



# **Innovation in pediatric trial design in rare autoimmune diseases**

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NJ ASA Spring Symposium  
June 28, 2019**

# Outline of talk

- Goals and challenges of trial designs in pediatric autoimmune disease
- Design types with some success
  - Flare designs
  - Withdrawal/tapering designs
  - Master Protocols
- Extrapolation Approaches
  - Bayesian Methods
  - Frequentist Methods
  - Others
- Summary & Future Directions

# **Key goals of designing clinical trials in pediatric rare autoimmune diseases**

- Understanding the pathophysiology of disease to determine if the full range of pediatric patients need to be studied
- Minimizing the exposure to placebo, with endpoints that allow for early escape/switching to active treatment
- Use of modeling and simulation to determine the best starting dose for treatment
- Allow pediatric patients to be treated for their condition with monotherapy (steroid and background immunosuppressant withdrawal)
- Optimizing the use of patients across the Phase III development program through master protocol designs (platform, basket, umbrella)

# What have been the biggest challenges?

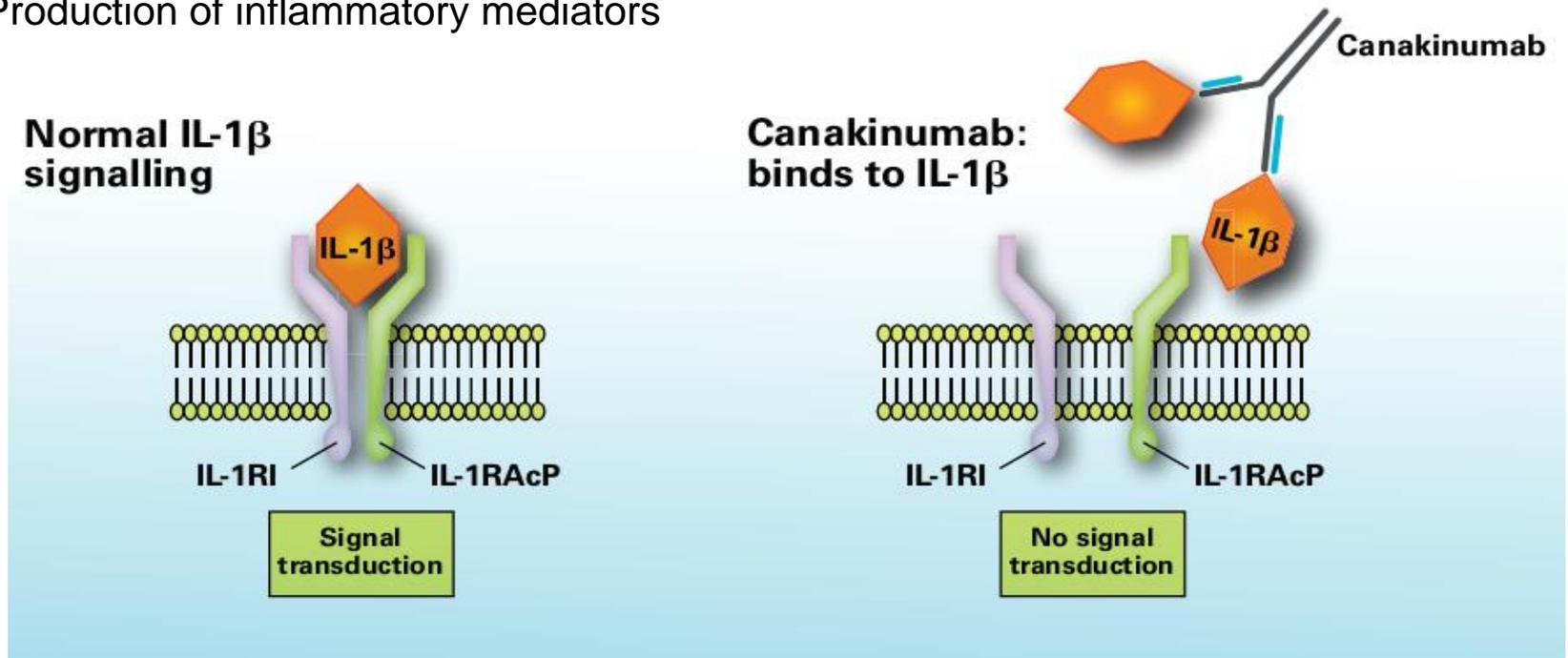
- Recruiting the required number of patients required to demonstrate effectiveness
- Determining the best dose(s) to study without doing formal dose ranging studies
- Defining a meaningful estimand
- Determining whether or not the criteria for full or partial extrapolation from adult patients can be met

# The pediatric drug develop paradigm is changing

- The traditional regulatory pathway is to develop a pediatric plan and begin studies once the clinical efficacy and safety data is available for adults
- Unmet need is changing this paradigm where increasingly pediatrics indications are arriving much earlier in the drug development cycle
- When this happens the opportunity is there to be innovative in how best to design and demonstrate treatments are safe and effective in pediatric patient populations

# Canakinumab Selectively Inhibits IL-1 $\beta$ -mediated Inflammation

- A fully human selective anti-IL-1 $\beta$  monoclonal antibody
- Canakinumab binds with high affinity selectively to IL-1 $\beta$ , preventing<sup>1-3</sup> :
  - Interaction between IL-1 $\beta$  and IL-1 receptor<sup>2,3</sup>
  - IL-1-induced gene activation
  - Production of inflammatory mediators



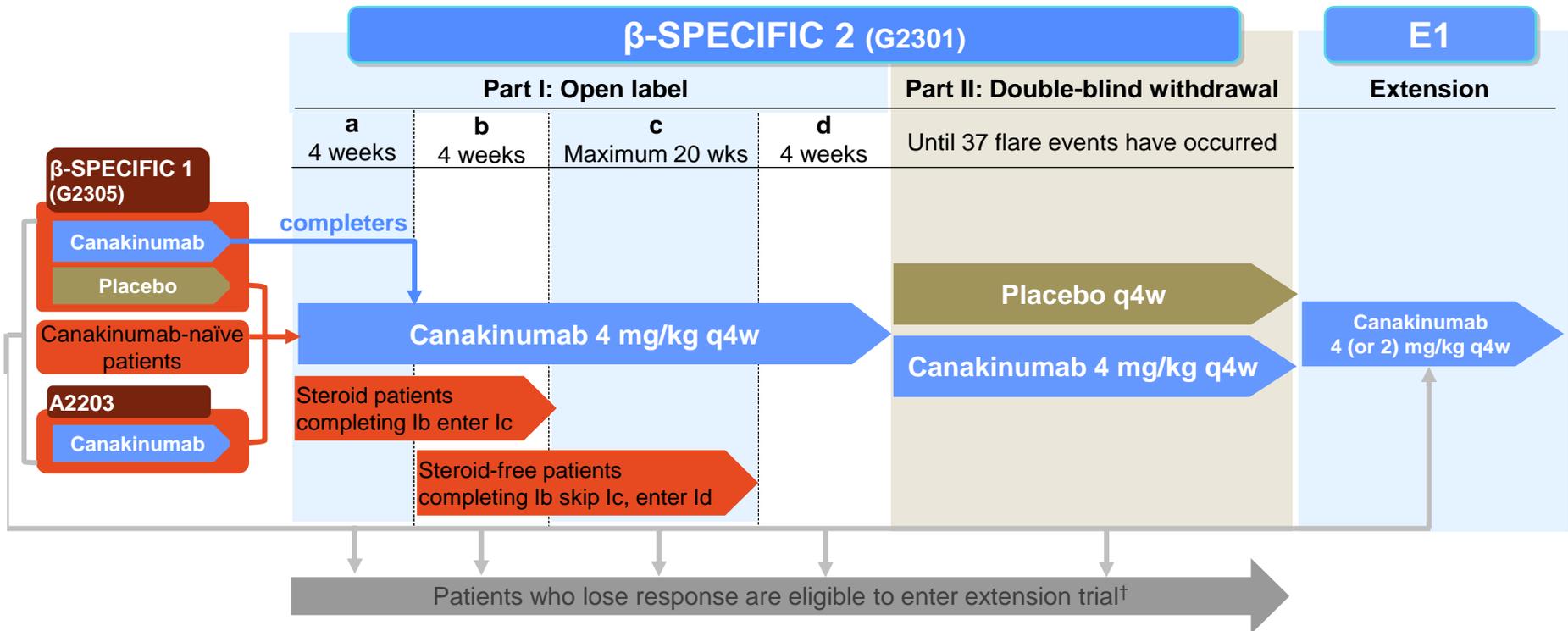
# Why has drug development with canakinumab been special?

- Although canakinumab has been studied in many different conditions where it was believed that the treatment of inflammation could have a positive effect on the clinical disease state, all of the approved indications for which it has been developed are in pediatric conditions.
- A strong network of pediatric rheumatologists have recognized the importance of treatments for rare autoimmune conditions and found that by blocking anti-IL1 $\beta$  this can have a positive effect on many patients
- Excellent health authority interaction to design efficient clinical trials to answer important questions in treating patients with these conditions

# Example 1: Systemic juvenile idiopathic arthritis (SJIA)

- Make the best use of all patients available to do a full development program that includes:
  - ✓ Dose-ranging
  - ✓ Steroid tapering
  - ✓ Treatment of disease flares
  - ✓ Withdrawal of treatment and dose-optimization
- Have flexibility that different patients can enter the development program in multiple studies and join at different points in time depending on how they are currently being treated and their current disease stat

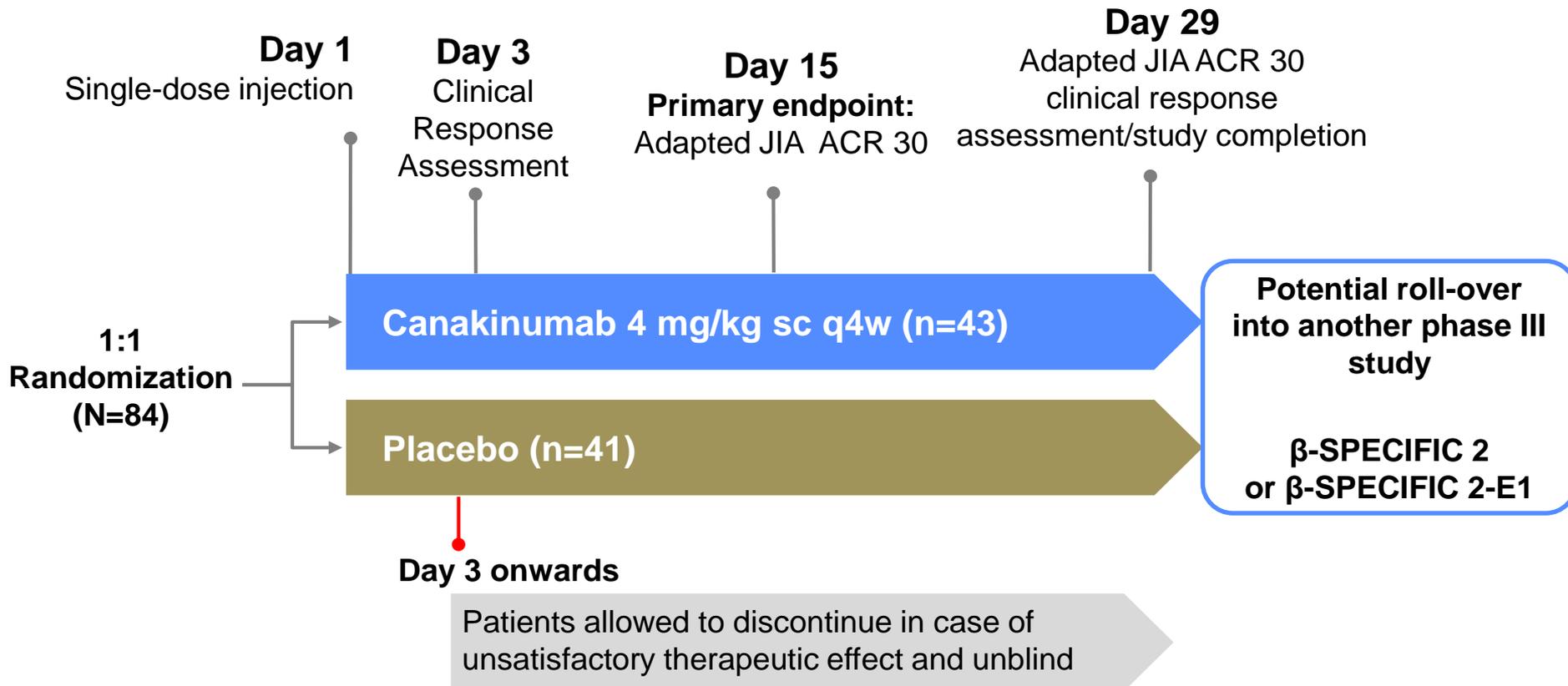
# Canakinumab Phase II/III Program in Systemic Juvenile Idiopathic Arthritis (SJIA)



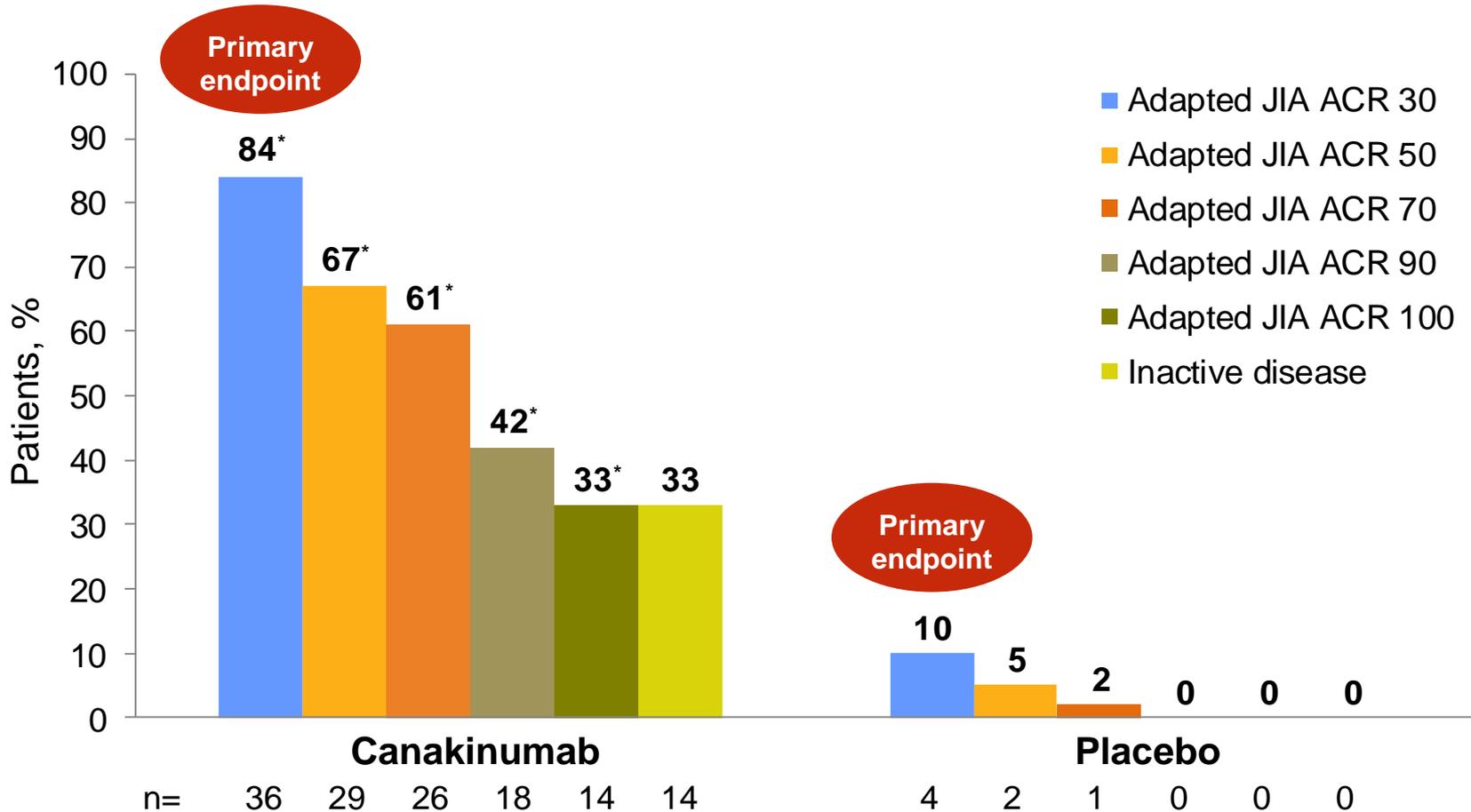
- A Phase IV study was conducted with patients from  $\beta$ -SPECIFIC 2 and canakinumab-naïve patients to investigate dose tapering and dosing-interval spacing.

## β-SPECIFIC 1

# Phase III, 4-Week, Randomized, Double-Blind, Single-Dose, Placebo-Controlled Study



# Canakinumab Induced Strong and Significant Clinical Response at Day 15

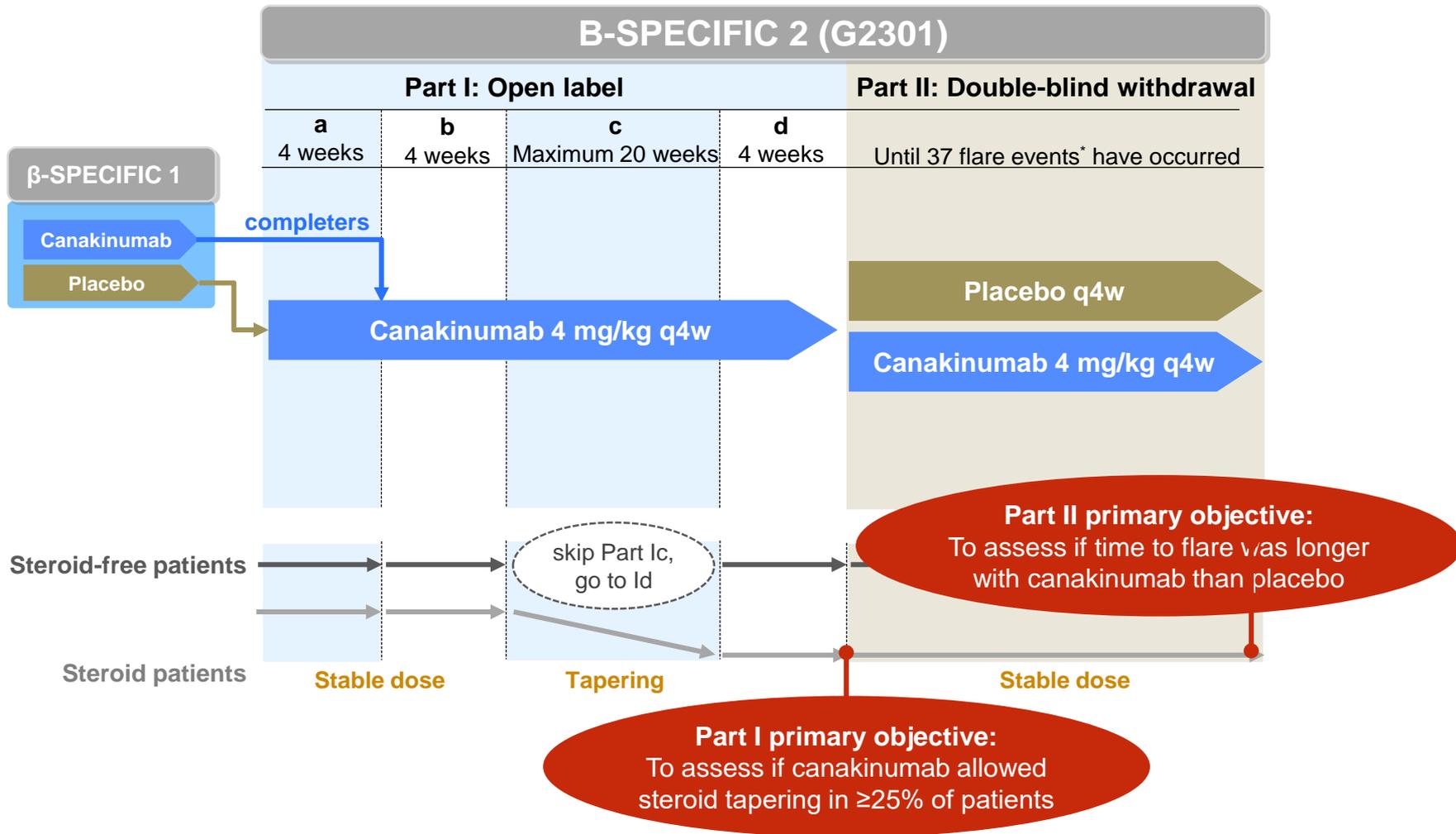


\*P < 0.001. P value not determined for comparison of inactive disease.

Adapted JIA ACR criteria include absence of fever.

- Ruperto N, et al. *N Engl J Med.* 2012;367:2396-406.

# 2-Part Study Design With Distinct Primary Objectives



\*Flare events included protocol-defined flares and discontinuations for any reason other than inactive disease. Adapted from Ruperto N, et al. *N Engl J Med.* 2012;367:2396-406.

## β-SPECIFIC 2: Part I

# Steroid Tapering Guidelines

Prednisone (or equivalent) dose, mg/kg/d	Amount of Reduction
>0.1	Taper at 0.1 mg/kg/wk until at dose of 0.1 mg/kg/d
0.1	Taper to dose of 0.05 mg/kg/d for 1 week
≤0.05	Alternate dosing days (ie, every 48 h) for 2 wk, then discontinue

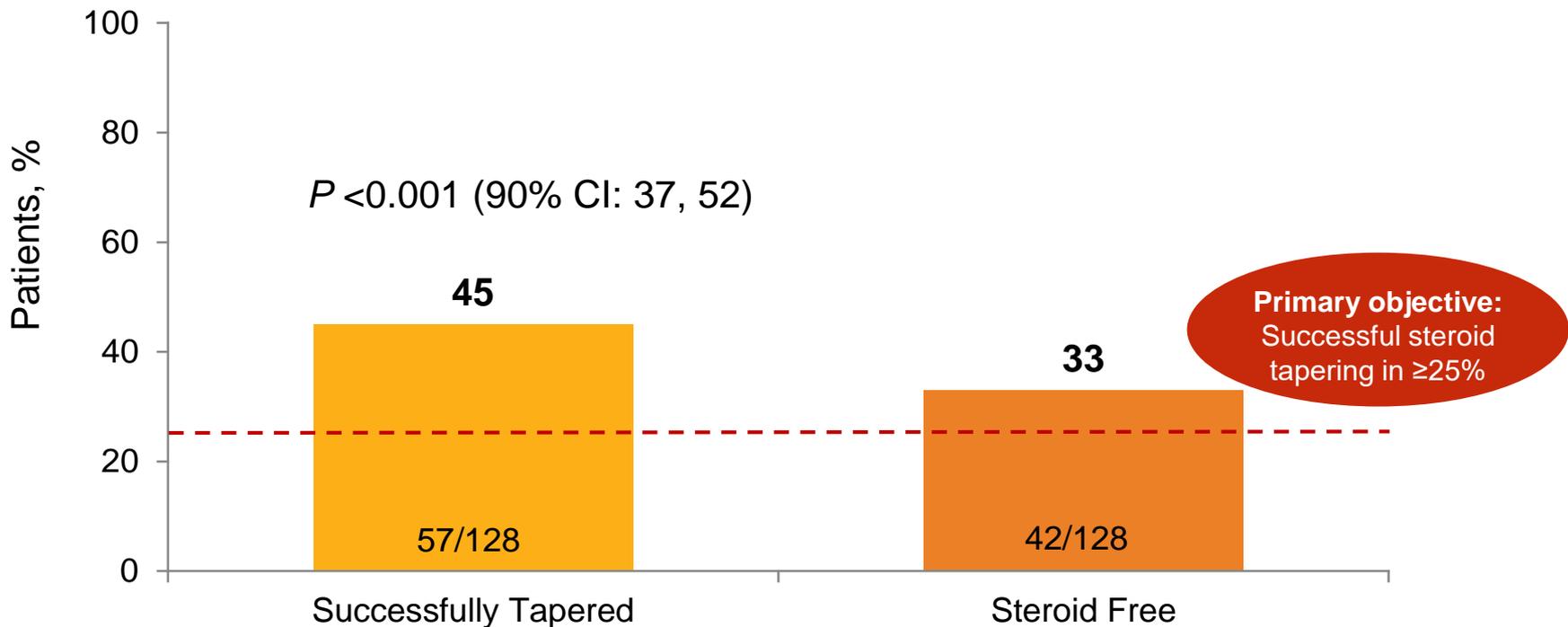
- Tapering could continue if patient
  - Did not flare
  - Maintained adapted JIA ACR 50 response, with no fever
- Tapering was stopped if patient
  - Failed 3 tapering attempts (eg, flare, CRP >30 mg/L, loss of adapted JIA ACR 30 response, change from minimum adapted JIA ACR 50 to 30 response)
  - Reached 20 weeks (maximum duration permitted)

### Successful taper:

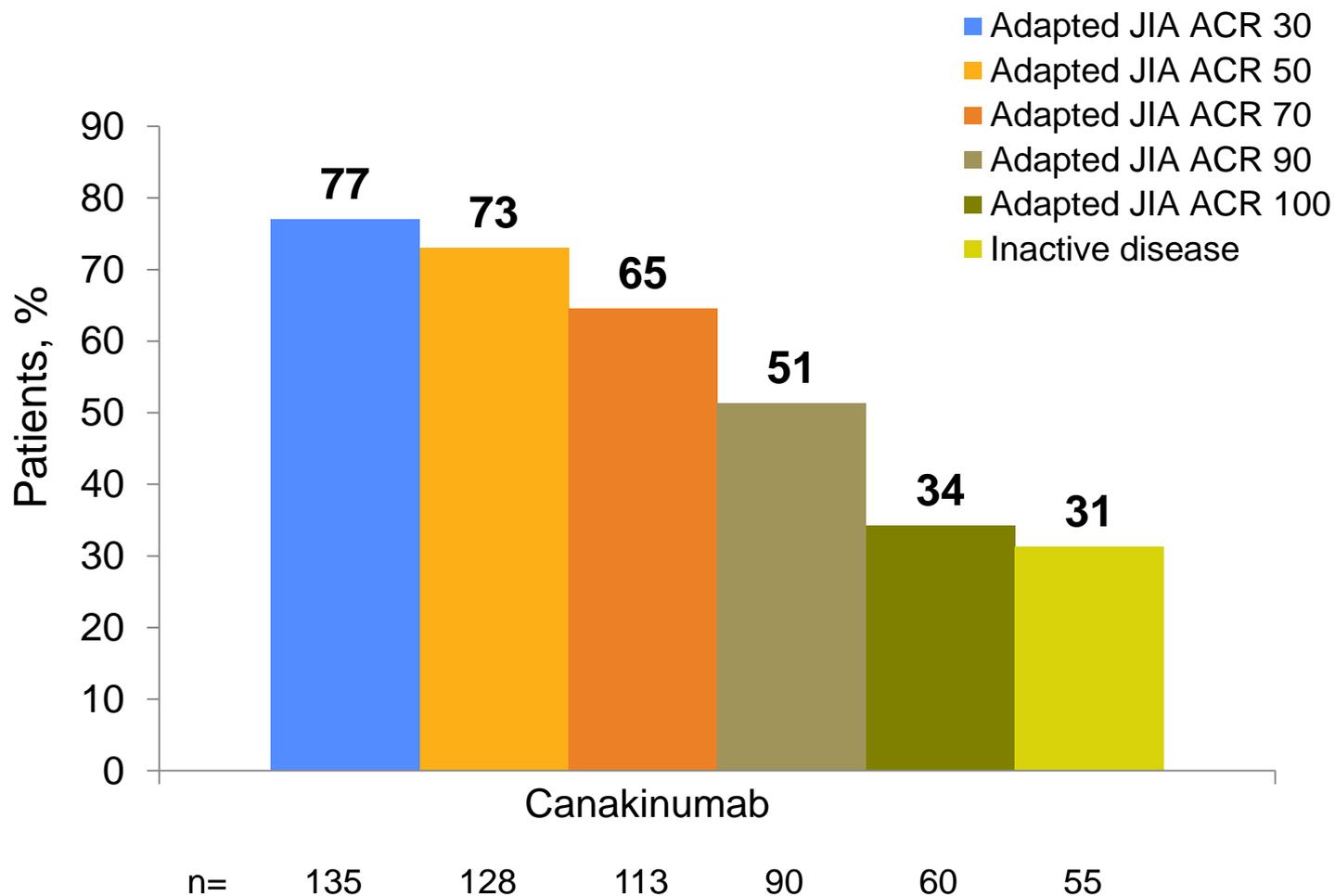
- >0.8 to ≤0.5 mg/kg/d or
- ≥0.5 and ≤0.8 by ≥0.3 mg/kg/d or
- Any initial dose to ≤0.2 mg/kg/d

# Primary Endpoint Met: 45% of Patients on Steroids at Entry Successfully Tapered Within 5 Months

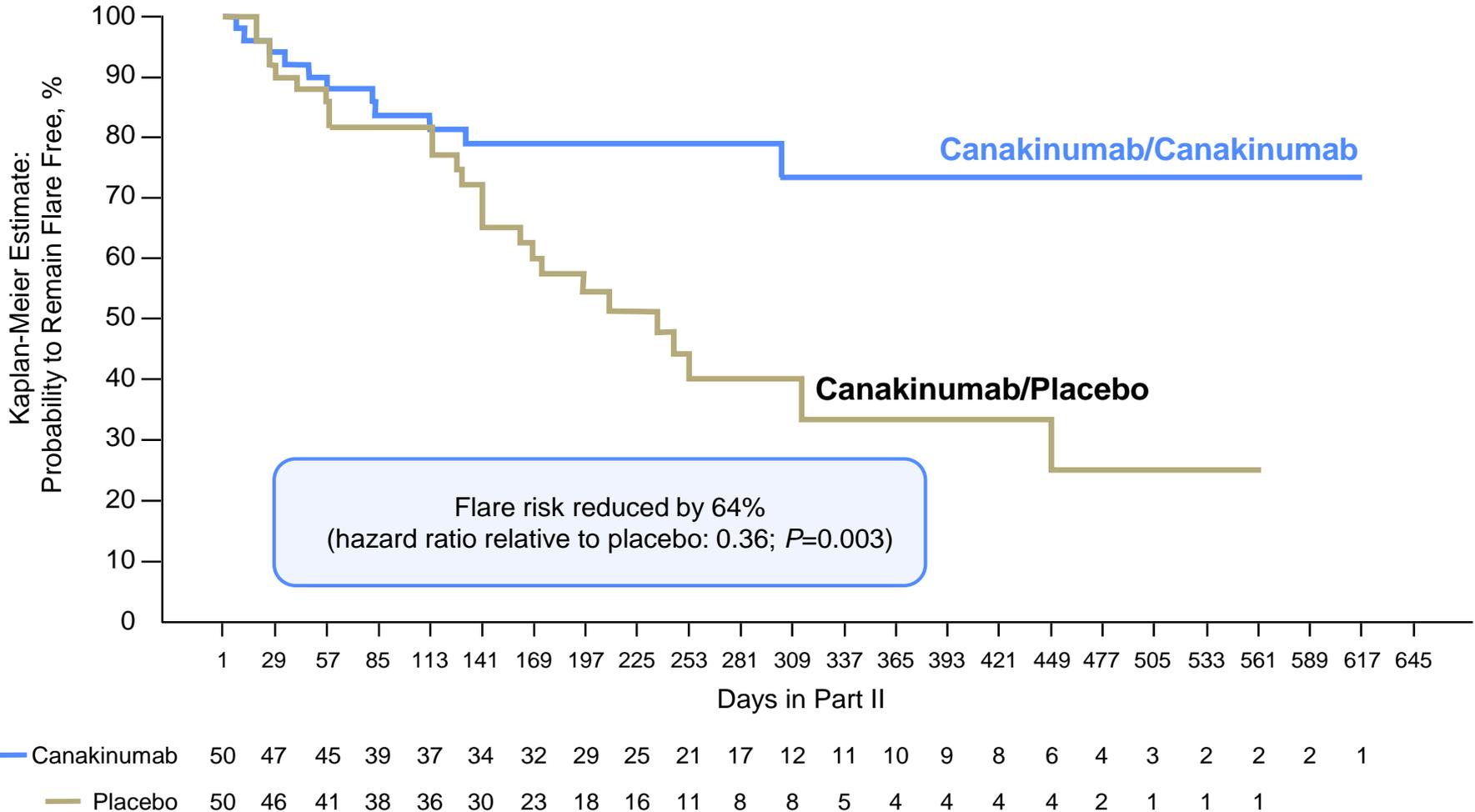
Mean daily dose of steroids decreased from 0.34 to 0.05 mg/kg in patients who successfully tapered



# One-third of Canakinumab-treated Patients Achieved Inactive Disease at the End of Part I



# Primary Endpoint Met: Canakinumab Prolonged Time to Flare Compared With Placebo



Patients were also allowed to take concomitant medications during this period.

Ruperto N, et al. *N Engl J Med.* 2012;367:2396-406.

# **Pediatric master protocols (Lavange, FDA Pediatric Master Protocol Workshop 2016)**

- When one has multiple diseases, multiple patient subgroups defined by biomarkers, and/or multiple therapies studied under one study protocol this is often referred to as a master protocol
- In general these can be broken down into two subgroupings
  - Umbrella or platform trials: One disease (possibly multiple subpopulations), multiple drugs
  - Basket trials: One drug multiple disease cohorts
- Until recently, such designs have almost been exclusively conducted in oncology and anti-infectives
- Advancements in innovation have occurred due to
  - Establishment of clinical trial networks with the infrastructure to streamline trial logistics, improve data quality, and facilitate data sharing and new data collection (e.g. Transcelerate Placebo Standard of Care)
  - Development of a common protocol for the network that integrates innovative statistical approaches to study design and data analysis

## **Example 2: Hereditary period fevers (HPF) with Canakinumab**

- Evidence existed from local Phase IV studies that canakinumab showed some evidence of efficacy in several rare auto-immune diseases where treatment was successful because of the ability to regulate IL-1 pathway and reduces inflammatory activity
- All subjects with the different HPF conditions have regular flares of disease so efficacy could be demonstrate by resolving and preventing new flares
- The endpoints to evaluate the efficacy of the different conditions are the same with only minor differences in inclusion/exclusion criteria
- Lends itself to basket trial approach

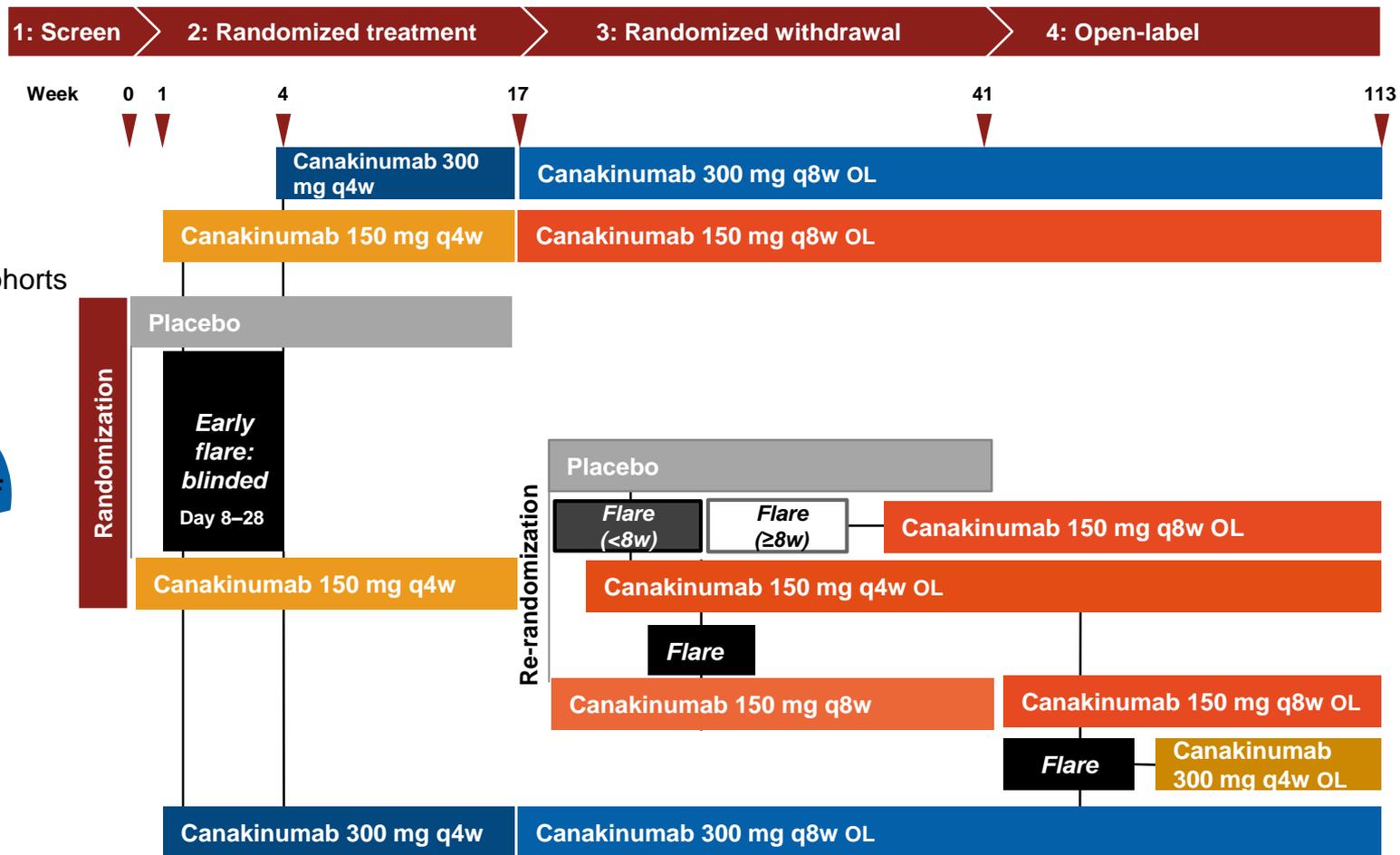
# Periodic Fever Syndromes – FMF, TRAPS and HIDS overview

Monogenic autoinflammatory syndromes: comparison of clinical manifestations			
	FMF	TRAPS	HIDS
Age at Dx	15 ±13 years (onset) 23 ±13 years (diagnosis)	3 years (range 1 month - 53 years)	0.5 years (median)
Fever duration	1–3 days	>5-14 days	3–7 days
Periodicity of attacks	10–12 per year	3–6 per year	9–10 per year
Serositis	++	++	+
Musculoskeletal	Monoarthritis	Monoarthritis, localized myalgia	Polyarthralgia/polyarthritis
Cutaneous	Erysipeloid	Erysipeloid	Maculopapular rash
Amyloidosis risk	+++ (up to 60%)	++ (15-20%)	+ (~15%)
Gene	<i>MEFV</i>	<i>TNFRSF1A</i>	<i>MVK</i>
Mode of inheritance	Recessive	Dominant	Recessive
Response to therapy			
Colchicine	Excellent	Poor	Poor
Steroids	Poor	Good	Poor

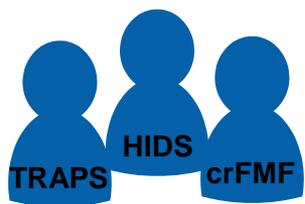
Drenth JP, van der Meer JW. N Engl J Med 2001;345:1748–57  
 Adapted from Yao Q, Furst DE. Rheumatology 2008;47:946–51  
 Aróstegui JI. Reumatol Clin 2011;7:45–50

+	Less extensive clinical manifestations
++	Moderately extensive
+++	Very extensive clinical manifestations

# CACZ885N2301 pivotal study for crFMF, TRAPS and HIDS (Study Design)



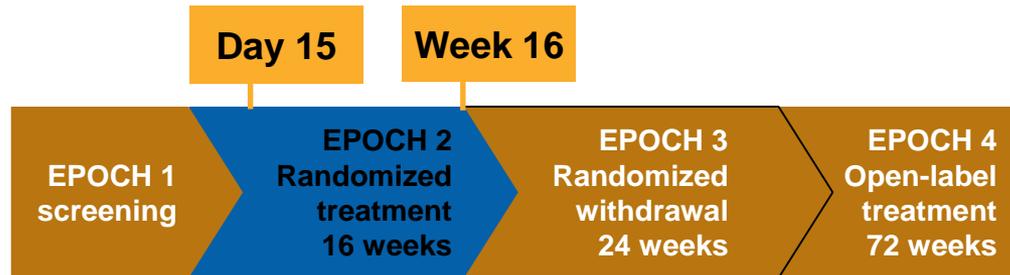
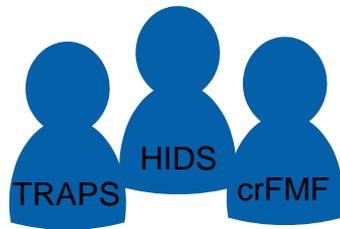
Identical for all 3 cohorts



# **CACZ885N2301 – Study Population**

- Male and female patients at least 2 years of age at the time of the screening visit will be enrolled in the randomized-treatment arm
- Male and female patients >28 days but <2 years old with bodyweight  $\geq 3.75$  kg at the time of the screening visit will be enrolled in the open-label arm only
- Clinical diagnosis and mutation of TRAPS, HIDS, or colchicine-resistant FMF and active clinical flare as evidenced by “mild”, “moderate”, or “severe” disease activity (PGA  $\geq 2$ )
- For FMF patients, colchicine resistance is defined as one of the following two:
  - Documented active disease despite colchicine therapy (from a minimum of 1.5 mg up to 3.0 mg/day or equivalent pediatric age/weight-adjusted dosing regimen depending on local guidelines or local standard practice)
  - Documented intolerance to effective doses of colchicine (from a minimum of 1.5 mg up to 3.0 mg/day or equivalent pediatric age/weight-adjusted dosing regimen depending on local guidelines or local standard practice)

# CACZ885N2301 – Primary Objective



## Primary objective

*To demonstrate superiority of canakinumab 150 mg q4w vs placebo in reducing disease activity by resolving flare by Day 15 and inhibiting new flares over 16 weeks of treatment*

## Responder definition

*(co-primary endpoints)*

- (1) Resolution of index flare at Day 15
  - a) PGA <2, AND
  - b) CRP normalization or 70% reduction

AND

- (1) No new flare from the resolution of the index flare until Week 16

### Index flare:

PGA  $\geq$ 2 and CRP >10 mg/L

### Resolution of index flare:

PGA <2 **and** CRP normalization ( $\leq$ 10 mg/L), or reduction by  $\geq$ 70% from baseline

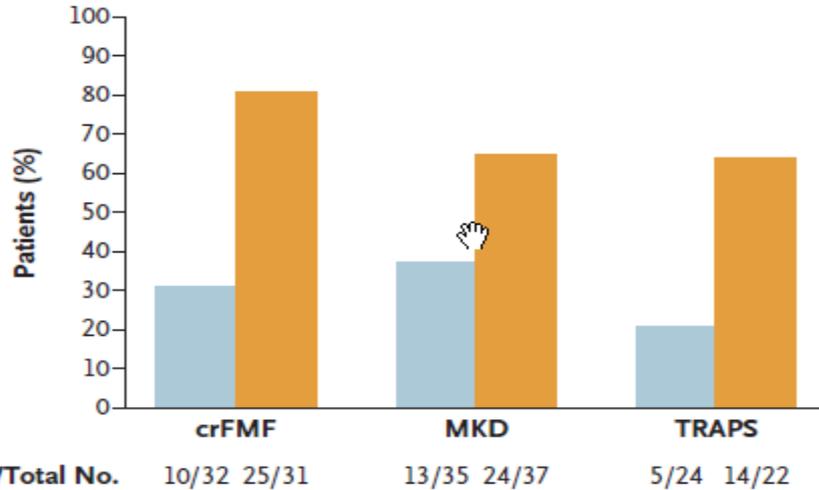
### New flare

PGA  $\geq$ 2 and CRP  $\geq$ 30 mg/L

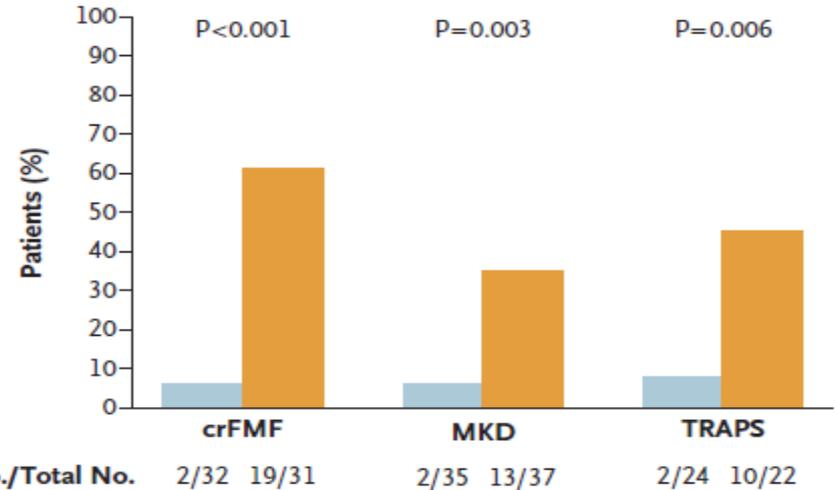
# Results: De Benedetti (NEJM 2018)

■ Placebo ■ Canakinumab, 150 mg every 4 wk

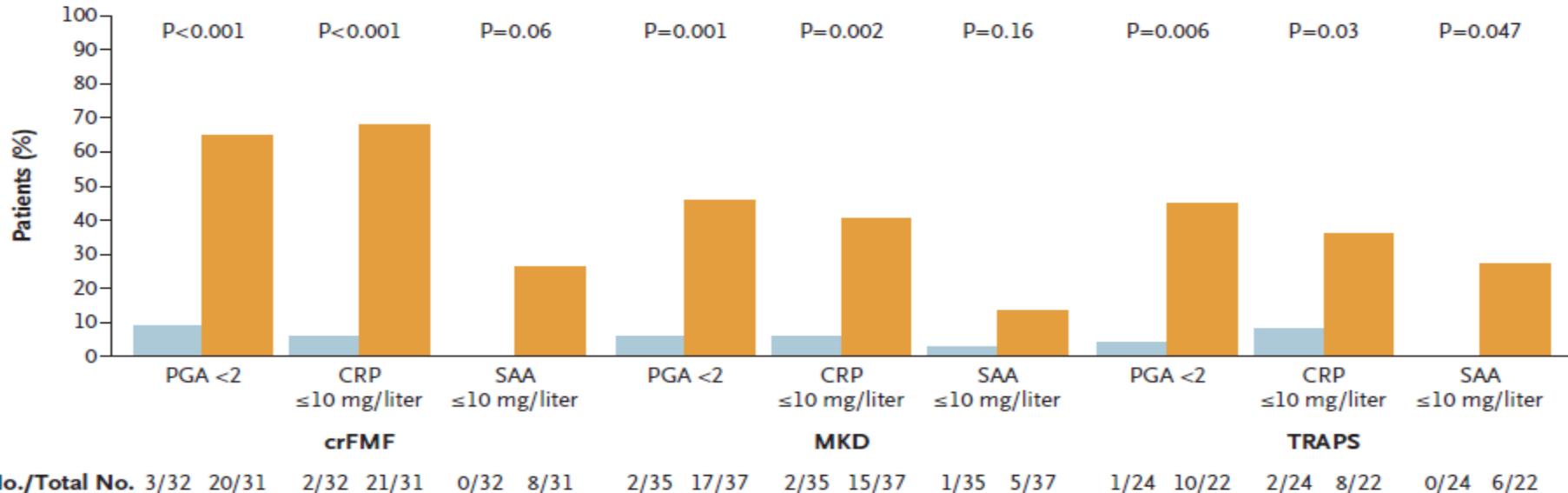
## A Resolution of Baseline Flare



## B Complete Response



## C Secondary Outcomes



# Reward for innovation

## Novartis Receives Three FDA Breakthrough Therapy Designations For Ilaris

4/27/2016 1:30 AM ET

Novartis ([NVS](#)) announced that the US Food and Drug Administration has granted three Breakthrough Therapy Designations for Ilaris or canakinumab to treat three rare types of Periodic Fever Syndromes, also known as Hereditary Periodic Fevers.

Periodic Fever Syndromes are a group of autoinflammatory diseases that cause disabling and recurrent fevers, which may be accompanied by joint pain and swelling, muscle pain and skin rashes, with complications that can be life-threatening. Most patients present with symptoms in infancy or childhood.

The three conditions for which Ilaris is being reviewed are Tumor Necrosis Factor-Receptor Associated Periodic Syndrome (TRAPS) and Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), as well as Familial Mediterranean Fever (FMF) not adequately controlled with colchicine.

The Breakthrough Therapy Designations were granted based on the pivotal Phase III CLUSTER trial. Based on this study Novartis submitted three supplemental Biologic License Applications in the US to register Ilaris for use in these indications.

by RTT Staff Writer

# What did we learn from this type of trial design?

- Basket designs are useful with rare autoimmune diseases if it is known that they can be treated by blocking the same pathway (IL-1 $\beta$ ) and efficacy can be evaluated by the same endpoint
- If historical data exists of a potential strong treatment effect, study can be done with relatively small sample size
- Flare designs which are common in autoimmune disease have challenges in defining meaningful estimands due to intercurrent events of treatment rescue and treatment switching

# Keys to successful master protocols in pediatric development

- Understanding the pathophysiology of the disease and selecting an endpoint that is able to assess clinically meaningful effectiveness
- Ability of sharing of placebo/standard of care patients across cohorts
- Evaluating of multiple orphan conditions that can be treated by blocking the same pathway
- Ability to make early decisions that treatments are highly efficacious or if demonstrating efficacy is futile

# **Extrapolation in Pediatric Drug Development**

# Why is extrapolation in pediatric drug development important

- Finding an adequate number of children (and their families) willing to participate in clinical trials is one of the most significant challenges in pediatric drug development, especially in diseases with serious outcomes.
- Often a proposal of a pediatric plan of proposed trials and age ranges for generating data on pediatric use is specified prior to starting Phase 3 in adults when generating such data is needed before a treatment can be used in pediatric patients
- Sample sizes are often based on feasibility (often 50-100 patients in transplantation) and the need to generate a minimum adequate amount of safety data.
- When it is known up front that recruiting the necessary patients may be difficult careful thought needs to be done to determine if extrapolation can be used to bridge the efficacy between adult and pediatric patients.

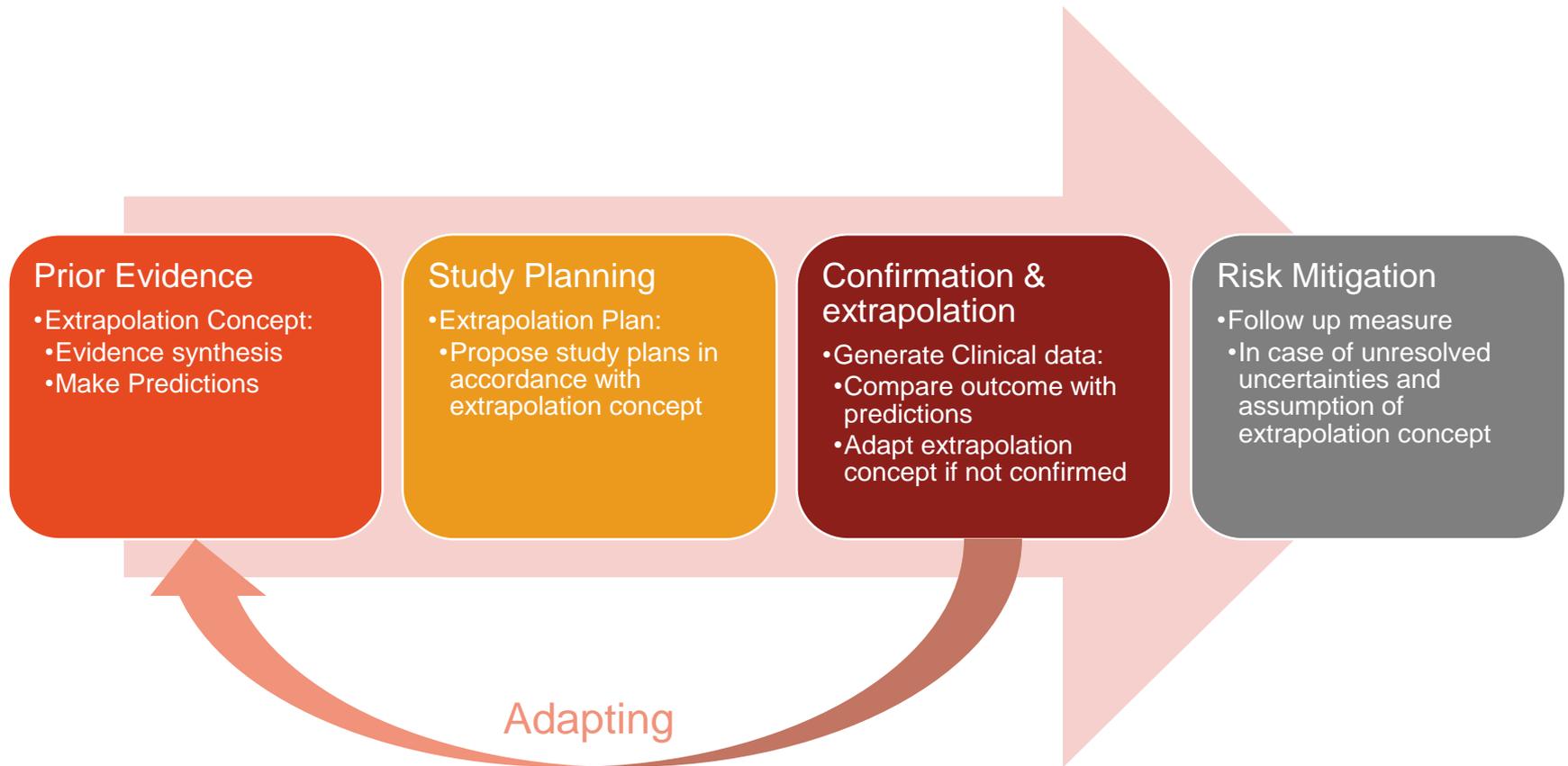
# Terminology & US background

- Generally understood, extrapolation is an inference from the known to the unknown.
  - to use known facts as the starting point from which to draw inferences or conclusions about something unknown
  - to predict by projecting past experience or known data
- Extrapolation of pediatric efficacy has a specific US legal definition.
  - “If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, [FDA] may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies.” (21 CFR §355c)

# EMA Reflection paper

- **Extrapolation:**
  - To build on a systematic synthesis of all available data, including the use of modelling and simulation approaches, with the aim of developing explicit predictions regarding differences of pharmacokinetics/pharmacodynamics (PK/PD), disease progression, and clinical response to treatment between source and target populations.
- **Aim:**
  - conclude on appropriate doses in the various age groups
  - conclude on efficacy and safety and the benefit-risk balance in the target population
- **Objective:**
  - to propose a framework that supports an explicit and systematic approach to extrapolation which sets out i) when, ii) to what extent, and iii) how extrapolation can be applied and validated.

# EMA Reflection paper: framework

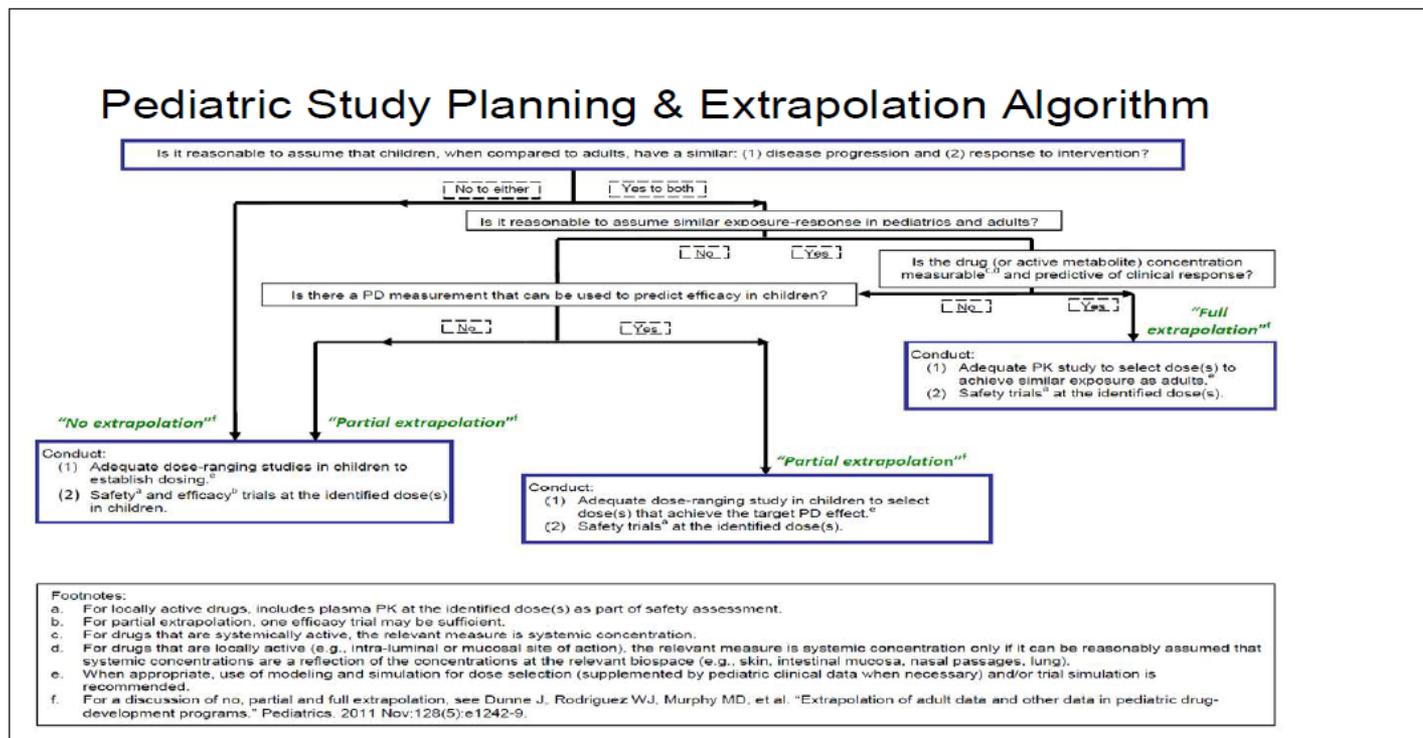


# FDA Guidance

- Extrapolation:

- is detailed in the draft 2014 guidance “General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products”

APPENDIX<sup>44</sup>



<sup>44</sup> See the Guidance for Industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (Footnote 13).

# FDA Guidance: Extrapolation Approaches

- Full Extrapolation (PK only):
  - Assumptions: that children, when compared to adults, have
    - a similar progression of disease;
    - a similar response of the disease to treatment;
    - a similar exposure-response relationship; and
    - the drug (or active metabolite) concentration is measureable and predictive of the clinical response.
  - Supporting evidence:
    - Common pathophysiology and natural history of disease
    - Common drug metabolism
    - Experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions
  - Requirements:
    - Conduct of PK study to select dose to achieve similar exposure as adult
    - Conduct safety trials at identified dose(s)

# FDA Guidance: Extrapolation Approaches

- Partial Extrapolation (PK and PD):
  - Assumptions:
    - disease and intervention are believed to behave similarly in pediatric patients and adults
    - exposure-response relationship in pediatric patients is either inadequately defined OR thought not to be sufficiently similar
    - PD measurement can be used to predict efficacy in children
  - Requirements if efficacy PD measure available:
    - Exposure-response relationship in adults should be well-characterized
    - Dose-ranging study in children to select dose(s) that achieve target PD effect
    - Safety trials at the identified dose(s)
  - Requirements if no efficacy PD measurement is available:
    - Dose-ranging studies in children to establish dosing
    - Safety and efficacy trials at identified dose(s) in children

# Approaches to extrapolation at FDA between 1998 and 2008

Success Rate



Extrapolation	Supportive Evidence Requested From Pediatric Studies	Products n/N (%)	New or Expanded Indication
None 17%	Two adequate, well-controlled, efficacy and safety trials plus PK data.	19/166 (11)	7/19 (37)
	Oncology products only: sequential approach starting with phase 1/2. Do not proceed if no evidence of response.	10/166 (6)	3/10 (30)
Partial 68%	Single, adequate, well-controlled, efficacy and safety trial (powered for efficacy) plus PK data.	67/166 (40)	35/67 (52)
	Single, controlled or uncontrolled, efficacy and safety trial (qualitative data) plus PK data.	20/166 (12)	15/20 (75)
	Single exposure-response trial (not powered for efficacy) plus PK and safety data, PK/PD and uncontrolled efficacy plus safety data, or PK/PD plus safety data.	26/166 (16)	19/26 (73)
Complete 14%	PK and safety data.	10/166 (6)	9/10 (90)
	Safety data only.	14/166 (8)	6/14 (43)

# EMA Extrapolation Workshop 2016

- Goal of the meeting was
  - to agree on recommendations for clinicians, modelers and statisticians which should result in an explicit and systematic approach for decision making alongside the life cycle.
  - to gather input from European stakeholders with invited observers, including experts from the ICH E11 (R1) guideline.
- Presentations are available under:
  - [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/events/2015/10/event\\_detail\\_001230.jsp&mid=WC0b01ac058004d5c3](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2015/10/event_detail_001230.jsp&mid=WC0b01ac058004d5c3)

# Extrapolation Approaches

- Bayesian Methods
  - To create an informative prior distribution for a parameter of a target population
  - assessing the appropriateness of parameters of source and target population
- Frequentist Methods
  - Synthesizing data across populations using a joint model,
  - Use of weighted test statistic across populations
  - Assess consistency of parameters between source and target population
- Others
  - Empirical models: popPK, PKPD models
  - Non-empirical PBPK models

# Bayes: Informative prior distribution for a parameter of a target population

- Method 1: Adaptive down-weighting of data from the source population
  - Example 1: Power Priors (and their 10 variations, not shown here)
    - Hierarchical power priors are formed by raising the likelihood  $L$  of the historical source data  $x_s$  to a power  $a_0 \in [0, 1]$ .
$$\pi^{PP}(\theta, a_0 | x_s) \propto L(\theta | x_s)^{a_0} \pi_0(\theta) \pi(a_0)$$
    - Prior  $\pi_0(\theta)$  represents the prior before historical source data become available, prior  $\pi(a_0)$  captures prior uncertainty on the appropriateness of parameters of historical and contemporary data.
    - Once data from the new trial become available, they are used to derive a posterior distribution for  $\theta$  and  $a_0$  given trial data  $x_T$  and source data  $x_s$ .
  - Similar or other concepts: comensurable priors (CP), meta-analytic predictive priors (MAP), mixture priors

# Bayes: Informative prior distribution for a parameter of a target population

- Method 2: Non-adaptive down-weighting of data from the source population
  - These methods use existing data from a source population to formulate an informative prior for  $\theta_T$ , down-weighting these data in a non-adaptive, pre-specified manner.
  - Example 1: Conditional Power priors (CPP)
    - Hierarchical power priors are formed by raising the likelihood  $L$  of the historical source data  $x_s$  to a power  $a_0 \in [0, 1]$ .
$$\pi^{CPP}(\theta, a_0 | x_s) \propto L(\theta | x_s)^{a_0} \pi_0(\theta) a_0$$
    - Prior  $\pi_0(\theta)$  denotes represents the prior before historical source data become available,  $a_0$  captures prior uncertainty on the appropriateness of parameters of historical and contemporary data.

# Bayes: Assessing the appropriateness of parameters of source and target populations

- Method 3: No down-weighting of data from the source population
  - Data from source and target population will be pooled once available to derive a posteriori distribution for  $\theta_T$ .
  - For this approach special a assessment of consistency between source and target population is required.
    - Examples: comparable PK levels by quantiles, posterior predictive probabilities

# Frequentist: Synthesizing data across populations

- Method 1: Synthesis of source and target population data by joint models
  - Parameters  $\theta_S$  and  $\theta_T$  can represent in this approach short/long-term treatment effects or distribution of 2 endpoints.
  - A group sequential test monitoring a long-term outcome in the target population is informed by data of the correlated short-term endpoint.
  - A joint likelihood is maximized by paired observations from source and target population.

# Frequentist: Using weighted statistics across populations

- Method 2: Combine of source and target population data by weighted test statistics
  - Let  $Z_T$  and  $Z_S$  test statistics of target and source populations comparing treatment against placebo following aprox. Standard normal distribution.
  - A weighted test statistics  $Z_w$  is proposed to test  $H_0: \theta=0$ .
  - $Z_w = \sqrt{\omega}Z_S + \sqrt{1 - \omega}Z_T$  with  $0 < \omega < 1$
  - And assuming that  $|Z_w| > Z_{1-\alpha/2}$  implies the results of the bridging study (in target population) are consistent with those of the reference study (in source population) which demonstrated efficacy of the new treatment relative to placebo.
  - The weight  $\omega$  should be pre-specified.

# Frequentist: Assess consistency across populations

- Method 3: Assess consistency between key parameter in source and target population.
  - If consistency is shown pooling data across population may be justified
    1. Global Methods:  
Assessment of consistency based on a test statistic combining data across all populations.
    2. Multivariate quantitative methods:  
Assessment of consistency by considering all pairwise differences between region-specific effect estimates
    3. Multivariate qualitative methods:  
Assessment whether patients from all populations can benefit from a new treatment.
  - All methods assume normal response variable. Let  $\Delta_j$  the difference in mean response of treatment E and C of population  $j=1, \dots, s$  and  $\Delta = \sum_j n_j \Delta_j / n$  the overall treatment effect.

# Frequentist: Assess consistency across populations

- Global Method:

- Utilize Cochran's Q statistics testing  $H_0: \Delta_1 = \Delta_2 = \dots = \Delta_s = \Delta$

- $Q = \sum_{j=1}^s \frac{(\hat{\Delta}_j - \hat{\Delta})^2}{2/n_j} < \chi^2_{s-1; 1-\alpha}$

- Some modifications of Q available

- Multivariate quantitative methods

- Testing  $H_0: \Delta_1 = \Delta_2 = \dots = \Delta_s = \Delta$  and declare treatment effect being consistent if no significant pairwise differences between effect estimates:

- $|\hat{\Delta}_i - \hat{\Delta}_j| < z_{\alpha/2} \sqrt{2(n_j + n_i)/(n_i n_j)}$  for  $i, j = 1, \dots, s \ i \neq j$

- Variations of the approach available

# Frequentist: Assess consistency across populations

- Multivariate qualitative methods:
  - Several similar methods to check for consistency are available. Methods are derived from checking consistency between regions.
  - Example 1 Non-inferiority approach:
    - Testing  $H_0: \Delta_1 \leq \delta\Delta$  or ... or  $\Delta_s \leq \delta\Delta$
    - Example 2 Confidence interval coverage:
      - $\hat{\Delta}_j > \pi\hat{\Delta} - z_{\alpha/2}\sqrt{2/n_j}$
    - Example 3 reproducibility probability:
      - Reproducibility power defined as the power of the bridging study to detect a treatment effect equal to the estimated effect from the source study which itself produced a significant result.
      - If the reproducibility probability exceeds a critical value (determined by a regulatory agency) then the target study may be considered unnecessary, that is clinical data from the original source population can be completely extrapolated to the new population to support claims of efficacy.

Ian Wadsworth, Lisa V Hampson and Thomas Jaki, 2016 Extrapolation of efficacy and other data to support the development of new medicines for children: A systematic review of methods, SMMR early view

# popPK Models to predict exposure

- Non-linear mixed effect models (popPK) are frequently used to predict drug concentrations and PD effects in children extrapolating from source to target age groups and consequently derive the required dose and regimen.
- Assumptions:
  - Comparable correlations between pharmacokinetic parameters and covariates across the entire age range
  - Comparable link between exposure and response

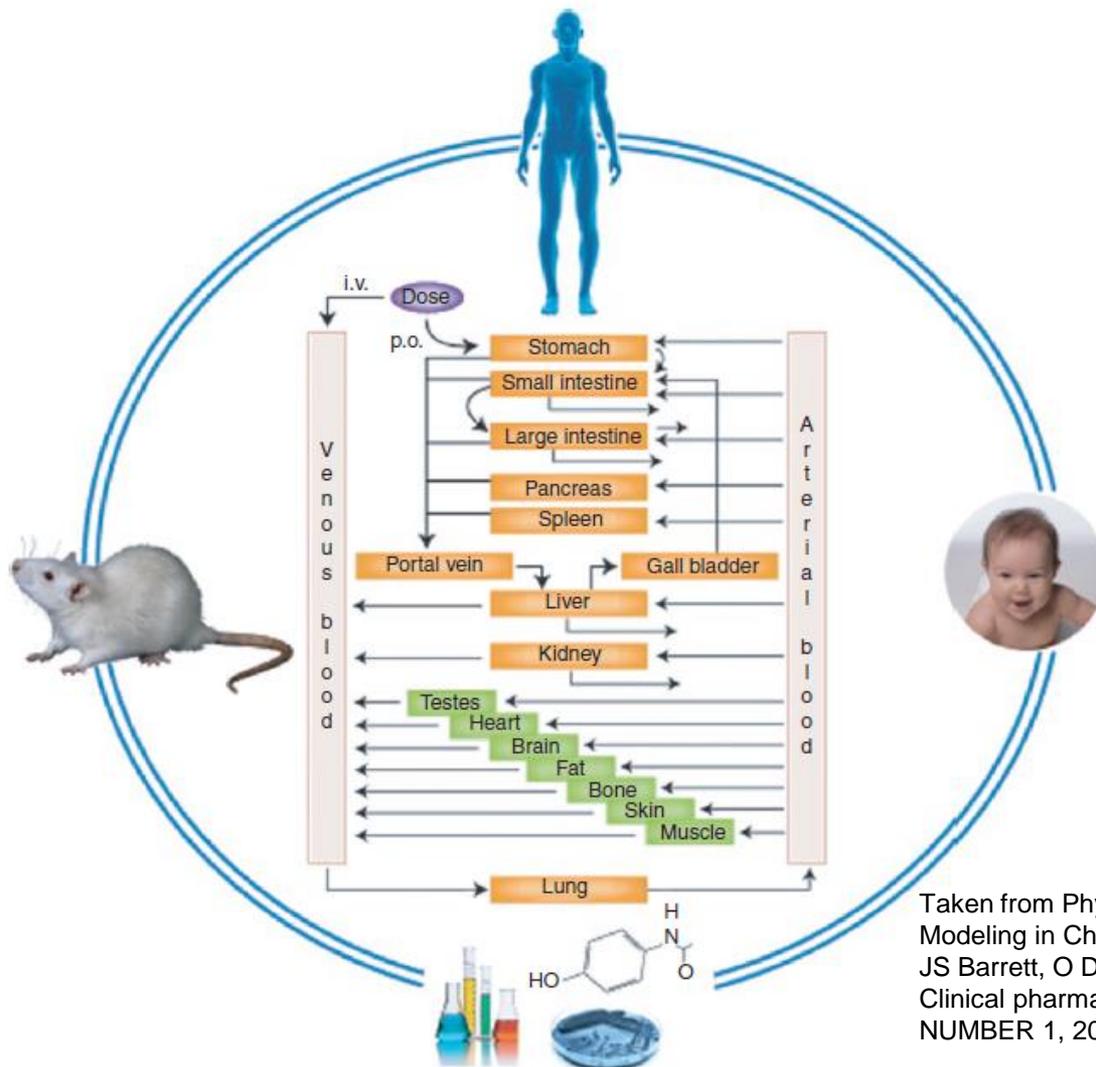
# PBPK models to predict exposure

- Physiologically based pharmacokinetic (PBPK) model provides a computational engine for predicting dose-exposure relationships in children.
  - Mass balance equations for each organ describe drug appearance in the organ from arterial blood and its exit into venous blood. The PBPK model is also constructed to incorporate relevant physiological, pharmacogenetic, biochemical, and thermodynamic parameters in a way that organizes much of the knowledge of the drug–body system
  - The approach is to modify a PBPK model that has been validated with adult PK data and then to incorporate the differences in growth and maturation that can affect all relevant aspects of drug disposition and PD.
    - E.g. changes in drug absorption, drug distribution, hepatic metabolism, renal excretion of drugs and drug metabolites.

Ref: Physiologically Based Pharmacokinetic (PBPK) Modeling in Children

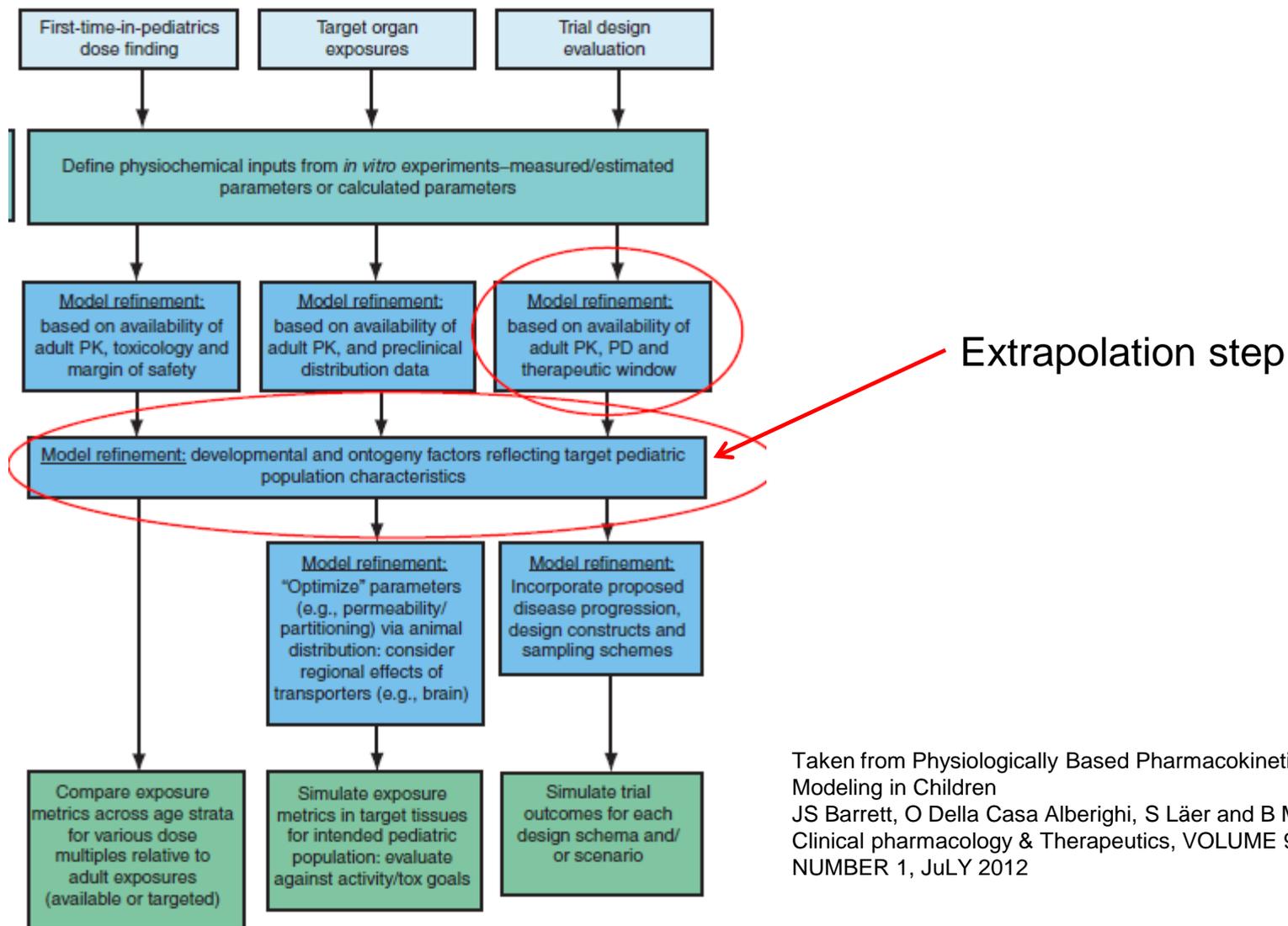
JS Barrett, O Della Casa Alberighi, S Läer and B Meibohm, Clinical pharmacology & Therapeutics, VOLUME 92 NUMBER 1, 2012

# PBPK models to predict exposure

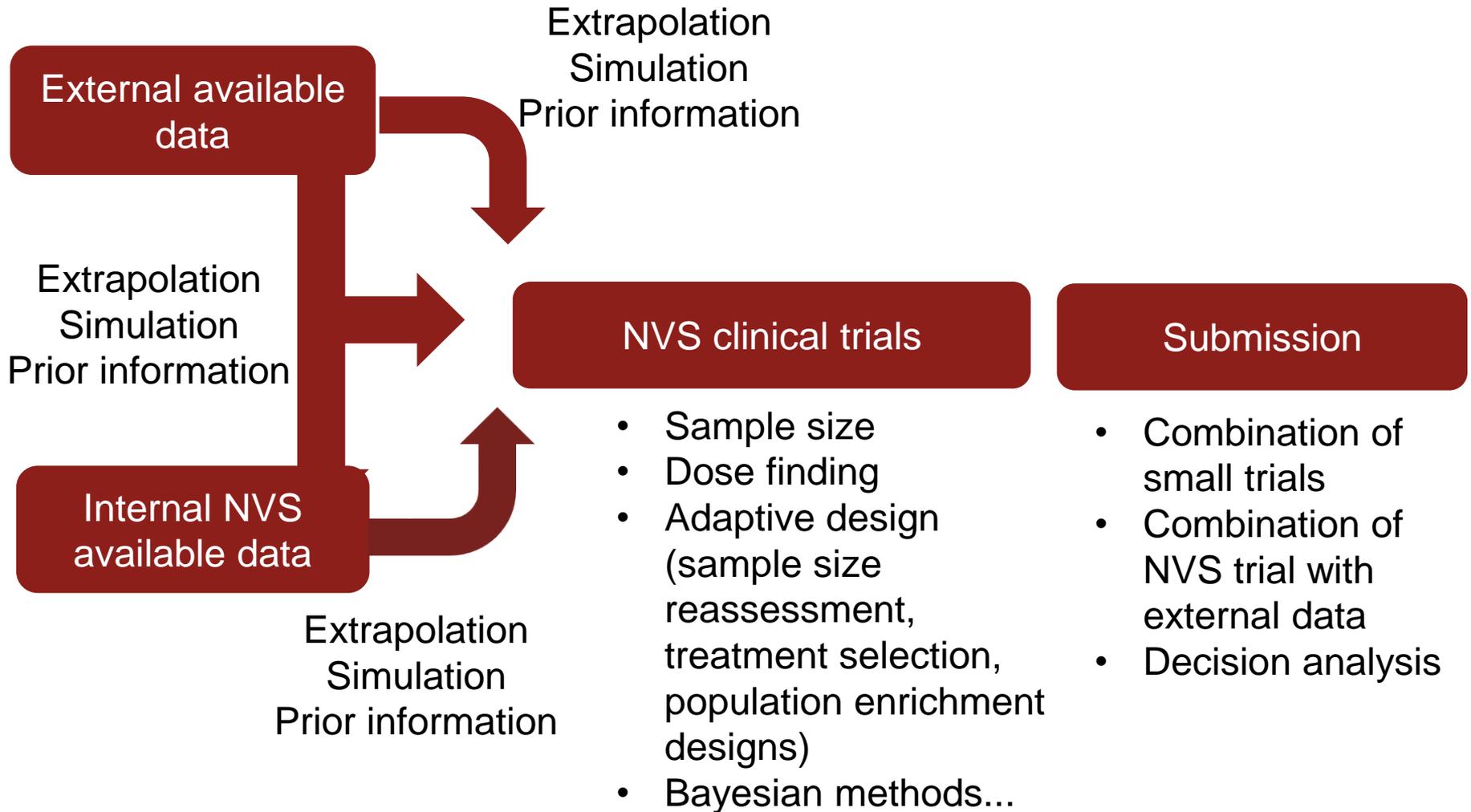


Taken from Physiologically Based Pharmacokinetic (PBPK) Modeling in Children  
JS Barrett, O Della Casa Alberighi, S Läer and B Meibohm,  
Clinical pharmacology & Therapeutics, VOLUME 92  
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# PBPK models to predict exposure



# Evidence synthesis



# Case study for extrapolation in pediatric kidney transplantation

- Extrapolation in de Novo kidney transplantation with everolimus from adult population to pediatric population to account for challenges in recruiting pediatric transplant patients
- Two step process of prediction and validation

## Prediction Step:

- A Bayesian meta-analysis was performed from adult data to derive the posterior predictive distribution
- Derived posterior distribution is used to predict outcomes in a matched pediatric population

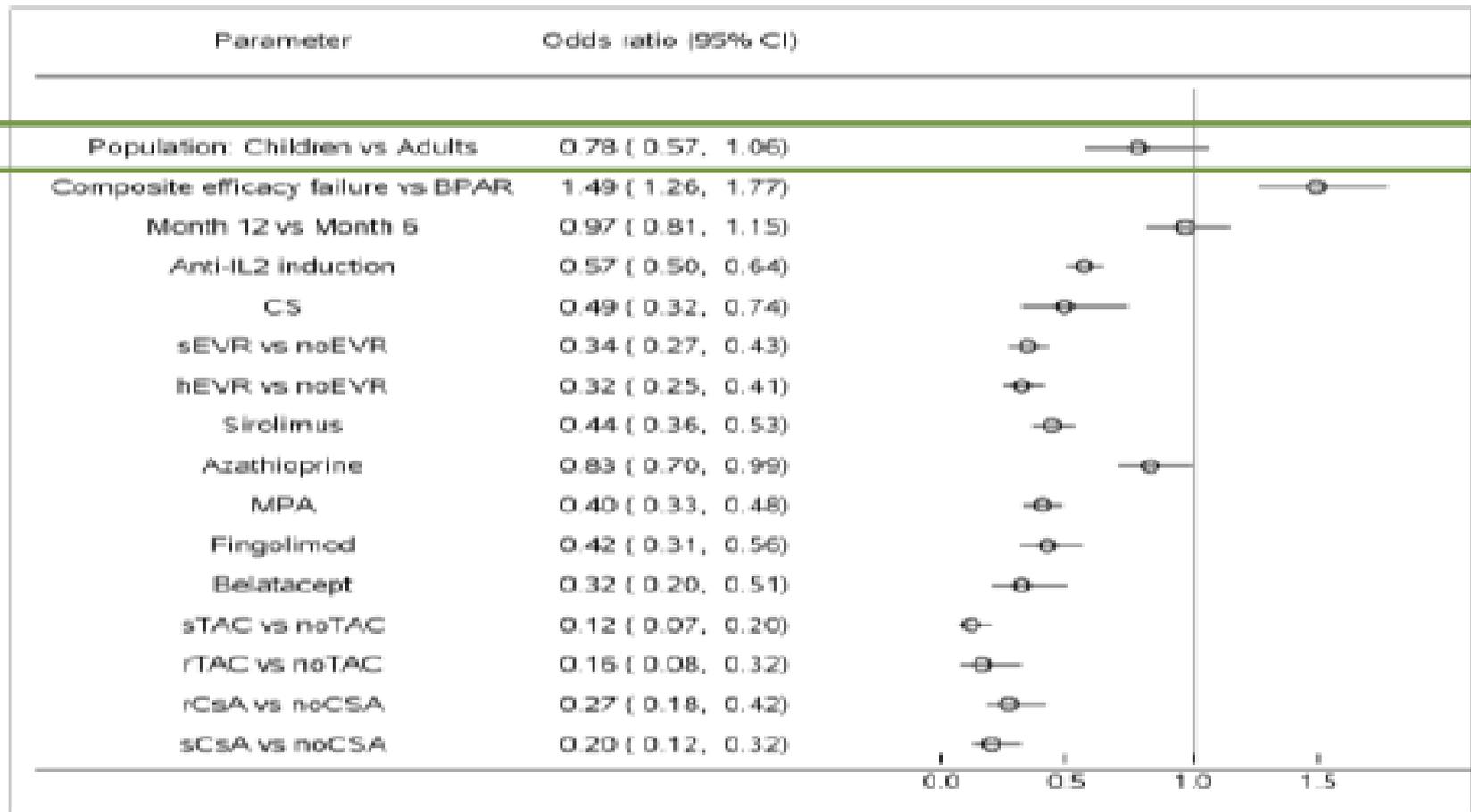
## Validation Step:

- The predicted pediatric outcomes based on adult data compared with outcomes observed in partially completed pediatric trials
- Demonstrate observed data are similar to what is predicted
- Combined with pharmacometric exposure-response modeling, evidence of similarity is used to argue that the partial sample size is adequate to satisfy the pediatric plan

# How was this implemented?

- ML Estimation of between adults and children in rejection rates
- Mixed effects logistic regression model of rejection event rate (Witte 2011)
- Kidney transplant study level data: 57 adult & 7 pediatric studies (>652 children, 19720 adults)
- Kidney transplant patient level data: 6 adult & 4 pediatric studies (72 children, 2052 adults)

# Estimated odds ratios for efficacy failures in kidney transplantation



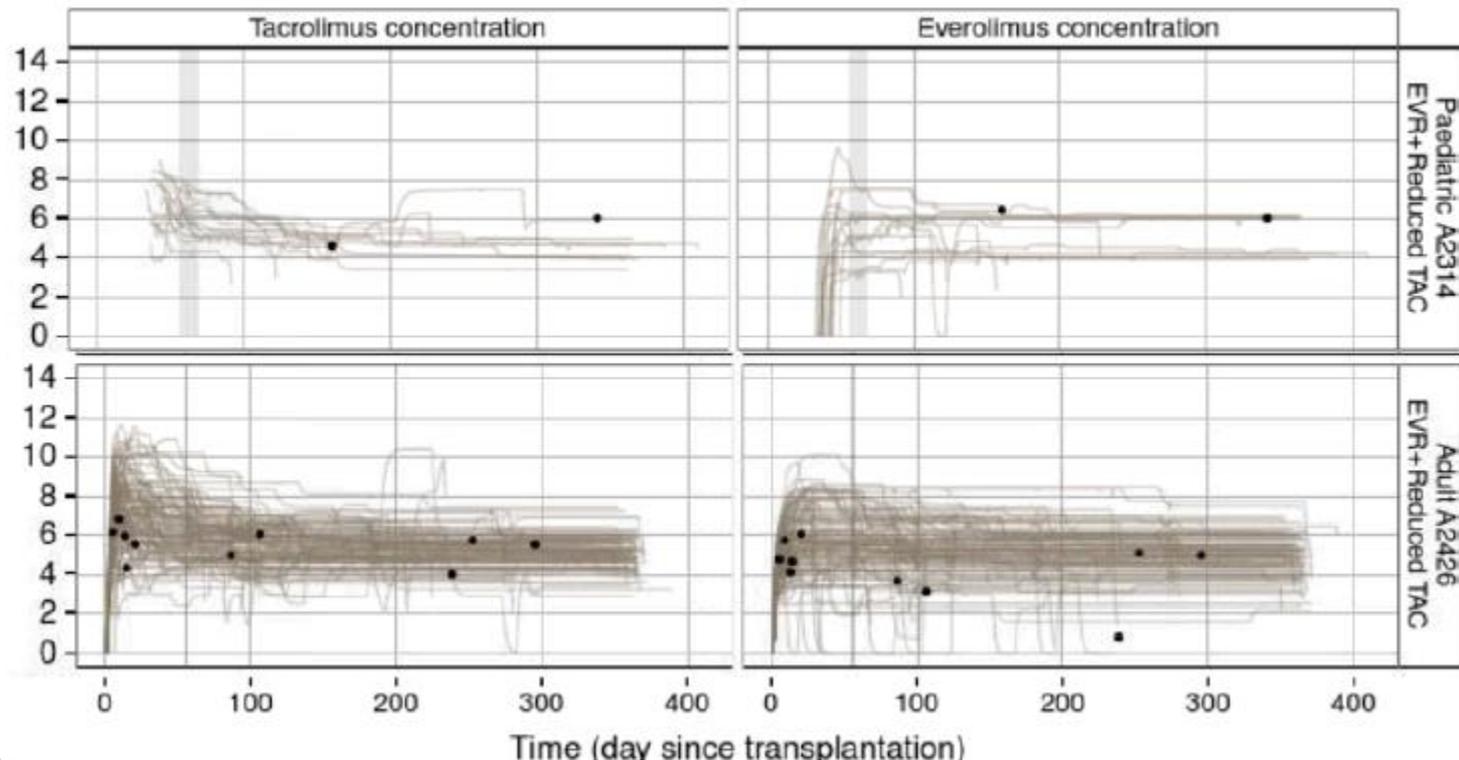
Pediatrics were estimated to have a slightly smaller (better) event rate, and similarity could not be excluded since the CI contained 1.



# Extrapolation based on exposure-response from adults to pediatrics

- The predicted tacrolimus + everolimus C<sub>min</sub> of the pediatric patients on days prior to the days with events were similar to those of the adult patients at the same time after transplantation

Time-course of predicted tacrolimus + everolimus C<sub>min</sub> concentration (kidney)



# What shall we do?

Evidence available?

Comparator? Or single arm?

Sample size? Power?

Statistical methods?

# Summary & Conclusions

- The complex innovative design initiative with the FDA is an ideal opportunity to provide new and innovative ways of studying the safety and effectiveness of treatments in pediatric patient populations
- Applying the extrapolation methods may reduce pediatric data requirements.
- Regulatory frameworks are available for US and EU
- Several Bayesian and frequentistic methods have been published to bridge statistics from adults to children or between different age groups.
- Modeling and Simulations can be applied under some assumptions
- Not one solution fits all in Rare diseases
- Choose the most appropriate method that will help to develop our drug in pediatric patients depending on the evidence already available.



