Treatment evolution
—from “alleviating & delaying” to “stopping” disease progression —

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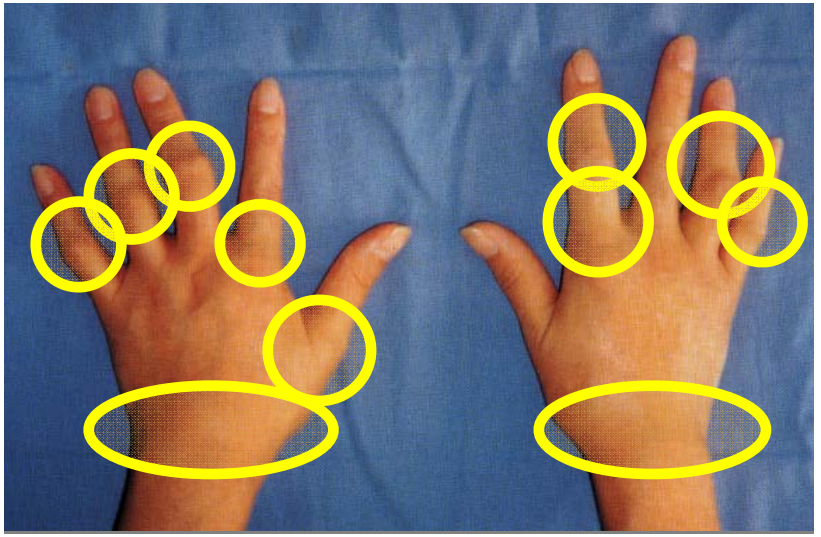
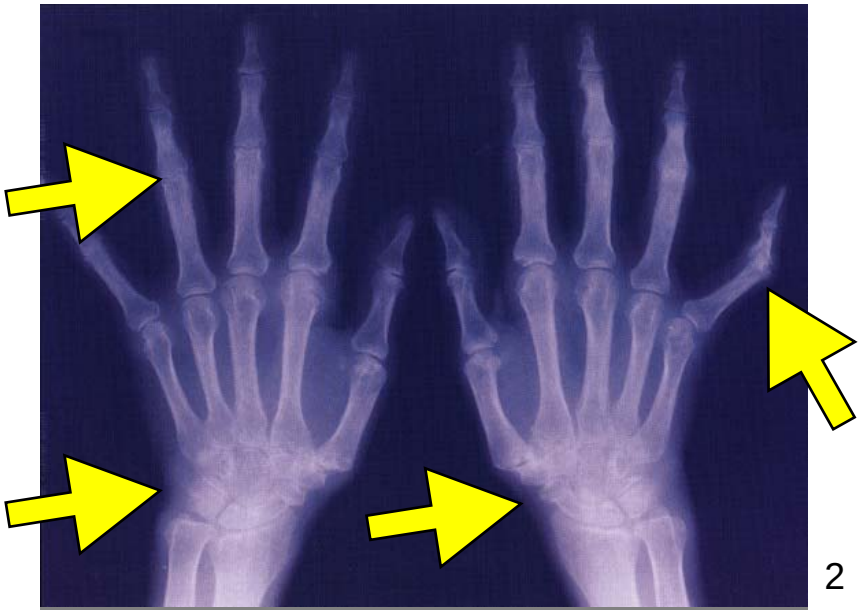
Epidemiology of Connective Tissue Disease and Rheumatic Disease

	No. of patients	Ratio (male : female)
Rheumatoid arthritis (RA)	700,000	1 : 4
Sjogren's syndrome (SjS)	50,000	1 : 14
Systemic lupus erythematosus (SLE)	50,000	1 : 8
Scleroderma (SSc)	14,000	1 : 7
Polymyositis/dermatomyositis (PM/DM)	10,000	1 : 2
Mixed connective tissue disease(MCTD)	7,000	1 : 14~16
Vasculitis		
Polyarteritis nodosa (PN)	1,000	1 : 1
Wegener's granulomatosis (WG)	6,000	1 : 1
Microscopic polyangitis (MPA)	4,000	1 : 2

Rheumatoid Arthritis:RA

- Progressive, systemic, inflammatory diseases
- Symmetrical, erosive, destructive arthritis
- Various systemic symptoms
- Prevalence rate 0.5 ~ 1.0%, 1:4 male-female ratio
- Does not spread through blood transfusion
- Half of patients will be bedridden in 10 years with advanced symptoms

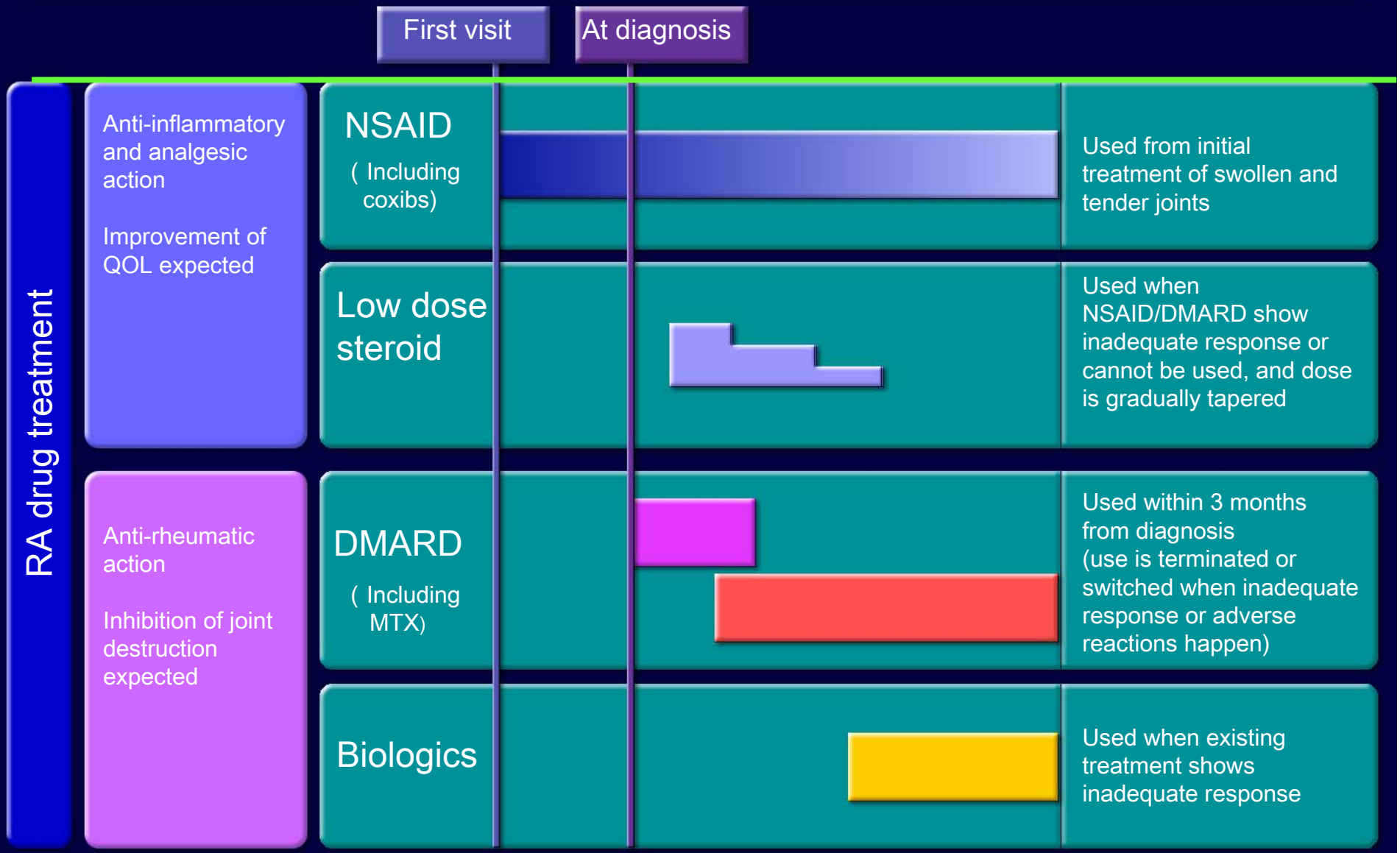




Current Situation Surrounding RA

- Rheumatoid arthritis (RA) is a severe and progressive disease.
- Poor prognosis
  - 50% of patients are bedridden in 10 years
  - Life expectancy is reduced by 10 years
  - Severity is similar to Hodgkin's disease stage IV or three-vessel coronary artery disease
- Medical cost is very high and patients cannot work for very long
- Many patients become incapable of working even before seeing a rheumatologist → Need to raise public awareness
- Joint damage begins at early stage and deteriorates → Need to start treatment at early stage

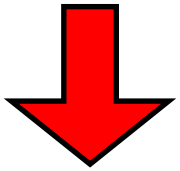
New Strategy of Drug Treatment for RA



Goals of RA Treatment

- Short-term: Improve patient QOL, reduce pain, swelling and stiffness of joints
  (achieve better clinical effect in short time → clinical remission)

- Mid- to long-term: inhibit joint damage and maintain physical functions
  (arrest progression of joint damage → true remission)



NSAIDs and steroids → only for alleviating symptoms
Anti-rheumatic drugs → change the natural course of the disease
Aim is to suppress arthritis and joint damage with anti-rheumatic drugs

Remission becomes a realistic target by using biological agents!

Goals of RA Treatment

EULAR2005

"The main goal of therapy is remission"

EULAR2006

"Remission is realistic goal in early RA"

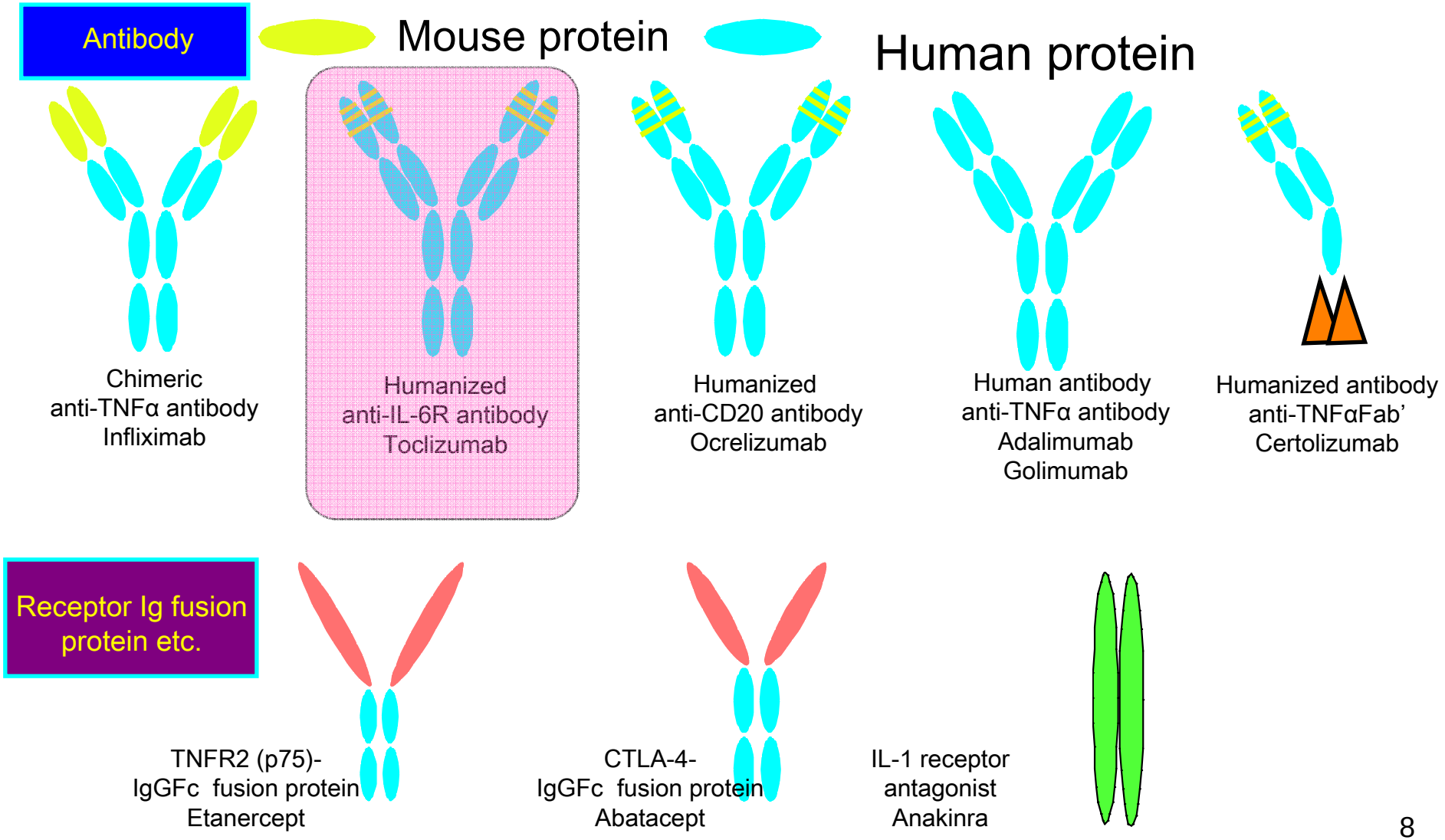
"Drug free Remission is possible for pts with early active RA" (2007')

Goals of RA Treatment

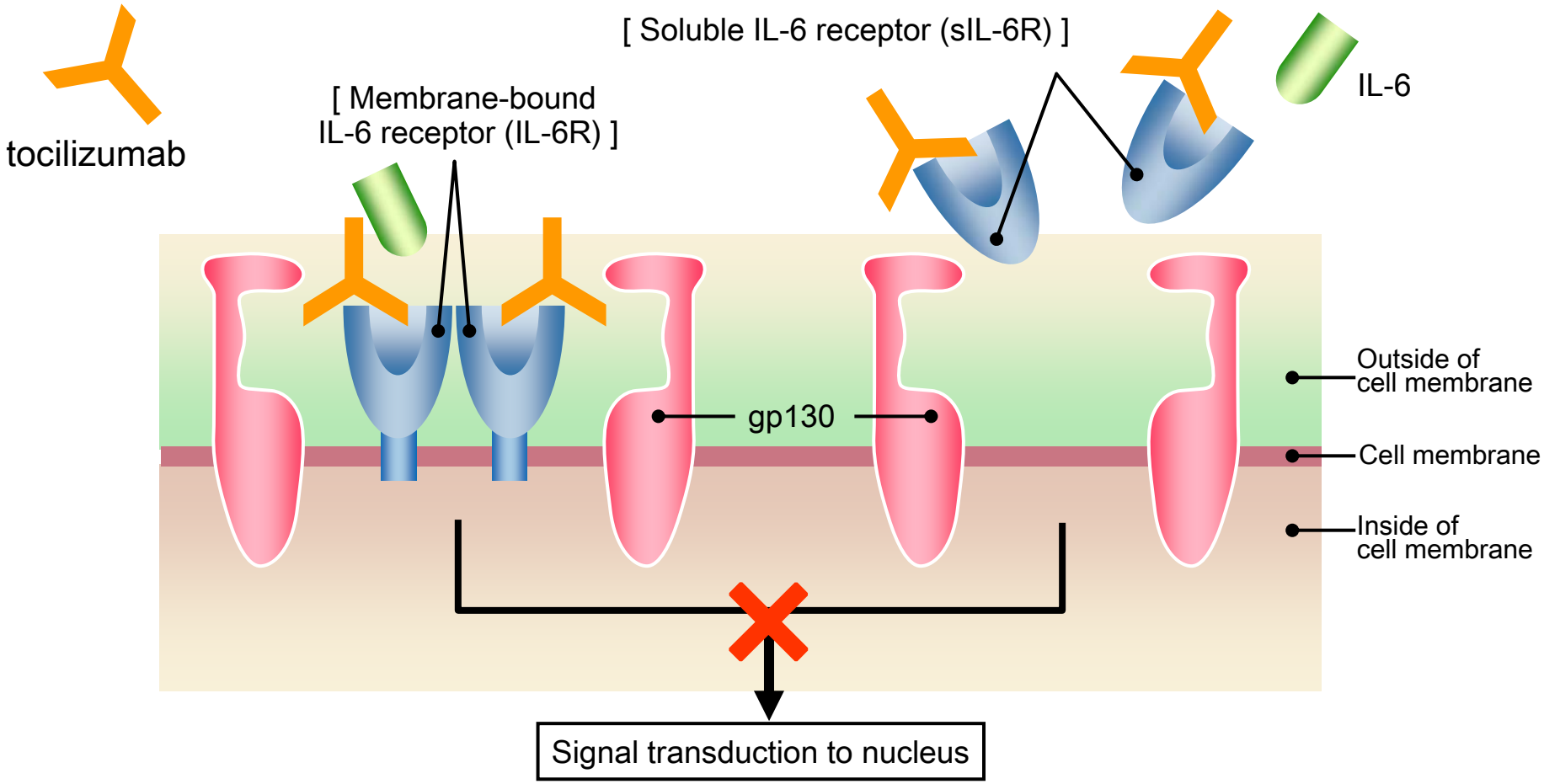
- **Clinical remission:** normal inflammatory response + no synovitis present clinically, ACR/DAS remission criteria
- **Radiographic remission:** no synovitis detected with super-sensitive imaging
- **True remission:** Low RA activity with no progression of joint damage

MTX and biological agents are the driving forces!

Structure and Target of Biological Agents

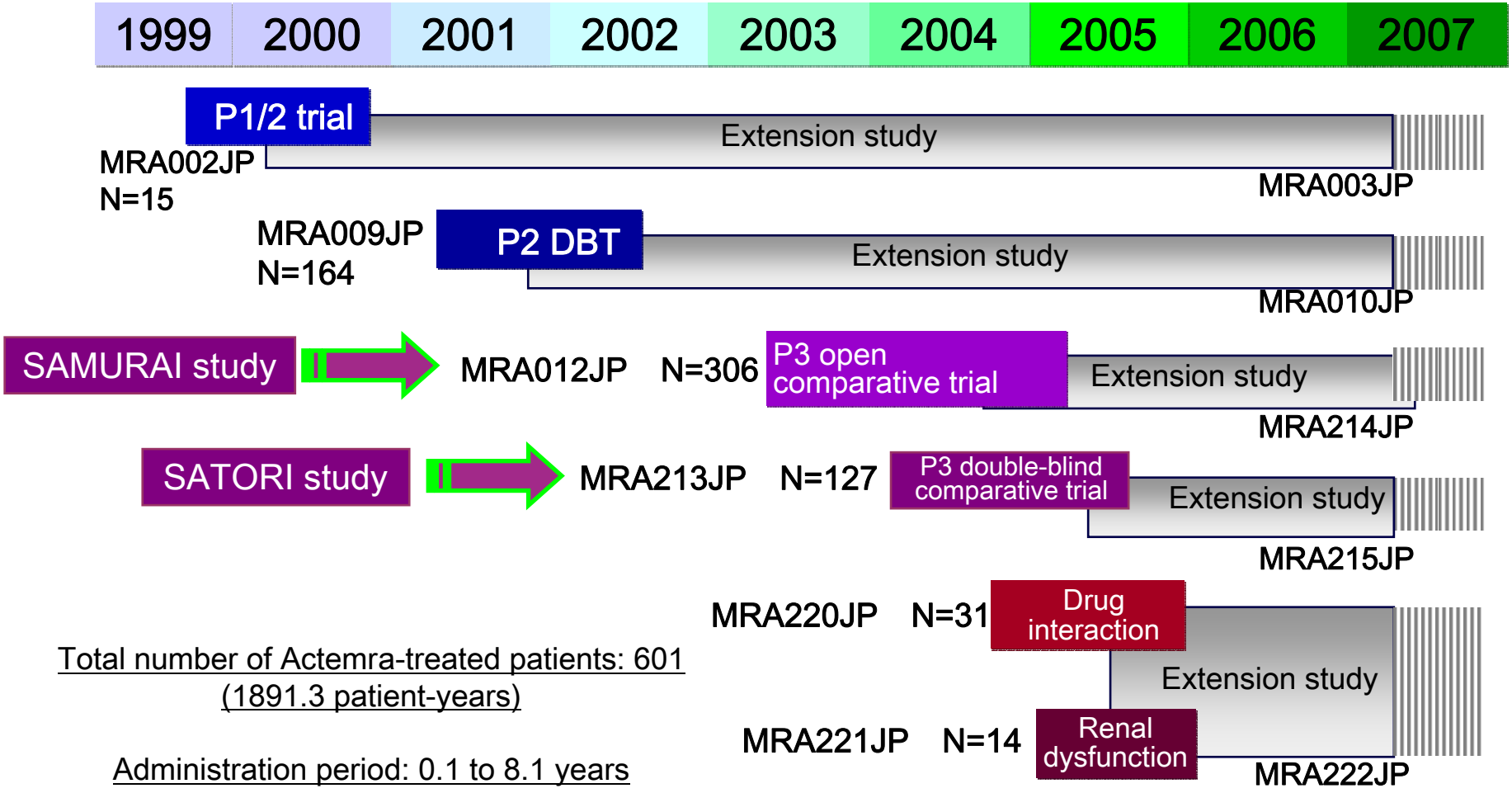


Mechanism of Action of Actemra (anti-IL6 receptor antibody)



Results of Clinical Studies

Overview of Clinical Studies Conducted in Japan (RA)



Total number of Actemra-treated patients: 601
(1891.3 patient-years)

Administration period: 0.1 to 8.1 years
Median: 2.9 years

Overview of Clinical Studies Conducted Outside of Japan (RA)

Name of study	Clinical study design/target	Comparators	No. of patients	Primary endpoints
OPTION	Double blind comparative study MTX inadequate responders	TCZ 4mg/kg+MTX TCZ 8mg/kg+MTX MTX+ placebo	623	ACR20 (24 weeks)
TOWARD	Double blind comparative study DMARDs inadequate responders	TCZ 8mg/kg+DMARDs DMARDs+ placebo	1220	ACR20 (24 weeks)
AMBITION	Double blind comparative study Not used MTX for previous 6 months	TCZ 8mg/kg+MTX placebo MTX+ TCZ placebo	673	ACR20 (24 weeks)
RADIATE	Double blind comparative study TNF α inhibitors inadequate responders	TCZ 4mg/kg+MTX TCZ 8mg/kg+MTX MTX+ placebo	499	ACR20 (24 weeks)
LITHE	Double blind comparative study Moderate and severe RA/ X-ray study	TCZ 4mg/kg+MTX TCZ 8mg/kg+MTX MTX+ TCZ placebo	1196	ACR20 (24 weeks) TSS (52 weeks) HAQ (52 weeks)

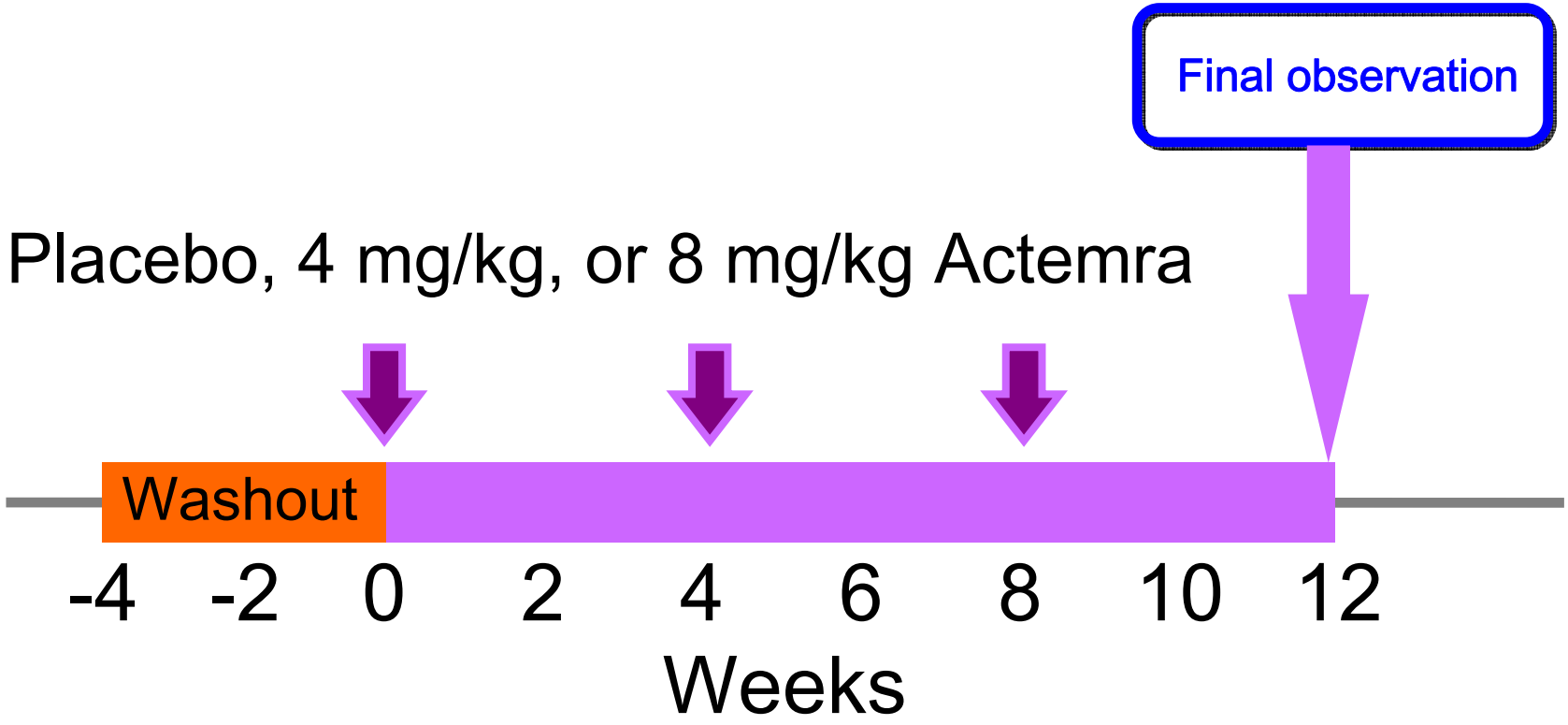
Phase II Trial

Overview of Study (Phase II trial)

Objective	To investigate optimal dose based on efficacy and safety
Type	Double-blind, controlled trial
Subjects	Patients with active RA for at least 6 months duration with inadequate response to one or more DMARDs or immunosuppressants
Method	Patients were randomized to receive placebo, 4 mg/kg Actemra or 8 mg/kg Actemra once every four weeks given intravenously (total: three doses).
Number of patients	164

Arthritis Rheum, 50:1761-9 2004

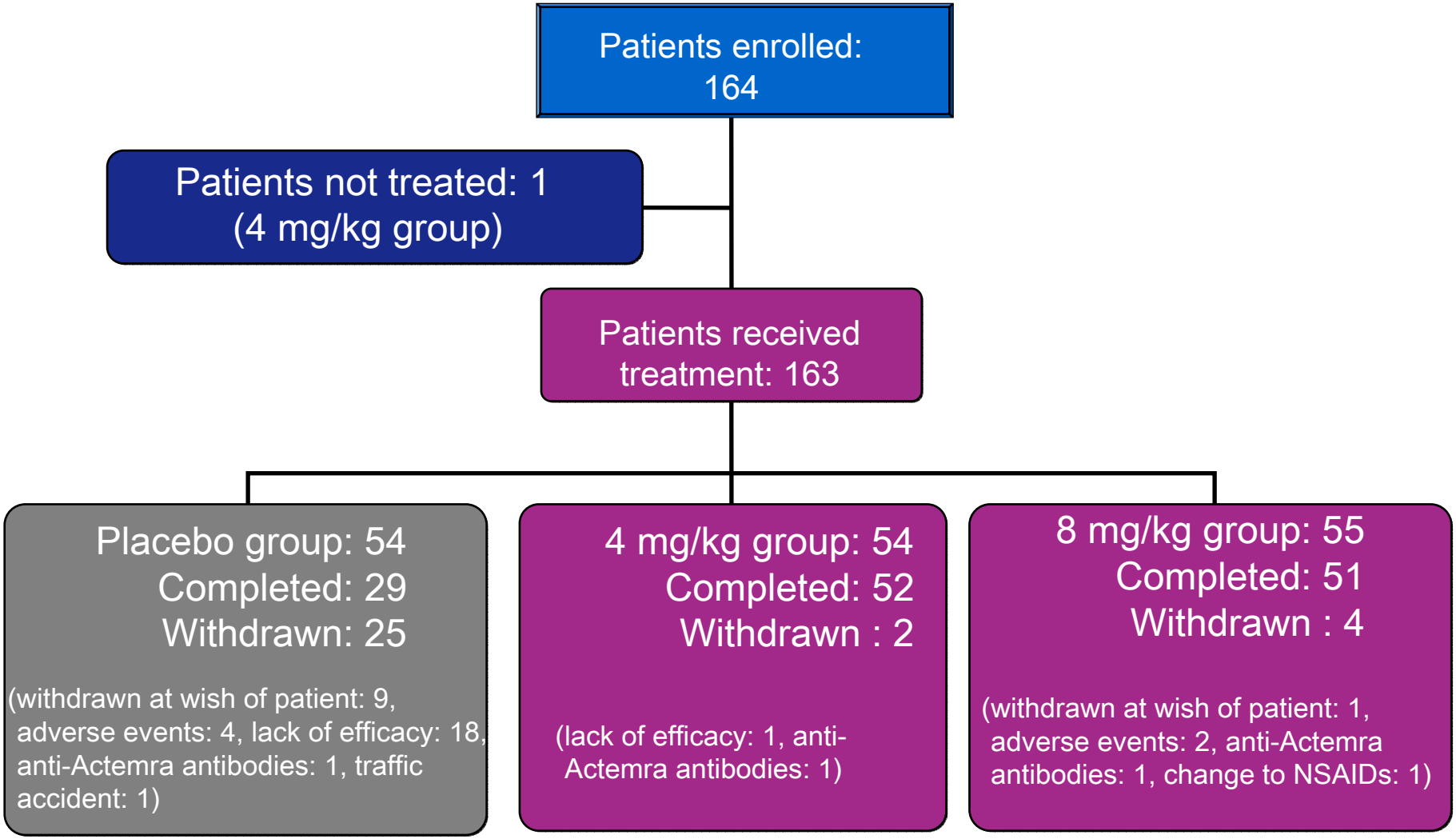
Study Design (Phase II trial)



Primary endpoint: ACR 20 response rate

Arthritis Rheum, 50:1761-9 2004

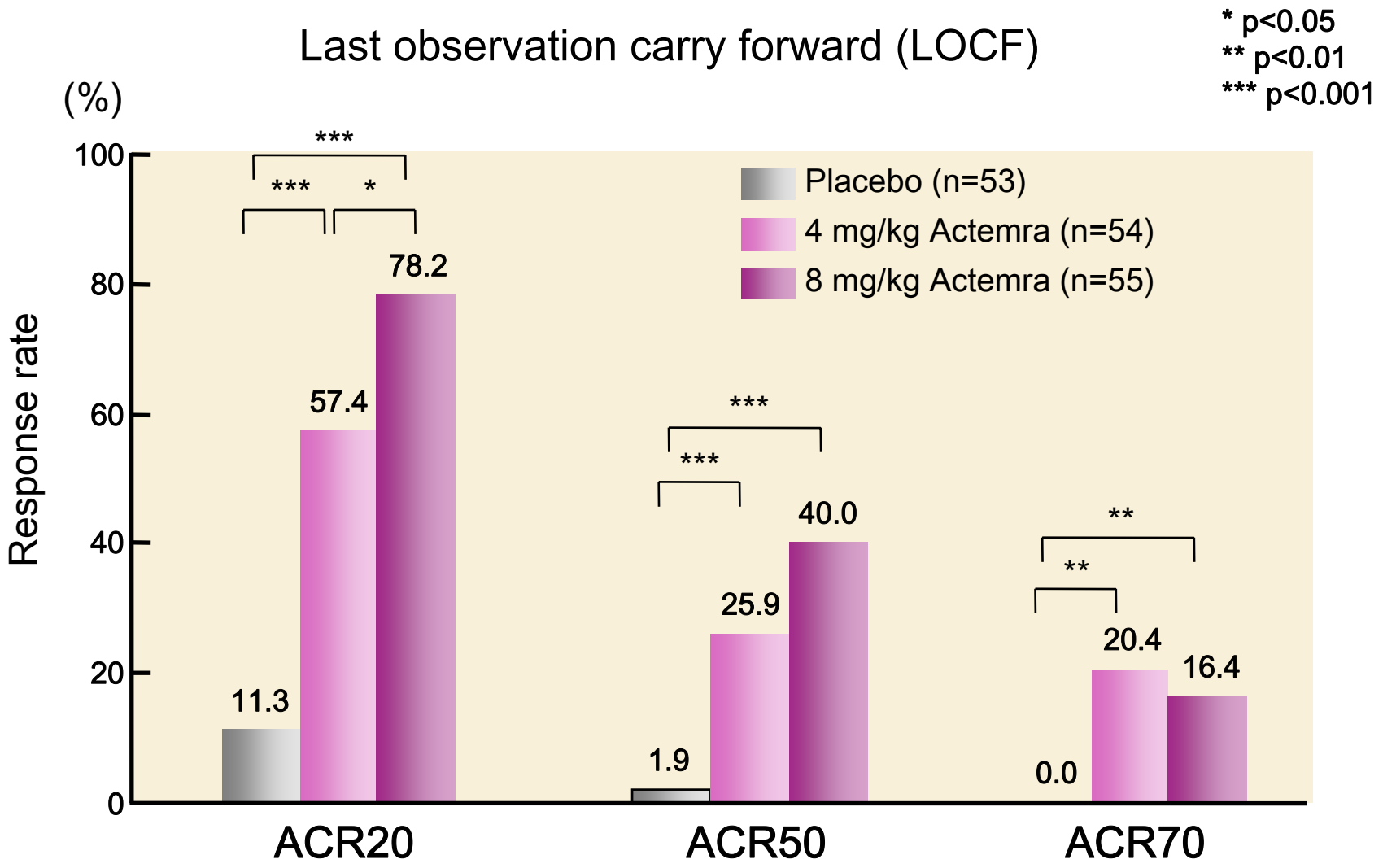
Disposition of Patients (Phase II trial)



Note: multiple reasons were given for in some withdrawn cases.

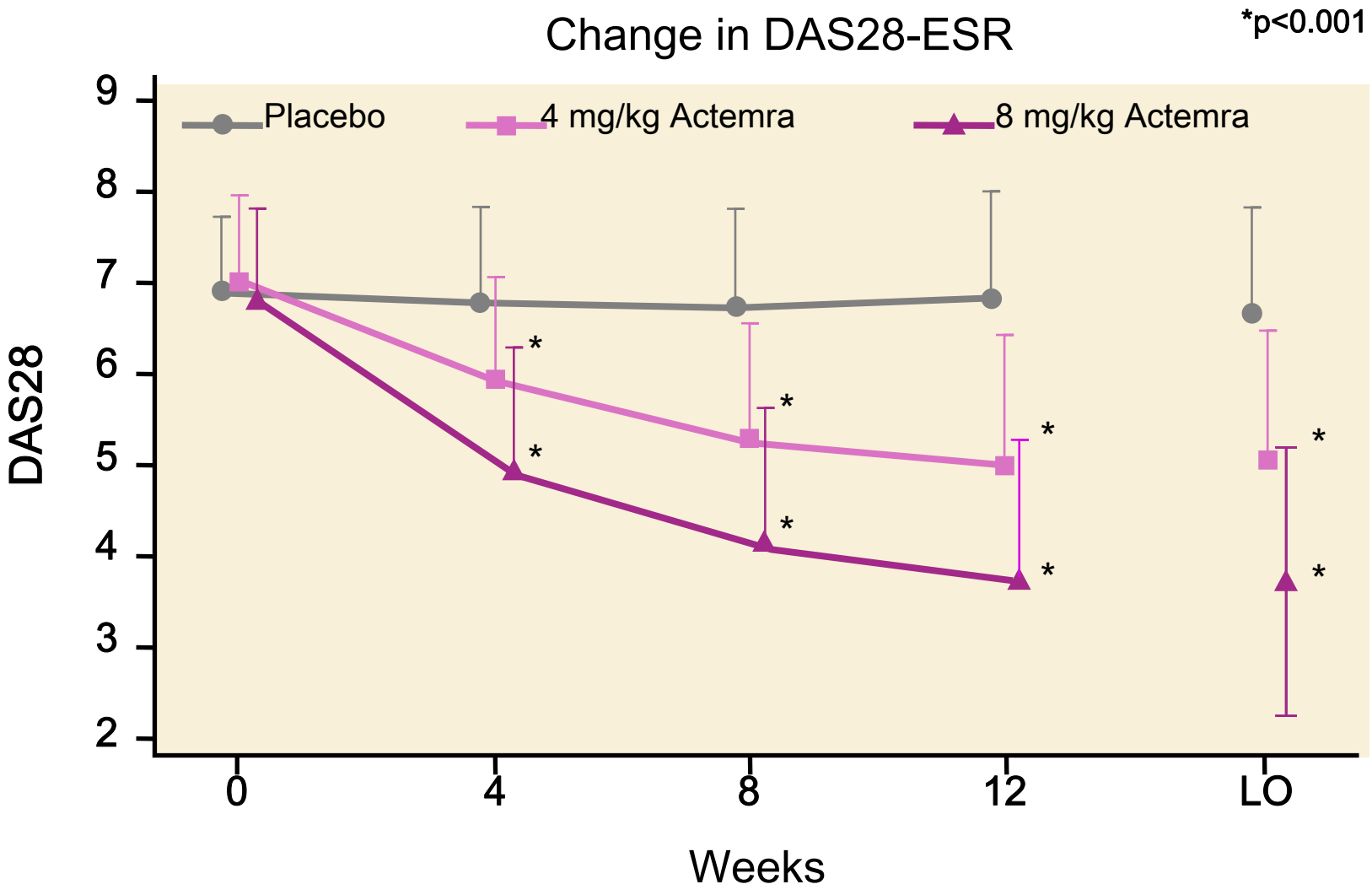
Arthritis Rheum, 50:1761-9 2004

ACR Response Rate (Phase II trial)



Arthritis Rheum, 50:1761-9 2004

Change in DAS28 (Phase II trial)



Arthritis Rheum, 50:1761-9 2004

Phase III Clinical Trial —SAMURAI

S*tudy of*
A*ctive controlled*
M*onotherapy*
U*sed for*
R*heumatoid*
A*rthritis, an*
I*L-6 inhibitor* (SAMURAI)

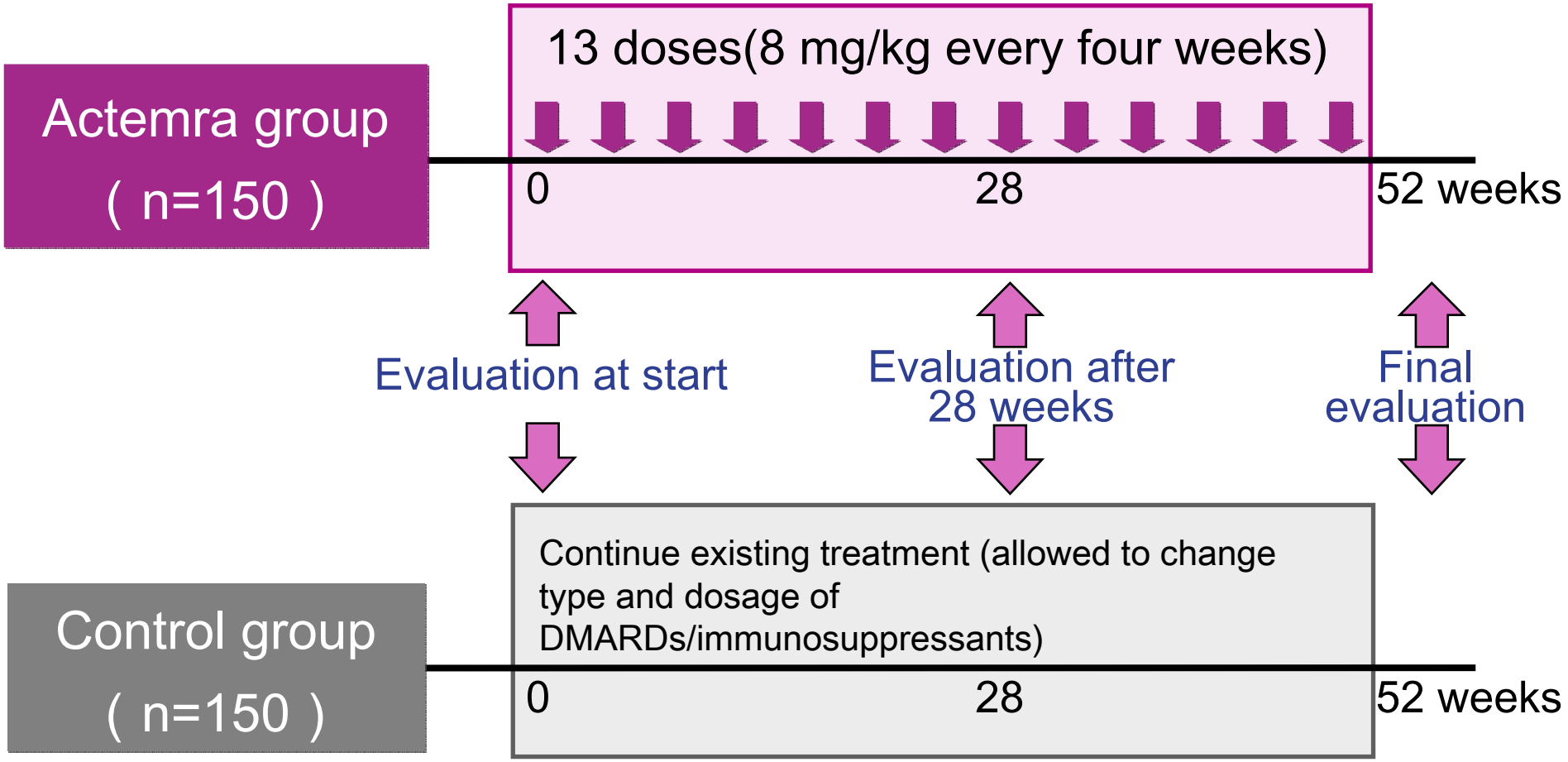
Overview of Study (Phase III trial)—SAMURAI

Objective	To investigate efficacy of inhibition of structural damage, reducing signs and symptoms of RA, and safety
Type	Open parallel-group trial (radiograph reader-blinded controlled trial)
Subjects	Patients with active RA for at least 6 months duration but no more than 5 years who showed an inadequate response to one or more DMARDs or immunosuppressants
Method	(1) Control group: Continue existing treatment (52 weeks) (2) Actemra group: Receive 8 mg/kg Actemra intravenously every four weeks for a total of 13 doses over 52 weeks
Number of patients	306

Ann Rheum Dis, 66:1162-7 2007

Study Design—SAMURAI

Radiograph reader-blinded controlled trial



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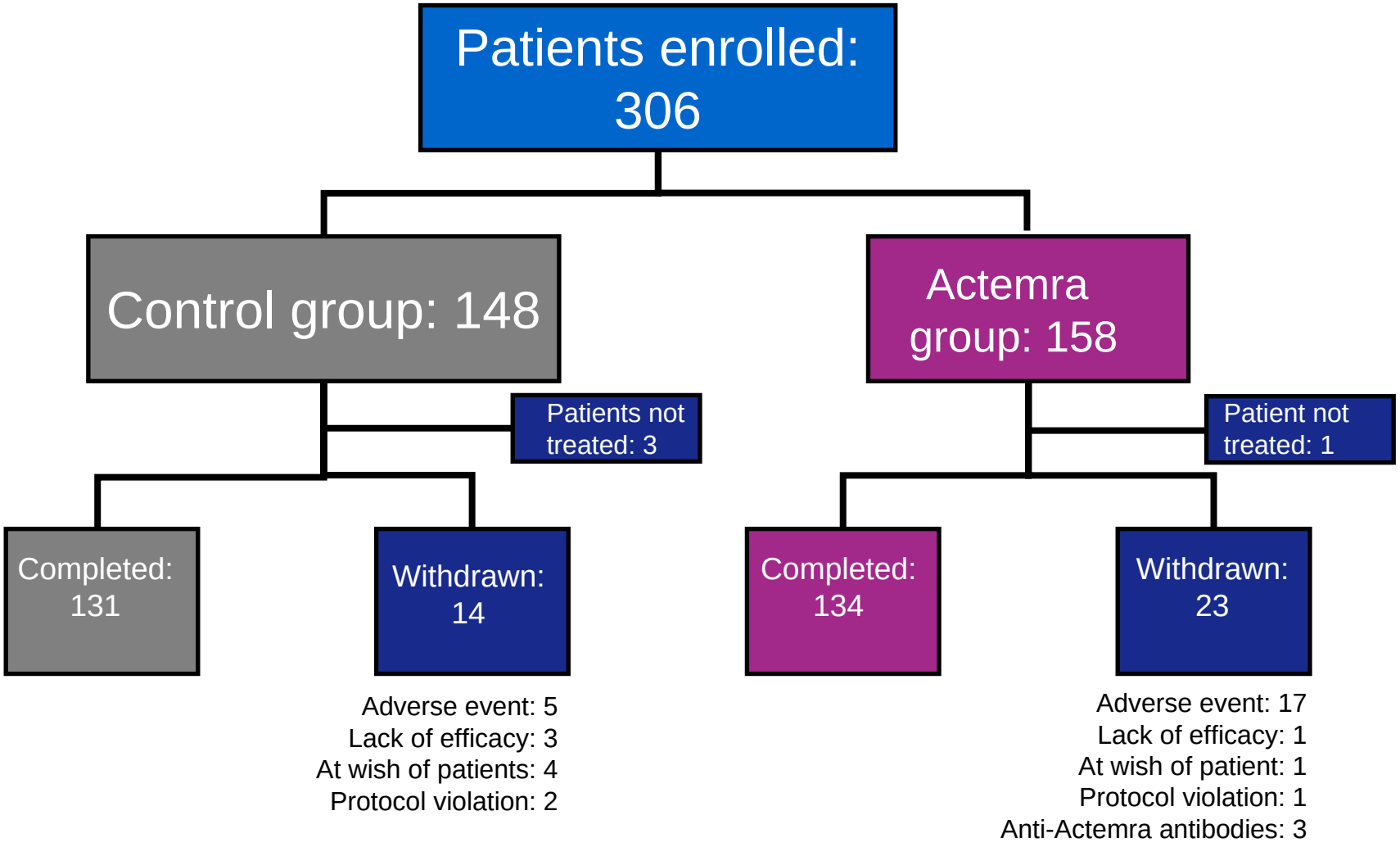
Disposition of Patients—SAMURAI



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Baseline Patient Characteristics—SAMURAI

	Control group	Actemra group
Patients on MTX or DMARDs N(%)	53 (37)	43 (27)
Patients on MTX monotherapy N(%)	44 (30)	73 (46)
Patients on DMARDs and immunosuppressant drugs N(%)	32 (22)	30 (19)
MTX dosage mg(range)	7.1 (4-13)	6.9 (2-13)
Baseline total Sharp score TSS(range)	30.6 (0-209)	28.3 (0-261)
Steroid dose in prednisolone equivalent mg(mean±SD)	5.4±3.2	5.4±3.1

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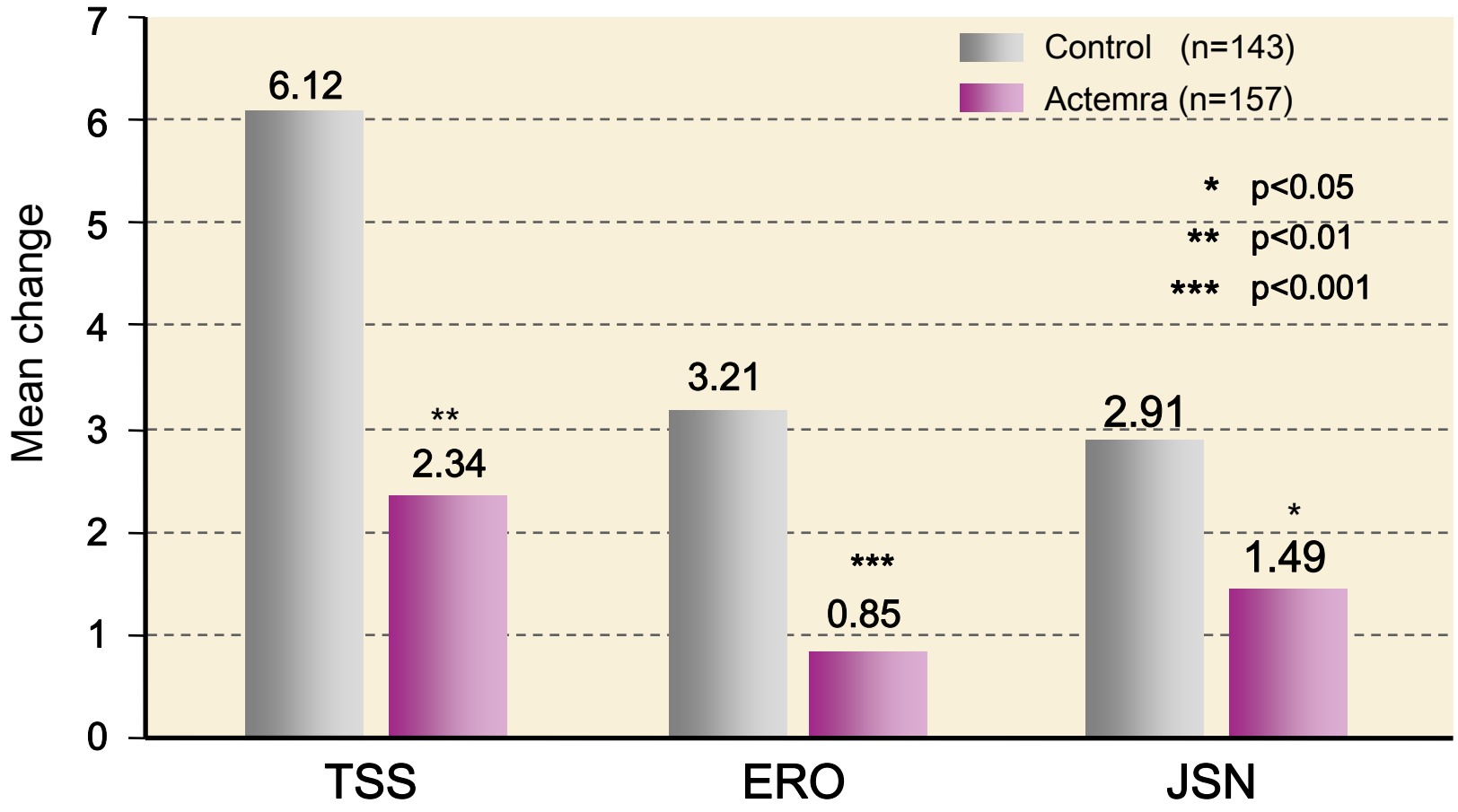
Mean Change in Radiographic Scores (Total Sharp Score: TSS) (after 52 weeks)



ERO = Erosion, JSN = Joint Space Narrowing

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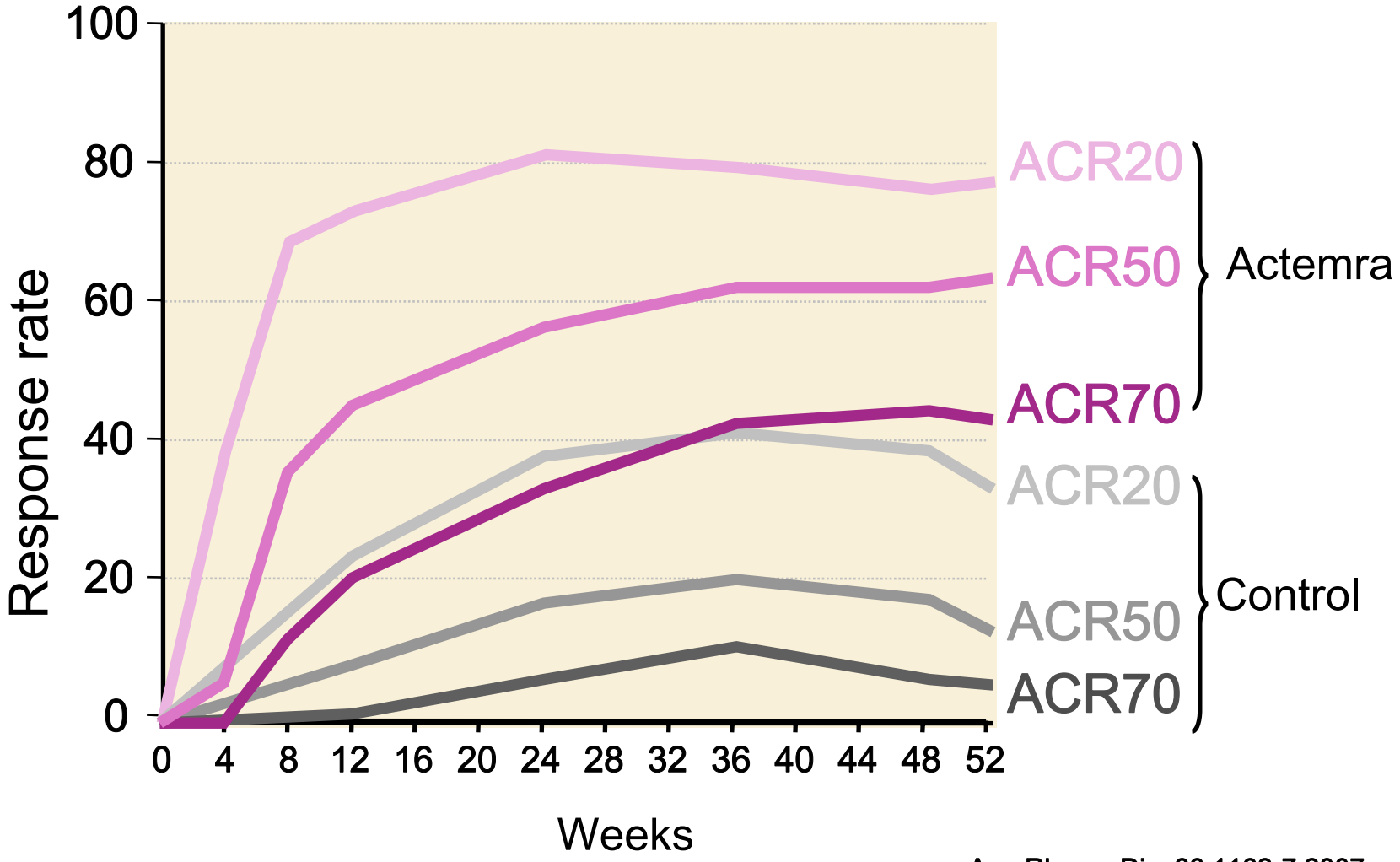
Change in ACR Response Rate (ITT: 52 weeks)



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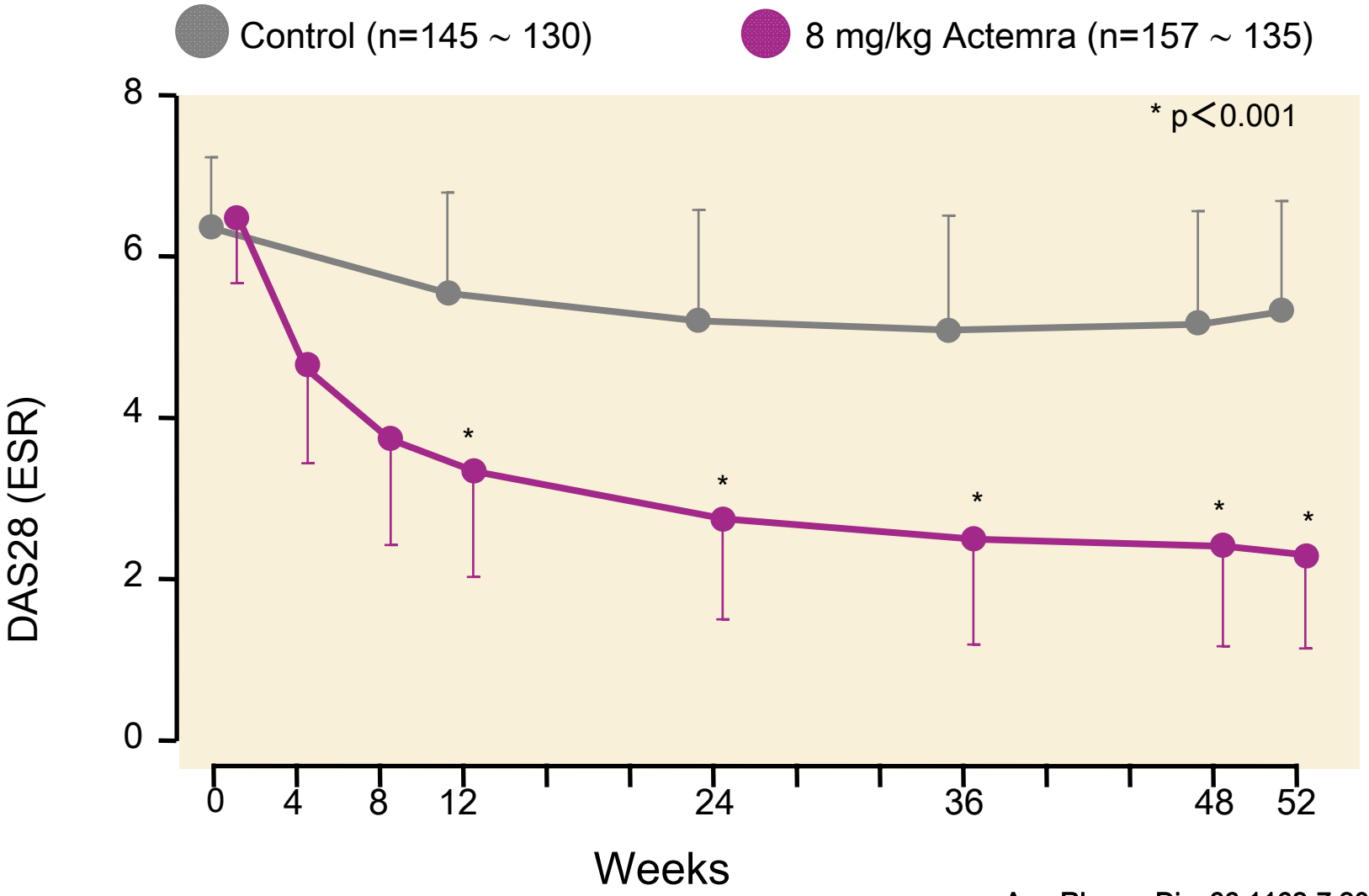
Change in DAS28(ESR)



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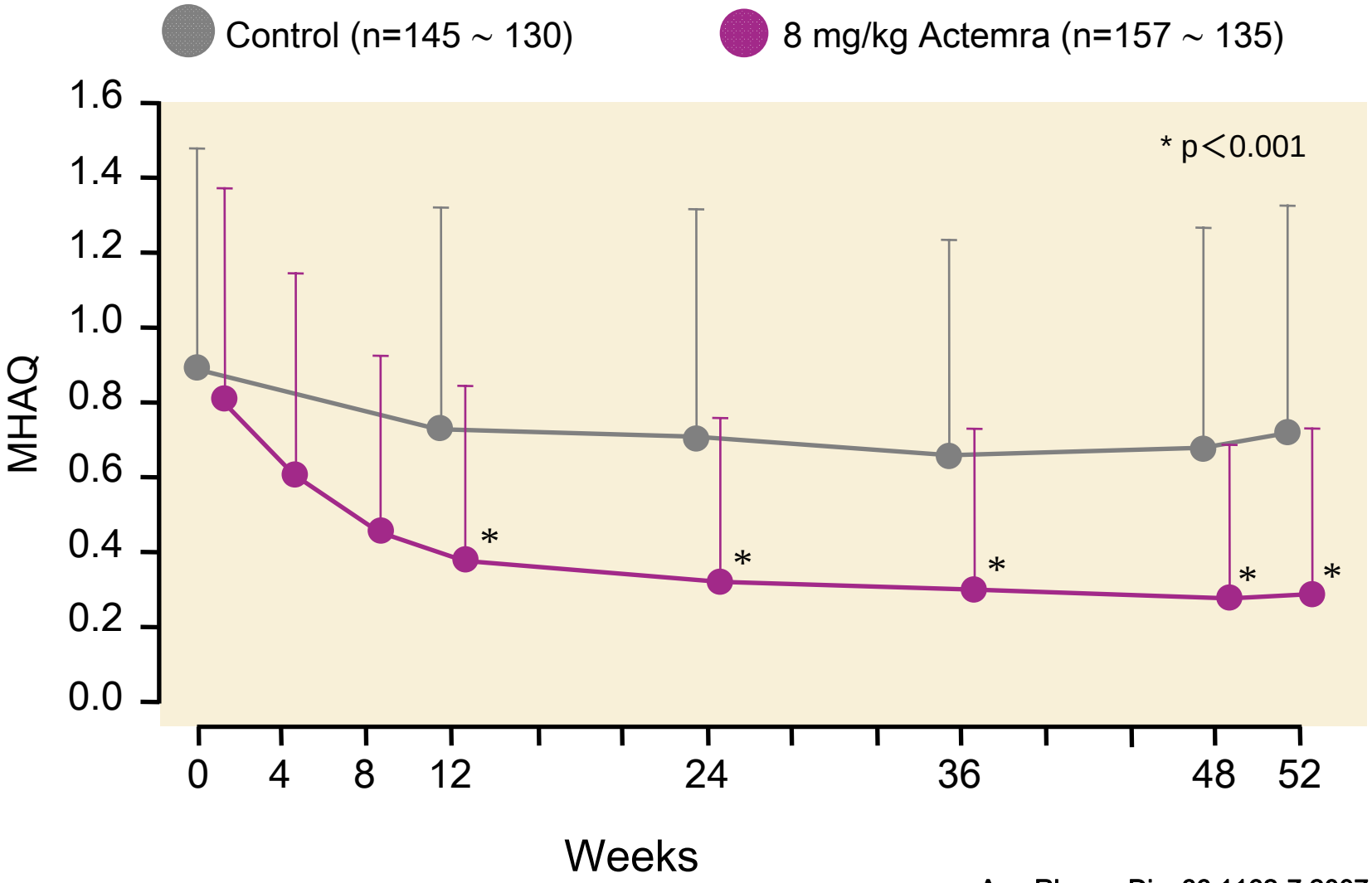
Change in MHAQ



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Adverse Events (frequency of 5% or greater)

	Control (n=145)	Actemra (n=157)
Number of patients (%)	119 (82.1)	140 (89.2)
Adverse event (≥5%) Number of patients (%)		
Nasopharyngitis	47 (32.4)	56 (35.7)
Rash	6 (4.1)	17 (10.8)
Diarrhea	13 (9.0)	13 (8.3)
Headache	3 (2.1)	11 (7.0)
Stomatitis	13 (9.0)	9 (5.7)
Eczema	6 (4.1)	9 (5.7)
Nausea	2 (1.4)	9 (5.7)
Pruritus	2 (1.4)	9 (5.7)
Paronchia	1 (0.7)	9 (5.7)
Vomiting	5 (3.4)	8 (5.1)
Vertebral compression fracture	8 (5.5)	3 (1.9)

Ann Rheum Dis, 66:1162-7 2007

Phase III Double-blind Parallel Group Trial on MRA for Treatment of RA

S*tudy of*
A*ctive controlled*
TO*cilizumab monotherapy for*
R*heumatoid arthritis patients with an*
I*nadequate response to MTX* (SATORI)

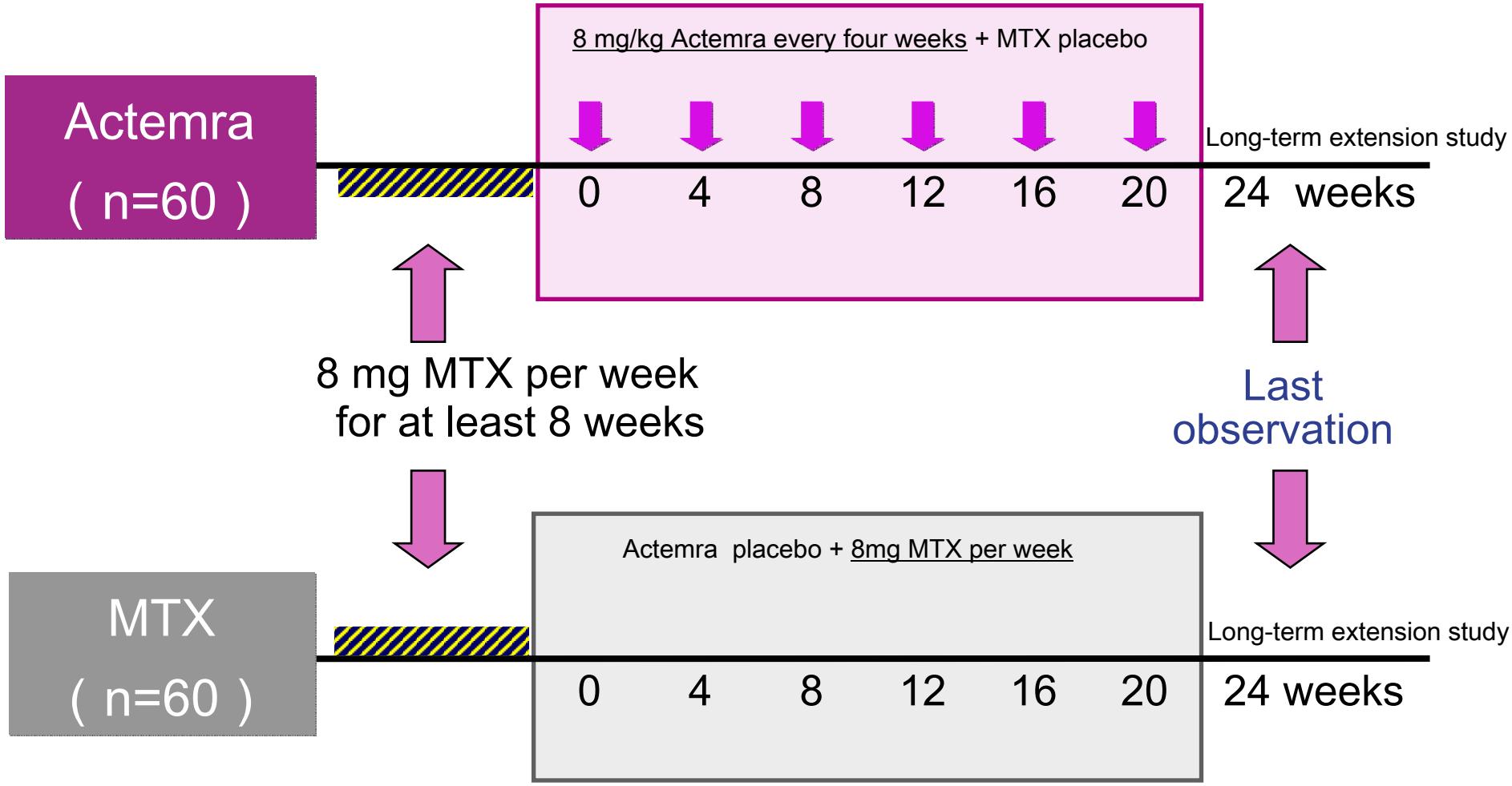
Overview of Study (Phase III trial)—SATORI

Objective	To investigate efficacy and safety (Verify superiority compared to group given methotrexate)
Type	Double-blind controlled trial
Subjects	Patients with a certain level of RA activity who had been given methotrexate
Method	Patients were randomized to receive either 8 mg of methotrexate every week for a total of 24 doses or 8 mg/kg Actemra at four week intervals for a total of 6 doses (total 24 weeks).
Number of patients	127

Source: CHUGAI PHARMACEUTICAL in-house data

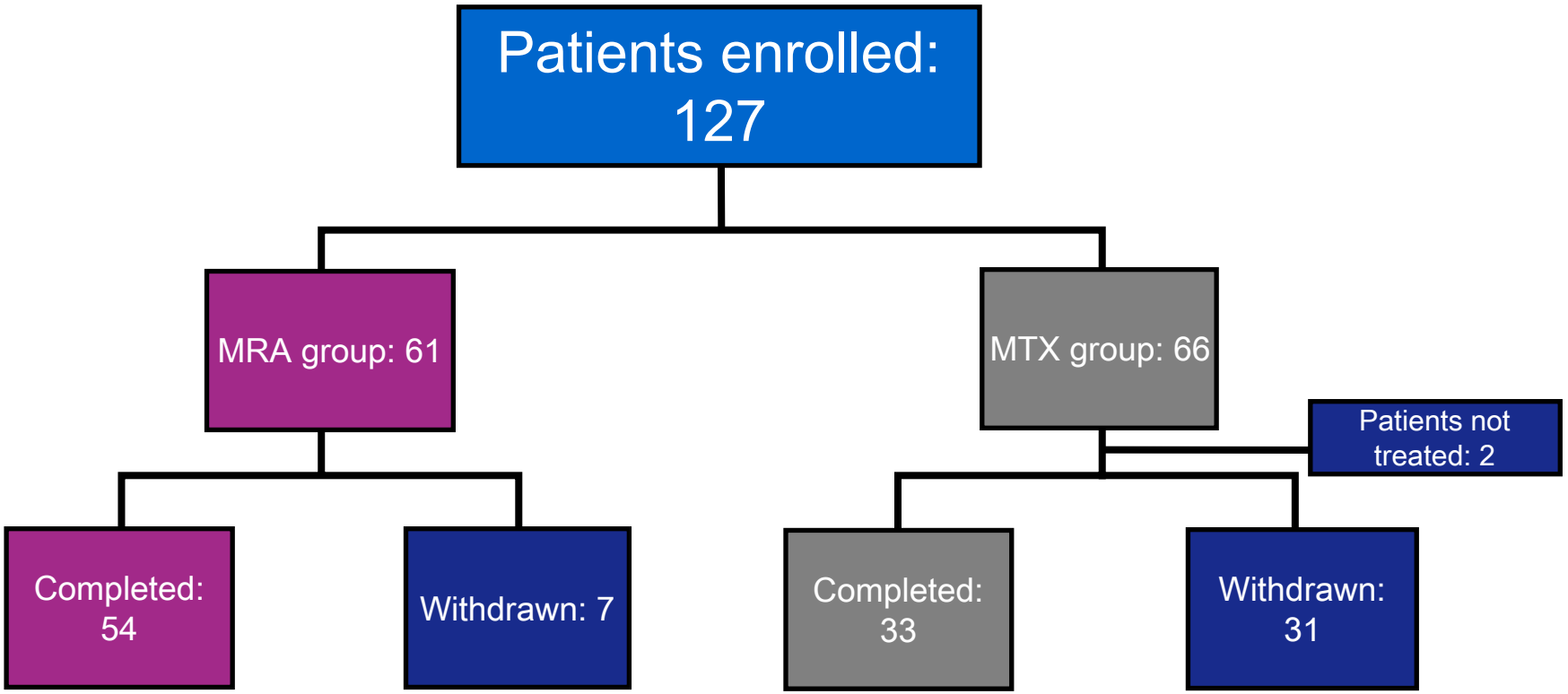
Study Design—SATORI

・ Double-blind　　・ Double-dummy



Source: CHUGAI PHARMACEUTICAL in-house data

Disposition of Patients —SATORI

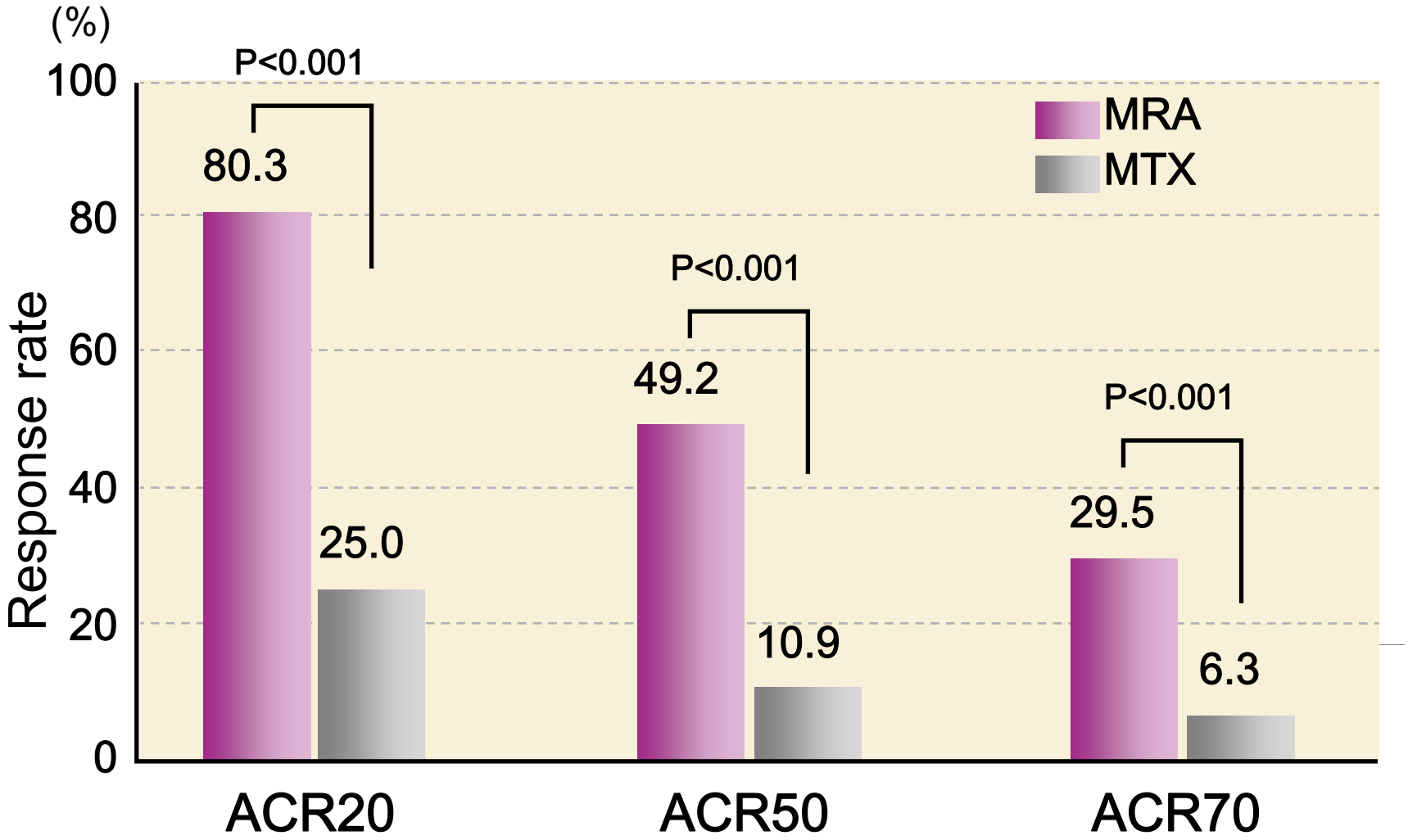


Lack of efficacy: 1
Adverse events: 2
Protocol violation: 2
Others: 2

Lack of efficacy: 20
Adverse events: 3
Withdrawn at wish of patients: 3
Protocol violation: 4
Others: 1

Source: CHUGAI PHARMACEUTICAL in-house data

ACR Response Rate (Last observation)



Source: CHUGAI PHARMACEUTICAL in-house data

Adverse Events

	Actemra (61 patients)	MTX (64 patients)
Adverse events	211 cases	104 cases
Infections	31 cases	19 cases
Serious adverse events	4 cases	3 cases
Infections	2 cases	1 case

Source: CHUGAI PHARMACEUTICAL in-house data

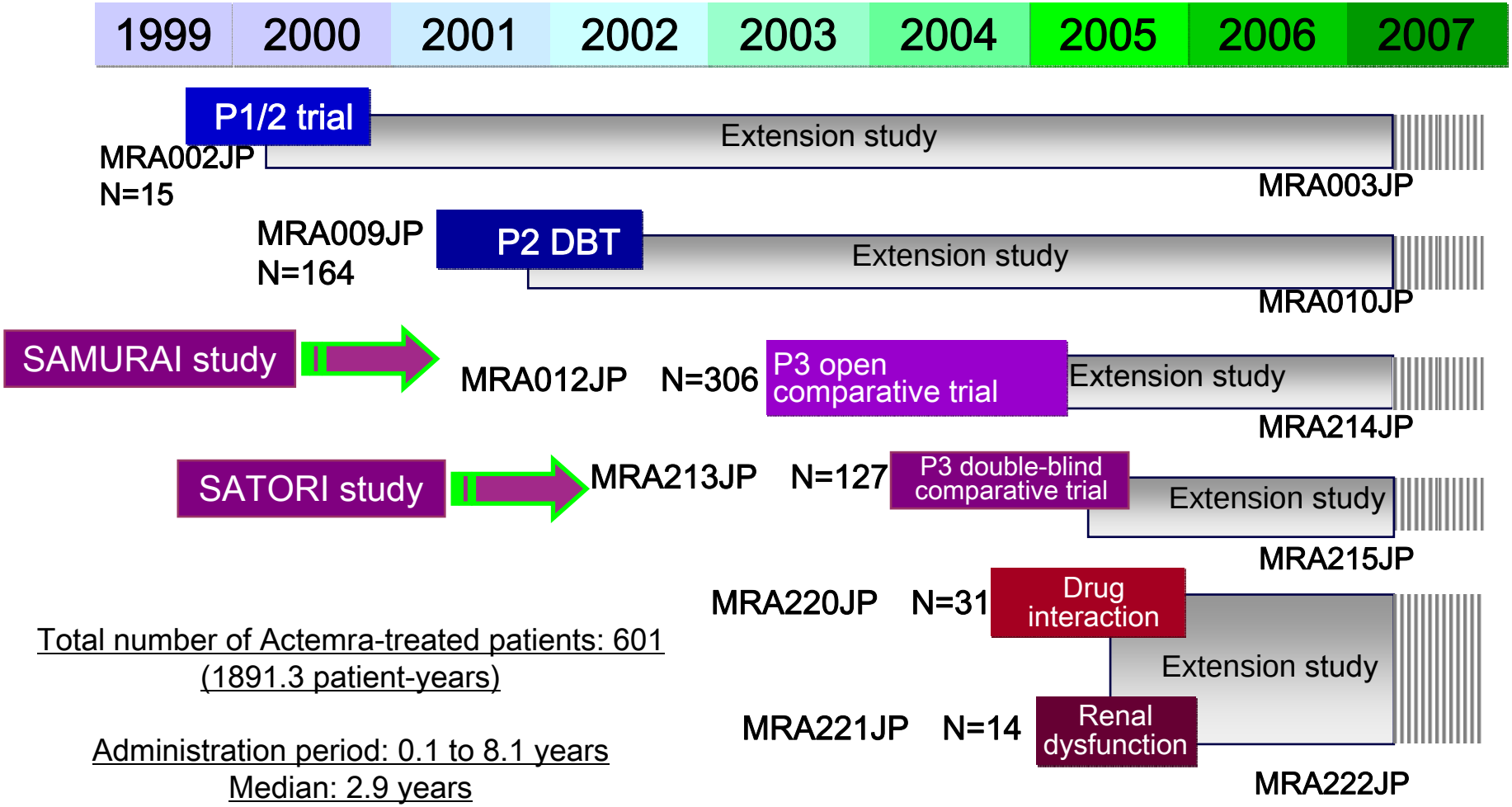
Efficacy—a Summary

Results of clinical studies revealed that Actemra monotherapy:

- offers a high degree of efficacy for patients who show an inadequate response to existing therapies
- is effective in inhibiting structural joint damage
- is associated with a high continuation rate
- maintains its effectiveness over the long-term

Safety Report

Overview of Clinical Studies Conducted in Japan (RA)



Total number of Actemra-treated patients: 601
(1891.3 patient-years)

Administration period: 0.1 to 8.1 years
Median: 2.9 years

Disposition of RA Patients in Japan (n=601)

Age (years)		53.1±11.4 *	
		54.0 (21-80)**	* Mean±SD
Percentage of women out of total		80.4 %	**Median (range)
Duration of illness (years)		6.5±7.1 *	
		4.1 **	
Class	I	8.2 %	
	II	72.2 %	
	III	19.6 %	
Stage	I	4.3 %	
	II	33.9 %	
	III	29.6 %	
	IV	22.6 %	
Total patient-years		1891.3	

Source: CHUGAI PHARMACEUTICAL in-house data

Adverse Drug Reactions (RA)

	Number of patients	Number of ADRs
Total ADRs	585 (97.3%)	5,822
	307.8 / 100 patient-years	
Serious ADRs	114 (19.0%)	191
	10.1 / 100 patient-years	

Source: CHUGAI PHARMACEUTICAL in-house data

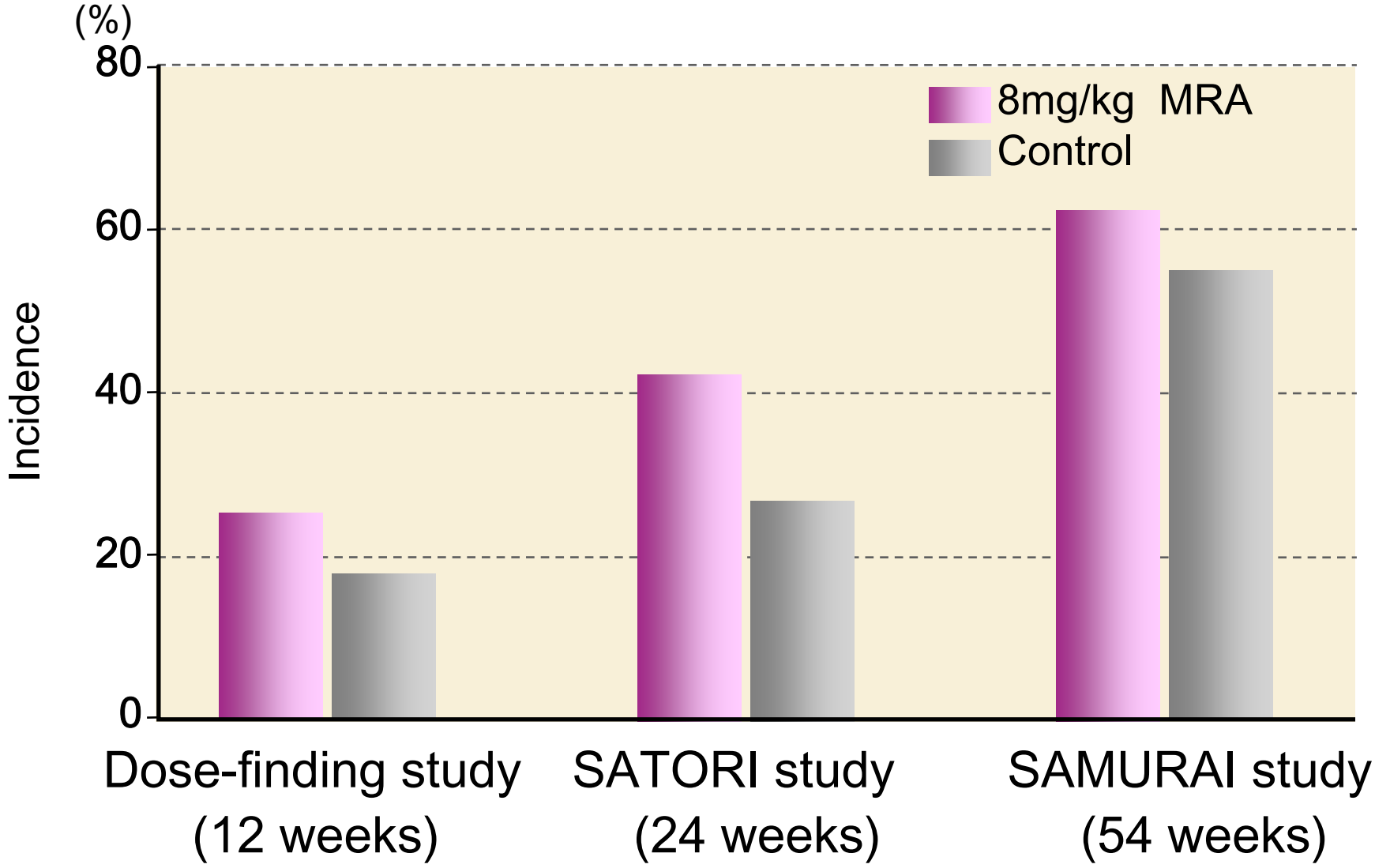
Major ADRs in RA Patients in Japan

By SOC (system organ class)	Number of ADRs	Events/ 100patient-year
Infections and infestations	1888	99.8
Neoplasms benign, malignant and unspecified	30	1.6
Nervous system disorders	254	13.4
Eye disorders	125	6.6
Cardiac disorders	37	2.0
Vascular disorders	84	4.4
Respiratory, thoracic and mediastinal disorders	326	17.2
Gastrointestinal disorders	506	26.8
Skin and subcutaneous tissue disorders	403	21.3
Musculoskeletal and connective tissue disorders	106	5.6
General disorders and administration site conditions	171	9.0
Investigations	1632	86.3

total patient-years: 1891.3

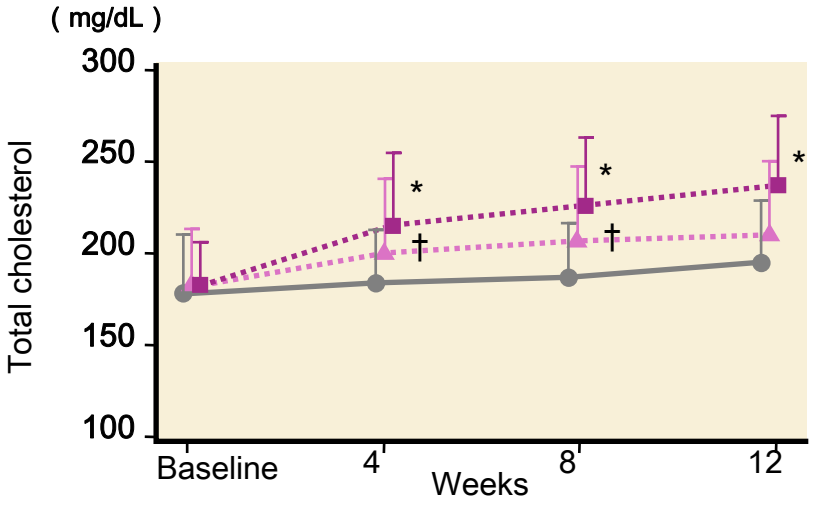
Source: CHUGAI PHARMACEUTICAL in-house data

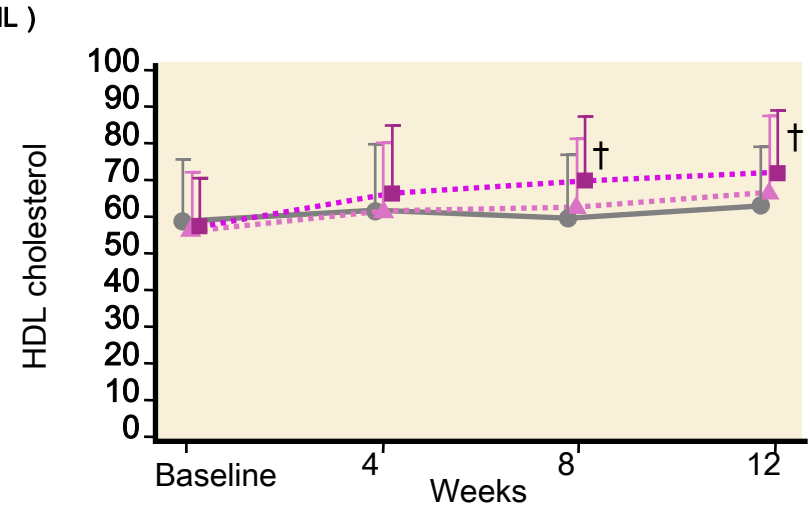
Incidence of Infectious ADRs in Controlled Trials

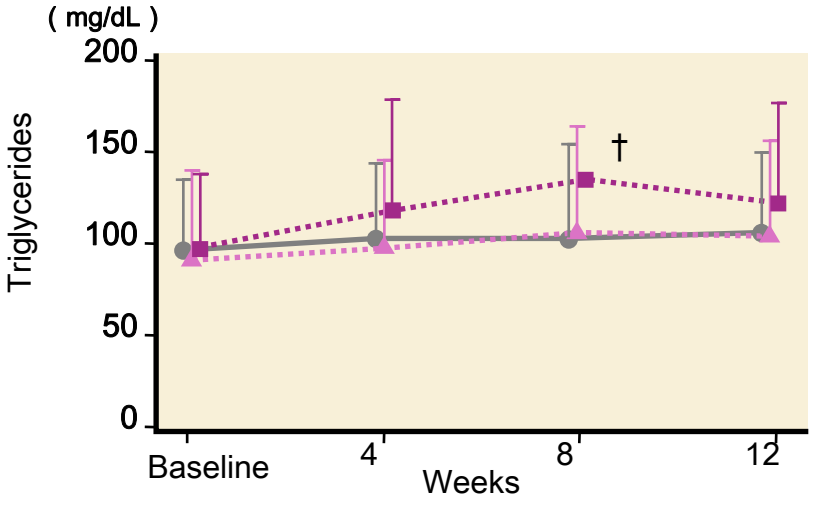


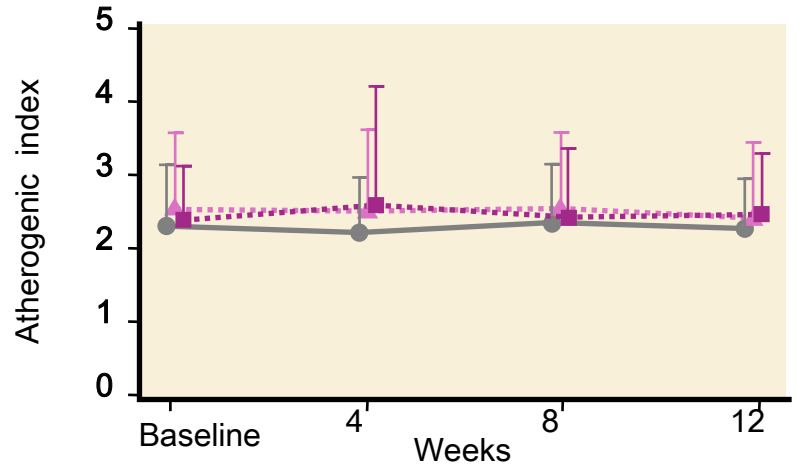
Source: CHUGAI PHARMACEUTICAL in-house data

Lipid Parameters (Phase II trial)









Placebo 4 mg/kg 8mg/kg

*p<0.001 †p<0.05

Arthritis Rheum, 50:1761-9 2004

Incidence of Anti-tocilizumab Antibodies in Japan

	Neutralizing antibodies Number of patients (%)	IgE antibodies Number of patients(%)	Anti-Actemra antibodies Number of patients (%)
2 mg/kg	0/5 (0.0)	0/5 (0.0)	0/5 (0.0)
4 mg/kg	0/59 (0.0)	3/59 (5.1)	3/59 (5.1)
8 mg/kg	5/556 (0.9)	11/556 (2.0)	16/556 (2.9)
Total	5/620 (0.8)	14/620 (2.3)	19/620 (3.1)

RA: 18 out of 601 patients (3.0%)
Polyarticular-course JIA: 1 out of 19 patients (5.3%)

Source: CHUGAI PHARMACEUTICAL in-house data

Incidence of Anti-Actemra Antibodies in Phase II Clinical Trials for RA in Europe

	Actemra (mg/kg)	Neutralizing antibodies Number of patients (%)	IgE antibodies Number of patients (%)	Anti-Actemra antibodies Number of patients (%)	Total Number of patients (%)
MTX (-)	2	10/53 (18.9)	9/53 (17.0)	14/53 (26.4)	22 /159 (13.8%)
	4	2/54 (3.7)	7/54 (13.0)	8/54 (14.8)	
	8	0/52 (0.0)	0/52 (0.0)	0/52 (0.0)	
MTX (+)	2	0/52 (0.0)	2/52 (3.8)	2/52 (3.8)	3 /151 (2.0%)
	4	1/49 (2.0)	0/49 (0.0)	1/49 (2.0)	
	8	0/50 (0.0)	0/50 (0.0)	0/50 (0.0)	

No antibodies were observed in the 8 mg/kg group even when MTX was not administered concomitantly.

Arthritis Rheum, 54:2817-29 2006

Safety (ADRs)

- ADRs were observed in 751 out of 783 patients (95.9%).
  - Castleman's disease: 35 patients
  - RA: 601 patients
  - Polyarticular-course JIA: 19 patients
  - Systemic-onset JIA: 128 patients

- Major ADRs
  - Nasopharyngitis: 421 patients (53.8%)
  - Increase in cholesterol: 292 patients (37.3%)
  - Increase in LDL: 148 patients (18.9%)
  - Increase in triglycerides: 126 patients (16.1%)
  - Increase in ALT(GPT): 119 patients (15.2%)

Safety (Important ADRs)

- Anaphylactic shock (incidence unknown[1)]),
  Anaphylactic symptoms (0.4%)
- Infections:

– Pneumonia (7.8%), herpes zoster (6.4%), infective gastroenteritis (3.4%), cellulitis (3.3%), infectious arthritis (0.9%), sepsis (0.4%) and, nontuberculous mycobacteria (0.4%), tuberculosis (0.3%) and pneumocystis jirovecii pneumonia (0.1%)

- Intestinal perforation (incidence unknown[1)])
- Neutropenia（7.0%）
- Cardiac failure (incidence unknown[2)])

1) Presented as 'incidence unknown' because ADRs occurred in overseas clinical studies, for which incidence cannot be calculated.
2) Presented as 'incidence unknown' because the ADR occurred during off-label use, for which incidence cannot be calculated.

Indications

- The following diseases which do not show sufficient response to the existing therapies

  - Rheumatoid arthritis[1)]
    (including inhibition of progression of structural joint damage)
  - Polyarticular-course juvenile idiopathic arthritis [1)]
  - Systemic juvenile idiopathic arthritis[2)]

1) Actemra should be administered to patients who have failed to show sufficient response in the past despite receiving appropriate treatment with one or more anti-rheumatic drugs.
2) Actemra should be administered to patients who have failed to show sufficient response in the past despite receiving appropriate treatment with corticosteroids.