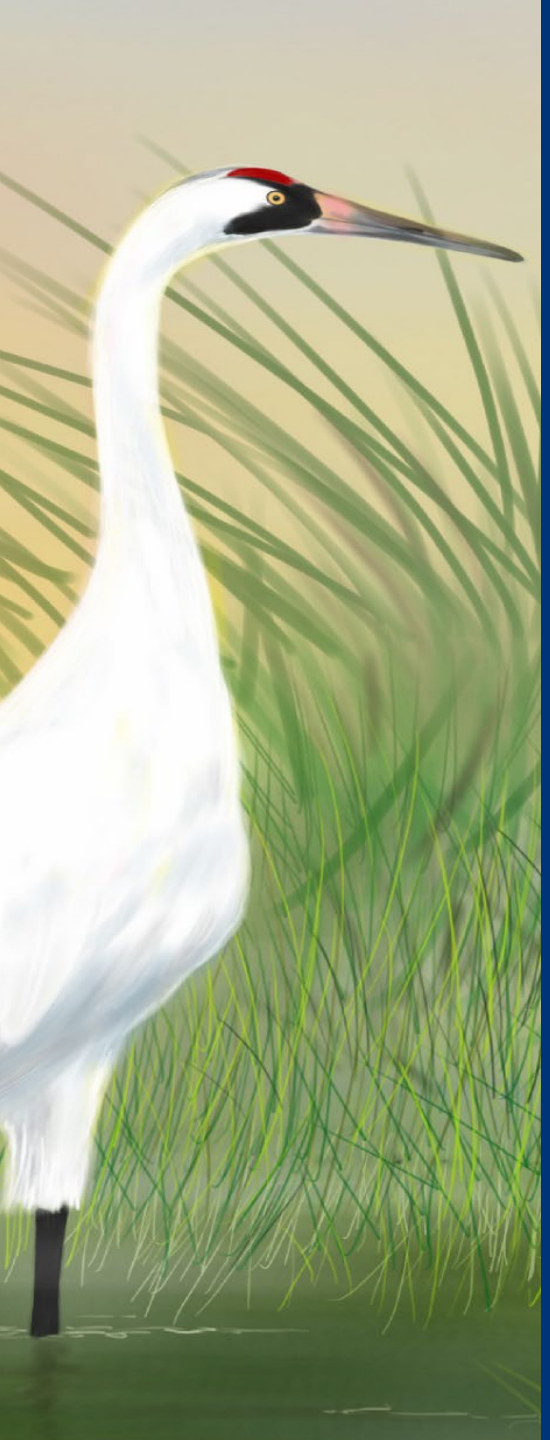

Two Well-Controlled Phase 3 Trials in Patients With Juvenile Idiopathic Arthritis: Challenges and Lessons Learned

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Disclaimer/Disclosure

- This presentation is intended for educational purposes only. Statements of fact and opinions expressed are those of the participant individually and, unless expressly stated to the contrary, are not the opinion or position of any company, institution or third party entity.
- Jocelyn H. Leu, PharmD, PhD, is a full-time employee of Janssen Research and Development and stock holder of Johnson & Johnson.

Outline

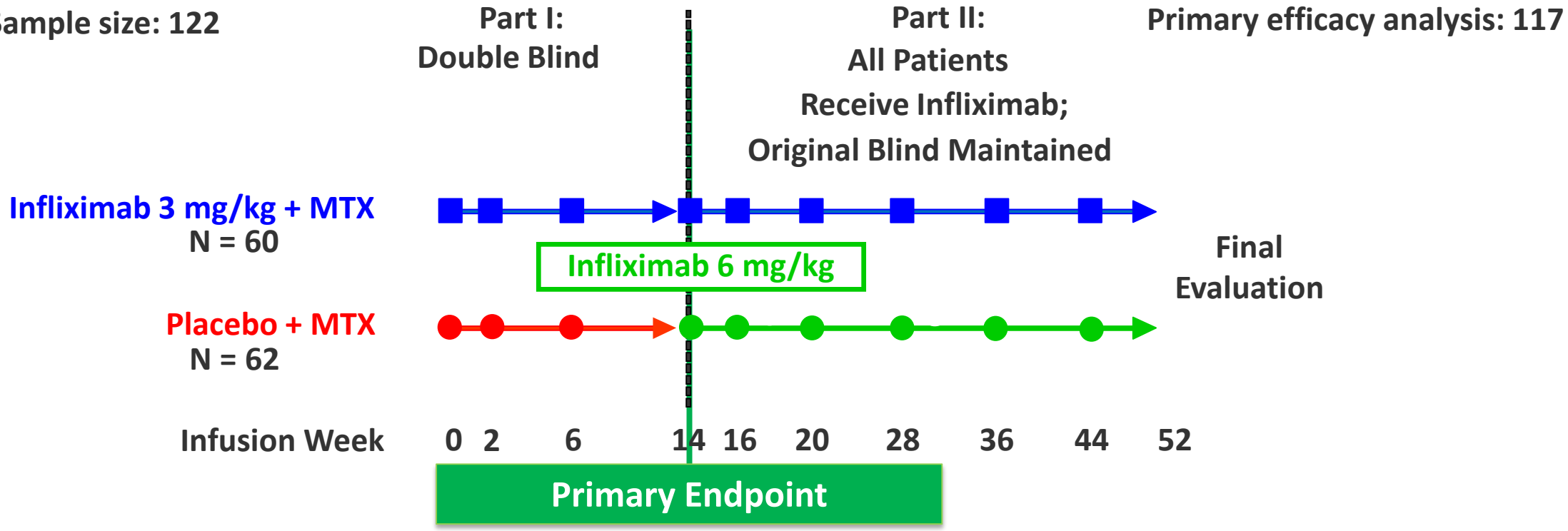
- Case 1: Remicade pJRA
  - Lessons learned from the double-blind, placebo-controlled Phase 3 trial
- Case 2: Simponi pJIA (SC)
  - Lessons learned from the randomized-withdrawal Phase 3 trial
- Challenges in pediatric research

A Randomized, Double-blind, Trial of Infliximab in Combination with Methotrexate for the Treatment of Patients with Polyarticular Juvenile Rheumatoid Arthritis

Study Name: JRA

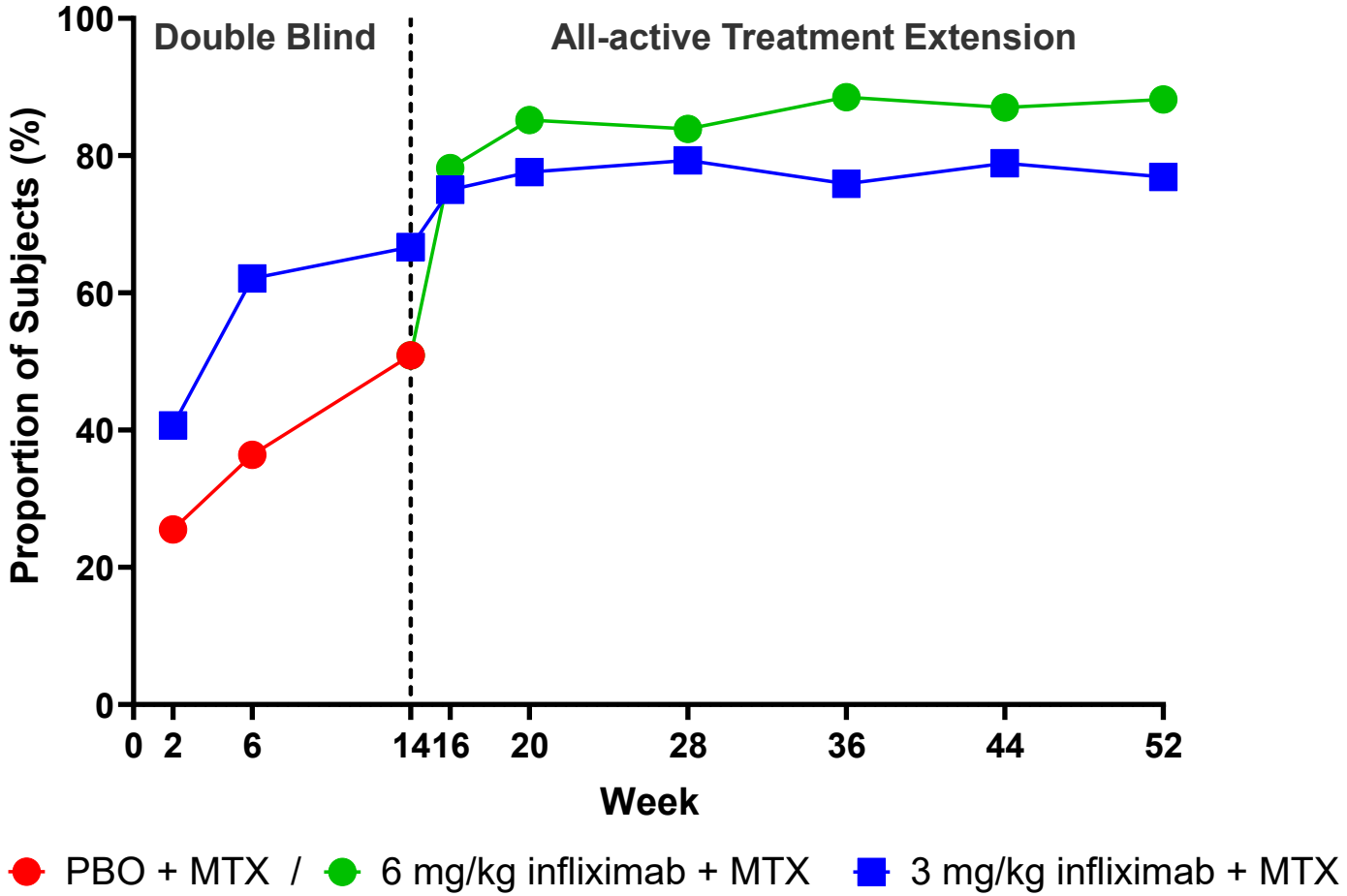
EudraCT No: 2004-000758-22
Study Start: 19 October 2001
Study Completed: 01 April 2004

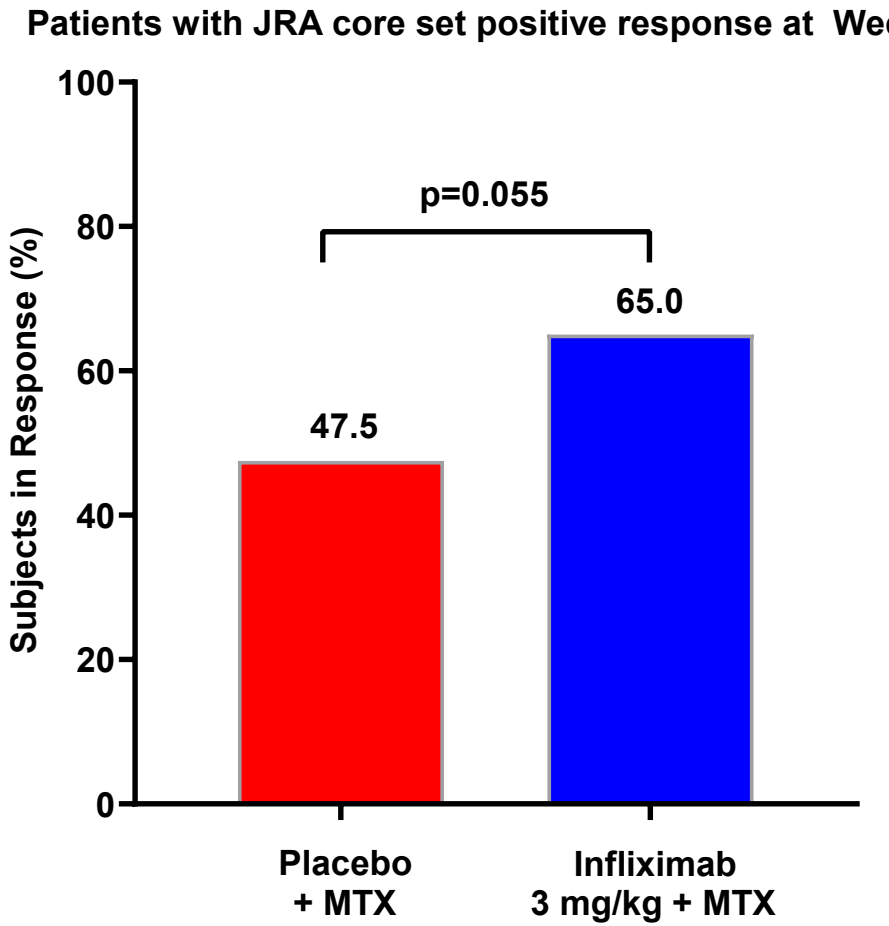
Infliximab pJRA Phase 3 Study



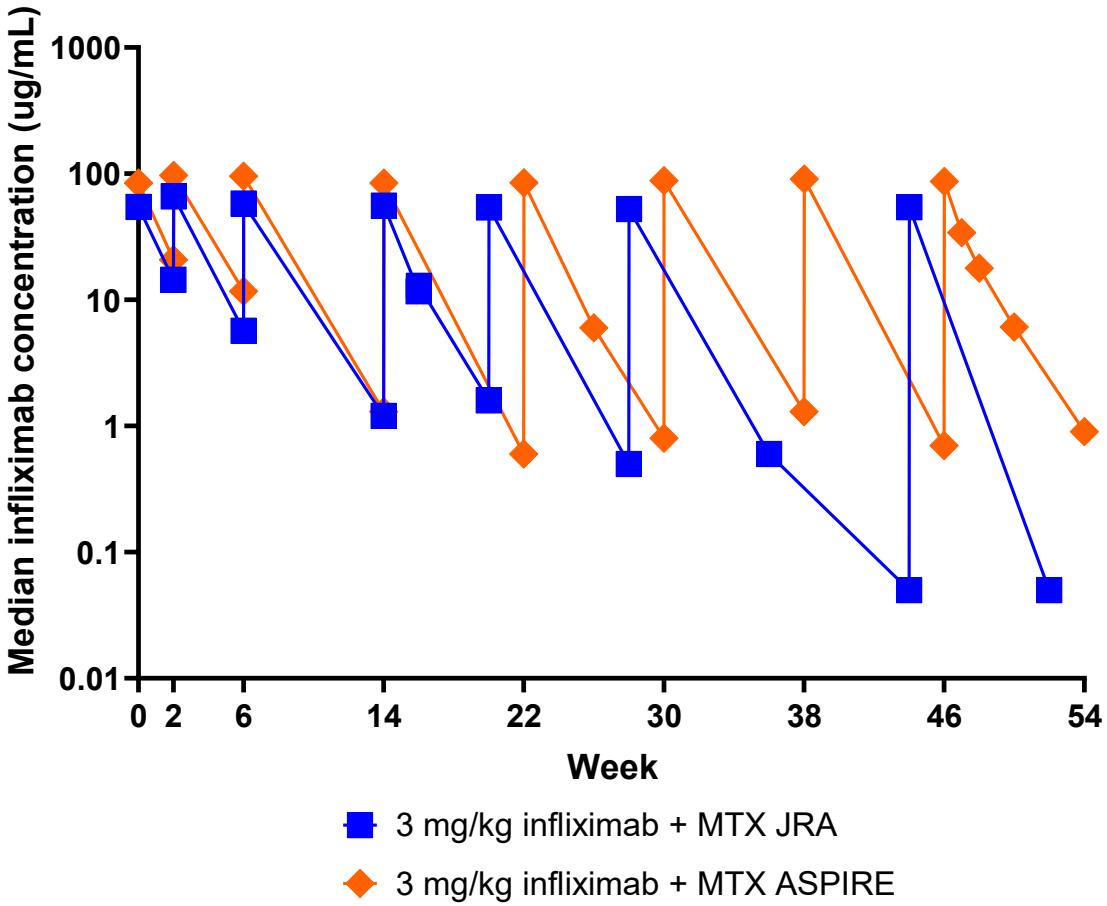
- At Week 14, subjects on infliximab 3 mg/kg + MTX remained on the same dose; subjects on placebo + MTX → Infliximab 6 mg/kg + MTX

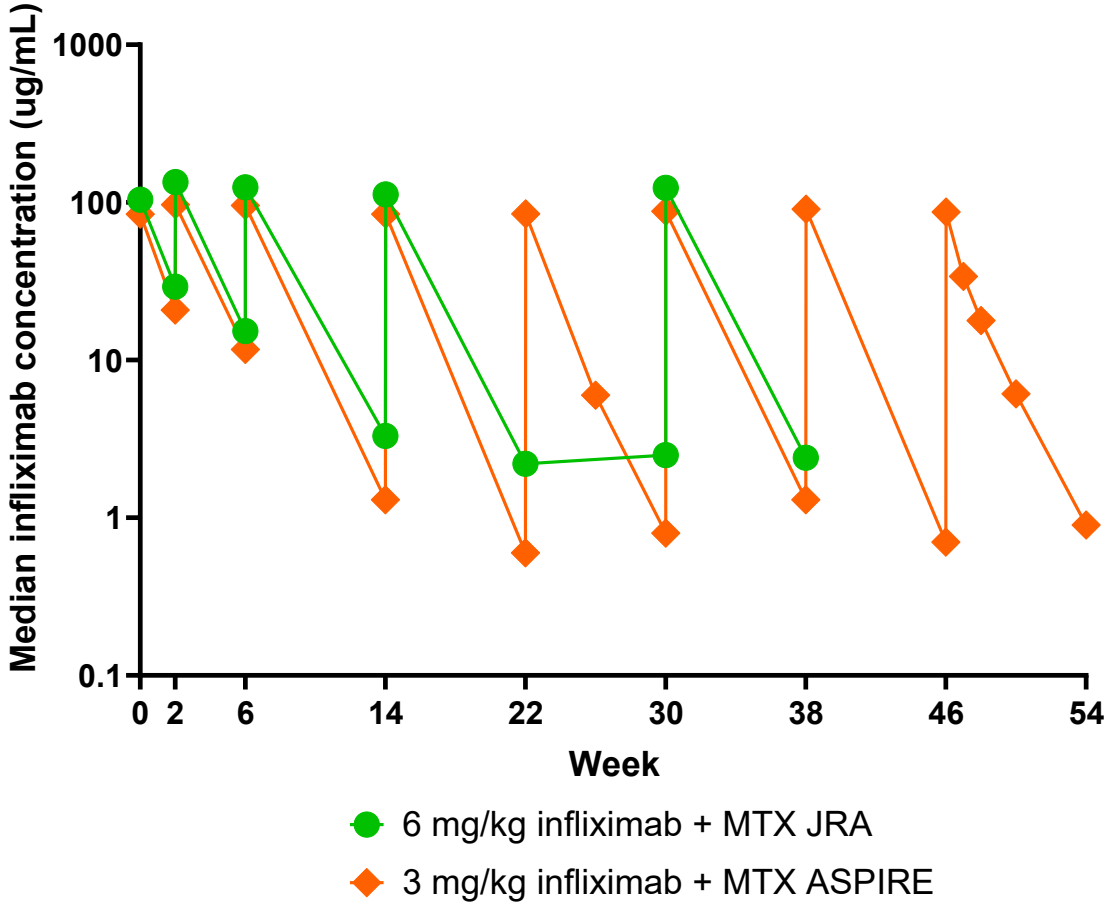
Primary Endpoint: ACR Pediatric 30 Response





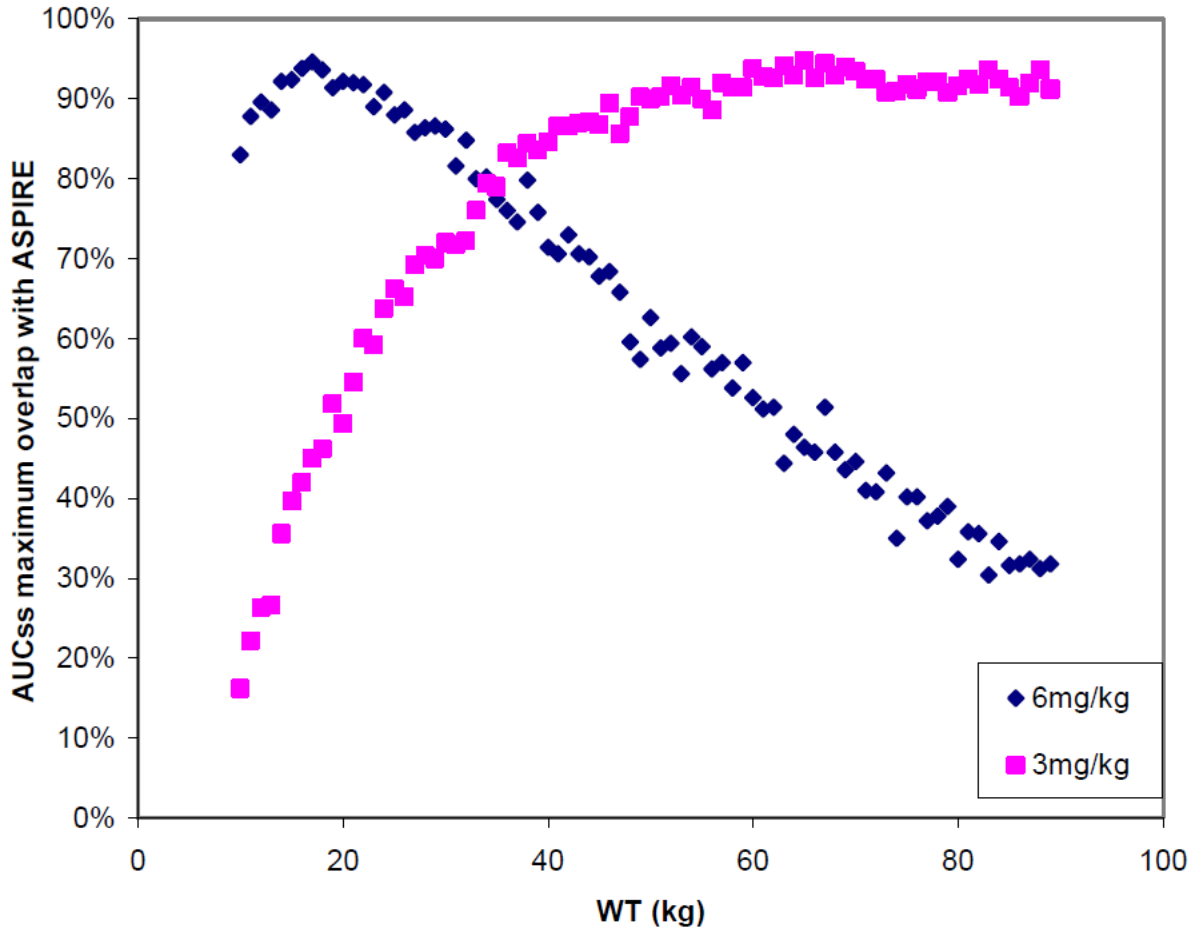
Infliximab PK Profiles
3 and 6 mg/kg JRA vs. 3 mg/kg Adult RA (ASPIRE)





% Overlap in Simulated AUCss Between JRA and ASPIRE

- Simulated AUCss for 500 virtual subjects for each body weight applying the validated population PK model.
- % AUCss overlap between JRA and ASPIRE was calculated.
- To achieve a minimum of 80% AUCss overlap between JRA and ASPIRE:
  - ≥34 kg would require a dose of 3 mg/kg
  - <34 kg would require a dose of 6 mg/kg



Lessons Learned from the Infliximab JRA trial

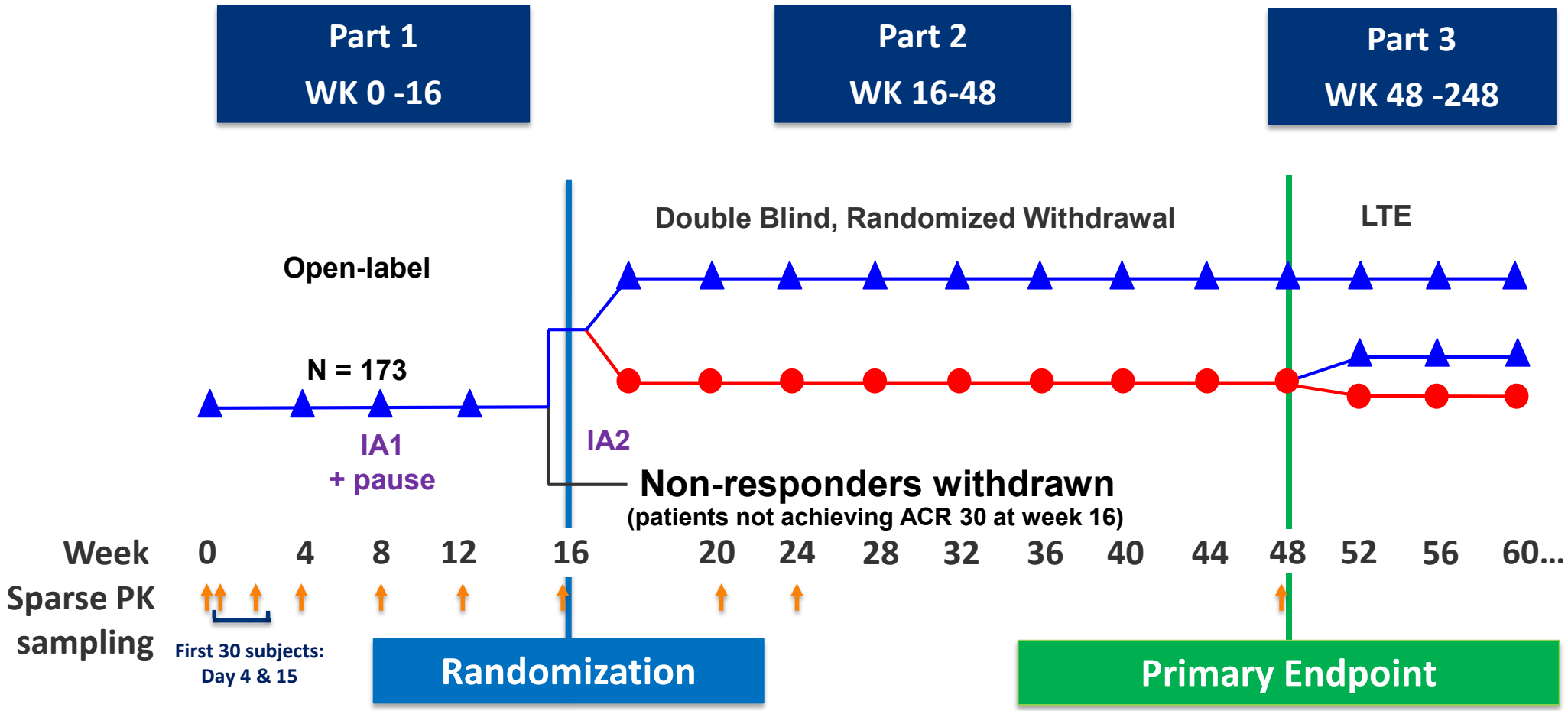
- Durable efficacy seen at 1 year but primary efficacy endpoint at 3 months not met
- High placebo response rate
  - Seen before in JIA DMARD trials using the same design
- The same mg/kg dose in adults did not produce comparable PK exposure in children with lower body weights
  - a higher mg/kg dose may be required, particularly when the approved adult dosage is the minimum efficacious dose
- Confirmation of PK/PD needed
  - Analyze PK/PD in the initial subjects in future Phase 3 trials with interruption of enrollment until PK/PD results are available

A Double-blind, Randomized-Withdrawal Trial of Subcutaneous Golimumab in Pediatric Subjects with Active Polyarticular Course Juvenile Idiopathic Arthritis Despite Methotrexate Therapy

Study Name: GO-KIDS

EudraCT No: 2009-015019-42
Study Start: 01 December 2010
Study Completed: 27 May 2014

GO-KIDS Study Design



Patient Population: Major Inclusion Criteria

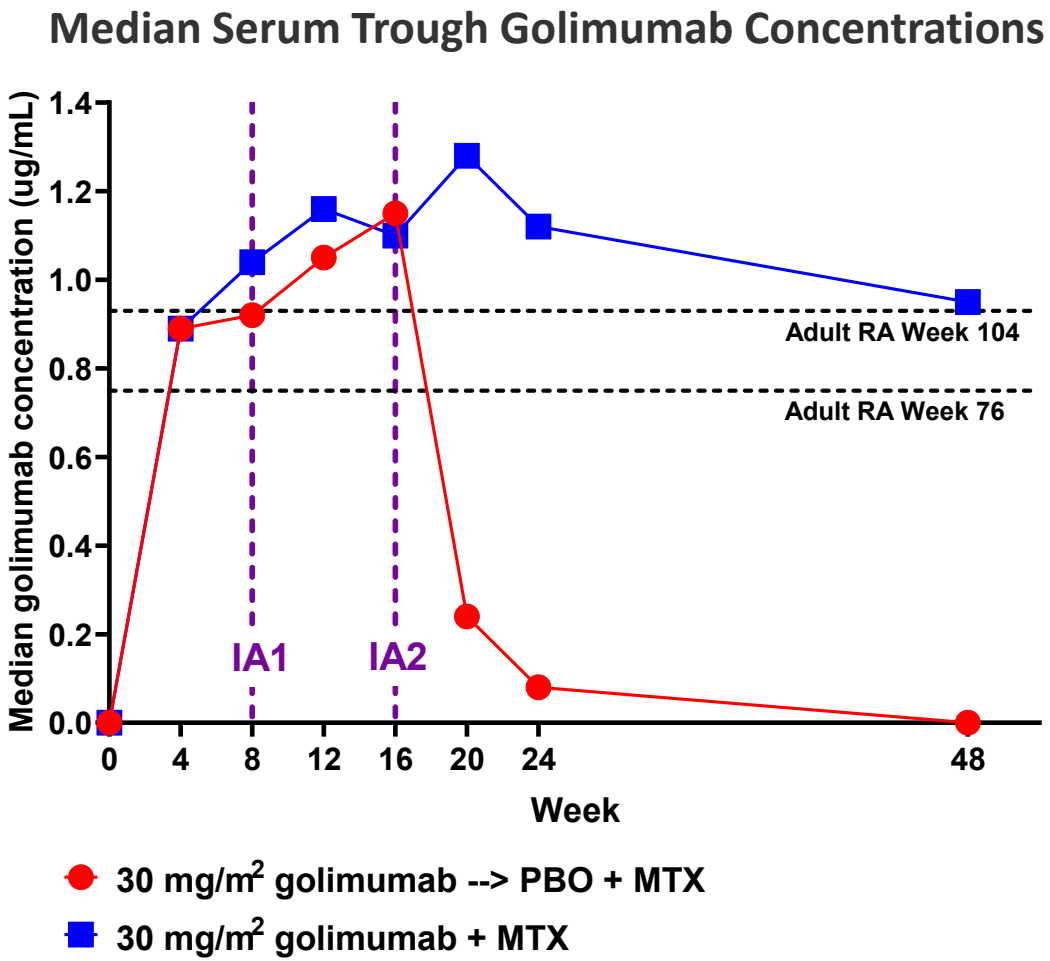
- Children aged 2-17 years with polyarticular course of JIA[#] for ≥ 6 months
  - Polyarticular JIA RF+ or RF-
  - Psoriatic sub-group JIA
  - Extended oligoarticular JIA
  - Systemic JIA without systemic features or MAS for ≥ 6 months
- Active arthritis ≥5 joints despite >3 months of MTX
  - Subjects currently on MTX (weekly 10 to 30 mg/m^2), must receive a stable dose of methotrexate for ≥4 weeks before screening. Subjects with BSA ≥1.67 m^2 must receive a minimum of 15 mg/week of MTX.
- Prior exposure to one anti-TNF agent permitted
- Allowed concomitant medications
  - NSAIDs
  - Stable dose of prednisone at ≤ 0.2mg/kg/day (max 10 mg)
- No requirement for elevated CRP or ESR at study entry
  - Consistent with studies performed with other biologics in pJIA

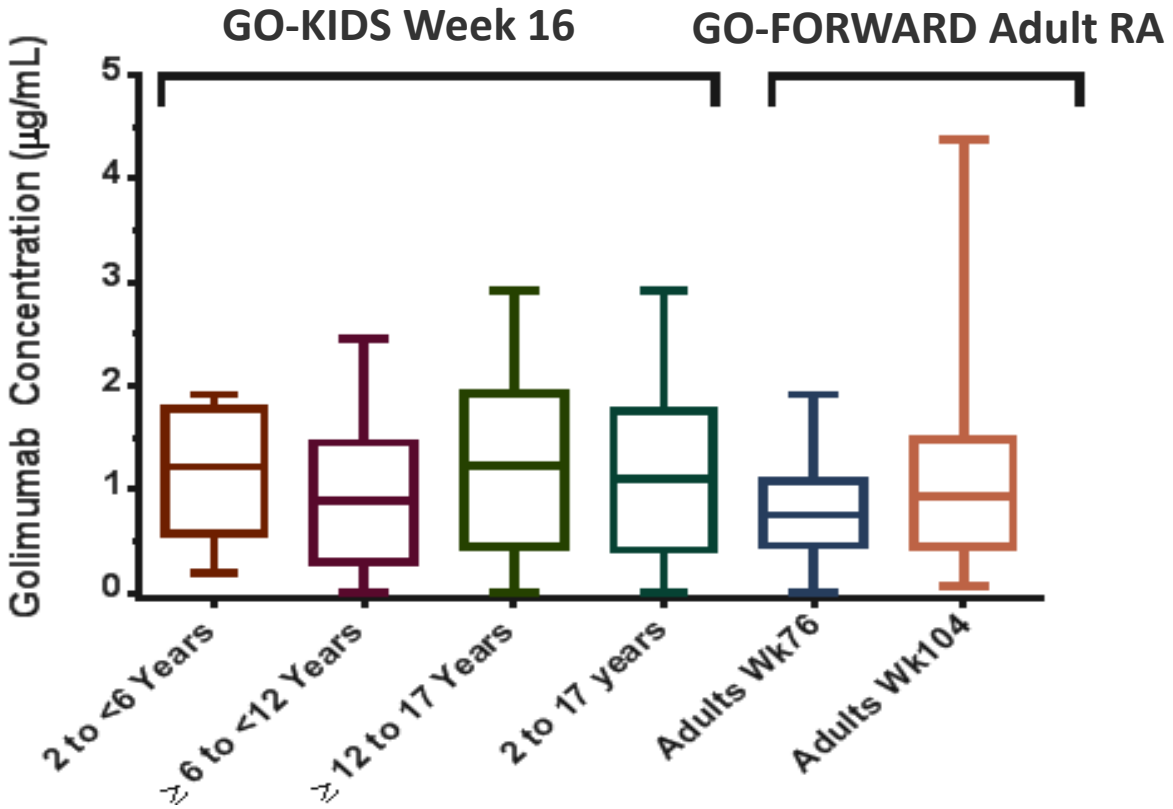
[#] as per ILAR Criteria; Petty RE, et al. J Rheumatol. 2004;31:390-392

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MAS: macrophage activation syndrome

Two Interim Analyses to Check PK/PD in GO-KIDS (1)

IA1– paused enrollment to evaluate 30 subjects reaching Week 8
IA2 – Futility analysis: 120 subjects reaching Week 16

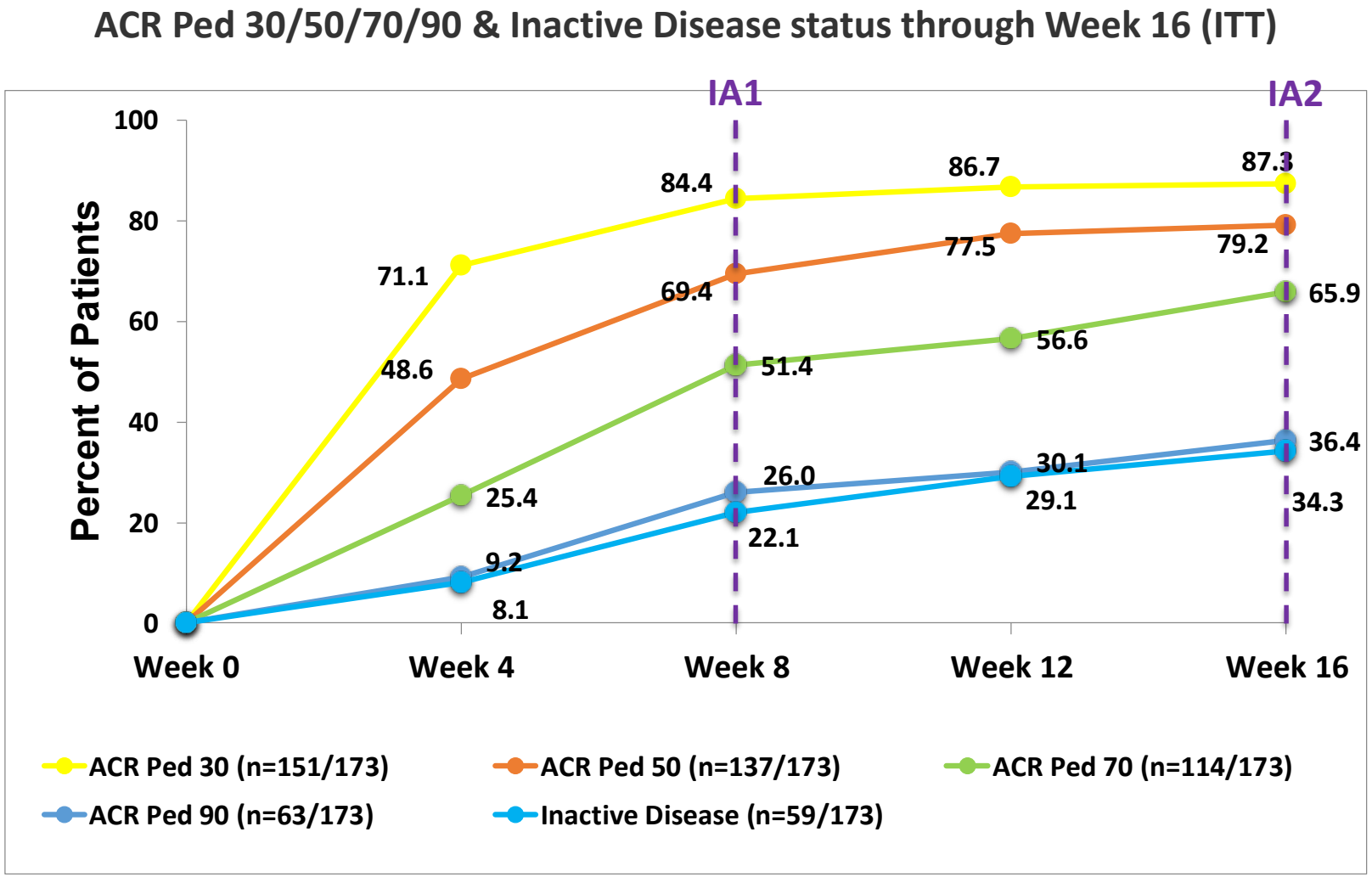




Bioanalysis with the same PK assay (MSD)

- Week 16 GO-KIDS SC golimumab 30 mg/m^2 + MTX Q4W
- Week 76 & 104 GO-FORWARD SC golimumab 50 mg + MTX Q4W

Two Interim Analyses to Check PK/PD in GO-KIDS (2)



GO-KIDS Safety Results

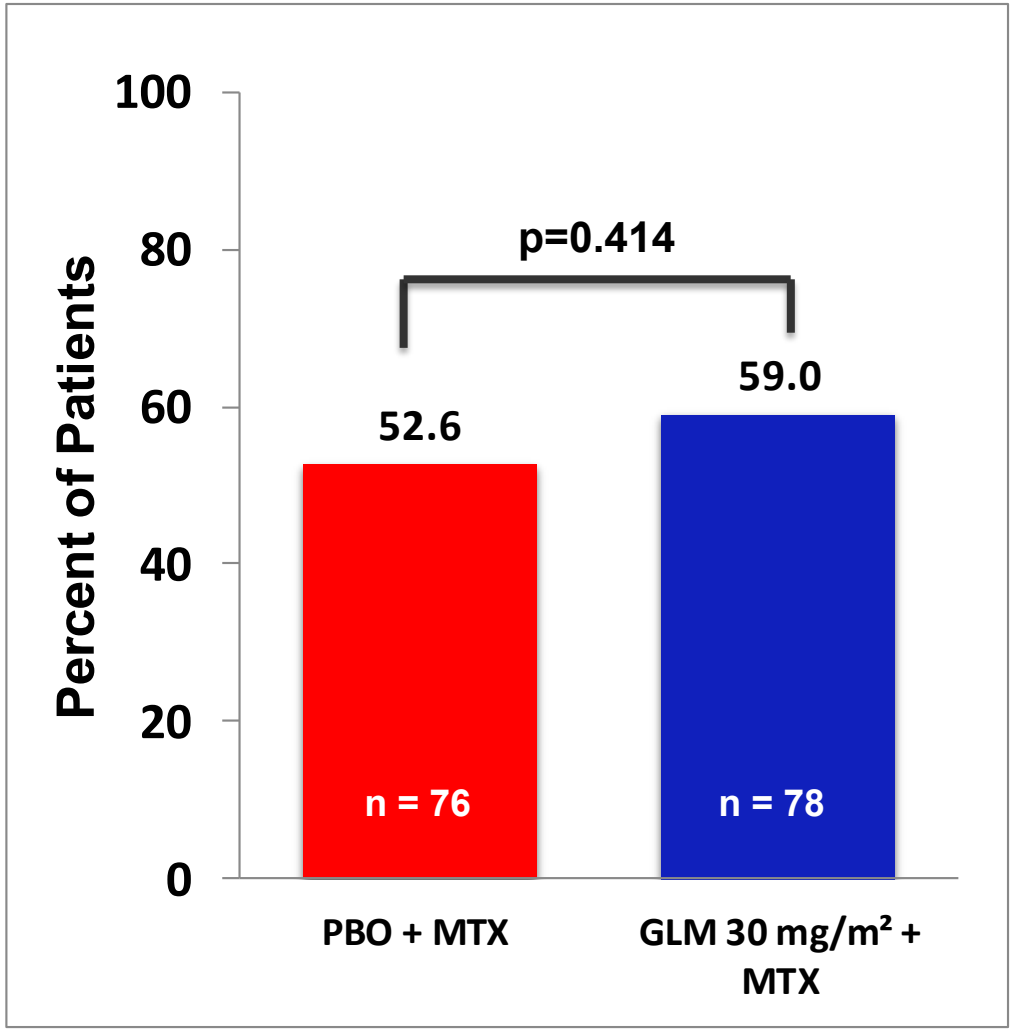
- Safety profile from GO-KIDS was consistent with the established safety profile of SIMPONI® in adults, as well as other anti-TNF agents in adult and pediatric patients.
- No new safety signals or adverse drug reactions identified for SIMPONI® in pediatric patients versus adult patients.

➢ **No new safety concerns different than those reported for the class of anti-TNF therapies in the treatment of pJIA/JRA.**

GO-KIDS Primary Endpoint

Proportion of patients who are ACR Ped 30 responders at Week 16 who do not experience a flare of disease between Weeks 16 and 48

ITT: In Part 2 (Week 16 – 48) patients were randomized to continue GLM or switch to PBO q4wks and GLM restarted upon flare



Hypotheses for the Study Outcome

- Inadequate inflammatory burden at baseline
- Randomized withdrawal study design
  - Length of randomized withdrawal period
  - Switching PBO patients to GLM upon flare
- PK / PD effects
  - Ruled out: inadequate dosing
- Ruled out: Data entry errors, medication errors, training of investigators.

Comparison of baseline disease characteristics across pJIA studies with biologics

	Golimumab	Tocilizumab	Adalimumab	Etanercept	Abatacept
Sample Size (OL/RW)	173/154	188/163	85/80	69/51	190/122
Active joints	12	20	15	28	15
Limited ROM joints	8	18	8	10	14
CHAQ	0.9	1.4	0.9	1.4	1.2
Parent Assessment of Disease (cm)	4.5	5.3	4.3	5.0	4.0
Physician Assessment of Disease (cm)	5.4	6.1	5.8	7.0	5.3
ESR (mm/hr)	16	35	-	35	30
CRP (median)	0.17 mg/dL	78% of subjects with CRP >1.0 mg/dL	0.7-0.8 mg/dL	3.5 mg/dL	3.2 mg/dL

Inadequate inflammatory burden of pJIA patients

- In subgroups of patients with higher baseline CRP levels, the proportion of subjects who did not flare was greater in the golimumab group versus the placebo group (baseline CRP > 1.0 mg/mL was pre-specified)

Table 2: Number of subjects who did not flare from Week 16 through Week 48 by CRP levels at baseline; randomized subjects

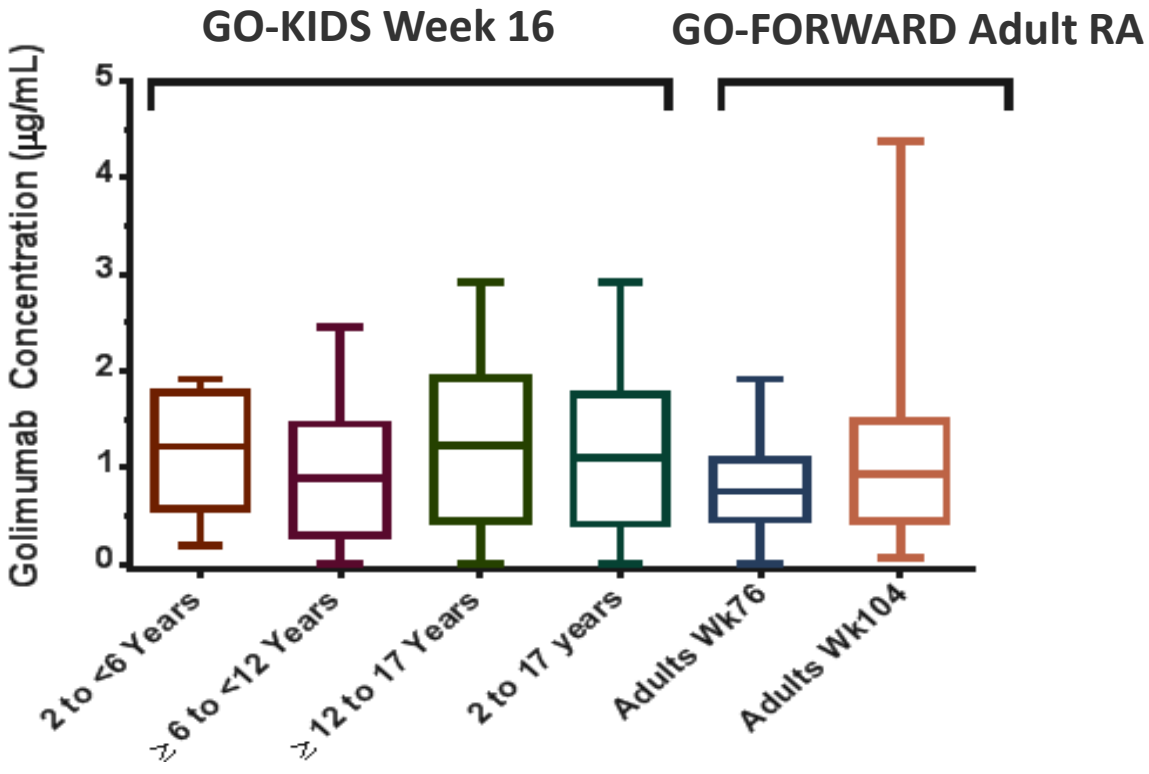
	Golimumab Administered Prior to Randomization at Week 16		
	Placebo + MTX	Golimumab 30 mg/m^2 + MTX	p-value
Subjects randomized	76	78	-
Subjects who did not flare			
baseline CRP >= 0.02 mg/dL	37/72 (51.4%)	46/75 (61.3%)	0.196
baseline CRP >= 0.1 mg/dL	14/38 (36.8%)	27/44 (61.4%)	0.020
baseline CRP >= 0.2 mg/dL	12/33 (36.4%)	20/36 (55.6%)	0.100
baseline CRP >= 0.3 mg/dL	10/30 (33.3%)	19/33 (57.6%)	0.050
baseline CRP >= 0.4 mg/dL	6/26 (23.1%)	17/28 (60.7%)	0.003
baseline CRP >= 0.5 mg/dL	5/25 (20.0%)	15/26 (57.7%)	0.003
baseline CRP >= 0.6 mg/dL	5/22 (22.7%)	14/23 (60.9%)	0.005
baseline CRP >= 0.7 mg/dL	4/20 (20.0%)	13/20 (65.0%)	0.004
baseline CRP >= 0.8 mg/dL	2/18 (11.1%)	12/19 (63.2%)	0.001
baseline CRP >= 0.9 mg/dL	2/17 (11.8%)	11/18 (61.1%)	0.004
baseline CRP >= 1.0 mg/dL	2/15 (13.3%)	9/15 (60.0%)	0.007

Randomized Withdrawal Study Design

- Most biologics (e.g. etanercept, adalimumab, abatacept, tocilizumab) used RWD
  - Open-label portion in which all patients received drug for 12 to 16 wks, followed by randomized withdrawal to drug or placebo for 16 to 32 wks
  - These other biologics demonstrated treatment benefit vs placebo using this design with similar length of randomized withdrawal period as used in GO-KIDS
  - Considered the best study design circa late 90's early 2000's.
- Length of the randomized withdrawal period:
  - Possibility of prolonged PD effect in placebo-treated subjects after the initial 16 weeks of golimumab treatment
  - Longer withdrawal duration could have helped to discern treatment effect of Simponi from placebo
- Treatment of GLM was re-instated upon flare in a blinded manner for placebo treated patients

PK/PD - Dosing

- Dosing with GLM 30 mg/m^2 every 4 weeks resulted in GLM levels similar or higher compared to adults with RA
- Immunogenicity
  - Did not affect GLM levels with exception of patients with high titers of ADA
  - Did not affect efficacy unless titers were >1:1000 (n=6)
- There is no identified mechanistic basis for prolonged PD effect in anti-TNF agents



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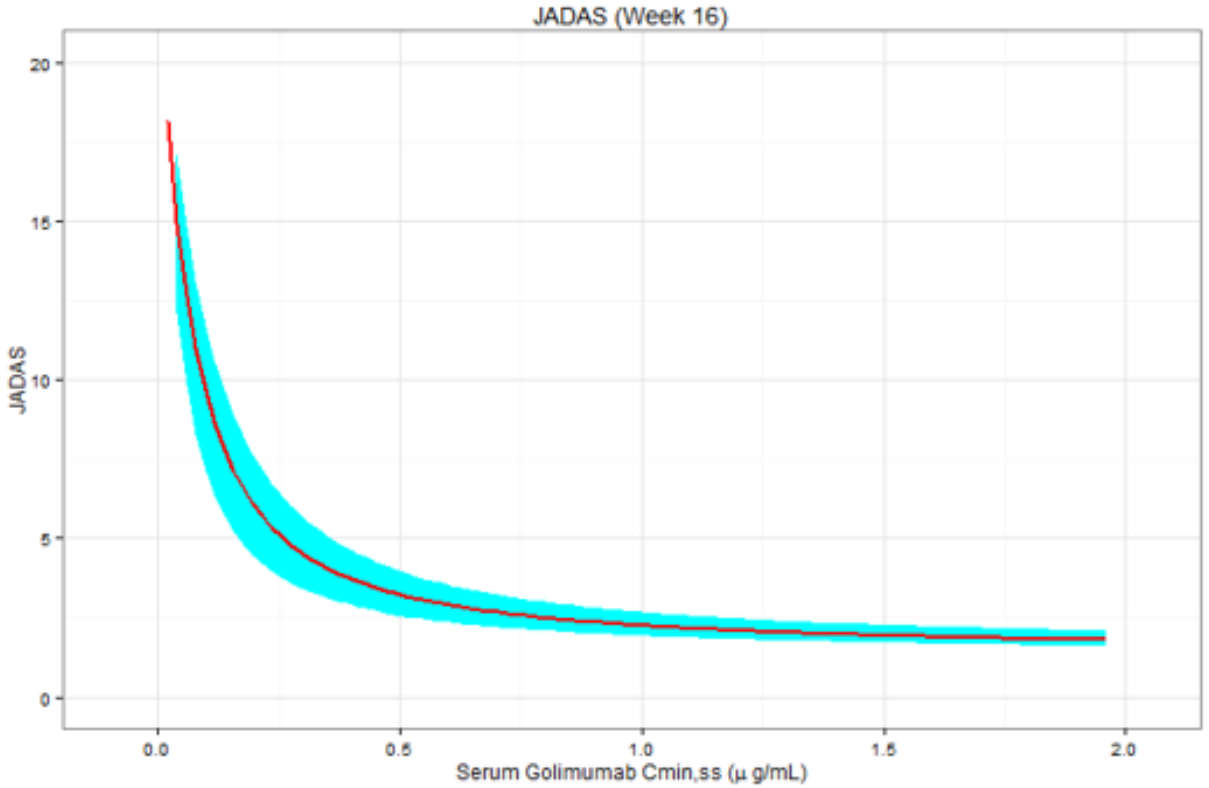
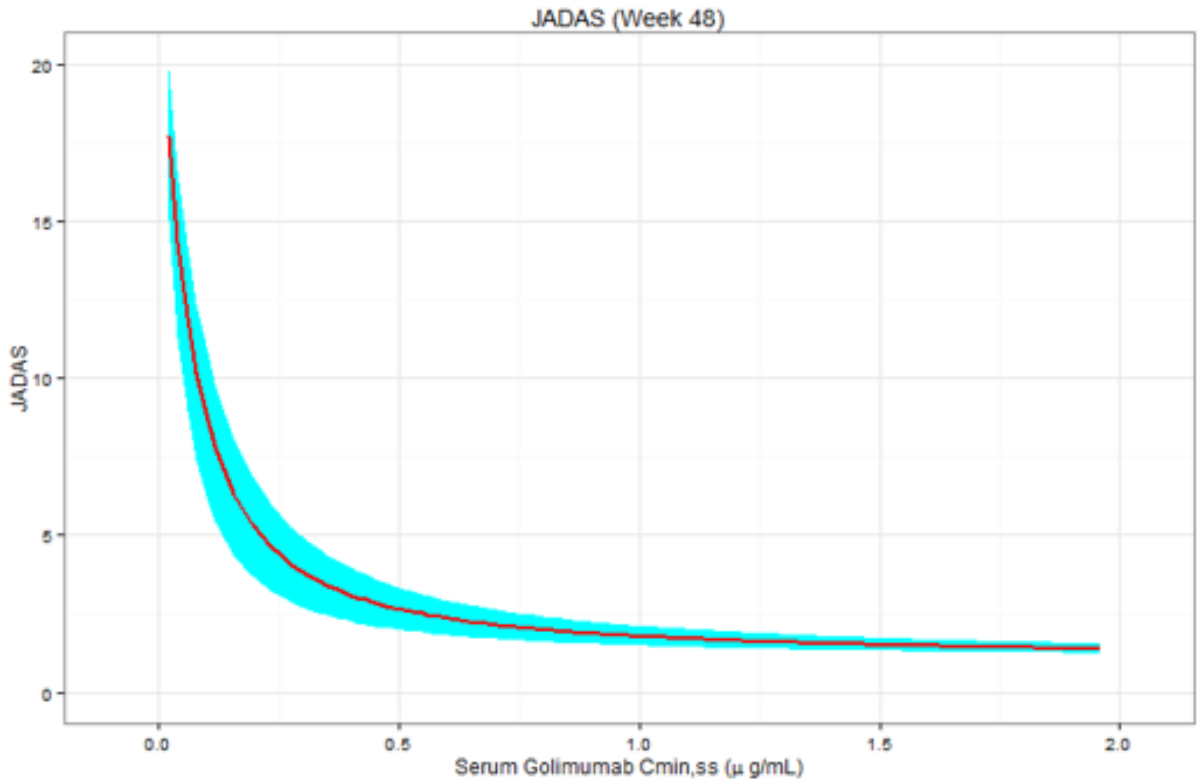
- Week 76 & 104 GO-FORWARD SC golimumab 50 mg + MTX Q4W

E-R Relationship for JADAS-71

Open Label



Randomized Withdrawal



Simponi SC for pJIA Epilogue

- EMA: Path forward for approval based on **totality of evidence** including the post-hoc analyses and PK/PD modeling to support the benefit/risk evaluation.
- Submitted in 49 ROW countries and approved in 37 of these countries for the pJIA patients who can use the adult presentation. To be followed with submissions for the Simponi 45mg/0.45mL solution for injection in prefilled pen
- FDA did not view the data from the current study alone as being supportive of an indication.
  - Extrapolation based approach of the open label data alone not adequate to support an indication in this case since the study didn't meet endpoints.
- sBLA filed to fulfill required updates to Section 8.4 of USPI to describe study outcome. No indication claim was sought.
- Post-marketing requirement listed in April 24, 2009 was deemed fulfilled on June 22, 2017

Challenges with Pediatric Research

- Both well-controlled trials did not meet their primary endpoints
  - Saw evidence for efficacy in pJIA without substantial difference between children and adults - however could not file for a claim (Simponi SC in US)
- Ethics of testing pediatric patients but no path to get this treatment
  - Frustration particularly of parents of children and physicians who have seen transformative improvement on golimumab and do not want to see these children suffer longer
  - Single patient INDs
  - Countries without access
- Fewer treatment options for pJIA patients compared to adults
- Additional clinical trials involves more testing in a vulnerable population, time to recruit and run another trial, and further delay of useful treatment to the children who need them.
- Lots of valuable information collected in the trials
  - "totality of evidence" approach rather than more studies
  - Use of modeling and simulation: Population PK and exposure-response modeling

Thank you