Model Informed Drug Development: Is there a need to repaint the canvas?

Regulatory Perspectives

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Disclosures and Acknowledgements

- Disclosures
  - The views expressed in this presentation are that of the speaker and do not reflect the official policy of the FDA. No official endorsement by the FDA is intended nor should be inferred.

- Contributors to the ideas presented today
  - Division of Pharmacometrics
  - Office of Clinical Pharmacology
  - Ongoing thinking and evolving policy at CDER
  - Data presented is public – Reviews, Advisory Proceedings

Outline

I.   Regulation and Pharmacometrics at the FDA

II.   Current Status of Physiologically Based PK Models

III. Examples –

- EOP2A , Tapentadol

- Adalimumab – Ulcerative Colitis

- Dose Selection in Oncology

- Orphan Drugs – Pasireotide for Cushings' Disease

IV. Regulatory Submissions

The Concept of Drug Regulation and the Role Of FDA Continuously Evolves

- Societal expectations of regulators change each decade

- Science also evolves (complex molecules, Human efficacy trials)

- Broader initiatives such as FDA's Critical Path, Safety First, and Safe Use initiatives reflect recent changes

- *Entering an era of comparative effectiveness and greater individualization*

A New Approach is Needed for Drug Development and Drug Evaluation

- Incorporate new biomedical science into preclinical and clinical drug development to improve prediction and information yield
- Rapidly incorporate new science into evaluation of existing interventions
  - Targeting therapies: who benefits?
  - Biomarkers for drug toxicity: who is at risk?
  - Improve predictability in outcomes

  Improve the **value** of old and new drugs
  Improve the **success rate** of drug development

Drug Development and Evaluation

- 27 NMEs approved in 2013
  - Labeling
  - Approvability decisions
  - PMC/R negotiations

- ~ same number of "complete responses"/withdrawals
  - Unfavorable benefit-risk (supported by exposure-response analyses)
  - Sub-efficacious doses
  - Deficiency in bridging the clinical trial and to-be-marketed formulations
  - Lack of information on drug interaction potential
  - Improper dosing in specific populations

Original Investigation

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

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

The Questions Drive the Strategy For A Model Informed Analysis

- **NDA/BLA reviews**
- **IND reviews**
  - **Dose-Finding trials**
  - **Registration trials**
- **QT Reviews**
  - **Central QT team**
- **EOP2A**
- **Model-based drug development tool evaluation**
- **Research**
  - **Disease Models**
  - **Pediatrics**
  - **PBPK**
- **Knowledge Management**

- ➢ Merits of pursuing a pharmacological target
- ➢ Integration of knowledge and data and systematic reduction of uncertainty
- ➢ Assessment of benefit –risk : predictions in unstudied scenarios
- ➢ Generate a body of evidence that usually is supportive and sometimes primary support of effectiveness

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- Target Concentration and Therapeutic Window
- Dose Selection and Justification
- Dose Optimization in Specific Populations
- Clinical Trial Design

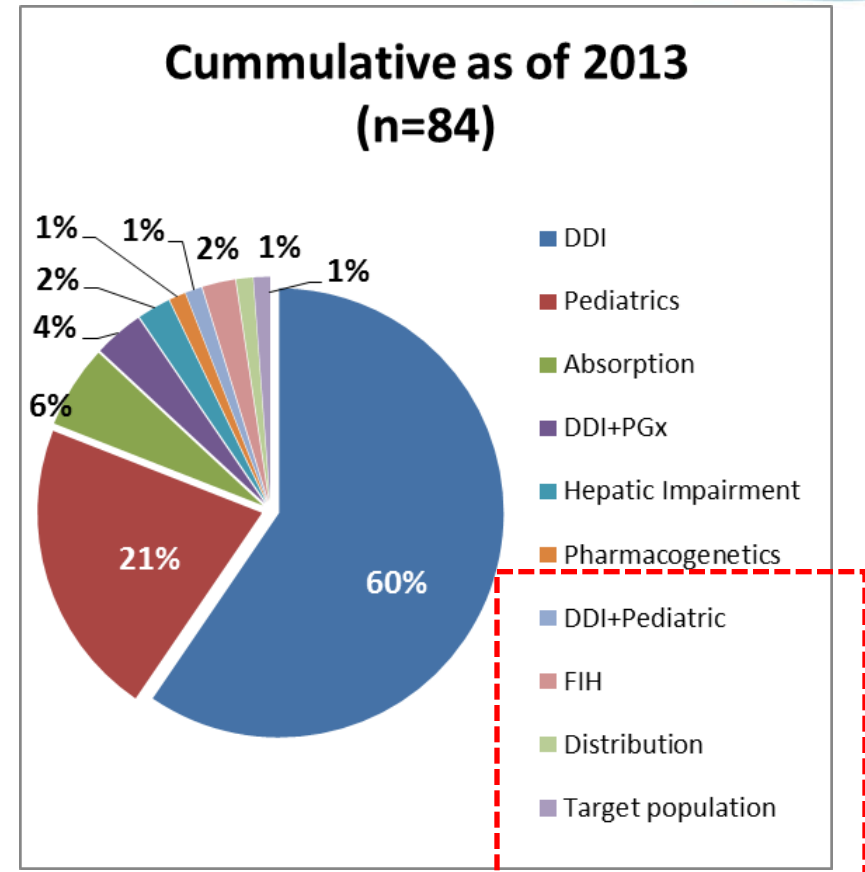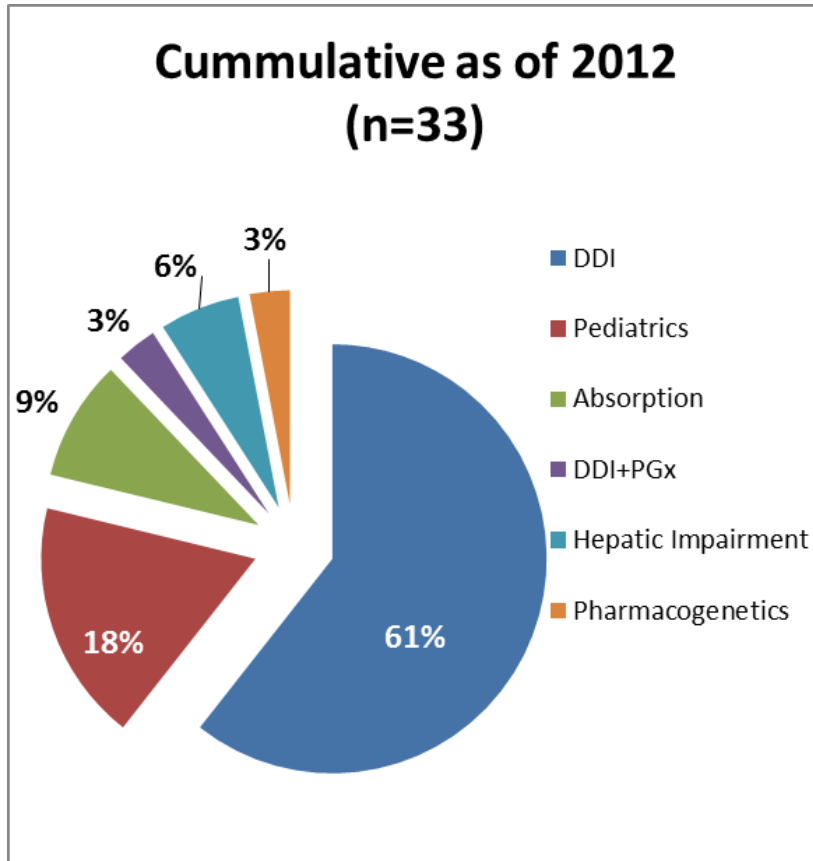March 10, 2014
White Oak, Maryland

FDA Public Workshop

Application of Physiologically-based Pharmacokinetic (PBPK) Modeling to Support Dose Selection

Innovative Approaches to Pediatric Drug Development and Pediatric Medical Counter Measures (MCM): A Role for Physiologically-Based PK?

Monday, May 5, 2014
FDA White Oak

By Sponsors, How is PBPK Being Utilized?

Cummulative as of 2012 (n=33)

- DDI — 61%
- Pediatrics — 18%
- Absorption — 9%
- DDI+PGx — 3%
- Hepatic Impairment — 6%
- Pharmacogenetics — 3%

Huang et al, J Pharm Sci, 2013

Cummulative as of 2013 (n=84)

- DDI — 60%
- Pediatrics — 21%
- Absorption — 6%
- DDI+PGx — 4%
- Hepatic Impairment — 2%
- Pharmacogenetics — 1%
- DDI+Pediatric — 1%
- FIH — 2%
- Distribution — 1%
- Target population — 1%

Pan, ASCPT Annual Meeting, 2014, Atlanta, GA

- **Increased use of PBPK by drug developers**
- **Majority of the cases were related to drug-drug interactions (~ 60%); pediatrics ranks the second**

PBPK applications: Current status

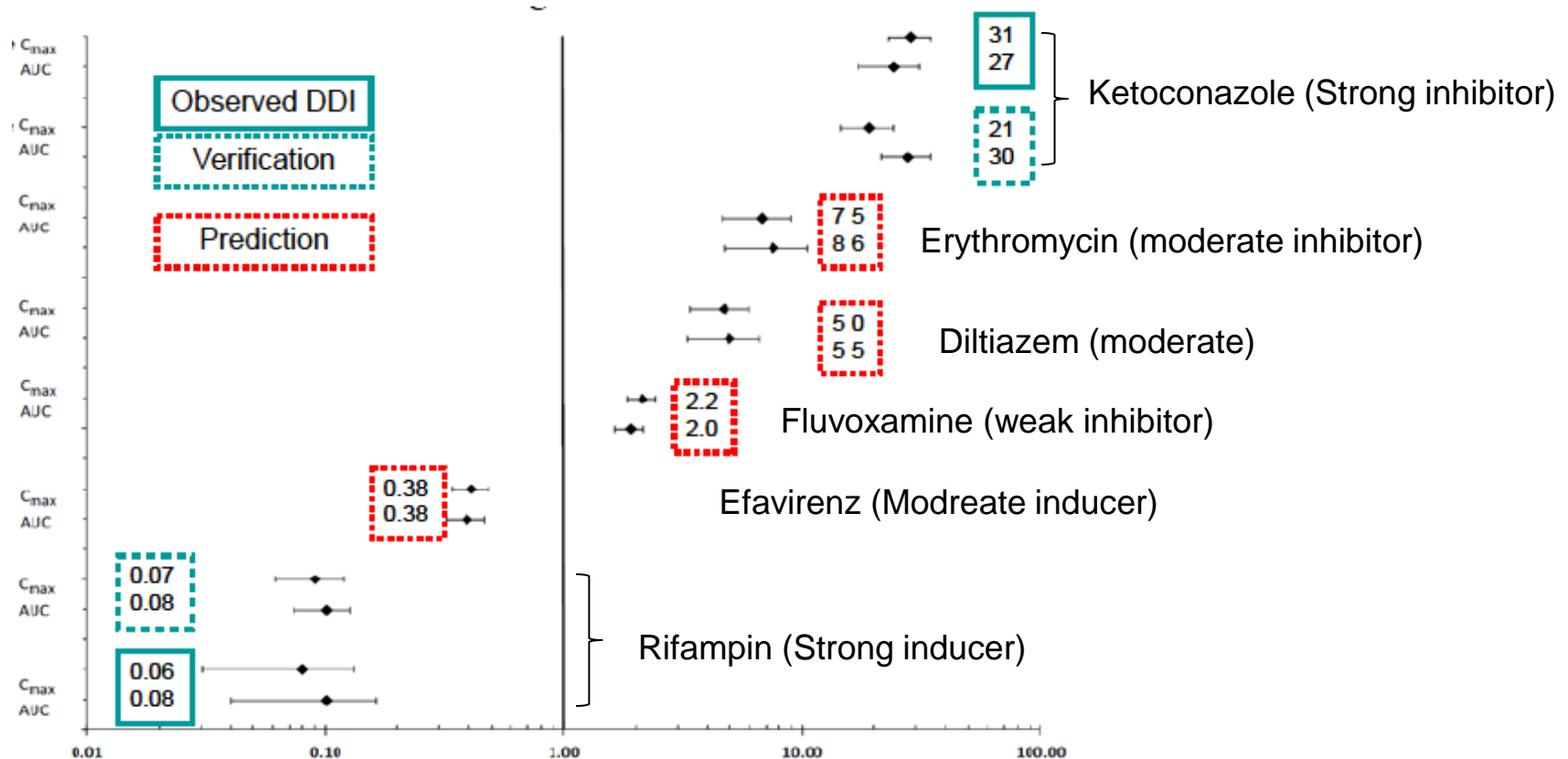| Applications		Status
Drug-drug Intearctions	*Drug as enzyme substrate*	• *Substrate/inhibitor models verified with key clinical data can be used to simulate untested scenarios and support labeling*
	Drug as enzyme perpetrator	• *Use to confirm the lack of enzyme inhibition* • *Additional evidence needed to confirm predictive performance for positive interactions*
	Transporter-based	• *In vitro-in vivo extrapolation not mature due to lack of information,* • *Complicated by transporter-enzyme interplay* • *Predictive performance yet to be demonstrated*
Specific populations	*Organ impairments (hepatic and renal)*	• *Predictive performance yet to be improved* • *System component needs more information*
	Pediatrics	• *Allometry is reasonable for PK down to 2 years old* • *Less than 2 years old ontogeny and maturation need to be considered*
Additional specific populations and situations	**Pregnancy, ethnicity, geriatrics, obesity, disease states** **Food effect, formulation change, PH effect (including DDIs on gastric pH)** **Tissue concentration**	• *Yet to be determined*

PBPK: FDA review of ibrutinib

❑ Predominantly metabolized by CYP3A

❑ Clinical drug interaction studies:

- *With strong CYP3A inhibitor ketoconazole: AUC increased by 24-fold*

- *With strong CYP3A inducer rifampin: AUC decreased by 90%*

What are exposure changes by other CYP3A inhibitors or inducers?

How do we manage this if patients have to take CYP3A inhibitors or inducers?

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205552Orig1s000ClinPharmR.pdf

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

PBPK-Simulated and observed Cmax and AUC ratios (mean and 95% confidence interval)

Ibrutinib: Package Insert

What are exposure changes by other CYP3A inhibitors or inducers?

How do we manage this if patients have to take 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"

Section 2.4: "…strong CYP3A inhibitors which would be taken chronically…is not recommended. For short-term use (treatment for 7 days or less) of strong CYP3A inhibitors (e.g., antifungals and antibiotics) consider interrupting IMBRUVICA therapy until the CYP3A inhibitor is no longer needed…Reduce IMBRUVICA dose to 140 mg if a moderate CYP3A inhibitor must be used…Patients taking concomitant strong or moderate CYP3A inhibitors should be monitored more closely for signs of IMBRUVICA toxicity."

And more in Section 7…

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

Adalimumab

- Adalimumab is the third TNF inhibitor to be approved in the United States.

- It binds to Tumor necrosis factor-alpha (TNFα), preventing it from activating TNF receptors and was constructed from a fully human monoclonal antibody

- TNFα inactivation has proven to be important in down regulating the inflammatory reactions associated with autoimmune diseases.

➢ Problem
  – No adequate Phase 2 dose ranging studies conducted to establish dose of adalimumab for the treatment of ulcerative colitis

  – At a pre-Phase 3 meeting for the UC indication, the FDA expressed concern about proceeding with the same dosing regimen as approved for Crohn's disease.

  ➢ Modest but statistically significant effect (16.5% remission rate for adalimumab compared to 9.3% for placebo) for the induction of clinical remission in the registration trial.

Adalimumab: Higher Induction Dose For Ulcerative Colitis
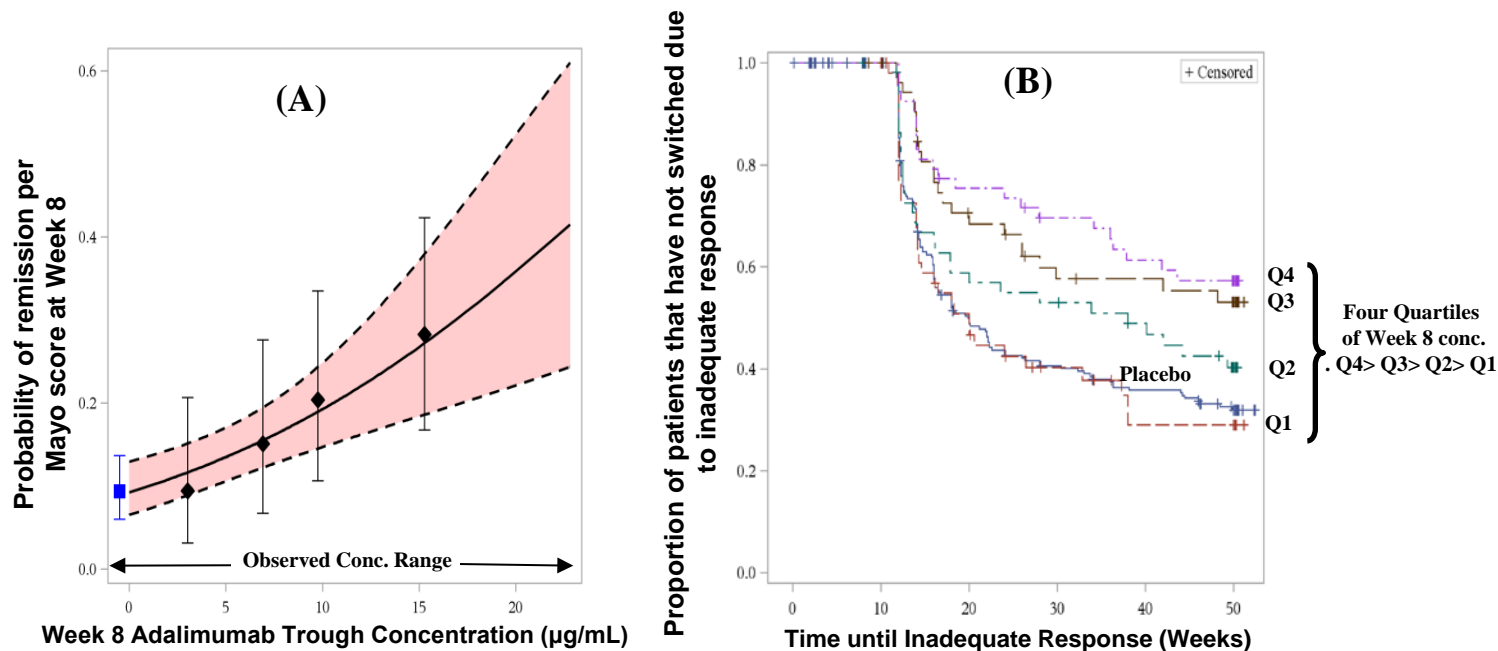
> Trend of increasing remission rate with increasing adalimumab concentrations

> Patients with lower concentrations in the induction phase exhibited inadequate response earlier.

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Dose Selection in Oncology

- Early Drug development
  - Identify optimal concentrations (IC_{50}, IC_{90}) for target effects
  - Determine correlation of human PK to
    - in vivo biomarker
    - in vitro target concentrations
- Phase 2 Development
  - Adaptive design to explore more than one dose
    - Optimal biologic dose
    - Near MTD dose
    - Collect PK and evaluate exposure activity and safety relationships
- Phase 3 Development
  - Sparse PK samples in all patients
    - Evaluate relationships between covariates influencing exposure and key clinical outcome
    - Develop rationale for dose escalation or reduction for approval and labeling
- Post-Marketing Trials
  - Refine dose if not optimized during development (difficult to do)
  - Sparse PK sampling in all patients
    - Evaluate relationships between exposure and **long term toxicity**

Courtesy – Dr. Rahman, FOCR, 2013

Cabozantinib (Progressive Metastatic Medullary Thyroid Cancer)

- Inhibits multiple kinases
- Dosing regimen: Start at 140 mg QD with reduction to 100 mg and then 60 mg based on tolerability
- 140 mg is the MTD
- Substantial proportion of patients had dose modifications in the pivotal trial
    - PPE (Palmar-plantar erythrodysaesthesia syndrome)
    - Diarrhea
    - Fatigue

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203756Orig1s000ClinPharmR.pdf
Presented at ASCO meeting (2013)

Higher Exposure Associated with Earlier Dose Modifications

Starting dose (140 mg)

– No dose change before first dose modification

- Multivariate Cox model identified initial AUC as a significant covariate (p<0.0001) for prediction of time to the first dose modification

    – Hazard ratio: 1.95, 95% CI [1.47-2.59]*

    * Adjusted for age, sex, body size, smoking status, Asian status, and ECOG performance

Regulatory Decision

- Post marketing requirement to study lower doses

  - Clinical dose led to ~ 80% dose reduction and 69% patients suffered grade 3 or 4 toxicities in the registration trial

  - Lower exposure does not appear to be associated with shorter PFS

  - Higher exposure was associated with earlier dose modification

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203756Orig1s000Approv.pdf

Challenges in Orphan Drug Development

- Small number of patients
- Many rare diseases are serious and life-threatening
- Lack of regulatory precedence/established endpoints
- Novel products
- Many diseases primarily affect pediatric patients
- Logistical trial challenges
- Heterogeneity in disease pathology

Cushing's Disease (Pasireotide)

- Orphan disease: ~ 17, 000 patients in the US
- Due to ACTH secreting pituitary adenoma
  - Stimulates cortisol Production
- Clinical signs/symptoms
  - Moon face
  - Central fat deposits
  - Muscle weakness
  - Infections
  - **Hyperglycemia**
  - Hypertension

- Mean of 24 hr Urinary Free Cortisol (mUFC) (unit: nmol/day)
  - High intra-subject variability
  - Average of four 24 hr UFC measurements

- Treatment target: Reduce cortisol level < 145 nmol/day (ULN: Upper Limit of Normal)

Efficacy Results

- **Pre-specified criterion of success (primary efficacy endpoint)**: The lower limit of the 95% CI of proportion of responder within treatment arm> **15.0%**

- Pivotal trial result demonstrated that 900 ug met the pre-specified primary endpoint.

  - 900 ug BID: 21/80, 26.3% (**16.6**, 35.9)
  - 600 ug BID:12/82, 14.6% (**7.0**, 22.3)
   **600 ug failed to meet the pre-specified primary efficacy endpoint**

Can 600 ug be Approved as Starting Dose?

- Stringent criterion for success: The lower limit of the 95% CI of proportion of responder within dose arm > **15.0%**

  - No statistical comparison between two dose arms

- 50% higher baseline mUFC in 600 ug arm than 900 ug arm

- Remarkable hyperglycemic effects on treatment (1.4% mean absolute change of HbA1c levels):

  - Hyperglycemia: 38% in 600 ug BID vs 43% in 900 ug BID

- Substantial overlap in exposure between two doses (600 ug and 900 ug BID)

  - High inter-individual PK variability

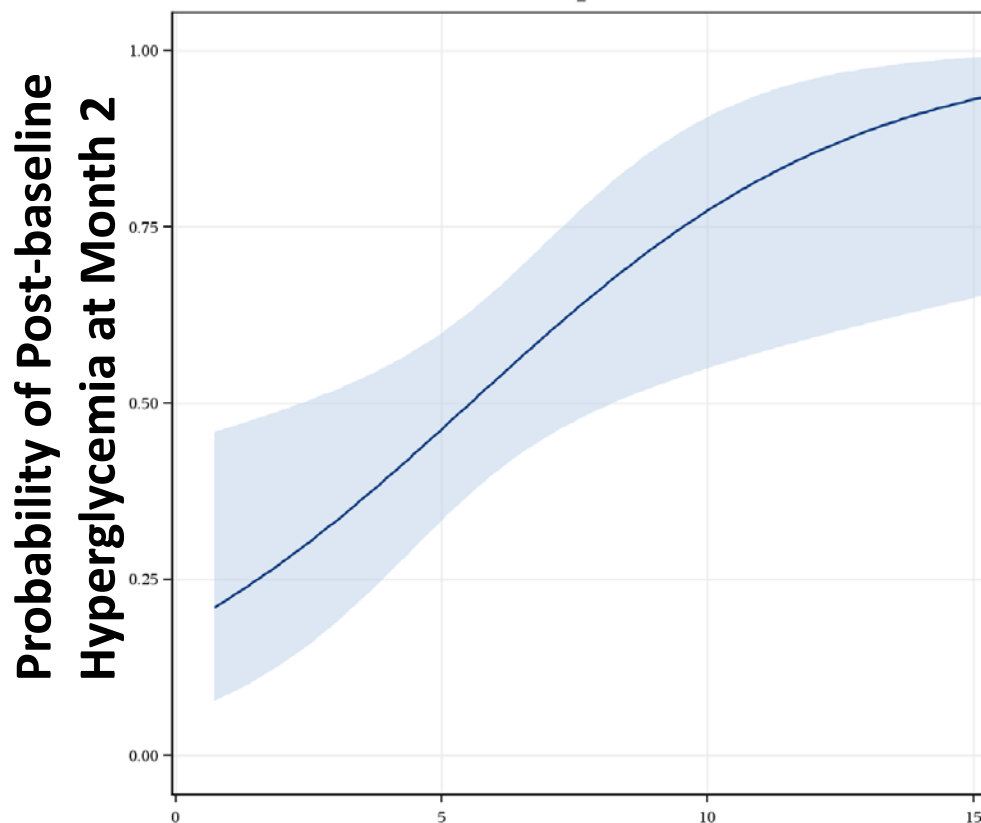**Can E-R analysis provide additional insight on dose selection?**

Flat E-R Relationship for Efficacy after Adjusting for Baseline mUFC (Multivariate analysis)

At BLUFC=828.4
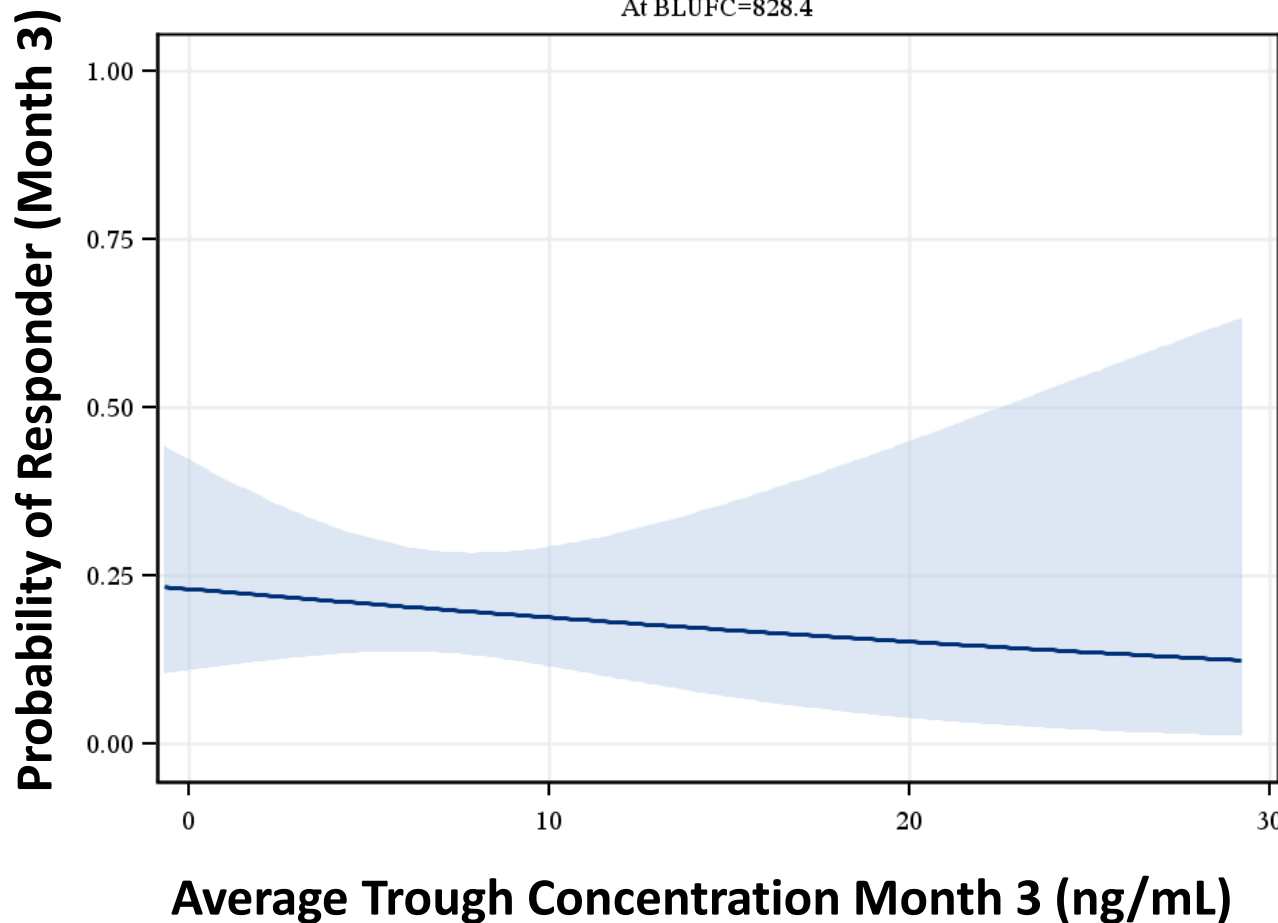
Starting dose (600 ug vs 900 ug): similiar in efficacy

Significant E-R Relationship for Safety (hyperglycemia) in Patients with normal baseline HbA1c

At BLVAL_1N=5.246

Post-baseline hyperglycemia: >1% HbA1c increase from baseline

**Starting dose:
600 ug is better than 900 ug in safety
Sponsor proposed: 900 ug
FDA approved: 600 ug or 900**

Average Trough Concentration at Month 2 (ng/mL)

Probability of Post-baseline Hyperglycemia at Month 2

Regulatory Decision

- Dose optimization-Approval of both 600 and 900ug as starting dose
  - Supported the approval of a starting dose that failed to meet pre-specified primary efficacy endpoint
    - 600 ug vs 900 ug: better safety, comparable efficacy
      - Flat E-R relationship for efficacy
      - Significant E-R relationship for hyperglycemia
  - 900ug remains an option
- Review provided supportive evidence (E-R for hyperglycemia) for the PMR of a "long-term prospective observational cohort study"

Pharmacometrics in Regulatory Submissions: IND Phase

- Typical mode of information is *via* briefing documents
- EOP 2A – Submission of datasets, codes, model files
- EOP2 is a critical meeting (typically other issues predominate) – **Dose Justification**
- Early interaction is encouraged to be prospective and deliberative in using model based approaches

- Wide variance in type and content of information
- Range from "is a model or plan adequate?" to " do you agree with selected dose ?". There should be a drive to type of decisions being made and then discuss models.
- Quality and clarity of graphics, result presentation is varied and often models are not contextualized with the key development questions.
- If models are the sole basis of decisions then, presentation of results and inferences are critical:
- ➢ Review cycles are short, we get limited time to review and make recommendations for such meetings
- ➢ Specifically ask for participation from the Division of Pharmacometrics

Pharmacometrics in Regulatory Submissions: NDA/BLAs (1 of 2)

❑ Population pharmacokinetics is routine in most applications (exceptions are rare diseases, small subject numbers)

o The goal of population PK should be to link exposure to response (analysis)

o Typically used to rule out covariates (no dose adjustments) and if a clinically significant covariate is identified, dose adjustment is made based on "matching" exposures to a "normal" population

o Consider using models to provide additional information – missed doses, alternative dosing regimens

o Model based analysis is supportive if the decision can be made from other sources/observations.

➢ Design of sparse sampling should be adequate to estimate parameters. If a subset is being sampled, it should be representative of the overall population (outcomes, incidence risk)

Pharmacometrics in Regulatory Submissions: NDA/BLAs (2 of 2)

❑ Exposure-Response (ER)

o Exposure-QT is done for all submissions.

o E-R for efficacy and safety – must be considered to support the dose for Phase 3 trials and for approval for submissions

o Context of analysis (differentiate extent done for internal decision making vs. regulatory decision making)

o Leverage E-R analysis (time course) to support approval of a lower dose or unstudied regimens (alternate titration designs) if tolerability and safety profiles can be improved.

o We expect comprehensive ER analysis for pediatric submissions as an approach to inform dosing and study design considerations.

o Relate ER to other parts of the submission- ER should corroborate and explain dose response (variability in response)

Thank you !