Dose-Response and Extrapolation of Efficacy from Older Pediatric Patients

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Disclaimer

The views expressed in this presentation are those of the presenter and do not necessarily represent the official position of the U.S. Food and Drug Administration.

Pediatric Extrapolation — Regulatory Framework

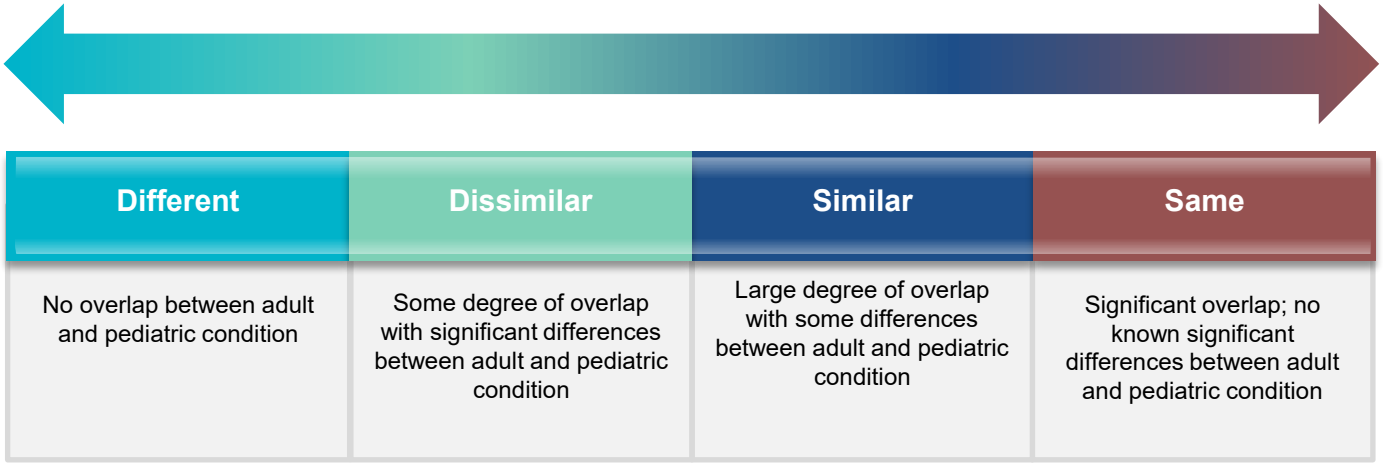
- Pediatric drug development has the same basic standard as for adults:
  - Substantial evidence of effectiveness and evidence indicating that the drug is safe for its intended use (benefits outweigh risks)

- We can rely on the concept of extrapolation to provide evidence in support of effective and safe use of drugs in the pediatric population if:
  - the disease is similar
  - the drug's pharmacology is similar
  - response to treatment is similar

  → vs. reference: adult or other pediatric subset

- The consensus on the level of similarity of the adult and pediatric conditions and treatment response falls on a spectrum

Extrapolation of Efficacy



Adapted from E11A Pediatric Extrapolation Guidance, December 2024

Challenges in Antihypertensive Drug Evaluation in Pediatric Patients

Unmet Medical Need

- Hypertension occurs in 2–5% of all pediatric patients; one of the top five chronic diseases in children
- Many pediatric patients are misdiagnosed in primary care settings
- Long-term consequences: heart disease, kidney disease, stroke

Operational and Scientific Challenges

- Off-label use
- Ethical constraints on placebo use
- Characterization of PK in youngest children; rapid physiologic changes and organ maturation
- Need for age-appropriate formulations
- Pediatric hypertension uses age-, sex-, and height-adjusted BP percentiles, complicating trial enrollment

Approved Antihypertensive Therapies in Pediatric Patients

ACEi	ARB	β-blocker	CCB	Renin inhibitor
Enalapril (Vasotec)	Losartan (Cozaar)	Metoprolol (Toprol XL)	Amlodipine (Norvasc)	Aliskiren (Tekturna)
Fosinopril (Monopril)	Olmesartan (Benicar)			
Lisinopril (Prinivil, Zestril)	Candesartan (Atacand)			
Benazepril (Lotensin)	Valsartan (Diovan)			

Approved in <6 years of age

ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker

Objective

- To compare the response to treatment between older and younger pediatric patients (6 to <17 years vs. 1 to <6 years of age)

Choice of Drugs

- Candesartan and valsartan - two drugs from the same class having dose/exposure-response data across the entire pediatric age range

Choice of Reference Group

- Older pediatric patients are closer in the age continuum
- Inaccessibility of data from the adult trials

Available Data and Study Designs

Candesartan

Age	Study # & Sample size	Design	Duration DB phase	Dosing (L/M/H)	Formulation	PK data	Primary efficacy variable
6 to <17 y	261A N=240	Randomized, double-blind (DB), placebo controlled	4 weeks	<50 kg 2/8/16 mg ≥50 kg 4/16/32 mg	Tablets	Yes sub-study (trough concentration)	mean seated SBP
1 to <6 y	328 N=93	Randomized, double-blind	4 weeks	0.05, 0.2, 0.4 mg/kg	Extemporaneous suspension		

https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-pediatric-assessments-conducted-under-prea-2007
Reviews of Pediatric Studies Conducted under BPCA and Pediatric assessments conducted under PREA from 2012 – present | FDA

Trachtman H, et al. J Clin Hypertens (Greenwich). 2008
Schaefer F, et al. J Hypertens. 2010
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Available Data and Study Designs

Valsartan

Age	Study # & Sample size	Design	Duration DB phase	Duration RPBW phase	Dosing (L/M/H)	Formulation	PK data	Primary efficacy variable
6 to <16 y	A2302 N=261	Randomized, double-blind (DB) + Randomized placebo withdrawal (PBW)	2 weeks	2 weeks	<35 kg 10/40/80 mg ≥35 kg 20/80/160 mg	Tablets	×*	mean seated SBP
1 to 5 y	A2307 N=90		2 weeks	2 weeks	<18 kg 5/20/40 mg ≥18 kg 10/40/80 mg	Extemporaneous suspension		
0.5 to 5 y	K2303 N=75		6 weeks	2 weeks	0.25, 1, 4 mg/kg			
1 to 5 y	K2306 N=127	Randomized, double-blind (DB)	6 weeks	×	0.25, 4 mg/kg	Oral solution		

* Single-dose PK data available but not as a part of the efficacy trial

Comparison of Inclusion/Exclusion Criteria: Older vs. Younger Pediatric Patients

Key Similarities

- Inclusion criterion for BP (naïve and treated): seated SBP and/or DBP ≥95th percentile for age, sex, and height; includes upper BP threshold; average of 2 or 3 measurements
- Exclusion of secondary hypertension (coarctation of the aorta, pheochromocytoma, hyperthyroidism, Cushing's syndrome, use of corticosteroids) – candesartan studies
- Exclusion of renal artery stenosis, nephrotic syndrome not in remission (candesartan), clinically significant arrhythmia
- Exclusion based on eGFR; cut-offs slightly varied b/w studies but mostly in the range of 30 to 50 mL/min (Schwartz equation)
- Inclusion of patients with renal transplant provided >6 mo. or 1 y prior to enrollment
- Exclusion of patients with impaired liver function and known hypersensitivity to ARBs

Notable Caveats

- Children <1 year excluded due to safety risk with RAS inhibitors in immature kidney
- CKD patients – 50% enrollment specified in K2306 but not specified in other studies

Overall, inclusion/exclusion criteria are broadly similar, supporting comparability of enrolled populations across age groups

Methodology and Variables

Objective

- Compare dose-response and exposure-response relationships between older (6 to <17 years) and younger (1 to <6 years) pediatric patients for candesartan and valsartan

Primary Efficacy Variable

- Change in seated systolic blood pressure (SBP) from baseline to last treatment visit (trough)

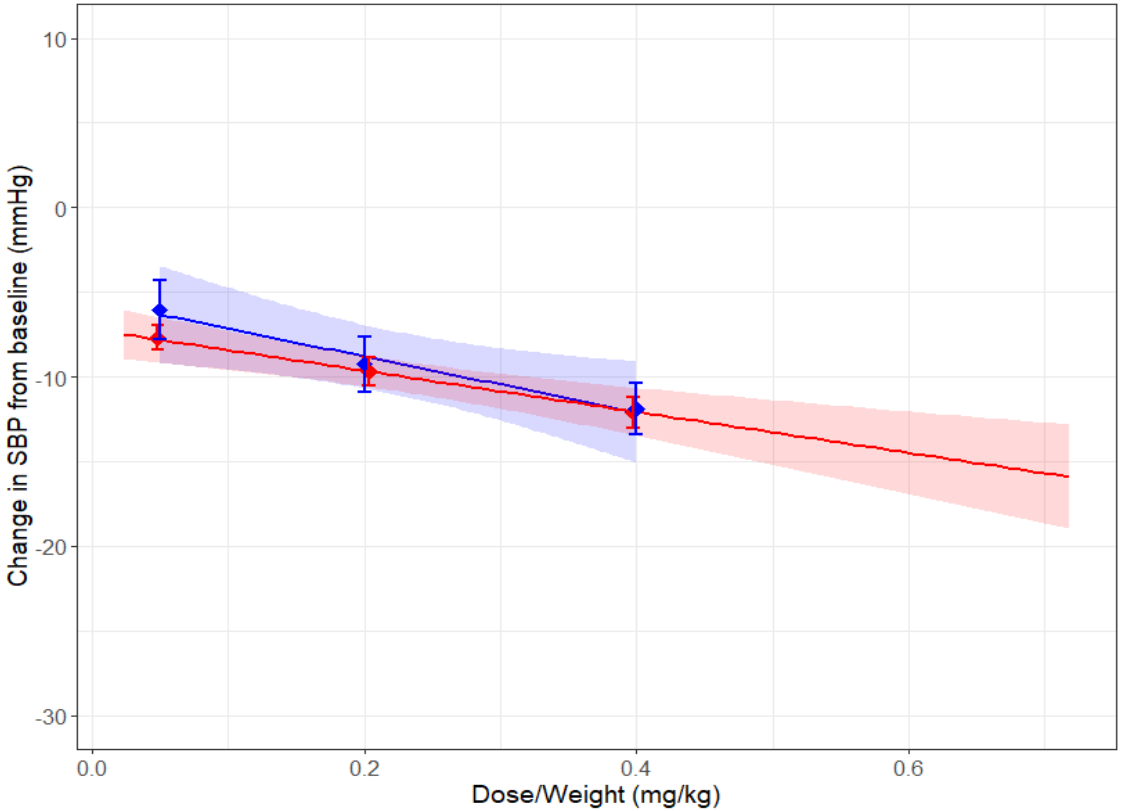
Dose-Response Analysis

- Simple linear regression of change in SBP vs. dose (mg/kg)
- Separate models for 1 to <6 years and 6 to <17 years
- Similarity assessed by comparing slope and intercept

Exposure-Response Analysis (Candesartan)

- Trough plasma concentration used as exposure metric (from PK sub-study in Study 328)
- Simple linear regression of change in SBP vs. trough concentration
  - Pooled and separate models by age group
- Similarity assessed by comparing slope and intercept

Similarity in dose-response relation between older and younger pediatric patients for candesartan



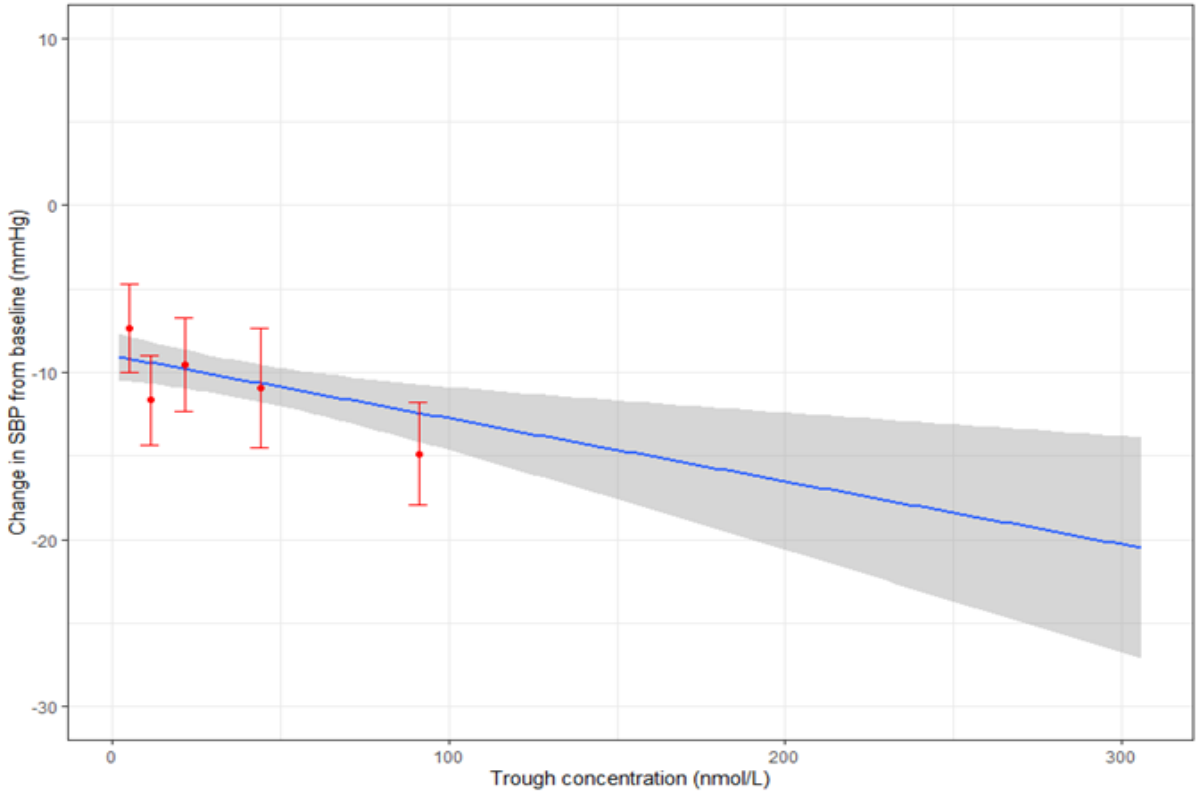
Age Group (years)

1 to <6

6 to <17

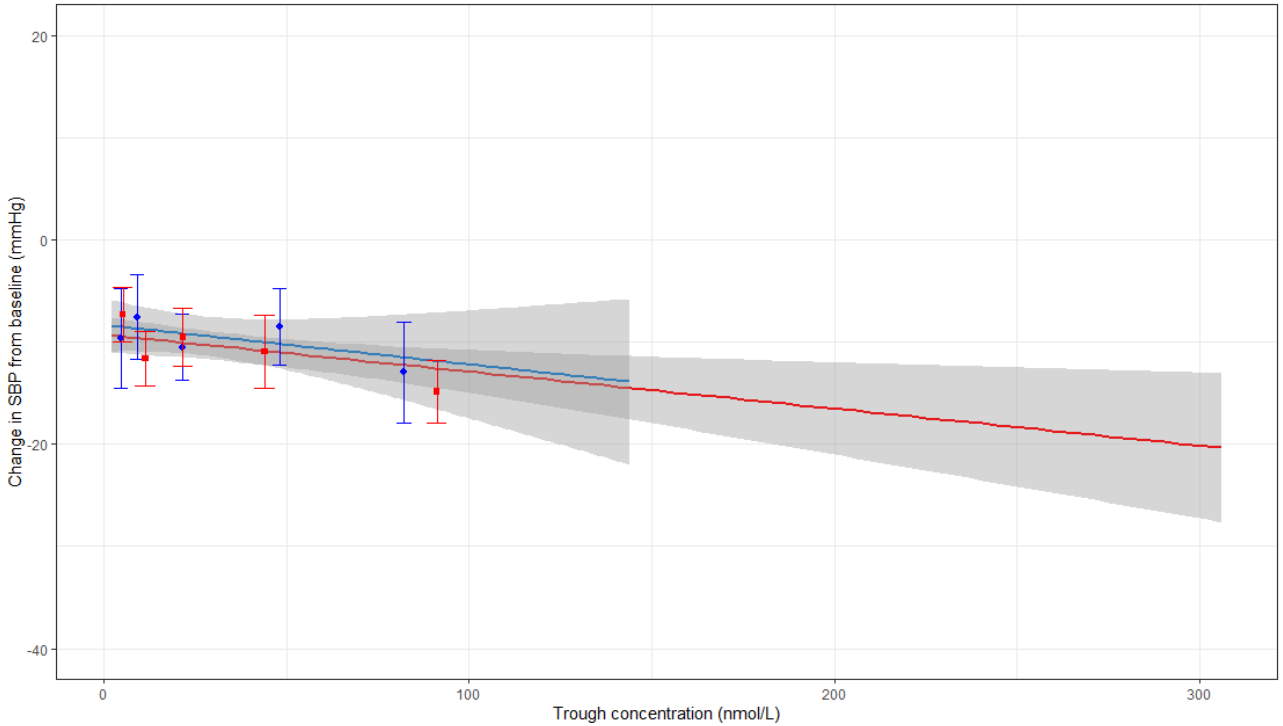
	Estimate	SE
Intercept	-5.50	± 1.72
Slope	-16.5	± 6.55
Intercept	-7.21	± 0.793
Slope	-12.1	± 2.98

Pooled exposure-response relation for changes in SBP from baseline for candesartan in pediatric patients



	Estimate	SE
Intercept	-8.98	± 0.722
Slope	-0.037	± 0.012

Similarity in exposure-response relation between older and younger pediatric patients for candesartan



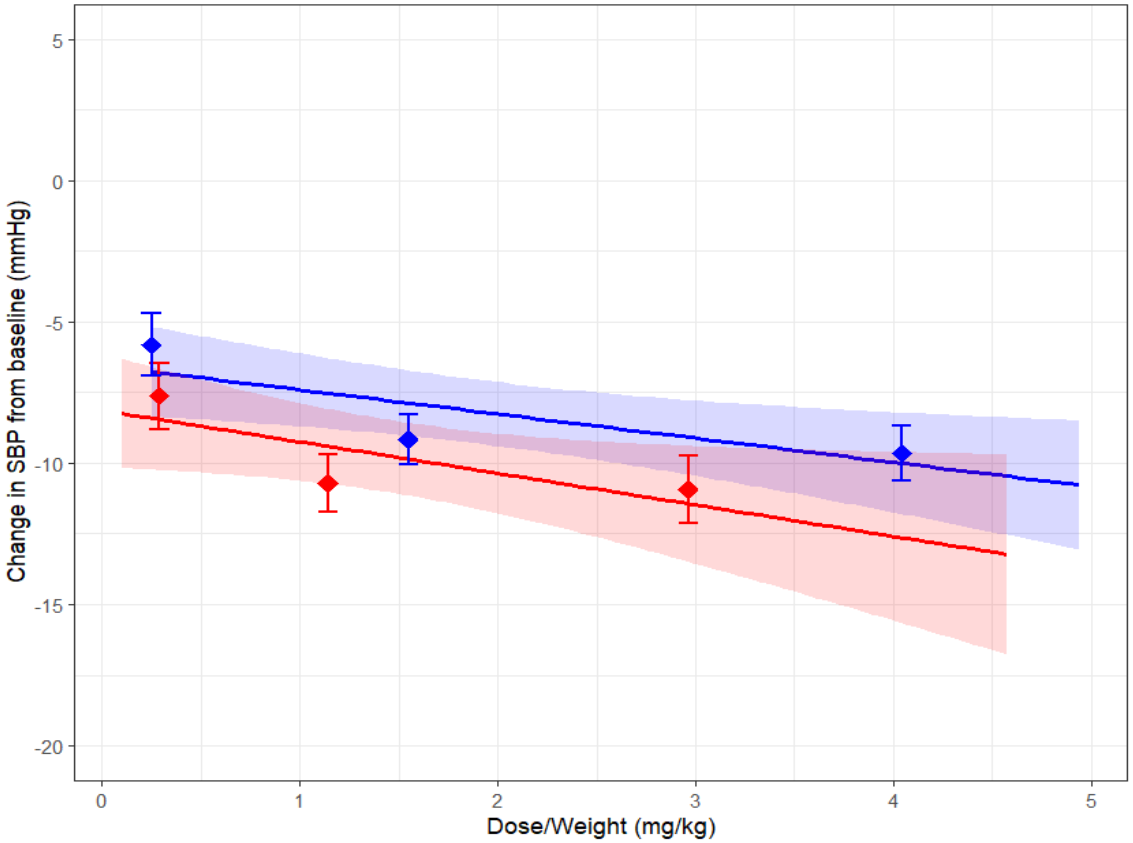
Age Group (years)

1 to <6

6 to <17

	Estimate	SE
Intercept	-8.35	± 1.32
Slope	-0.0386	± 0.0337
Intercept	-9.28	± 0.889
Slope	-0.0362	± 0.0137

Similarity in dose-response relation between older and younger pediatric patients for valsartan



Age Group (years)

1 to <6

6 to <17

	Estimate	SE
Intercept	-6.54	± 0.870
Slope	-0.856	± 0.336
Intercept	-8.12	± 1.02
Slope	-1.11	± 0.538

Conclusions and Implications

Support for Pediatric Extrapolation of Efficacy for ARBs

- Response to treatment is similar between older and younger pediatric patients
  - Similarity in dose/exposure-response relationship for candesartan and valsartan
- Lays the foundation for extrapolation of efficacy from older pediatric patients provided the disease is similar between the two groups

Implications

- Findings can inform other ARB pediatric programs entering via the 505(b)(2) pathway with pediatric friendly formulations to support an indication in pediatric patients.

What is Still Required?

- A pharmacokinetic (PK) study to determine a dosing regimen that provides drug exposures in younger patients similar to those effective in older pediatric patients
- Safety data focusing on the known adverse effects of the drug (ARB) class

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