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Landscape of pJIA drug development: Regulatory perspective

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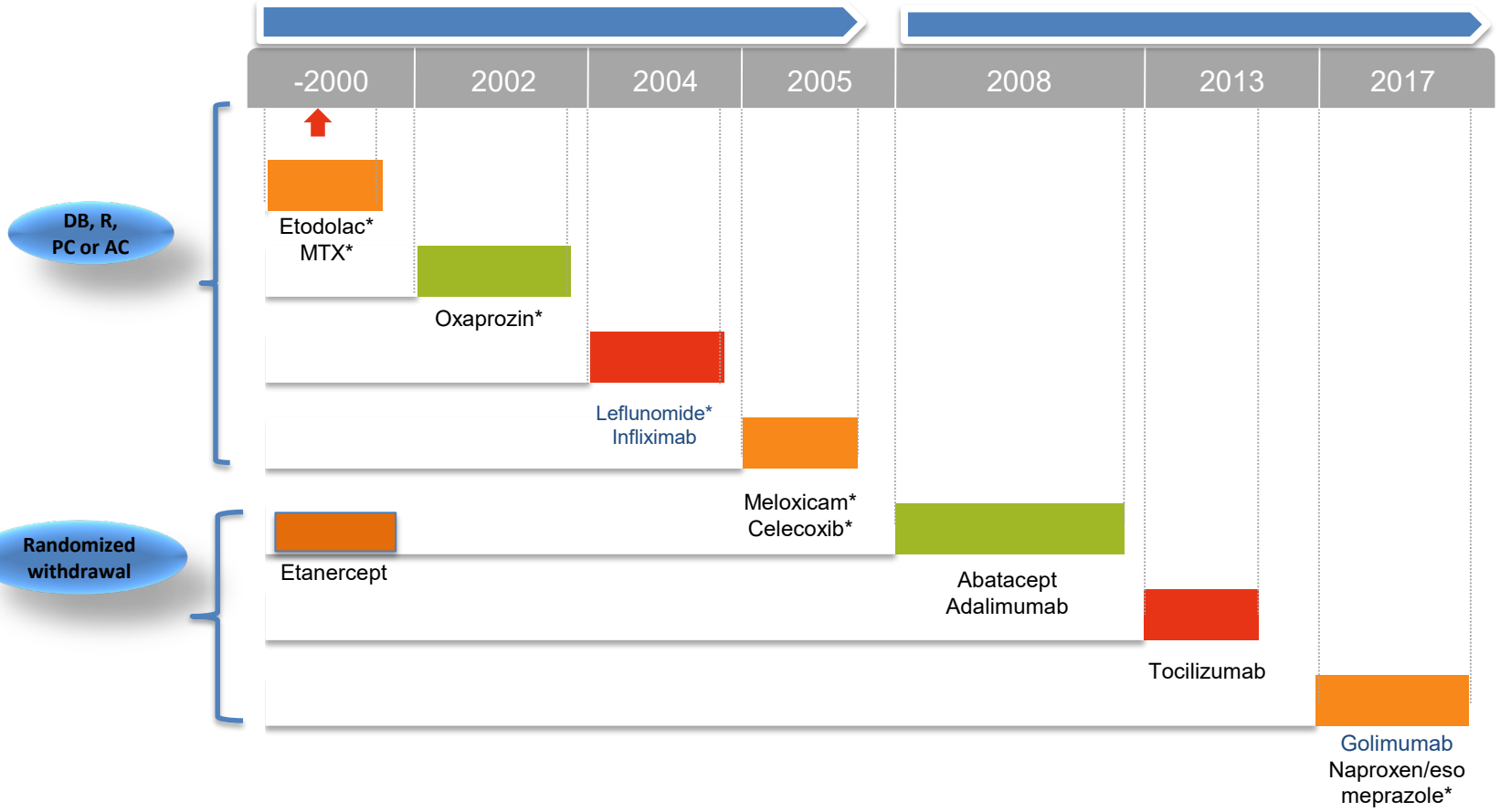
Pediatric submissions (pJIA)

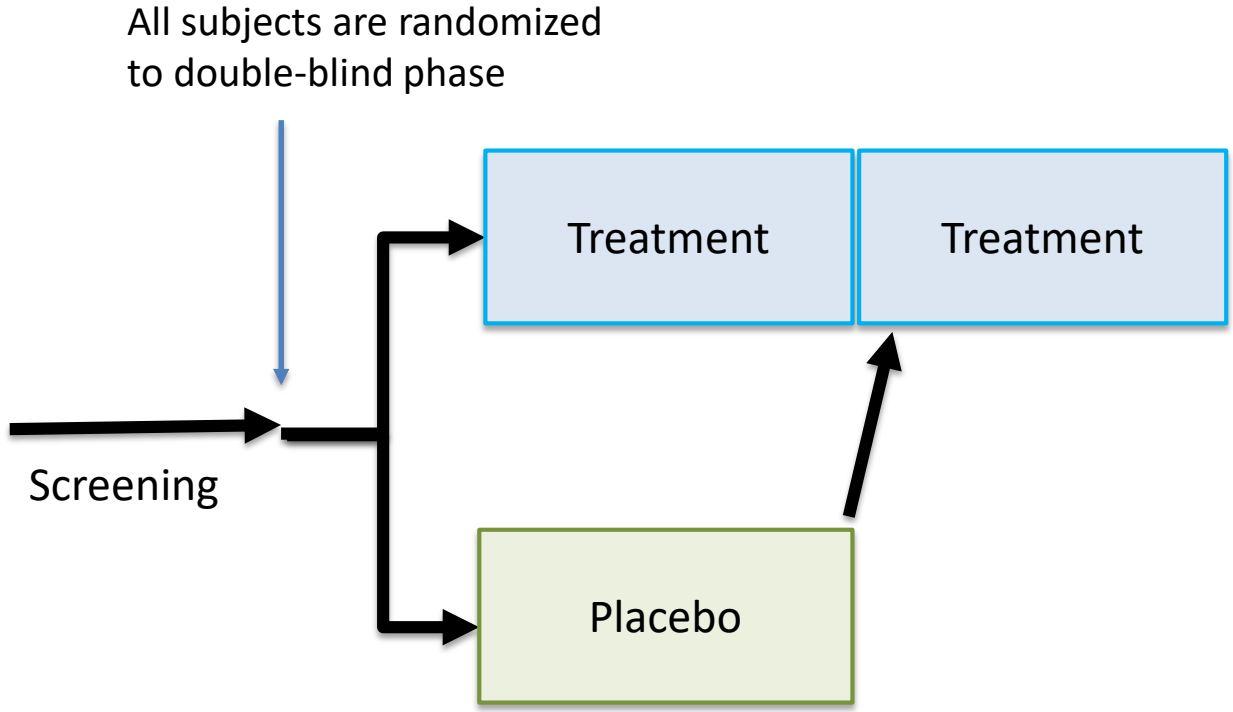


Negative trials: leflunomide, infliximab, golimumab
*small molecules

Ongoing/planned PJIA development program

- JAK inhibitors
  - Tofacitinib
  - Baricitinib
  - Upadacitinib
  - …
- Biologics
  - Sarilumab
  - …

Case 1: Parallel double blind design



- All Adult registration trials are parallel trial design

Methotrexate: Double blind, placebo controlled, parallel design

- Objectives: Efficacy and safety
- Patients: age range 2-17 yrs, N=127
- Design: 6-month, double-blind, placebo-controlled, multicenter study
- Primary endpoint: composite index, articular-severity score, physician's global assessment
- Dosing selection:
  - Adult RA: starting at 7.5 mg once weekly, may titrate up
  - PJIA:
    - methotrexate: 5 mg/m^2, QW, N=40
    - methotrexate: 10 mg/m^2, QW, N=46
    - Placebo, N=41

Methotrexate 10 mg/m2 , but not 5 mg/m2 QW demonstrated efficacy in pediatric patients

Physician global assessment

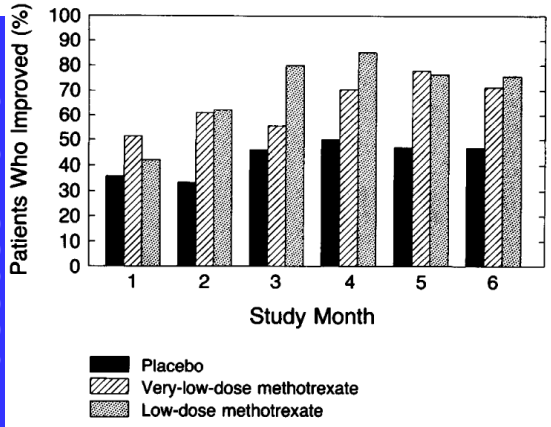


Figure 1. Physicians' Global Assessment of Patients' Response to Therapy.

Articular severity

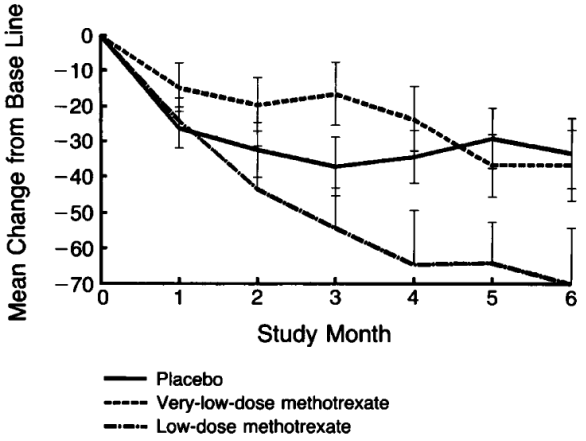


Figure 2. Mean (±SE) Change from Base Line in the Articular-Severity Score.

Composite index

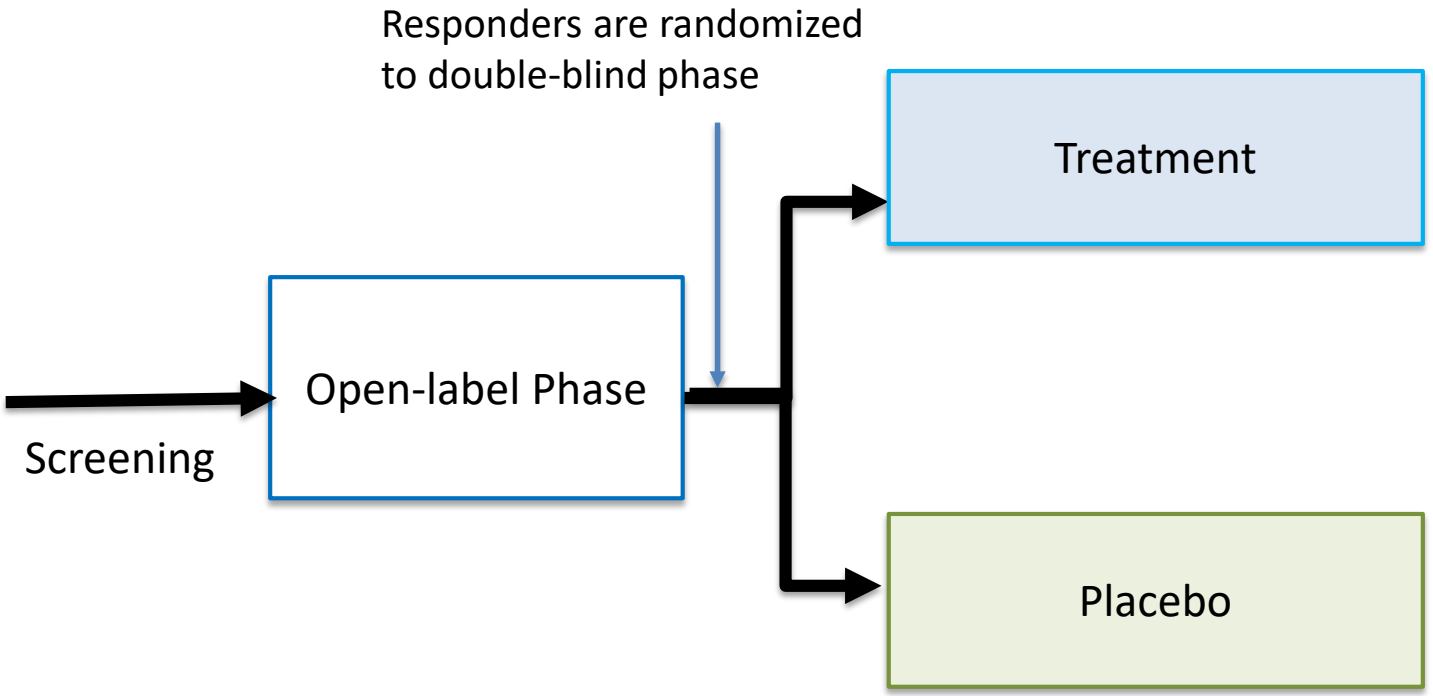
Table 2. Changes in the Indexes of Articular Disease at the Final Visit, According to Study Group.

Index	Low-Dose Methotrexate (N = 38)	Very-Low-Dose Methotrexate (N = 37)	Placebo (N = 39)	P Value*
	mean (±SE) and median changes from base line			
No. of joints with swelling	−7.1±1.8, −5.5	−4.9±1.7, −2	−4.3±1.4, −4	>0.3
Severity of swelling	−14.5±3.3, −10	−9.3±2.6, −4	−9.2±2.3, −8	>0.3
No. of joints with pain on motion	−11.0±2.2, −5	−3.0±1.7, −1	−7.1±2.1, −3	0.016
Severity of pain on motion	−19.0±4.4, −10	−6.1±2.5, −2	−11.5±3.1, −5	0.02
No. of joints with tenderness	−9.0±2.1, −6.5	−4.9±1.7, −2	−5.2±2.1, −2	0.257
Severity of tenderness	−17.1±4.6, −9	−7.7±2.4, −4	−9.0±2.7, −4	0.109
No. of joints with limitation of motion	−5.4±1.7, −3.5	−0.5±1.6, 0	−0.7±1.3, −1	0.04
Severity of limitation of motion	−12.2±4.4, −10	−5.0±2.9, −6	−4.1±2.4, −3	0.166
No. of joints with active arthritis	−7.5±2.6, −7	−5.2±2.0, −1	−5.2±1.5, −4	>0.3
Articular-severity score	−63.0±15.0, −52	−28.0±9.0, −17	−36.4±8.8, −24	0.077
Duration of morning stiffness (min)	−52.3±11.8, −30	−50.5±22.9, −18.5	−41.8±15.1, −20	>0.3

*By unadjusted analysis of variance.

Giannini EH, et al. The New England Journal of Medicine, Apr 1992. Vol326(16), 1043-49

Case 2: Randomized Withdrawal Design



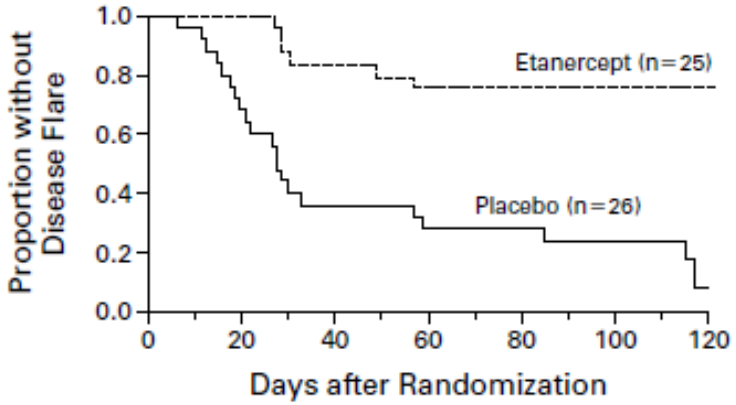
- All Adult registration trials are parallel trial design

Case 2: Enbrel (Etanercept): Randomized withdrawal design

- Objectives: Efficacy, safety, and PK
- Patients: PJIA patients 2-17 years, N=69
- Design: 90 day open-label lead-in phase, followed with a 4-month randomized double-blind phase
- Primary endpoint: Time to flare
- Dose selection:
  - Adult RA: 25 mg SC twice weekly
  - PJIA:
    - Etanercept 0.4 mg/kg up to 25 mg SC twice weekly
    - Placebo
  - Later, dose for adult RA: 50 mg SC once weekly
  - PJIA: Dose change accordingly to match adult
    - Etanercept 0.8 mg/kg once weekly

Etanercept Pediatric Trial Results

Efficacy



Etanercept group significantly better than placebo for efficacy, comparable for safety

Safety

- Well tolerated
- No significant differences in the frequencies of adverse events between patients who received etanercept and those who received placebo.

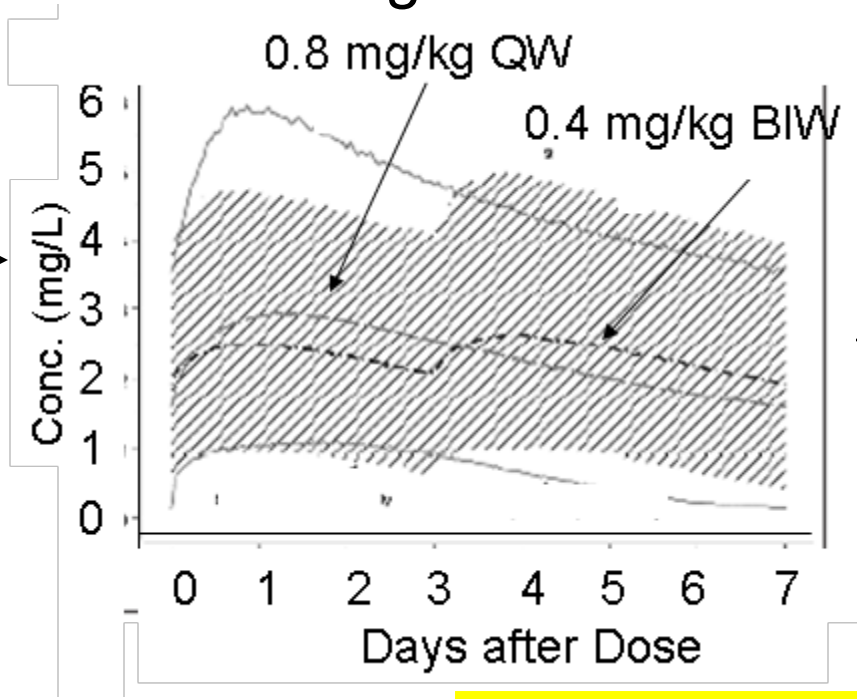
Lovell DJ, N Engl J Med 2000; 342:763-769

Etanercept Dosing Recommendation in Pediatric Patients

Efficacy trial

0.4 mg/kg BIW approved for PJIA

PK modeling and simulation



0.8 mg/kg QW approved for PJIA

Yim DS, et al. J Clin Pharmacol. 2005 Mar;45(3):246-56.

Different placebo effect across PJIA programs

Drug	Patient Characteristics	JIA ACR response (end of OL phase)	Flare rates	Response withdrawal (treatment/placebo)
Golimumab	2 – 17 years of age with MTX-IR active PJIA	ACR 30: 89.0% ACR 50: 79.2% ACR 70: 65.9%	GLM: 41% PBO: 47.4%	ACR 30: 55%/52% ACR 50: 54%/51% ACR 70: 47%/47%
Etanercept	4 – 17 years of age with MTX-IR active PJIA	ACR 30: 74% ACR 50: 64% ACR 70: 36%	ETA: 24% PBO: 77%	ACR 30: 80%/35% ACR 50: 72%/23% ACR 70: 44%/19%
Adalimumab	4 – 17 years of age with MTX-IR active PJIA and naïve MTX treatment	ACR 30*: 94% ACR 50*: 91% ACR 70*: 71%	ADA: 37% PBO: 65%	ACR 30*: 63%/38% ACR 50*: 63%/38% ACR 70*: 63%/27%
Tocilizumab	2 – 17 years of age with MTX-IR active PJIA	ACR 30: 89% ACR 50: 83% ACR 70: 62%	TCZ: 26% PBO: 48%	ACR 30: 74%/54% ACR 50: 73%/52% ACR 70: 65%/42%

*Patients receiving MTX

Product labels and literature:

- Golimumab: Brunner HI, et al. Ann Rheum Dis 2018;77:21–29
- Etanercept: Lovell DJ, N Engl J Med 2000; 342:763-769
- Adalimumab: Lovell DJ, N Engl J Med 2008; 359:810-820
- Tocilizumab: Brunner HI, et al. Ann Rheum Dis 2015;74: 1110–1117

Double-blind vs open-label ACR response

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Etanercept	4 – 17 years of age with MTX-IR active PJIA	ACR 30: 74% ACR 50: 64% ACR 70: 36%	ETA: 24% PBO: 77%	ACR 30: 80%/35% ACR 50: 72%/23% ACR 70: 44%/19%
Adalimumab	4 – 17 years of age with MTX-IR active PJIA and naïve MTX treatment	ACR 30*: 94% ACR 50*: 91% ACR 70*: 71%	ADA: 37% PBO: 65%	ACR 30*: 63%/38% ACR 50*: 63%/38% ACR 70*: 63%/27%
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Case 3: Extrapolation of Efficacy

- The extrapolation of efficacy in PJIA for ≤4-6 yrs age from >4-6 yrs age
  - Adalimumab
  - Abatacept

- The extrapolation of efficacy in PJIA for SC route from IV route
  - Tocilizumab
  - Abatacept

- Evaluation of extrapolation of efficacy in PJIA from adult RA ?
  - EMA PJIA guideline (came into effect Jun 2016)

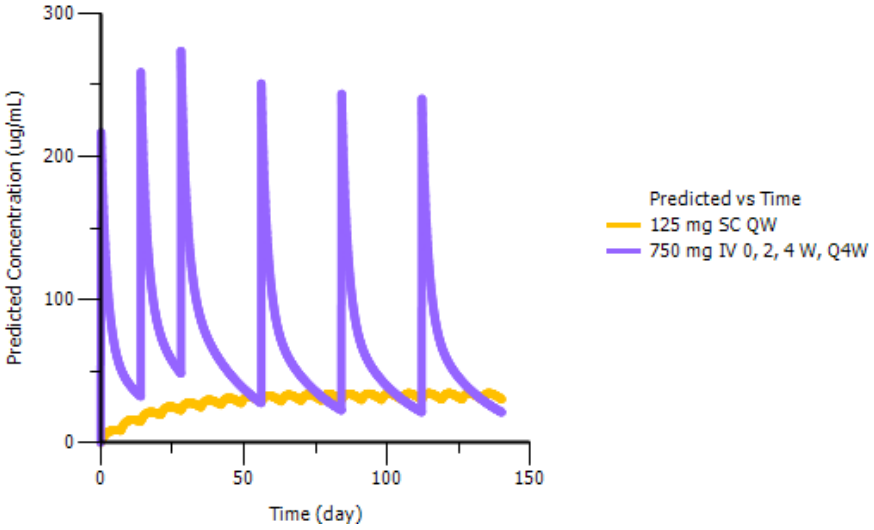
Case 3:ORENCIA (Abatacept)

Route	RA	PJIA (≥6 yr)
IV (Initial approval 2005; approved for PJIA 2008, lyophilized powder)	< 60 kg, 500 mg; 60-100 kg,750 mg; >100 kg ,1000 mg W2, W4, Q4W thereafter	<75kg, 10 mg/kg; ≥75 kg, adult dose W2, W4, Q4W thereafter
Subcutaneous (PFS, approved 2011; Autoinjector 125 mg)	125 mg QW Optional IV loading dose	E, S 10 to< 25 kg, 50 mg; 25 to <50 kg, 87.5mg; ≥50 kg ,125 mg QW

- SC: Efficacy extrapolation based on Cmin

Dose selection for abatacept SC: To match the steady state Cmin

- Written request: Efficacy of SC abatacept will be supported by demonstrating the proposed SC abatacept regimen is able to achieve the **steady state trough concentration (Cmin)** associated with efficacy in the IV abatacept PJIA study used to support the approval of abatacept for PJIA.



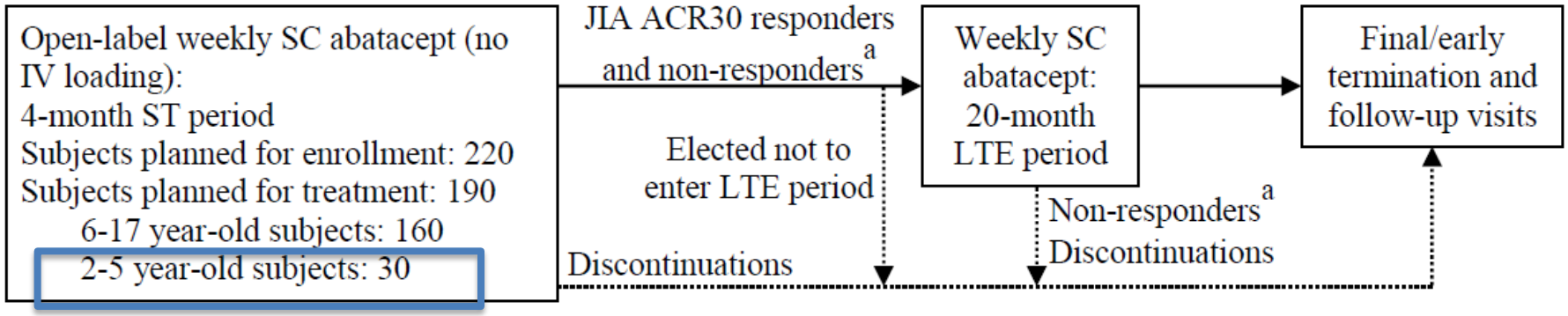
PK Parameter	SC	IV
AUC (TAU) (µg•h/mL) [b,c]	5875.5 (1261.0, 13068.4)	41981.5 (18315.6, 88991.5)
Observed Cmax (µg/mL) [b]	48.1 (9.8, 132.4)	231.6 (123.1, 458.9) [d]
Observed Cmin (µg/mL) [b,e]	32.5 (6.6, 113.8)	22.3 (1.2, 80.6)

Approval in 2-5 year-old

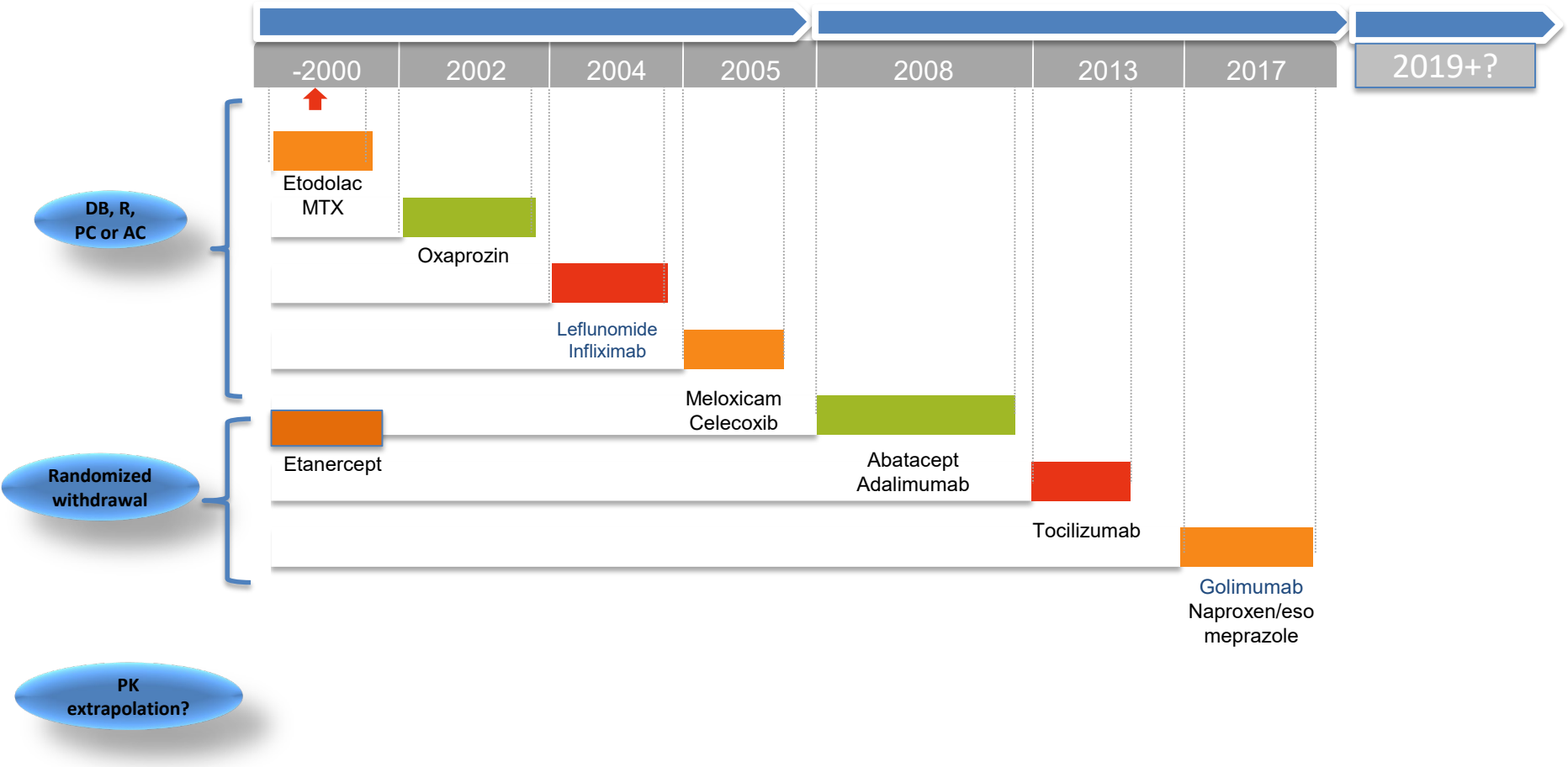
- Phase 3 Study IM101301 is an open-label study that evaluated the pharmacokinetics (PK), safety, efficacy, and immunogenicity of a weekly weight-tiered SC abatacept dosing regimen in subjects 2-17 yrs old with JIA.

- The efficacy for SC abatacept is extrapolated from the IV study (101033) in PJIA. In the IV study, the youngest is 5 yr old and the lowest weight is 14 kg.

- Consistent PK, efficacy (OL) and safety in 2-5 yrs old.

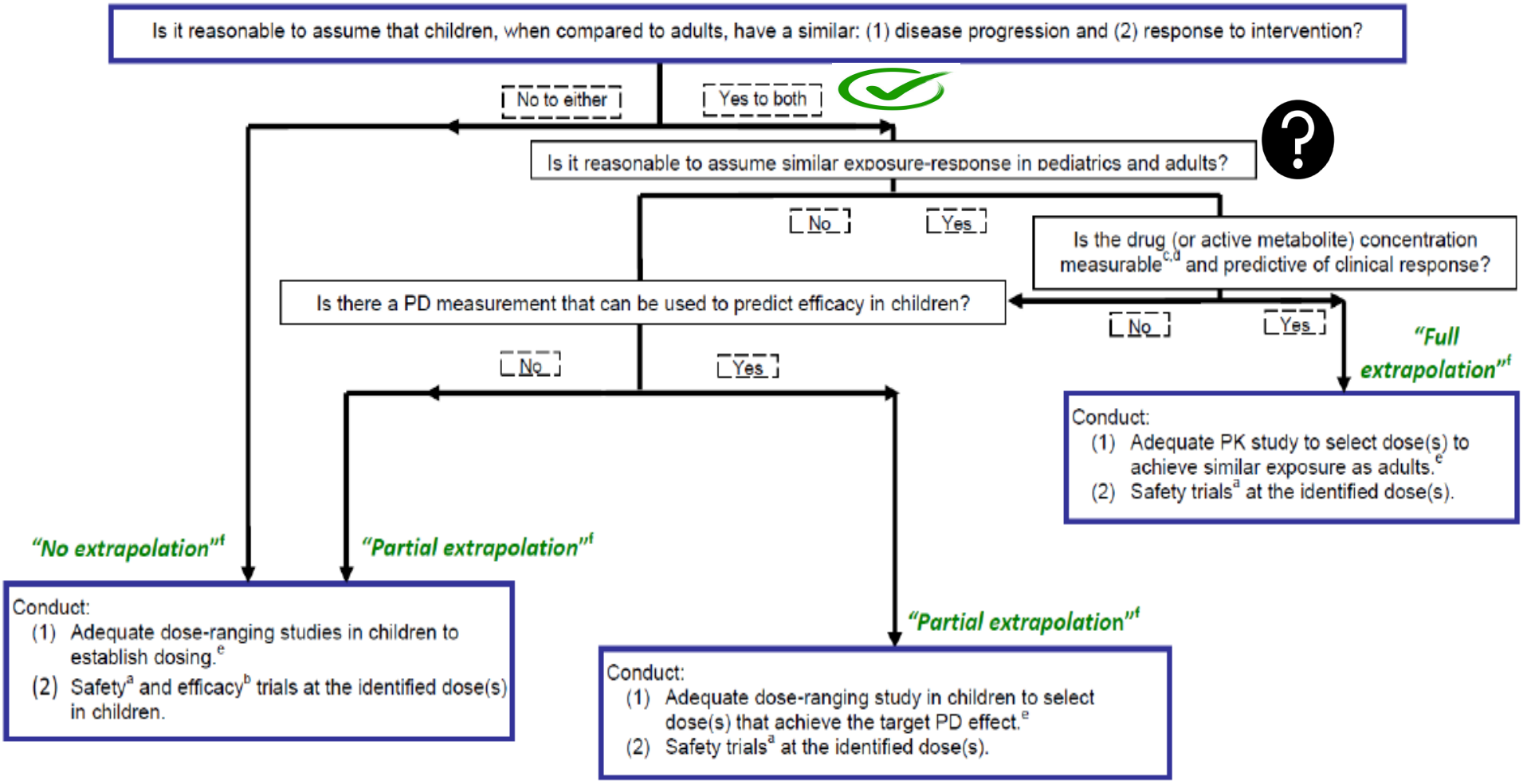


Pediatric submissions (pJIA)



Negative trials: leflunomide, infliximab, golimumab

Pediatric Study Planning & Extrapolation Algorithm



Source- FDA guidance - General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products

Framework of Full Extrapolation of Efficacy from RA

Disease Similarity	• Session 1
Exposure Similarity	?
Response Similarity	?

PK parameters

- Biologics
  - Cmin
  - AUC

- Small molecule
  - Cmax
  - AUC
  - Cmin

Dose selection for PJIA

- In general, PJIA programs did not have dedicated phase 2 dose ranging for efficacy.

- The pivotal efficacy study may assess more than one dose, as the methotrexate case. For more recent programs, typically only one dose is assessed with the randomized withdrawal study design.

- Dose selection rationale is to match the exposure of the approved adult RA dosing regimen
  - For biologics with linear PK, the dose is usually based on similar weight based dosing/BSA based dosing/PK simulation.
  - For small molecules and biologics with nonlinear PK, it's common to have a small scale PK study to confirm that the pediatric doses will match the exposure of the approved adult RA dosing regimen, before the pivotal phase 3 study in PJIA.

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
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)

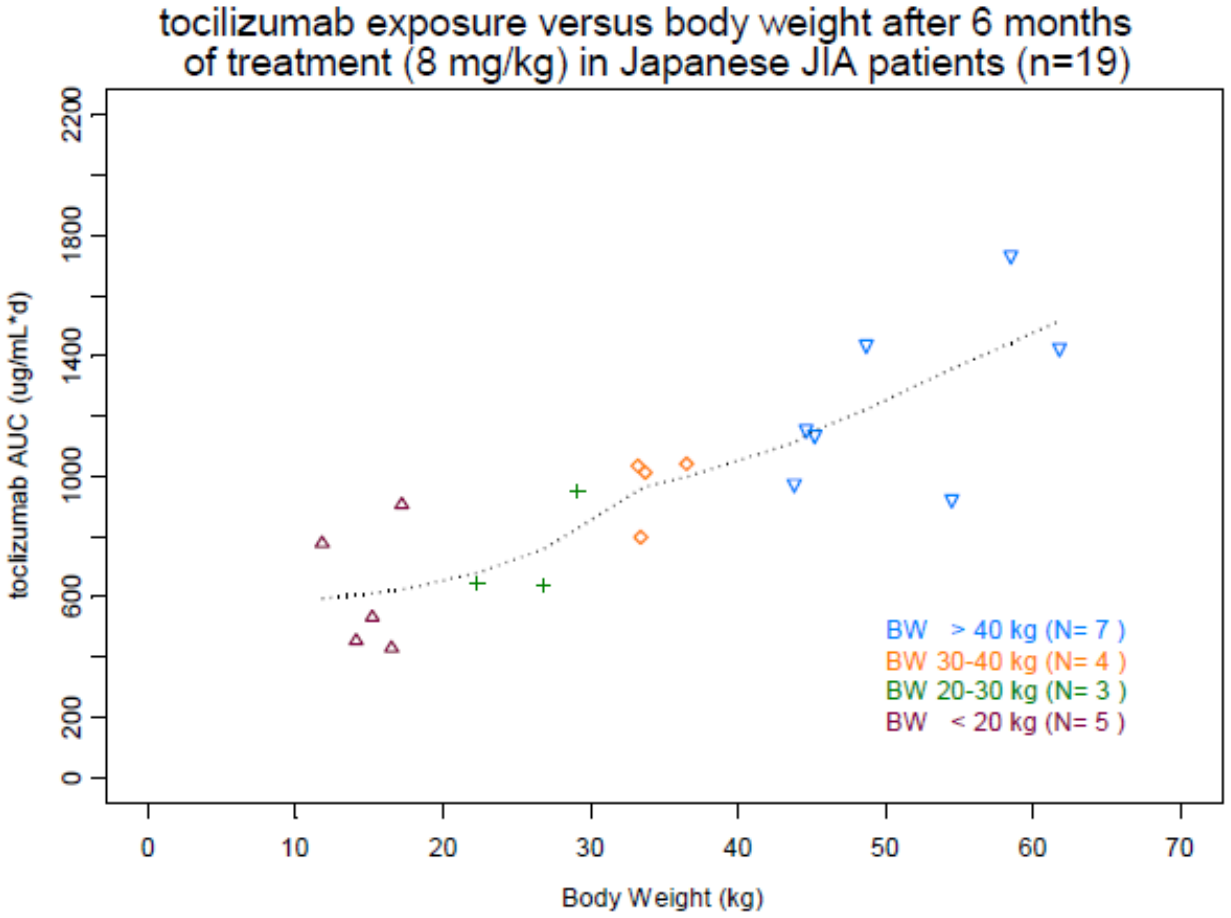
Drug	Ctrough (ug/mL)		Cmean(ug/mL)	
	RA	PJIA	RA	PJIA
Etanercept	1.4	-	1.9	2.1
Adalimumab	5, w/o MTX	6.6-6.8, w/o MTX	-	-
	8-9, with MTX	8.1-10.9, with MTX		
Abatacept (SC)	12.6 w/o loading dose 32.5 with loading dose	38.5-46.6	-	-
Abatacept (IV)	24	11.9	-	-
Tocilizumab (SC)	4.1 (162 mg q2w) 42.9 (162 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)

Framework of Full Extrapolation of Efficacy

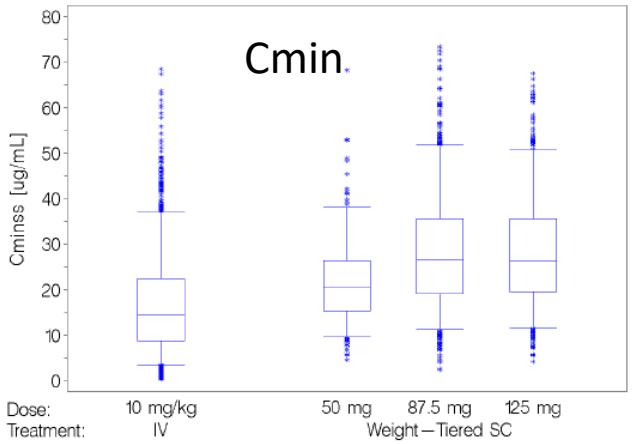
Disease Similarity	• Session 1
Exposure Similarity	• Approved PJIA medications are within the range of therapeutic exposure of approved adult RA doses
Response Similarity	

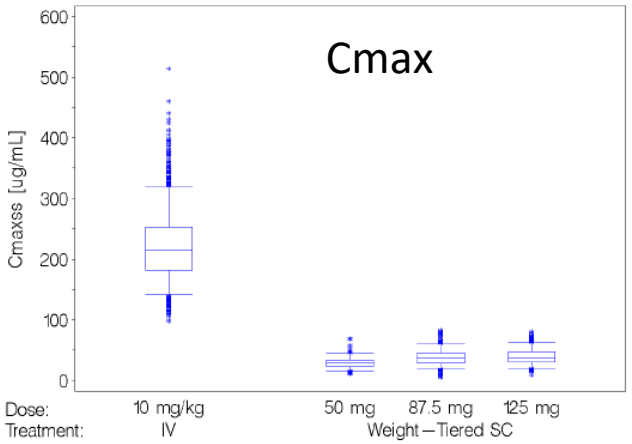
Backup

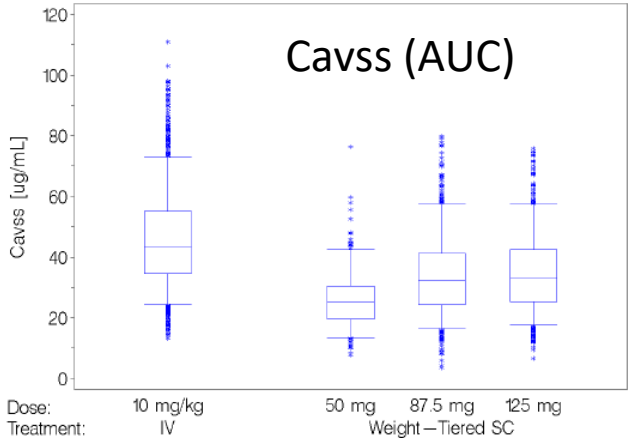
Study WA19977



Comparable Cmin with IV (approved in PJIA) or SC in PJIA







- Comparable/ higher Cmin.
- Much lower Cmax
- Slightly lower AUC of SC

PK trend expected due to different dosing frequency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