Learn & confirm' in JIA:
Modeling and Simulations to Support Development and Extrapolation

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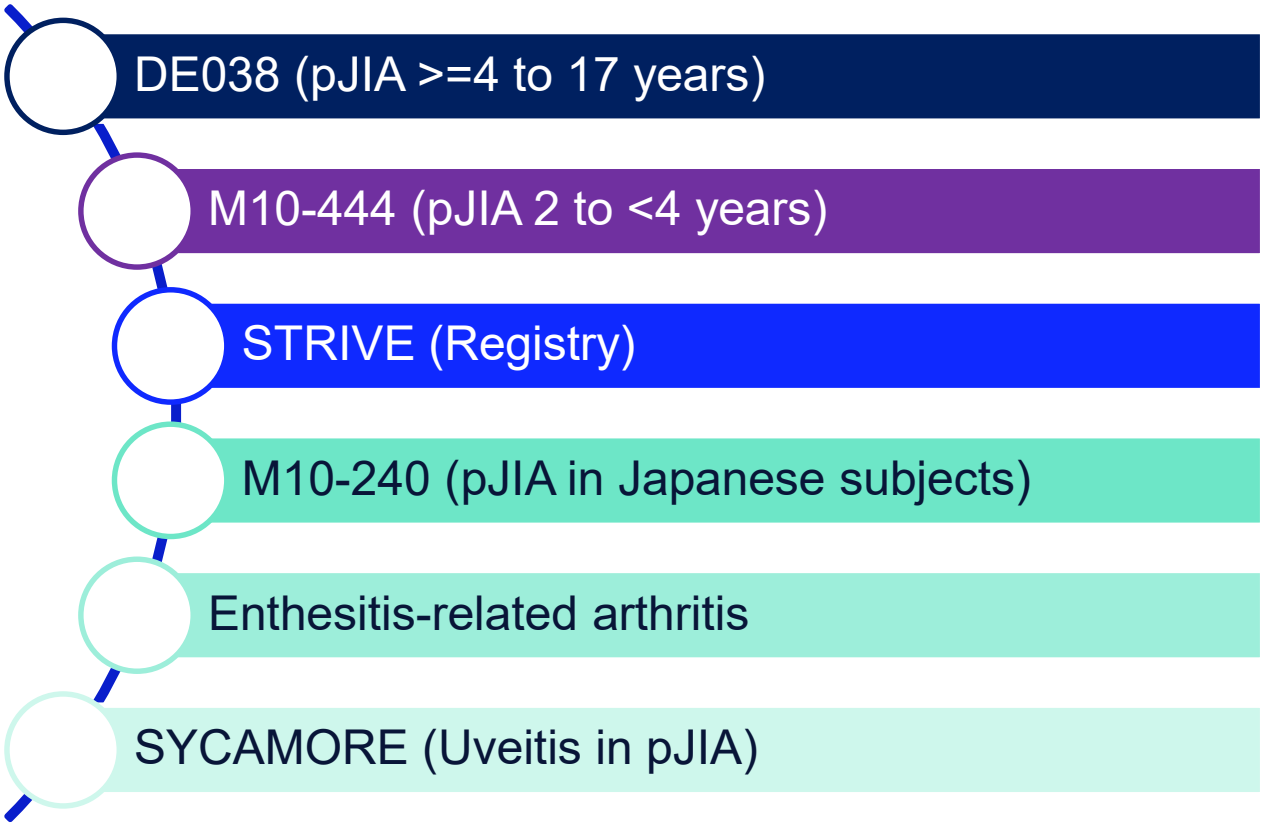
The Beginning

- Adalimumab ‘about to be’ approved (2002) for rheumatoid arthritis in adults with/without methotrexate
- Adult studies in adults with Crohn’s disease (underway) and plaque psoriasis (planned)
- First subject in the first study of JIA program was enrolled in Sep 2002 (completed in Jun 2010)
- No other pediatric studies for adalimumab at the time

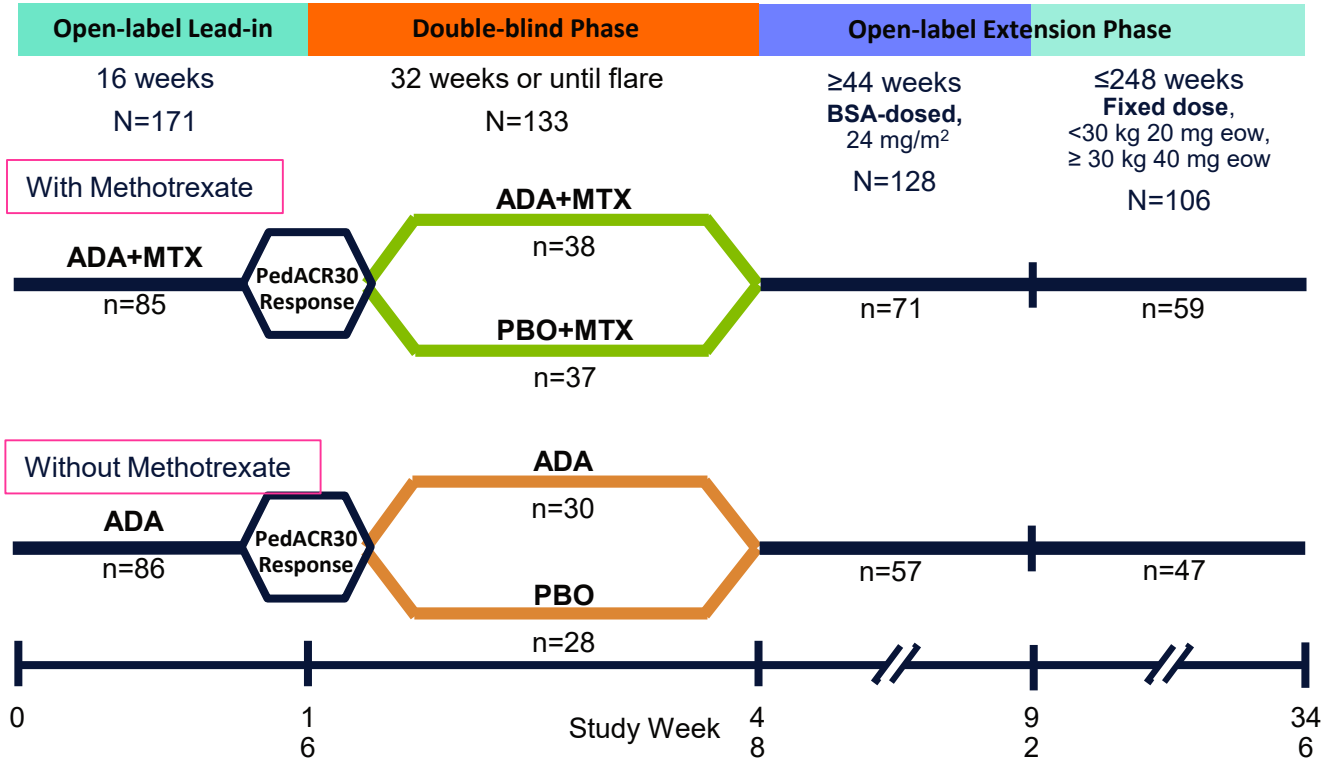
Adalimumab pJIA Program



Study DE038: Study Design (1)

- Randomized, double-blind, parallel − group study in 171 children (4-17 years old) with pJIA
- In the open-label lead-in phase (OL LI) patients were stratified into two groups: MTX (methotrexate)-treated or non-MTX-treated (naïve or withdrawn from MTX > two weeks prior to study)
- Patients remained on stable doses of NSAIDs and or prednisone (≤ 0.2 mg/kg/day or 10 mg/day maximum).
- In the OL LI phase all patients received adalimumab 24 mg/m^2 (BSA) up to a maximum of 40 mg every other week for 16 weeks.
- Patients with Pediatric ACR 30 response at Week 16 were randomized into DB phase and received either adalimumab or placebo every other week for an additional 32 weeks or until disease flare (worsening of ≥ 30% from baseline in ≥ 3 of 6 Pediatric ACR core criteria, ≥ 2 active joints, and improvement of > 30% in no more than 1 of the 6 criteria).
- After 32 weeks or at disease flare, patients were eligible to enroll into the open label extension (OLE) phase (initially by BSA and subsequently by fixed dose). Patients were followed up over 6 years.

Study DE038: Study Design (2)



Randomized, double-blind, placebo-controlled, multicentre, medication-withdrawal study

ADA: 24 mg/m^2 eow; MTX: ≥10 mg/m^2 weekly

ADA, adalimumab; BSA, body surface area; eow, every other week; PBO, placebo

Adalimumab with or without methotrexate in juvenile idiopathic arthritis.
Lovell DJ, et al. N Engl J Med 2008;359:810–820

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adalimumab with or without Methotrexate in Juvenile Rheumatoid Arthritis

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ABSTRACT

BACKGROUND

Tumor necrosis factor (TNF) has a pathogenic role in juvenile rheumatoid arthritis. We evaluated the efficacy and safety of adalimumab, a fully human monoclonal anti-TNF antibody, in children with polyarticular-course juvenile rheumatoid arthritis.

METHODS

Patients 4 to 17 years of age with active juvenile rheumatoid arthritis who had previously received treatment with nonsteroidal antiinflammatory drugs underwent stratification according to methotrexate use and received 24 mg of adalimumab per square meter of body-surface area (maximum dose, 40 mg) subcutaneously every other week for 16 weeks. We randomly assigned patients with an American College of Rheumatology Pediatric 30% (ACR Pedi 30) response at week 16 to receive adalimumab or placebo in a double-blind fashion every other week for up to 32 weeks.

RESULTS

Seventy-four percent of patients not receiving methotrexate (64 of 86) and 94% of those receiving methotrexate (80 of 85) had an ACR Pedi 30 response at week 16 and were eligible for double-blind treatment. Among patients not receiving methotrexate, disease flares (the primary outcome) occurred in 45% of those receiving adalimumab and 71% of those receiving placebo (P=0.03). Among patients receiving methotrexate, flares occurred in 37% of those receiving adalimumab and 65% of those receiving placebo (P=0.02). At 48 weeks, the percentages of patients treated with methotrexate who had ACR Pedi 30, 50, 70, or 90 responses were significantly greater for those receiving adalimumab than for those receiving placebo; the differences between patients not treated with methotrexate who received adalimumab and those who received placebo were not significant. Response rates were sustained after 104 weeks of treatment. Serious adverse events possibly related to adalimumab occurred in 14 patients.

CONCLUSIONS

Adalimumab therapy seems to be an efficacious option for the treatment of children with juvenile rheumatoid arthritis. (ClinicalTrials.gov number, NCT00048542.)

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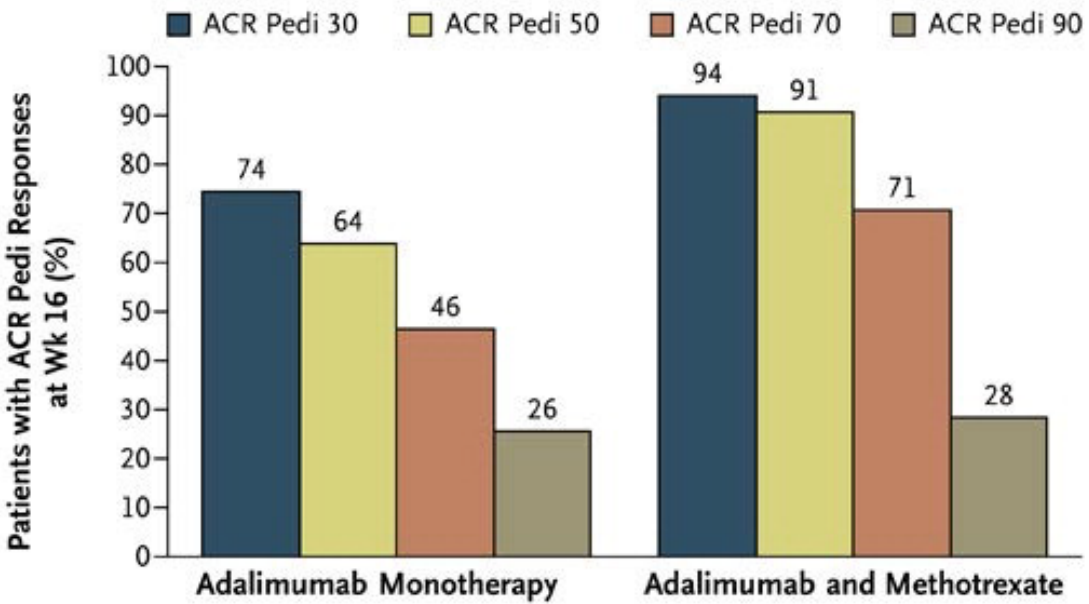
Drs. Lovell and Ruperto contributed equally to this article.

N Engl J Med 2008;359:810-20.

Study DE038: Results
Ped ACR30/50/70/90 at Week 16 - end of the OL LI

Patients treated with concomitant MTX achieved somewhat higher response rates than were seen with adalimumab monotherapy.

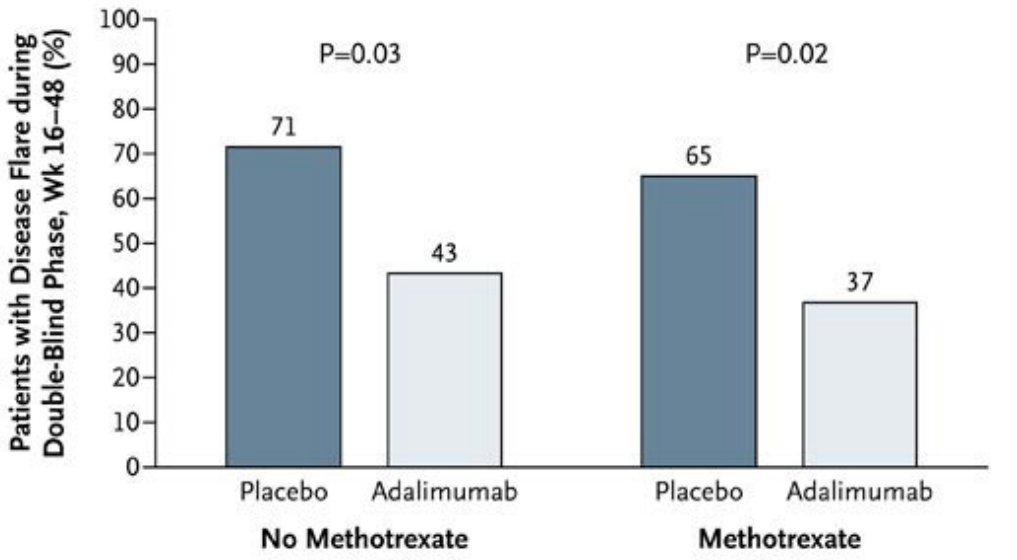


Modified from Lovell D et al. N Engl J Med. 2008;359(8):810-20

Study DE038: Results

Percentages of Patients in the Placebo and Adalimumab Groups with Disease Flare during the DB Phase (Week 16 through 48)

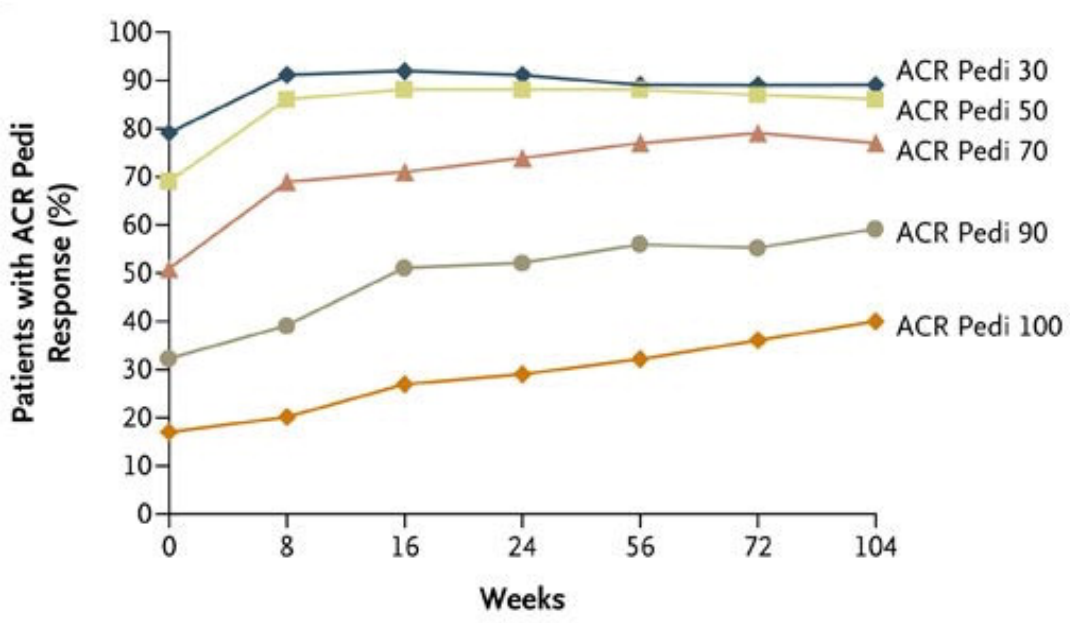
Adalimumab treatment resulted in significant improvement in flare rates (p=0.015 for MTX stratum, p=0.031 for non-MTX stratum) and time to flare compared to placebo, in monotherapy as well as in combination with MTX.



Lovell D et al. N Engl J Med. 2008;359(8):810-20

Study DE038: Results
Ped ACR 30/50/70/90/100 responses during the first 104 weeks of the OLE

Adalimumab provided sustained improvement in signs and symptoms regardless of whether patients were dosed by body surface or weight category (fixed dosing)



Lovell D et al. N Engl J Med. 2008;359(8):810-20

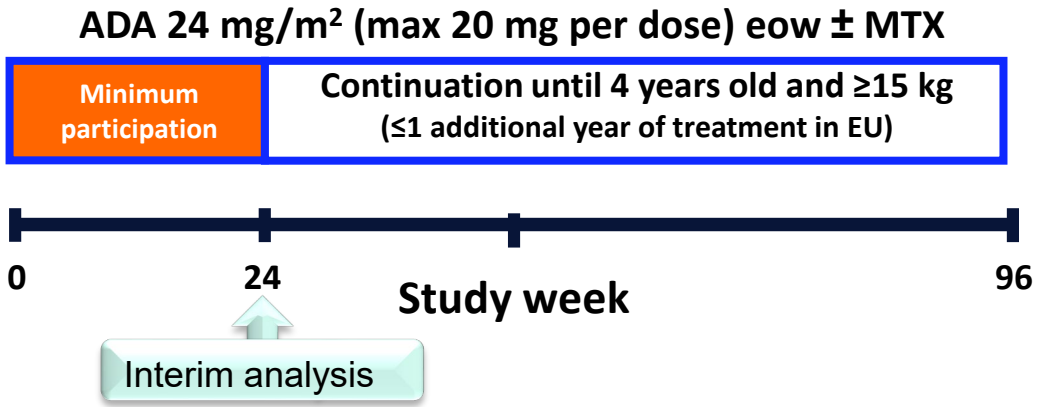
Study DE038: Key Safety Results in the Double Blind Phase

Event	MTX		Non-MTX	
	ADA (n = 38)	Placebo (n = 37)	ADA (n = 30)	Placebo (n = 28)
Any adverse event (AE)	32 (84.2%)	27 (73.0%)	28 (93.3%)	21 (75.0%)
Serious AE	3 (7.9%)	2 (5.4%)	1 (3.3%)	0
Severe AE	2 (5.3%)	0	1 (3.3%)	0
AE leading to discontinuation	0	0	0	0
Infectious AE	22 (57.9%)	19 (51.4%)	19 (63.3%)	11 (39.3%)
Serious Infections	1 (2.6%)	0	1 (3.3%)	0
Opportunistic Infections (incl. TB)	0	0	0	0
Injection site reactions	14 (36.8%)	9 (24.3%)	11 (36.7%)	4 (14.3%)
Malignancies	0	0	0	0
Death	0	0	0	0

Study M10-444: Design

- Open label study in 32 children ± MTX with moderately to severely active pJIA N = 32 (age 2 to < 4 years or 4 years and above weighing < 15 kg)
- Patients received adalimumab 24 mg/m^2 BSA up to a maximum of 20 mg eow SC for at least 24 weeks.

- **Patients aged 2–4 years or ≥4 years weighing <15 kg**
- **Moderately to severely active polyarticular JIA**



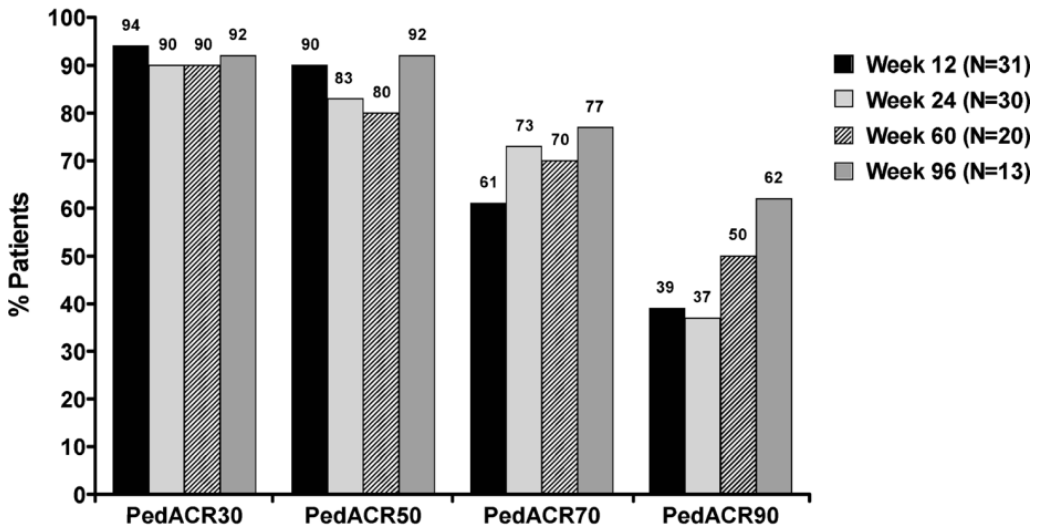
Study M10-444: Key Results

Efficacy

At Wk 12 and 24, Ped ACR30 response was 93.5% and 90.0%, respectively (observed)
Among those who had a Ped ACR 30 at Week 24 (27 of 30 pts), Ped ACR 30 was maintained for up to 60 weeks in the OLE phase in patients who received adalimumab throughout this time period.
Overall, 20 subjects were treated for 60 weeks or longer.

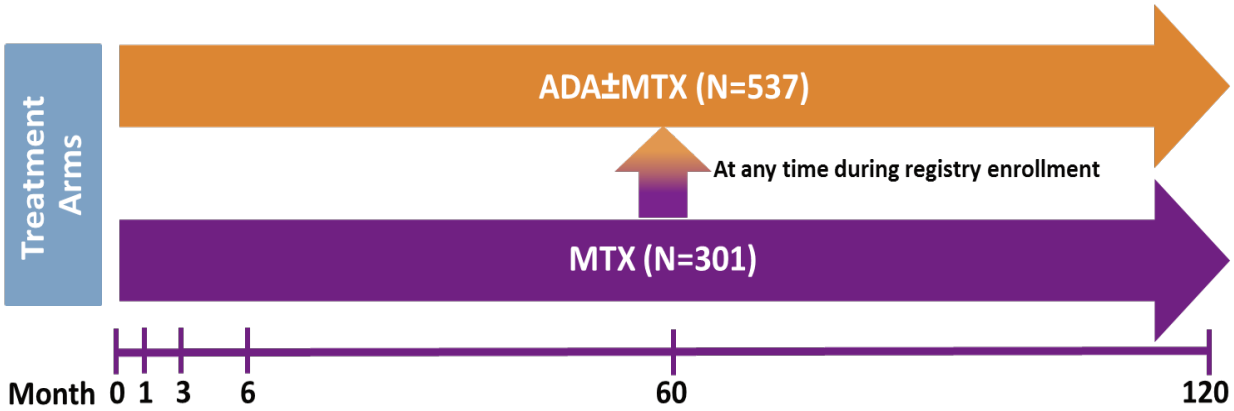
Safety

Safety of adalimumab in this patient population was similar to that observed in older JIA patients.
No new safety signals occurred in this study. No events of opportunistic infections/TB, malignancies, or deaths were reported.

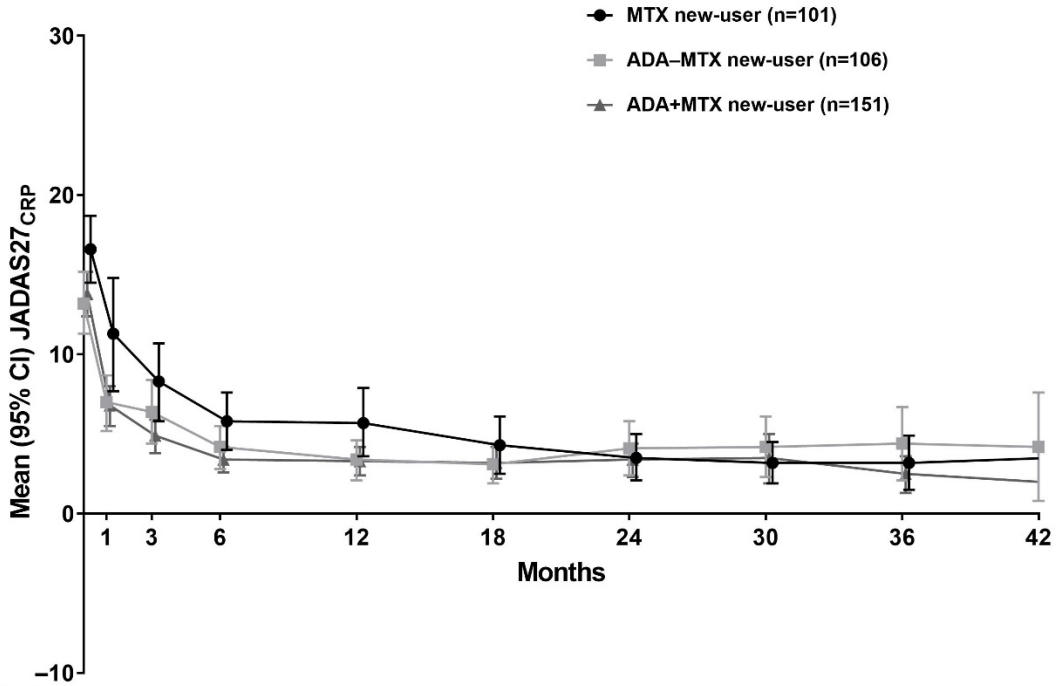


STRIVE (Study P10-262): Design

- (STRIVE) is a JIA registry to assess long-term safety (up to 10 years) and effectiveness in patients with pJIA receiving Humira® in accordance with the approved local product label under routine clinical setting conditions (i.e., FD or BSA-based dosing regimens).
- A cohort of patients who initiated MTX therapy was enrolled and used for comparison.



STRIVE: Efficacy Results

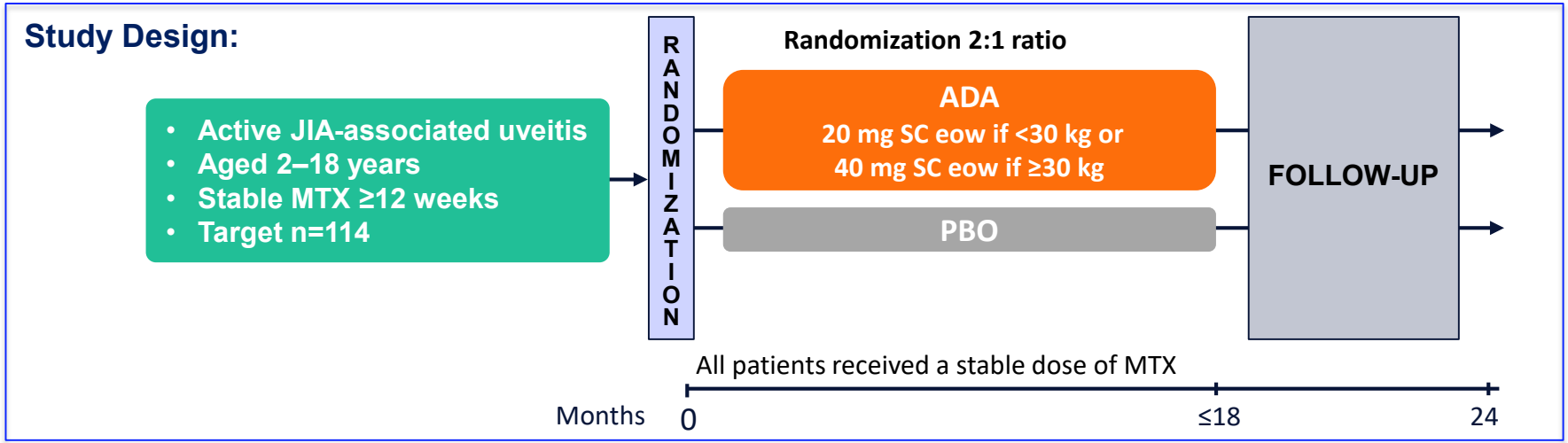


Number of patients										
MTX new-user	63	31	33	32	27	26	28	21	17	10
ADA–MTX new-user	68	52	52	47	46	44	39	30	20	16
ADA+MTX new-user	110	71	81	81	71	61	55	43	31	22

STRIVE (Study P10-262): Key Safety Results

	MTX		ADA ± MTX			
			ADA only		ADA + MTX[#]	
	N=301 n (%)	PYs=1170.3 E (E/100 PYs)	N=160 n (%)	PYs=517.0 E (E/100 PYs)	N=377 n (%)	PYs=1338.5 E (E/100 PYs)
Any AE	157 (52.2)	**505 (43.2)**	66 (41.3)	**216 (41.8)**	178 (47.2)	**553 (41.3)**
At least "possibly drug related" per the investigator	87 (28.9)	**197 (16.8)**	30 (18.8)	**66 (12.8)**	88 (23.3)	**177 (13.2)**
Severe AE	17 (5.6)	**23 (2.0)**	14 (8.8)	**22 (4.3)**	25 (6.6)	**41 (3.1)**
Serious AE	32 (10.6)	**52 (4.4)**	21 (13.1)	**39 (7.5)**	56 (14.9)	**95 (7.1)**
AE leading to discontinuation of study drug or study	28 (9.3)	**36 (3.1)**	13 (8.1)	**19 (3.7)**	25 (6.6)	**40 (3.0)**
Infectious AE	87 (28.9)	**179 (15.3)**	38 (23.8)	**75 (14.5)**	105 (27.9)	**187 (14.0)**
Serious infectious AE	14 (4.7)	**17 (1.5)**	6 (3.8)	**8 (1.5)**	22 (5.8)	**30 (2.2)**
Injection site-related AE	6 (2.0)*	**8 (0.7)**	5 (3.1)	**6 (1.2)**	24 (6.4)	**32 (2.4)**

SYCAMORE is an IIS Assessing the Use of Adalimumab in JIA Uveitis (UK)



Ramanan AV et al. N Engl J Med. 2017 Apr 27;376(17):1637-1646

Major Inclusion Criteria:

- Age ≥ 2 and <18 years with diagnosis of JIA (ILAR)
- Active anterior uveitis: Sustained grade of cellular infiltrate in anterior chamber of the SUN criteria grade ≥1+ or more during the preceding 12 weeks, Failed MTX: Been on MTX for at least 12 weeks and stable dose for preceding 4 weeks
- No disease modifying immunosuppressive drugs, other than MTX, in the 4 weeks prior to screening

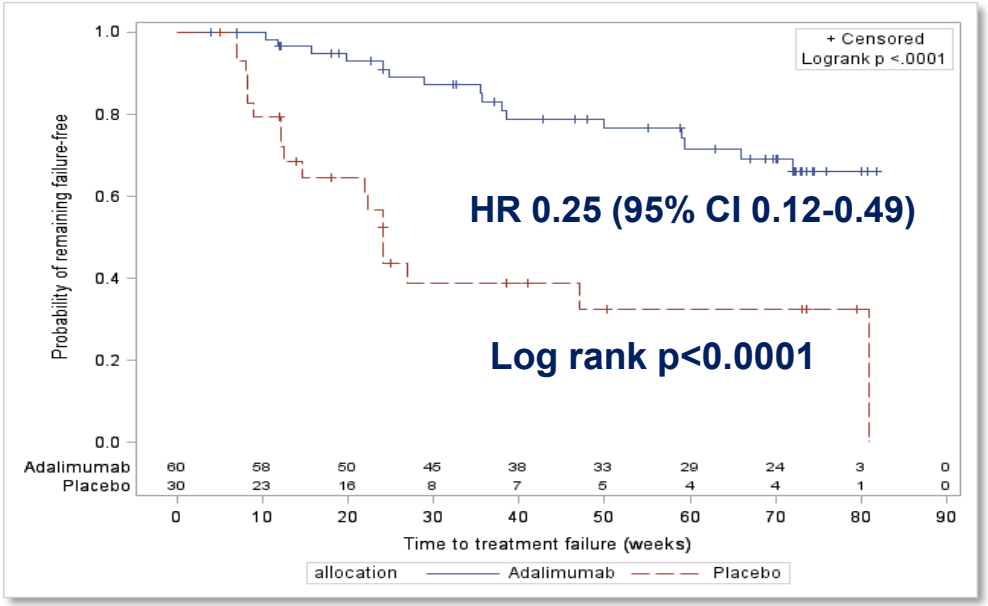
SYCAMORE: Key Efficacy Results

The trial was stopped after 90 patients (60 on adalimumab, 30 on placebo) had been randomised

- Interim efficacy analysis met the pre-specified statistical stopping boundary

Total of 34 treatment failures

- 16 treatment failures in 60 patients on adalimumab (26.7%)
- 18 treatment failures in 30 patients on placebo (60%)

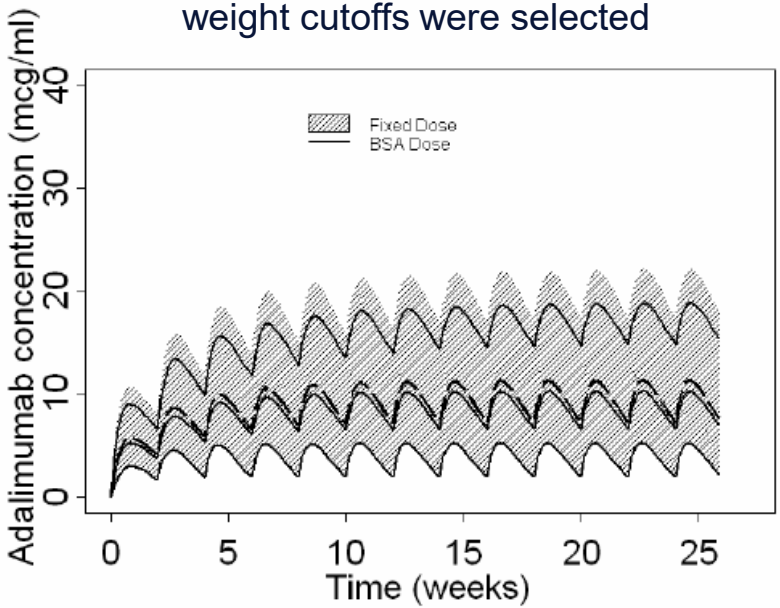


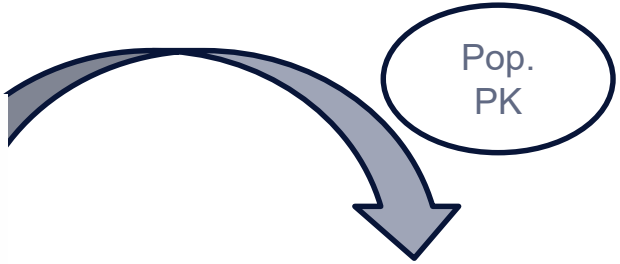
Where Do We Go from Here?

Dosing of Adalimumab in Patients with pJIA (US)

Remember:
Dosing of adalimumab in DE038 was based on BSA ➔ patients could switch to fixed dose by body weight cutoff in OLE phase

Through PK modeling, doses and body weight cutoffs were selected





USPI

DOSAGE AND ADMINISTRATION

- Administered by subcutaneous injection (2)

Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis (2.1):

- 40 mg every other week.
  - Some patients with RA not receiving methotrexate may benefit from increasing the frequency to 40 mg every week.

Juvenile Idiopathic Arthritis or Pediatric Uveitis (2.2):

- *10 kg (22 lbs) to <15 kg (33 lbs):* 10 mg every other week
- *15 kg (33 lbs) to < 30 kg (66 lbs):* 20 mg every other week
- *≥ 30 kg (66 lbs):* 40 mg every other week

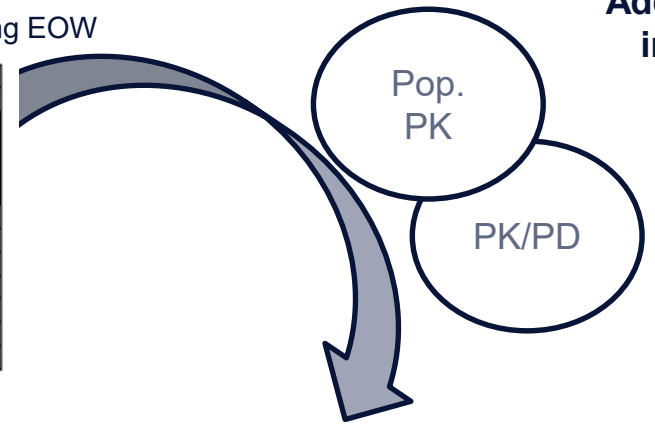
Alignment of Dosing Regimen for pJIA in EU

Initially in the EU: BSA regimen, 24 mg/m² up to a maximum of 40 mg EOW

Height (cm)	Total Body Weight (kg)												
	10	15	20	25	30	35	40	45	50	55	60	65	70
80	0.2	0.3	0.3	0.3									
90	0.2	0.3	0.3	0.4	0.4	0.4							
100	0.3	0.3	0.3	0.4	0.4	0.4	0.5	0.5					
110	0.3	0.3	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.6	0.6		
120	0.3	0.4	0.4	0.4	0.5	0.5	0.5	0.6	0.6	0.6	0.6	0.7	0.7
130		0.4	0.4	0.5	0.5	0.5	0.6	0.6	0.6	0.6	0.7	0.7	0.7
140		0.4	0.4	0.5	0.5	0.6	0.6	0.6	0.7	0.7	0.7	0.7	0.8*
150			0.5	0.5	0.6	0.6	0.6	0.7	0.7	0.7	0.7	0.8*	0.8*
160			0.5	0.5	0.6	0.6	0.7	0.7	0.7	0.8*	0.8*	0.8*	0.8*
170				0.6	0.6	0.6	0.7	0.7	0.8*	0.8*	0.8*	0.8*	0.8*
180					0.6	0.7	0.7	0.8*	0.8*	0.8*	0.8*	0.8*	0.8*

*Maximum single dose is 40 mg (0.8 ml)

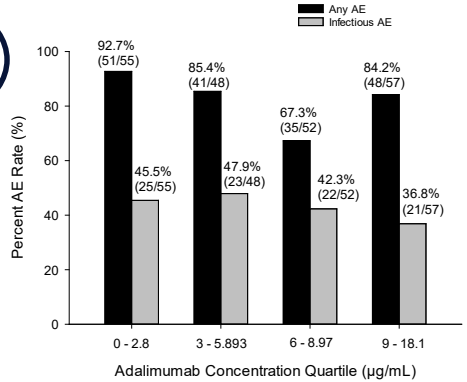
Humira Dose in Milliliters (mL) by Height and Weight of Patients for pJIA



Additional Data in Pediatric Patients

Lack of E-R

JIA (Week 0 to Week 12/16)



Polyarticular juvenile idiopathic arthritis from 2 years of age

The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis from 2 years of age is based on body weight (Table 1). Humira is administered every other week via subcutaneous injection.

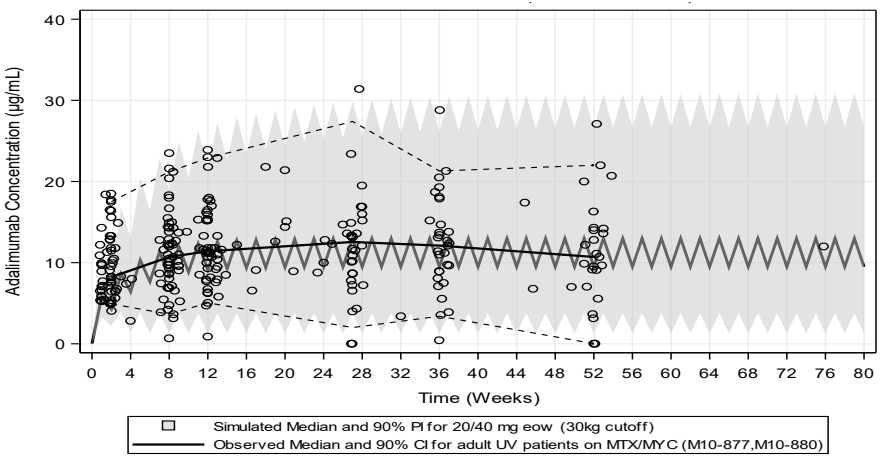
Table 1. Humira Dose for Patients with Polyarticular Juvenile Idiopathic Arthritis

Patient Weight	Dosing Regimen
10 kg to < 30 kg	20 mg every other week
≥ 30 kg	40 mg every other week

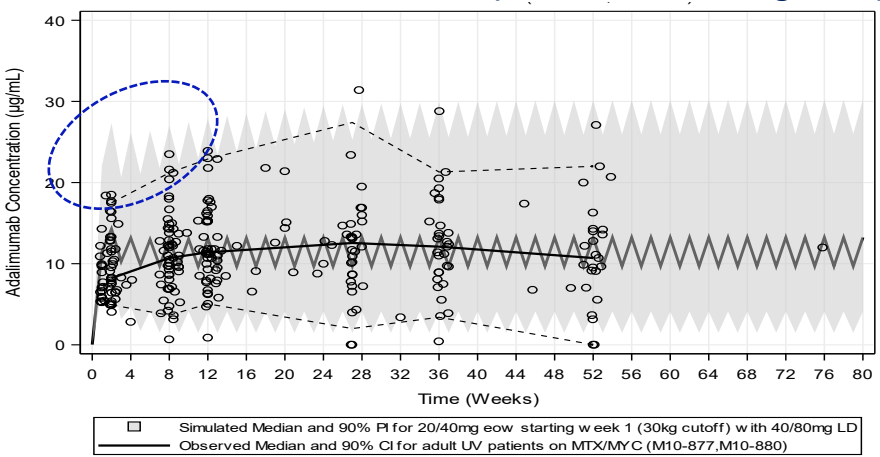
Pharmacokinetic Simulations to Support Dosing Recommendation in JIA Uveitis

- In JIA uveitis, PK simulations were used to demonstrate that
  - expected concentrations in pediatric patients with uveitis is similar to those observed in adults
  - support the used of an optional loading dose (not studied) to help achieve steady state concentration faster

Pediatric Uveitis Patients (with MTX)



Pediatric Uveitis Patients (with MTX + loading dose)



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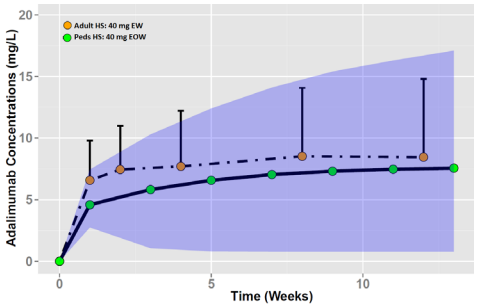
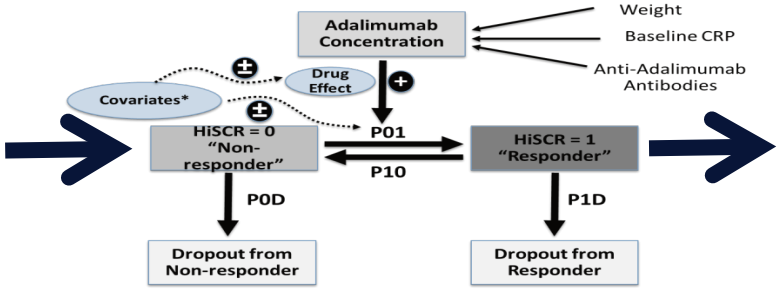
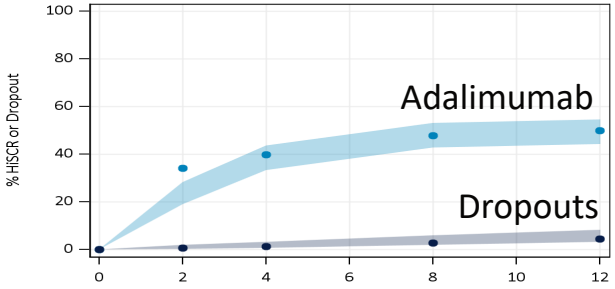
MTX: Methotrexate

Full Extrapolation in Adolescents with Hidradenitis Suppurativa





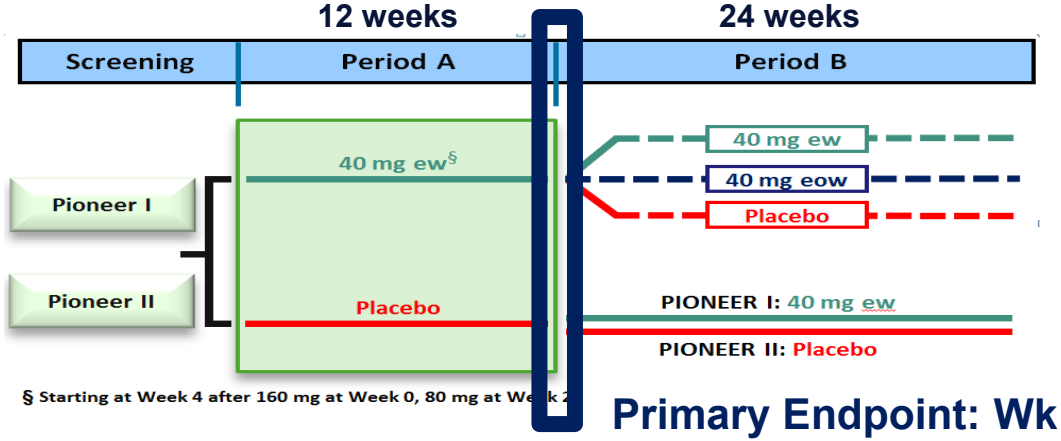


Adalimumab Exposure and HiSCR Response for Adult (Observed) vs Adolescent (Simulated) HS Patients

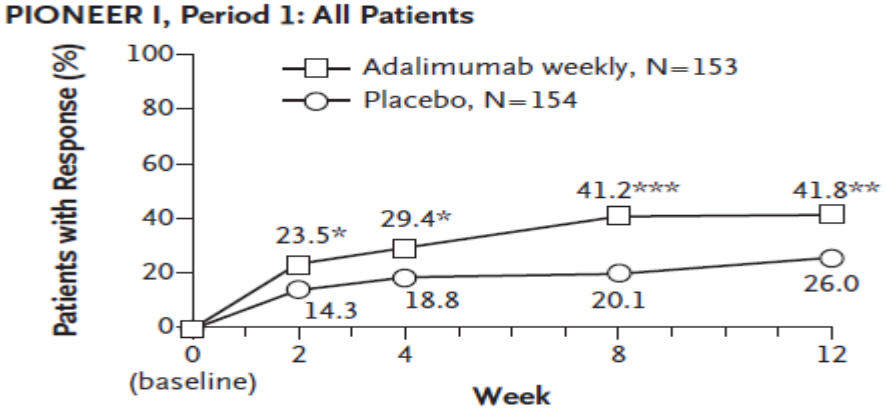
Week 12 Endpoint	Observed Adult (M11-313)	Observed Adult (M11-810)	Observed Adult (Combined)	Sim. Adolescent (80 mg at Week 0 and 40 mg eow starting at Week 1) Median and 90% PI)
Adalimumab Concentration (µg/mL)	8.66 ± 6.39*	8.95 ± 6.27*	8.81 ± 6.32*	8.4 (0.8 – 18)
HiSCR "Adalimumab"	41.8%	58.9%	51%	55% (51 - 58)
HiSCR "Placebo"	26%	27.6%	26.8%	28% (24 - 32)

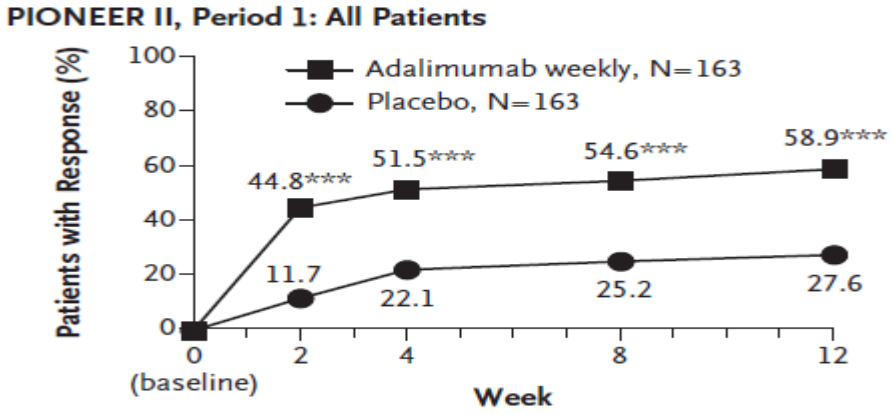
*(Mean±SD)

Efficacy of Adalimumab in Adult Patients with HS



Primary Endpoint: Wk 12 HiSCR





Kimball, *et al,* 2016.

Data available from Adult and Pediatric Patients for Extrapolation in HS

- Large clinical studies in adult patients with HS (~600) and psoriasis (~900)
- Clinical trials in 3 different pediatric populations with >500 patients combined (juvenile idiopathic arthritis, psoriasis, CD)
- Patient registry in patients with HS (included adolescents, different drugs)
- Elaborate extrapolation plan
  - Population PK model in pediatrics – used simulate exposure in adolescent HS
  - Combined adult HS and PS Pop PK model - quantify any indication effect on adalimumab PK independent of demographic covariate effects
  - Select a pediatric dose ➔ similar exposure to adults ➔ predict HiSCR response in adolescent HS population

Summary

- Efficacy of adalimumab was established in RA in adults then in pJIA patients ages 2 and older
- The safety profile of adalimumab in the pediatric patient population is consistent with what has been observed in adults, expected for the underlying disease, and presented in the current Humira® label
- No new safety signals or unexpected trends specific to the pediatric population were identified.
- A flat dosing regimen by body weight cutoffs was established
- Population PK and PK/PD analyses was used to support dose selection and extrapolation across age groups in JIA and across indications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