A Randomized, Double-blind Trial of Anti-TNF Chimeric Monoclonal Antibody (Infliximab) in Combination With Methotrexate for the Treatment of Patients With Polyarticular Juvenile Rheumatoid Arthritis

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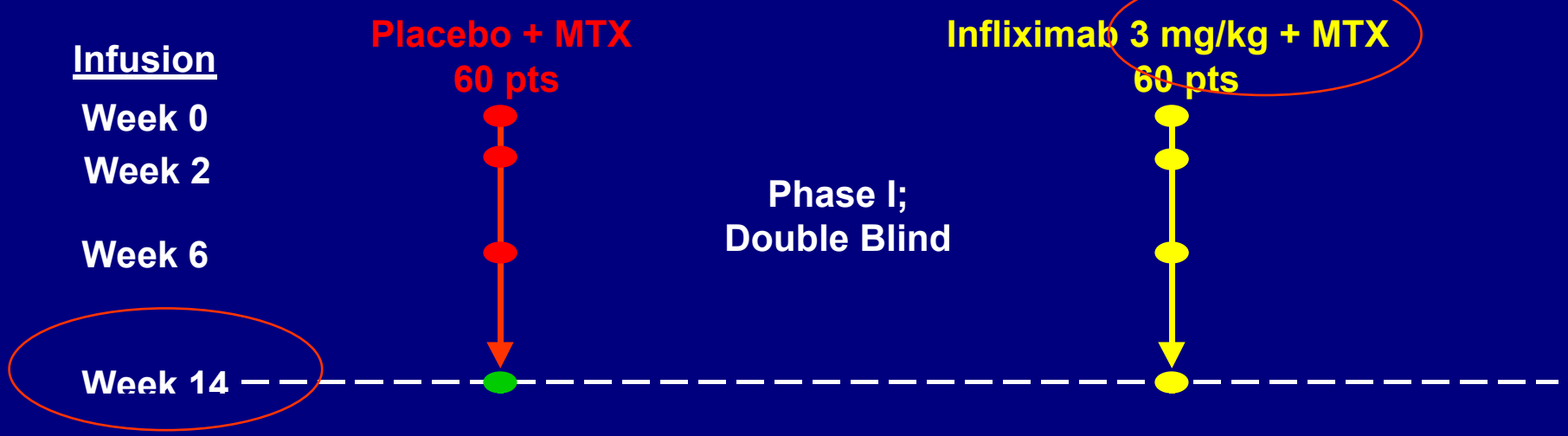
EMA 2010

JRA Study Design (40 centres)



Inclusion/Exclusion Criteria

Inclusion Criteria

- Polyarticular JRA
- At least 5 active joints
- Low dose prednisone (≤10 mg or 0.2 mg/kg/day) for >4 weeks
- Methotrexate: stable dose and route, Initiated at least 3 months prior to first study infusion

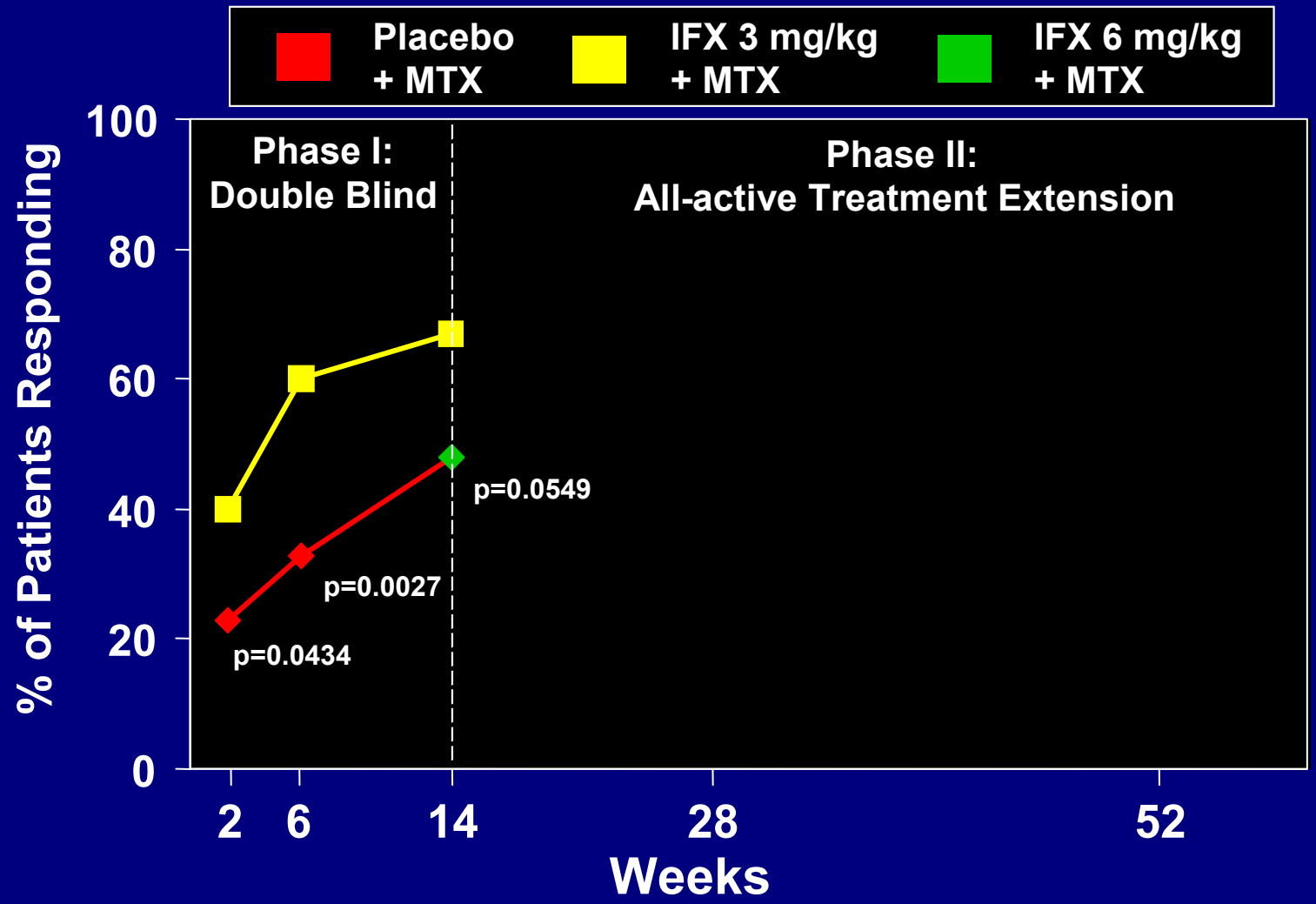
Exclusion Criteria

- No systemic manifestation
- No joints injections 4 w before
- No previous infliximab or other biologics
- No previous use of cyclophosphamide, nitrogen mustard, chlorambucil
- No DMARDs other than MTX

Endpoints

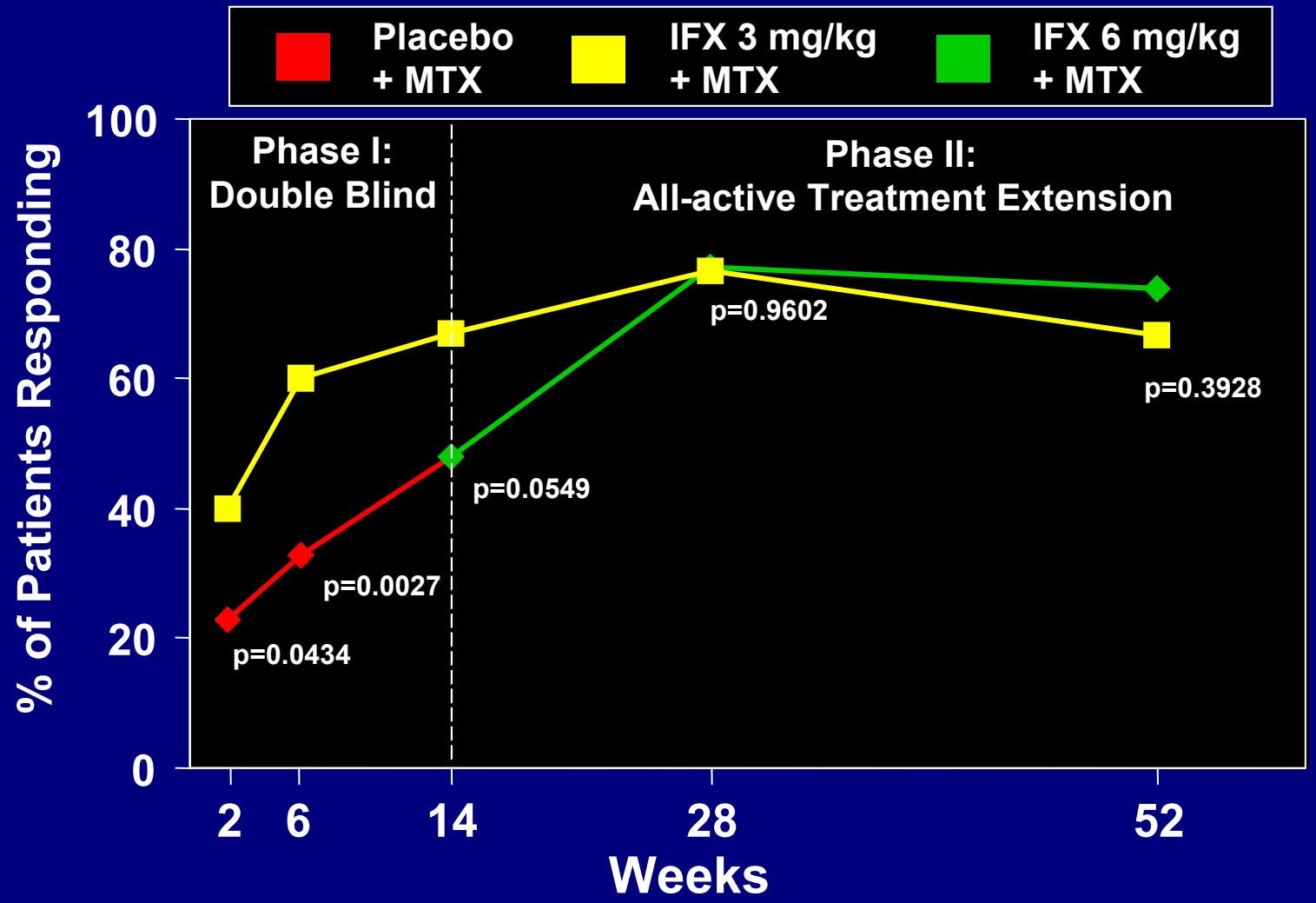
- Primary Endpoint
  - The proportion of patients achieving ACR pediatric 30 response at Week 14 in the placebo/6 mg/kg infliximab + MTX group (Group I) compared with the 3 mg/kg infliximab + MTX group (Group II)
- Major Secondary Endpoints
  - Infliximab pharmacokinetics
  - Adverse event profile of infliximab in the JRA population

ACR-pediatric 30 Using ESR*



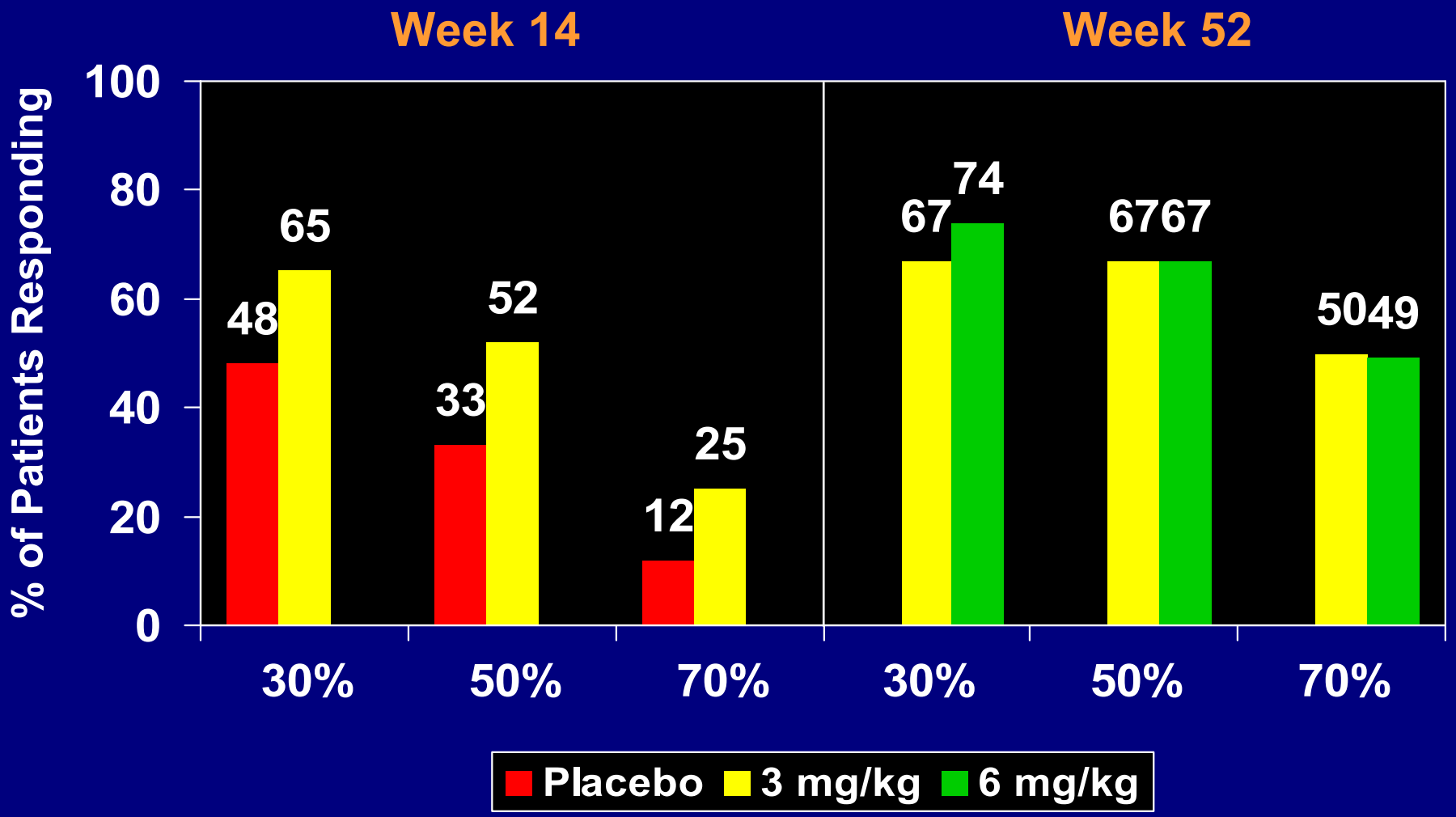
*ESR: protocol specified analyses

ACR-pediatric 30 Using ESR*

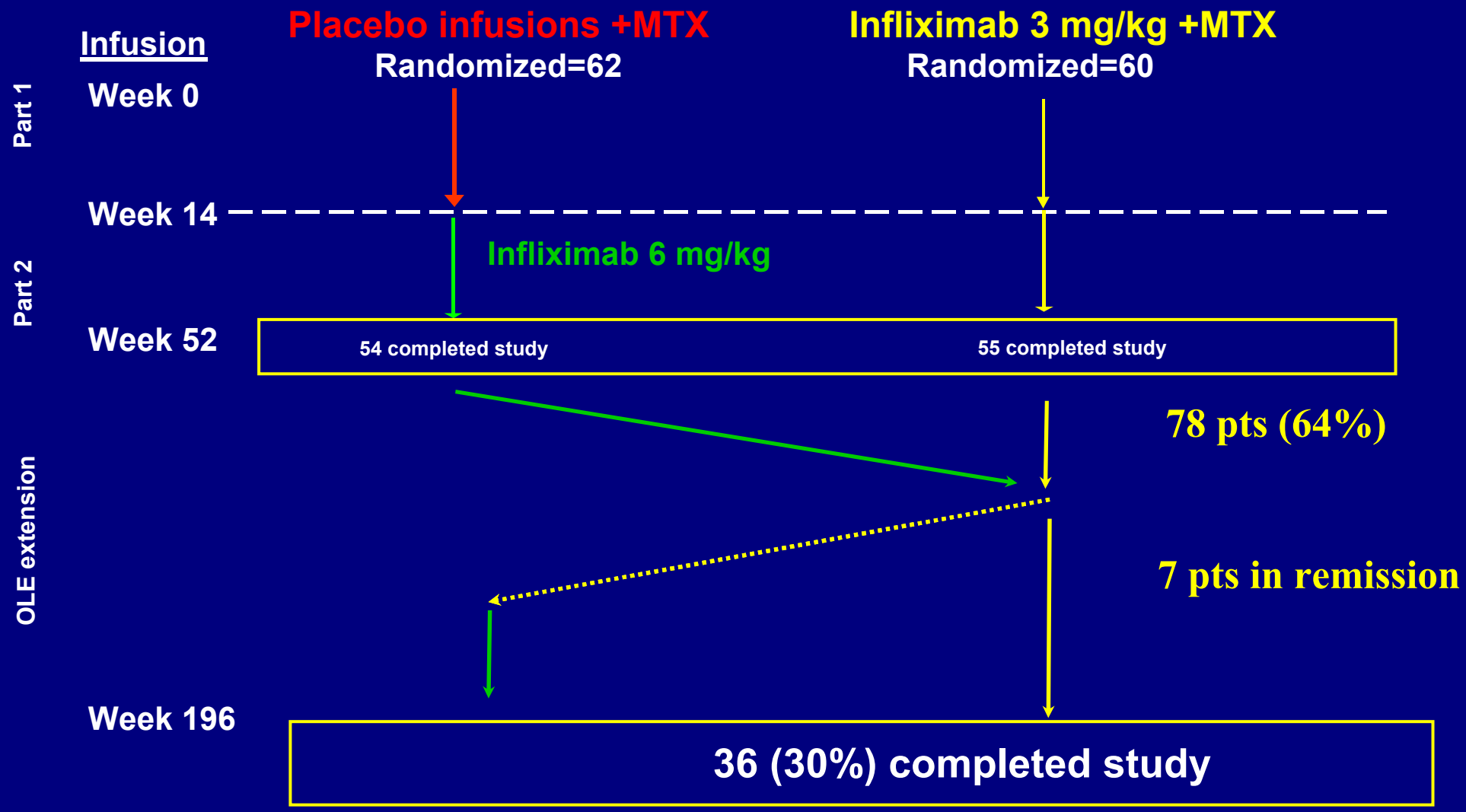


*ESR: protocol specified analyses

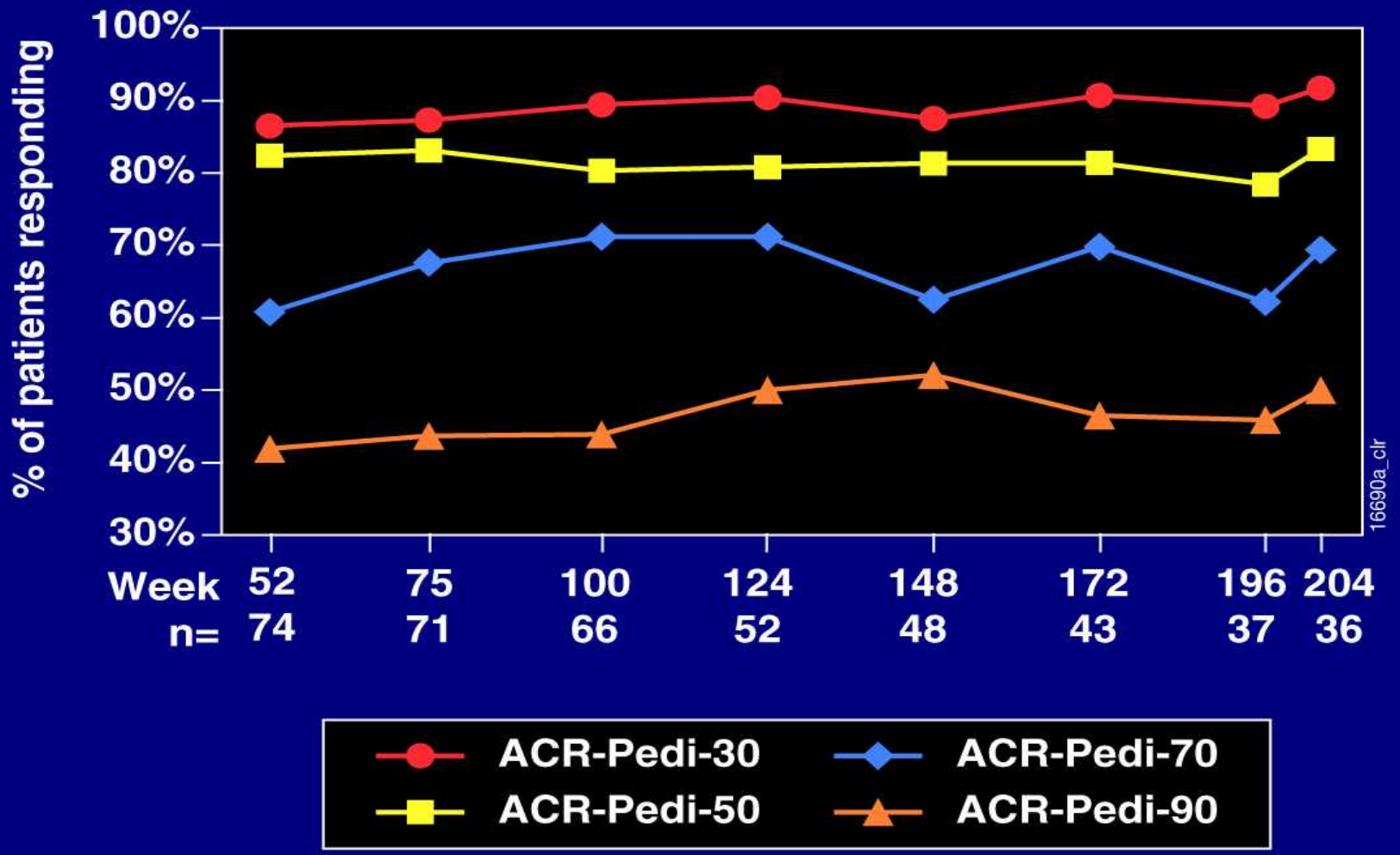
ACR-pedi 30, 50, and 70 Using ESR



JRA Study Design



Improvement in ACR-Pedi-30, 50, 70, 90



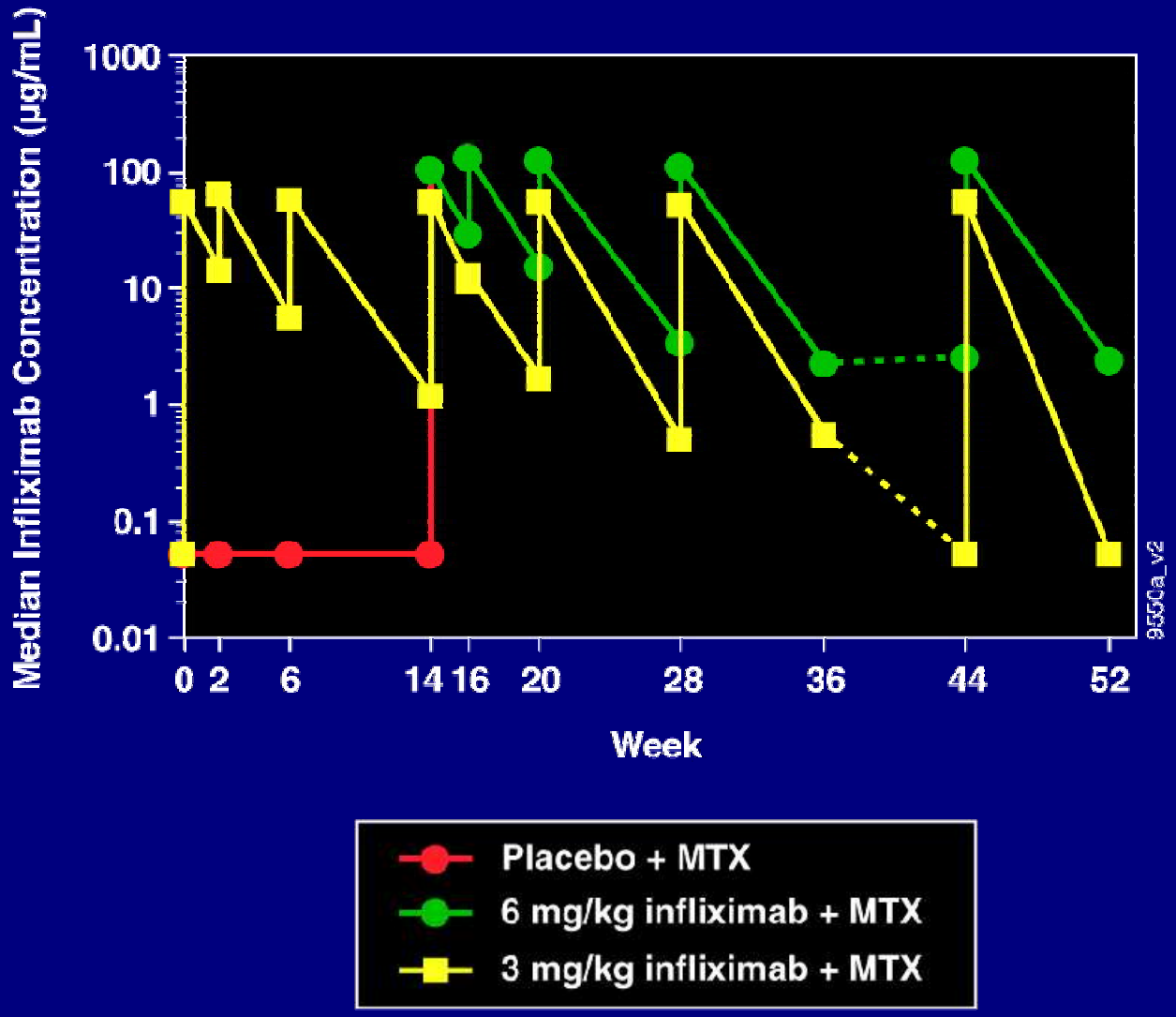
Infusion reactions/immunogenicity 0-52 w

- Infusions with infusion reactions
  - Infliximab 3 mg/kg (Week 0-52) = 46 (9.1%)
  - 6 mg/kg (Week 14-52) = 13 (4.2%)
- Serious infusion reactions
  - Infliximab 6 mg/kg = 2 (3.5%)
  - Infliximab 3 mg/kg = 4 (6.7%)
- Higher anti-infliximab antibody incidence in 3 mg/kg than in 6 mg/kg group
  - 37.7% in 3 mg/kg and 12.2% in 6 mg/kg
  - Incidence for 6 mg/kg group is similar to 3 mg/kg in adults with RA (ASPIRE trial data)
- Antibody positive patients had lower serum infliximab concentrations

Infliximab immunogenicity

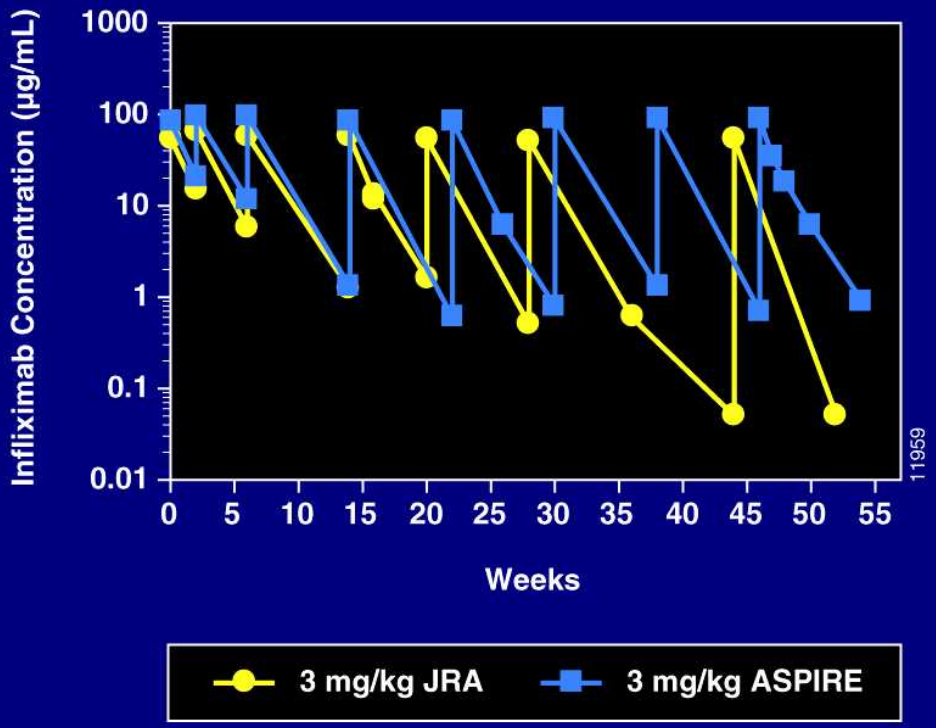
Infusion Reactions Week 52- 204	Infliximab + MTX (n=78)
Subjects POSITIVE for ATIs from Week 52 through Week 216	26/71 (36.6%)
Infusion Reactions	15 (57.7%)
Serious Infusion Reactions (possible anaphylactic reaction)	1 (3.8%)
Subjects negative for ATIs from Week 52 through Week 216	22/71 (31%)
Infusion Reactions	5 (22.7%)
Serious Infusion Reactions	1 (4.5%)
Antinuclear antibodies (titer >1:320)	
Newly positive from Weeks 52-204	15/58 (25.9)
Antibody to double-stranded DNA	
Newly positive from Weeks 52-204	4/61 (6.6)

Comparison of PK Profile in the 3 mg/kg group vs. 6 mg/kg group in JRA



Data on File; Centocor, Inc.

Comparison of PK Profile 3 and 6 mg/kg JRA vs. 3 mg/kg ASPIRE (Adult Early RA Study)



Data on File; Centocor, Inc.

Reasons for failure to achieve primary objectives

- Errors in sample size assumptions
  - 5 patients excluded from efficacy analysis 1 for consent withdrawn and 4 for potential unblinding issues
  - Higher than anticipated placebo response (48%)

ADDITIONAL REASONS

- Errors in time to assess primary outcome (14 weeks too short)
- Failure to have an adequate pK/safety model specific for children prior to the phase III trial