

*REMICADE® (infliximab)*

# Centocor Presentation

---

**REMICADE® (infliximab)**  
**Chimeric Monoclonal Antibody**  
**Against Human Tumor Necrosis Factor  $\alpha$**

*REMICADE® (infliximab)*

# Rheumatoid Arthritis

---

- **Current therapies**
  - **Treat signs and symptoms**
  - **Slow progression of structural damage**
- **Unmet medical need**
  - **Prevent structural damage and improve physical function in patients with active disease despite DMARD therapies**

**REMICADE® (infliximab)**

# **Rheumatoid Arthritis**

---

- **REMICADE®**, in combination with methotrexate,
  - **Significantly prevents structural damage (erosions and joint space narrowing)**
  - **Improves physical function (HAQ and physical components of SF-36)**

*REMICADE® (infliximab)*

# Approved Indications

---

August 1998

- **Moderately to severely active Crohn's Disease**
  - Treatment of signs and symptoms
- **Fistulizing Crohn's Disease**
  - Reducing the number of draining enterocutaneous fistulas

**REMICADE® (infliximab)**

# **Approved Indications**

---

November 1999

- **Rheumatoid Arthritis (RA)**
  - **In combination with methotrexate, for reduction of signs and symptoms in patients who have had an inadequate response to methotrexate**
  - **3 mg/kg followed with additional 3 mg/kg doses at 2 and 6 weeks then every 8 weeks thereafter**

**REMICADE® (infliximab)**

# **ATTRACT Trial**

---

- **Study design**
  - **2 years treatment**
  - **Placebo controlled**
  - **Double blind**
  - **Randomized**
  - **Concomitant methotrexate therapy**
  - **Patients with inadequate response to methotrexate**

**REMICADE® (infliximab)**

# **ATTRACT Trial**

---

- **FDA Guidance to Industry defines potential claims, including prevention of structural damage**
- **ATTRACT design and endpoints to support indication based on FDA Guidance to Industry**
- **Primary endpoints**
  - **Treatment of signs and symptoms (30 weeks)**
  - **Prevention of structural damage (54 weeks)**
  - **Improvement in physical function (102 weeks)**

**REMICADE® (infliximab)**

# **Proposed RA Indication Expansion**

---

- **Prevention of structural damage**
  - **Erosions**
  - **Joint space narrowing**
- **Improvement in physical function**

**REMICADE® (infliximab)**

# **Agenda of Speakers**

---

**Introduction**

**Martin Page**  
**Vice President, Worldwide Regulatory Affairs**  
**Centocor**

**Scientific Rationale and  
Clinical Pharmacology**

**Professor Ravinder Maini, M.D., FRCP**  
**Kennedy Institute of Rheumatology**  
**London, UK**

**Efficacy and Safety**

**Gregory Harriman, M.D.**  
**Senior Director, Immunology Clinical Research**  
**Centocor**

**Significance of  
Radiographic Results**

**Désirée M.F.M. van der Heijde, M.D., Ph.D.**  
**Professor of Rheumatology**  
**University Hospital Maastricht, The Netherlands**

**Clinical Perspective**

**E. William St. Clair, M.D.**  
**Associate Professor of Medicine**  
**Duke University School of Medicine, Durham, NC**

**Concluding Remarks**

**Martin Page**

**REMICADE® (Infliximab)**

# **Centocor Consultants**

---

**Paul Emery, M.D.**

**Professor of Rheumatology  
Leeds General Infirmary  
Leeds, U.K.**

**John Sharp, M.D.**

**Affiliate Professor of Medicine  
University of Washington  
Seattle, WA**

**Frederick Wolfe, M.D.**

**Clinical Professor of Internal Medicine and  
Family and Community Medicine  
University of Kansas School of Medicine  
Wichita, KA**

**REMICADE® (infliximab)**

# **Agenda of Speakers**

---

**Introduction**

**Martin Page**

**Vice President, Worldwide Regulatory Affairs  
Centocor**

**Scientific Rationale and  
Clinical Pharmacology**

**Professor Ravinder Maini, M.D., FRCP  
Kennedy Institute of Rheumatology  
London, UK**

**Efficacy and Safety**

**Gregory Harriman, M.D.**

**Senior Director, Immunology Clinical Research  
Centocor**

**Significance of  
Radiographic Results**

**Désirée M.F.M. van der Heijde, M.D., Ph.D.**

**Professor of Rheumatology  
University Hospital Maastricht, The Netherlands**

**Clinical Perspective**

**E. William St. Clair, M.D.**

**Associate Professor of Medicine  
Duke University School of Medicine, Durham, NC**

**Concluding Remarks**

**Martin Page**

# **REMICADE<sup>®</sup> (infliximab)**

---

## **Scientific Rationale**

*REMICADE® (infliximab)*

# Scientific Rationale and Clinical Pharmacology

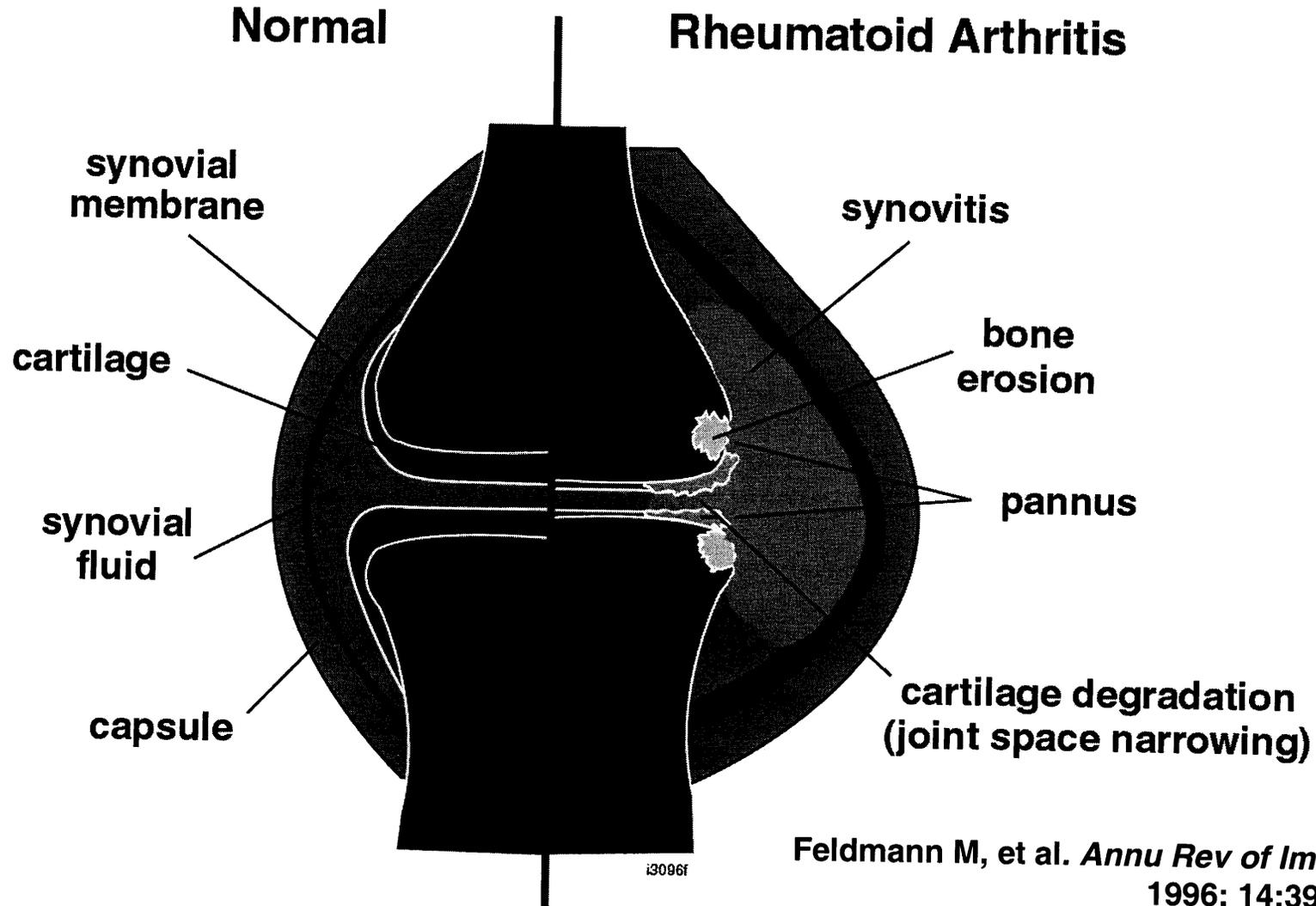
---

- **Preclinical evidence for prevention and reversal of structural damage to both bone and cartilage**
- **Pharmacodynamic data from clinical trials show that REMICADE® down-regulates mediators of joint destruction**

*Scientific Rationale*

# The Pathology of Rheumatoid Arthritis

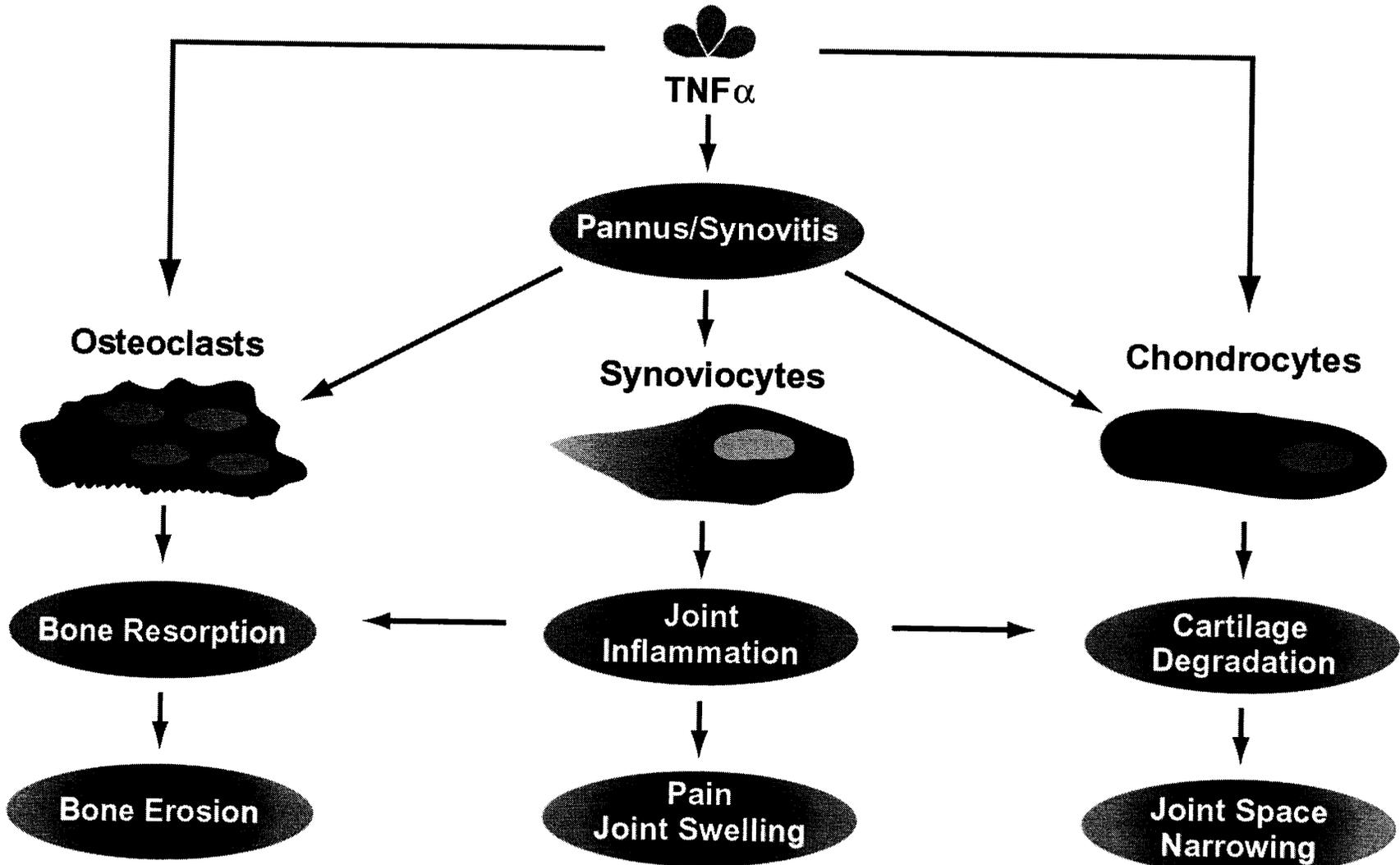
---



Feldmann M, et al. *Annu Rev of Immuno.* 1996; 14:397-440.

*Scientific Rationale*

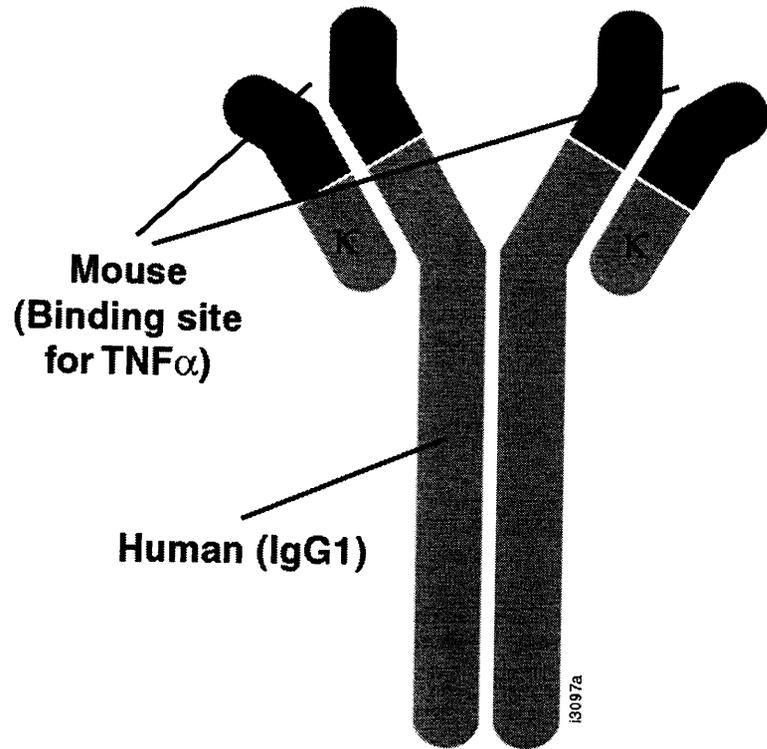
# Central Role of TNF $\alpha$ in RA



**Scientific Rationale**

# REMICADE® (infliximab)

---



- **Chimeric IgG1 monoclonal antibody**
- **High affinity binding to TNF $\alpha$  ( $K_a = 10^{10}M^{-1}$ )**

*Scientific Rationale*

# Unique Features of REMICADE<sup>®</sup> (infliximab)

---

	<u>REMICADE<sup>®</sup></u>	<u>p75-Receptor Construct</u>
<b>Specificity</b>	<b>Neutralizes only TNF<math>\alpha</math><sup>1</sup></b>	<b>Binds to TNF<math>\alpha</math> and LT<math>\alpha</math><sup>2</sup></b>
<b>Avidity</b>	<b>Highly stable complexes<sup>3</sup></b>	<b>Dissociation of TNF-complexes in the presence of free TNF or receptor<sup>4</sup></b>
<b>Cytolytic activity</b>	<b>Selective lysis of activated TNF<math>\alpha</math>-expressing cells<sup>5</sup></b>	<b>No cell lysis<sup>6</sup></b>

<sup>1</sup>Knight DM, et al. *Molec Immunol*. 1993. 16:1443-53. <sup>2</sup>Mohler KM, et al. *J Immunol*. 1993. 151:1548-61.

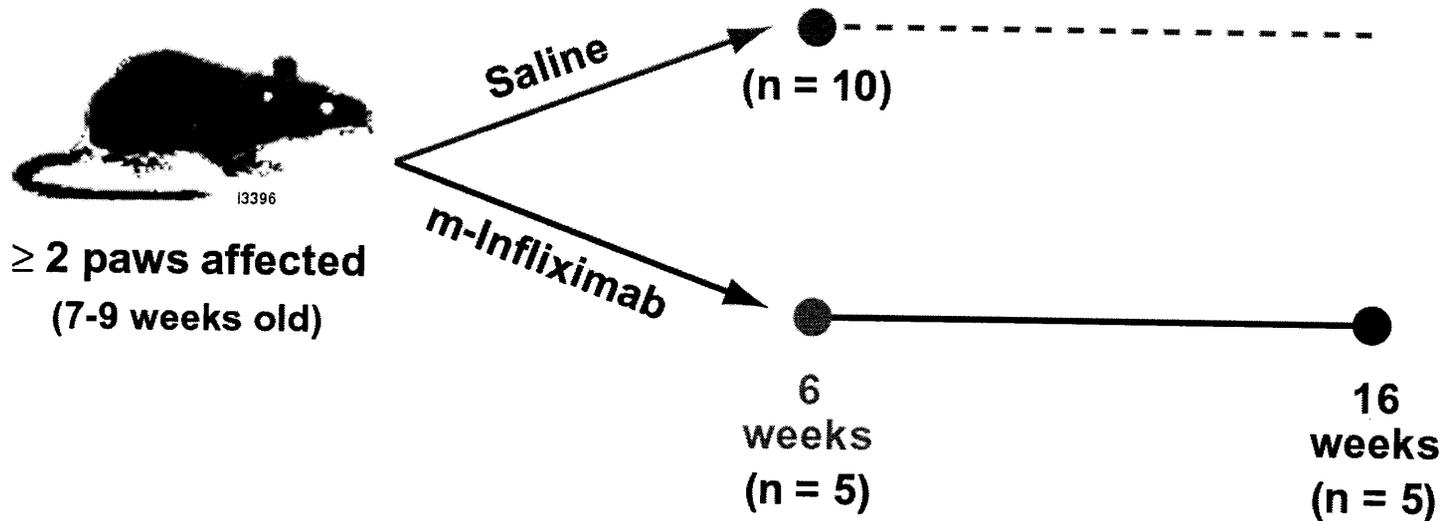
<sup>3</sup>Data on file; <sup>4</sup>Evans TJ, et al. *J Exp Med*. 1994. 180:2173-79. <sup>5</sup>Scallon BJ, et al. *Cytokine*. 1995. 7:251-9.

<sup>6</sup>Barone D, et al. *Arthritis Rheum*. 1999. 42 (Suppl) S90.

*Scientific Rationale*

# Reversal of Structural Damage in RA Mouse Model

Tg197 Transgenic Mice Express Human TNF $\alpha$  and Develop Polyarthritis

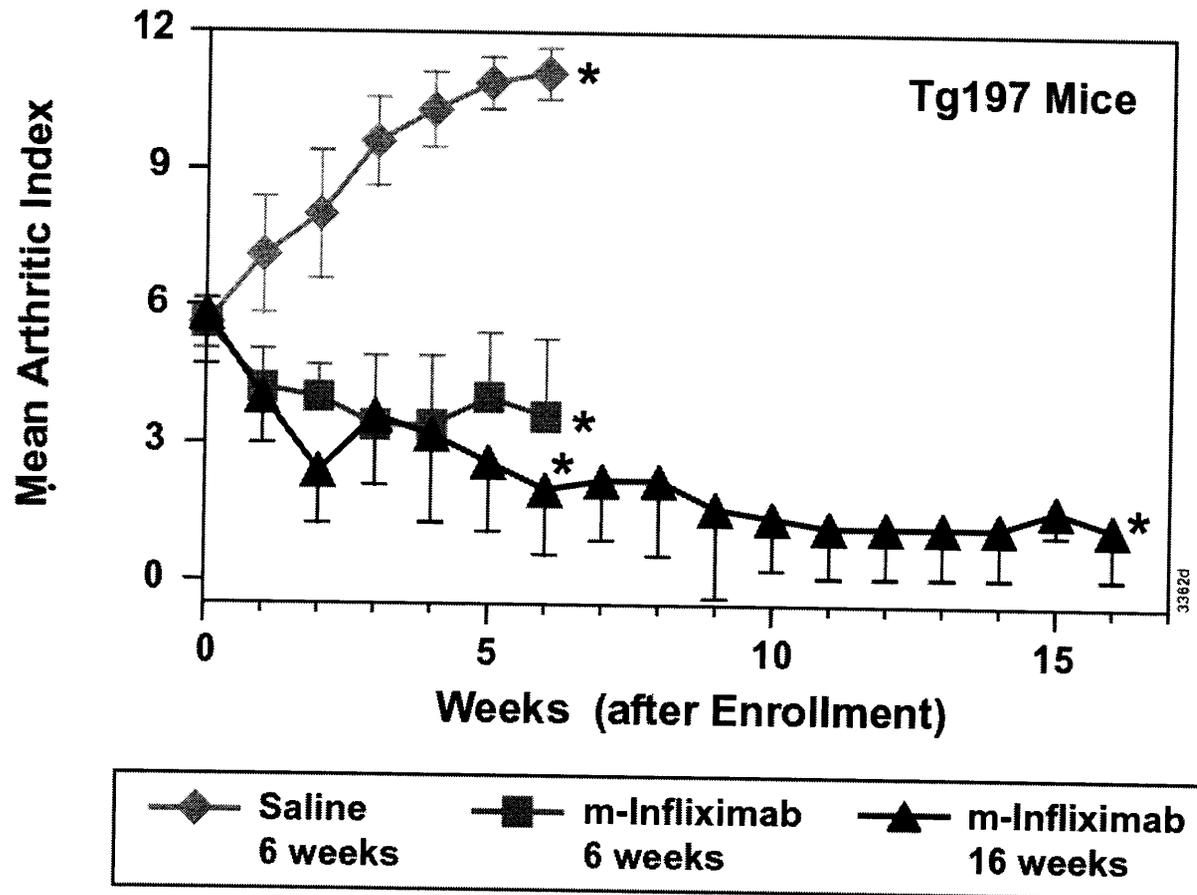


- Paws clinically scored weekly
- 16 week saline group sacrificed at 6 weeks for ethical reasons

Scientific Rationale

# m-Infliximab Reverses Arthritis

## Arthritic Index

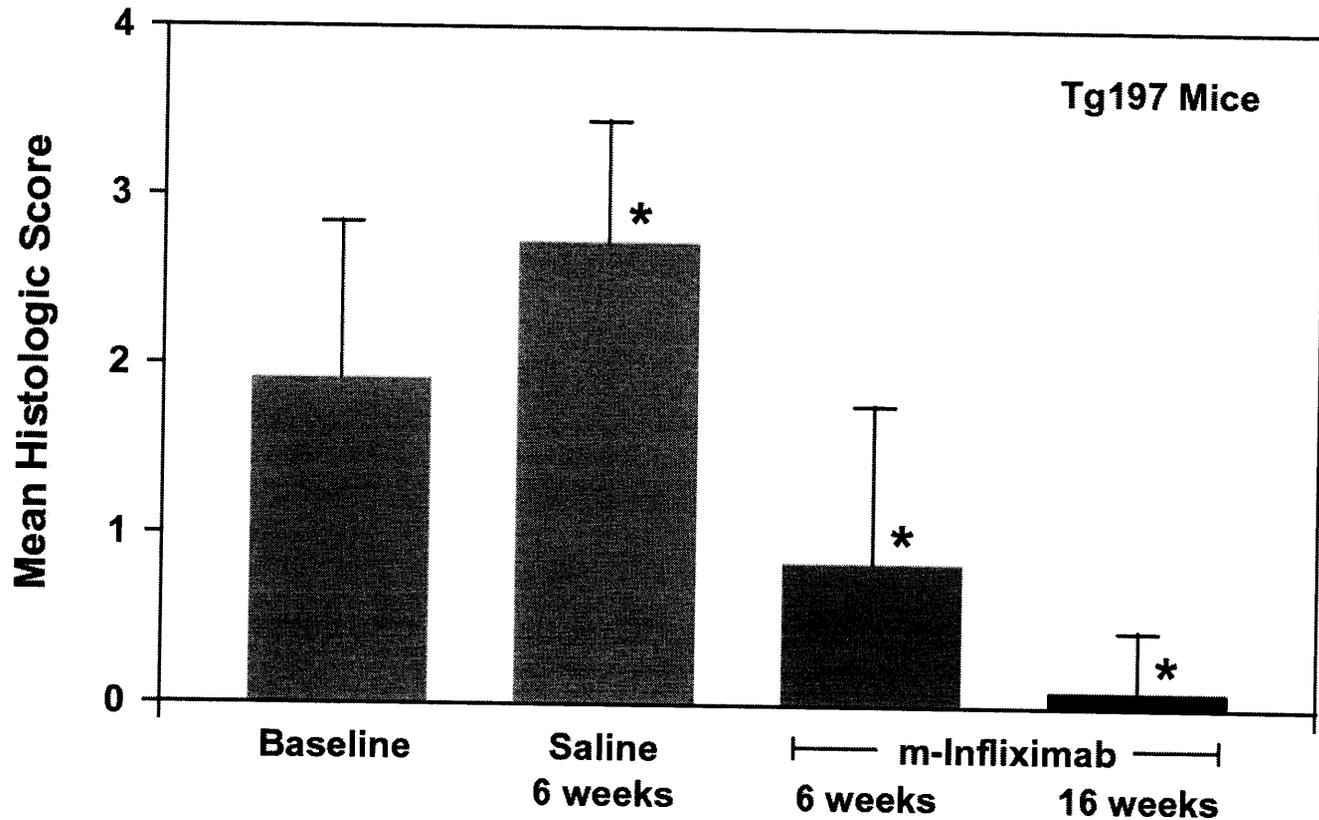


\*p-value vs. baseline < 0.05

*Scientific Rationale*

# m-Infliximab Reverses Structural Damage

## Synovitis

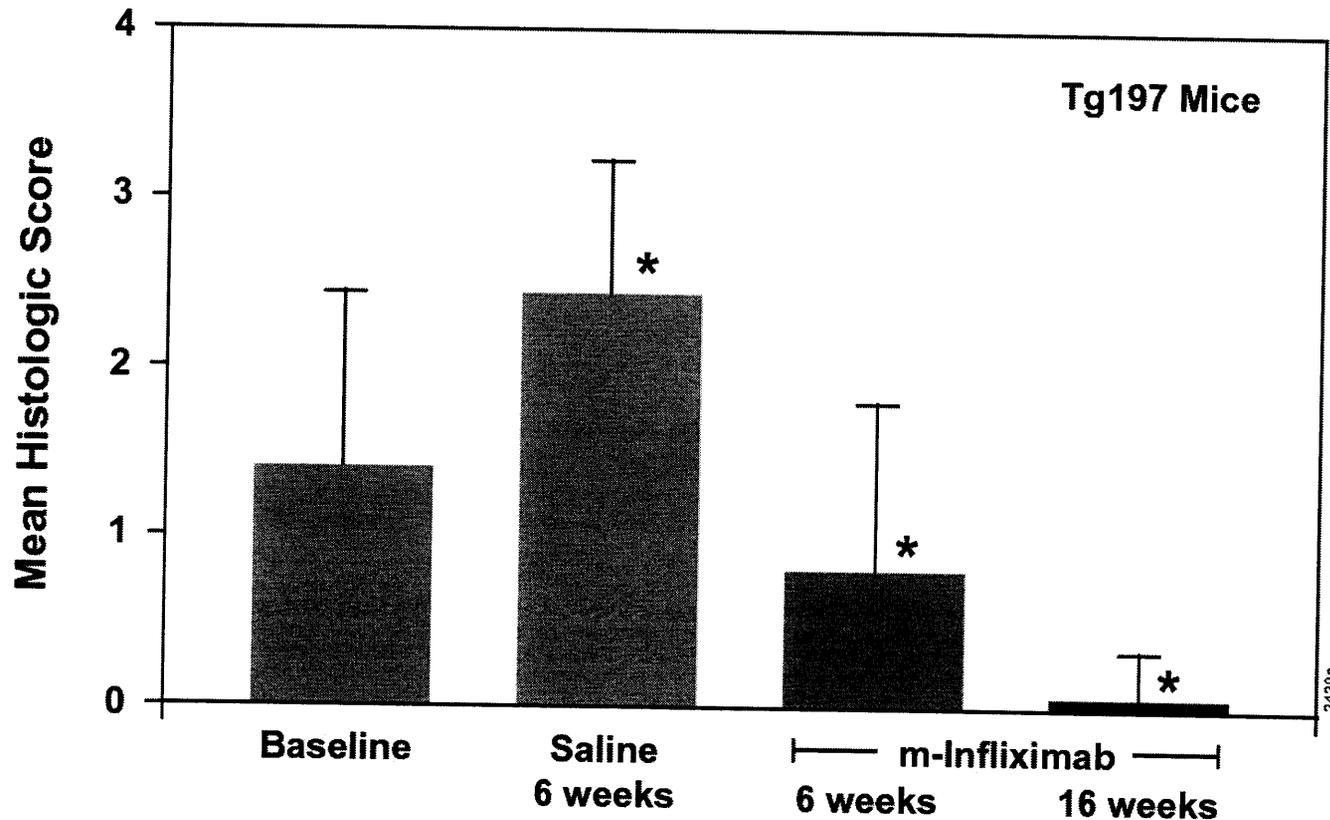


\*p-value vs. baseline < 0.001

*Scientific Rationale*

# m-Infliximab Reverses Structural Damage

## Bone Erosions

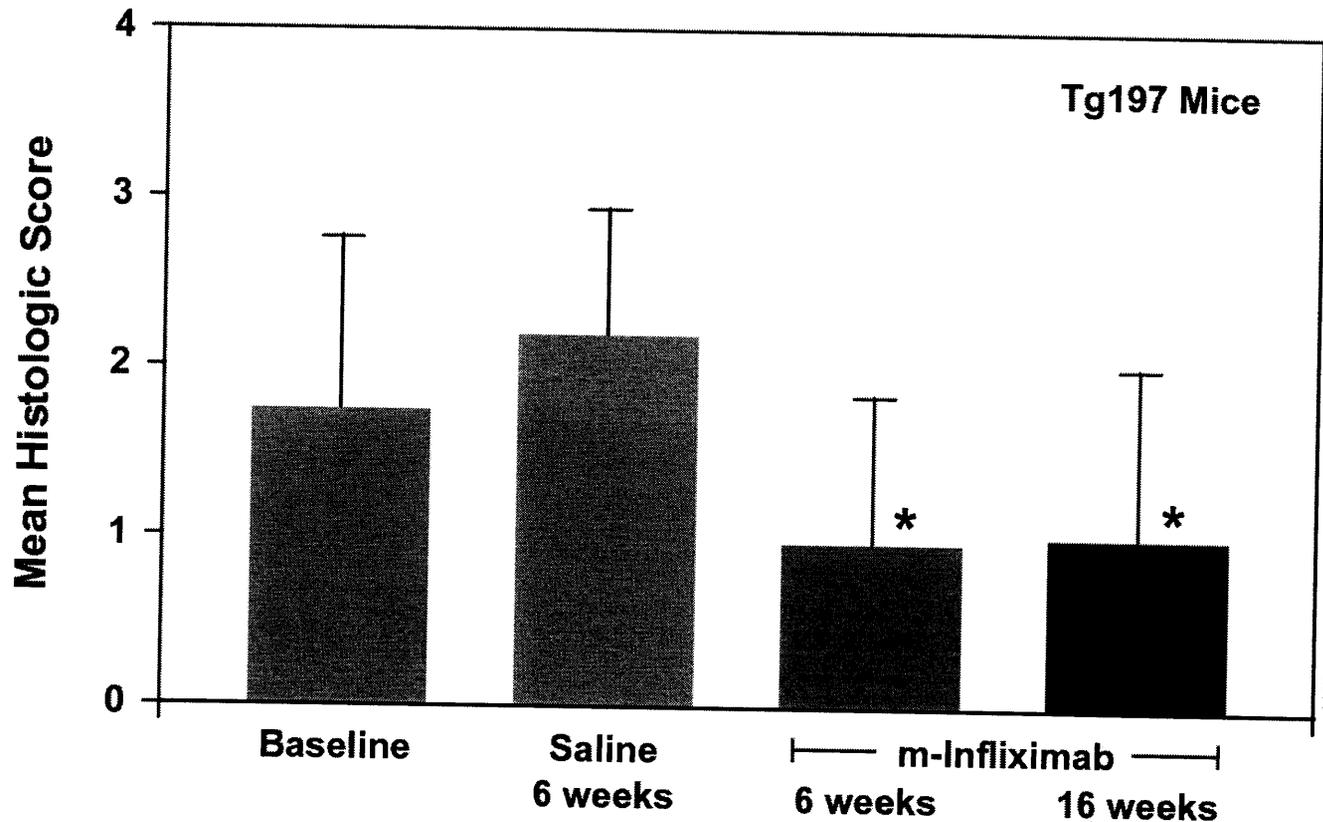


\*p-value vs. baseline < 0.01

*Scientific Rationale*

# m-Infliximab Reverses Structural Damage

## Cartilage Degradation



\*p-value vs. baseline < 0.01

*Scientific Rationale*

# **m-Infliximab Reverses Structural Damage**

## Synovitis, Erosions and Cartilage Degradation



**Baseline**



**6 wk Saline**



**6 wk m-Infliximab**

*Scientific Rationale*

# m-Infliximab Reverses Structural Damage

## Cartilage Degradation



**Baseline**



**6 wk Saline**



**6 wk m-Infliximab**

# **REMICADE<sup>®</sup> (infliximab)**

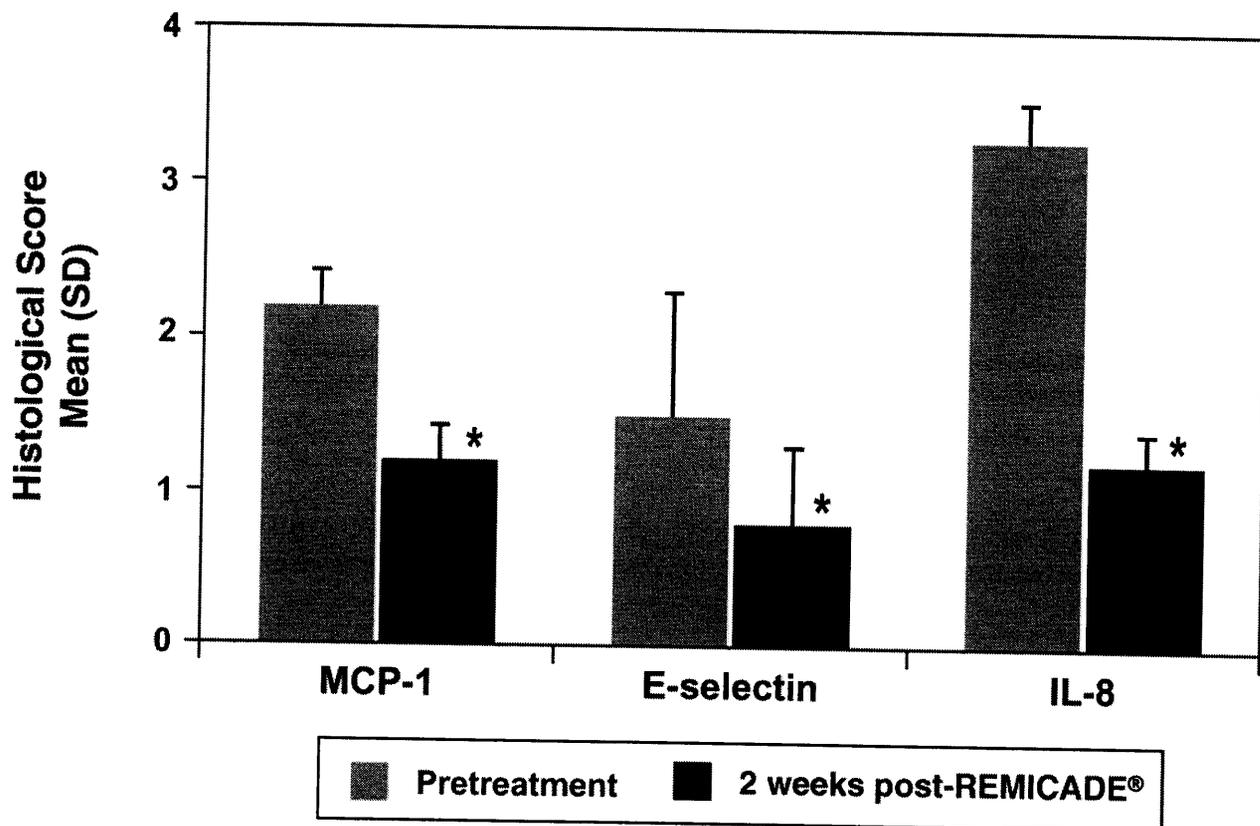
---

## **Clinical Pharmacodynamics in RA Patients**

Clinical Pharmacology

# REMICADE<sup>®</sup> Reduces Mediators of Inflammation

## RA Patient Synovial Biopsies

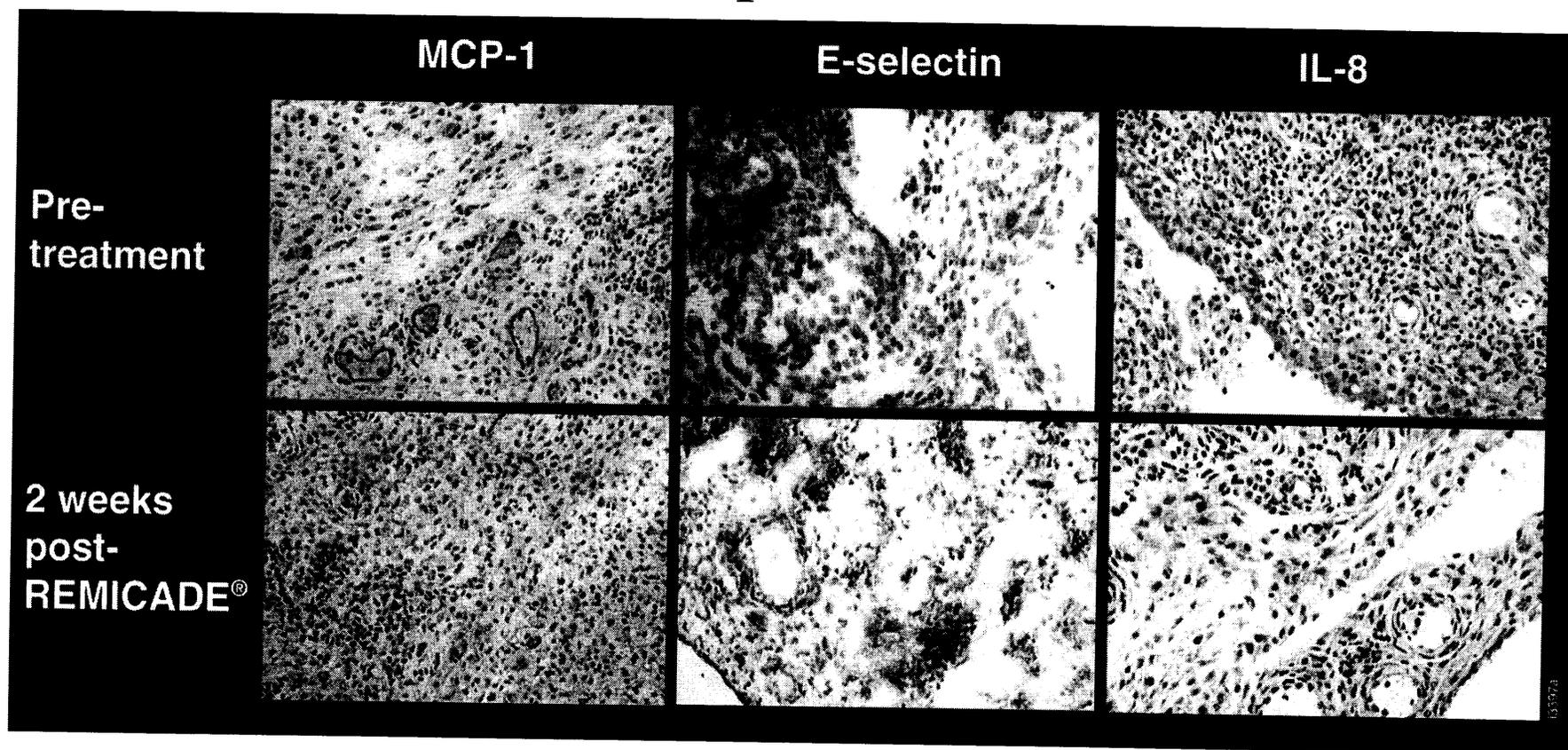


\*p-value vs. pretreatment < 0.05

*Clinical Pharmacology*

# REMICADE® Reduces Mediators of Inflammation in Synovial Tissue

## RA Patient Synovial Biopsies

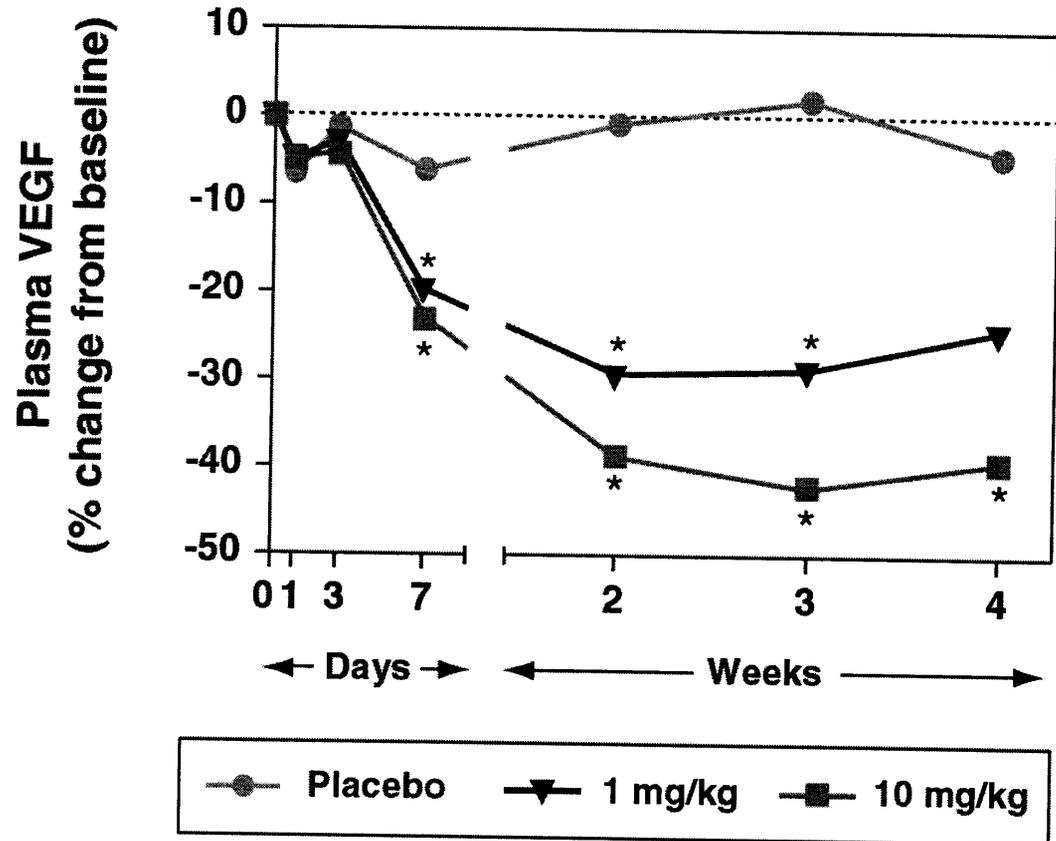


C0168T18

Clinical Pharmacology

# REMICADE<sup>®</sup> Reduces Mediators of Pannus Formation in RA Patients

## Angiogenic Factor – VEGF



\*p-value vs. placebo < 0.05

RA3071m

C0168T09

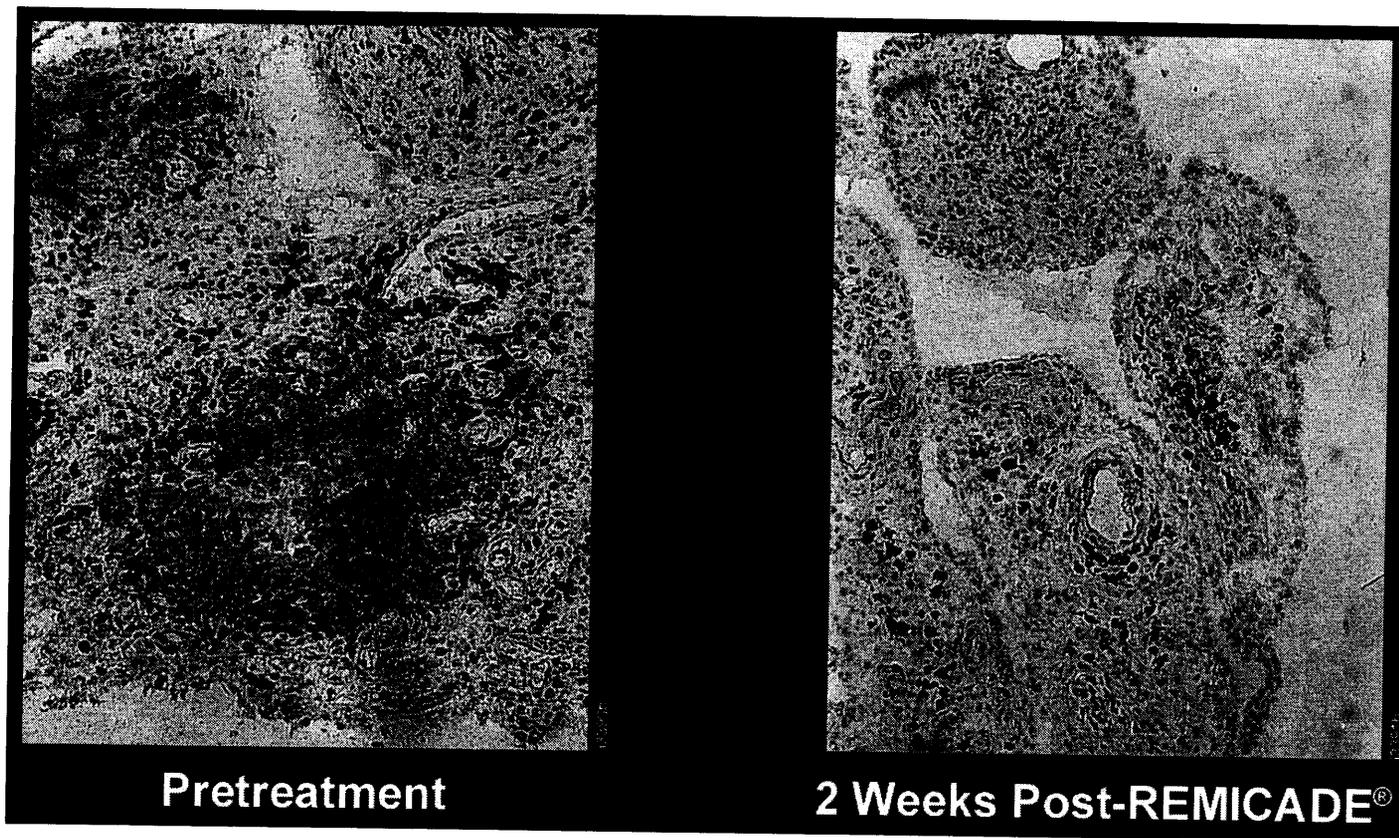
07/12/00 FINAL MAIN C 28

*Clinical Pharmacology*

# REMICADE<sup>®</sup> Reduces Mediators of Pannus Formation in RA Patients

---

## CD3<sup>+</sup> T-cell Infiltration



Tak P. *Arthritis Rheum.* 1996; 39(7):1077-1081.

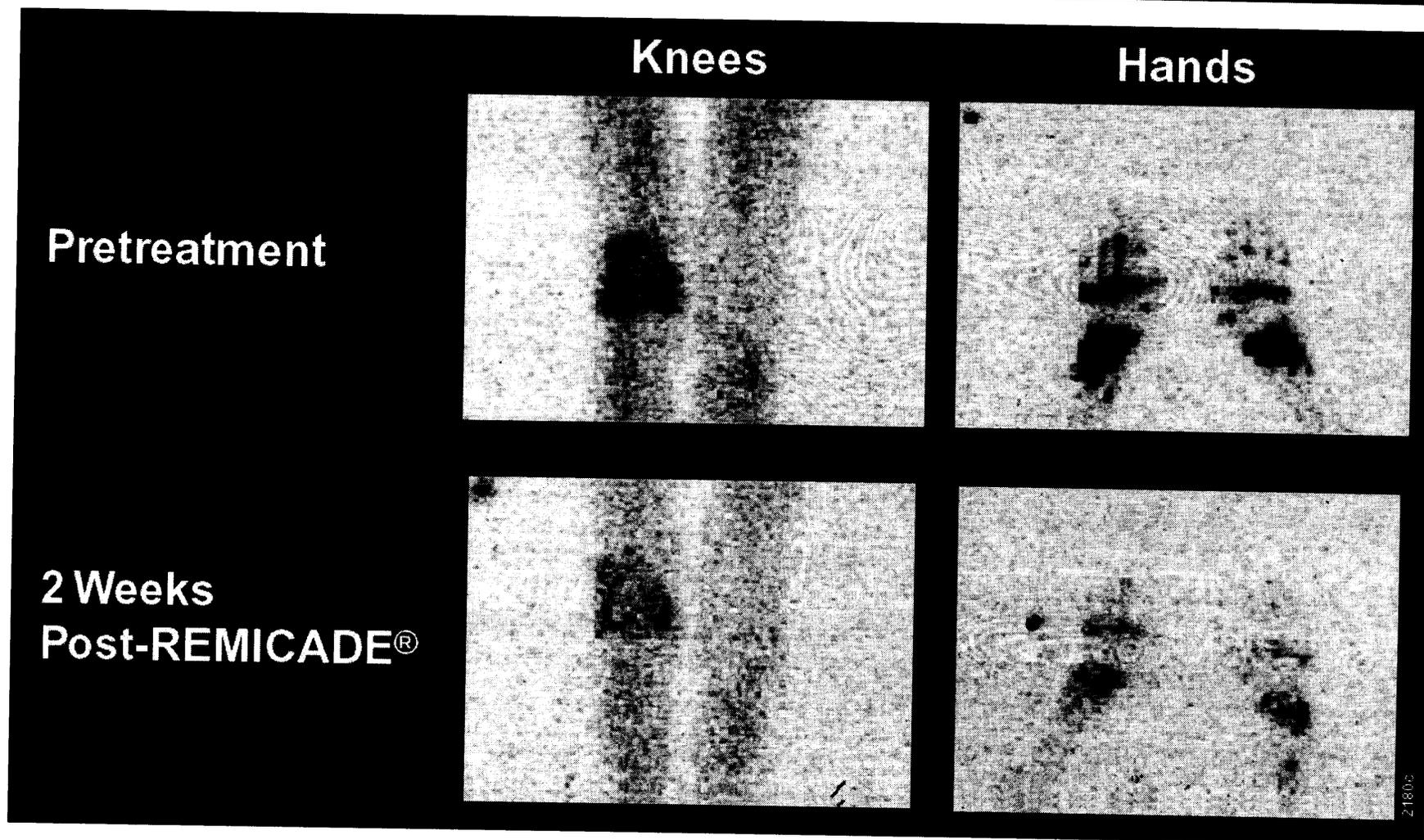
RA3083g

C0168T18

07/12/00 FINAL MAIN C 29

*Clinical Pharmacology*

# REMICADE® Reduces Cell Infiltration



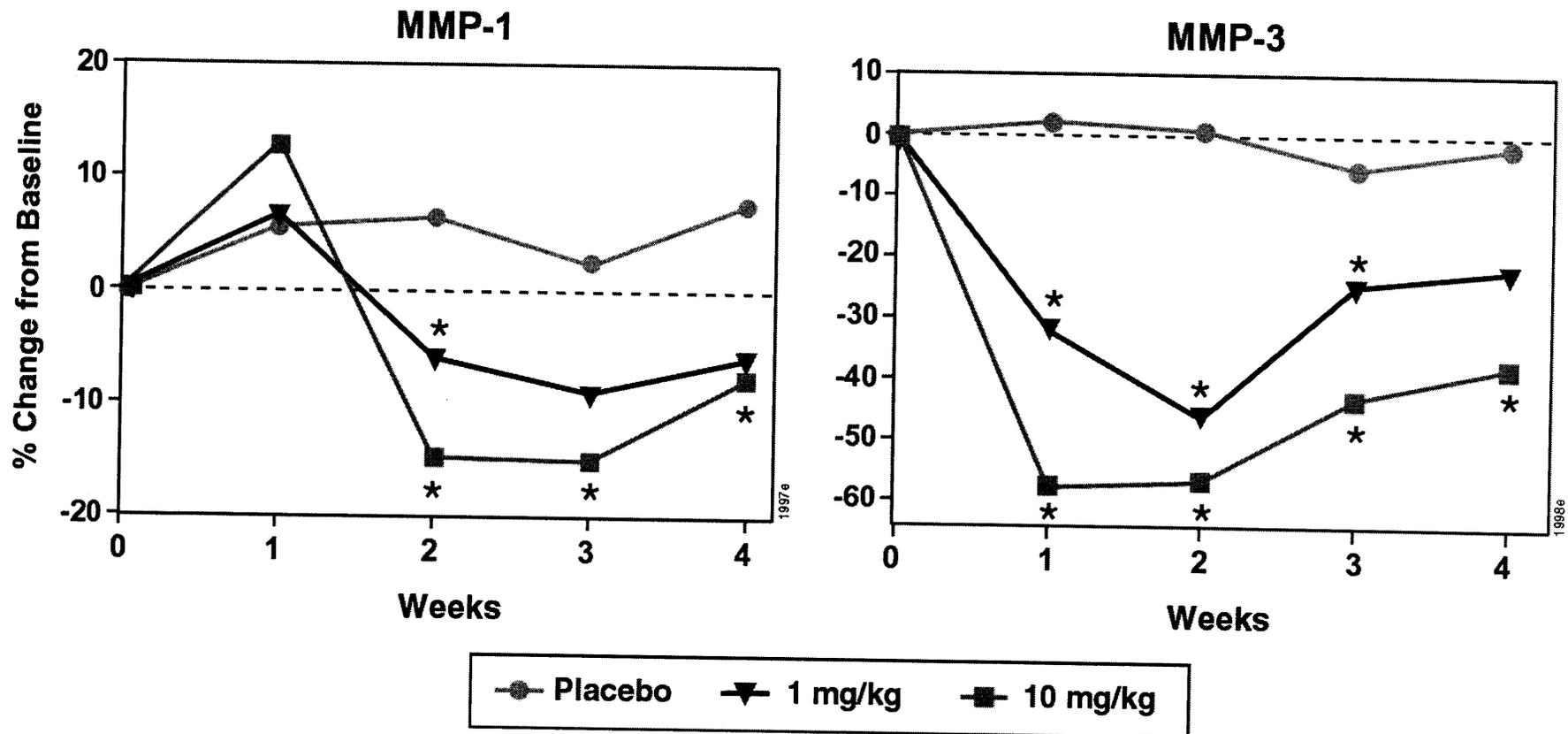
C0168T18

Taylor P, et al. *Arthritis Rheum*, 2000; 43(1):38-47.

Clinical Pharmacology

# REMICADE<sup>®</sup> Reduces Mediators of Cartilage Degradation

## Serum Metalloproteinases (Pro-MMP-1, Pro-MMP-3)

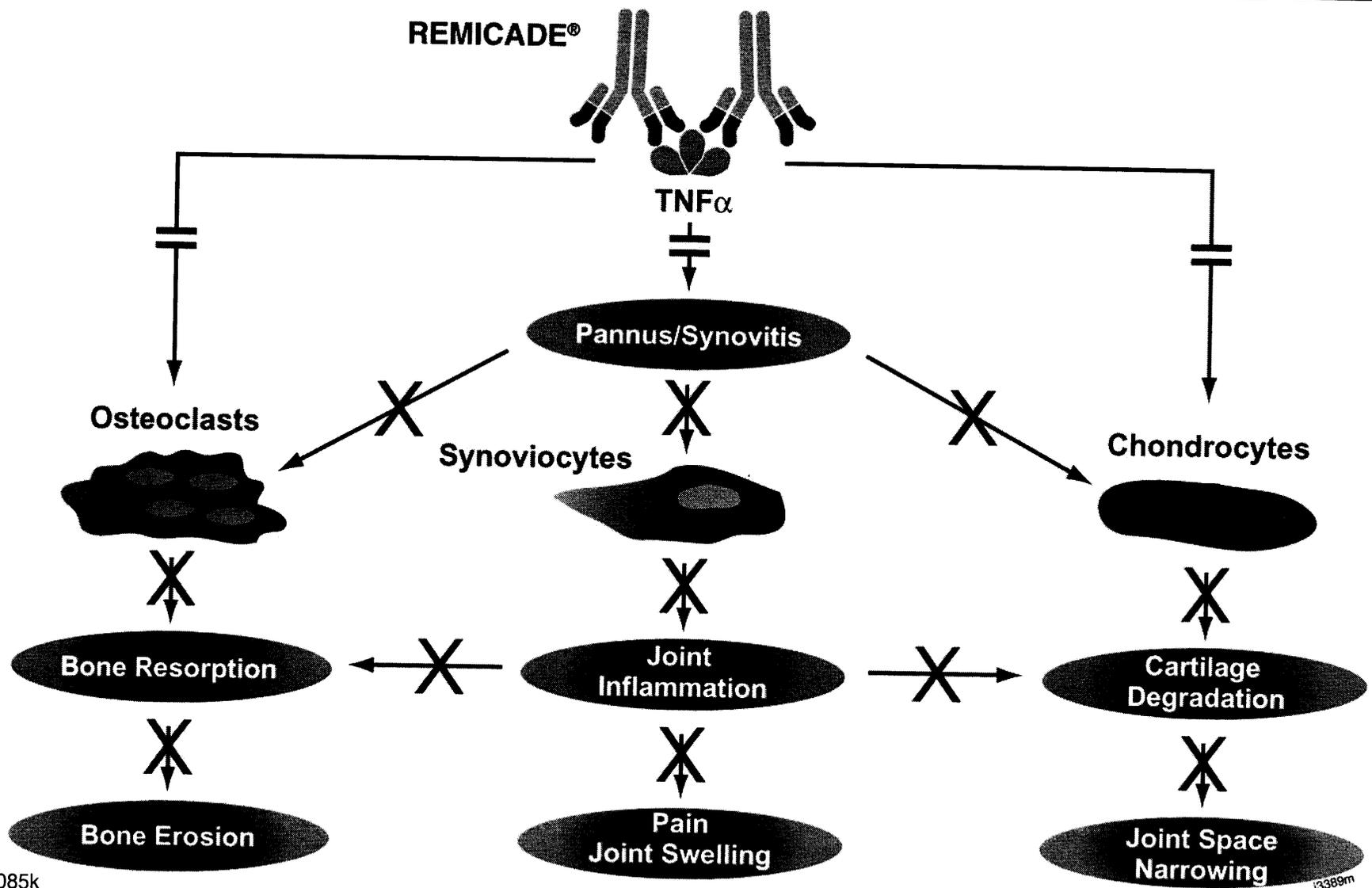


\*p-value vs. placebo < 0.05

RA3200g

C0168T09

# REMICADE® Prevents Joint Destruction



**REMICADE® (infliximab)**

# Summary

---

## Scientific Rationale and Clinical Pharmacology

- **TNF $\alpha$  mediates joint destruction in RA**
- **m-Infliximab prevented and reversed structural damage to bone and cartilage in a mouse model of arthritis**
- **REMICADE® reduced mediators of joint destruction in RA patients**
  - **Synovitis/pannus formation**
  - **Bone erosion**
  - **Cartilage degradation**

**REMICADE® (infliximab)**

# **Agenda of Speakers**

---

**Introduction**

**Martin Page**  
**Vice President, Worldwide Regulatory Affairs**  
**Centocor**

**Scientific Rationale and  
Clinical Pharmacology**

**Professor Ravinder Maini, M.D., FRCP**  
**Kennedy Institute of Rheumatology**  
**London, UK**

**Efficacy and Safety**

**Gregory Harriman, M.D.**  
**Senior Director, Immunology Clinical Research**  
**Centocor**

**Significance of  
Radiographic Results**

**Désirée M.F.M. van der Heijde, M.D., Ph.D.**  
**Professor of Rheumatology**  
**University Hospital Maastricht, The Netherlands**

**Clinical Perspective**

**E. William St. Clair, M.D.**  
**Associate Professor of Medicine**  
**Duke University School of Medicine, Durham, NC**

**Concluding Remarks**

**Martin Page**

**REMICADE®**

# Clinical Experience

---

## Efficacy and Safety

- **Prevention of structural damage**
- **Sustained reduction in signs and symptoms**
- **Improvement in physical function**
- **Safe and well-tolerated**

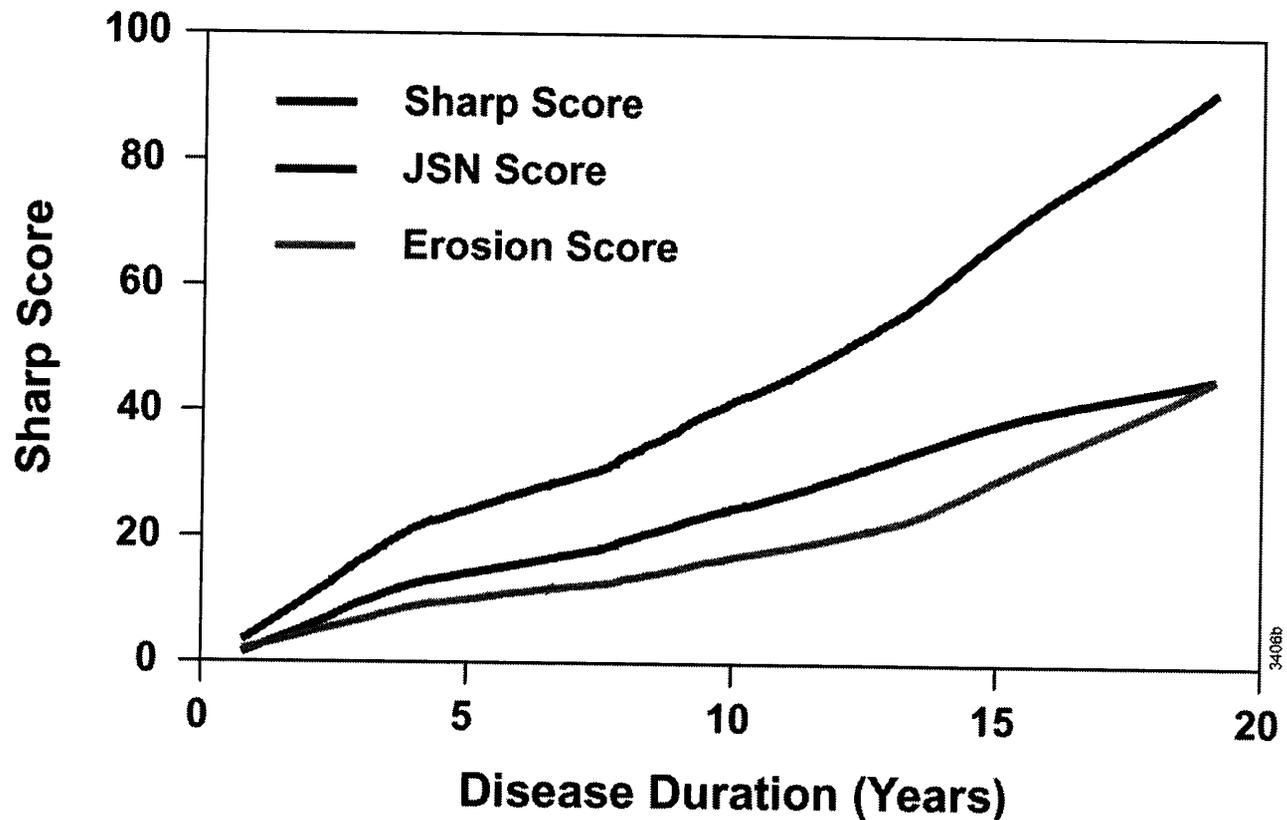
# **FDA Guidance for Industry**

---

- **Outcome measures to support prevention of structural damage claim**
  - **slowing x-ray progression using either Larsen, the modified Sharp or another validated radiographic index**
  - **prevention of new x-ray erosions – maintaining an erosion-free state or preventing new erosions**
  - **other measurement tools (e.g. MRI)**
- **Primary endpoint in ATTRACT for prevention of structural damage claim**
  - **change from baseline to 54 weeks in the modified Sharp score (van der Heijde)**

# Structural Damage = Erosions + Joint Space Narrowing (JSN)

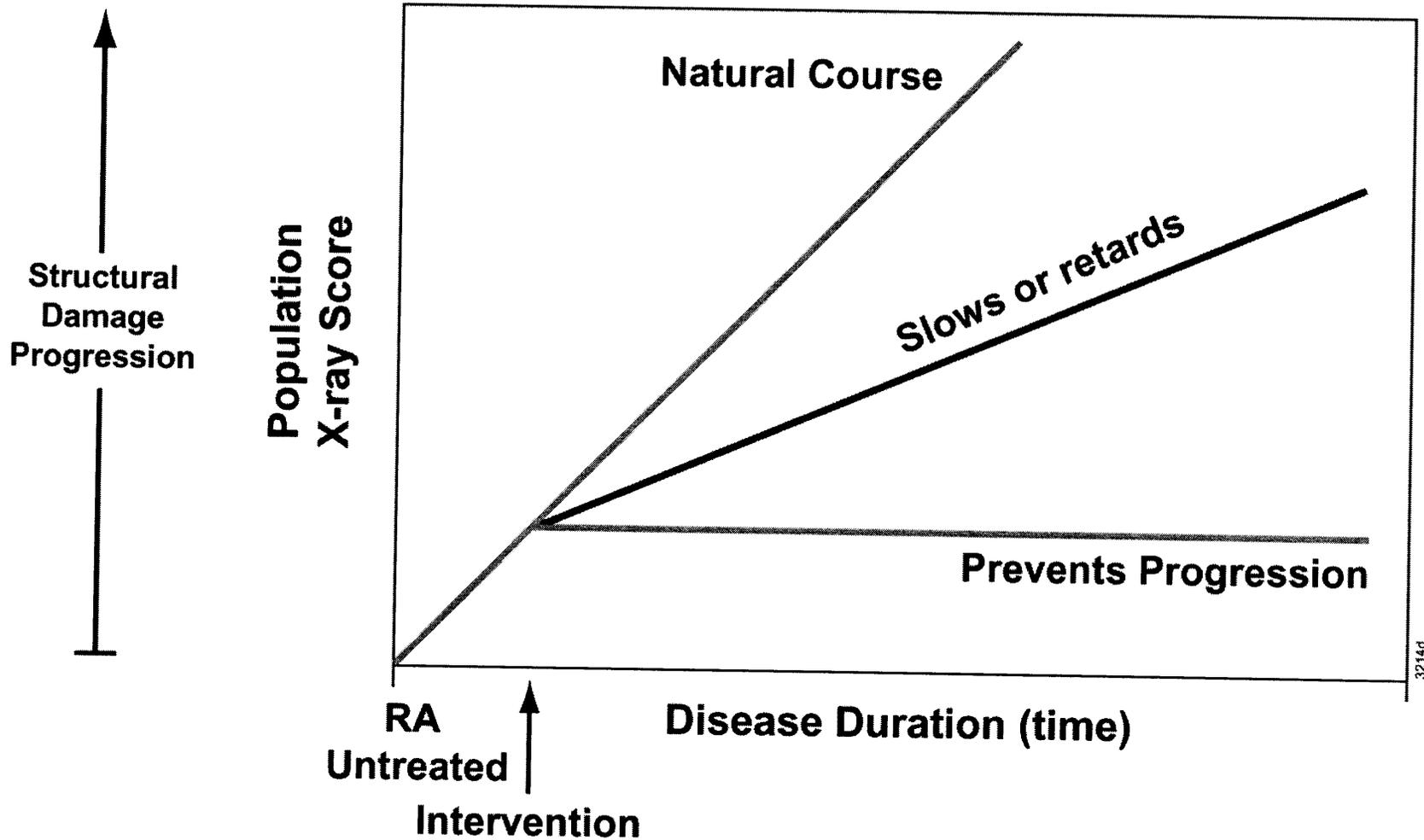
Natural Course in Patients Receiving Therapy



Wolfe F and Sharp J, *Arthritis Rheum.* 1998; 41(9):1571-82.

*Structural Damage*

# Rheumatoid Arthritis Disease Progression



**REMICADE®**

---

# **ATTRACT**

**Anti-TNF $\alpha$  Trial in Rheumatoid Arthritis  
with Concomitant Therapy**

# Study Overview

---

- **International, multicenter study**
- **Randomized, double-blind, placebo-controlled study**
- **Four REMICADE® dose regimens**
- **All patients continued on stable doses of concomitant MTX**
- **Three co-primary endpoints to assess**
  - **Improvement of signs and symptoms**
  - **Prevention of structural damage**
  - **Improvement in physical function/disability**

**ATTRACT**

# **Study Organization**

---

**Study Chairmen:**

**Ravinder Maini, M.D.  
Peter Lipsky, M.D.**

**Steering Committee:**

**Ferdinand Breedveld, M.D.  
Daniel Furst, M.D.  
Joachim Kalden, M.D.  
Josef Smolen, M.D.  
E. William St. Clair, M.D.  
Michael Weisman, M.D.**

**Safety Monitoring Committee:**

**David Felson, M.D. (chair)  
Frank Wolheim, M.D.  
Charles Goldsmith, Ph.D.**

**Radiographic Scoring:**

**Désirée van der Heijde, M.D., Ph.D.**

**Central Laboratories:**

**BARC and Mayo - Routine Labs  
Bioluminescence Imaging Technologies Inc. (BITI) -  
Radiographs**

# Target Study Population

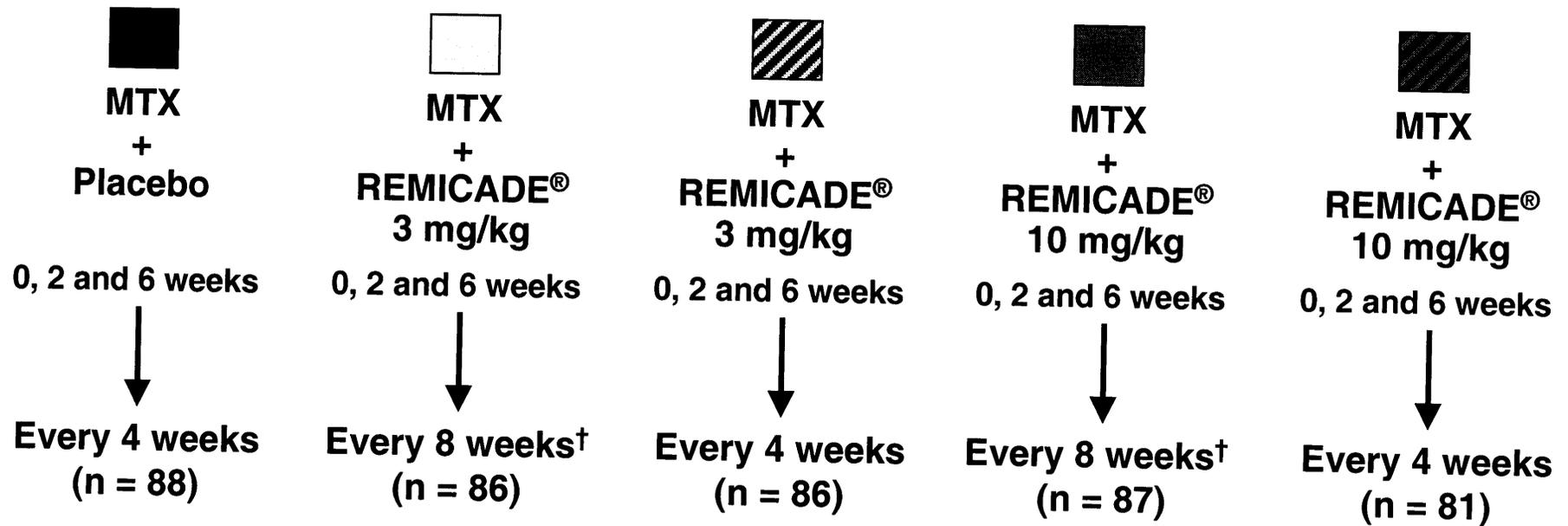
---

- **Active RA despite MTX**
  - **$\geq 6$  swollen and tender joints**
  - **At least two of the following: morning stiffness  $\geq 45$  minutes, ESR  $\geq 28$  mm/hr, CRP  $\geq 2.0$  mg/dL**
- **MTX for  $\geq 3$  months and  $\geq 12.5$  mg/week stable dose for at least four weeks**
- **No other concomitant DMARDs**
- **Stable corticosteroids ( $\leq 10$  mg/day) and NSAIDs**

# Study Design

---

## Randomized Treatment Groups (n = 428)

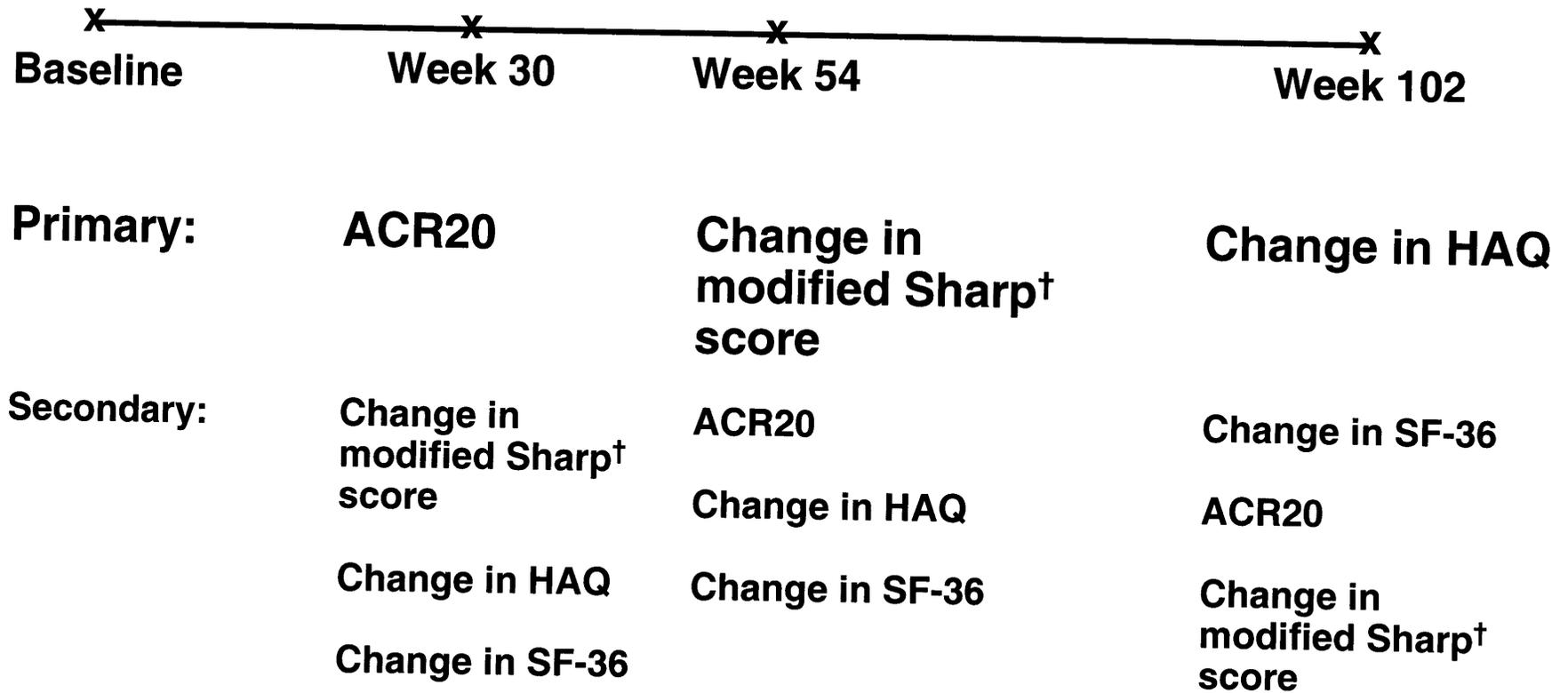


**Efficacy and Safety Assessments through 102 weeks**

† With placebo infusions at 4-week interim visits

# Study Endpoints

---



<sup>†</sup>van der Heijde modification of Sharp score

# **Methods for Radiographic Analysis**

---

- **van der Heijde-modified Sharp score**
- **Two experienced readers evaluated all patients' films**
- **Readers were blinded as to patient's treatment assignment and film sequence**
- **Each patient's films (baseline, 30 weeks and 54 weeks) were read independently by each reader as a set**

# **Methods for Radiographic Analysis**

---

- **44 joints scored for erosions**
- **40 joints scored for joint space narrowing (JSN)**
- **Erosion and JSN summary scores are sums of individual joint scores**
- **Total score is sum of the erosion and JSN summary scores**
- **Final patient score is the average of the two readers' scores**

# Methods for Radiographic Analysis

---

- **88% of patients had radiographs at baseline and week 54**
- **82% of patients included in primary endpoint analysis**
- **Reasons for exclusion**
  - **Incomplete set of x-rays or views (15%)**
  - **Insufficient number of evaluable joints due to prior surgery or image quality (3%)**

# Statistical Methods

---

- **Hypothesis testing**
  - **Overall test comparing five treatment groups**
  - **If significant, pairwise comparisons between Placebo + MTX versus REMICADE<sup>®</sup> + MTX groups were made**
  - **Two-sided testing using intention to treat principle**
- **The overall Type 1 error rate for the three co-primary endpoints was controlled at the 0.05 level**

# Primary Week 54 Analysis

---

- **Primary endpoint for prevention of structural damage was the change from baseline to week 54 in van der Heijde modified Sharp score**
- **Primary analysis compared treatment groups using nonparametric analysis of variance at alpha level 0.025**
- **All patients with evaluable sets of x-rays at weeks 0 and 54 included according to randomized treatment group**

***ATTRACT***

---

# **Study Population**

*ATTRACT Study Population*

# Baseline Patient Characteristics

---

<b>Age (yrs)</b>	<b>54 (19 - 80)</b>
<b>Gender (female)</b>	<b>78%</b>
<b>RF positivity</b>	<b>81%</b>
<b>No. of prior DMARDs (including MTX)</b>	<b>3 (2 - 8)</b>
<b>MTX (mg/week)</b>	<b>15 (10 - 35)</b>
<b>Swollen joints</b>	<b>20 (2 - 64)</b>
<b>Tender joints</b>	<b>31 (1 - 68)</b>
<b>CRP (mg/dL)</b>	<b>2.6 (0.1 - 25.9)</b>
<b>HAQ</b>	<b>1.8 (0.0 - 3.0)</b>

Unless otherwise indicated, values are medians (ranges).

***ATTRACT Study Population***

# **Baseline Patient Characteristics**

---

<b>Disease duration (yrs)</b>	<b>8.4 (0.5 - 49.9)</b>
<b>Disease duration <math>\leq</math> 3 yrs</b>	<b>19%</b>
<b>Functional class</b>	
<b>I</b>	<b>4.7%</b>
<b>II</b>	<b>46.0%</b>
<b>III</b>	<b>48.6%</b>
<b>IV</b>	<b>0.7%</b>
<b>Baseline radiographic score</b>	<b>51 (0 - 382)</b>
<b>Annual radiographic progression</b>	<b>7.2 (0 - 77)</b>

**Unless otherwise indicated, values are medians (ranges).**

## ATTRACT Study Population

# Treatment Discontinuation

## Discontinuation of Study Treatment through 54 Weeks

	REMICADE®					
	Placebo (n = 88)	3 mg/kg q 8 wks (n = 86)	3 mg/kg q 4 wks (n = 86)	10 mg/kg q 8 wks (n = 87)	10 mg/kg q 4 wks (n = 81)	All REMICADE® (n = 340)
<b>Patients d/c treatment</b>	<b>44 (50%)</b>	<b>23 (27%)</b>	<b>20 (23%)</b>	<b>12 (14%)</b>	<b>16 (20%)</b>	<b>71 (21%)</b>
<b>Reason:</b>						
<b>Lack of efficacy</b>	<b>36%</b>	<b>20%</b>	<b>12%</b>	<b>7%</b>	<b>9%</b>	<b>12%</b>
<b>Adverse event</b>	<b>8%</b>	<b>6%</b>	<b>10%</b>	<b>5%</b>	<b>10%</b>	<b>8%</b>
<b>Other</b>	<b>6%</b>	<b>1%</b>	<b>1%</b>	<b>2%</b>	<b>1%</b>	<b>1%</b>

All patients received concomitant MTX

## ATTRACT Study Population

# Protocol Compliance

At 54 Weeks

		REMICADE®				
	Placebo (n = 88)	3 mg/kg q 8 wks (n = 86)	3 mg/kg q 4 wks (n = 86)	10 mg/kg q 8 wks (n = 87)	10 mg/kg q 4 wks (n = 81)	All REMICADE® (n = 340)
<b>Pts returning at 54 wks</b>	<b>69 (78%)</b>	<b>77 (90%)</b>	<b>80 (93%)</b>	<b>82 (94%)</b>	<b>74 (91%)</b>	<b>313 (92%)</b>
<b>Pts receiving MTX at last visit</b>	<b>84 (95%)</b>	<b>83 (97%)</b>	<b>81 (94%)</b>	<b>83 (95%)</b>	<b>77 (95%)</b>	<b>324 (95%)</b>
<b>MTX dose at last visit (median)</b>	<b>15.0</b>	<b>15.0</b>	<b>15.0</b>	<b>15.0</b>	<b>15.0</b>	<b>15.0</b>

***ATTRACT***

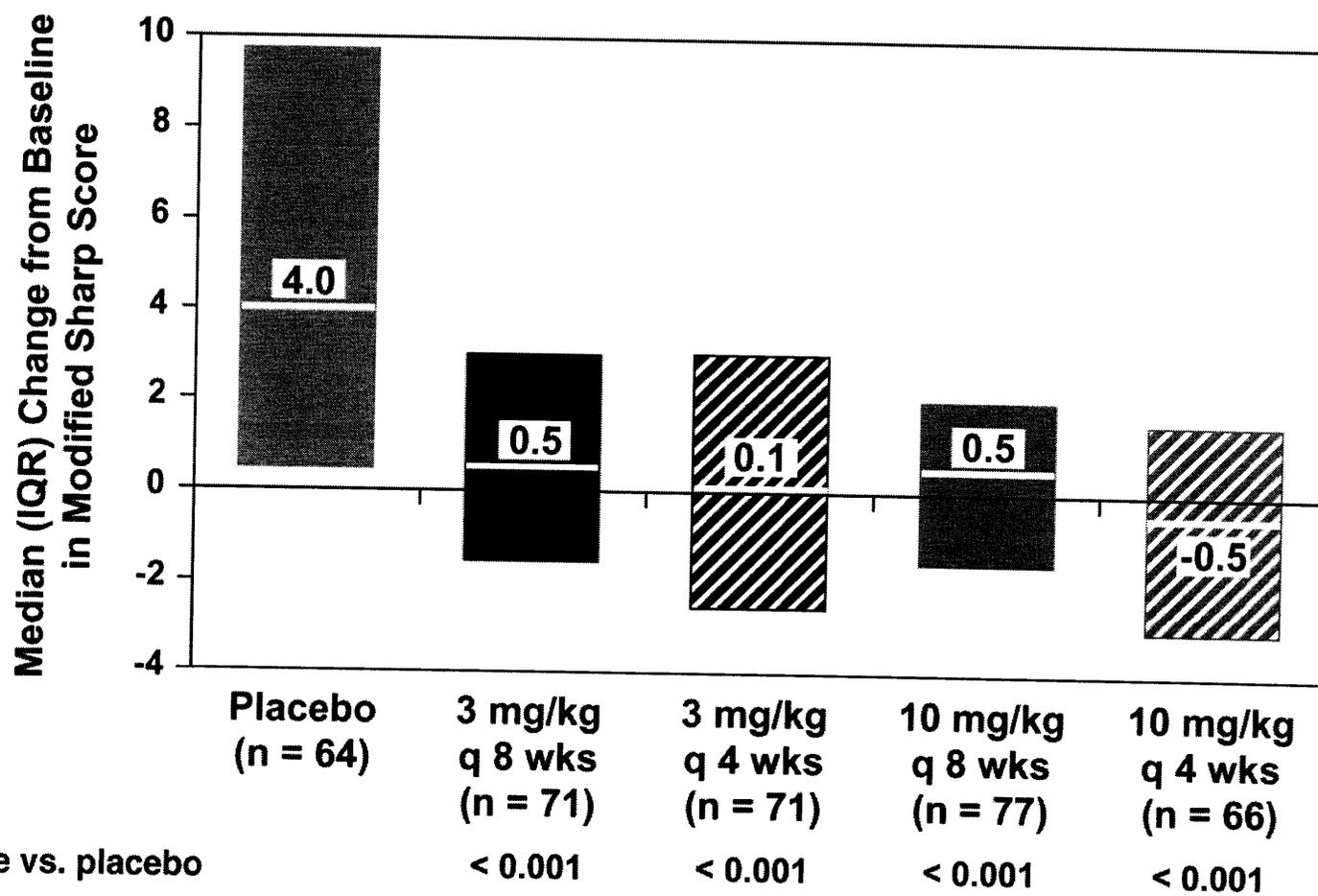
---

# **Efficacy Results**

## **Prevention of Structural Damage**

# Prevention of Structural Damage

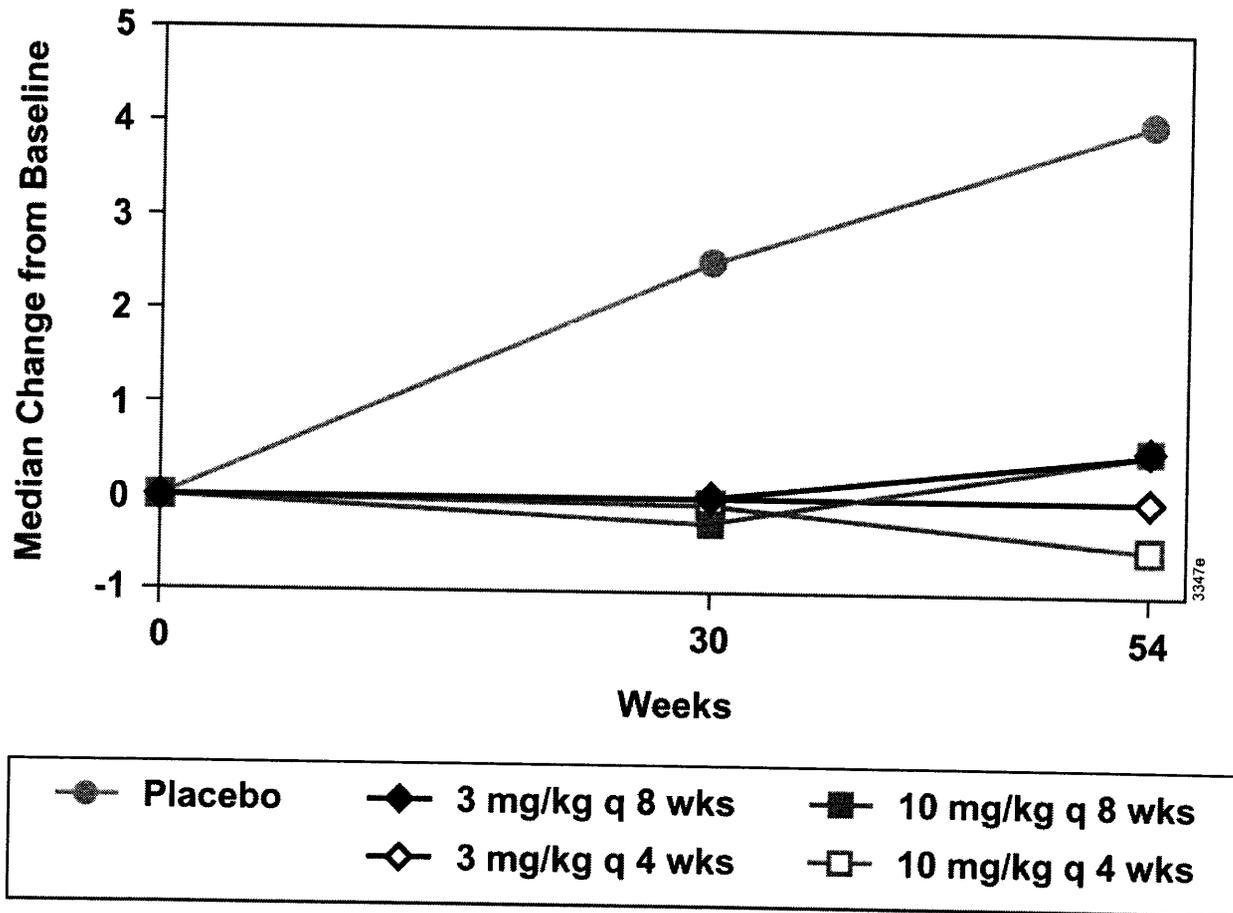
## Primary Radiographic Endpoint at 54 Weeks



All patients received concomitant MTX

# Prevention of Structural Damage

## Change in Modified Sharp Score through 54 Weeks

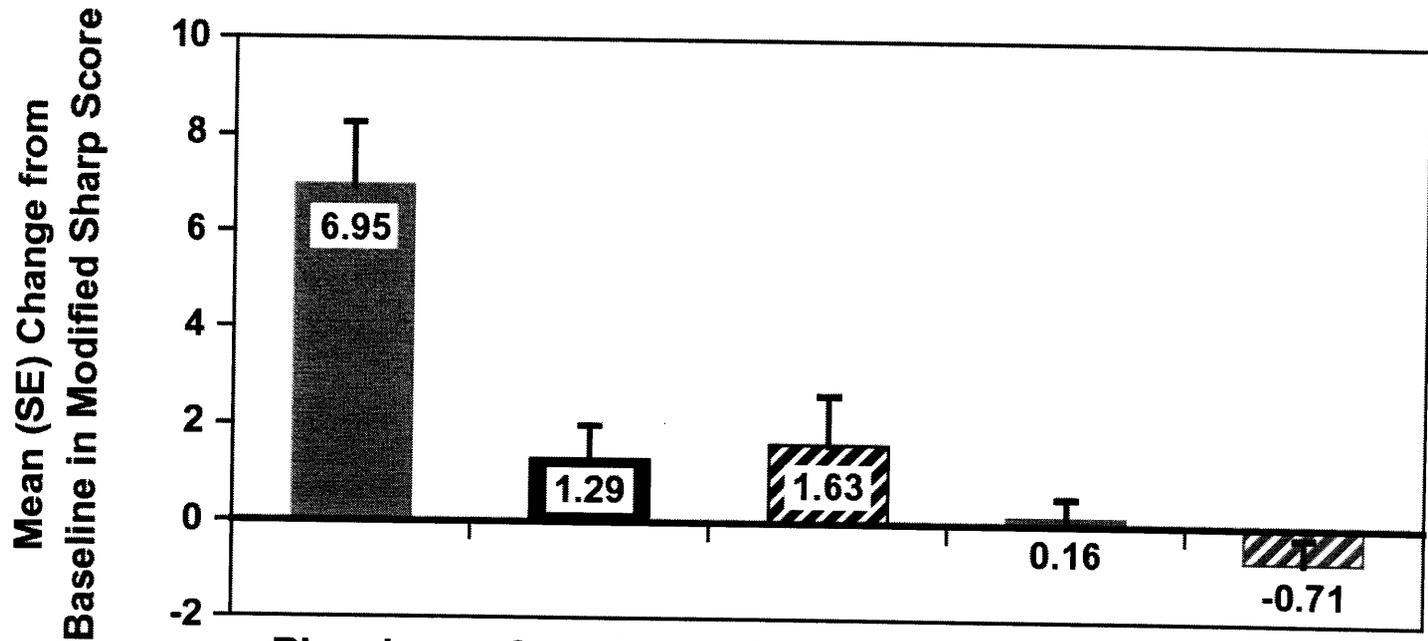


All patients received concomitant MTX

**ATTRACT Efficacy**

# Prevention of Structural Damage

## Primary Radiographic Endpoint at 54 Weeks



3154k

	Placebo (n = 64)	3 mg/kg q 8 wks (n = 71)	3 mg/kg q 4 wks (n = 71)	10 mg/kg q 8 wks (n = 77)	10 mg/kg q 4 wks (n = 66)
p-value vs. placebo		< 0.001	< 0.001	< 0.001	< 0.001

All patients received concomitant MTX

# Effects of Missing Data

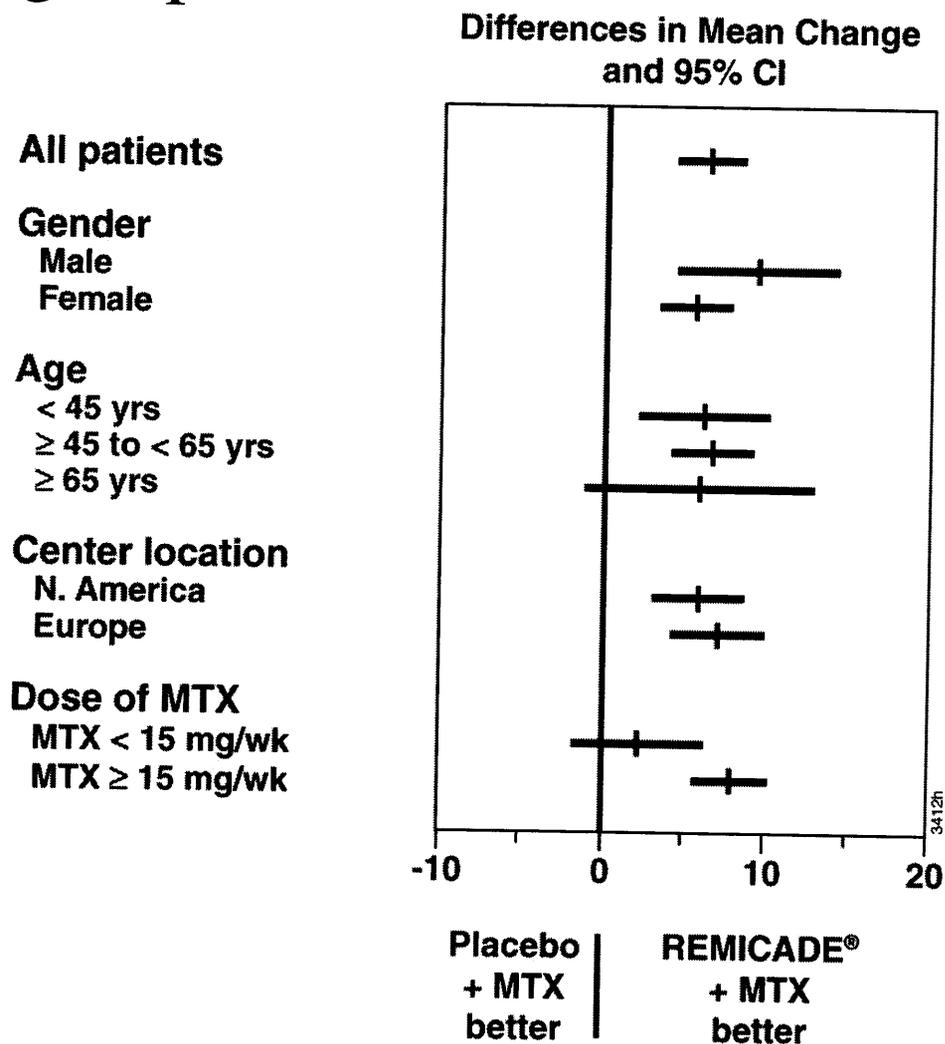
---

- **Given the patient population, availability of radiographic data was good**
- **Additional analyses performed to assess effects of missing data**
  - **Derive results for missing data using extrapolations from available data**
  - **Replace missing values using worst-case assumptions**
- **Results from these analyses are consistent with primary analysis**

# Consistency of Results

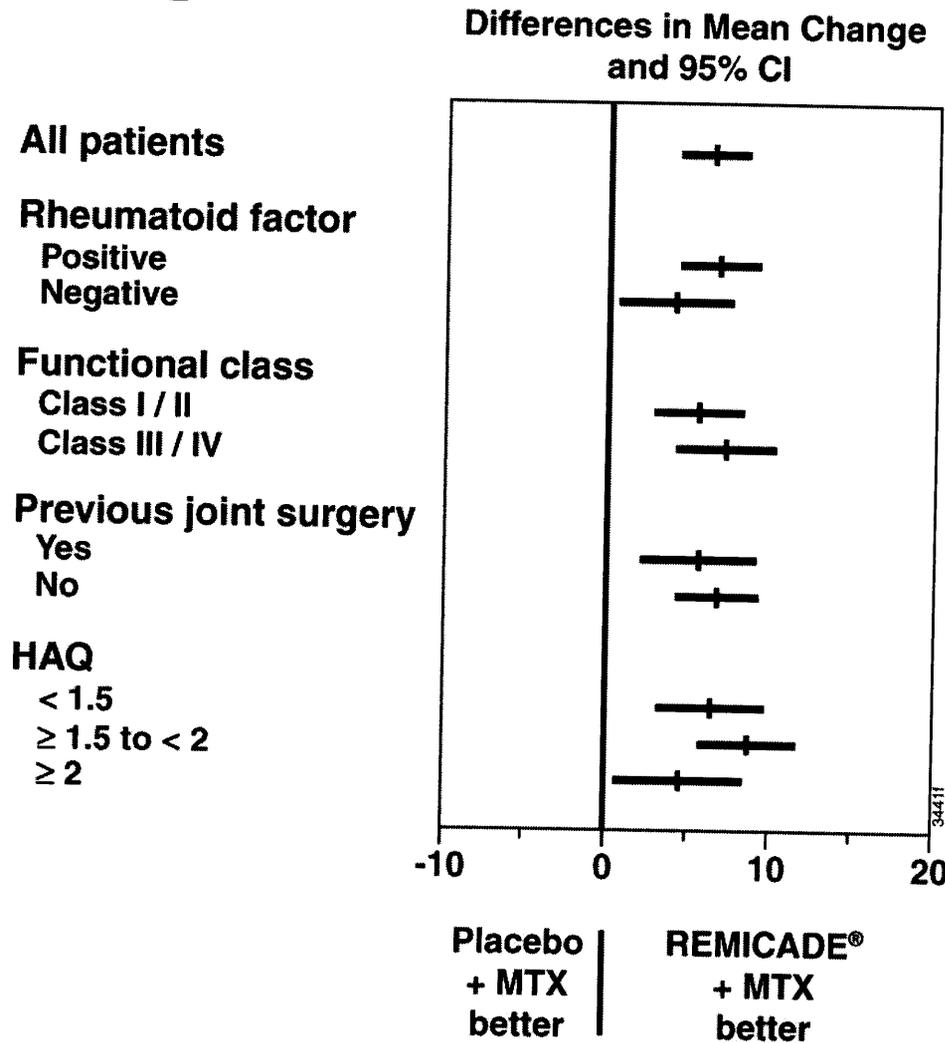
# Consistent Structural Damage Benefit

## Patient Subgroups



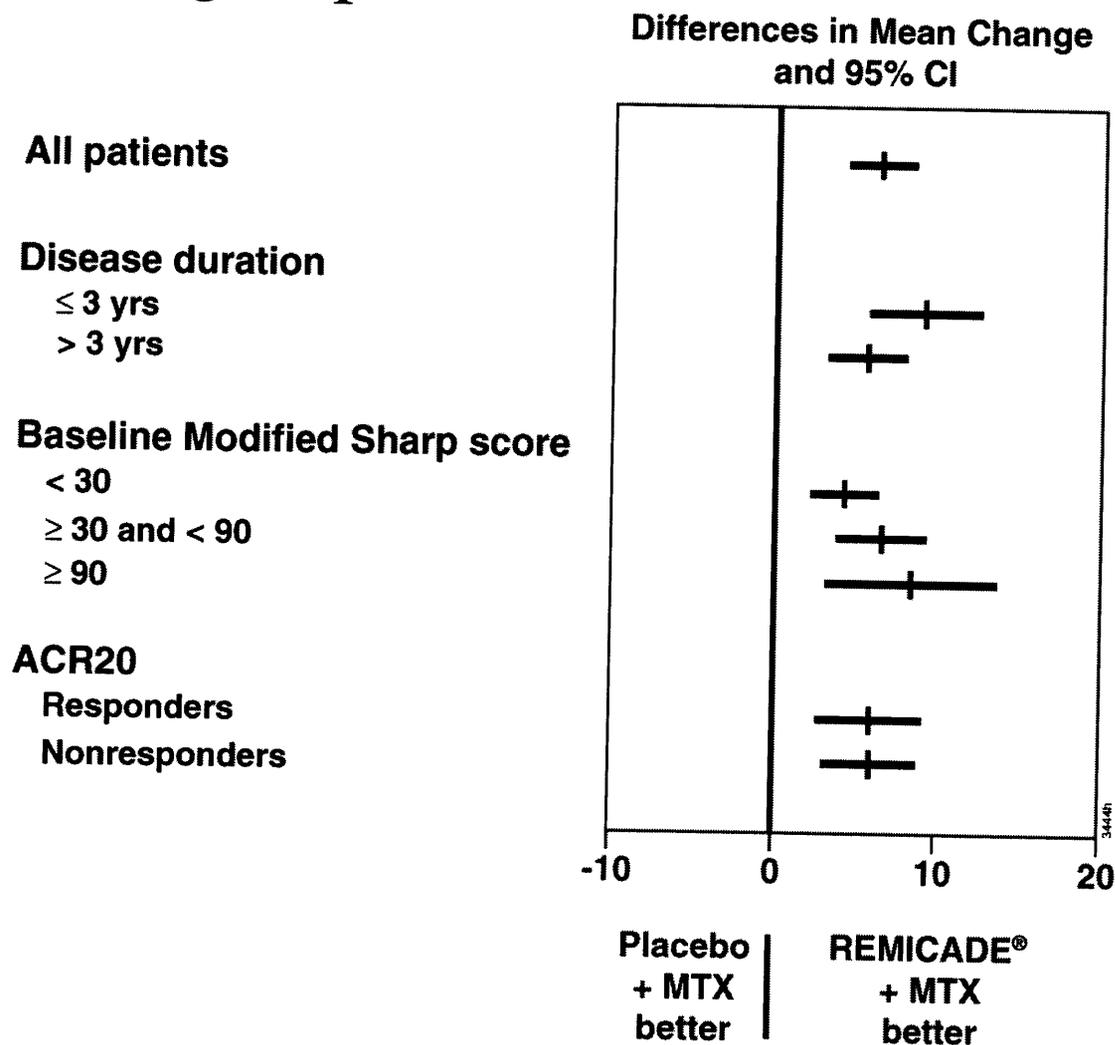
# Consistent Structural Damage Benefit

## Patient Subgroups



# Consistent Structural Damage Benefit

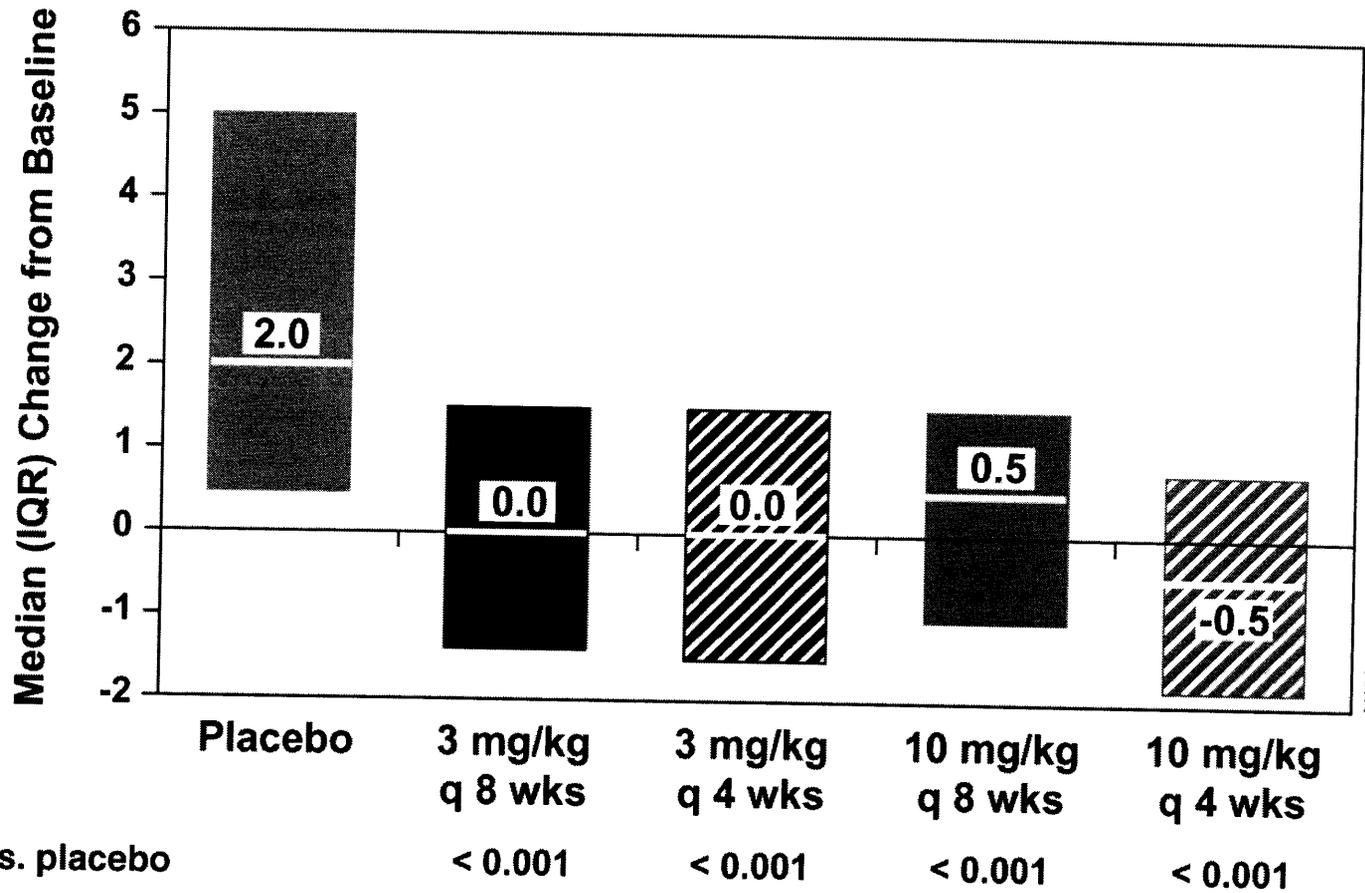
## Patient Subgroups



# **Components of the Primary Endpoint**

# Prevention of Structural Damage

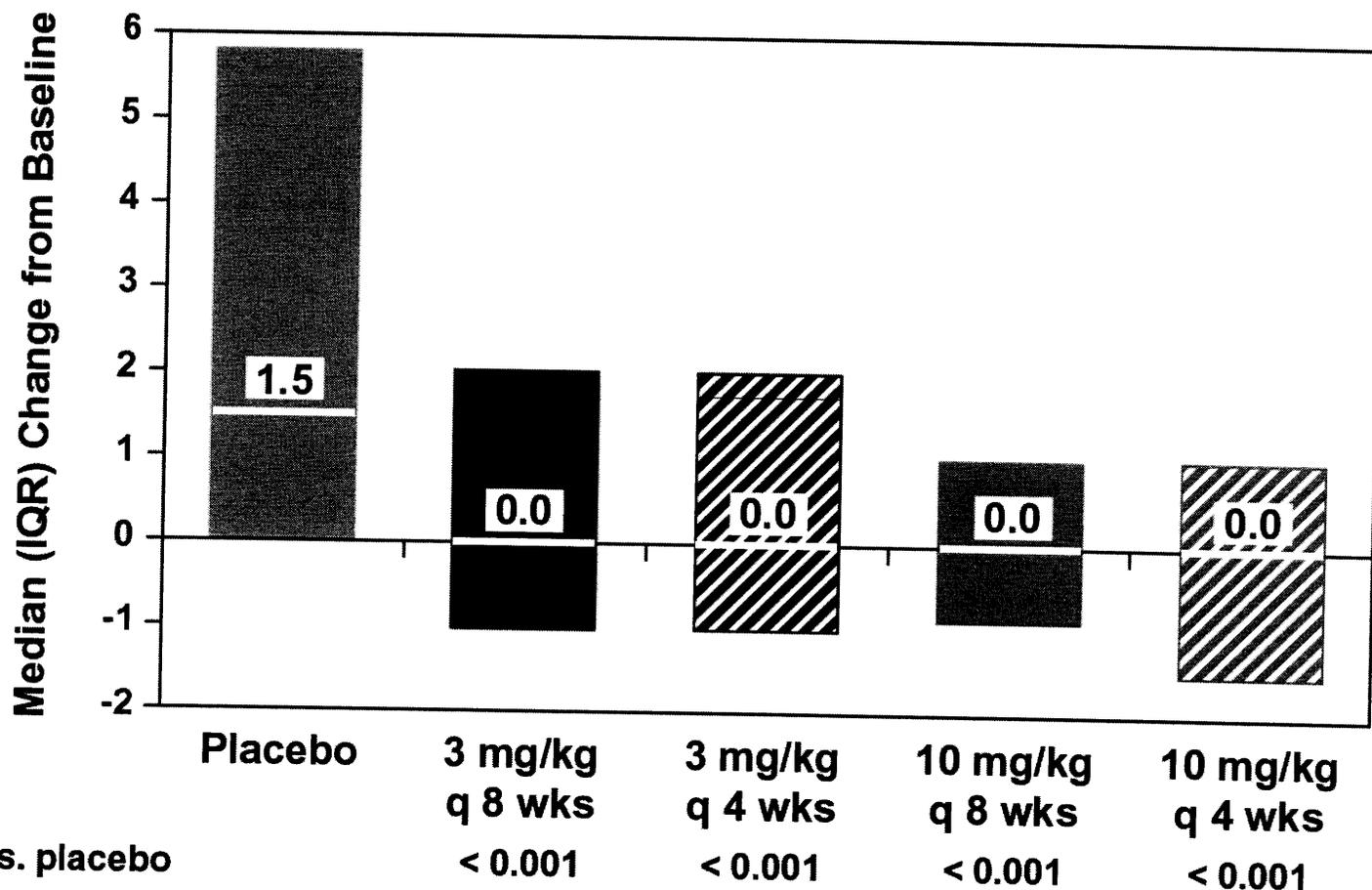
## Change in Erosions at 54 Weeks



All patients received concomitant MTX

# Prevention of Structural Damage

## Change in Joint Space Narrowing at 54 Weeks

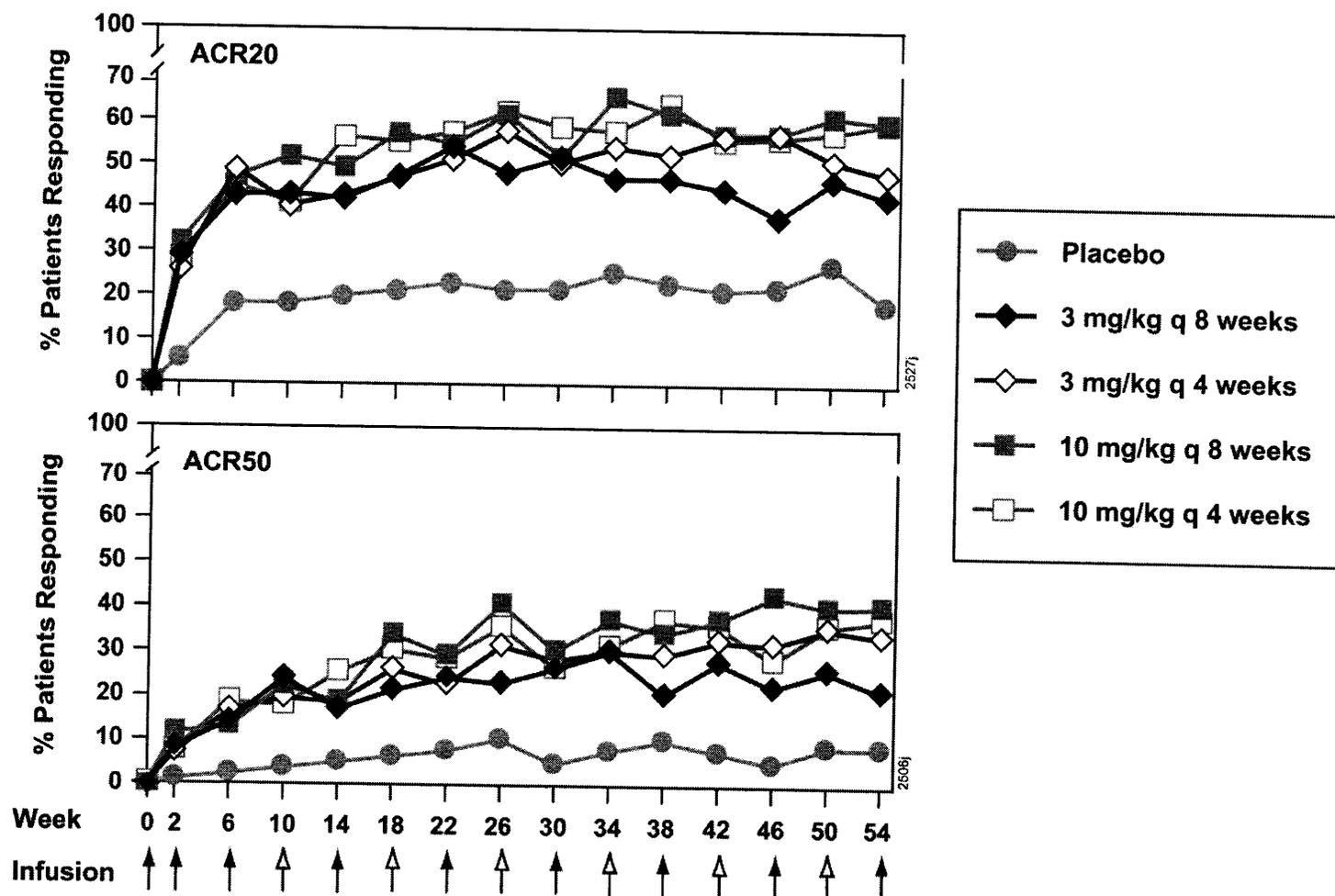


All patients received concomitant MTX.

## ATTRACT Efficacy

# Sustained Reduction in Signs and Symptoms

## Through 54 Weeks



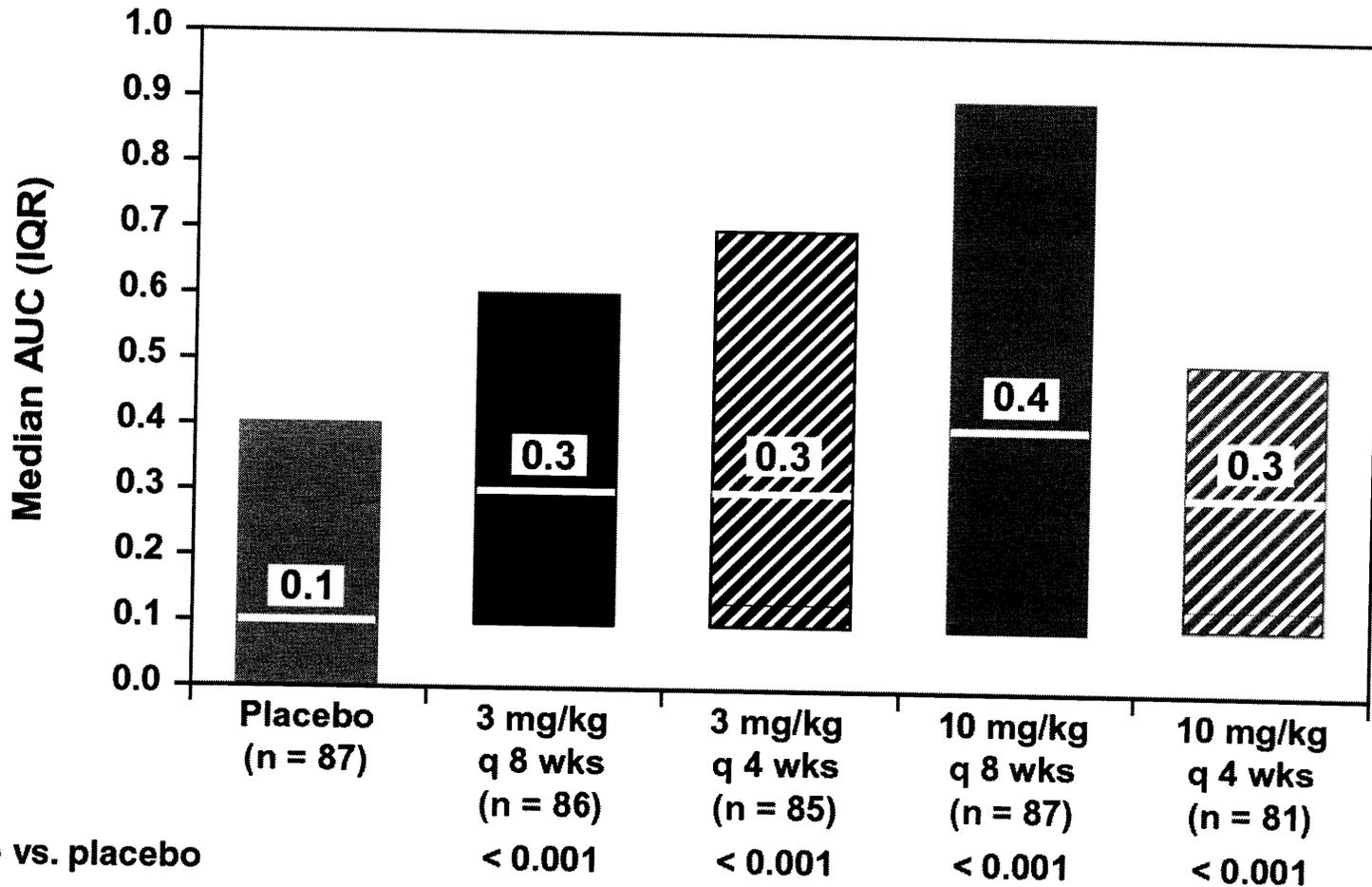
# **Efficacy Results**

## **Improvement in Physical Function**

**ATTRACT Efficacy**

# Improvement in Physical Function

Change in HAQ through 54 Weeks (AUC)



p-value vs. placebo

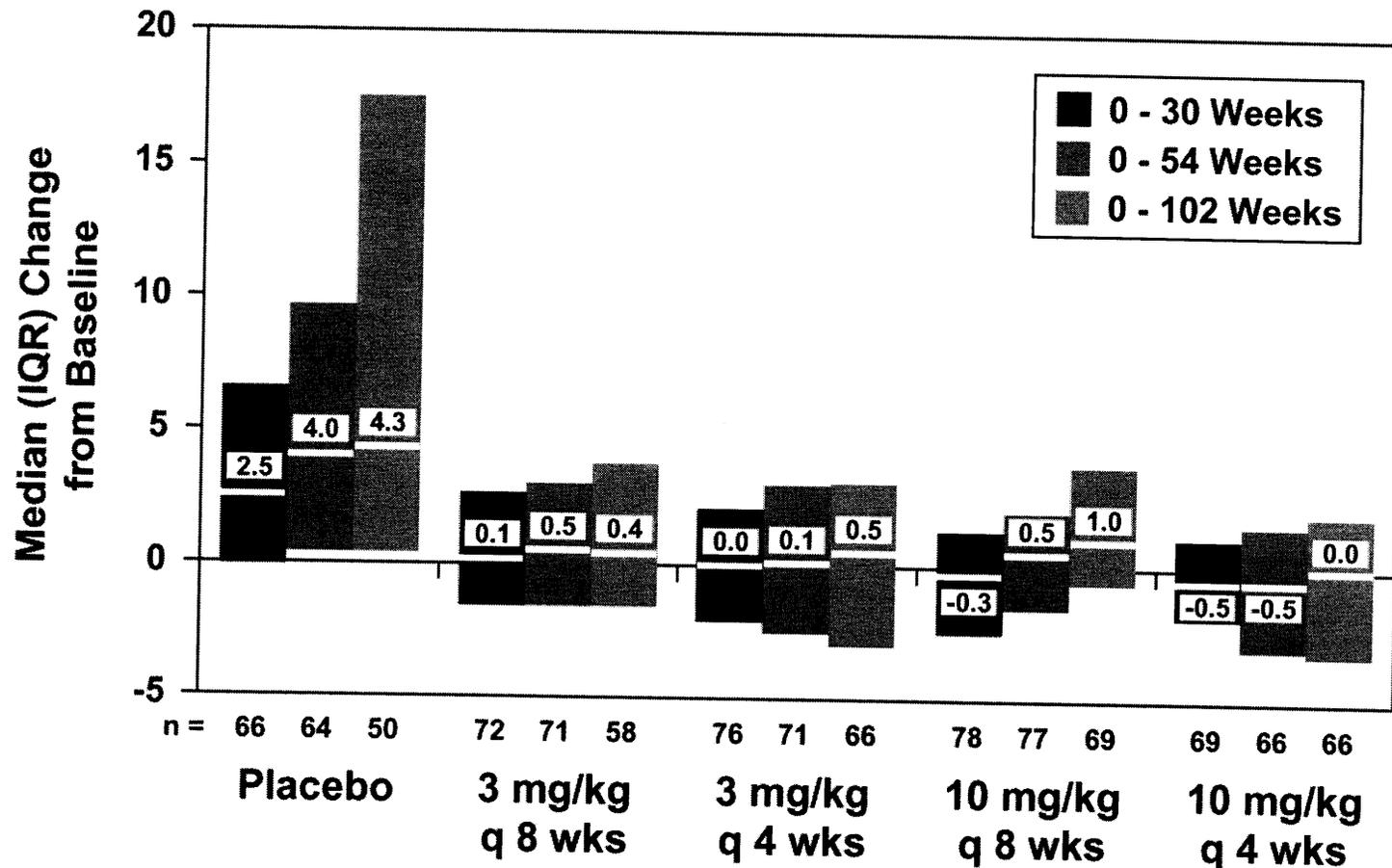
All patients received concomitant MTX

**Efficacy at 102 Weeks  
Sustained Prevention of  
Structural Damage**

**ATTRACT Efficacy**

# Sustained Prevention of Structural Damage

## Median Change in Modified Sharp Scores

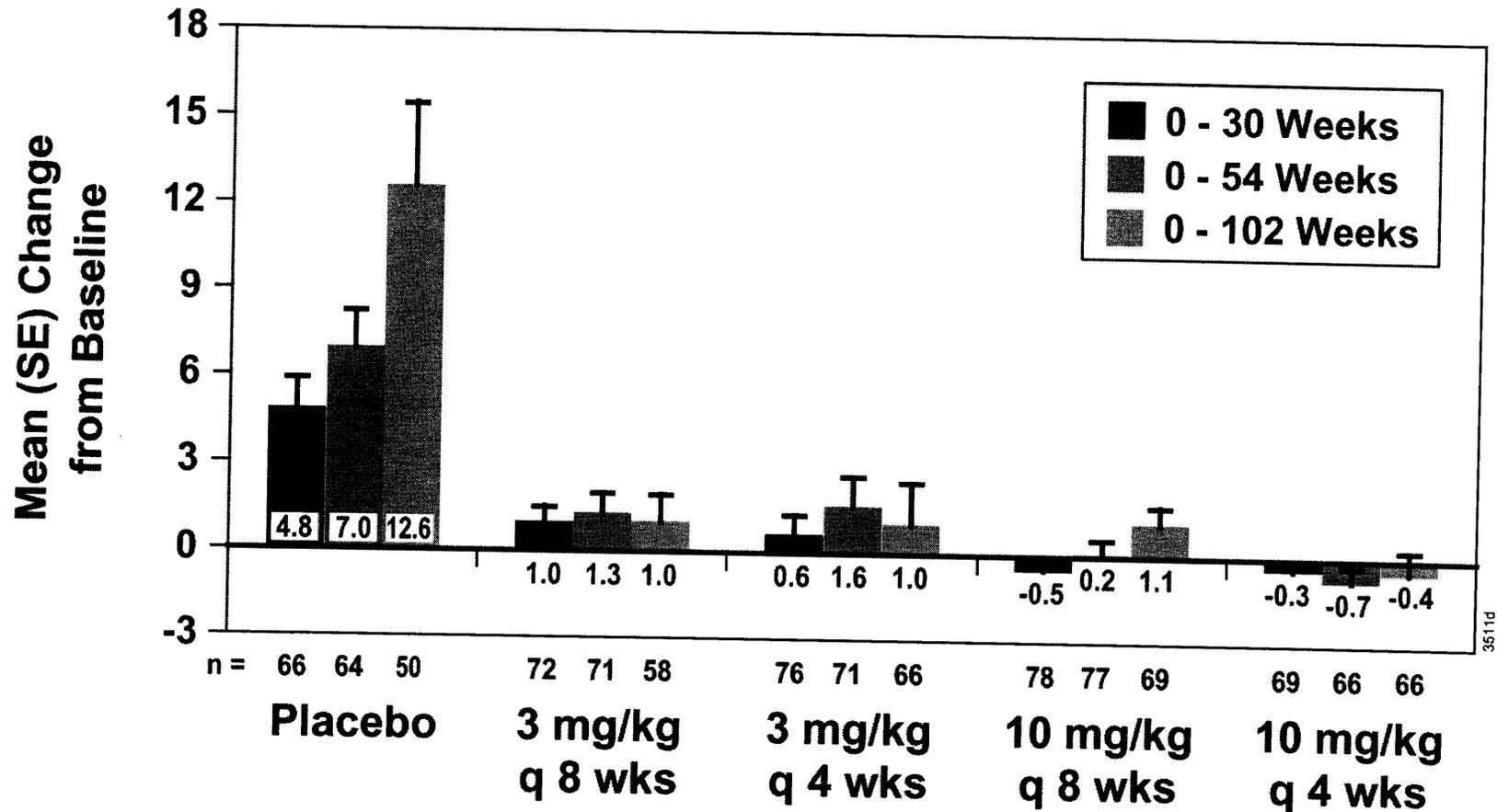


All patients received concomitant MTX

**ATTRACT Efficacy**

# Sustained Prevention of Structural Damage

## Mean Change in Modified Sharp Scores



All patients received concomitant MTX

# Other Endpoints at 102 Weeks

---

- **Reduction in signs and symptoms sustained through 102 weeks in all REMICADE<sup>®</sup> treatment groups**
- **Improvement in physical function (HAQ) sustained through 102 weeks in all REMICADE<sup>®</sup> treatment groups**

# **Overall Efficacy Conclusions**

---

**REMICADE<sup>®</sup> in Combination with MTX Superior to Placebo + MTX**

- **Prevention of structural damage (erosions and JSN)**
  - **Results robust**
  - **Results consistent across patient subgroups**
  - **Supported by sustained reduction in signs and symptoms**
- **Improvement in physical function**

**SAFETY RESULTS**  
**Clinical Trial Experience**  
**Postmarketing Experience**

# **Safety in REMICADE® Clinical Trials**

---

## Patient Population

- **Pooled safety data**
  - 771 REMICADE®-treated patients
  - 192 control patients
- **Summation from 12 clinical trials in 913 patients:**
  - 6 in rheumatoid arthritis (n = 660)
  - 4 in Crohn's disease (n = 233)
  - 2 in other inflammatory diseases (n = 20)
- **Postmarketing safety in > 62,000 patients**

## ATTRACT Safety

# Adverse Events through 54 Weeks<sup>†</sup>

	REMICADE®					
	Placebo (n = 86)	3 mg/kg q 8 wks (n = 88)	3 mg/kg q 4 wks (n = 86)	10 mg/kg q 8 wks (n = 87)	10 mg/kg q 4 wks (n = 81)	All REMICADE® (n = 342)
<b>Pts with ≥ 1 AE</b>	<b>94%</b>	<b>92%</b>	<b>92%</b>	<b>98%</b>	<b>98%</b>	<b>95%</b>
URI	22%	40%	27%	38%	32%	34%
Headache	16%	25%	26%	25%	28%	26%
Nausea	21%	20%	19%	20%	19%	19%
Sinusitis	6%	19%	12%	20%	19%	17%
Diarrhea	16%	11%	15%	14%	19%	15%
Coughing	7%	11%	11%	20%	17%	15%
Rash	6%	9%	13%	21%	15%	14%
Abdominal pain	9%	8%	16%	11%	12%	12%
Fatigue	7%	16%	10%	6%	15%	12%
Dizziness	12%	9%	10%	16%	10%	11%
Pharyngitis	6%	8%	9%	13%	16%	11%
Pain	11%	9%	8%	14%	11%	11%
Rhinitis	11%	10%	6%	14%	11%	10%

<sup>†</sup>Occurring in at least 10% of ATTRACT REMICADE®-treated patients

All patients received concomitant MTX

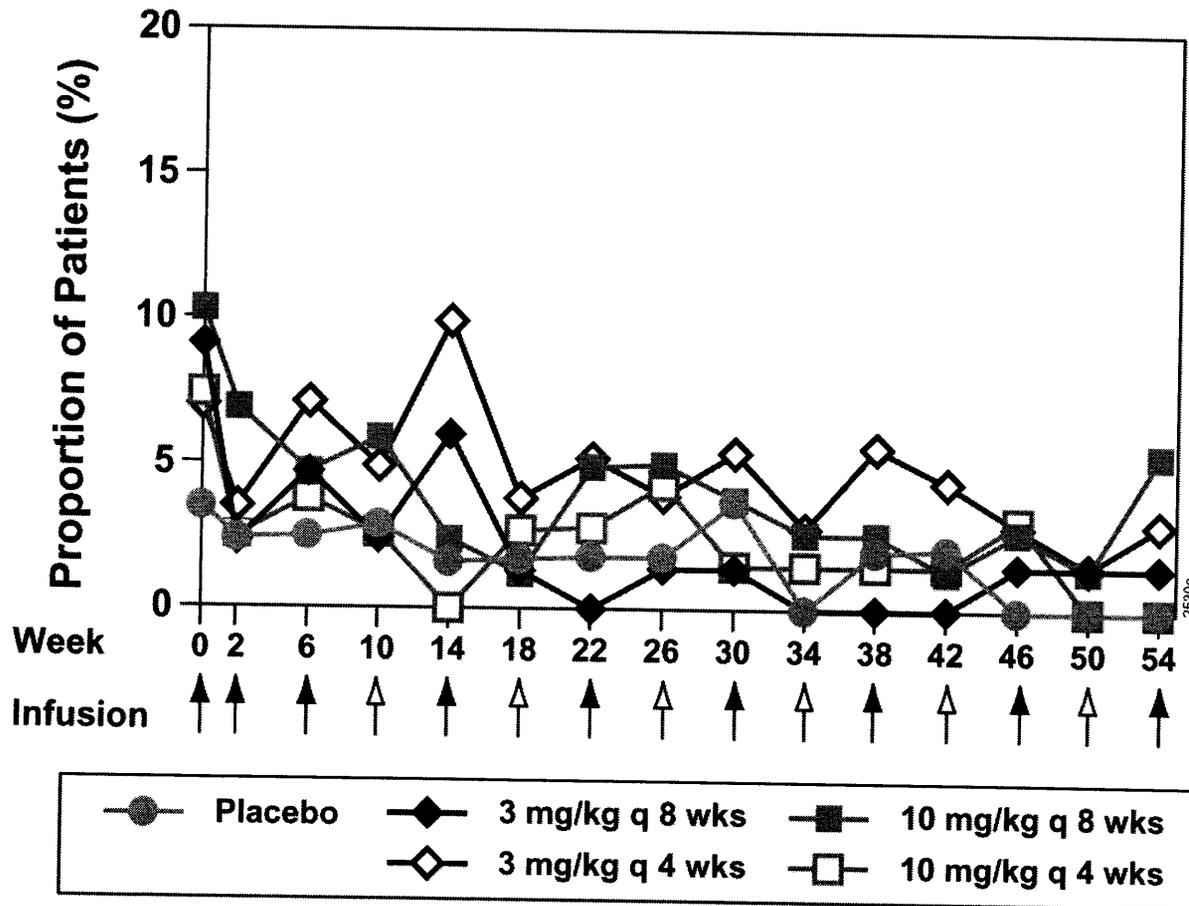
# **Infusion Reactions in REMICADE® Clinical Trials**

---

	<b>ATTRACT</b>		<b>All studies</b>	
	<b>Placebo + MTX</b>	<b>REMICADE® + MTX</b>	<b>Control</b>	<b>REMICADE®</b>
<b>Number of patients</b>	<b>86</b>	<b>342</b>	<b>220</b>	<b>771</b>
<b>Infusions</b>	<b>884</b>	<b>3,614</b>	<b>1,192</b>	<b>4,797</b>
<b>Infusions with reactions</b>	<b>1.9%</b>	<b>3.8%</b>	<b>2.2%</b>	<b>4.8%</b>
<b>Patients with serious reactions</b>	<b>0%</b>	<b>0%</b>	<b>0%</b>	<b>0.5%</b>
<b>Patients with reactions leading to discontinuation</b>	<b>0%</b>	<b>1.5%</b>	<b>0%</b>	<b>1.9%</b>

# Infusion Reactions by Treatment Cycle

Through 54 Weeks



All patients received concomitant MTX

**ATTRACT Safety**

# Serious Adverse Events (SAE)

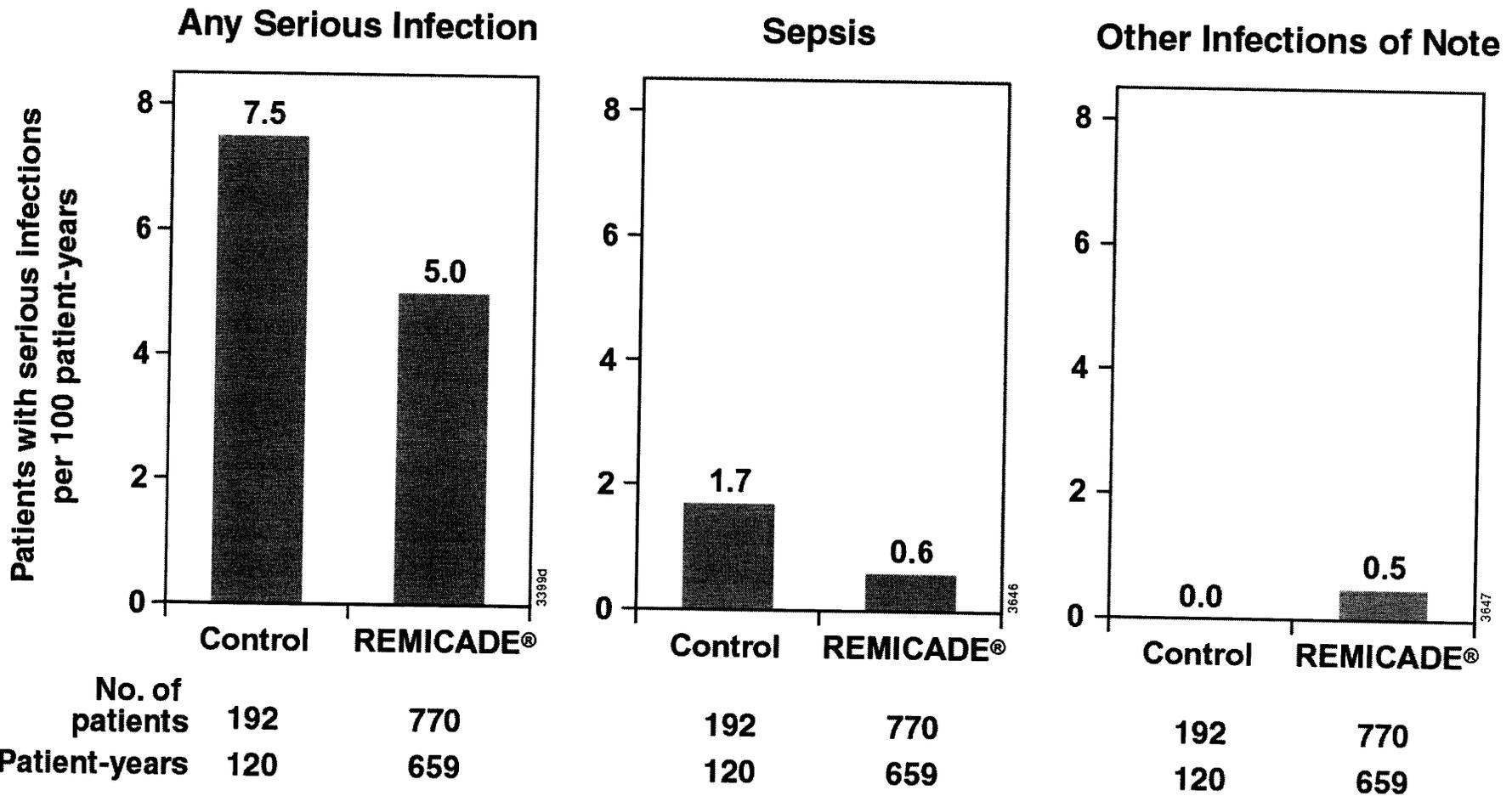
Through 54 Weeks

	Placebo (n = 86)	REMICADE®				All REMICADE® (n = 342)
		3 mg/kg q 8 wks (n = 88)	3 mg/kg q 4 wks (n = 86)	10 mg/kg q 8 wks (n = 87)	10 mg/kg q 4 wks (n = 81)	
<b>Pts with ≥ 1 SAE</b>	<b>18 (21%)</b>	<b>10 (11%)</b>	<b>14 (16%)</b>	<b>17 (20%)</b>	<b>16 (20%)</b>	<b>57 (17%)</b>
<b>Pts with ≥ 1 serious infection</b>	<b>7 (8%)</b>	<b>2 (2%)</b>	<b>6 (7%)</b>	<b>7 (8%)</b>	<b>6 (7%)</b>	<b>21 (6%)</b>
<b>Pneumonia</b>	<b>1 (1.2%)</b>	<b>0 (0.0%)</b>	<b>2 (2.3%)</b>	<b>2 (2.3%)</b>	<b>1 (1.2%)</b>	<b>5 (1.5%)</b>
<b>Cellulitis</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>1 (1.2%)</b>	<b>1 (1.1%)</b>	<b>1 (1.2%)</b>	<b>3 (0.9%)</b>
<b>UTI/pyelonephritis</b>	<b>2 (2.3%)</b>	<b>0 (0.0%)</b>	<b>1 (1.2%)</b>	<b>0 (0.0%)</b>	<b>1 (1.2%)</b>	<b>2 (0.6%)</b>
<b>Bacterial infection</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>1 (1.2%)</b>	<b>0 (0.0%)</b>	<b>1 (1.2%)</b>	<b>2 (0.6%)</b>
<b>Sepsis</b>	<b>2 (2.3%)</b>	<b>0 (0.0%)</b>	<b>1 (1.2%)</b>	<b>0 (0.0%)</b>	<b>1 (1.2%)</b>	<b>2 (0.6%)</b>
<b>Herpes zoster</b>	<b>0 (0.0%)</b>	<b>1 (1.1%)</b>	<b>0 (0.0%)</b>	<b>1 (1.1%)</b>	<b>0 (0.0%)</b>	<b>2 (0.6%)</b>

All patients received concomitant MTX

# Serious Infections – All Studies

Through 6-month Long-term Follow-up



# **Laboratory Results in Clinical Trials**

---

- **Hematology measurements**
  - **Mild increase in hemoglobin**
  - **Mild to moderate decrease in neutrophils**
  - **Mild increase in lymphocytes and monocytes**
- **Chemistry measurements**
  - **Mild decrease in alkaline phosphatase**
  - **Minimal increase in AST and ALT**

# **Anti-dsDNA Antibodies in Clinical Trials**

---

## **Percent Positive During Study**

	<b><u>REMICADE®</u></b>
<b>ATTRACT</b>	<b>9.7%</b>
<b>Other RA &amp; Crohn's disease</b>	<b>9.1%</b>

- **Three of 771 patients (0.39%) developed lupus-like symptoms while on study - all with full resolution of symptoms**
- **No autoimmune conditions, other than underlying disease, observed during the long-term follow-up period**

# **Antibodies to REMICADE® in Clinical Trials**

---

- **13% in Crohn's disease clinical trials**
- **8.3% in ATTRACT**
- **Majority are low titer**
- **2-3 fold increase in risk of having infusion reaction**

# **Malignancies – Lymphomas**

---

Through 3-year Long-term Follow-up

- **One non-Hodgkin's lymphoma (NHL) in ATTRACT (prior to week 30)**
- **Two other NHL (1 RA, 1 Crohn's disease)**
- **One Hodgkin's lymphoma (RA)**
- **2 to 20 fold increased incidence in NHL in RA**
- **Risk correlates with severity of rheumatoid arthritis and use of immunosuppressants**
- **Lymphomas occurred in patients with varying doses and latency periods**

# Malignancies – Other

Through 3-year Long-term Follow-up

	<b>ATTRACT</b>		<b>All studies</b>	
	<b>Placebo + MTX (n = 86)</b>	<b>REMICADE® + MTX (n = 342)</b>	<b>Control (n = 192)</b>	<b>REMICADE® (n = 770)</b>
<b>Patient-years of follow up</b>	<b>83</b>	<b>346</b>	<b>189</b>	<b>1,385</b>
<b>Expected number of patients with non- lymphoma malignancies (NIH SEER)</b>	<b>1</b>	<b>3</b>	<b>1</b>	<b>8</b>
<b>Observed number of patients with non- lymphoma malignancies</b>	<b>0</b>	<b>3</b>	<b>1</b>	<b>9</b>

# Deaths

## Through 3-year Long-term Follow-up

	<b>ATTRACT</b>		<b>All studies</b>	
	<b>Placebo + MTX (n = 86)</b>	<b>REMICADE® + MTX (n = 342)</b>	<b>Control (n = 192)</b>	<b>REMICADE® (n = 770)</b>
<b>Deaths/patient-years of follow-up</b>	<b>3/83</b>	<b>5/346</b>	<b>3/189</b>	<b>15/1,385</b>
<b>Incidence per patient-year of follow-up</b>	<b>0.04</b>	<b>0.01</b>	<b>0.02</b>	<b>0.01</b>

# Postmarketing Experience

---

> 62,000 Patients Treated through May 2000

<b>Infections</b>	<b>0.69%</b>
<b>Serious infections</b>	<b>0.36%</b>
<b>Sepsis</b>	<b>0.05%</b>
<b>Other infections of note</b>	<b>0.04%</b>
<b>Malignancies</b>	<b>0.04%</b>
<b>Deaths</b>	<b>0.06%</b>

**REMICADE® (infliximab)**

## **Additional RA Studies (n > 6,400)**

---

	<u>Number of Patients</u>		<u>Status</u>
	<u>REMICADE®</u>	<u>Control</u>	
<b>PROMPT (open-label U.S. study in RA)</b>	<b>547</b>	<b>0</b>	<b>ongoing</b>
<b>ASPIRE (early RA combination study)</b>	<b>750</b>	<b>300</b>	<b>ongoing</b>
<b>Early RA monotherapy study</b>	<b>~100</b>	<b>~50</b>	<b>planned</b>
<b>Early RA pilot studies</b>	<b>22</b>	<b>22</b>	<b>ongoing</b>
<b>JRA</b>	<b>~50</b>	<b>~50</b>	<b>planned</b>
<b>European and Canadian expanded access programs</b>	<b>&gt; 2,500</b>	<b>0</b>	<b>ongoing</b>
<b>US patient registry</b>	<b>~2,500</b>	<b>~2,500</b>	<b>planned</b>

**REMICADE® (infliximab)**

## **Other REMICADE® Studies (n > 7,900)**

---

	<u>Number of Patients</u>		<u>Status</u>
	<u>REMICADE®</u>	<u>Control</u>	
<b>ACCENT I (Crohn's disease maintenance trial)</b>	<b>580</b>	<b>0</b>	<b>ongoing</b>
<b>ACCENT II (Fistulizing Crohn's disease maintenance trial)</b>	<b>300</b>	<b>0</b>	<b>ongoing</b>
<b>TREAT (U.S. Crohn's disease registry)</b>	<b>~2,500</b>	<b>~2,500</b>	<b>ongoing</b>
<b>Pediatric Crohn's disease studies</b>	<b>~95</b>	<b>0</b>	<b>ongoing/planned</b>
<b>Psoriasis studies</b>	<b>~320</b>	<b>~210</b>	<b>ongoing/planned</b>
<b>European and Canadian expanded access programs</b>	<b>&gt; 3,000</b>	<b>0</b>	<b>ongoing</b>
<b>Other</b>	<b>&gt; 1,150</b>	<b>&gt; 1,050</b>	<b>ongoing/planned</b>

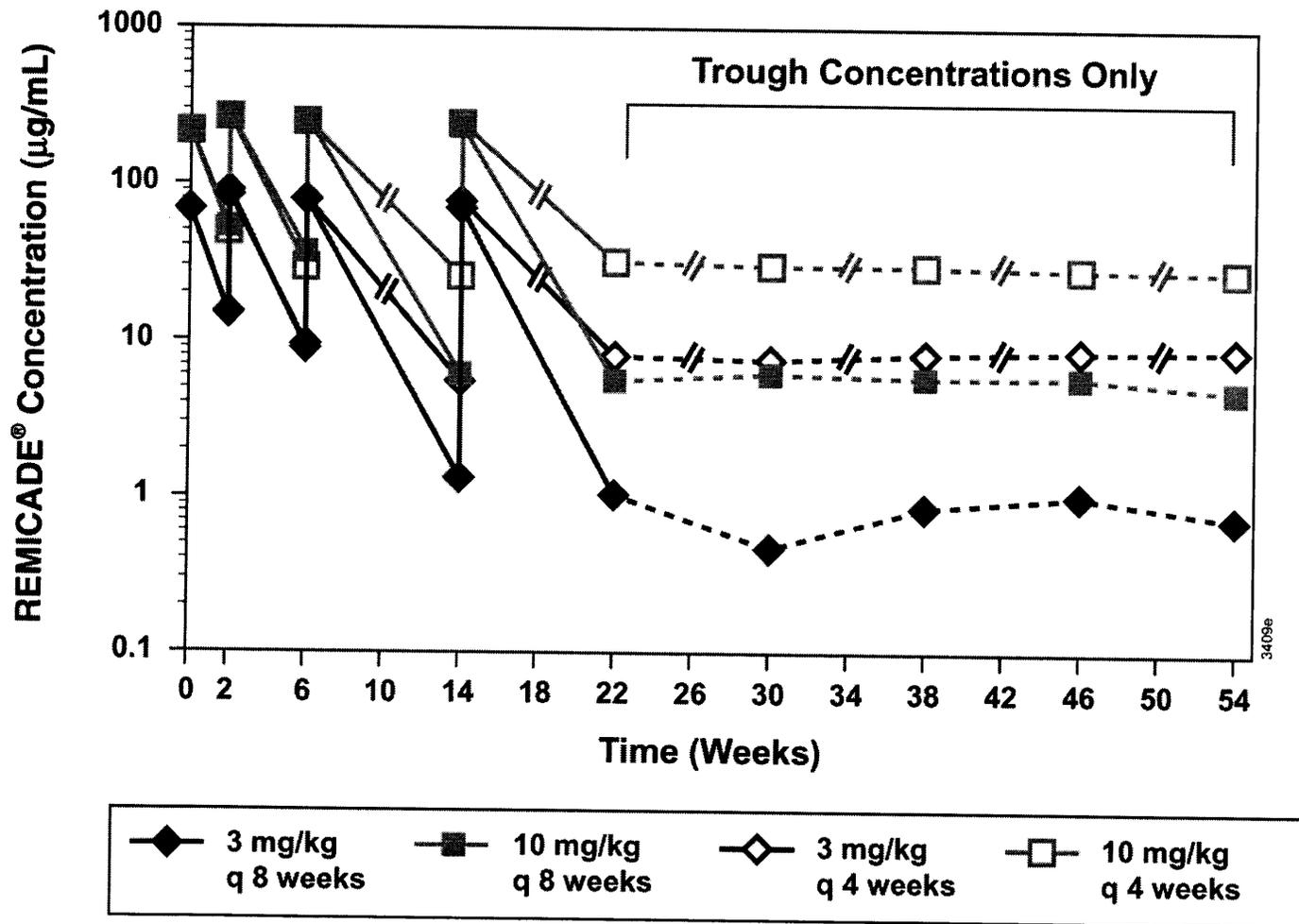
***ATTRACT***

---

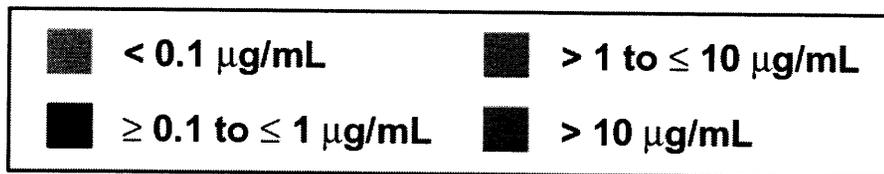
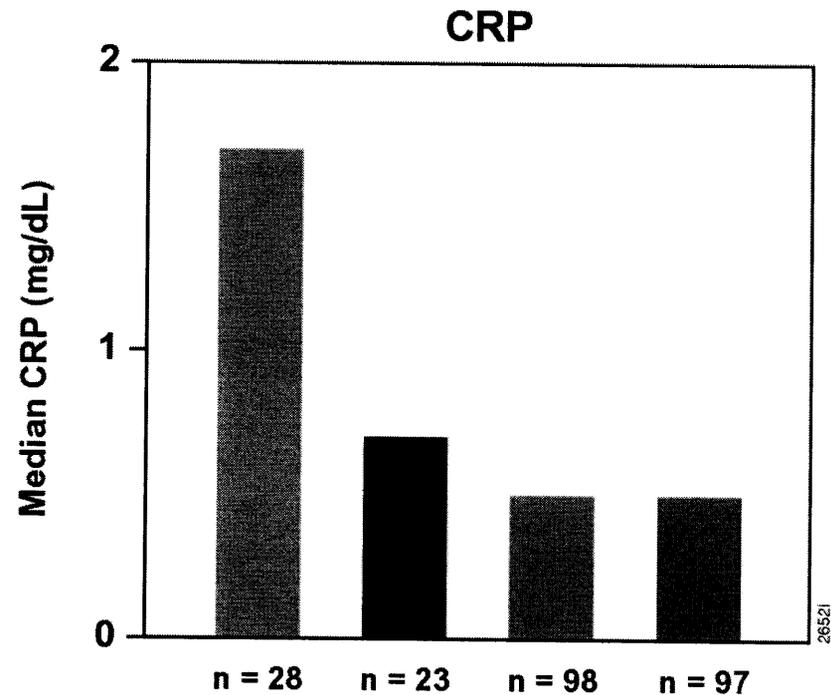
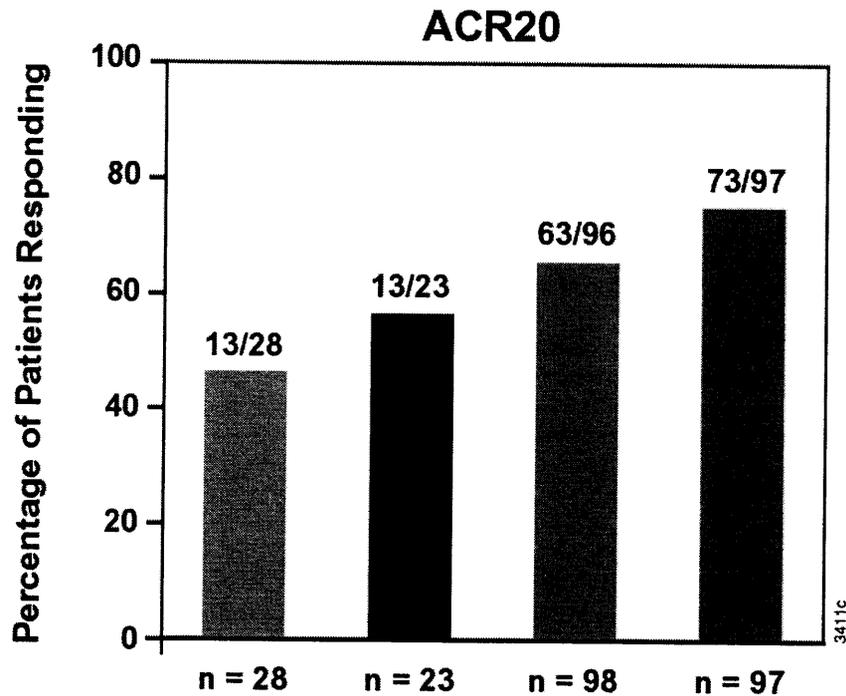
# **Dose Rationale**

REMICADE® (Infliximab)

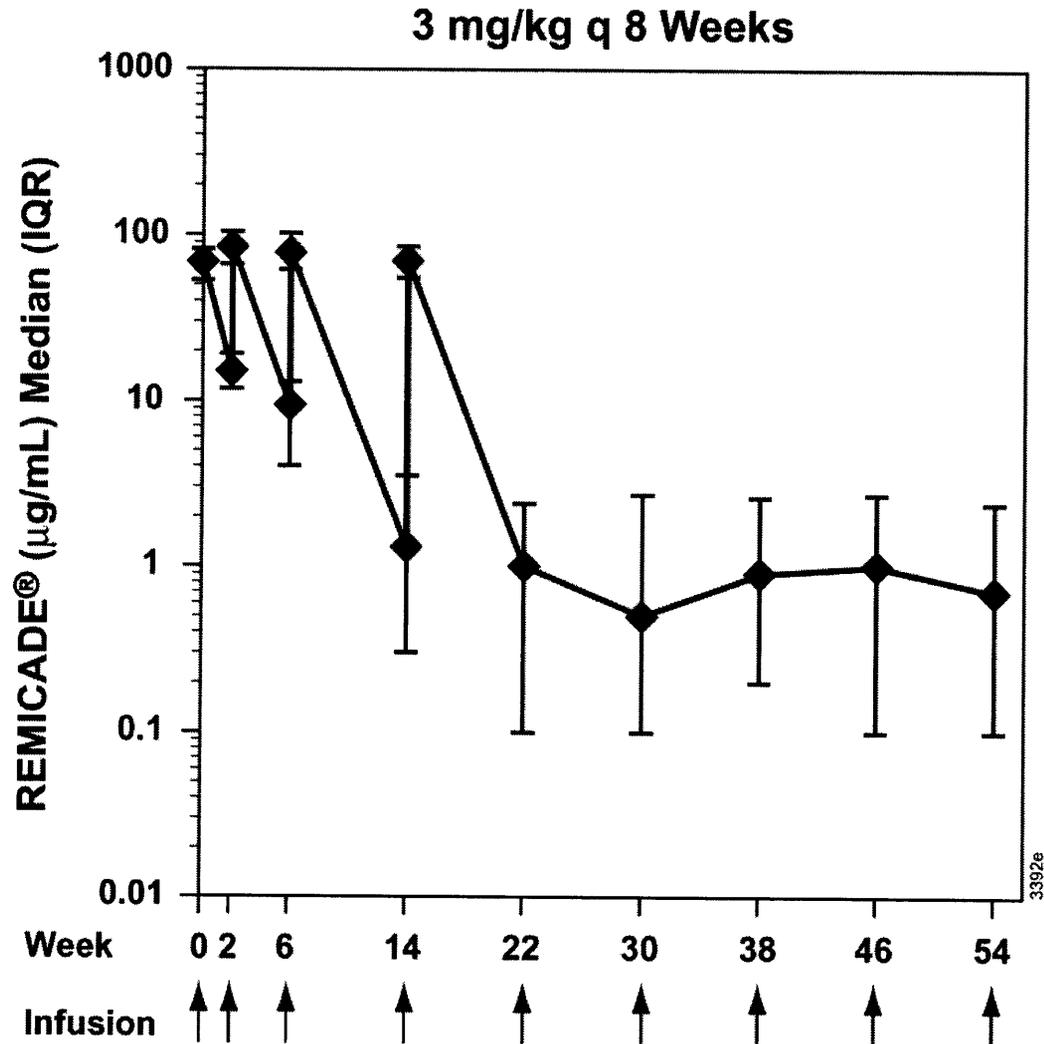
# Serum REMICADE® Concentrations in ATTRACT



# Relation of REMICADE<sup>®</sup> Concentration to ACR20 and CRP



# ATTRACT Pharmacokinetics



# **Dose Recommendation**

---

- **Starting Dose:**

**3 mg/kg given as intravenous infusion, followed with additional 3 mg/kg doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.**

- **Maintenance Dose:**

**Maintenance of clinical response in some patients might require decreased infusion interval and/or increased dose up to 10 mg/kg.**

# **Conclusions**

---

**In patients with active RA despite treatment with MTX, REMICADE® at a dose of 3 mg/kg every eight weeks in combination with MTX provides the following benefits through 54 weeks:**

- Prevention of structural damage (erosions and joint space narrowing)**
- Sustained improvement in signs and symptoms**
- Improvement in physical function/disability**
- Safe and well-tolerated**

**REMICADE® (infliximab)**

# **Agenda of Speakers**

---

**Introduction**

**Martin Page**  
**Vice President, Worldwide Regulatory Affairs**  
**Centocor**

**Scientific Rationale and  
Clinical Pharmacology**

**Professor Ravinder Maini, M.D., FRCP**  
**Kennedy Institute of Rheumatology**  
**London, UK**

**Efficacy and Safety**

**Gregory Harriman, M.D.**  
**Senior Director, Immunology Clinical Research**  
**Centocor**

**Significance of  
Radiographic Results**

**Désirée M.F.M. van der Heijde, M.D., Ph.D.**  
**Professor of Rheumatology**  
**University Hospital Maastricht, The Netherlands**

**Clinical Perspective**

**E. William St. Clair, M.D.**  
**Associate Professor of Medicine**  
**Duke University School of Medicine, Durham, NC**

**Concluding Remarks**

**Martin Page**

# **Significance of Radiologic Findings**

---

- **Size and quality of the ATTRACT radiographic data set**
- **Structural outcome measurements**
- **Specific features of the ATTRACT data**

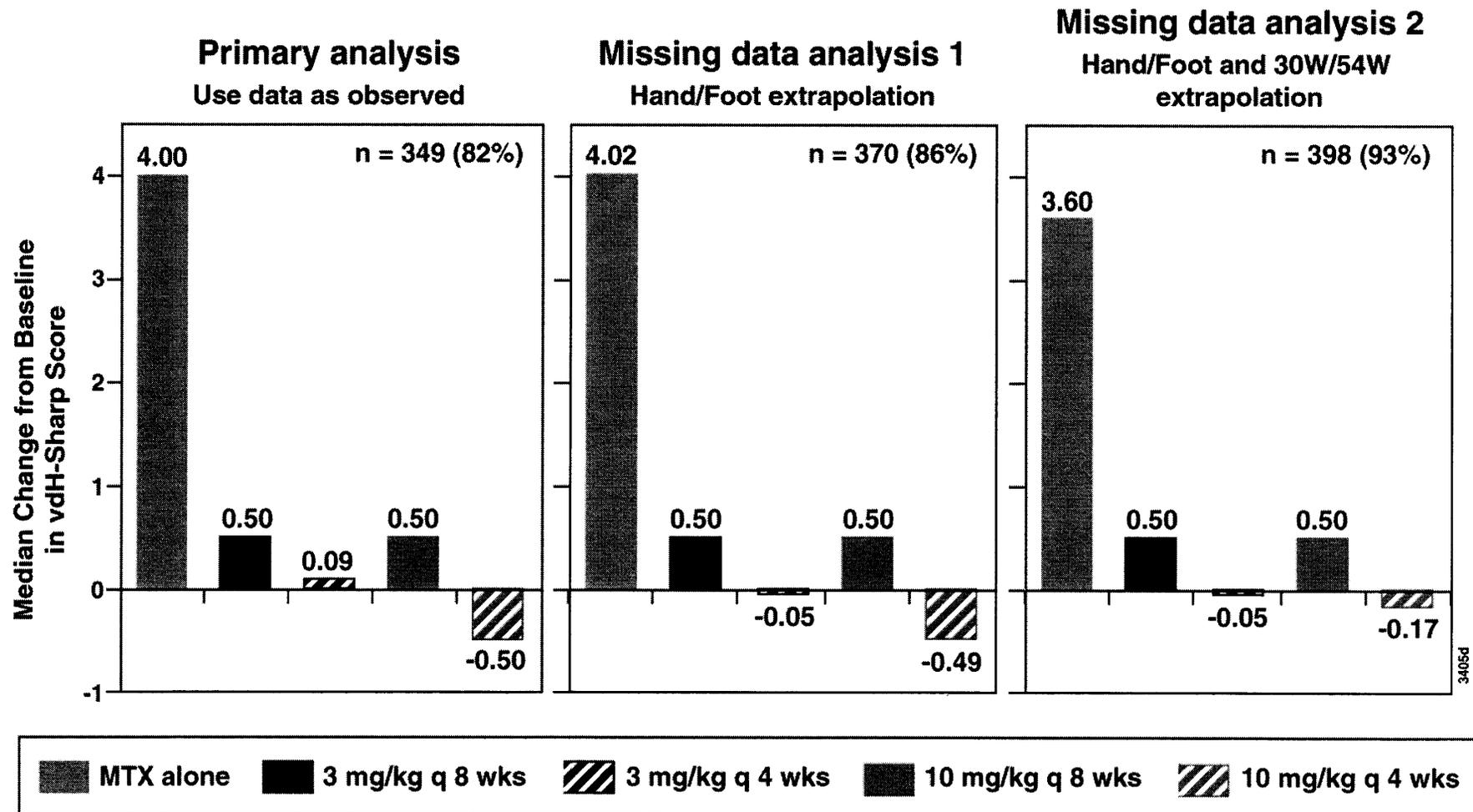
# **ATTRACT Study**

---

## **Data Quality**

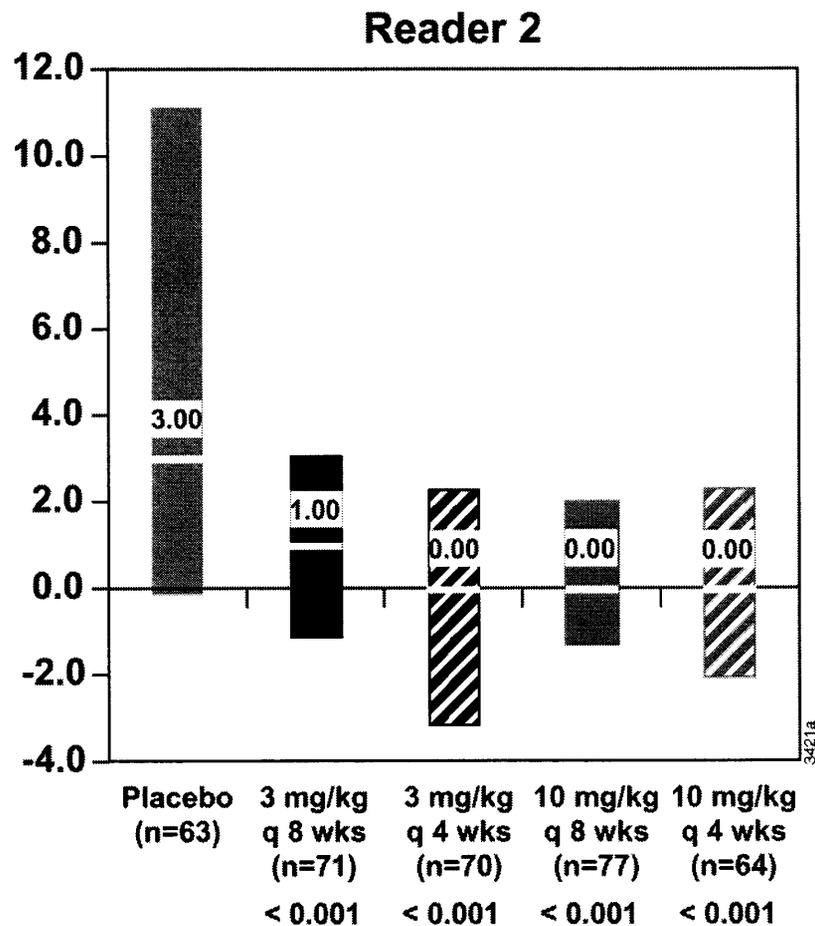
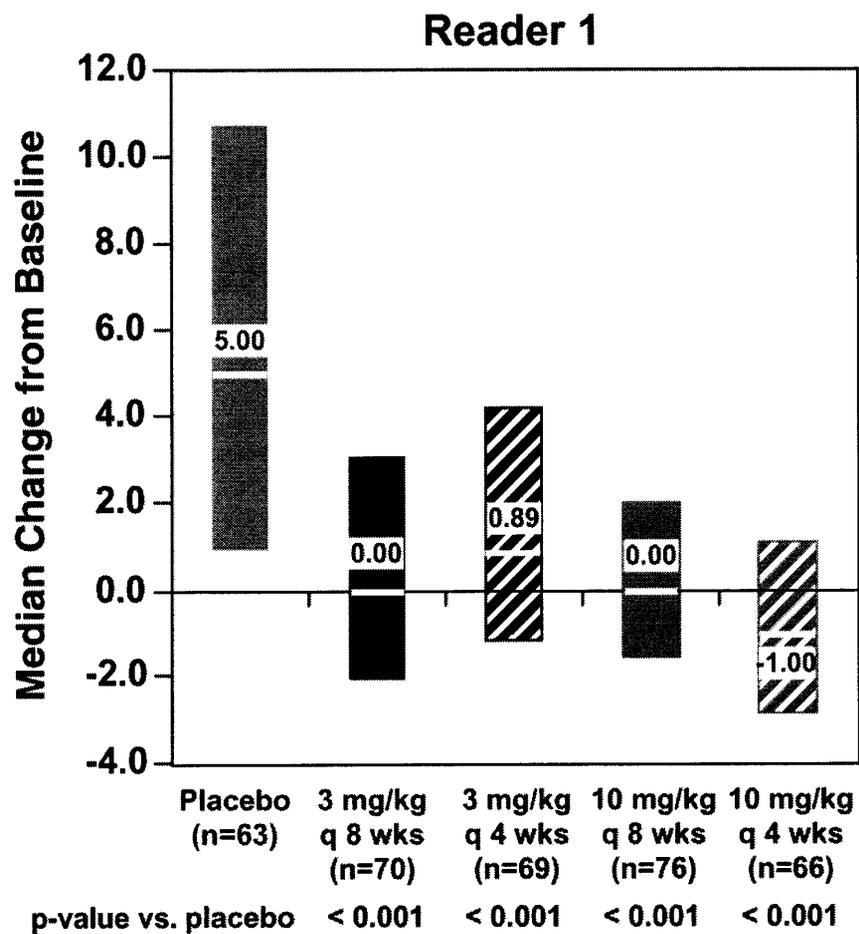
## ATTRACT Efficacy

# Robust Results When Accounting for Missing Data



## Radiographic Perspective

# Consistent Results between Readers



All patients received concomitant MTX

# **Radiographic Results are Robust**

---

- **Sensitivity analyses**
- **Excluding patients with medication changes**
- **Consistency across patient sub-groups**

# Structural Outcome Measurements

---

- **Both bone erosions and joint space narrowing give independent and additive information**
  - **Different pathologic processes may be involved**
- **The van der Heijde-modified Sharp total score captures both of these aspects**
  - **More sensitive to change**
  - **More reliable**

# **ATTRACT Study**

---

## **Specific Features of Radiographic Findings**

# **Effective in Medically Resistant Population**

---

Factors Associated with Decreased Response to Medical Treatment in RA:

- **Increased disease duration**
- **More severe functional class**
- **Prior DMARD use**

# Patient Populations in Recent Studies Measuring Structural Damage

---

## Baseline Characteristics

	<b>MTX/SSZ/CCS (COBRA)</b>	<b>Leflunomide (US301)</b>	<b>Etanercept (ERA)</b>	<b>REMICADE® (ATTRACT)</b>
<b>Study duration (wks)</b>	<b>80</b>	<b>52</b>	<b>52</b>	<b>54</b>
<b>Disease duration (yrs)</b>	<b>0.3</b>	<b>7.0</b>	<b>≤ 1</b>	<b>8.4</b>
<b>Prior DMARDs</b>	<b>0.2</b>	<b>0.8</b>	<b>0.5</b>	<b>3</b>
<b>MTX naive</b>	<b>yes</b>	<b>yes</b>	<b>yes</b>	<b>no</b>
<b>Functional class III</b>	<b>†</b>	<b>12%</b>	<b>†</b>	<b>49%</b>
<b>Baseline Sharp score</b>	<b>3</b>	<b>23</b>	<b>12</b>	<b>70</b>

†Not reported

# **Specific Features of Radiologic Benefit**

---

- **Effective in medically resistant population**
- **Benefits both bone erosion and cartilage damage**
- **Durable through 2 years**
- **Consistent benefit in all patient subgroups**
- **Provides significant structural damage benefit**

**REMICADE® (infliximab)**

# **Agenda of Speakers**

---

**Introduction**

**Martin Page**  
**Vice President, Worldwide Regulatory Affairs**  
**Centocor**

**Scientific Rationale and  
Clinical Pharmacology**

**Professor Ravinder Maini, M.D., FRCP**  
**Kennedy Institute of Rheumatology**  
**London, UK**

**Efficacy and Safety**

**Gregory Harriman, M.D.**  
**Senior Director, Immunology Clinical Research**  
**Centocor**

**Significance of  
Radiographic Results**

**Désirée M.F.M. van der Heijde, M.D., Ph.D.**  
**Professor of Rheumatology**  
**University Hospital Maastricht, The Netherlands**

**Clinical Perspective**

**E. William St. Clair, M.D.**  
**Associate Professor of Medicine**  
**Duke University School of Medicine, Durham, NC**

**Concluding Remarks**

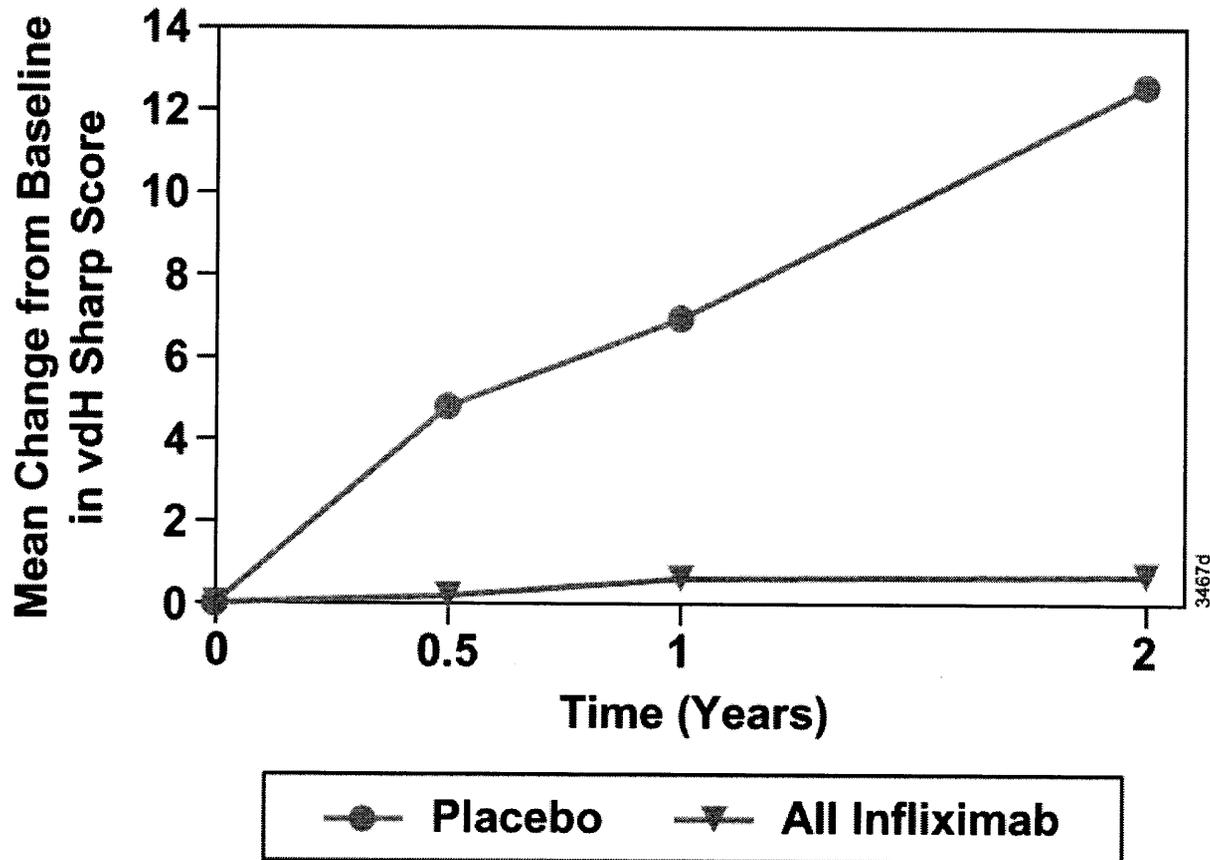
**Martin Page**

# **Infliximab Therapy for Rheumatoid Arthritis**

---

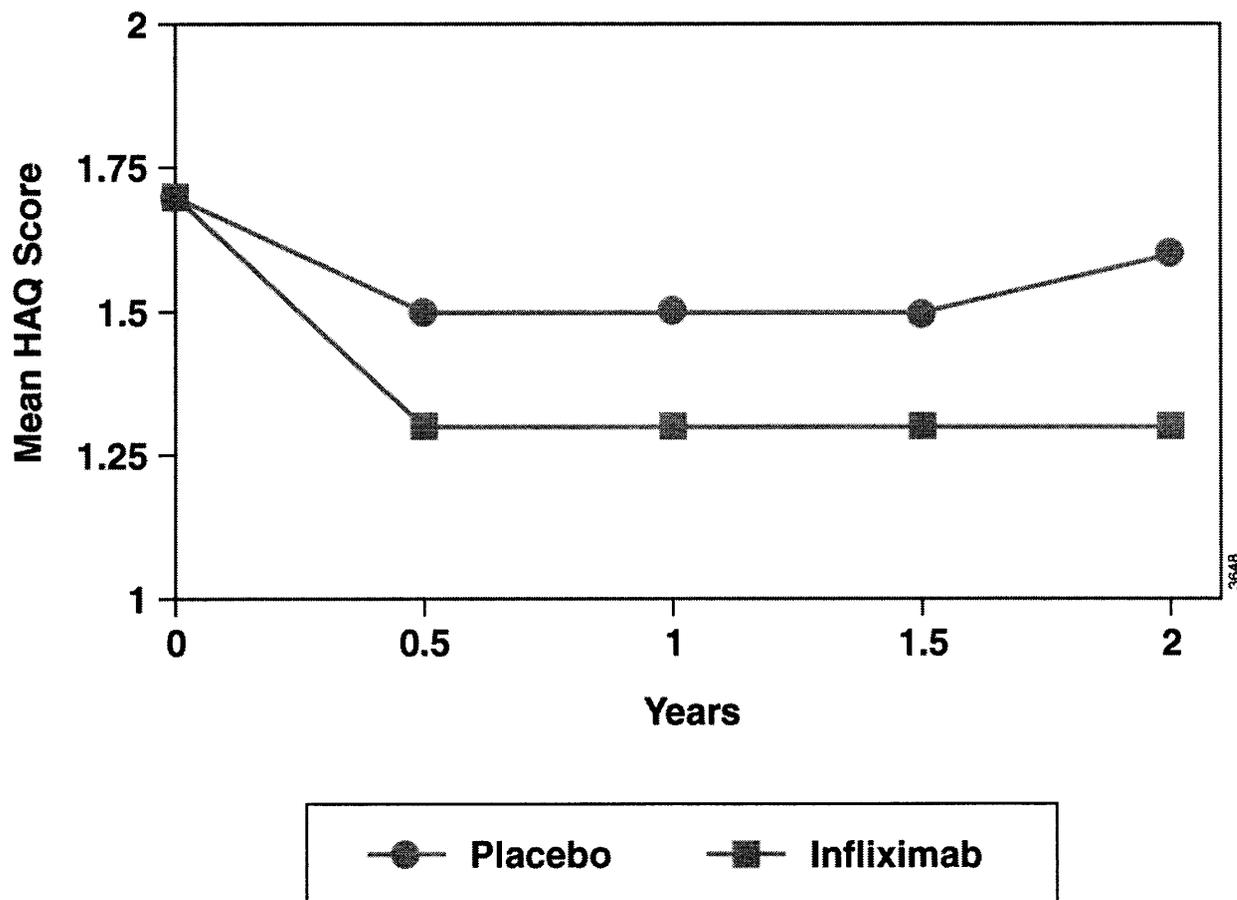
## **Clinical Perspective**

# Radiographic Progression Over 2 Years in ATTRACT



All patients received concomitant MTX

# Mean HAQ Scores Over Time



All patients received concomitant MTX

# Potential Risks of Anti-TNF Therapy

---

- **Infusion reactions**
- **Autoimmunity**
- **Immunogenicity**
- **Infections**
- **Malignancies**

# Treatment Recommendations

---

- **Initial dose: 3 mg/kg 0, 2, 6 and 14 weeks**
- **Maintenance dosing**
  - **3 mg/kg every 8 wk group has a lower proportion of ACR50 responses than other infliximab dosage groups**
  - **Trough serum levels of infliximab > 1 µg/mL associated with higher likelihood of ACR response**
  - **3 mg/kg every 4 weeks and 10 mg/kg every 8 weeks produce trough serum infliximab levels > 1 µg/mL in more than 80% of patients**
- **Options for increasing serum trough levels of infliximab**
  - **↑ dose**
  - **↓ interval**

# **Infliximab Therapy for Rheumatoid Arthritis**

---

## **Final Thoughts**

**REMICADE® (infliximab)**

# **Agenda of Speakers**

---

**Introduction**

**Martin Page**  
**Vice President, Worldwide Regulatory Affairs**  
**Centocor**

**Scientific Rationale and  
Clinical Pharmacology**

**Professor Ravinder Maini, M.D., FRCP**  
**Kennedy Institute of Rheumatology**  
**London, UK**

**Efficacy and Safety**

**Gregory Harriman, M.D.**  
**Senior Director, Immunology Clinical Research**  
**Centocor**

**Significance of  
Radiographic Results**

**Désirée M.F.M. van der Heijde, M.D., Ph.D.**  
**Professor of Rheumatology**  
**University Hospital Maastricht, The Netherlands**

**Clinical Perspective**

**E. William St. Clair, M.D.**  
**Associate Professor of Medicine**  
**Duke University School of Medicine, Durham, NC**

**Concluding Remarks**

**Martin Page**

**REMICADE® (infliximab)**

---

## **Concluding Remarks**

# REMICADE<sup>®</sup> (infliximab)

---

## Proposed Expanded Indication

**REMICADE<sup>®</sup> in combination with methotrexate is indicated for the reduction in signs and symptoms, prevention of structural damage (erosions and joint space narrowing) and improvement in physical function in patients who have had an inadequate response to methotrexate.**