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Pediatric Extrapolation:
Little by Little Becomes a Lot

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Pediatric Extrapolation: Little by Little Becomes a Lot

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- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA

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Outline

- Background and History
- Current Thinking
- Case Examples

U.S. Evidentiary Standard for Approval

- For approval, pediatric product development is held to same evidentiary standard as adult product development:
- A product approved for children must:
  - Demonstrate substantial evidence of effectiveness/clinical benefit (21CFR 314.50)
  - Clinical benefit:
    - The impact of treatment on how patient feels, functions or survives
    - Improvement or delay in progression of clinically meaningful aspects of the disease
- Evidence of effectiveness [section 351 of PHS Act, 505(b)(1) of the FD&C Act]
  - Evidence consisting of adequate and well-controlled investigations on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports to have under the conditions of use prescribed, recommended, or suggested in the labeling
- Adequate safety information must be included in the application to allow for appropriate risk benefit analysis [FD&C 505(d)(1)]

Special Considerations for Pediatric Product Development

- Ethical considerations
  - Children should only be enrolled in a clinical trial if the scientific and/or public health objectives cannot be met through enrolling subjects who can provide informed consent personally (i.e., adults)
  - Absent a prospect of direct therapeutic benefit, the risks to which a child would be exposed in a clinical trial must be “low”
  - Children should not be placed at a disadvantage after being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary health care
  - Ethical considerations do play a role in the need to correctly apply pediatric extrapolation
- Feasibility considerations
  - The prevalence and/or incidence of a condition is generally much lower compared to adult populations
  - Feasibility, by itself, is not a scientific justification for use of extrapolation

Pediatric Extrapolation

- 1994: Final Regulation: Pediatric Labeling Rule
- "A pediatric use statement may also be based on adequate and well-controlled studies in adults, provided that the agency concludes that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dosage, and additional pediatric safety information must also be submitted"
- Efficacy may be extrapolated from adequate and well-controlled studies in adults to pediatric patients if:
  - The course of the disease is sufficiently similar
  - The response to therapy is sufficiently similar
- Dosing cannot be fully extrapolated
- Safety cannot be fully extrapolated

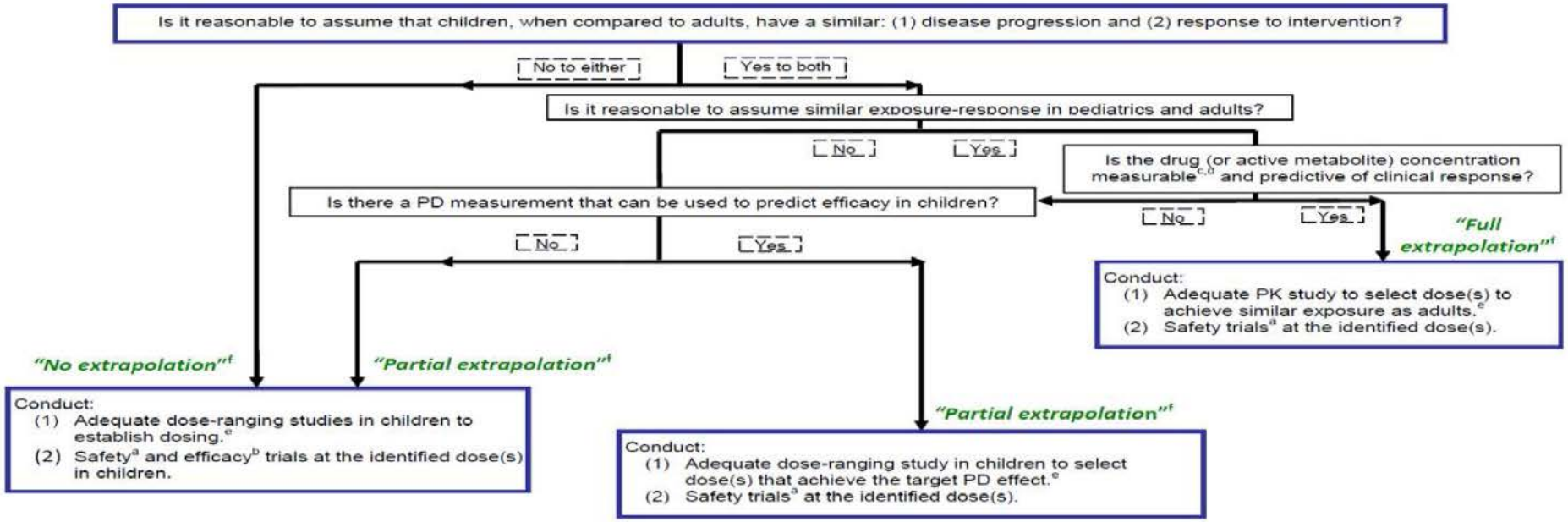
A Brief History

Early 1990's	• Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children
1994	• FDA Pediatric Labeling rule
1997	• FDAMA: First incentives for Pediatric Studies
2000	• ICH E11: Investigation of Medicinal Products in Pediatric Populations
2002	• BPCA: Legislative Incentives for Pediatric Studies
2003	• PREA : Legislative Requirements for Pediatric Studies • Extrapolation Algorithm appeared in FDA Guidance
2007	• Pediatric Regulation (EMA)

A Brief History

2011	• Dunne et al, Extrapolation of Adult Data and Other Data in Pediatric Drug Development Programs
2013	• Milligan, P.A. et al Model-based drug development: a rational approach to efficiently accelerate drug development. Clin. Pharmacol. Ther. 93, 502–514 (2013)
2014	• FDA Guidance: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products (CDER)
2015	• FDA Guidance: Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices (CDRH/CBER)
August, 2017	• ICH E11(R1) adopted Clinical Investigation of Medicinal Products in the Pediatric Population
October, 2017	• EMA Reflection Paper Pediatric Extrapolation
October, 2017	• ICH E11A Pediatric Extrapolation Expert Working Group Formed

Pediatric Study Planning & Extrapolation Algorithm



Footnotes:

a. For locally active drugs, includes plasma PK at the identified dose(s) as part of safety assessment.
b. For partial extrapolation, one efficacy trial may be sufficient.
c. For drugs that are systemically active, the relevant measure is systemic concentration.
d. For drugs that are locally active (e.g., intra-luminal or mucosal site of action), the relevant measure is systemic concentration only if it can be reasonably assumed that systemic concentrations are a reflection of the concentrations at the relevant biospace (e.g., skin, intestinal mucosa, nasal passages, lung).
e. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.
f. For a discussion of no, partial and full extrapolation, see Dunne J, Rodriguez WJ, Murphy MD, et al. "Extrapolation of adult data and other data in pediatric drug-development programs." Pediatrics. 2011 Nov;128(5):e1242-9.

FDA Draft Guidance: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, December 2014

EMA Reflection Paper

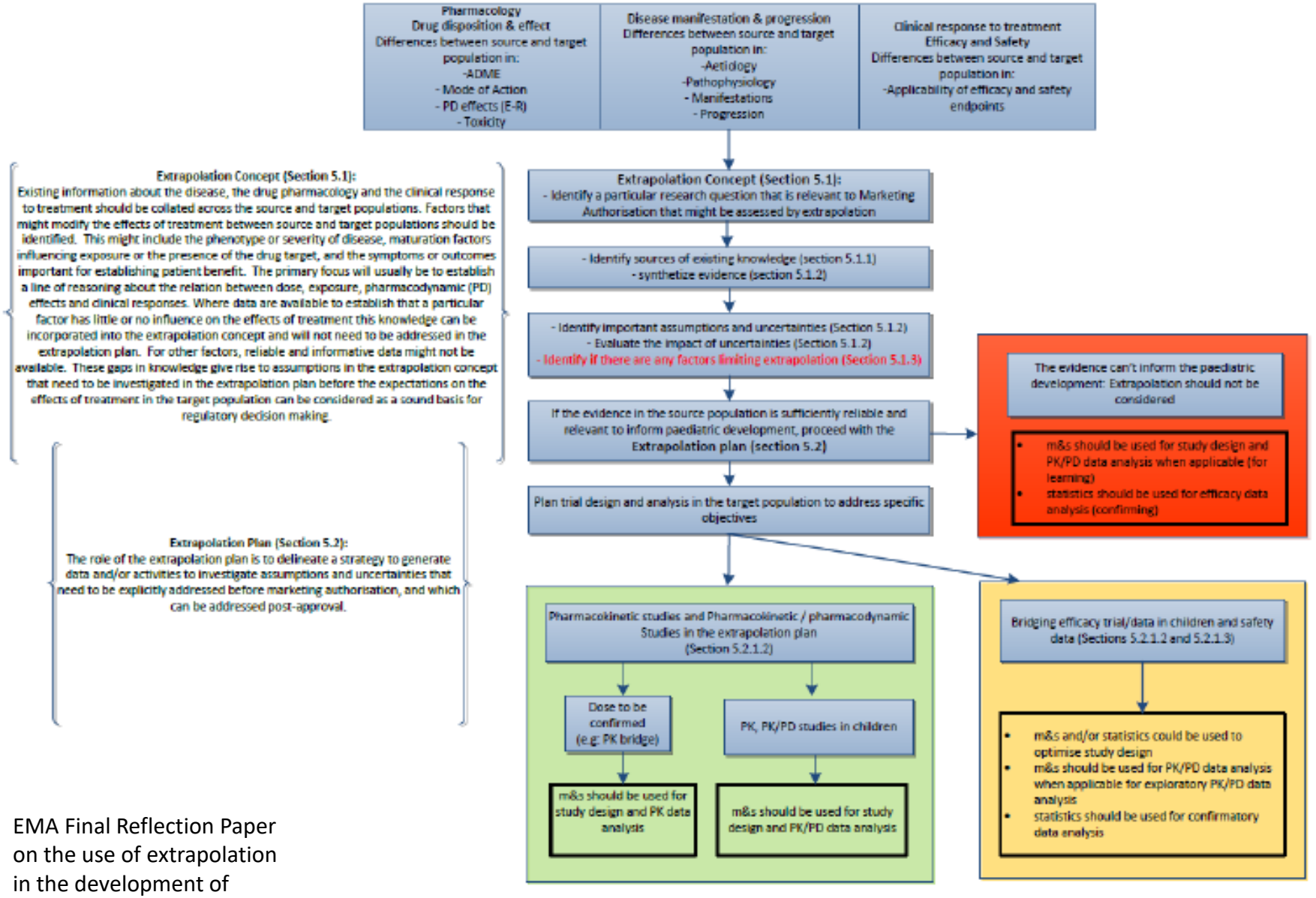
- Published as draft in October 2017 and Finalized October 2018
- Addresses the use of quantitative methods to help assess the relevance of existing information in a source population to one or more target population(s)
  - Extrapolation Concept
  - Intended to identify gaps in knowledge
  - Strength of evidence available
- Address gaps in knowledge and assumptions, so that the totality of available evidence can address the scientific questions of interest for marketing authorisation in the target population
  - Extrapolation Plan
  - Studies to be conducted/Information to be collected to address gaps in knowledge
- Validation of the Extrapolation Concept and Mitigation of Risks associated with Extrapolation
- Does not discuss “categories” of extrapolation (i.e., full or partial extrapolation)

Extrapolation framework table

			Pharmacology Drug disposition & effect	Disease manifestation & progression	Clinical response to treatment Efficacy & safety
SOURCE POULATION Adults and/or paediatric	Extrapolation concept	Mechanisms	Age-related differences in - ADME - mode of action - PD effects (E-R) - toxicity	- Age-related differences in - aetiology - pathophysiology - manifestation - progression - indicators	Age-related - differences, - applicability, - validation of efficacy & safety endpoints
		Quantitative evidence	PB-PK/PD models Pop-PK/PD models Covariates: - age, maturation, etc - disease, comorbidity,	Quantitative synthesis of natural disease data Disease progression models Covariates: - age - disease types, severity - comorbidity	Quantitative synthesis or meta-analysis of treatment data Disease response models Covariates: - age - disease types, severity - comorbidity
			➢ existing data ➢ progressive input of emerging data		
TARGET POPULATION Children, different paediatric subgroups		Prediction	Predict doses to achieve - similar exposure, or - similar PD effect, and - acceptable safety per paediatric subgroup	Describe/predict differences in natural course of disease progression by paediatric subgroup	Given similar drug exposure or PD response, predict degree of differences in - efficacy - safety - benefit-risk balance by paediatric subgroup
			➢ refine predictions using emerging data		
	Extrapolation plan		PK studies or PK/PD studies needed for confirmation of doses in target population	Epidemiological data - natural disease course - SOC treatment in target population	- Design of clinical studies - Sample size(s) required in target population to conclude on benefit-risk balance
	Validation & Extrapolation		Validate - modelling approaches - modelling assumptions - confirm predicted differences in PK and PD Establish appropriate doses in the target population	Confirm predicted differences in disease progression Conclude on disease progression in target population	Confirm predicted differences in clinical response Conclude on positive benefit-risk in target population
			➢ alternatively, adapt extrapolation concept and plan		
	Further validation		PK/PD data from - phase III trials - post MA studies	Epidemiological data Other drug developments	Post MA studies Prospective meta-analyses Pharmacoepidemiological data Other drug developments

EMA Reflection paper on the use of extrapolation in the development of medicines for paediatrics, October, 2017

EMA Decision Process for Extrapolation



EMA Final Reflection Paper on the use of extrapolation in the development of medicines for paediatrics, October, 2018

Extrapolation in Pediatric Medical Devices

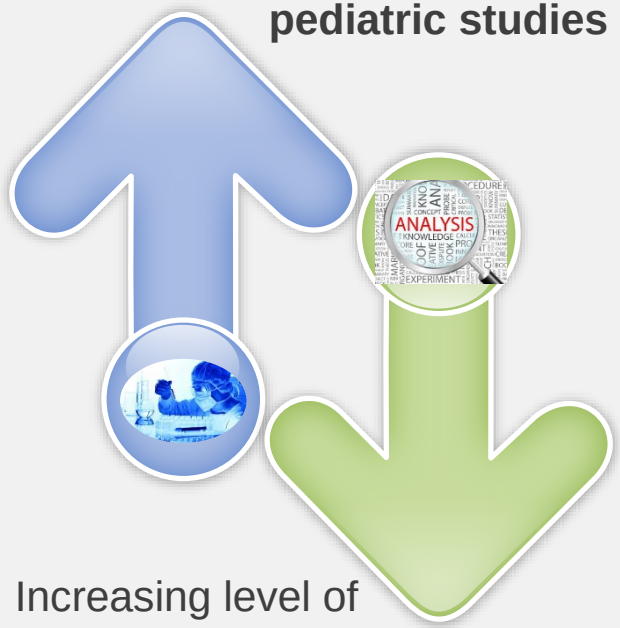
- Guidance published "Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices"
  - Draft published 2015; final guidance published 2016
  - https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm444591.pdf
- Medical device approval regulations different from drug approval regulations
- Introduces Bayesian concept of borrowing from one population or data set (e.g., prior adult information) to come to a posterior conclusion about another population (e.g., pediatric effectiveness or safety)

ICH E11(A): Pediatric Extrapolation

- Recently finalized E11(R1) Addendum recognized the need for more detailed ICH guidance on Pediatric Extrapolation
- Concept Paper finalized in October 2017
- Expert Working Group assembled
  - Global Regulatory Authorities and Drug Development Organizations
- Align terminology
- Systematic approach to use pediatric extrapolation
- Study designs, statistical methodologies, and Modeling and Simulation strategies that can be considered

Extrapolation approaches in pediatric programs

Increasing level of **evidence required from pediatric studies**



Increasing level of **confidence in similarity of disease/response**

~60% Pediatric Programs
require at least 1 adequate, well-controlled efficacy trial (clinical or surrogate endpoint)

1 or more adequate-well controlled studies powered on a clinically meaningful endpoint
Bipolar disorder, systemic juvenile idiopathic arthritis, major depression, migraine, polyarticular JIA (pJIA), bronchopulmonary dysplasia, ADHD, nausea/vomiting, partial seizures (<4 y/o), respiratory syncytial virus, prophylaxis of venous thromboembolism, atopic dermatitis, etc.

1 or more adequate-well controlled studies powered on a surrogate endpoint
Diabetes, anemia, idiopathic thrombocytopenia, treatment of venous thromboembolism, hypertension, hypercholesterolemia, asthma, etc.

Controlled study without formal statistical power
Community acquired pneumonia, nosocomial infections, skin and skin structure infections, etc.

Descriptive efficacy study without concurrent control
Plaque psoriasis, Neurogenic detrusor over-activity, pJIA (NSAIDs), etc.

Small dose-ranging studies (randomization to multiple dose levels)
Sedation, ulcerative colitis, Crohn's, etc.

Small PK/PD studies (single dose level matching adult exposures)
HIV, erosive esophagitis (infants), anesthetics, pulmonary arterial hypertension,

PK/safety only (single dose level matching adult exposures)
gastroesophageal reflux disease, bacterial sinusitis, herpes simplex, analgesics/anesthetics (well known MOAs; over 2 y/o), imaging products, melanoma (adolescents)

List partially adapted from Dunne et al. *Pediatrics* 2011

Assessment of Disease Similarity and Response to Intervention

- The assessment is not a simple “yes or no”
- Quantitative assessment of differences between target and source population
  - Evidence of common pathophysiology, natural history
  - Similarity in response as assessed by similar endpoints, mode of action, or biological pathway, experience with drugs in the same therapeutic class
- What assumptions or uncertainties exist in this assessment
  - Quantity of evidence
  - Quality of evidence
- Degree of confidence in similarity will affect the information that will need to be collected to support efficacy

Extrapolation and Bayesian Approaches

- Bayesian Approach Applied to Pediatric Trials
  - Make use of, or borrow, prior information in pediatric trials
  - Provides a formal approach for incorporating prior information into the planning and the analysis of the next study
- Clinical input on whether prior information is reliable
- Similarity
  - Population
    - Baseline characteristics and demographic information
  - Disease progression
    - Baseline disease characteristics
    - Placebo information
  - Treatment effect (both disease and MOA)
    - Treatment group information
- Uncertainty regarding the validity of prior information can be accounted for in Bayesian statistical modeling
- Sometimes Bayesian modeling will allow for few patients in a clinical trial but not always

Approaches Pediatric Trial Design

- Trial should be designed to fill gaps in knowledge
  - Amount of information needed will be based on the confidence in assumptions about disease similarity and response to intervention
- Modeling and Simulation
- Innovative Statistical Analyses including Bayesian Approaches
  - Make use of, or borrow, existing information to increase efficiency of pediatric drug development
- Confidence in both of these approaches depends on multiple factors
  - Quality and quantity of data used
  - Accuracy of assumptions made
- Availability of pediatric-specific biomarkers and endpoints may also affect clinical trial design
- Availability of patients, existing therapies, and operational issues may also affect trial design

Extrapolation of Efficacy:

Disease/response "similarity" is a continuum

Different	Dissimilar	Similar	Same
No overlap between adult and pediatric condition	Some degree of overlap with significant differences between adult and pediatric condition	Large degree of overlap with some differences between adult and pediatric condition	Significant overlap; no known significant differences between adult and pediatric condition

Increasing relevance of adult information to pediatric population with increasing confidence in similarity between adult and pediatric condition

Pediatric RCT(s)

Pharmacodynamic markers, Bayesian methodologies, etc.

Exposure matching

Recent Case Examples

- Pediatric Schizophrenia
  - Use of modeling to evaluate disease similarity between adult and pediatric populations
- Pediatric Heart Failure
  - Use of pharmacodynamic marker to bridge efficacy between adult and pediatric populations
- Systemic Lupus Erythematosis
  - Use of novel statistical approach to leverage adult efficacy information

Schizophrenia

- Clinical Presentation
  - Peak age at onset is early to mid-20s for males and late-20s for females; onset below age 13 is very rare
  - Estimated prevalence 0.04% for <13 years, 0.5% for age 13-17 years, and 0.5-1% for adults
- Disease Similarity
  - Symptomatology similar between adult and adolescent schizophrenia
  - Same DSM-5 diagnostic criteria
- Uncertainties:
  - Earlier age of onset predictor of worse prognosis - schizophrenia with adolescent onset may represent more severe form of illness

- Qualitative assessment is often general approach to establishing disease similarity

A Quantitative Justification of Similarity in Placebo Response Between Adults and Adolescents With Acute Exacerbation of Schizophrenia in Clinical Trials

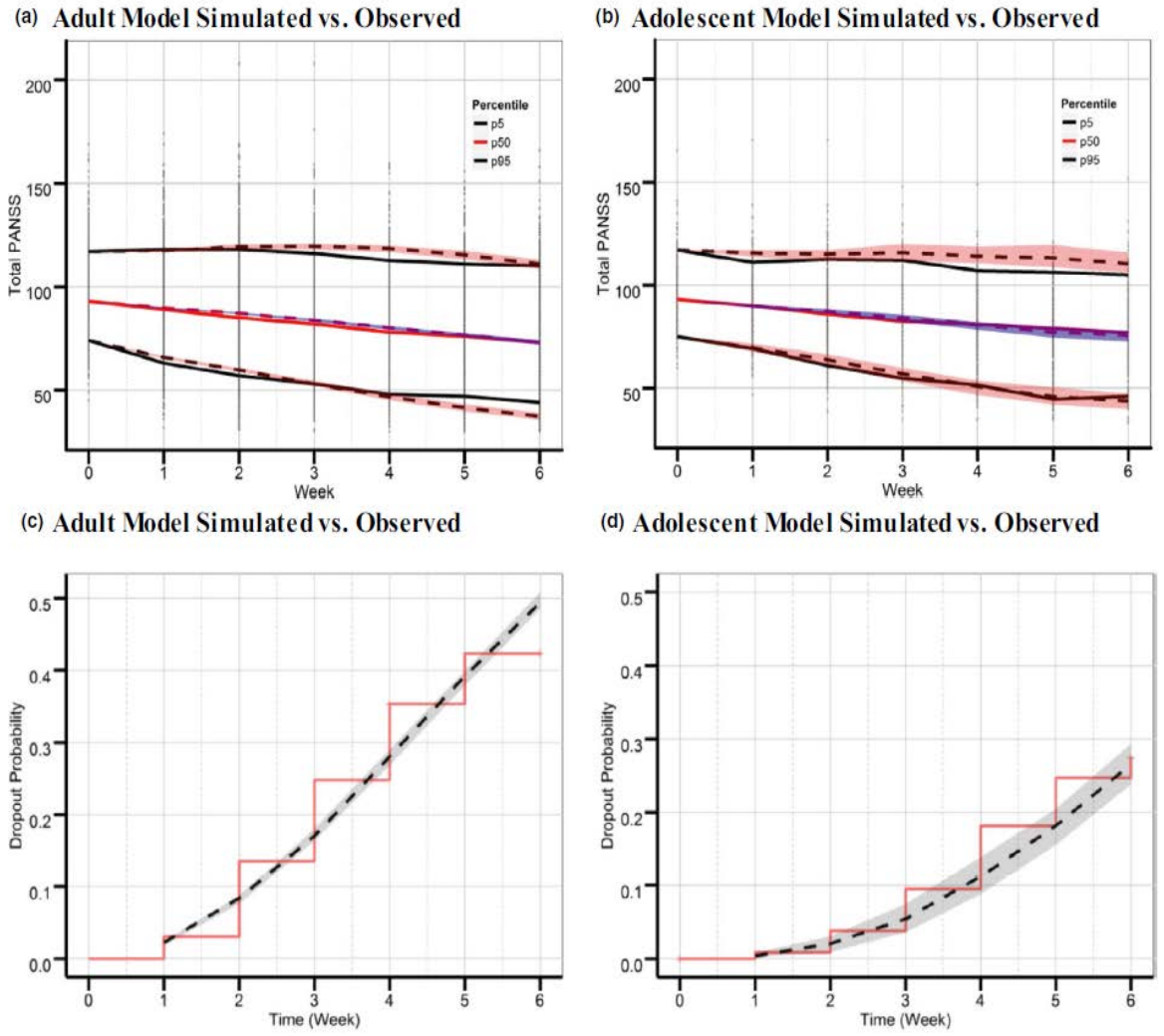
Shamir N. Kalaria[1], Hao Zhu[2,*], Tiffany R. Farchione[3], Mitchell V. Mathis[3,†], Mathangi Gopalakrishnan[1], Ramana Uppoor[2], Mehul Mehta[2] and Islam Younis[2,†]

- Developed a model-based approach to evaluate disease similarity by evaluating the placebo arms of adult vs. pediatric studies
  - Assume that placebo arm can be viewed as a proxy for natural course of the disease after acute exacerbation
- Reviewed adult and placebo data sets from 34 adult (n=3,733) and 7 pediatric trials (n-579)
- Model developed to evaluate longitudinal PANSS scores
  - Utilized data from both adult and adolescent placebo response and dropouts
  - Included dropouts because changes in PANSS scores different between placebo and early dropout (lower placebo effect in dropout group)

Comparison of placebo response between adults and adolescents

Adult and Adolescent Placebo and Dropout Models

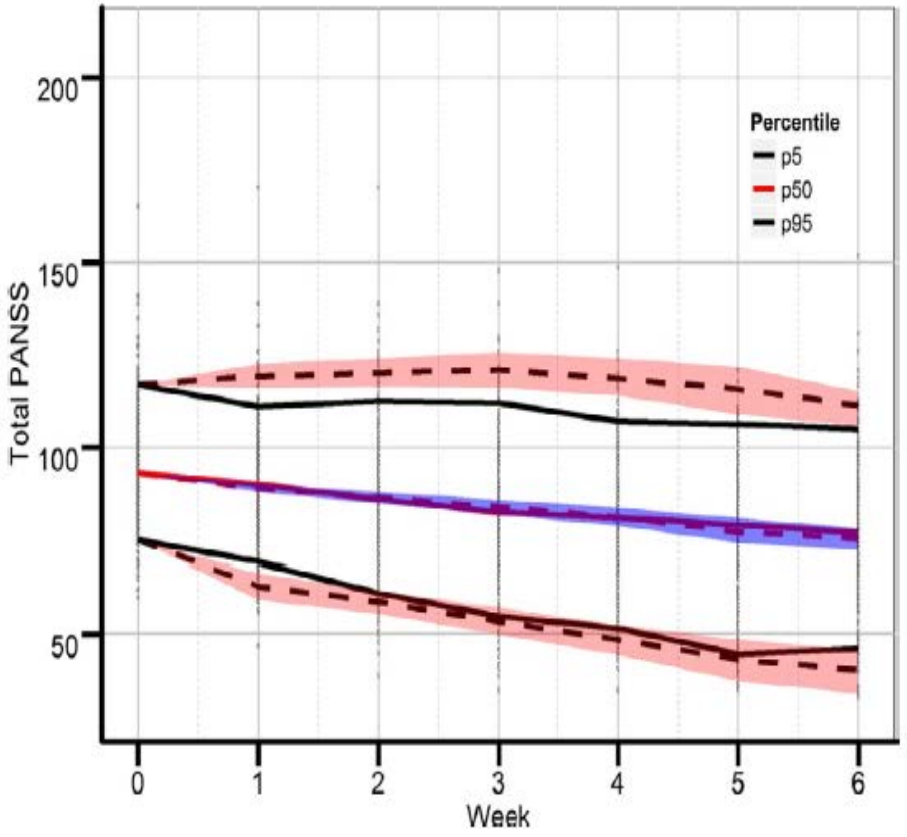
- Adult Placebo Model and Adult Drop out Model reasonably predict PANSS scores over time
- Adolescent Placebo Mode and Adolescent Drop Out Model also reasonably predict PANSS scores over time



Model Based Simulations to Evaluate Placebo Response between Adult and Pediatric Populations

- Developed a combined disease-trial model
  - Adult placebo model (disease)
  - Adolescent dropout model (trial)
- Describe the longitudinal trend in total PANSS scores
- Simulations based on this combined model demonstrate that the two populations share similar placebo response profiles

Predicted vs. Observed total PANSS scores



Similarity of Response to Therapy

- Brexpiprazole, cariprazine, olanzapine, risperidone, aripiprazole, quetiapine, quetiapine XR, paliperidone, ziprasidone, and asenapine have been studied in both adults and adolescents (age 12 or 13 to 17 years)

- Of 34 adult trials for the above drugs, 74% positive. Of adolescent trials, all positive except for asenapine (underpowered study) and ziprasidone (data integrity and dose selection concerns)

- The dose ranges are similar between adolescents and adults for atypical antipsychotics approved for both populations

Approved Doses in Pediatric Atypical Antipsychotic Drugs

Drug	Age Range (years)	Recommended Dose in Adolescents (mg/day)	Recommended Dose in Adults (mg/day)
Paliperidone ER	12-17	Weight <51 kg: 3-6 Weight >51 kg: 3-12	3-12
Quetiapine	13-17	400-800	400-800
Risperidone	13-17	1-6	4-16
Aripiprazole	13-17	10-30	10-30
Lurasidone	13-17	40-80	40-160
Olanzapine	13-17	10	10

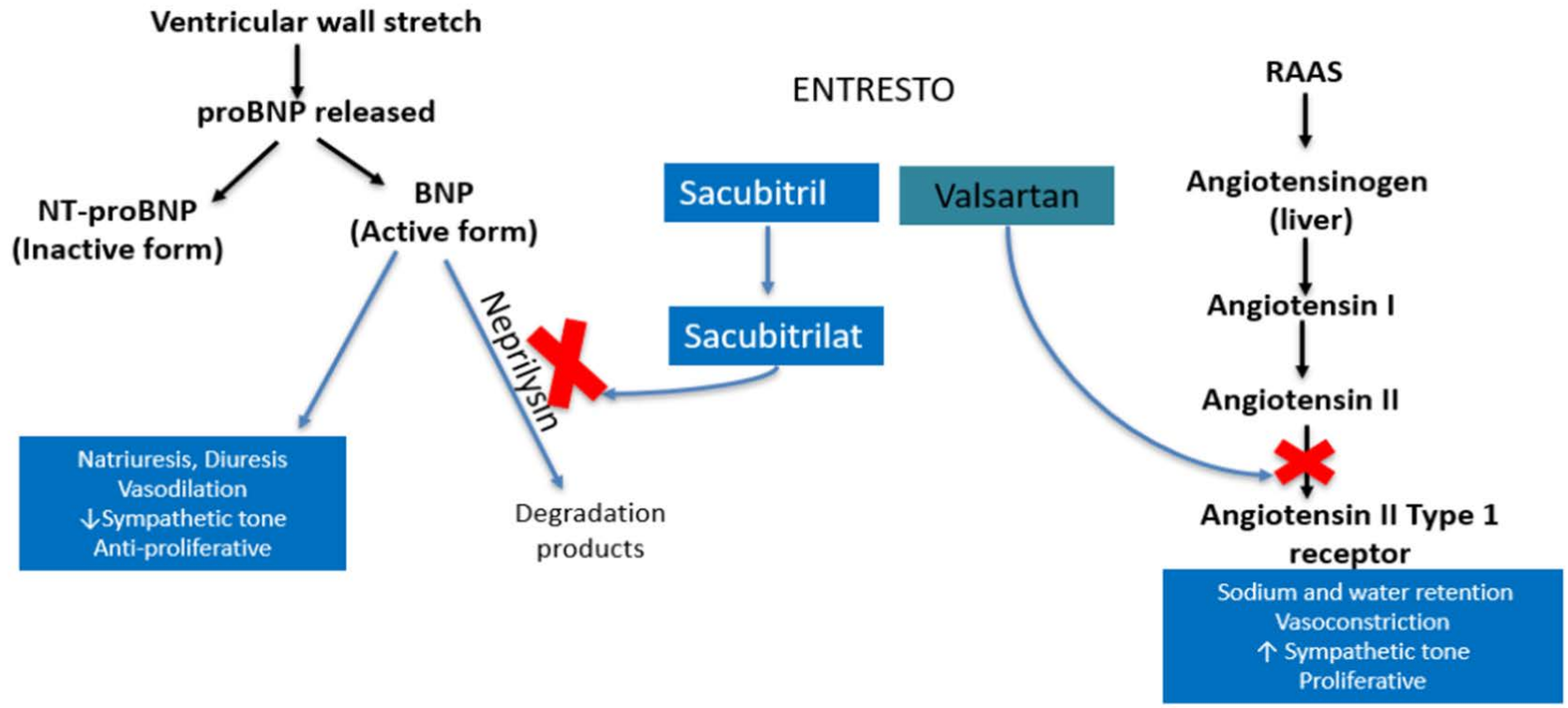
Division of Psychiatry Pediatric Development Policies

- Atypical Antipsychotics for Schizophrenia
- No efficacy studies in pediatric patients (age 13-17 years) are required if:
  - An approved indication in adults
  - A PK analysis to determine a dosing regimen that provides similar drug exposures as effective in adults
- Long-term open-label safety study required for pediatric patients (age 13 to 17 years)
- New policy implemented January 2020

Sacubitril/Valsartan (Entresto)

Sacubitril/Valsartan

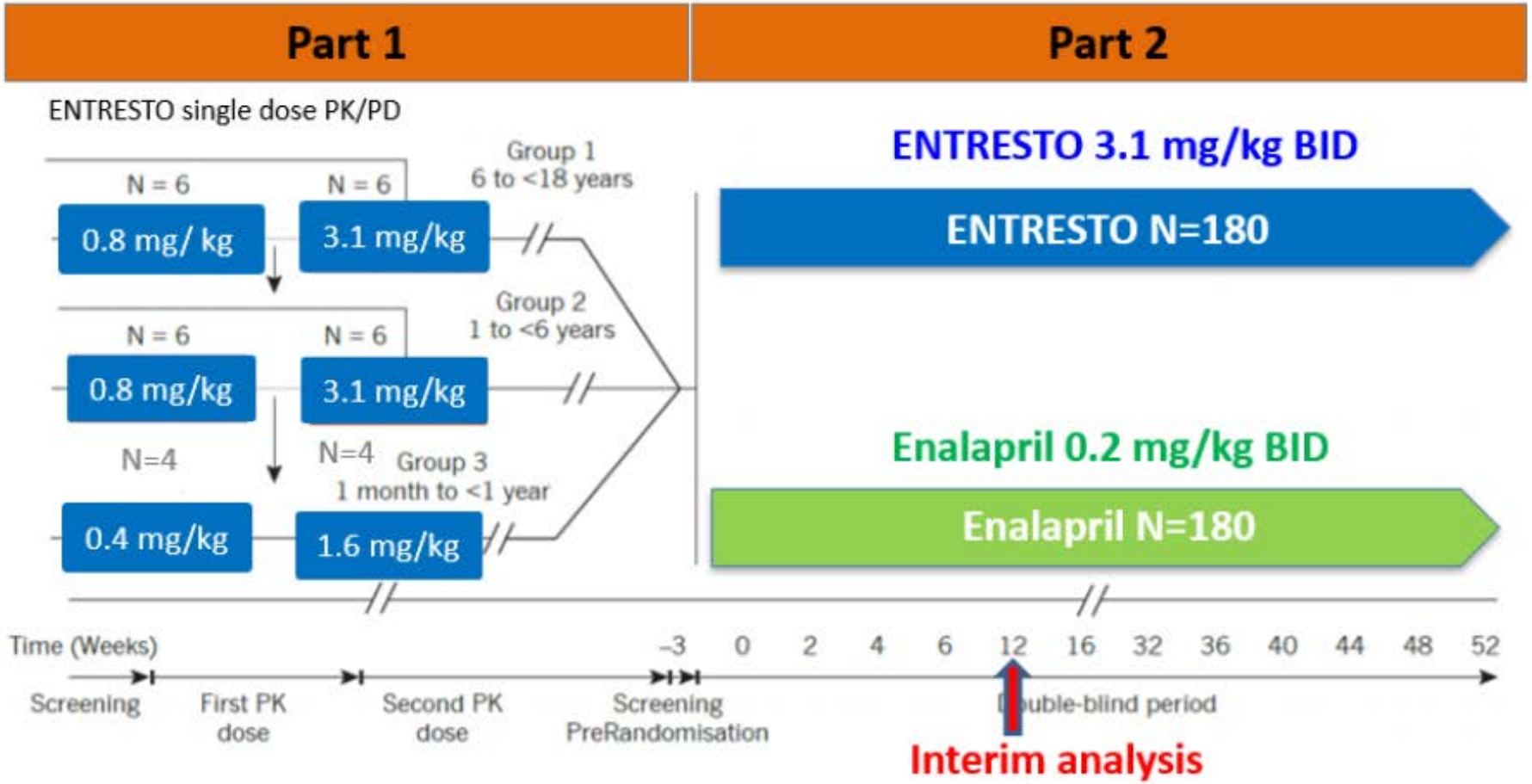
- Sacubitril/valsartan is a first-in-class angiotensin receptor neprilysin inhibitor approved in 2015 for treatment of adult patients with chronic heart failure and reduced ejection fraction (HFrEF)



Similarity of HFrEF between Adult and Pediatric Patients

- Uncertainty about the similarities between adult and pediatric patients existed at the time of design of pediatric studies (2015)
- HF etiologies differ between adult and pediatric patients
- Presentation and clinical course are usually different
- Pediatric extrapolation not accepted at that time (2015)
- Original study was design
  - Double-blind, randomized, active-controlled study of sacubitril/valsartan compared to enalapril in pediatric patients with heart failure due to systemic left ventricular dysfunction
  - Original endpoint was a time to event of Global Rank Endpoint based on death, requirement for heart transplant or life support assistance, worsening heart failure and measures of functional status and quality of life

Pediatric Study: PANORAMA –HF Study

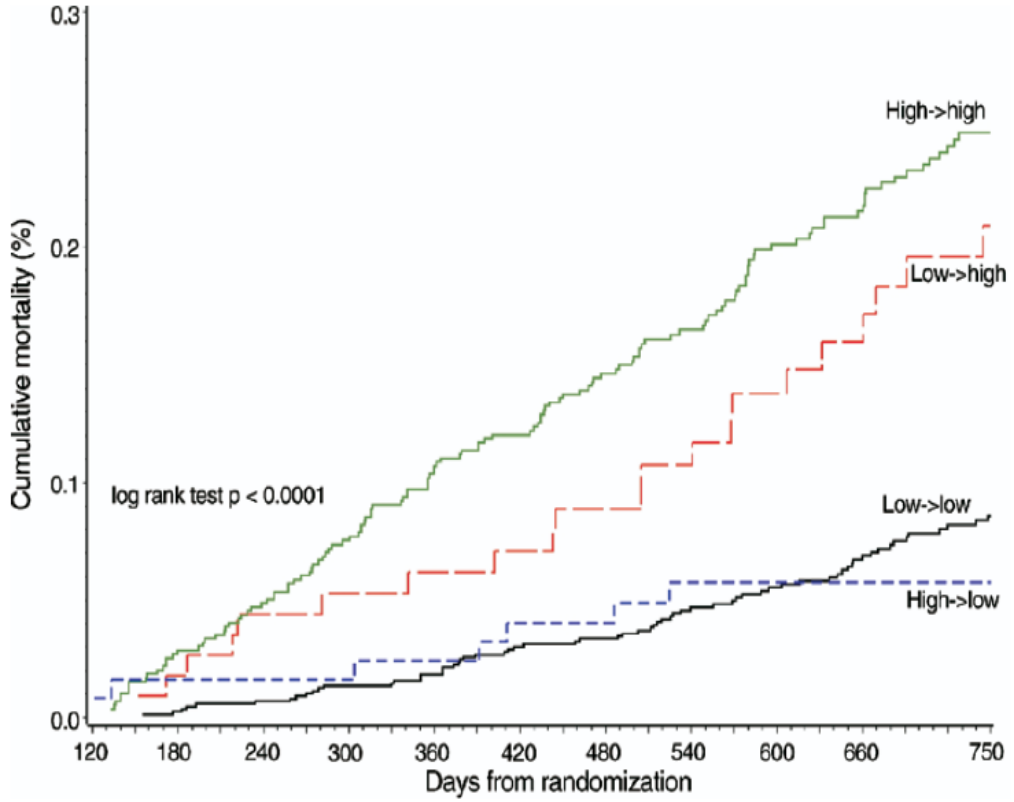


Advances in Understanding of Heart Failure in Adult and Pediatric Patients

- Based on the understanding that pathophysiology between pediatric HF patients with DCM and adult HFrEF DCM patients is similar (FDA/M-CERSI pediatric workshop in October 2017)
- Dilated Cardiomyopathy (DCM)
  - Occurs in both adult and pediatric patients
  - Neurohormonal pathophysiologic derangements in DCM are sufficiently similar between adult and pediatric patients
  - Would expect similar responses to HF therapies targeting these neurohormonal pathways
- Pediatric extrapolation could be considered in a subset of patients with DCM if data in adult patients with DCM demonstrate efficacy
- Uncertainties: Adult trials were not powered to evaluate treatment effects in this subset of patients

Adult Data to support Use of NT-proBNP

- Valsartan Heart Failure trial
  - R, PC, DB trial in adult patients with symptomatic heart failure
  - Post-hoc analysis of 1742 patient receiving placebo to evaluate association of changes in NT-proBNP with outcome

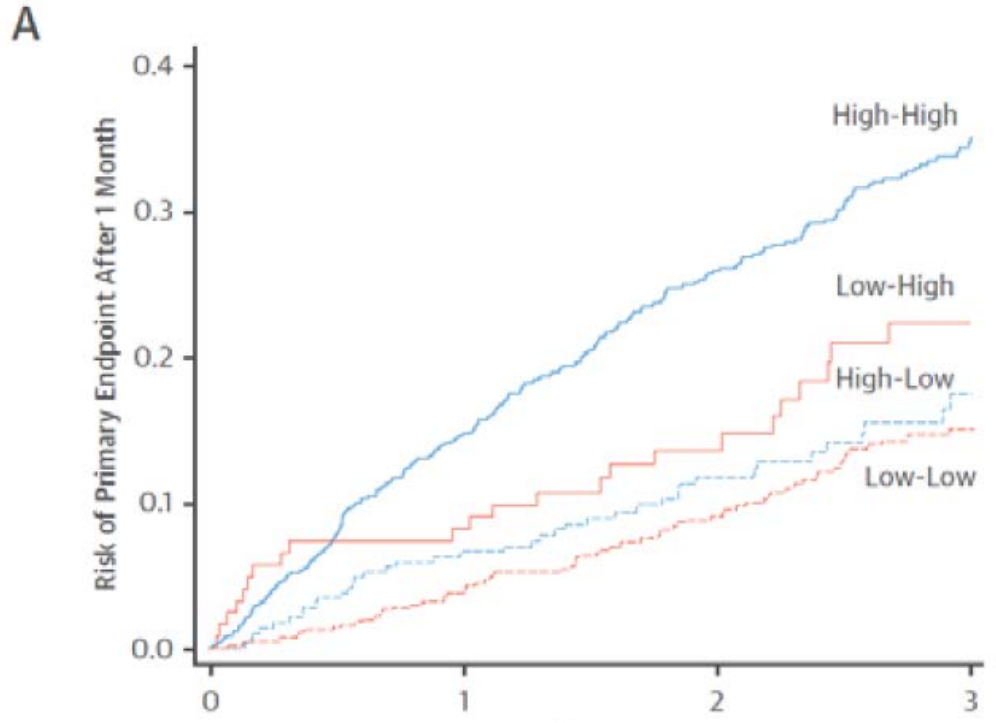


Source: Figure 3, Masson S, et al., J Am Coll Cardiol. 2008

FDA Office of Clinical Pharmacology Review; 9/20/2019, located at: https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2012-present

Adult Data to Support Use of NT-proBNP

- PARADIGM-HF trial
- R, DB, Active-controlled trial evaluating efficacy and safety compared to enalapril
- Patients received 4-6 weeks of single-blind enalapril run-in followed by an additional 4-6 weeks of single-blind treatment with enalapril + sacubitril/valsartan
- Re-randomized to receive either one drug or the other
- Post-hoc analysis of 2080 patients to evaluate changes in NT-proBNP and clinical outcomes (morbidity and mortality)



Number at risk				
High-High	903	746	476	191
High-Low	287	263	174	74
Low-High	122	111	78	36
Low-Low	611	581	390	182

FDA Office of Clinical Pharmacology Review; 9/20/2019, located at: https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2012-present

Pediatric Data to Support Use of NT-proBNP

- Rusconi et al. Retrospective Study in Peds DCM (Am Heart J. 2010 Oct;160(4):776-83)
  - A 10-fold increase in NT-proBNP was associated with a 9.8% decrease in LVEF and increased odds of being in functional class III/IV (OR 85.5; 95% CI, 10.9 to 671.0)
  - NT-proBNP >1000 pg/mL predictive of children with constant or intermittent functional class III-IV
- den Boer et al. Retrospective Study in Peds DCM (Am J Cardiol. 2016 Dec 1;118(11):1723-1729 2016)
  - Results showed a direct relationship between risk for cardiac death and increase/decrease in NT-proBNP serum levels

Changes to Study Design

- Sponsor requested a change in the primary endpoint from a clinical endpoint to change in NT-proBNP at 12 weeks
- FDA agreed to the change in primary endpoint to change in NT-proBNP based on:
  - Changes in NT-proBNP are correlated with heart failure outcomes in adults
  - Changes in NT-proBNP are correlated with markers of left ventricular systolic function and heart failure outcomes in pediatric patients

Primary Efficacy Results

Adjusted geometric mean NT-proBNP at Week 12/ NT-proBNP at baseline (95%CI)		**Adjusted geometric mean ratio (95% CI)**
ENTRESTO (N=54)	Enalapril (N=54)	ENTRESTO/ Enalapril
0.56 (0.48 – 0.67)	0.67 (0.57 – 0.79)	0.84 (0.67– 1.06) (p=0.15)

FDA Office of Clinical Pharmacology Review; 9/20/2019, located at: https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2012-present

Comparison between Adult and Pediatric Change from baseline NT-proBNP

Patient population (N-ENTRESTO arm, N-enalapril arm)	Time post-randomization	Adjusted geometric mean NT-proBNP/ NT-proBNP at baseline (95%CI)		Adjusted geometric mean ratio (95% CI)
		ENTRESTO	Enalapril	ENTRESTO/ Enalapril
Pediatrics 1 to <18 years N=54, N=54	Week 12	0.56 (0.48 – 0.67)	0.67 (0.57 – 0.79)	0.84 (0.67– 1.06)
Adults-DCM subgroup N=213, 192	Month 1	0.57 (0.52 – 0.62)	0.92 (0.84 – 1.0)	0.62 (0.55 – 0.71)
Adults-DCM subgroup N=178, 167	Month 8	0.48 (0.42 – 0.56)	0.79 (0.68 – 0.91)	0.61 (0.50 – 0.75)
Adults N=971, N=971	Month 1	0.68 (0.66 – 0.71)	0.93 (0.89 – 0.96)	0.75 (0.70 – 0.78)
Adults N=885, N=874	Month 8	0.65 (0.62 – 0.69)	0.87 (0.82 – 0.91)	0.75 (0.70 – 0.81)

FDA Office of Clinical Pharmacology Review; 9/20/2019, located at: https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2012-present

Conclusions

- Based on the totality of evidence in adults and children, FDA concluded that NT-proBNP could be used a pharmacodynamic marker that could be used to bridge from adult efficacy in HFrEF to pediatric patients with DCM
  - Change in NT-proBNP similar between adults with HFrEF and pediatric patients with DCM
- Remaining uncertainties
  - Active comparator, enalapril, not approved for a HF treatment indication in pediatric patients but used as standard of care
  - Treatment effect on NT-proBNP with enalapril in pediatric patients with HF unknown

Application of Bayesian Analyses to Support Approval of Intravenous Belimumab in Children with Systemic Lupus Erythematosus in the U.S.

Pottackal G, Travis J, Neuner N, Rothwell R, Levin G, Niu J, Marathe A, Nikolov NP
Office of New Drugs
Office of Biostatistics
CDER

Belimumab

- Monoclonal antibody that inhibits B-lymphocyte stimulator (BLyS)
- Originally approved in 2011 for the treatment of adults with active, autoantibody-positive SLE
- Use of pediatric extrapolation was considered but uncertainties existed about the degree of similarity between adult and pediatric SLE

Different	Dissimilar	Similar	Same

Disease Similarities
Similarities: Disease pathophysiology, Diagnostic criteria
Dissimilarities: Natural history, Clinical management

Response Similarities
Belimumab mechanism of action expected to be similar between adult and pediatric SLE
Uncertainties: Novel drug, dose-response similarity/exposure-response similarity

Increasing relevance of adult information to pediatric population with increasing confidence in similarity between adult and pediatric condition

Pediatric RCT(s) → "Bridging biomarkers", Bayesian approaches, → Exposure matching

Study Design

Study	Design Objectives	Study Population	Dosing Regimens	Key Endpoints
Pediatric BEL114055 (C1109) 52-week	MC, R, DB, PC PK, safety and efficacy**	93 SLE subjects 5 to 17 yo (SELENA/SLEDAI score ≥6)	• Belimumab 10 mg/kg • Placebo	SRI-4 at Week 52

** The trial was underpowered by design due to feasibility issues

Dose-Exposure Similarity

Patients	N	$C_{max,ss}$ (µg/mL) Geoetric Mean (95% CI)	$C_{min,ss}$ (µg/mL) Geometric Mean (95% CI)	$C_{avg,ss}$ (µg/mL) Geometric Mean (95% CI)	AUC_{tau} (day·µg/mL) Geometric Mean (95% CI)
Pediatrics (5-11 yo)	10	305 (267-350)	42 (30-60)	92 (71-118)	2569 (1992-3314)
Pediatrics (12-17 yo)	43	317 (288-350)	52 (43-63)	112 (99-126)	3126 (2765-3533)
Adults P3 studies	563	311 (306-316)	46 (44-48)	100 (98-103)	2811 (2734-2890)

Efficacy Similarity

SRI-4 response rates at Week 52

	C1056 (Adult)		C1057 (Adult)		C1109 (Pediatric)	
	Placebo N=275	Belimumab 10 mg/kg N=273	Placebo N=287	Belimumab 10 mg/kg N=290	Placebo N=40	Belimumab 10 mg/kg N=53
Response, n (%)	93 (34)	118 (43)	125 (44)	167 (58)	17 (44)	28 (53)
Observed difference	-	9.41	-	14.03	-	9.24
Odds ratio (95% CI)	-	1.52 (1.07, 2.15)	-	1.83 (1.30, 2.59)	-	**1.49 (0.64, 3.46)**

Study Design Similarity

- The pediatric SLE study C1109 design was similar to that of the adult IV confirmatory studies, C1056 and 1057
  - Double-blind, randomized, placebo (add on to standard of care)-controlled, multicenter, efficacy, safety, immunogenicity, and PK studies
  - Similar eligibility criteria:
    - Active, sero-positive SLE patients
    - Stable background standard of care therapies
    - Excluded severe lupus phenotypes, i.e. severe renal or CNS involvement
  - Similar dosing regimen: 10 mg/kg
  - Key efficacy endpoints, including SRI-4 at Week 52

Bayesian Analysis

- A *prior* for the treatment effect in the pediatric population was constructed using a weighted combination of the treatment effect estimate distribution in adults and a skeptical prior
  - The weight represents the degree of belief in the similarity of the pediatric and treatment effects estimated:

$$w * f(b) + (1 - w) * f(sp)$$

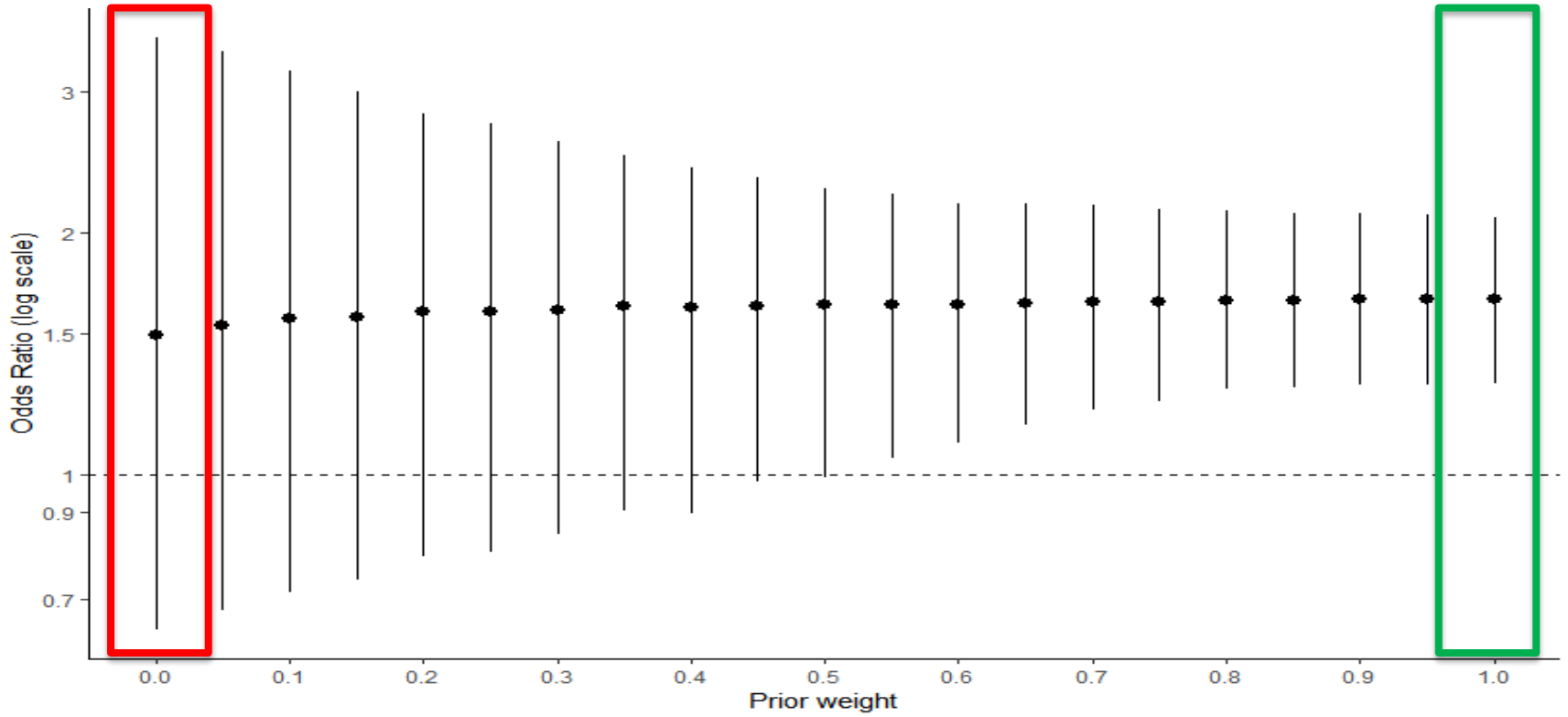
  - b = borrowed information, sp = skeptical prior

Bayesian Analysis

- A Bayesian logistic regression model was used to analyze the treatment effect in SLE Responder Index (SRI) response in pediatric patients, which adjusted covariates for:
  - Treatment group
  - Baseline SELENA SLEDAI score (<13 vs ≥13)
  - Age group (5-11 vs 12-17 years of age)

Results: Bayesian Analysis

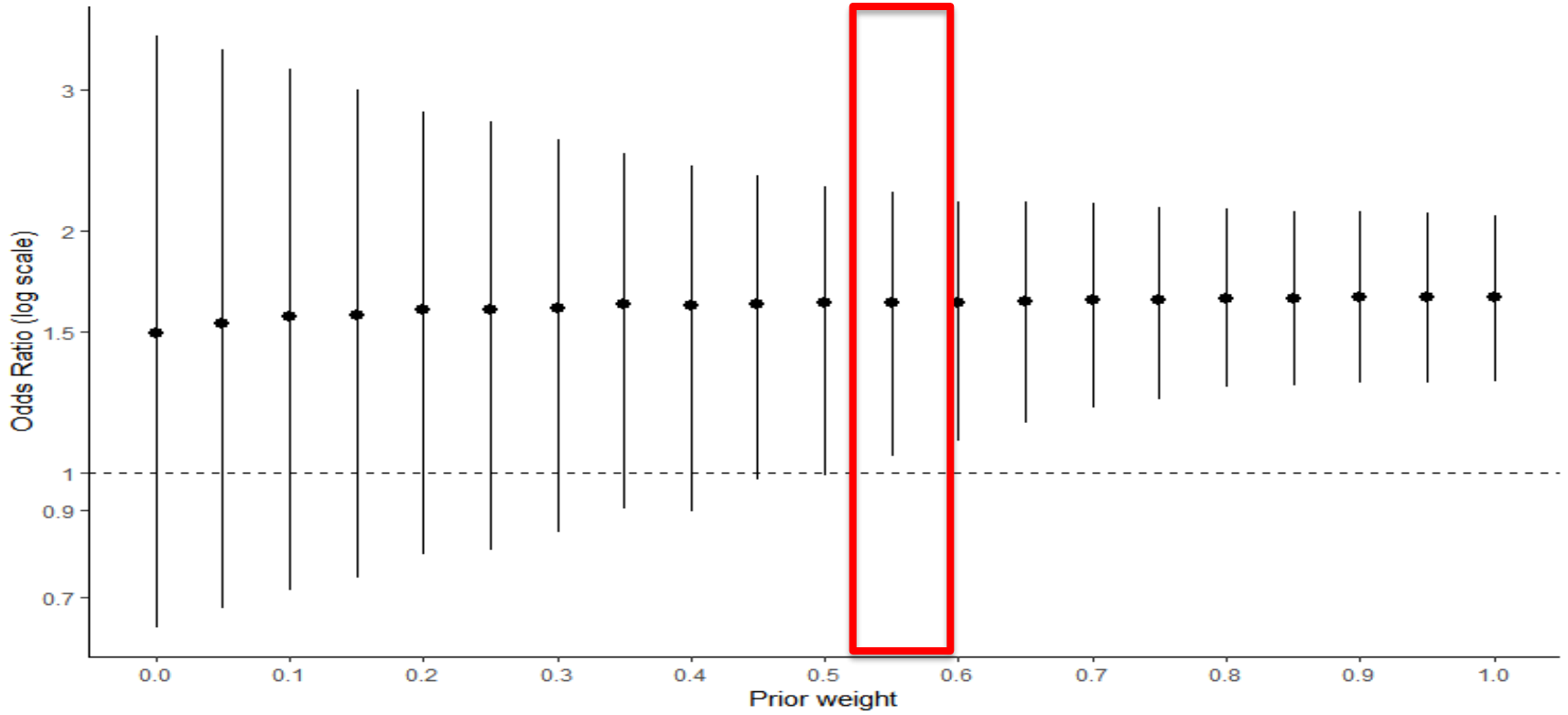
Posterior mean and 95% credibility intervals of the odds ratio of SRI response in belimumab to placebo for several prior weights ranging from 0 to 1



FDA analysis and figure generated from Applicant submission

Results: Bayesian Analysis

***Posterior* mean and 95% credibility intervals of the odds ratio of SRI response in belimumab to placebo for several prior weights ranging from 0 to 1**



FDA analysis and figure generated from Applicant submission

Conclusions

- The results of the post-hoc Bayesian analysis supported a conclusion that the treatment effect of IV belimumab in the pediatric population favored belimumab 10 mg/kg as compared to placebo
- Bayesian approaches should be considered early to obtain regulatory agreement
  - May help expedite clinical development in pediatric rheumatic diseases, and address some of the challenges with conducting trials in the setting of these rare conditions

Summary

- Pediatric extrapolation can be used to maximize the efficiency of pediatric product development while maintaining important regulatory standards for approval
- Pediatric extrapolation has matured “little by little” over the last 20 years
- No standard, harmonized regulatory “recipe”
- FDA continues to review assumptions about the acceptability of pediatric extrapolation approaches based on new knowledge gained
- Use of well-conceived and well-designed models and statistical methodologies can greatly aid in addressing gaps in knowledge in pediatric extrapolation approaches
  - Early discussions with regulatory authorities encouraged
  - Convening of workshops in specific disease areas with input from all stakeholders can be of benefit

U.S. FOOD & DRUG ADMINISTRATION

Thank you

Back Up Slides

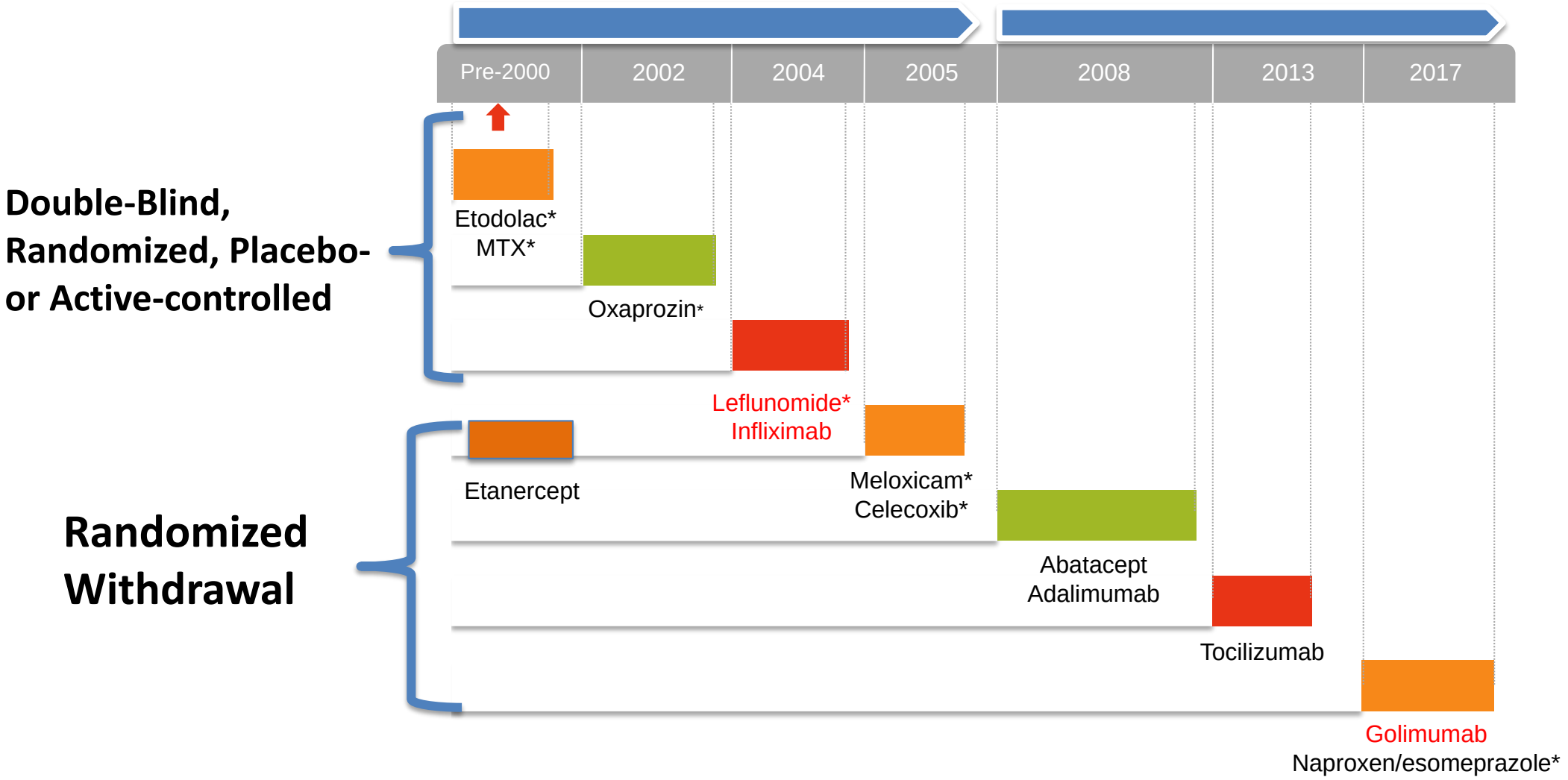
Juvenile Idiopathic Arthritis

JIA and RA Comparison

- Accelerating Drug Development for Polyarticular Juvenile Idiopathic Arthritis (pJIA) Workshop
  - Sponsored by UMD CERSI and FDA
  - Discussed use of pediatric extrapolation, trial design considerations, dose selection, modeling and simulation, and level of evidence required to establish safety and effectiveness in pediatric patients with pJIA

- Disease Similarity
  - Age 16 cutoff was never founded on data of any kind
  - Similarities between pJIA and RA:
    - F>M
    - Small + large joints, C-spine, but sparing axial skeleton
    - Synovial fluid / infiltrates: CD4, CD8, B cells, fibroblast expansion, fluid neutrophils
    - HLA II association
    - Some are RF+; these are also often ACPA+, share joint distribution, nodules
    - Response to Tx: MTX, SSZ, TNFi, CTLA4-IG, IL-6R blockade
- Similarity of Response
  - Drug exposure in pJIA trials generally within therapeutic exposure range from RA pivotal trials.
  - In general, response (ACR and subcomponents) was similar or better in PJIA when compared to RA
  - The approved RA dose/s are generally at the top of the E-R curve

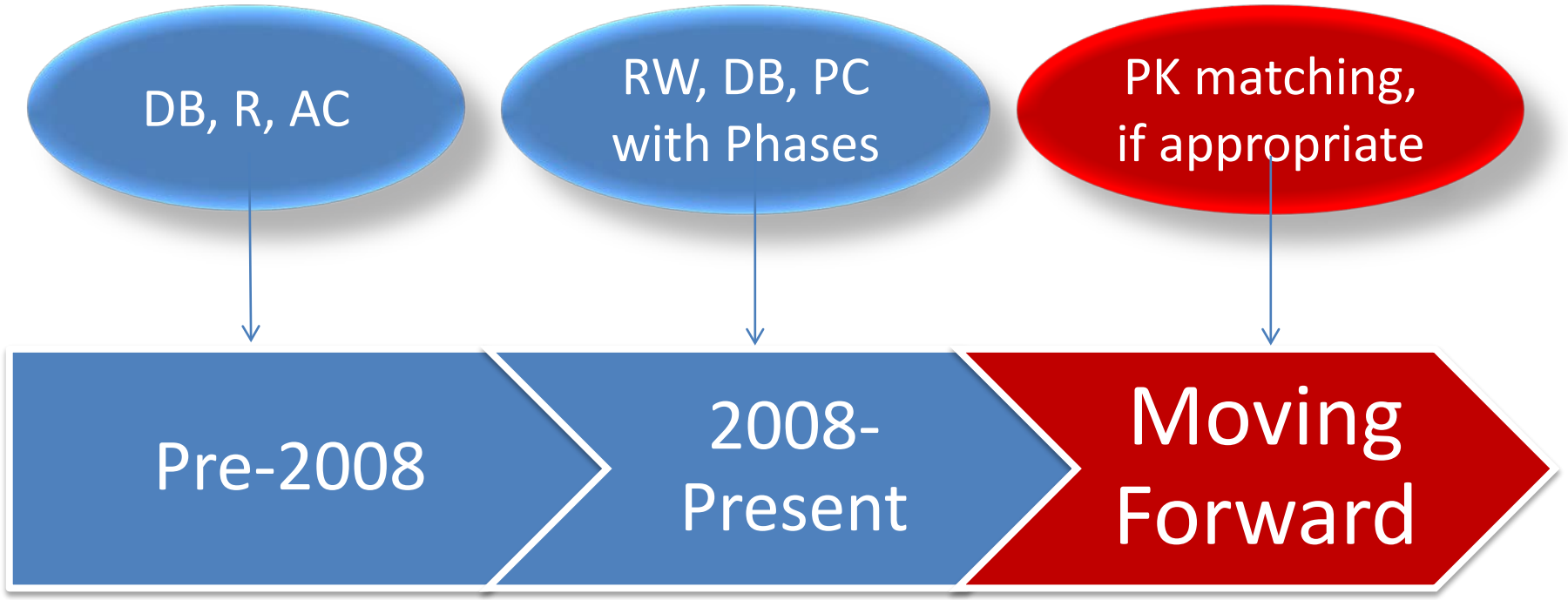
Evolution in the Understanding of Polyarticular Juvenile Idiopathic Arthritis (pJIA)



Negative trials: leflunomide, infliximab, golimumab

***small molecules**

Evolution in the Study Designs for Polyarticular Juvenile Idiopathic Arthritis (pJIA)



DB: Double Blind, R: Randomized, PC: Placebo Controlled, RW: Randomized Withdrawal, AC: Active Controlled, PK: Pharmacokinetic

Dose selection: match the exposure of the approved

Drug	Approved dose for RA	Dose in pivotal PJIA	Approved Dose in PJIA
MTX	Start at 7.5 mg qw, titrate up	• 5mg/m^2 qw, • 10 mg/m^2 qw	10 mg/m^2 qw
Adalimumab	40 mg q2w	24mg/m^2 q2w, Fixed dose in extended open label study	• 10 kg to <15 kg: 10 mg q2w • 15 kg to < 30 kg: 20 mg q2w • ≥ 30 kg: 40 mg q2w
Etanercept	25 mg SC twice weekly 50 mg qw	0.4 mg/kg up to 25 mg SC twice weekly	0.8 mg/kg per week (<63 kg) Or 50 mg weekly (≥63 kg)
Abatacept IV	• <60 kg, 500 mg • 60 to 100 kg, 750 mg • >100 kg, 1000 mg at week 0, 2, 4 w, and q4w after	10 mg/kg, not to exceed 1000 mg, at week 0, 2, 4 w, and q4w thereafter	10 mg/kg, not to exceed 1000 mg, at week 0, 2, 4 w, and q4w thereafter
Abatacept SC	125 mg qw, optional IV loading dose	• 10 to <25 kg, 50 mg qw • 25 to <50 kg, 87.5 mg qw • ≥ 50 kg, 125 mg qw	• 10 to <25 kg, 50 mg qw • 25 to <50 kg, 87.5 mg qw • ≥ 50 kg, 125 mg qw

For biologics with linear PK, the approved dose in PJIA is usually based on similar weight based dosing/BSA based dosing as RA

Dose selection: match the exposure of the approved adult RA dosing regimen

Drug	Approved dose for RA	Dose in pivotal PJIA	Approved Dose in PJIA
Tocilizumab IV*	4 and 8 mg/kg	• <30kg, 8mg/kg, or 10 mg/kg • ≥30 kg, 8mg/kg	• <30kg, 10 mg/kg • ≥30 kg, 8mg/kg
Tocilizumab SC**	<100 kg, 162 mg q2w, titrate up to qw ≥100 kg, 162 mg qw	• <30kg, 162 mg q3w • ≥30 kg, 162 mg q2w	• <30kg, 162 mg q3w • ≥30 kg, 162 mg q2w
Infliximab	3 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks	Doses of 3 mg/kg of infliximab IV at Weeks 0, 2, 6 and 14. Patients randomized to placebo crossed-over to receive 6 mg/kg of infliximab at Weeks 14, 16, and 20, and then every 8 weeks through Week 44.	NA
Golimumab	50 mg q4w	30 mg/m^2 (maximum 50 mg) q4w	NA

*A pilot PJIA study in Japan showed that with 8mg/kg, lower weight patients got lower exposure.
**No pilot study in PJIA. Prior to PJIA study, PK data available in SJIA study, to inform the dosing in PJIA

Exposure comparison: PJIA vs RA-Biologics (label statement)

Drug	Ctrough (ug/mL)		Cmean(ug/mL)	
	RA	PJIA	RA	PJIA
Etanercept	1.4	-	1.9	2.1
Adalimumab	5, w/o MTX	6.6-6.8, w/o MTX	-	-
	8-9, with MTX	8.1-10.9, with MTX		
Abatacept (SC)	12.6 w/o loading dose 32.5 with loading dose	38.5-46.6	-	-
Abatacept (IV)	24	11.9	-	-
Tocilizumab (SC)	4.1 (162 mg q2w) 42.9 (162 mg qw)	13.4 (162 mg q3w, <30kg) 12.7(162 mg q2w, ≥30kg)	9.2 (162 mg q2w) 47.3 (162 mg qw)	35.7 (162 mg q3w, <30kg) 23.0 (162 mg q2w, ≥30kg)
Tocilizumab (IV)	0.1 (4mg/kg) 13.4 (8 mg/kg)	0.35 (10 mg/kg, <30kg) 3.3 (8 mg/kg, ≥30kg)	18.0 (4mg/kg) 54.0 (8 mg/kg)	30.8 (10 mg/kg, <30kg) 38.6 (8 mg/kg, ≥30kg)

- Example of Disease similarity and careful evaluation of dose similarity between adult and pediatric patients
- Dose Response similarity

- The efficacy of ENTRESTO was evaluated in a multinational, randomized, double-blind trial comparing ENTRESTO and enalapril based on an analysis in 110 pediatric patients 1 to < 18 years old with heart failure (NYHA/Ross class II-IV) due to systemic left ventricular systolic dysfunction (LVEF ≤ 40%). Patients with systemic right ventricles and single ventricles were excluded from the trial. The target maintenance dose of ENTRESTO in pediatric patients 1 to < 18 years old was 3.1 mg/kg twice daily.
- The endpoint was the between-group difference in the change in plasma NT-proBNP from baseline to 12 weeks. The reduction from baseline in NT-proBNP was 44% and 33% in the ENTRESTO and enalapril groups, respectively. While the between-group difference was not statistically significant, the reductions for ENTRESTO and enalapril were similar to or larger than what was seen in adults; these reductions did not appear to be attributable to post-baseline changes in background therapy.
- Because ENTRESTO improved outcomes and reduced NT-proBNP in PARADIGM-HF, the effect on NT-proBNP was considered a reasonable basis to infer improved cardiovascular outcomes in pediatric patients.

Background

- On April 26, 2019 FDA approved intravenous (IV) belimumab for children with SLE under a priority review
  - https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-pediatric-patients-lupus
  - BLA 125370/s-064 Multi-disciplinary Review and Evaluation: https://www.fda.gov/media/127912/download
- Belimumab is a B-lymphocyte stimulator (BLyS)-specific inhibitor indicated for the treatment of patients ***aged 5 years and older*** with active, autoantibody positive SLE who are receiving standard therapy
- Dosage and administration
  - 10 mg/kg IV at 2-week intervals for first 3 doses and every 4 weeks thereafter