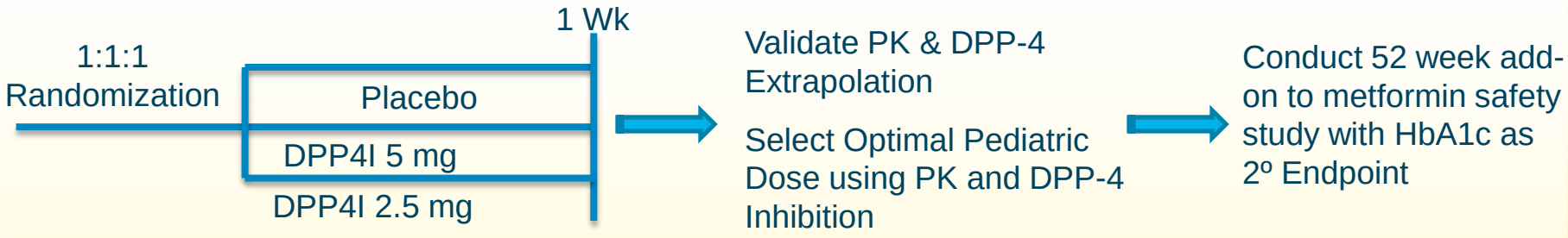
DPP-4 Inhibitor	No. Trials	No. Patients
Saxagliptin	2	1315
Alogliptin	5	2106
Sitagliptin	12	5970
Vidagliptin	14	4447
Total	33	13838

WAI = predicted weighted average inhibition

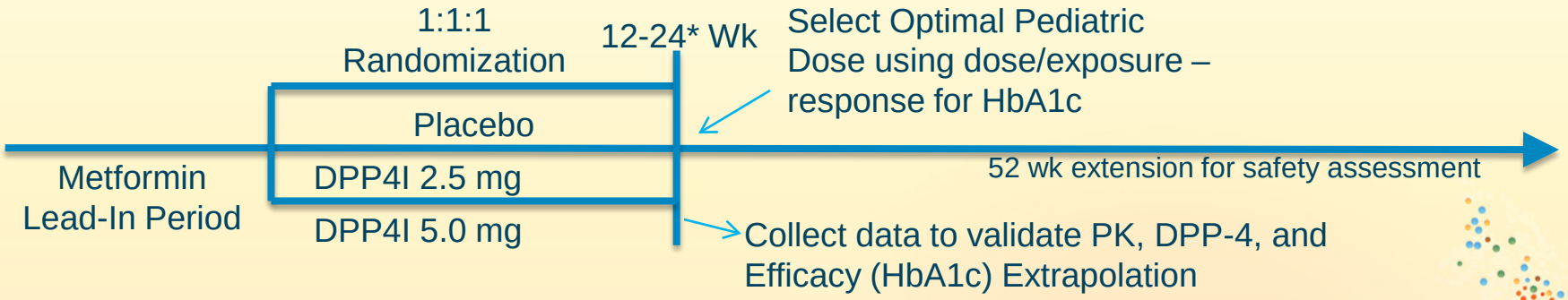
*Gibbs JP, Fredrickson J, Barbee T, Correa I, Smith B, Lin SL, Gibbs MA. Quantitative model of the relationship between dipeptidyl peptidase-4 (DPP-4) inhibition and response: meta-analysis of alogliptin, saxagliptin, sitagliptin, and vildagliptin efficacy results. J Clin Pharmacol. 2012 Oct;52(10):1494-505. Epub 2011 Dec 12.

Evaluate Potential Approaches to Validate Extrapolation

Example 1: PK/PD study followed by long term safety study (model if no need to validate efficacy)



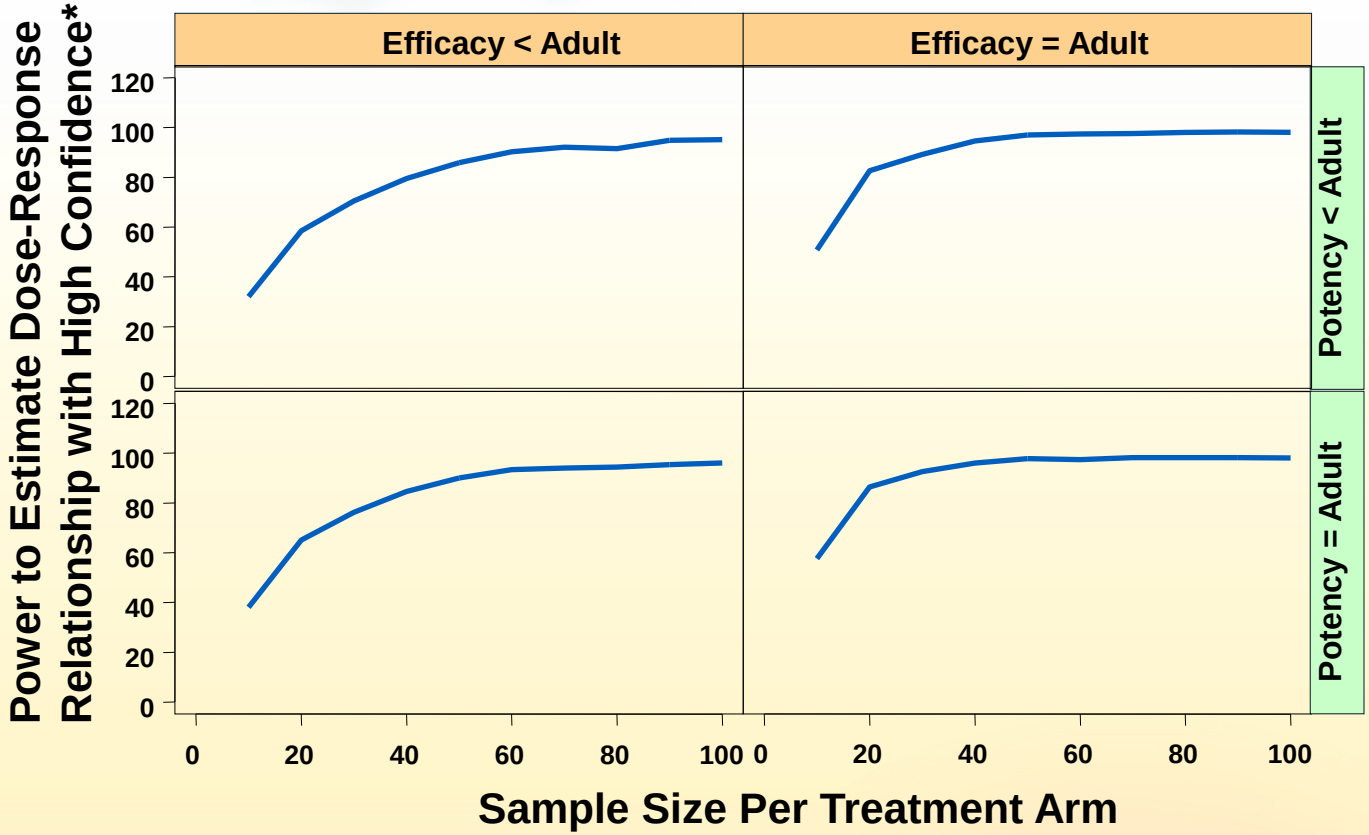
Example 2: Confirmatory efficacy study powered for dose-response as add-on therapy to metformin followed by long term safety extension



Any alternative pediatric study designs may be evaluated using clinical trial simulations

*simulation performed for 24 weeks

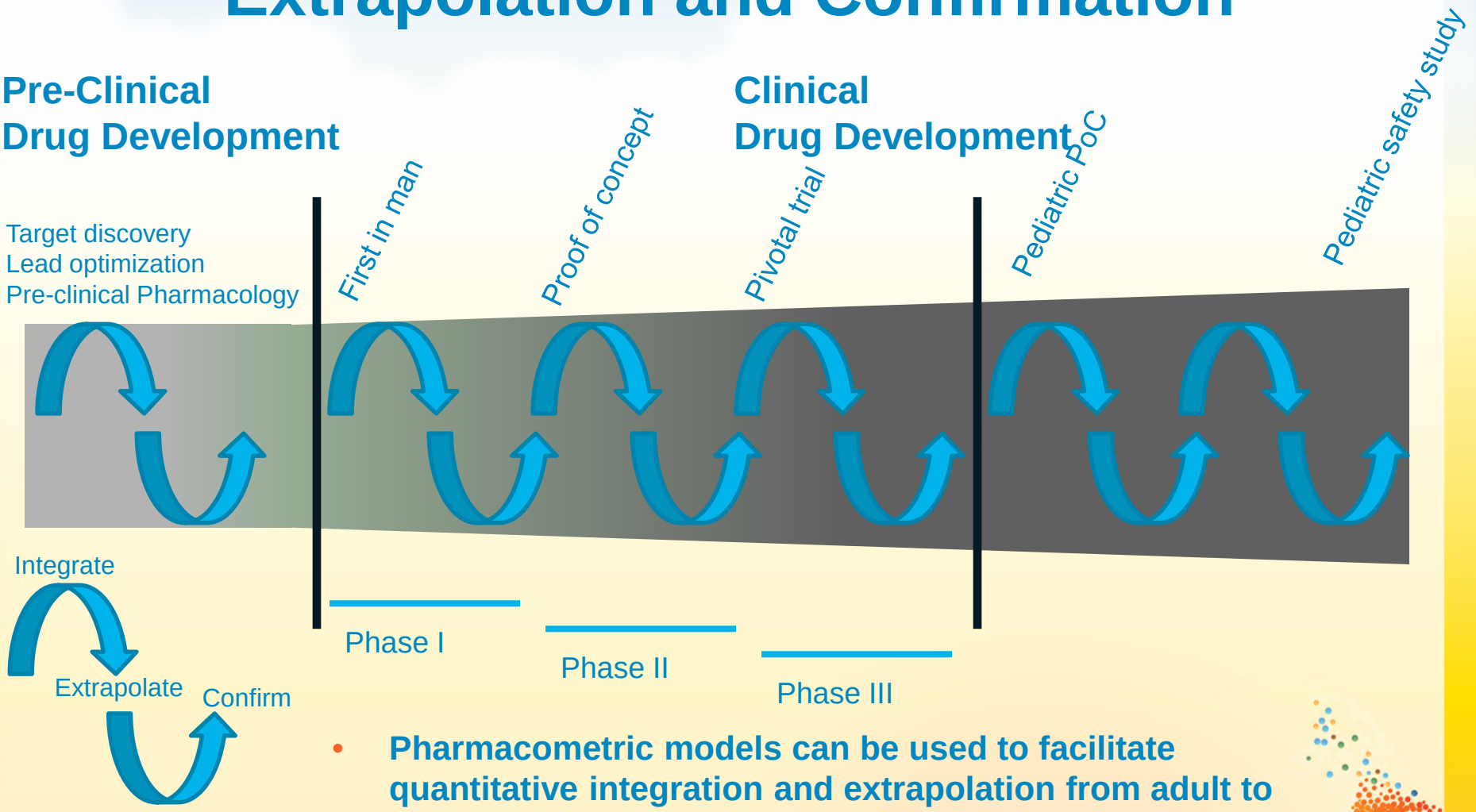
Exploration of Power/Sample Size using Clinical Trial Simulations



- **To achieve ~ 80% power:** total sample size of 51 (efficacy/potency equivalent to adult) to 120 (low efficacy and potency)
- **Total sample size of N = 90 subjects:** power of ~ 70% (low efficacy and potency) to 93% (efficacy/potency equivalent to adult)

*95% confidence interval for estimate of placebo anchored dose-response slope does not include zero.

Summary: Quantitative Integration, Extrapolation and Confirmation



- **Pharmacometric models can be used to facilitate quantitative integration and extrapolation from adult to pediatric subjects**
- **Robust models exist for DPP-4 inhibitors to support extrapolation for T2DM**

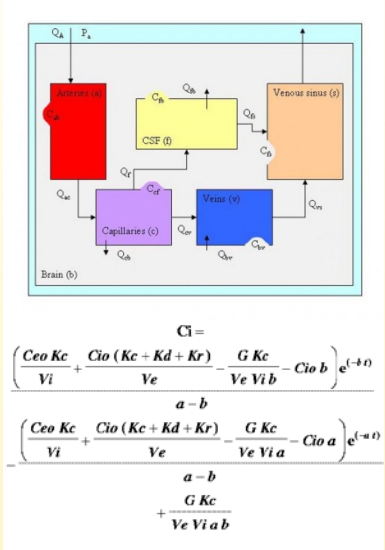
Back-up for questions

Pharmacometrics Facilitates Quantitative Extrapolation

Prior Knowledge from Adult Trials, Preclinical Data and Literature

- Adult Phase 1 Data (PK/PD, Intrinsic/Extrinsic PK/PD Effects)
- Adult Patient Data (Efficacy/Safety)
- Literature (Clinical & Pre-Clinical Data from Similar MoA)
- Pre-Clinical (Target/Disease Biology)

Pharmacometric Model



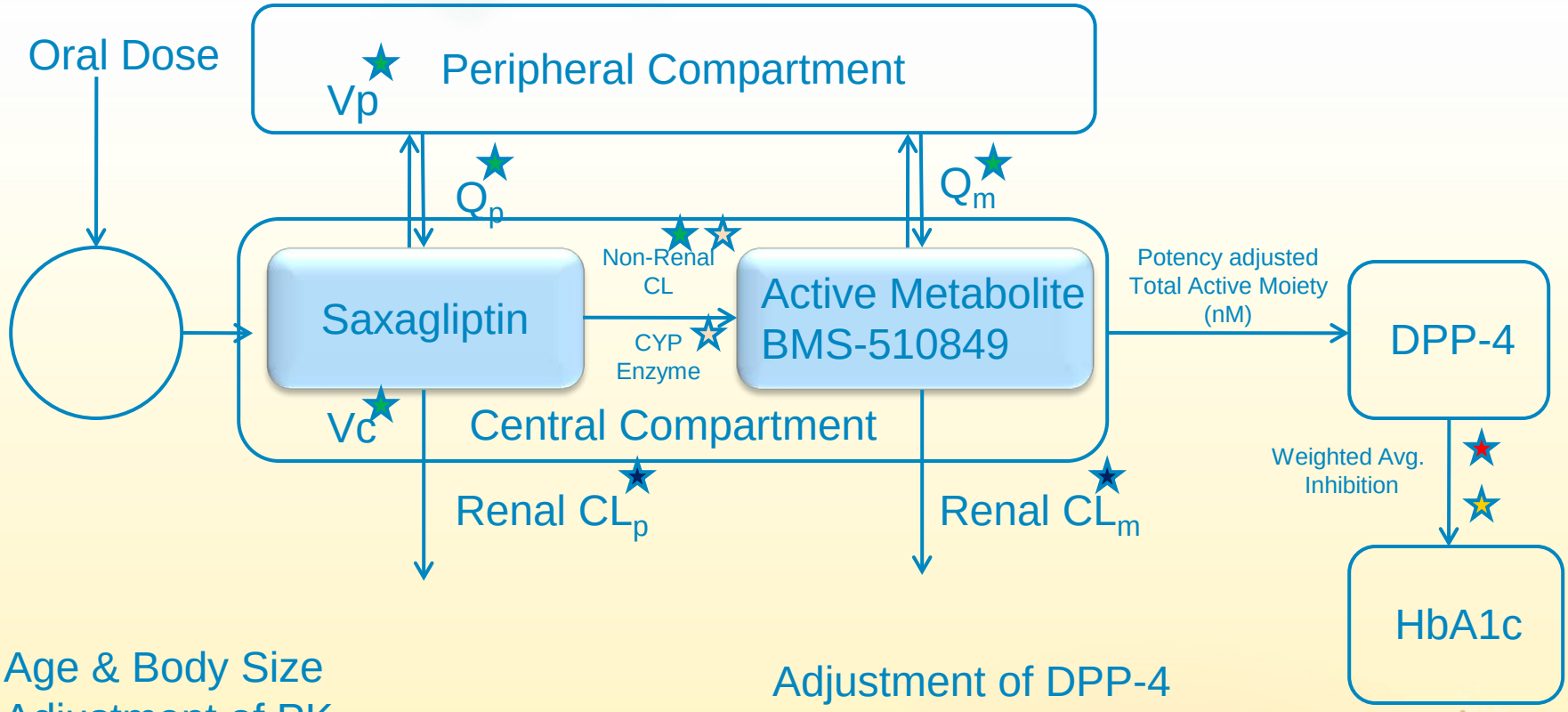
$$Ci = \frac{\left(\frac{Ceo\,Kc}{Vi} + \frac{Cio\,(Kc+Kd+Kr)}{Ve} - \frac{G\,Kc}{Ve\,Vi\,b} - Cio\,b\right)e^{(-b\,t)}}{a-b} - \frac{\left(\frac{Ceo\,Kc}{Vi} + \frac{Cio\,(Kc+Kd+Kr)}{Ve} - \frac{G\,Kc}{Ve\,Vi\,a} - Cio\,a\right)e^{(-a\,t)}}{a-b} + \frac{G\,Kc}{Ve\,Vi\,a\,b}$$

- **Quantitative Integration of Prior Evidence**
- **Hypothesis evaluation**
- **Extrapolation**

Pediatric Investigation

- ✓Dose selection
- ✓Biomarker selection
- ✓Sample size
- ✓Power
- ✓Inclusion/exclusion criteria

Extrapolation from Adult to Pediatric for Saxagliptin for Trial Simulation



Age & Body Size Adjustment of PK

- ★ $(WT/75)^{0.75}$
- ☆ $AGE^{0.83}/(0.31+AGE^{0.83})$
- ★ $(CrCL/82.8)^{1.28}$ ~Saxa, $(CrCL/82.8)^{0.44}$ ~Metabolite

Adjustment of DPP-4 PD for Age/Disease

- ★ ED_{50}
- ★ EMax

Application of Pharmacometric Model in Pediatric Trial Design

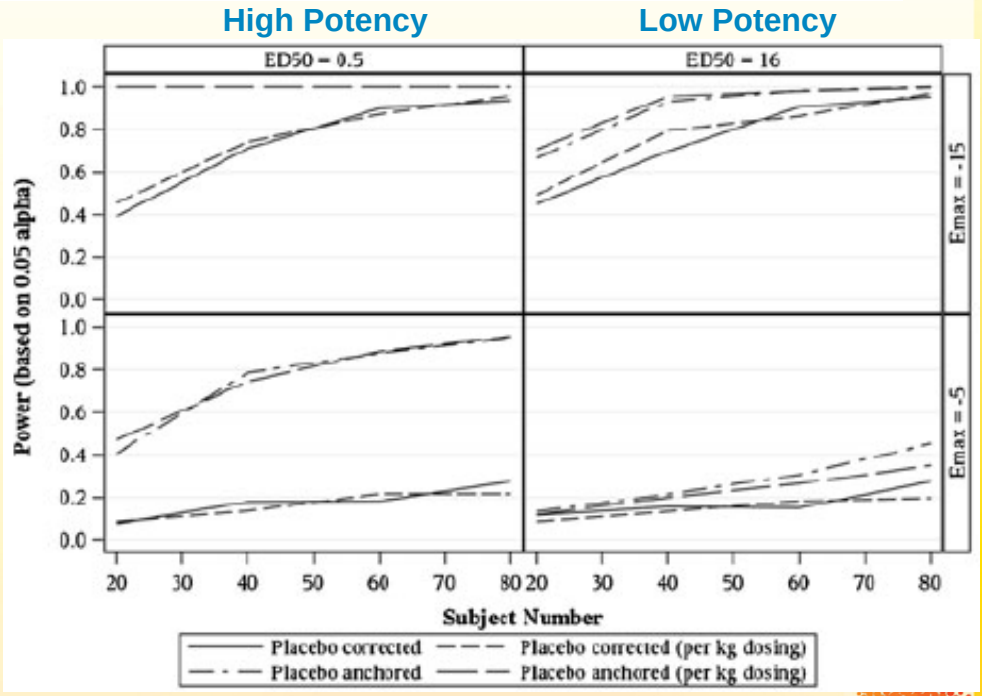
Improper Selection of a Pre-specified Primary Dose–Response Analysis Delays Regulatory Drug Approval

Jiang Liu,[1,2] Pravin Jadhav,[1] Yaning Wang,[1] and Jogarao Gobburu[1]

Exposure-response model for Candesartan and Metoprolol in pediatric subjects

$$E_i = \left(E_{Placebo} + \frac{E_{max} \times D_i' \times \left(\frac{Wt_i}{Wt_{ref}}\right)^{1-\lambda}}{ED_{50} + D_i' \times \left(\frac{Wt_i}{Wt_{ref}}\right)^{1-\lambda}} \right) + \varepsilon_i$$

Clinical Trial Simulation



Test different assumptions of drug potency/efficacy on power & sample size for a dose-response trial

AAPS J. 2013 Jan 10. [Epub ahead of print